A Straightforward Route to Ibophyllidine Alkaloids by a Double Transannular Cyclization

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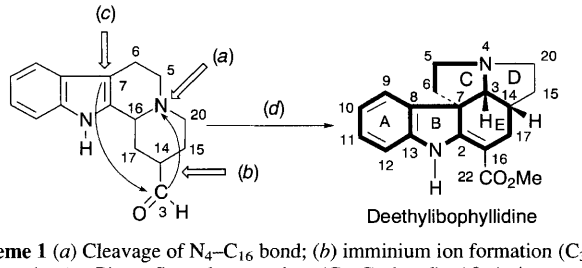
Ring cleavage of indolo[2,3-*a*]quinolizidine **4** to an octahydroazecino[5,4-*b*]indole system, followed by introduction of a cyano substituent and double transannular cyclization gives (±)-deethylibophyllidine.

The synthesis of monoterpenoid indole alkaloids possessing a pyrrolo[2,3-*d*]carbazole moiety (ABCE rings), *e.g. Aspidosperma, Strychnos* and ibophyllidine alkaloids, has been extensively explored during the last twenty years. The construction of the characteristic 2,3,3-trisubstituted indoline unit by formation of the quaternary stereocentre at C-7[1] is usually the crucial step of the synthesis.[2]

In this paper we describe a new, straightforward synthetic entry to 2,3,3-trisubstituted indole alkaloids embodying the pyrrolo[2,3-*d*]carbazole skeleton based on the transannular Pictet–Spengler cyclization (bond formed C-3–C-7) of an iminium ion generated intramolecularly (bond formed C-3–N-4) from an appropriately substituted azecino[5,4-*b*]indole. The usefulness of this strategy is exemplified by a synthesis of the alkaloid deethylibophyllidine.[3] Our approach constitutes a 'criss-cross'-type annulation,[4] in which the key octahydroazecino[5,4-*b*]indole intermediate is prepared by ring cleavage (bond cleaved N-4–C-16) of a readily accessible octahydroindolo[2,3-*a*]quinolizine (Scheme 1).

The synthesis starts with 2-formylindolo[2,3-*a*]quinolizidine **3**, which was prepared from tryptophyl bromide and pyridine acetal **1** by $NaBH_4$ reduction of the initially formed pyridinium salt **2** with further treatment of the resulting 1,2,3,6-tetrahydropyridine with acetic acid.[5] The latter process brought about deprotection of the acetal function, isomerization of the double bond to give an enamine,[6] and cyclization *via* an iminium ion. Aldehyde **3** was isolated as a 7:2 mixture of epimers and, without purification, was protected as an ethylene acetal using Amberlyst-15[7] as the catalyst. The resulting acetals **4a** and **4b**† were separated by column chromatography (the first in this reaction sequence). Although this separation is not strictly necessary from the synthetic standpoint since C-16 (corresponding to C-12b in the indolo[2,3-*a*]quinolizidine system) is not a stereogenic centre in the final product, it is convenient from the practical point of view due to the slightly different reactivity of both epimers (see below). The overall yield for the four initial steps (i–iv in Scheme 2) was 36%.

