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The Pummerer Cyclization Route to the Ibophyllidine Alkaloids. Total Synthesis of (±)-Deethylibophyllidine

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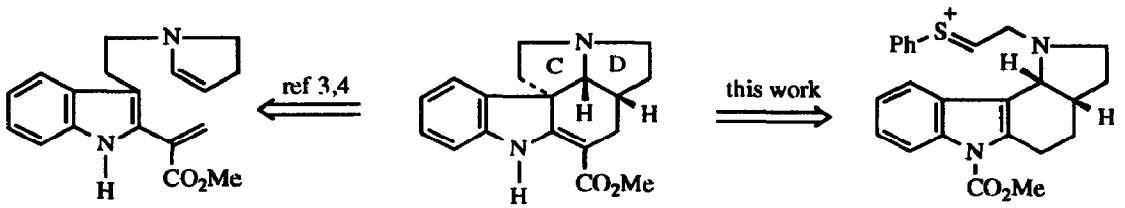
Abstract: Pummerer cyclization of β-aminoethyl sulfoxide **6** was effectively achieved using TFAA-TFA in toluene at 80 °C. The cyclized product **7** was then converted to the alkaloid deethylibophyllidine. The required pyrrolo[3,2-*c*]carbazole **6** was prepared in five steps from 4-methoxyphenethylamine.

The ibophyllidine alkaloids constitute a small group of indole alkaloids of the ibogan type[1] characterized by the presence of the structurally unusual pyrrolizino[1,7-*cd*]carbazole ring system, which incorporates a pyrrolidine D-nor ring[2] instead of the piperidine ring usually found in the monoterpenoid indole alkaloids.

The ibophyllidine alkaloids have previously been synthesized through a synthetic strategy[3,4] involving the simultaneous formation of the C and E rings by an intramolecular Diels-Alder reaction. In this work we describe the total synthesis of (±)-deethylibophyllidine[1b] from an appropriately substituted octahydropyrrolo[2,3-*a*]carbazole through a new synthetic approach which implies a tandem process: a Pummerer rearrangement[5] followed by a thionium ion cyclization upon a 2,3-disubstituted indole.[6]



Deethylibophyllidine (**1**)

