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STEREOCONTROLLED ACCESS TO DASYCARPIDAN-TYPE COMPOUNDS AND FORMAL TOTAL SYNTHESIS OF *STRYCHNOS* INDOLE ALKALOIDS OF THE STRYCHNAN-TYPE

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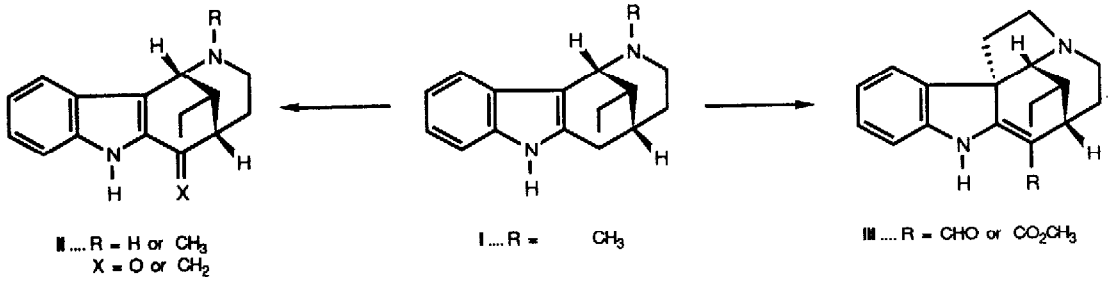
An efficient, stereocontrolled synthesis of the tetracyclic bases **1** and **2** by cyclization of the regioisomeric cyanopiperidines **4** and **5**, prepared from the common *cis*-3-ethyl-4-(2-indolylmethyl)piperidine intermediate **3**, is reported.

The tetracyclic ring system defined by the dasycarpidan stereoparent (**I**, *S*-configuration at the bridge carbon) is present in the uleine group of indole alkaloids (**II**)[1] as well as in the *Strychnos* indole alkaloids[2] having the Aspidospermatan skeleton (**III**). The stereocontrolled synthesis of tetracyclic compounds derived from the stereoparent **I** has had limited success so far.[3,4]

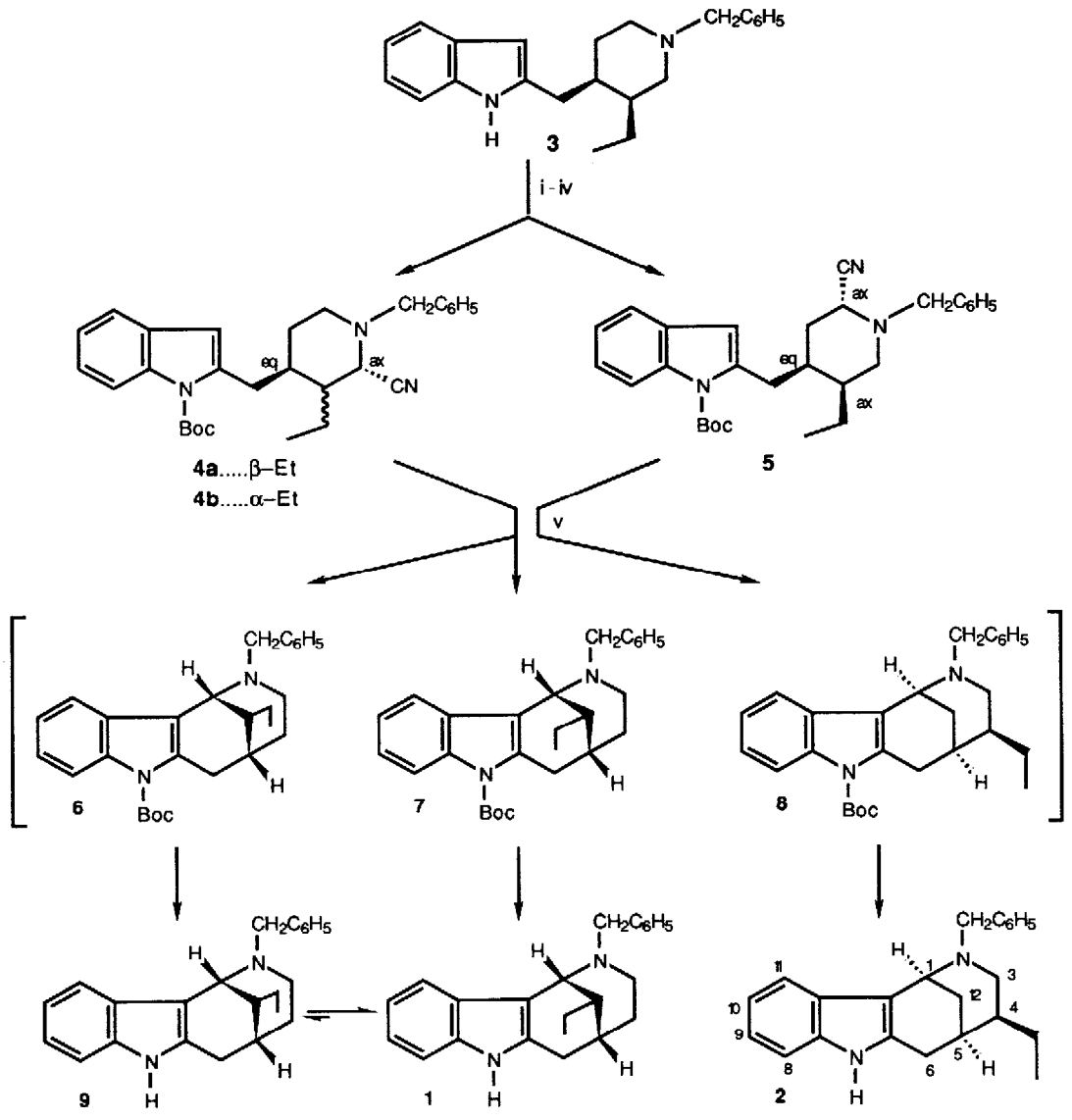
In the preceeding paper,[5] we have reported the usefulness of cyanopiperidines for the stereocontrolled synthesis of functionalized 4- and 9-ethyl-2-azabicyclo[3.3.1]nonanes. Using a similar strategy, we describe in this Letter the stereocontrolled synthesis of the tetracyclic base **1** (**I**, R=$CH_2C_6H_5$) and an alternative synthesis of its regioisomer **2**. Further elaboration of compound **1** could result in a new synthetic entry both to the uleine alkaloids and to the Aspidospermatan-type of *Strychnos* alkaloids, whereas the synthesis of **2** constitutes a formal total synthesis of the *Strychnos* alkaloids having the Strychnan skeleton tubifolidine,[6] tubifoline,[7] and 19,20-dihydroakuammicine.[8]

