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Diastereoselective Bis-Alkylation of Chiral Non-Racemic α,β-Unsaturated γ-Lactams

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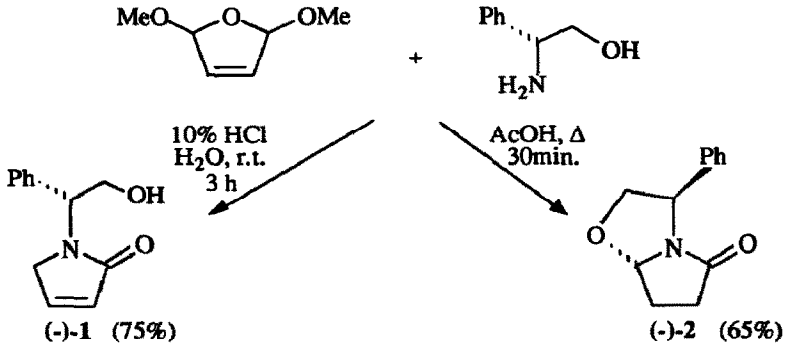
Abstract: A new chiral non-racemic γ-lactam **1** easily prepared in one step from (*R*)-(-)-phenylglycinol was bis-alkylated α to the carbonyl function in very high to complete diastereoselectivity. The stereochemistry at the so-formed chiral quaternary center was ascertained through an X-ray crystallographic study.

In the course of our research on new chiral starting materials for the asymmetric synthesis of piperidine and pyrrolidine derivatives[1], we investigated the condensation of dimethoxydihydrofuran with (*R*)-(-)-phenylglycinol. To our surprise, lactam **1**[2] was found to be formed in a 75% yield, under reaction in water at pH 1. This compound resulted in an intramolecular oxido-reduction similar to a Cannizzaro reaction and thus a 1,2 or 1,3-hydride shift may account for the formation of **1** (a similar reaction, between phtalaldehyde and amines has been reported).[3] When the reaction was conducted in refluxing acetic acid, bicyclic lactam **2**[4] was obtained in 65% yield.

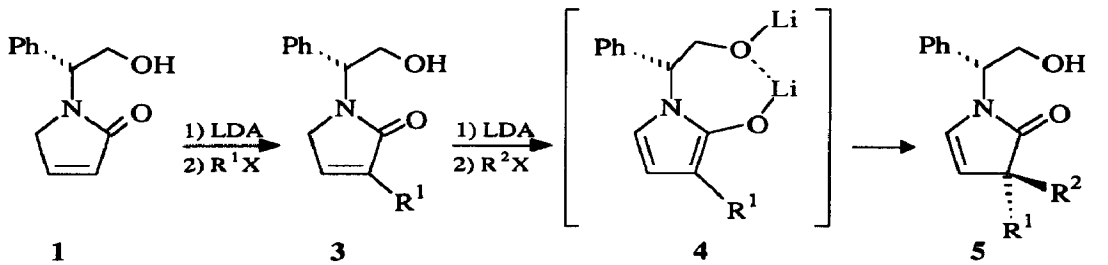


Scheme 1

With compound **1** in hand, we decided to examine its reactivity since, *a priori*, it could be substituted at each center of the pyrrolidine ring by means of electrophilic and nucleophilic attacks. This would give access to highly substituted pyrrolidines in a diastereoselective fashion.

Thus mono-alkylation of the enolate generated *in situ* from **1** (2.2 eq. of LDA, THF, -78°C) and quenching with various primary alkyl halides (Scheme 2) gave compound **3** in good yields (see Table). Formation of C-5-alkylated derivative was not observed in this reaction. Under the same conditions a second alkyl group

was introduced at C-3 of **3** to give compound **5** which possesses a chiral quaternary center α to the carbonyl function. This bis-alkylation was found to be very highly diastereoselective. Compound **5a** (R^1=CH_3, R^2=$CH_2CH_2CH_3$)[5] was formed as a single diastereoisomer on the basis of careful examination of the crude reaction mixture (HPLC and NMR means) and further, by comparison with **5b** (R^1=$CH_2CH_2CH_3$, R^2=CH_3)[5] also obtained as an unique product from **1** by changing the order in introducing electrophiles. When one of the R group was a benzyl, the diastereoselectivity was not as high but still very good and easily determined by NMR on the crude reaction mixture (see Table, entries c and d).



