Pergamon

SCIENCE DIRECT®

Tetrahedron: *Asymmetry* 14 (2003) 293–295

TETRAHEDRON: *ASYMMETRY*

On the configuration of (3*R*,8a*S*)-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine

Mercedes Amat,[a,*] Núria Llor,[a] Carmen Escolano,[a] Marta Huguet,[a] Maria Pérez,[a] Elies Molins[b] and Joan Bosch[a,*]

[a]*Laboratory of Organic Chemistry, Faculty of Pharmacy, University of Barcelona, E-08028 Barcelona, Spain*
[b]*Institut de Ciència de Materials (CSIC), Campus UAB, E-08193 Cerdanyola, Spain*

Received 4 November 2002; revised 9 December 2002; accepted 10 December 2002

Abstract—The configuration of (3*R*,8a*S*)-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine **2** has been unambiguously confirmed by X-ray crystallographic analysis. A ^{1}H NMR-based method for the stereochemical assignment of 3,8a-*cis* and *trans* phenylglycinol-derived bicyclic lactams is also proposed.

The preparation of both (3*R*,8a*R*)- and (3*R*,8a*S*)-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]-pyridine (**1** and **2**, respectively, Fig. 1) and their enantiomers was published some years ago.[1–4]

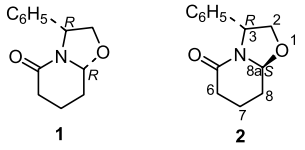
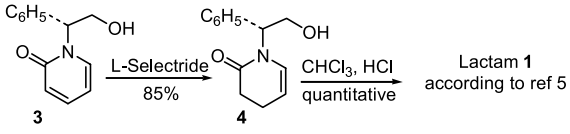


Figure 1.

Recently, a new procedure for the preparation of this class of phenylglycinol-derived bicyclic lactams has been reported, involving the selective reduction of pyridone **3** to give acyl enamine **4**, followed by closure of the oxazolidine ring under acidic conditions[5] (Scheme 1). On the basis of ^{1}H NMR 1D NOE and ROESY experiments, the resulting lactam was assigned as **1**, with a *cis*-3,8a relationship, although, as the authors point out, the ^{1}H and ^{13}C NMR data of this lactam were identical to those previously reported[1–3] for the *trans* isomer **2**. Furthermore, the specific rotation value of this lactam was also very similar {$[\alpha]_D^{20}$ −92 (*c* 1.0, CH_2Cl_2)} to that reported for **2** {$[\alpha]_D^{22}$ −90.8 (*c* 0.6, CH_2Cl_2);[1b] $[\alpha]_D$ −88 (*c* 0.6, CH_2Cl_2)[2]}, but quite different from that reported for **1** {$[\alpha]_D^{22}$ −45.8 (*c* 2.2, CH_2Cl_2);[1b] $[\alpha]_D$ −51 (*c* 2.2, CH_2Cl_2)[2]}. This would mean that the configuration at C-8a of the previously reported lactams **1** and **2** should be reversed.



Scheme 1.

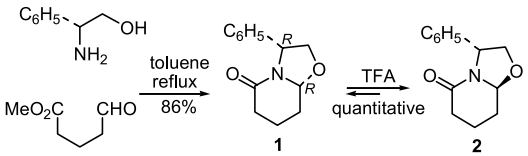
In this communication, we confirm the previously assigned[1–4] configuration of both **1** and **2**.

