A New Synthetic Entry to the Alkaloids of the Mavacurine Group. First Total Synthesis of (±)-2,7-Dihydropleiocarpamine

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The total synthesis of the mavacurine alkaloid 2,7-dihydropleiocarpamine **9** has been achieved by photocyclization of the tetracyclic chloroacetamide **5** as the key step.

The mavacurine type alkaloids[1] constitute a small subgroup of *Corynanthe* indole alkaloids that has received little attention from a synthetic standpoint. To date all syntheses reported for these alkaloids and related pentacyclic structures involve as the key reaction either a skeletal rearrangement from a norfluorocurine system[2,3] or closure of the *E* ring by formation of C(16)–N(1) bond (biogenetic numbering)[4] from an indolo[2,3-*a*]quinolizidine derivative, in most cases after *C/D* ring cleavage with final reclosing of the C(3)–N(4) bond by transannular cyclization.[5–8]

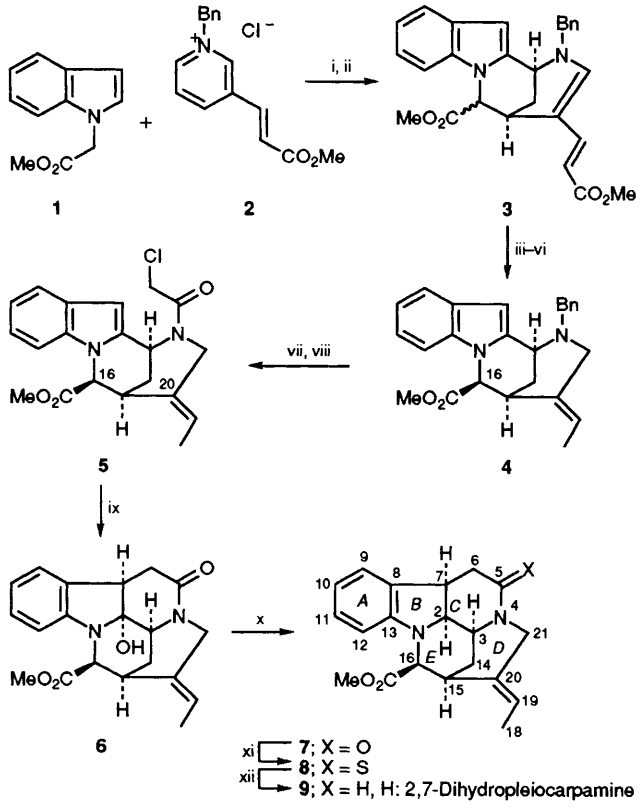
We report here a different strategy for the synthesis of the pentacyclic ring system of mavacurine alkaloids, which has been successfully applied to the synthesis of 2,7-dihydropleiocarpamine, an alkaloid isolated from *Alstonia muelleriana* in 1973.[1,9] The synthesis implies closure of the *C* ring by photocyclization upon the indole 3-position from a suitably functionalized *N*-(chloroacetyl) derivative **5** that embodies rings *ABDE* of the alkaloid and possesses both the correct relative stereochemistry at C(16) and the natural (*E*)-configuration for the C(20)-ethylidene substituent. A previous, similar approach involving closure of the *C* ring by electrophilic cyclization had resulted in failure.[10]

