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Unprecedented Oxidation of a Phenylglycinol-Derived 2-Pyridone: Enantioselective Synthesis of Polyhydroxypiperidines

Mercedes Amat,*,† Núria Llor,† Marta Huguet,† Elies Molins,‡ Enrique Espinosa,‡ and Joan Bosch†

Laboratory of Organic Chemistry, Faculty of Pharmacy, University of Barcelona, 08028-Barcelona, Spain, and Institut de Ciència de Materials (CSIC), Campus UAB, 08193-Cerdanyola, Spain

amat@farmacia.far.ub.es

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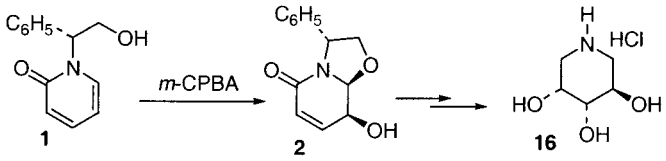
ABSTRACT



The phenylglycinol-derived 2-pyridone 1 undergoes *m*-CPBA oxidation steroselectively leading to the chiral nonracemic unsaturated bicyclic hydroxylactam 2, from which the enantioselective synthesis of (3*R*,5*R*)-3,4,5-trihydroxypiperidine (16) and the formal synthesis of the azasugar epiisofagomine are described. The enantioselective synthesis of (*S*)-*N*-Boc-3-hydroxypiperidine and (3*R*,4*S*)-3,4-dihydroxypiperidine is also reported.

Both naturally occurring (e.g., deoxynojirimycin, fagomine) and synthetic (e.g., miglitol, epiisofagomine) polyhydroxylated piperidines, pyrrolidines, and indolizidines[1] have been shown to be specific and potent inhibitors of glycosidases[2] and have been demonstrated to have a great potential as drugs to treat a variety of carbohydrate-mediated diseases such as diabetes,[3] viral infections including HIV,[4] and cancer metastasis[5] (Figure 1). As a consequence, in recent years there has been a great deal of interest not only in the synthesis of the natural products themselves but also in that of chemically modified analogues. However, most of the methodologies described for the synthesis of these compounds, which can be regarded as azasugars (also called iminosugars), start from carbohydrates and, in general, require a large number of steps to reach a specific target. Thus, the development of new methods for the enantioselective synthesis of polyhydroxylated piperidines constitutes an area of current interest.[6]

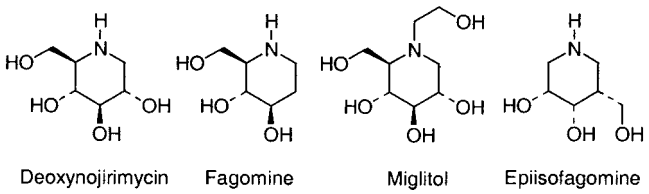


Figure 1. Natural and synthetic azasugars as glycosidase inhibitors.

† University of Barcelona.
‡ Institut de Ciència de Materials.

(1) (a) Nash, R. J.; Watson, A. A.; Asano, N. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Elsevier: Oxford, 1996; Vol. 11, pp 345−376. (b) Elbein, A. D.; Molyneux, R. J. In *Comprehensive Natural Products*; Barton, D., Nakanishi, K., Eds.; Elsevier: New York, 1999; Vol. 3, pp 129−160.

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(3) (a) Horii, S.; Fukase, H.; Matsuo, T.; Kameda, Y.; Asano, N.; Matsui, K. *J. Med. Chem.* **1986**, *29*, 1038. (b) *Drugs Future* **1986**, *11*, 1039; **1987**, *12*, 1157. (c) Robinson, K. M.; Begovic, M. E.; Reinhart, B. L.; Heineke, E. W.; Ducep, J.-B.; Kastner, P. R.; Marshall, F. N.; Danzin, C. *Diabetes* **1991**, *40*, 825.