Scheme 2 outlines the route developed in our laboratory[1b] for the preparation of these lactams. Cyclocondensation of (*R*)-phenylglycinol with methyl 5-oxopentanoate under neutral conditions afforded lactams **1** and **2** in an 85:15 ratio, respectively. However, when the crude mixture was treated under acidic conditions (TFA–CH_2Cl_2) a reversal in the ratio of isomeric lactams **1** and **2** was observed (14:86, respectively).[6] Both lactams could be efficiently separated by column chromatography. Thus, pure lactam **1** can be directly obtained (73% yield) by cyclodehydration whereas lactam **2** is accessible (74% overall yield) by cyclodehydration followed by equilibration of the initially formed reaction mixture under acidic conditions.[7]

Scheme 3 shows two different routes, developed by Royer and Husson,[2] leading to either the *cis* (**1**) or the

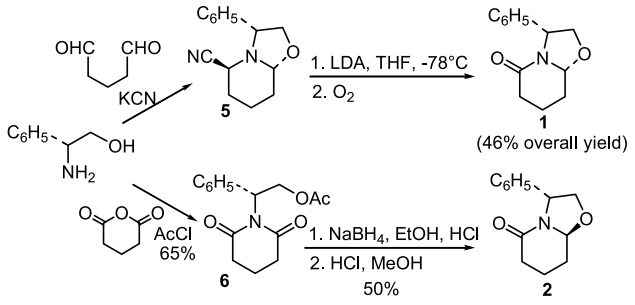
* Corresponding authors. Tel.: +34 93 402 45 40; fax: +34 93 402 45 39; e-mail: amat@farmacia.far.ub.es; jbosch@farmacia.far.ub.es

0957-4166/03/$ - see front matter
PII: S0957-4166(02)00837-6



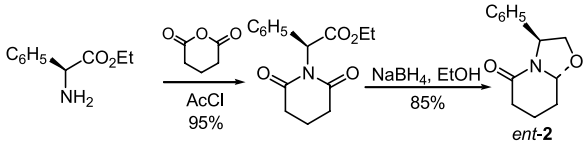
Scheme 2.

trans (**2**) isomer. Oxidation of the anion derived from 5-cyanooxazolo[3,2-*a*]piperidine **5**, of known configuration, gives **1** as a unique stereoisomer. On the other hand, partial reduction of (*R*)-phenylglycinol-derived glutarimide **6**, followed by treatment with a 1 M HCl solution in MeOH affords isomer **2**. The use of a 1:1 85% HCO_2H–85% H_3PO_4 mixture in the second step gave a 3:7 mixture of isomers **1** and **2**, respectively, in 47% yield.[1a]



Scheme 3.

Finally, Scheme 4 shows a more convenient route reported by Quirion and Husson[3] for the *trans* isomer in the enantiomeric series (*ent*-**2**).



Scheme 4.

In previous work lactam **2** had been converted into lactams **7**,[1b] **8**,[4] **9**,[8] and **10**[9] (Fig. 2), all of them with a 3,8a-*trans* relationship unambiguously established by X-ray crystallographic analysis. Consequently, it seems reasonable to assume that the 3,8a relative configuration of lactam **2** is also *trans*.

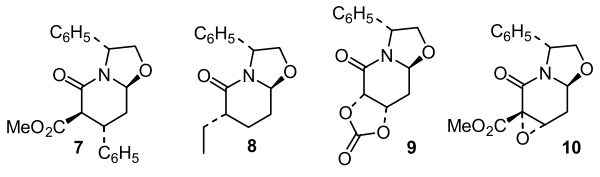


Figure 2.

This has now been unambiguously proven by X-ray crystallography: the configuration of **2** in the crystal lattice (Fig. 3) shows that the methine hydrogens at the 3 and 8a positions are in a *trans* disposition.[10] Consequently, the previous stereochemical assignments[1–4] for lactams **1** (3,8a-*cis*) and **2** (3,8a-*trans*), and their enantiomers, must be maintained, and the lactam resulting from the reaction sequence depicted in Scheme 1 is the *trans* isomer **2**.

