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Asymmetric Synthesis. XXX[1]. Synthesis of 3-Substituted Piperidines from Chiral Non-racemic Lactams.

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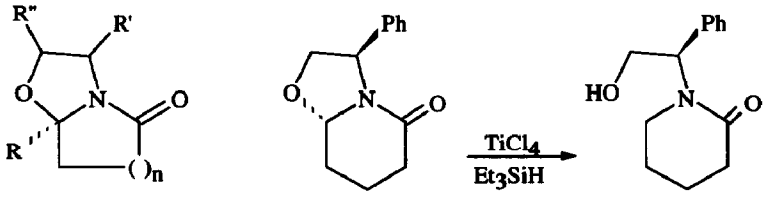
Key-words : Asymmetric synthesis; 3-substituted piperidines, diastereoselective alkylation of lactams, stenusine.

Abstract A series of 3-substituted piperidines in enantiomerically pure form has been synthetized from lactam **3** by a stereospecific route involving a postulated rigid amide enolate. This strategy has been applied to the synthesis of (+)-stenusine **10**.

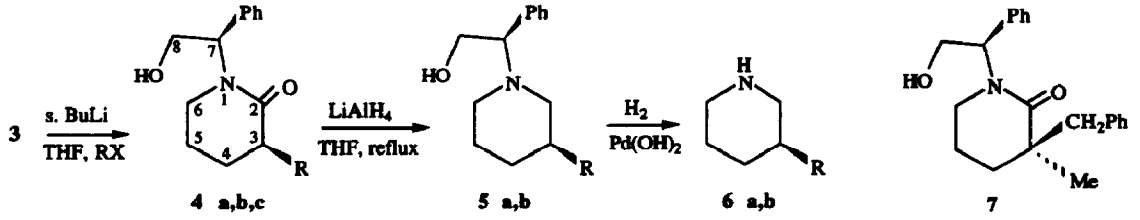
As part of a program dealing with the asymmetric synthesis of alkaloids we were interested in the development of a convenient method for the preparation of enantiomerically pure 3-substituted piperidines. Although several methods exist for the asymmetric synthesis of 2-alkylated piperidines[2], to our knowledge there is still no general method for the preparation of 3-substituted compounds. Although the synthesis of such compounds has been reported[3], these methods lack versatility and seem restricted to simple compounds. Their application to optically active compounds and polysubstituted derivatives appears to be difficult. Meyers[4] developped chiral non-racemic bicyclic lactams **1** as precursors of mono and di-substituted lactams. This method allowed the preparation of five membered ring derivatives with an excellent diastereoselectivity. However the application of this strategy to six-membered lactams was limited by the availability of starting material and the lower selectivities obtained during alkylation, especially for the first alkylation.



1 **2** **3**

Recently we studied a new method for the preparation of bicyclic lactam **2**,[5] an optically active potential acyl iminium ion.[6] Surprisingly when this compound was submitted to Meyers alkylation conditions[4] (LDA or s-BuLi, RX) no substitution was observed.

As the presence of a free hydroxyl group is compatible with the above-mentioned conditions,[7] we decided to explore the reactivity of hydroxy lactam **3** obtained in 84 % yield by reduction of **2** following Meyers' procedure. Deprotonation of **3** in THF solution with 2.5 equivalents of s.BuLi at -78°C followed by addition of alkyl halide led to substituted products **4** (Table) in moderate to good yields[8] as the only isomer detected in the ^{1}H and ^{13}C NMR spectra (and HPLC for compound **4a**). When benzyl bromide was used as an electrophile a better yield was observed if LiBr (1 equivalent) was added to the reaction mixture.

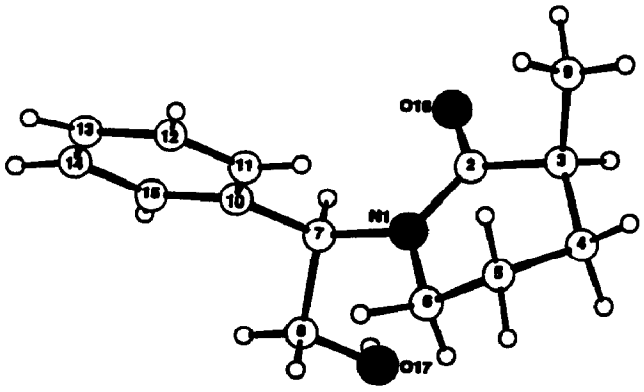


Table

RX	compound	yield[a](%)	de(%)	compound	yield[a](%)	compound	yield[d](%)
CH_3I	**4a**	96	≥ 98[b]	**5a**	88	**6a**	96
$PhCH_2Br$	**4b**	75	≥ 95[c]	**5b**	85	**6b**	94
$CH_2{=}CHCH_2Br$	**4c**	40	≥ 95[c]	-	-	-	-

a) Based on isolated products ; b) Determined by HPLC and NMR ; c) Determined by ^{1}H and ^{13}C-NMR ; d) Isolated as hydrochloride salt.