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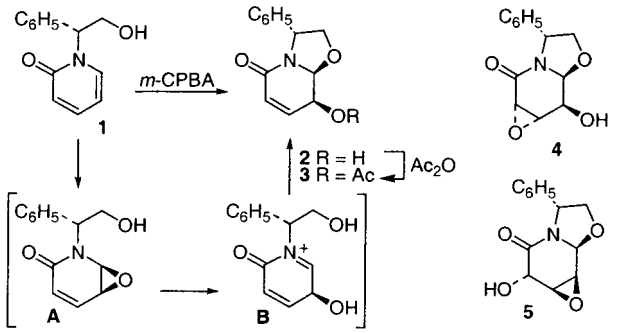
The potential of chiral nonracemic bicyclic lactams derived from (*R*)- or (*S*)-phenylglycinol as versatile building blocks for the enantioselective synthesis of piperidine derivatives has previously been demonstrated with the synthesis of diversely substituted piperidines. In these syntheses the oxazolopiperidine ring system is usually generated by cyclocondensation of a 5-oxoacid derivative with phenylglycinol. A subsequent introduction of substituents on the carbon atoms of the piperidine ring is achieved by α-amidoalkylation, enolate or homoenolate alkylations, manipulation of the amide carbonyl group, or addition to the corresponding α,*β*-unsaturated lactams.[7] We describe here the one-pot generation of the highly functionalized chiral bicyclic hydroxylactam **2** by an alternative procedure involving an unprecedented diastereoselective oxidation of an (*R*)-phenylglycinol-derived 2-pyridone and its subsequent conversion into an enantiopure trihydroxypiperidine through a route that establishes a formal synthesis of epiisofagomine.

The starting pyridone **1** was prepared from the pyridine Zincke salt and (*R*)-phenylglycinol as previously described.[8] Oxidation of **1** with *m*-CPBA (4 equiv) in methylene chloride at room temperature for 4 days afforded the unsaturated hydroxylactam **2** in 35−40% yield as a single stereoisomer (Scheme 1).[9] Modification of the reaction conditions, such

Scheme 1. *m*-CPBA Oxidation of the (*R*)-Phenylglycinol-Derived Pyridone **1**

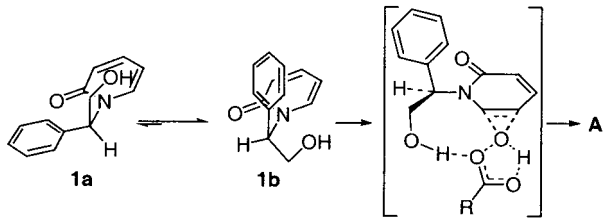


as the amount of reagent, time, or temperature, did not improve the yield.[10] In some runs, in which the yield of **2** was lower, small amounts of epoxides **4** (∼10%) and **5** (∼5%) were isolated after column chromatography on silica gel. Although the yield of **2** is only moderate, it should be noted that in a single step, from an easily accessible starting material, a lactam functionalized in all carbon positions of the piperidine ring, with a defined configuration in the two new stereogenic centers, has been formed.

The stereochemical assignment of compounds **2**, **4**, and **5** was inferred by NMR spectroscopy. Moreover, the configuration of **2** was confirmed by X-ray analysis of a crystal of the acetylated derivative **3**.[11]

Formation of the bicyclic lactam **2** can be rationalized by considering the initial regioselective epoxidation of the C_5-C_6 double bond of the pyridone ring, followed by ring cleavage of the resulting epoxide **A** promoted by the lone electron pair of the nitrogen, to give the acyliminium cation **B**, which would undergo the intramolecular attack of the hydroxy group present in the chiral inductor. The stereochemical outcome of this reaction can be attributed to the directing influence of the hydroxy group of the phenylglycinol moiety, which is capable of hydrogen bonding with the oxygen atom of the epoxidant. Thus, for pyridone **1** there are two conformations, **1a** and **1b**, in which the hydroxy group can stabilize the two possible diastereotopic transition states of the epoxidation step by hydrogen bonding (Scheme 2). The interactions between the phenyl ring and the carbonyl

Scheme 2. Diastereoselective Epoxidation of the Pyridone Ring



group in conformation **1a** favor the reaction taking place stereoselectively through conformation **1b**, on the *si-si* face, affording epoxide **A**. A subsequent epoxide cleavage and oxazolidine ring formation also takes place stereoselectively to give lactam **2**, with the thermodynamically more stable *trans*-3,8a configuration.[12] Although the directing effect of allylic and homoallylic hydrogen bond donating groups in the peracid epoxidation of alkenes is well documented, there are relatively few examples in which the directing group is

