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ASYMMETRIC SYNTHESIS X[1] : A CHIRAL PYRROLIDINE SYNTHON FOR A NEW APPROACH TO THE SYNTHESIS OF ALKALOIDS

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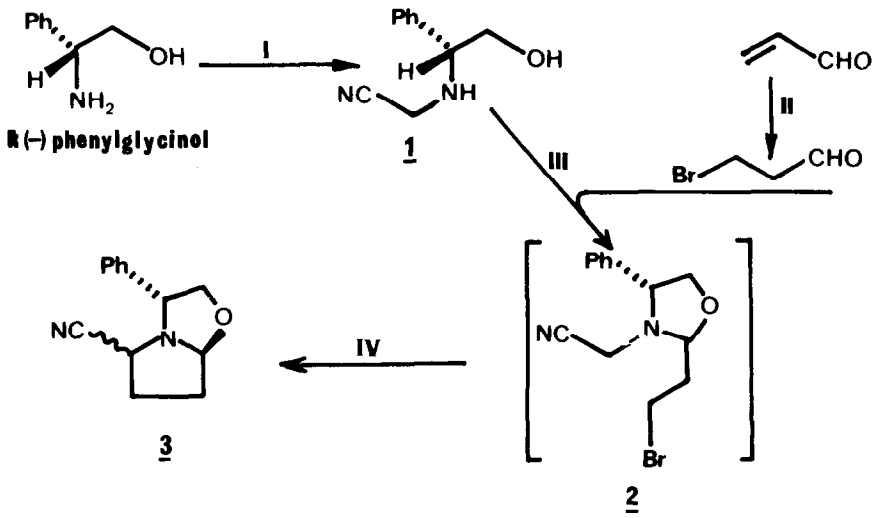
Abstract - The synthesis of chiral 2-cyano-5-oxazolopyrrolidine 3 is reported. The synthesis of the optically pure ant venom alkaloid, (+)-(S)-trans-2-heptyl-5-butyl-pyrrolidine 7, has been achieved from 3.

The development of synthetic methodologies in which preformed chiral building units are used, is gaining popularity. In connection with our studies directed towards the asymmetric synthesis of alkaloids[2] we now describe our results[3] aimed at a general approach to the enantiospecific synthesis of pyrrolidine, pyrrolizidine and indolizidine alkaloids from a chiral reactive intermediate 3 (Scheme 1).



Reagents : (I) HCHO, $NaHSO_3$; KCN, H_2O. (II) HBr, CH_2Cl_2, 0°, 3 h. (III) Br-CH_2-CH_2CHO, CH_2Cl_2, MS 4A, Δ, 1 h. (IV) LDA 1.8 equiv., THF, -78°C, 2 h.

Scheme 1

Recently there has been a resurgence of interest in the synthesis of 2,5-dialkylpyrrolidines (constituents of fire ant venom) and several approaches have been reported.[4]

Central to our synthetic plan was the development of a viable route to 3[5] (Scheme 1). The condensation of R(-) phenylglycinol (50 mmol) with formaldehyde (1 equiv.) in the presence of sodium bisulfite (1 equiv.) in water (10 ml) followed by KCN (1 equiv.) addition gave aminonitrile 1 in nearly quantitative yield.[7] Stirring of 1 in refluxing CH_2Cl_2 (1 mmol/1 ml) with freshly prepared 3-bromo-propionaldehyde[8] (1.2 equiv.) for one hour led to oxazolidine 2[9] which was cyclized *in situ* to 3 *via* its anion. Compound 3 (two diastereomers 1:1) was obtained in 35% overall yield from (-)phenylglycinol after purification by flash chromatography on silica gel.

The versatility of this new synthon is illustrated by the enantiospecific synthesis of (+)-*trans*-2,5-dialkylpyrrolidine ant venom alkaloid 7[10] (Scheme 2).

Alkylation of the anion of 3 with heptyl bromide produced compound 4 (1:1 diastereomeric ratio) in 60% yield after purification by flash chromatography.

