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# ASYMMETRIC SYNTHESIS XIV[1] : A SHORT AND EFFICIENT SYNTHESIS OF 3,5-DISUBSTITUTED PYRROLIZIDINE ALKALOIDS VIA THE CN(R,S) METHOD[2]

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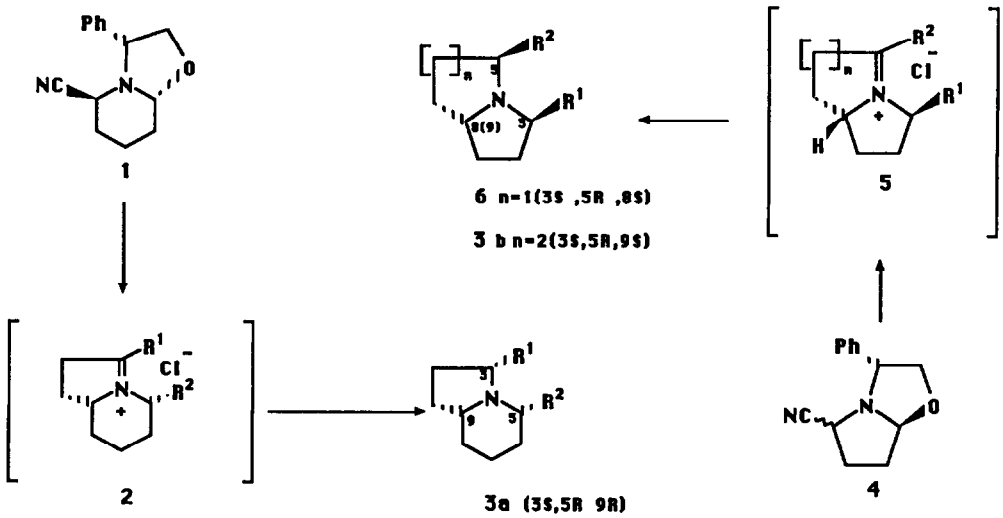
*Abstract* - *The enantiospecific synthesis of the dextrorotatory enantiomer of the ant venom alkaloid 3-heptyl-5-methylpyrrolidine 11 has been achieved in four steps and 31% overall yield from the chiral 2-cyano-5-oxazolopyrrolidine synthon 4. On the basis of previous results it was concluded that the absolute configuration of (+) 11 is 3S, 5R, 8S in disagreement with an earlier report.*

In continuation of our program of asymmetric syntheses based on the use of the chiral N-cyanomethyl-4-phenyl-1,3-oxazolidine system, we have now extended the potential of the CN(R,S) method[2] to the synthesis of pyrrolizidine alkaloids. The use of 2-cyano-6-oxazolopiperidine synthon 1 [3] was particularly noteworthy in elaboration of the five membered ring of indolizidine alkaloids 3a [4].

The key step of this reaction sequence was the acidic hydrogenolytic cleavage of the chiral auxiliary and reduction of the iminium intermediate 2 formed after concomitant liberation of the keto group (Scheme 1).