NMR studies did not allow the determination of the configuration of the newly created asymmetric center. This problem was solved by an X-ray analysis of the methylated derivative **4a**[9] (Figure).

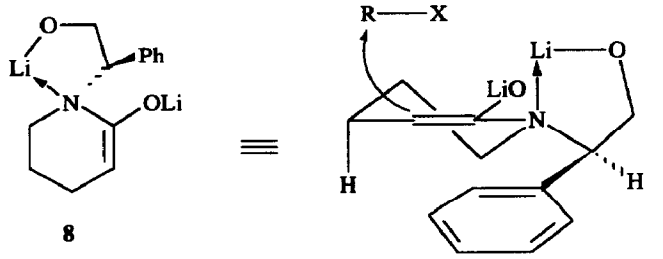


Figure

The lactam function of **4** could be reduced using $LiAlH_4$ without epimerization at C-3 furnishing piperidine derivatives **5** in excellent yield. Hydrogenolysis of **5** was performed with Pearlman catalyst and gave the 3-substituted piperidines **6a** and **6b** isolated as hydrochlorides.[10]

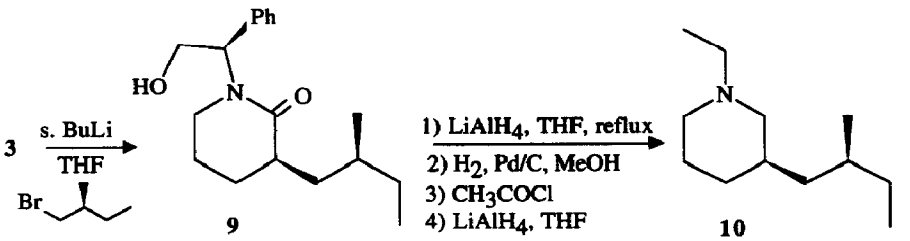
The dialkylated product **7** was obtained in greater than 97 % de, *via* alkylation of methyl derivative **4a** (s.BuLi, $PhCH_2Br$). Although it has beeen impossible to determine the configuration of the quaternary center, it is likely that the second substituent was introduced with the same configuration as the first one. The same selectivity was observed by Meyers[4, 11] during the bis alkylation of bicyclic lactams.

The excellent diastereoselectivity accompanying alkylation can be explained by a chelation process, as previously observed[7]. Nitrogen is known to be highly pyramidalized in amide enolates[12]. Consequently, the N-lone pair in the amide enolate makes a very good electron donor allowing the chelation with lithium and then enhancing the acidity of the proton α to the carbonyl. Conformation **8** was then favoured for steric reasons. During the alkylation, the alkyl halide approached the lactam enolate from the less hindered side under stereoelectronic control[13] leading to the observed stereochemistry. This hypothesis was confirmed by the diminution of reactivity and the loss of diastereoselectivity when the alkylation was performed with O-methyl or O-silyl derivatives.



8

This strategy was then applied to the synthesis of stenusine **10**[14], a spreading agent of *Stenus comma*. Alkylation of lactam **3** with commercially available (S)-(+)-1-bromo-2-methylbutane led to substituted lactam **9** in 77% yield as the only isomer detectable in ^{13}C and ^{1}H NMR. Reduction of the carbonyl function, followed by hydrogenolysis furnished a piperidine derivative which was N-substituted by a classical method. (2S,3R)-1-Ethyl-3-(2-methylbutyl)piperidine **10** identical to the product described by Enders[14b] (MS, $[\alpha]_D$, ^{1}H and ^{13}C NMR) was obtained in 46% yield from synthon **3**.



9 **10**

In conclusion the efficiency of our new method is highlighted by a rapid and convenient synthesis of (+)-stenusine **10**. The process should provide a practical route to optically pure polysubstituted piperidines due to potentialities of the starting oxazololactam **2**.