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(7) (a) Amat, M.; Llor, N.; Bosch, J. *Tetrahedron Lett.* **1994**, *35*, 2223. (b) Amat, M.; Llor, N.; Hidalgo, J.; Hernández, A.; Bosch, J. *Tetrahedron: Asymmetry* **1996**, *7*, 977. (c) Amat, M.; Pshenichnyi, G.; Bosch, J.; Molins, E.; Miravitlles, C. *Tetrahedron: Asymmetry* **1996**, *7*, 3091. (d) Amat, M.; Llor, N.; Bosch, J.; Solans, X. *Tetrahedron* **1997**, *53*, 719. (e) Amat, M.; Hidalgo, J.; Llor, N.; Bosch, J. *Tetrahedron: Asymmetry* **1998**, *9*, 2419. (f) 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. (g) Amat, M.; Pérez, M.; Llor, N.; Bosch, J.; Lago, E.; Molins, E. *Org. Lett.* **2001**, *3*, 611. For reviews, see: (h) Meyers, A. I.; Brengel, G. P. *Chem. Commun.* **1997**, 1. (i) Groaning, M. D.; Meyers, A. I. *Tetrahedron* **2000**, *56*, 9843. (j) For the use of related chiral bicyclic phenylglycinol-derived 2-cyanopiperidines, see: Husson, H.-P.; Royer, J. *Chem. Soc. Rev.* **1999**, *28*, 383.

(8) Gnecco, D.; Marazano, C.; Enríquez, R. G.; Terán, J. L.; Sánchez S., M. R.; Galindo, A. *Tetrahedron: Asymmetry* **1998**, *9*, 2027.

(9) All yields are from material purified by column chromatography. Satisfactory spectral (IR, ^{1}H and ^{13}C NMR), analytical, and/or HRMS data were obtained for all new compounds.

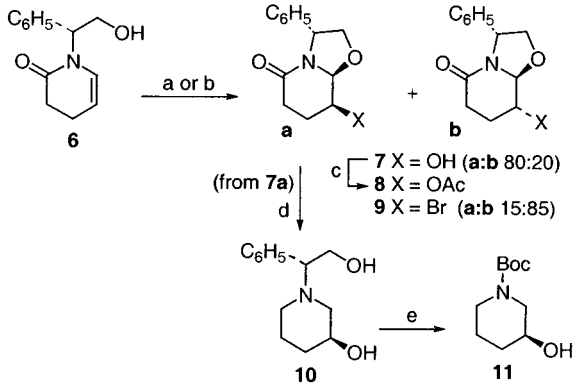
(10) Attempts to promote the oxidation of pyridone **1** using trifluoroperacetic acid, OsO_4 and NMO, DMD or UHP led only to the recovery of the starting material. Similarly, the *O*-silyl protected (TBDMS) lactam derived from **1** was recovered unchanged after exposure to *m*-CPBA.

located further away from the double bond.[13] It is also worth mentioning that, to our knowledge, this is the first example of oxidation of a 2-pyridone with *m*-CPBA.[14]

The minor compound **4** would be generated by epoxidation of the double bond of **2** with the excess of *m*-CPBA, whereas it is reasonable to asume that epoxide **5** is formed from **4** by intramolecular ring opening of the oxirane ring, probably during column chromatography, promoted by the hydroxy group in *anti*. In fact, treatment of the unsaturated lactam **2** with *m*-CPBA led to the epoxide **4** in 28% yield.

In accordance with the above mechanism involving hydrogen bonding by the phenylglycinol hydroxy group, *m*-CPBA oxidation of dihydropyridone **6**[15] took place with the same π-facial diastereoselectivity to give (51% yield) the saturated hydroxylactam **7** as a 4:1 mixture of epimers, **7a** and **7b**, in which the major one (**7a**) possessed the same stereochemistry as **2** (Scheme 3). The mixture of isomers

Scheme 3[a]

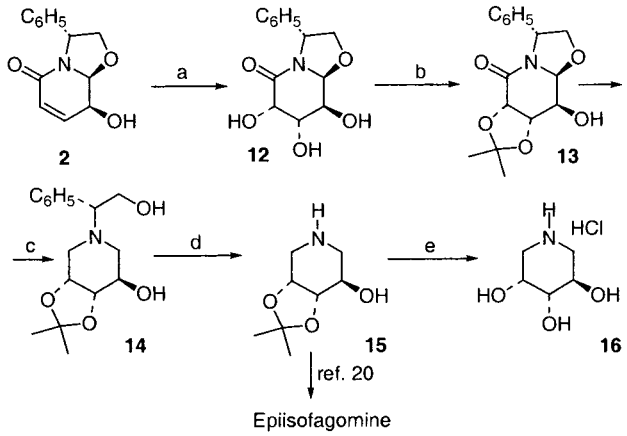


[a] Reagents and conditions: (a) *m*-CPBA (4 equiv), CH_2Cl_2, 25 °C, 2 h (**7**, 51%). (b) Br_2, NaOMe, MeOH, 25 °C, 3 h (**9**, 50%). (c) Ac_2O, pyr, DMAP, CH_2Cl_2, 25 °C, 3 h, 70%. (d) BH_3·THF, −78 °C (30 min) to 25 °C (3 h), 66%. (e) H_2, $Pd(OH)_2$, Boc_2O, AcOEt, 65%.