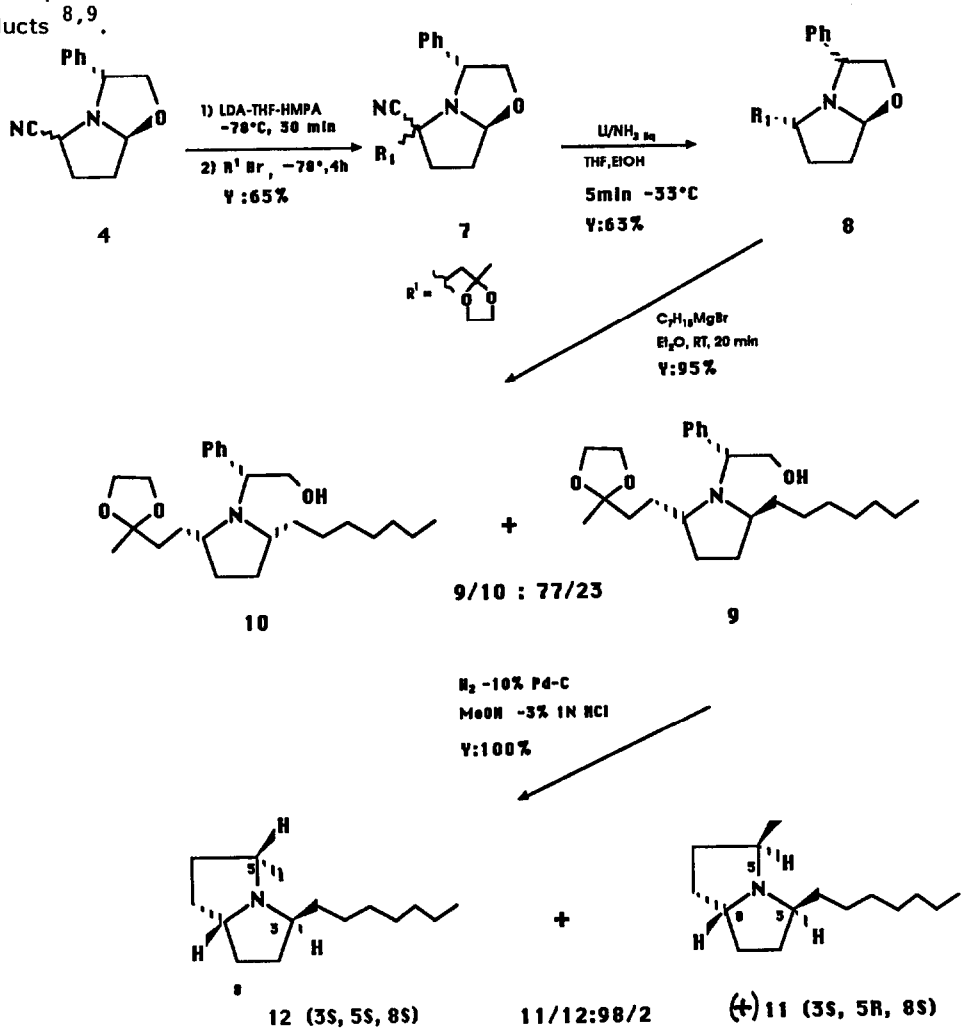



**Scheme 1**

The ease with which the 1-azabicycloalkane ring system was formed, stimulated us to apply the same strategy to the new 2-cyano-6-oxazolopyrrolidine synthon 4 [5,6]. It was felt that synthon 4 would be an ideal starting material for the construction of the disubstituted pyrrolizidine alkaloids of type 6. Indeed 4 can be converted in a stereoselective manner into trans α,α'-disubstituted pyrrolidines [5] precursors of 5.

Moreover the pyrrolidine synthon 4 can be used for the elaboration of the six membered piperidine moiety of indolizidines. In this event the opposite R configuration will be generated at the C-9 position giving the diastereomeric compound 3b with respect to the previously synthesized derivative 3a

Our initial studies, however, were devoted to the ant venom alkaloid 3-heptyl 5-methylpyrrolizidine [7] which has the relative stereochemistry depicted in 11. Stereoselective synthesis of 3,5-disubstituted pyrrolidines remains a challenging goal since relatively little work has been done on the synthesis of this rare series of natural products [8,9].




**Scheme 2**

Alkylation of the anion of 4 (Scheme 2) with 1-bromo-3,3-(ethylenedioxy)butane produced a mixture of stereomers 7 [10], isolated in 65 % yield after flash chromatography on silica gel. A stereospecific decyanation of the diastereomeric mixture 7 was achieved using Li-$NH_3$ reduction [5]. Compound 8 [11] was obtained in 63% yield as a single isomer. The S absolute configuration at the new asymmetric center was ascertained unambiguously on the basis of X-ray analysis performed on an analog of 8 [12] and by the use of 1D difference NOE and NOESY NMR techniques on 8. The heptyl chain was introduced at C-5 (pyrrolidine ring numbering) with $C_7H_{15}MgBr$ in 95 % yield providing predominantly the 2,5-trans-dialkylpyrrolidine 9 [13] accompanied by the cis isomer 10 [14] (9/10 : 77/23).

After separation of the two isomers by silica gel column chromatography compound 9 was submitted to catalytic hydrogenation conditions[4]. Thus the trans isomer 9 was converted in 98 % yield into 11 [15], which exhibited characteristic $^{13}C$ NMR resonances at 66.3, 65.0 and 61.8ppm [7] for the C-8, C-3 and C-5.

The epimeric pyrrolizidine 12 was also detected from an analysis of the $^{13}C$ NMR spectrum of the crude reaction mixture (approximately 2 %). Indeed the chemical shifts of the C-3, C-5 and C-8 in the NMR spectrum are quite diagnostic in differentiation of the four stereomers [7] (i.e. 66.2, 57.6 and 57.1ppm for 12).

The synthetic alkaloid 11 was found reproducibly to be dextrorotatory : $[\alpha]_D^{20}$ +9° (c 2.13, $CHCl_3$) ; this value is the opposite of that reported by TAKANO et al [8] for the same compound synthesized in an enantioselective fashion from a chiral epoxide.