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References and notes.

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8. Preparation of **4 a** is typical. To a solution of lactam **3** (500 mg, 2.3 mmol) in THF (25 ml) under nitrogen was added s.BuLi (2.5 eq) at - 78°C. The mixture was stirred for 20 min and MeI (3 eq, 430 µl) was then added dropwise. After stirring at - 78°C for 3 h, the mixture was treated with saturated NH_4Cl, extracted with CH_2Cl_2, washed with brine and concentrated to give a white solid which crystallized from toluene(511mg, 96%). **4 a**: mp 119°C (toluene), $[\alpha]_D^{20}$ = -75 (c= 0.7 ; $CHCl_3$); IR (film) 1622 cm^{-1}; MS (CI) : 234 (MH^+), 202 (M-31); ^1H NMR (δ ppm): 1.23 (d, Me, J = 7.2 Hz), 1.45 - 2.52 (m, 5H), 2.89 (td, H-6, J = 12.1 and 6.6 Hz), 3.20 (dt, H-6, J = 12.1 and 5,7 Hz), 3.75 (OH), 4.10 (m, 2xH-8), 5.81 (dd, H-7, J = 8.7 and 5.5 Hz), 7.2 - 7.4 (m, 5H ar). ^{13}C NMR: 18.3 (Me) 21.4 ; 28.9 (C4- C-5) 36.8 (C-3) 43.7 (C-6) 58.5 (C-7) 61.6 (C-8) 127.7 ; 127.9 ; 128.7 ; 137.2 (C ar) 175.4 (C-2).
9. **X- ray structure analysis** : Crystal data. $C_{14}H_{19}O_2N$, M_W = 233,31, orthorhombic, space group $P2_12_12_1$, Z = 4, a= 9.043 (8), b = 9.524 (8), c = 14.539 (12) Å , V = 1252 (2) $Å^3$, d_c = 1.24 g cm^{-3}, F(000) = 504, λ (Cu Kα) = 1.5418 Å, µ = 0.62 mm^{-1}; 2347 measured intensities, 1297 unique. Intensity data were measured on a Nonius CAD-4 diffractometer using graphite monochromated Cu Kα radiation and the (θ -2θ) scan technique up to θ = 66°. 1033 intensities with I > 3.0 σ(I) were considered as observed and kept in refinement calculations, σ(I) being derived from counting statistics. The structure was solved by direct methods using SHELXS86 and refined by full matrix least-squares with SHELX76, minimizing the function $\Sigma w (Fo- |Fc|)^2$. The hydrogen atoms, located in difference Fourier maps, were refined and assigned an isotopic thermal factor equivalent to that of the bonded carbon atom, plus 10%. Convergence was reached at R = 0.037 and R_W = 0.055 (with $Rw = \{\Sigma w(Fo- |Fc|)^2 / \Sigma wFo^2\}^{1/2}$ and $w= 1/[\sigma^2(Fo)+ 0.002745\ Fo^2]$. No residual was higher than 0.12 $eÅ^{-3}$ in the final difference map. In the structure, an intermolecular hydrogen bond is observed between the hydroxyl O17-H of one molecule and the oxygen atom O16 of the neighbouring one (distances O17...O16 = 2.726 (6), H17...O16 = 1.84 (6) Å, angle O17-H...O16 = 167°). Lists of the fractional atomic coordinates, thermal parameters, bond distances and angles have been deposited at the Cambridge Crystallographic Data Centre, U.K., as supplementary material.
10. **6a** (hydrochloride): ^1H NMR (CD_3OD, δ ppm): 1,08 (d, Me, J = 6.5 Hz), 1.30-2.01 (H-3ax, 2xH-4, 2xH-5), 2,65 (t, H-2ax, J =11.9 Hz), 2.93 (m, H-6 ax), 3.31-3.47 (m, H-6 eq, H-2 eq). ^{13}C NMR (CD_3OD): 19.1 (Me), 23.4; 31.6 (C-4, C-5), 30.1 (C-3), 45.1; 51.2 (C-2, C-6). $[\alpha]_D^{20}$ = -3 (c= 0.6, MeOH); MS : 99 (M^+), 84 (M-15) , 70 (M-29), 56. **6b** (hydrochloride) : $[\alpha]_D^{20}$ = -7 (c= 0.25 ; MeOH) ; MS : 175 (M^+), 91.
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