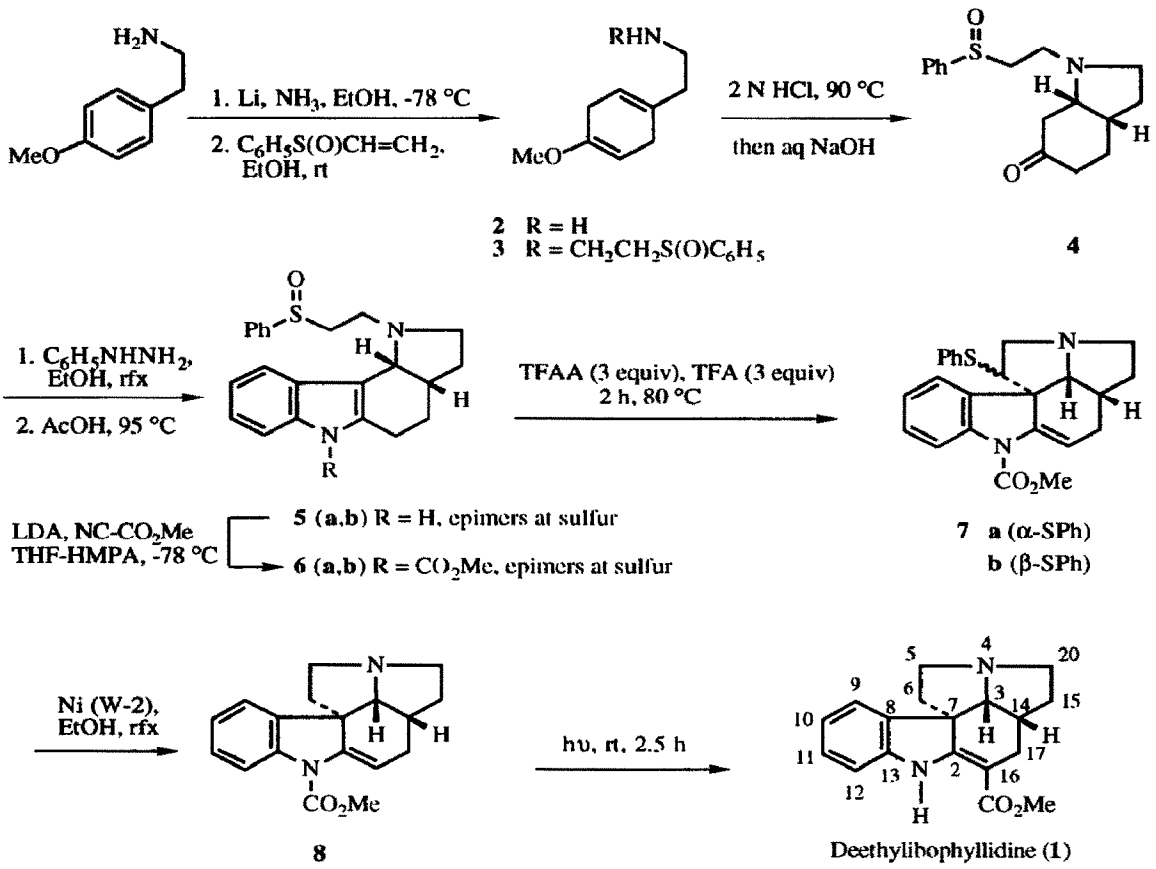
Scheme 1

The synthesis starts with 4-methoxyphenethylamine, which was converted to the dihydrobenzene **2**[7] by Birch reduction (Scheme 2). Addition of **2** to phenyl vinyl sulfoxide yielded β-aminoethyl sulfoxide **3** which, without further purification, was treated with 2 N HCl at 90 °C for 3 hours. After basification with sodium hydroxide[8] and flash chromatography on silica gel (EtOAc), *cis*-octahydroindolone **4**[9] was obtained in a stereoselective manner in 54% overall yield for the three steps.

The Fischer indolization from the phenylhydrazone of ketone **4** took place regioselectively when AcOH was used as an acid catalyst to afford the key tetracyclic derivative **5** (60% yield). The sequence of four steps developed here to obtain the pyrrolo[3,2-*c*]carbazole framework constitutes an efficient new entry to this tetracyclic skeleton.[10] It is noteworthy that the sulfoxide group did not undergo Pummerer rearrangement under the acidic conditions required for both the hydrolytic cleavage of the enol ether and the Fischer indolization. The stability of the β-amino sulfoxide moiety is in contrast with the higher reactivity of sulfoxides with an electron withdrawing substituent at the α-position and constitutes an advantage from the synthetic point of view because the sulfoxide group can be incorporated in an early stage of the synthesis with the required oxidation level at the methylene carbon adjacent to the nitrogen atom.

A limited number of examples of Pummerer reactions from β-amino sulfoxides have been reported so far.[6,11] In order to carry out the tandem process, the indole nitrogen of **5** was first protected as a N(1)-methoxycarbonyl derivative. This methoxycarbonylation was initially troublesome since the use of several standard procedures (LDA, $ClCO_2Me$ or dimethylcarbonic anhydride; $(CO_2Me)_2O$, CH_3CN, DMAP; or NaOH aq, TBAB, $ClCO_2Me$) caused the partial or total formation of carbazole derivatives by way of an additional methoxycarbonylation at N(4) and further gramine-type cleavage. The exclusive formation of the required protected indole **6** was achieved in good yields (76%) using LDA as a base and the less acylating agent methyl cyanoformate. The methoxycarbonyl group not only ensures the stability of the cyclized product but also allows for the elaboration of the anilinoacrylate moiety in the last step of the synthetis. The best results for the tandem Pummerer reaction-cyclization were obtained when a mixture of sulfoxides **6** was treated with an equimolecular mixture of TFA and TFAA (3 equiv) at 80 °C for 2 h. Under these experimental conditions the crucial quaternary center at C-7 was formed in a satisfactory manner[12] and the pentacyclic derivative **7**[13] was obtained in 63% yield as an epimeric mixture at C-6 (both epimers gave **8** on desulfurization). Similar results were obtained from the separate epimers **6a** or **6b**.