Since the relative stereochemistries at C-3, C-5 and C-8 of 11 are well established in both syntheses, the absolute configuration of the levorotatory compound [8] is brought into question.

In conclusion, these latest results illustrate once again the flexibility of the CN(R,S) method which compares very favorably with previously reported racemic [9] and asymmetric [8] syntheses by its shortness and efficiency.

## REFERENCES AND NOTES

1 - For part XIII see : S. ARSENIYADIS, P.Q. HUANG and H.-P. HUSSON, Tetrahedron Lett., accepted for publication.

2 - Since the publication of our first paper in this series [3] the N-cyanomethyl--4-phenyl-1,3-oxazolidine system has increasingly proved valuable as the reactive feature in chiral synthons designed for the asymmetric synthesis of a large variety of products. The generality of this approach, allowing a remarkable

stereocontrol for the formation of the new R or S asymmetric centers by CN elimination, has led us to call it "the CN(R,S) method" in recognition of the Centre National de la Recherche Scientifique which supports this research.

3 - L. GUERRIER, J. ROYER, D.S. GRIERSON and H.-P. HUSSON, J. Am. Chem. Soc., 1983, 105, 7754.

4 - J. ROYER and H.-P. HUSSON, J. Org. Chem., 1985, 50, 670.

5 - P.Q. HUANG, S. ARSENIYADIS and H.-P. HUSSON, Tetrahedron Lett., 1987, 28, 547.

6 - J. ROYER and H.-P. HUSSON, Tetrahedron Lett., 1987, 28, 6175.

7 - T.H. JONES, M.S. BLUM, H.M. FALES and C.R. THOMPSON, J. Org. Chem., 1980, 45, 4778.

8 - For the only enantioselective synthesis of 12 see : S. TAKANO, S. OTAKI and K. OGASAWARA, J. Chem. Soc. Chem. Comm., 1983, 1172.

9 - A stereoselective synthesis of (±) 11 has been recently published : D. LATHBURY and T. GALLAGHER, J. Chem. Soc. Chem. Comm., 1986, 1017.

10 - All new compounds gave satisfactory spectral (IR, $^{1}H$, $^{13}C$ NMR) and high resolution mass data. We thank Dr. S.K. KAN (Institut d'Electronique Fondamentale, Université de Paris-Sud) for the use of his 400 MHz NMR spectrometer).

11 - 8 : oil. $[\alpha]_D^{20}$ - 35° (c 1.4, $CHCl_3$). MS m/z E.I. 303 ($M^{+\cdot}$, 3), 288(10), 273(15), 260(29), 230(11), 189(49), 188(74), 159(44), 130(33), 104(75), 91(85), 68(69), 43(100) ; C.I. 304 ($MH^+$, 100), 184(33). $^{13}C$ NMR ($CDCl_3$, 50 MHz) δ (ppm) : 23.7, 30.2, 30.3, 35.6, 64.5, 66.7, 68.4, 73.0, 99.0, 110.1, 126.7, 127.9, 128.4, 143.3.

12 - S. ARSENIYADIS, P.Q. HUANG, D. PIVETEAU and H.-P. HUSSON, Tetrahedron accepted for publication.

13 - 9 : oil. $[\alpha]_D^{20}$ + 8° (c 1.0, $CHCl_3$). MS m/z E.I. 403 ($M^{+\cdot}$, 1), 372(100), 304(18), 288(14), 87(22) ; C.I. 404 ($MH^+$, 100), 386(22), 372(10). $^{13}C$ NMR ($CDCl_3$, 50 MHz) δ (ppm) : 14.0, 22.5, 23.7, 26.9, 27.7, 28.8, 29.1, 29.6, 31.7, 32.9, 36.2, 36.5, 60.8, 60.9, 62.3, 63.3, 64.5, 109.7, 127.4, 128.1, 129.1, 139.8.

14 - 10 : oil $[\alpha]_D^{20}$ - 26° (c 1.2, $CHCl_3$). MS m/z E.I. 403 ($M^{+\cdot}$ 1), 372(100), 304(43), 288(38), 260(21), 188(54), 168(24), 104(29), 87(43) ; C.I. 404 ($MH^+$, 100), 386(12), 304(29). $^{13}C$ NMR ($CDCl_3$, 50 MHz) δ (ppm) : 14.2, 22.7, 24.0, 26.8, 29.4, 29.8, 30.0, 31.9, 36.2, 58.2, 62.0, 64.2, 64.7, 65.2, 110.0, 127.9, 128.4, 129.1, 137.4.

15 - The spectral data of synthetic (+) 11 were identical to those previously reported for the racemic material [7].

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