1 **3** **4** **5**

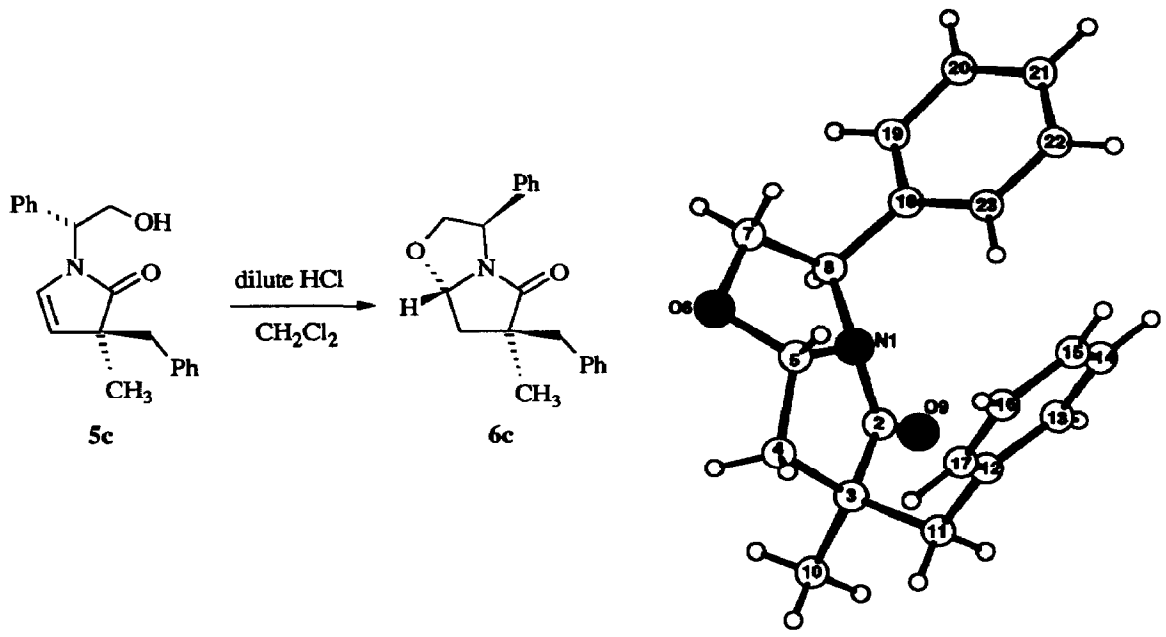
Scheme 2

entry	R^1X	3 (yield %)[a]	R^2X	5 (yield %)[a]	5 d.e. (%)[b]	$[\alpha]_D^{20}$(major)
a	CH_3I	80	$CH_3CH_2CH_2Br$	45	99[c]	5.2 (c 0.7, CH_2Cl_2)
b	$CH_3CH_2CH_2Br$	47	CH_3I	68	99[c]	-15.0 (c 1.2, CH_2Cl_2)
c	CH_3I	80	$PhCH_2Br$	70	73	47.0(c 0.8, CH_2Cl_2)
d	$PhCH_2Br$	70	CH_3I	61	93	

a) isolated yield. b) determined by HPLC on the crude reaction mixture. c) estimated value, no trace of the epimer was found by HPLC

Table: Diastereoselective bis-alkylation of lactam **1**

Considering that reaction of chelated enolate **4** could occur from less hindered face[6], the absolute configuration at the quaternary center of **5** was tentatively assigned as depicted in Scheme 2. This was confirmed by an X-ray analysis of a derivative of **5c**. The major bis-alkylated compound **5c** (R^1=CH_3, R^2=CH_2Ph) was easily obtained pure after flash chromatography (55% yield) and cyclized to single isomer **6c**[7] (quantitative yield). The structure of **6c** was obtained by X-ray crystallography[9] and reported in Scheme 3. This configuration was in full agreement with the assignment of stereochemistry at the quaternary center of **5** made from the chelated enolate **4**.



Scheme 3

In conclusion, we have prepared a new chiral γ-lactam which could be diastereoselectively bis-alkylated α to the carbonyl function. The absolute configuration at the quaternary chiral center has been determined by X-ray analysis. This constitutes a new approach in the asymmetric synthesis of substituted pyrrolidines and pyrrolidones precursors of γ-amino butyric acids derivatives.

References and notes:

1) For leading references in this topic, see: a) Guerrier, L.; Royer, J.; Grierson, D.S.; Husson, H.-P. *J. Am. Chem. Soc.*, **1983**, *105*, 7754-7755. b) Royer, J.; Husson, H.-P. *Tetrahedron Lett.*, **1987**, *27*, 6175-6178. c) Rouden, J.; Royer, J.; Husson, H.-P. *Tetrahedron Lett.*, **1989**, *30*, 5133-5136.

