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DIASTEREOSELECTIVE SYNTHESIS OF OPTICALLY ACTIVE PYRROLIZIDINE AND INDOLIZIDINE RING SYSTEMS THROUGH INTRAMOLECULAR ENE REACTION.

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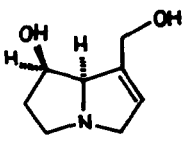
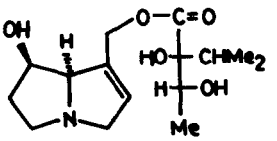
Abstract : Lewis acid catalyzed diastereoselective intramolecular ene cyclization of optically pure L-proline derived substrates provides asymmetric synthesis of Pyrrolizidine and Indolizidine ring systems.

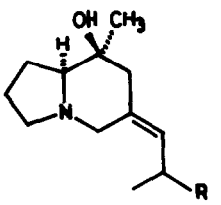
Pyrrolizidine and Indolizidine (pumiliotoxin-B) alkaloids possessing bicyclic skeleton occur widely in nature[1]. Potentially useful biological properties such as tumor inhibitory activity[2] of Inidicine-N-oxide render them attractive and largely pursued synthetic objectives.[3] One of the common structural features of these alkaloids is the presence of one or more hydroxy groups in the molecule.



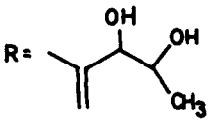
Retronecine



Indicine



Pumiliotoxin-B



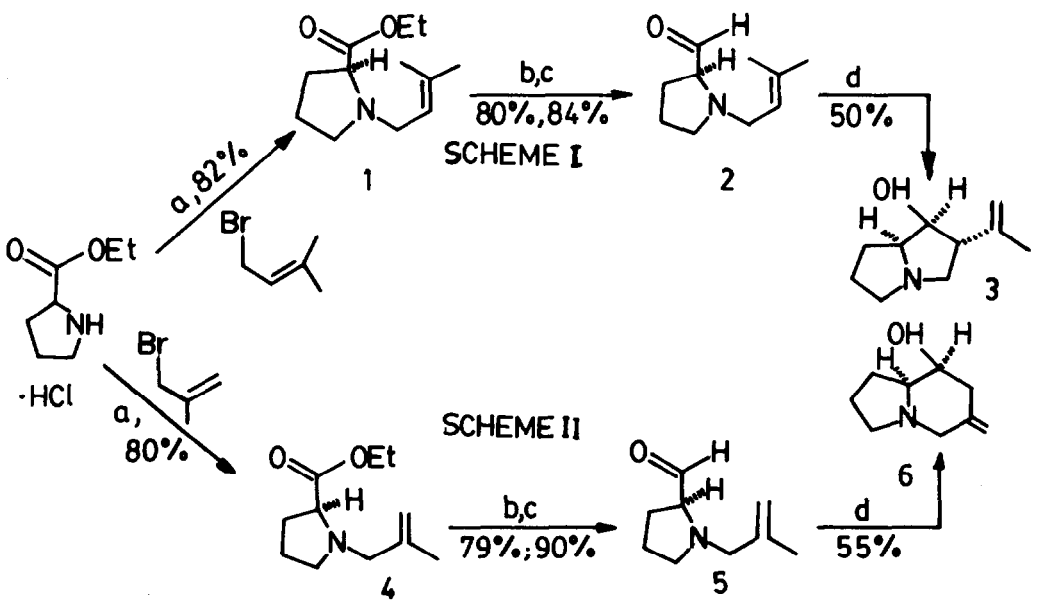
Although a variety of new methods has been explored[1,2,3] for their synthesis in racemic form, the synthesis of optically active pyrrolizidine alkaloids is of recent vintage i.e. beginning of the past decade[4]. Compared to other methods developed, the intramolecular ene reaction[5,6] has received far less attention and especially so in targeting molecules in their optically active form despite the enormous potential which it holds for alkaloid synthesis.

With this in mind we proceeded to investigate the application of this particular reaction to the construction of pyrrolizidine and indolizidine

ring systems in optically active form. Another interesting objective was to examine the diastereoselectivity of the ene cyclization.