The synthesis involves the construction of the fused morphan nucleus in the key step (bond formed C_1-C_{11b}) by cyclization of an iminium salt generated from a 1,3,4-trisubstituted 2-(or 6)cyanopiperidine.

Thus, after protecting the indole nitrogen in order to avoid interfering side-processes[9] during the following step, the easily accesible *cis*-2-(piper-



idylmethyl)indole **3**[10] was converted in 72% overall yield into a regioisomeric mixture of cyanopiperidines **4** and **5** (5:3 ratio)[11] by a Polonovski-Potier reaction followed by trapping of the resulting iminium salts with cyanide ion.[5]



Reagents: (i) $(Boc)_2O$, 50% aq NaOH, Bu_4NHSO_4, toluene, rt; (ii) m-CPBA, CH_2Cl_2, 0°C, 1 h; (iii) TFAA, -15°C, 1 h; (iv) aq KCN, NaOAc, pH 4-5, 30 min; (v) AcOH-H_2O-Dioxane (3:1:1), 90°C, 14 h.

As had already been observed in the 4-acetonylpiperidine series,[5] epimerization at the piperidine 3-position, through the corresponding enamine, occurs to a considerable extent in the regioisomer **4**, giving an epimeric mixture at C-3 in which the most stable *trans*-3,4-diequatorial epimer **4b** predominated (**4a**/**4b**: 2/3).[11]

Treatment of the above mixture of cyanopiperidines (**4** and **5**) with acetic acid in aqueous dioxane for 14 h accomplished both cyclization and deprotection of the indole ring to give a mixture of tetracycles **1** (46%) and **2** (26%), having the Aspidospermatan and the Strychnan skeletal types, respectively. The epimer **9** was formed only in yields lower than 4%.[12] When the cyclization step was conducted for shorter reaction times (2 h), the indole-protected tetracycles **6**, **7**, and **8** could also be isolated (*ca* 25% yield), thus indicating that cyclization, at least to some extent, takes place before deprotection.