2) **1**: mp: 98°C (heptane, AcOEt); $[\alpha]_D^{20}$ -21 (c 1, CH_2Cl_2); ^1H NMR ($CDCl_3$, 250 MHz) δ(ppm): 3.80 (d, J=20Hz, 1H), 4.05 (m, 2H), 4.10 (d, J=20Hz, 1H), 4.65 (m, 1H), 5.25 (dd, J=7.7Hz, 5.1Hz, 1H), 6.10 (d, J=5.9Hz, 1H), 7. 00 (d, J=5.9Hz, 1H), 7.30 (m, 5H).

3) a) Grigg, R.; Gunaratne, H.Q.N.; Sridharan, V. *J. Chem. Soc. Chem. Commun.*, **1985**, 1183-1184. b) DoMinh, T.; Johnson, A.L.; Jones, J.E.; Senise, P.P. *J. Org. Chem.*, **1977**, *42*, 4217-4221. c) Benachenhou, F.; Mesli, M.A.; El Borai, M.; Hanquet, B.; Guilard, R. *J. Heterocyclic Chem.*, **1988**, *25*, 1531-1534.

4) **2**: $[\alpha]_D^{20}$ -161 (c 1, EtOH). **Ent-2** has been previously obtained in two steps from succinic anhydride and (S)-(+)-phenylglycinol: Meyers, A.I.; Lefker, B.A.; Sowin, T.J.; Westrum, L.J. *J. Org. Chem.*, **1989**, *54*, 4243-4246. The homologue in the piperidine series has already been reported: Royer, J.; Husson, H.-P. *Heterocycles*, **1993**, *36*, 1493-1496

5) Compounds **5a** and **5b** were found different by means of chromatography (TLC and HPLC) and optical rotations but exhibit very similar ^1H and ^{13}C NMR spectra.

6) a) Micouin, L.; Varea, T.; Riche, C.; Chiaroni, A.; Quirion, J.-C.; Husson, H.-P. *Tetrahedron Lett.*, in press. b) Schanen, V.; Riche, C.; Chiaroni, A.; Quirion, J.-C.; Husson, H.-P. *Tetrahedron Lett.*, in press. c) Larchevêque, M.; Ignatova, E.; Cuvigny, T. *Tetrahedron Lett.*, **1978**, 3961-3964.d) Evans, D.A.; Takacs J.M. *Tetrahedron Lett.*, **1980**, *21*, 4233-4236

7) **Ent-6c** has been reported by A.I. Meyers[8] as we were preparing this manuscript. It has been obtained through the bis-alkylation of bicyclic lactam **ent-2** with 64% d.e.

8) Westrum, L.J.; Meyers, A.I. *Tetrahedron Lett.* **1994**, *35*, 973-976.

9) Crystal data. $C_{20}H_{21}NO_2$, M_w = 307.39, monoclinic, space group P 2_1, Z = 2 , a = 9.319 (4), b = 7.640 (4), c = 11.923 (8) Å, β = 93.65(3)°, V = 847.2(8) Å^3, d_c = 1.21 g cm^{-3}, F(000) = 328, λ (Cu Kα) = 1.5418 Å, μ = 0.58 mm^{-1} ; 2993 Nonius diffractometric intensities measured, 1566 unique of which 1439 with I > 3.0 σ(I) considered as observed.The structure was solved by direct methods using *SHELXS86*[10] and refined by full matrix least-squares with *SHELX76*[11] minimizing the function $\Sigma w (Fo-|Fc|)^2$. The hydrogen atoms, located in difference Fourier maps, were replaced at theoretical positions (d C-H = 1.00 Å) and assigned an isotropic thermal factor equivalent to that of the bonded carbon atom, plus 10%. Convergence was reached at R = 0.049 and R_w = 0.063 (with $R_w = \{\Sigma w(Fo-|Fc|)^2 / \Sigma wFo^2\}^{1/2}$ and $w = 1/[\sigma^2(Fo) + 0.000237\ Fo^2]$. No residual was higher than 0.17 e Å^{-3} in the final difference map. 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) Sheldrick, G.M. (1986).*SHELXS86*. Program for the solution of crystal structures. Univ. of Göttingen, Germany.

11) Sheldrick, G. M. (1976). *SHELX76*. Program for crystal structure determination. Univ. of Cambridge, England.

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