7a and **7b** could not be separated by conventional methods, but it was acetylated to give a mixture of **8a** and **8b**, from which the major isomer **8a** could be isolated. The stereochemistry of **7a** was unambiguously established by comparison of its spectroscopic data with those of a sample obtained by catalytic hydrogenation of the unsaturated lactam **2**. In contrast, treatment of dihydropyridone **6** with bromine afforded (50% yield) a mixture of bromo lactams **9a** and **9b**, the latter being the major product (15:85). The reversal of the diastereoselectivity can be accounted for in terms of an intramolecular hydrogen bonding between the hydroxy and carbonyl groups. To avoid steric interactions with the phenyl substituent, the bromonium intermediate is now formed by the opposite diastereotopic *re-re* face.[16] Hydroxylactam **7a** was converted into the *N*-Boc protected (*S*)-3-hydroxypiperidine **11** by simultaneous reduction of the lactam carbonyl and C−O bond with borane−THF complex followed by catalytic hydrogenation of the resulting piperidine **10** in the presence of di-*tert*-butyl dicarbonate.[17]

The synthetic potential of the unsaturated hydroxylactam **2** is illustrated by its conversion into the enantiopure trihydroxypiperidine **16**. Thus, the reaction of **2** with catalytic OsO_4 and NMO stereoselectively afforded the trihydroxylated lactam **12** as a sigle isomer in 78% yield (Scheme 4). The

Scheme 4. Synthesis of Enantiopure Trihydroxypiperidine **16**. Formal Synthesis of Epiisofagomine[a]



[a] Reagents and conditions: (a) OsO_4, NMO, aq MeCN, 25 °C, 24 h, 78%. (b) $Me_2C(OMe)_2$, *p*-TsOH, CH_2Cl_2, 25 °C, 24 h, 85%. (c) BH_3·THF, −78 °C (30 min) to 25 °C (3 h), 87%. (d) H_2, Pd/C, MeOH, 65%. (e) MeOH, HCl, 95%.

same *exo*-facial diastereoselectivity was also observed in the dihydroxylation of the unsaturated lactam **18**, lacking the hydroxy substituent, which was easily accessible from the known lactam **17**[7f] by treatment of the corresponding enolate

(11) The experiment was done on a Enraf-Nonius CAD4 diffractometer using graphite monochromated Mo Kα radiation. The structure was solved by direct methods (SHELXS-86) after applying Lorentz, polarization, and absorption (empirical PSI scan method) corrections. Full matrix least squares refinement (SHELXL-93) using anisotropic thermal parameters for non-H atoms and riding thermal parameters for H atoms (positioned at calculated positions) converged to a *R* factor of 0.0396 (for **3**) and 0.0733 (for **20**) (calculated for the reflections with $I > 2\sigma(I)$). **3** crystal data: $C_{15}H_{15}NO_4$, orthorhombic, space group $P2_12_12_1$, a = 5.8363(6), b = 14.926(2), c = 15.495(3) Å; V = 1349.8(3) Å^3, μ (Mo Kα) = 0.098 mm^{-1}, D_c = 1.345 g/cm^3. Approximate dimensions: 0.11 × 0.15 × 0.55 mm^3. Data collection was up to a resolution of $2\theta = 56.9°$ producing 1970 reflections. Maximum and minimum heights at the final difference Fourier synthesis were 0.168 and −0.158 e Å^{-3}. **20** crystal data: $C_{14}H_{13}NO_5$, orthorhombic, space group $P2_12_12_1$, a = 6.155(1), b = 12.016(1), c = 17.465(2) Å; V = 1291.7(3) Å^3, μ (Mo Kα) = 0.109 mm^{-1}, D_c = 1.415 g/cm^3. Approximate dimensions: 0.23 × 0.35 × 0.58 mm^3. Data collection was up to a resolution of $2\theta = 60.8°$ producing 2254 reflections. Maximum and minimum heights at the final difference Fourier synthesis were 0.585 and −0.450 e Å^{-3}.

(12) It has been demonstrated that related *cis*-3,8a bicyclic lactams equilibrate to the *trans* isomers; see ref 6f.