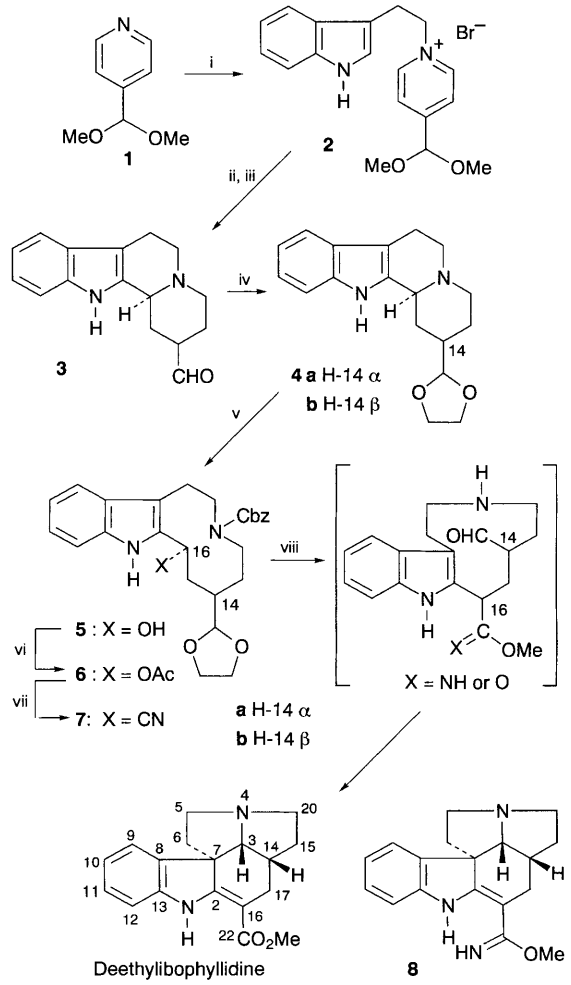
Acetals **4a** and **4b** were independently submitted to C/D ring cleavage[8,9] with benzyl chloroformate and excess water in THF in the presence of sodium carbonate to stereospecifically[8b] give the respective epimeric alcohols **5a** (72%) and **5b** (40%). For the introduction of the additional carbon (C-22), alcohol **5a** was converted to the corresponding acetate **6a** (92%) and then treated with NaCN in Me_2SO. A nearly equimolecular mixture of epimeric nitriles **7** (88%) was obtained, thus suggesting that the S_N1 process is preponderant. Operating in a similar manner from alcohol **5b**, a mixture of nitriles **7** was also obtained, although in lower overall yield (40%).



Scheme 1 (*a*) Cleavage of N_4–C_{16} bond; (*b*) imminium ion formation (C_3–N_4 bond); (*c*) Pictet–Spengler reaction (C_3–C_7 bond); (*d*) 'criss-cross' annulation

The NMR spectra of octahydroazecinoindoles (**5**–**7**) are very complicated due to the conformational flexibility of medium-sized rings and the duplicity of signals caused by the restricted rotation of the carbamate bond.‡

The crucial step of the synthesis was the simultaneous formation of rings CDE by a Pictet–Spengler reaction. This double transannular cyclization was satisfactorily accomplished by treatment of the mixture of nitriles **7** with HCl in methanol, followed by *in situ* acid hydrolysis.[10] The alkaloid deethylibophyllidine, which was identified by comparison with a sample prepared by an alternative route,[3d] was directly obtained in 30% yield (not optimized). This expeditious one-pot transformation involves six successive chemical processes: formation of an imidate from the cyano group, cleavage of the carbamate protecting group, hydrolysis of the acetal, generation of an iminium salt, hydrolysis of the imidate, and finally, cyclization upon the substituted indole β-position with isomerization of the



Scheme 2 *Reagents and conditions*: i, tryptophyl bromide, 90 °C, 16 h; ii, $NaBH_4$, MeOH; iii, aq. AcOH, room temp. 36 h; iv, $(CH_2OH)_2$, $CaCl_2$, Amberlyst-15, room temp., 3d; v, CbzCl, H_2O, THF, Na_2CO_3, 50 °C, 3 h; vi, Ac_2O, DMAP, 2 h, room temp.; vii, NaCN, Me_2SO, 95 °C, 7 h; viii, HCl (g), MeOH, 4 °C, 16 h; then H_2O, 90 min

resulting indolenine double bond to give the α-anilinoacrylate moiety.

It is worth mentioning that the pentacyclic imidate **8** was also isolated in 30% yield. However, **8** (a vinylogous *O*-methylurea) could not be further hydrolysed to deethylibophyllidine, thus suggesting that hydrolysis of the imidate occurs before cyclization.

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Footnotes

† Satisfactory analytical and spectral data were obtained for all new compounds.

‡ Aliphatic signals in the ^{13}C NMR spectrum of **5a**: (*Z*/*E* rotamers) δ 24.5/25.4 (C-6), 27.0 (C-15), 34.9/35.0 (C-14), 35.8/36.2 (C-17), 47.3/47.7 (C-20), 51.7/50.7 (C-5), 64.8/64.9 (OCH_2), 67.1/67.4 (CO_2CH_2), 67.5/67.6 (C-16), 106.0/106.2 (CH acetal)

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