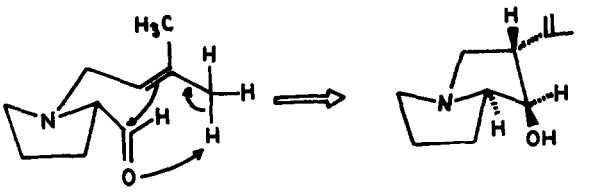
Scheme I details the preparation of the required olefinic aldehyde moiety from commercially available inexpensive L-proline. Ethyl prolinate hydrochloride was condensed with prenyl bromide in the presence of K_2CO_3 to get the alkylated proline ester in 82% yield ($[\alpha]_D$-77.3°, $CHCl_3$, C= 1.01). The latter was converted to the corresponding alcohol ($[\alpha]_D$-34.4°, $CHCl_3$, C=1.02) in 80% yield by the reduction with lithium aluminium hydride. Subsequent Swern oxidation afforded the desired aldehyde ($[\alpha]_D$-81.6° , $CHCl_3$, C = 1.02) in 84% yield.

Addition of the above described optically active aldehyde to a stirred suspension of $ZnBr_2$ in CH_2Cl_2 led to smooth cyclization (Figure 1) to the corresponding hydroxy pyrrolizidine [Chromatography; neutral alumina, hexane-ethyl acetate : methanol, 9:1:1, 50% yield]. A variety of other lewis acids like $BF_3.Et_2O$, $AlCl_3$, or $TiCl_4$ were either ineffective or gave poor yields. 3 was found to be homogeneous by TLC and GC analysis. This ene cyclization of 2 has generated two new chiral centres in addition to one already present in the molecule.



(a)K_2CO_3, Benzene Δ ; (b)$LiAlH_4$, ether, r.t. (c) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, -78°C; (d) $ZnBr_2$, CH_2Cl_2, r.t.

Figure 1



Further confirmation of the stereochemistry of the product was obtained from ^{1}H NMR wherein a signal at δ 3.82 (d, J=7.2 Hz) clearly showed the presence of assigned fused ring system.

A similar type of reaction sequence using 2-methyl-2-propenyl bromide giving the desired olefinic aldehyde is depicted in Scheme II. As described earlier $ZnBr_2$ induced intramolecular ene cyclization provided the corresponding hydroxy indolizidine **6**. GC analysis of the product after chromatography over neutral alumina (hexane-ethylacetate, methanol, 9:1:1) was found to be more than 94% pure. These results of cyclization providing 5,5 and 5,6 membered ring systems, clearly demonstrate that intramolecular ene type cyclization is highly diastereoselective in the aldehyde series. Since more than 1 eq. of Lewis acid is required for the reaction to go for completion it appears that the nitrogen and aldehydic carbonyl oxygen are coordinated to two separate molecules of $ZnBr_2$.

In conclusion, a simple synthesis that provides pyrrolizidine as well as indolizidine analogues of biologically important molecules in optically active form is described.

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- Presented at the National Seminar on "Heterocyclic Chemistry in Nature and Industry", Nagpur, India, September 26, 1988.

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8. New compounds were characterised by their IR, ^{1}H NMR, ^{13}C NMR. The data for selected compounds is

3 : IR (neat) cm^{-1}; 3350 (OH); 1650 (C=C) ^{1}H NMR ($CDCl_3$) δ : 1.12-2.25 (m, 8H); 2.35 - 2.6 (m, 2H, C_3H and C_6H); 3.12 - 3.5 (m, 3H, C_3 H, C_5 H, C_7H); 3.87 (2H, C_8H and OH), 5.0~5.2 (2H, m, C= CH_2) $[\alpha]_D$ + 18.0° ($CHCl_3$ C = .4). Anal. calcd. for $C_{10}H_{17}ON$: C, 71.85; H, 10.18; N, 8.%. Found : C, 72.05; H, 10.3; N, 8.3%.

6 : IR (neat), cm^{-1} ; 3600 3200 (OH); 1650 (C=C) ^{1}H NMR ($CDCl_3$, δ) : 1.7- 2.0 (m, 4H); 2.1~2.4 (m, 2H, C H); 2.4~2.6 (m, 3H, C_3 H, C_2CH_2); 3.2 3.4 (m, 2H, C_3 H C_8H); 3.9 (br.S, 2H, C_8 H, OH); 4.9~5.0 (m, 2H, C=CH_2; ^{13}C C_1 24.31; C_2 : 21.14; C_3 : 53.67; C_5 58.91; C_6 : 140.12; C_7 : 40.78; C_8 : 65.29; C_{8a} : 66.6; C_9 : 112.9; $[\alpha]_D$ - 7.2° ($CHCl_3$, C= 1.22). Anal. calcd. for $C_9H_{15}ON$: C, 70.59; H, 9.80; N, 9.15%. Found : C, 70.41; H, 10.10; N, 9.26%.

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