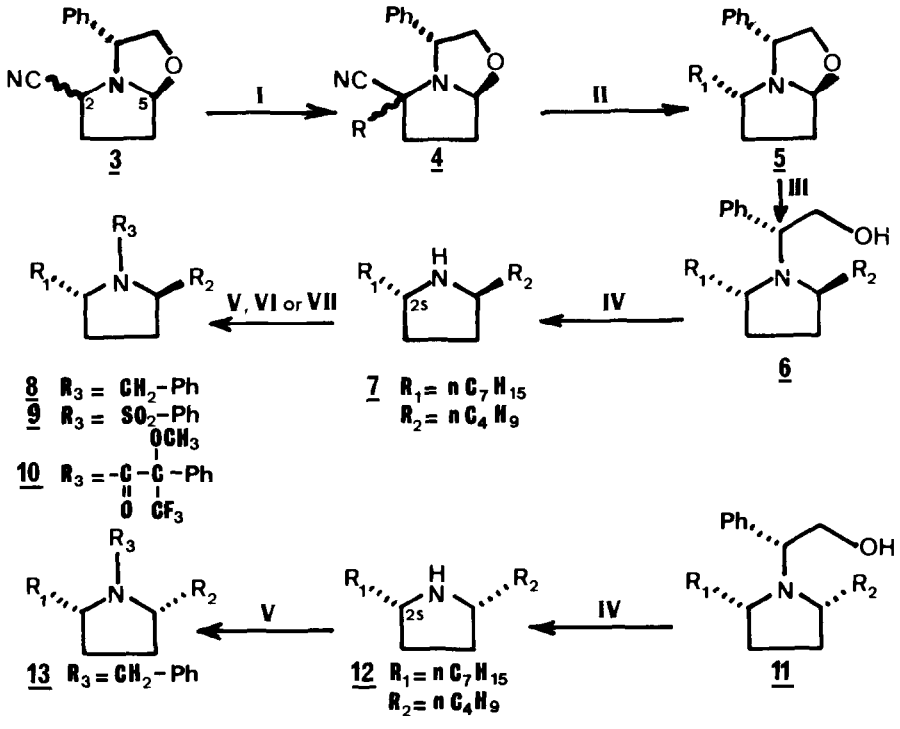
We encountered serious difficulties accomplishing the key step of our synthesis. $Zn(BH_4)_2$ reduction[6] of 4 turned out to be a rather difficult task. The expected product 5 was obtained in less than 10% yield and mostly unidentified low rf material was recovered. Instead, Li-NH_3 liq. reduction of 4 afforded 5 (amorphous, $[\alpha]_D^{20}$ -28°, c 0.96 $CHCl_3$) in 57% isolated yield with a remarkable stereocontrol.[11] A butyl side chain was introduced at C-5 on reaction of 5 with nBuMgBr providing predominantly the 2,5-*trans*-dialkylpyrrolidine 6 (amorphous, $[\alpha]_D^{20}$ +40°, c 1.02 CH_3OH) and its *cis* isomer 11 (Y > 95%; *trans/cis* : 72:28).

Under hydrogenolysis conditions the chiral auxiliary attached to the nitrogen of 6 was cleaved giving (2S)-*trans*-2-heptyl-5-butylpyrrolidine 7 (Y > 95%). In a similar fashion the 2,5-*cis* epimer 12 was prepared from the minor compound 11.

The structure and optical purity of compounds 7 and 12 were established as follows : the C-2/C-5 relative stereochemistry was determined by the method of Hill and Chan[12] based on the appearance of the respective N-$\underline{CH_2}$-C_6H_5 of the benzyl derivatives 8 and 13 (8 : AB quartet, J = 14 Hz, centered at δ 3.54 and 3.74 ppm; 13 singlet at δ 3.66 ppm).

The absolute configuration of 7 was inferred from the comparison of the optical rotation of its phenylsulfonyl derivative 9 with that of the previously assigned (2S)-*trans*-2-heptyl-5-butylpyrrolidine derivative (9 : $[\alpha]_D^{20}$ +58°; c 1.1, CH_2Cl_2; lit.[4a] + 59.7°; c 1.8, CH_2Cl_2).

Examination of the Mosher[13] amide derivative 10 showed that hydrogenolytic cleavage of the chiral auxiliary of pure stereomer 6 gave 7 without racemization to an appreciable extent.



Reagents : (I) LDA 1.2 equiv., TMEDA 1.8 equiv., THF, -78°C, 30 min.; R_1X, 2-3 equiv., -78°C, 2 h. (II) Li 2 equiv., NH_3 liq., THF, EtOH, -40°C, 5 min. (III) R^2MgBr, ether, r.t., 30 min. (IV) 10% Pd/C, H_2, AcOH, 50 psi, 6 h. (V) EtMgBr 1.15 equiv., Et_2O, r.t., 30 min., PhCOCl, r.t., 1 h.; LAH, Et_2O, Δ, 4 h. (VI) Ref 4a. (VII) (-)MTPA-Cl, 1.6 equiv., NEt_3 1.6 equiv., DMAP cat., CH_2Cl_2, r.t. 16 h.

Scheme 2

This six-step route from phenylglycinol represents an attractive alternative to a previous enantiospecific synthesis of dialkylpyrrolidine alkaloids.[4a] Further applications to the asymmetric synthesis of more complex alkaloid systems are currently under investigation.

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References and Notes

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