Some points about the stereochemical course of this cyclization are worthy of comment: a) As could be expected, the relative configuration at C-4 in the Strychnan-type tetracycles **8** and **2** is the natural one, i.e. *cis*-relationship between the hydrogens at the 4 and 5 positions. b) On the contrary, as a consequence of the epimerization at the piperidine 3-position in **4b**, the major Aspidospermatan-type epimer after the cyclization step (short reaction time) was **6**, which possesses the unnatural[13] relative configuration at C-12. However, interestingly, when the reaction time was long enough to accomplish the deprotection of the indole ring in the same synthetic operation, the Aspidospermatan-type tetracycle **1**, having the correct stereochemistry at C-12, was obtained as the major isomer, thus evidencing that a further epimerization had taken place after the deprotection step. Furthermore, it was demonstrated that the minor epimer **9** is converted, after an additional acidic treatment, into the major, desired stereoisomer **1**. This useful epimerization can be rationalized by considering that, when the indole ring is not deactivated,[14] the Pictet-Spengler reaction is reversible. Thus, after protonation at the indole 3-position in **9** and subsequent ring-opening, an iminium salt is formed. Epimerization at C-3 of the piperidine ring, through the corresponding enamine, followed by recyclization leads to **1**, which has the natural, more stable relative configuration at C-12.

In this manner, in four steps from an easily available *cis*-3-ethyl-4-piperidineacetate, through the common intermediate **3**, we have prepared the valuable tetracyclic indole derivatives **1** and **2** in 22% and 12% overall yields, respectively.

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2. For a review: Bosch, J.; Bonjoch, J. in "Studies in Natural Products Chemistry", vol.1, Atta-ur-Rahman, ed., Elsevier, Amsterdam, **1988**, pp 31-88.

3. Usually, a 12-epiderivative is the preponderant or exclusive stereoisomer formed in the syntheses of uleine-type alkaloids implying the formation of the C_6-C_{6a} bond in the last step. For a notable exception, see: Büchi, G.; Gould, S. J.; Näf, F. *J. Am. Chem. Soc.* **1971**, *93*, 2492.

4. The only precedent for the synthesis of uleine-type alkaloids by formation of the C_1-C_{11b} bond in the last step also affords an epimeric mixture at C-12: Jackson, A.; Wilson, N. D. V.; Gaskell, A. J.; Joule, J. A. *J. Chem. Soc. (C)* **1969**, 2738.

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10. This compound was prepared[a] from ethyl *cis*-1-benzyl-3-ethyl-4-piperidineacetate[b] in a 66% yield (3.5 g scale) employing the Smith indolization protocol.[c] (a) Bonjoch, J.; Quirante, J.; Linares, A.; Bosch, J. *Heterocycles* **1988**, *27*, 2883. (b) Bonjoch, J.; Linares, A.; Guardià, M.; Bosch, J. *Heterocycles* **1987**, *26*, 2165. (c) Smith, A. B. III; Visnick, M.; Haseltine, J. N.; Sprengeler, P. A. *Tetrahedron* **1986**, *42*, 2957.

11. Individual ratios were established from the integration of the $CH_2\underline{CH_3}$ signal in the ^{1}H-NMR (400 MHz) spectrum of the mixture.

12. All reported yields are for purified materials isolated from column chromatography and all compounds gave spectroscopic data in agreement with the assigned structures. Selected ^{13}C-NMR data include the following:

Compound	1-C	3-C	4-C	5-C	6-C	12-C	CH_2	CH_3
1[a]	55.7	43.8	33.8	29.2	25.9	43.8	23.8	11.9
2[a,b]	50.7	50.3	41.5	28.7	24.5	34.3	22.6	11.5
6[c]	52.5	44.4	28.3	29.9	34.5	42.7	23.4	12.3
7[c]	55.4	43.6	33.6	29.2	25.4	42.2	24.2	11.7
8[c]	50.4	50.1	41.5	29.3	25.5	33.6	23.7	11.4
9[a]	52.6	44.3	28.1	29.6	31.0	43.6	23.7	12.2

a. Measured at 50 MHz; b. Reference 10a; c. Measured at 100 MHz.

13. However, the isolation of epidasycarpidone and epiuleine as minor alkaloids has been reported: Gaskell, A. J.; Joule, J. A. *Chem. Ind. (London)* **1967**, 1089.

14. Similar cyclizations from 2-indolylcarbonyl derivatives have been reported[4,9a] to occur with retention of the relative configuration at the piperidine 3-position, and attempts to induce the type of epimerization here observed have failed.[4]

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