A C(16) diastereoisomeric mixture of tetracycles **3**, prepared as previously reported[10] by reaction of methyl 1-indoleacetate **1** and pyridinium chloride **2** followed by acid cyclization of the resulting 1,4-dihydropyridine, was stereoselectively converted by the usual[11] one-pot three-step sequence into a 3:2 mixture of (*E*)-ethylidene derivatives, **4** and its C(16) epimer, which were separated. Debenzylation of the major epimer **4** [H(15)–H(16) *cis*; H(16) δ 5.02, doublet, *J* 6 Hz] by hydrogenolysis, and subsequent acylation of the resultant secondary amine gave chloroacetamide **5**† which was irradiated for 15 min with a medium pressure mercury lamp to give (18%) the pentacyclic 2-hydroxyindoline **6**, ^{13}C NMR (50.3 MHz, $CDCl_3$) δ_C 13.0 (C-18), 23.1 (C-14), 31.0 (C-15), 36.2 (C-6), 41.6 (C-21), 45.8 (C-7), 51.4 (C-3), 51.7 (OMe), 57.6 (C-16), 92.1 (C-2), 107.9 (C-12), 118.5 (C-10), 120.7 (C-19), 124.7 (C-9), 127.6 (C-11), 129.7 (C-8), 134.3 (C-20), 147.8 (C-13), 170.3 and 170.9 (CO). No pentacyclic indole-containing products were detected. Although the starting material was recovered to some extent, longer reaction times or the use of aqueous MeCN as the solvent caused a decrease in the yield with concomitant loss of material.‡

Formation of hydroxyindoline **6** implies that the cation resulting from photocyclization[12] undergoes nucleophilic attack instead of aromatization, probably due to the strain associated with the pentacyclic mavacurine system.[1] Hydroxyindoline **6** proved to be very sensitive and, as could be expected from the above result, reluctant to undergo dehydration under several acid and neutral conditions. However, **6** could be converted to the indoline **7** (C-2 δ 67.0) by reduction with triethylsilane and then elaborated into the alkaloid 2,7-dihydropleiocarpamine **9** by removal of the amide carbonyl group through the corresponding thioamide **8**. Our synthetic material **9** showed an ^1H NMR spectrum identical with that reported for the natural product[1,9] and exhibited δ_C (50.3 MHz, $CDCl_3$) 12.6 (C-18), 20.2 (C-6), 31.2 (C-14 and C-15), 37.7 (C-7), 49.8 (C-5 and C-21), 52.1 (OMe), 60.6 (C-16), 63.1 (C-2), 108.9 (C-12), 119.5 (C-10), 123.5 (C-19), 123.6 (C-9), 127.5 (C-11), 131.0 (C-8), 133.6 (C-20), 147.7 (C-13) and 170.1 (CO).

† All new compounds gave satisfactory analytical and spectral data. All yields are from material purified by column chromatography.

‡ Attempted radical cyclization of 19,20-dihydro-**5** with Bu_3SnH resulted in failure and only the corresponding *N*-acetyl derivative was formed.



Scheme 1 *Reagents and conditions*: i, LDA–THF; ii, C_6H_6–HCl, room temp., 3 h, 33% from **2**; iii, 4 mol dm^{-3} HCl, 100 °C, 2 h; iv, 1.5 mol dm^{-3} MeOH–HCl, room temp., 20 h; v, $NaBH_4$, MeOH, 0 °C, 1 h, 34% from **3**; vi, separation of C(16) epimers, flash, SiO_2, 1 : 1 hexane–AcOEt; vii, H_2, $Pd(OH)_2$, MeOH, 24 h; viii, $ClCH_2COCl$, Et_3N, CH_2Cl_2, room temp., 2 h, 61% from **4**; ix, *hv*, 1 : 1 MeOH–H_2O (0.5 g dm^{-3}), 15 min, 18%; x, Et_3SiH, TFA, CH_2Cl_2, reflux, 2 h, 50%; xi, Lawesson's reagent, toluene, reflux, 2 h, 64%; xii, $NiCl_2 \cdot 6H_2O$, $NaBH_4$, MeOH–THF, −30 °C, 5 min, 45%; LDA = lithium diisopropylamide, TFA = trifluoroacetic acid

Although 2,7-dihydropleiocarpamine had been prepared previously by reduction of natural pleiocarpamine,[1] the synthesis here reported constitutes the first total synthesis of the former alkaloid. It also constitutes the first synthesis of a mavacurine type alkaloid with a H(15)–H(16) *cis*-stereochemistry.

Financial support from the DGICYT, Spain (projects PB88-0316 and PB91-0800) is gratefully acknowledged. Thanks are also due to the CIRIT (Catalonia) for Grants AR90-3454 and AR91-315.

Received, 22nd December 1992; Com. 2/06799D

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