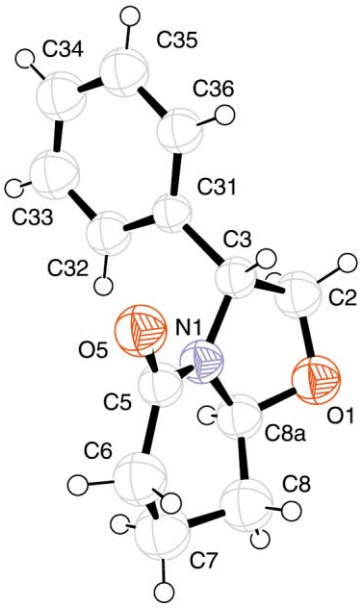
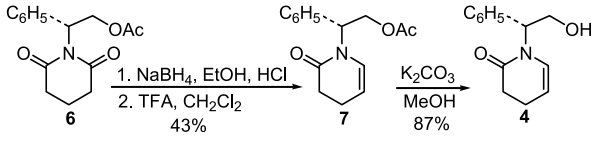


Figure 3. X-Ray structure of (3*R*,8a*S*)-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine **2**.

In fact, the propensity of the acyl enamine **4** to undergo cyclization had also been observed in our laboratory. Although this enamine, prepared from glutarimide **6**, via acetate **7**,[11] as shown in Scheme 5, could be oxidized with *m*-CPBA to give a bicyclic hydroxy lactam,[8] purification of **4** by column chromatography on silica gel caused its partial conversion to the *trans* lactam **2**.



Scheme 5.

Lactams **1** and **2**, as well as many other phenylglycinol-derived bicyclic δ-lactams, either 3,8a-*cis* or 3,8a-*trans*, have been extensively used in our laboratory[12] as starting materials or intermediates in the enantioselective synthesis of diversely substituted piperidine derivatives.[13] In the context of these studies we have observed that the chemical shift and coupling constants of the methine (H-3) and methylene (H-2) protons of the phenylglycinol moiety in these lactams are of diagnostic value in the assignment of the relative 3,8a stereochemistry. Thus, for the *cis* isomers, the C-2 methylene protons resonate at $\delta \sim 4.0$ and 4.2 as doublets of

doublets with a geminal coupling constant of about 9.0 Hz and vicinal coupling constants of about 1.5 and 7.0 Hz, respectively. In contrast, in the *trans* isomers the chemical shift difference between these protons is higher ($\delta \sim 3.8$ and 4.5), and they appear as doublets of doublets with two coupling constants of about 8.5 Hz. On the other hand, the methine H-3 proton appears as a doublet of doublets ($\delta \sim 4.9$; $J \sim 7.0$ and 1.5 Hz) in the *cis* isomers and, in contrast, as a more deshielded ($\delta \sim 5.35$) triplet ($J \sim 8.5$ Hz) in the *trans* isomers. This distinctive pattern can be observed in both the *cis* lactam **1** and the *trans* lactam **2**.[14]

The above ^{1}H NMR-based method provides an easy and practical way for the stereochemical assignment of 3,8a-*cis* and *trans* phenylglycinol-derived bicyclic lactams.

Acknowledgements

This work was supported by the DGICYT, Spain (BQU2000-0651). Thanks are also due to the DURSI, Generalitat de Catalunya, for Grant 2001SGR-0084 and to the Ministry of Education, Culture and Sport for fellowships to M.H. and M.P.