The *N*-(methoxycarbonyl)enamine function present in **7** allowed us to effect both the chemoselective hydrogenolysis of the phenylthio substituent without affecting the double bond at C-2 and the photochemical rearrangement[14] to the vinylogous carbamate moiety present in the ibophyllidine alkaloids. Thus, desulfurization of **7** using Raney nickel (W-2) in ethanol gave **8** (63% yield), which was then irradiated with a medium-pressure mercury lamp to give (±)-decthylibophyllidine **1**[15] in 50% yield. Our synthetic material **1** was identified by comparison of its ^1H NMR spectrum (500 MHz) with that of the natural product.[1b] The good yield in the formation of the anilinoacrylate unit in this series is in contrast with the moderate yields obtained in analogous photochemical rearrangements in the *Strychnos* series,[16] probably due to the greater coplanarity of the N-C(2)-C(16) unit in the ibophyllidine derivatives.



Scheme 2

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9. Compound **4** was a diastereomeric mixture at sulfur, which could not be separated at this stage. ^{13}C NMR: δ 26.2 (C-4), 29.2 and 29.3 (C-3), 35.2 (C-3a), 36.1 and 36.2 (C-5), 41.5 (C-7), 46.3 and 46.5 (CH_2SO), 52.6 and 53.2 (C-2), 56.3 and 56.7 (NCH_2), 62.0 and 62.8 (C-7a), 123.8, 124.1, 129.1, 129.2, 130.8, 131.0, 143.5, and 144.1 (Ar), 212.1 and 212.2 (C-6).
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13. Compound **7a** (α-epimer): ^{13}C NMR δ 27.6 (C-17), 31.6 (C-15), 38.3 (C-14), 52.6 (OCH_3), 55.1 (C-20), 55.7 (C-6), 56.5 (C-7), 58.0 (C-5), 74.2 (C-3), 107.1 (C-16), 115.2 (C-12), 123.4 (C-9), 123.5(C-10), 126.5 (C-11), 128.4, 128.6, 131.0, 133.0 (ArS), 135.2 (C-8), 141.8 (C-13), 142.9 (C-2), 152.6 (CO). Compound **7b** (β-epimer) ^{13}C NMR δ 30.6 (C-17), 31.5 (C-15), 37.3 (C-14), 52.6 (OCH_3), 55.2 (C-7), 62.9 (C-5), 63.0 (C-6), 75.5 (C-3), 113.0 (C-16), 115.2 (C-12), 121.8 (C-9), 124.0 (C-10), 126.2 (C-11), 128.1, 128.5, 129.9, 137.2 (ArS), 135.3 (C-8), 140.9 (C-13), 141.7 (C-2), 152.8(CO).
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15. (±)-Deethylibophyllidine: ^{13}C NMR δ 26.2 (C-17), 31.8 (C-15), 38.7 (C-14), 38.9 (C-6), 51.0 (OCH_3), 52.4 (C-5), 55.1 (C-20), 57.5 (C-7), 73.0 (C-3), 91.6 (C-16), 109.1 (C-12), 120.9 (C-10), 122.5 (C-9), 128.1 (C-11), 136.6 (C-8), 143.5 (C-13), 164.3 (C-2), 168.5 (CO). Assignments are based on DEPT, COSY, and HMQC data.
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