References

1. (a) Amat, M.; Llor, N.; Bosch, J. *Tetrahedron Lett*. **1994**, *35*, 2223–2226; (b) Amat, M.; Bosch, J.; Hidalgo, J.; Cantó, M.; Pérez, M.; Llor, N.; Molins, E.; Miravitlles, C.; Orozco, M.; Luque, J. *J. Org. Chem*. **2000**, *65*, 3074–3084.
2. Royer, J.; Husson, H.-P. *Heterocycles* **1993**, *36*, 1493–1496.
3. Micouin, L.; Quirion, J.-C.; Husson, H.-P. *Synth. Commun*. **1996**, *26*, 1605–1611.
4. Amat, M.; Pshenichnyi, G.; Bosch, J.; Molins, E.; Miravitlles, C. *Tetrahedron: Asymmetry* **1996**, *7*, 3091–3094.
5. Terán, J. L.; Gnecco, D.; Galindo, A.; Juárez, J.; Bernès, S.; Enríquez, R. G. *Tetrahedron: Asymmetry* **2001**, *12*, 357–360.
6. A similar result was observed when using 3N MeOH–HCl.
7. For the preparation of *ent*-**1** and *ent*-**2** from (*S*)-phenylglycinol following this procedure, see Ref. 4.
8. Amat, M.; Llor, N.; Huguet, M.; Molins, E.; Espinosa, E.; Bosch, J. *Org. Lett*. **2001**, *3*, 3257–3260.
9. Amat, M.; Llor, N.; Hidalgo, J.; Bosch, J.; Molins, E.; Miravitlles, C. *Tetrahedron: Asymmetry* **1996**, *7*, 2501–2504.
10. The experiment was done on an Enraf-Nonius CAD4 diffractometer using graphite monochromated Mo Kα radiation. The structure was solved by direct methods (SHELXS-97) after applying Lorentz, polarization, and absorption (semiempirical PSI scan method) corrections. Full-matrix least-squares refinement (SHELXL-97) with anisotropic thermal parameters for non-H atoms and riding thermal parameters for H-atoms (positioned at calculated positions) converged to an *R* factor of 0.0347 (calculated for the reflections with $I > 2\sigma(I)$). Crystal data: $C_{13}H_{15}NO_2$, orthorhombic, space group $P2_12_12_1$, $a = 8.329$, $b = 9.808$, $c = 14.108$ Å, $V = 1152.5$ Å^3, $Z = 4$, μ (Mo Kα) $= 0.084$ mm^{-1}, $D_{calcd} = 1.252$ g/cm^3. Data collection was up to a resolution of $2\sigma = 49.9°$ producing 1190 reflections. Largest peak and hole at the final difference Fourier synthesis were 0.097 and –0.153 e Å^{-3}.
11. Rodríguez, R.; Estiarte, M. A.; Diez, A.; Rubiralta, M.; Colell, A.; García-Ruiz, C.; Fernández-Checa, J. C. *Tetrahedron* **1996**, *52*, 7727–7736.
12. (a) Amat, M.; Pérez, M.; Llor, N.; Bosch, J.; Lago, E.; Molins, E. *Org. Lett*. **2001**, *3*, 611–614; (b) Amat, M.; Pérez, M.; Llor, N.; Bosch, J. *Org. Lett*. **2002**, *4*, 2787–2790; (c) Amat, M.; Cantó, M.; Llor, N.; Escolano, C.; Molins, E.; Espinosa, E.; Bosch, J. *J. Org. Chem*. **2002**, *67*, 5343–5351; (d) See also Refs. 1b, 4, 8, and 9.
13. For reviews on chiral, amino alcohol-derived bicyclic lactams, see: (a) Romo, D.; Meyers, A. I. *Tetrahedron* **1991**, *47*, 9503–9569; (b) Meyers, A. I.; Brengel, G. P. *Chem. Commun*. **1997**, 1–8; (c) Groaning, M. D.; Meyers, A. I. *Tetrahedron* **2000**, *56*, 9843–9873.
14. ^{1}H NMR data taken from Ref. 1b. Lactam **1**: δ 4.01 (dd, $J = 9.0$ and 1.5 Hz, 1H, H-2), δ 4.15 (dd, $J = 9.0$ and 7.0 Hz, 1H, H-2), δ 4.92 (dd, $J = 7.0$ and 1.5 Hz, 1H, H-3). Lactam **2**: δ 3.76 (dd, $J = 9.0$ and 8.0 Hz, 1H, H-2), δ 4.50 (dd, $J = 9.0$ and 8.0 Hz, 1H, H-2), δ 5.28 (t, $J = 8.0$ Hz, 1H, H-3).