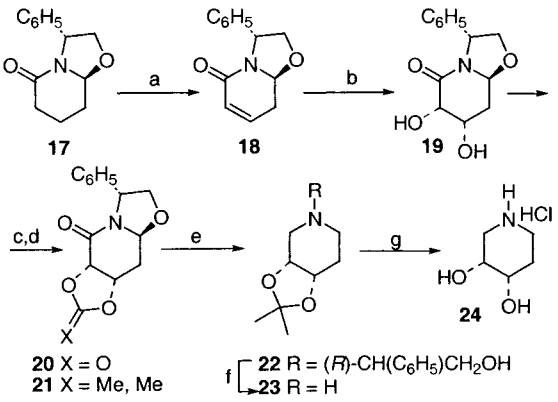
(13) (a) Schwesinger, R.; Willaredt, J.; Bauer, T. In *Stereoselective Synthesis (Houben-Weyl)*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Thieme: Stuttgart, 1996; Vol. 8, pp 4599−4697. (b) Adam, W.; Schambony, S. B. *Org. Lett.* **2001**, *3*, 79 and references therein.

(14) (a) For the Elbs peroxydisulfate oxidation of 2-pyridone to 5-hydroxy-2-pyridone, see: Behrman, E. J.; Pitt, B. M. *J. Am. Chem. Soc.* **1958**, *80*, 3717. (b) For the dioxygenase-catalyzed *cis*-dihydroxylation of *N*-methyl-2-pyridone, see: Modyanova, L.; Azerard, R. *Tetrahedron Lett.* **2000**, *41*, 3865.

(15) Rodríguez, R.; Estiarte, M. A.; Diez, A.; Rubiralta, M.; Colell, A.; García-Ruiz, C.; Fernández-Checa, J. C. *Tetrahedron* **1996**, *52*, 7727.

with methyl phenylsulfinate, followed by thermal elimination of the sulfoxide (Scheme 5). This stereoselectivity was not

Scheme 5. Synthesis of Enantiopure *cis*-3,4-Dihydroxypiperidine[a]



[a] Reagents and conditions: (a) KH, $PhSO_2Me$, THF, reflux, 90 min, then Na_2CO_3, toluene, reflux, 7 h, 90%. (b) OsO_4, NMO, aq MeCN, 25 °C, 24 h, 87%. (c) $(Cl_3CO)_2CO$, pyr, CH_2Cl_2, 25 °C, 90 min, (**20**: 72%). (d) $Me_2C(OMe)_2$, *p*-TsOH, CH_2Cl_2, 25 °C, 3 h, (**21**, 93%). (e) BH_3·THF, −78 °C (30 min) to 25 °C (2 h), 70%. (f) H_2, Pd/C, MeOH, 56%. (g) MeOH, HCl, 93%.

unexpected because it had already been observed both in the conjugate addition of lower order cyanocuprates to related unsaturated bicyclic lactams[7f,g] and in the dihydroxylation (OsO_4−NMO) of 8a-substituted derivatives.[18]

After formation of acetonide **13**, BH_3·THF reduction gave piperidine **14**, which was debenzylated to **15** and then converted by methanolysis to 3,4,5-trihydroxypiperidine **16** (1,5-dideoxy-1,5-imino-D-arabitol).[19] The fact that **16** was optically active confirmed the *exo*-facial configuration of the two new stereocenters generated in the dihydroxylation step.

Given that the protected intermediate **15** had previously been converted into epiisofagomine, an extremely potent inhibitor for β-galactosidase (K_i, 4.1 nM),[20] the above route represents a formal synthesis of this azasugar. 1,5-Dideoxy-1,5-imino-D-pentitols are known to have a moderate binding affinity for a broad range of glycosidases. In particular, 1,5-iminopentitol **16** selectively inhibits the α-L-fucosidase from human placenta.[19b]

On the other hand, the stereochemical identity of diol **19** was confirmed by X-ray crystallography[11] of a crystal of the corresponding carbonate **20**. Following a reaction sequence similar to that described above, diol **19** was converted via the acetonide derivative **21** to (3*R*,4*S*)-3,4-dihydroxypiperidine (**24**; 2-deoxy-1,5-iminopentitol),[21] which has been shown to be an inhibitor of β-glucosidase (K_i, 6 μM).[2]

The diastereoselective oxidation of chiral amino alcohol-derived 2-pyridones opens new possibilities for the straightforward preparation of highly functionalized bicyclic lactams, which are valuable chiral synthons for the synthesis of enantiopure piperidine derivatives and, in particular, azasugars.

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Supporting Information Available: Copies of ^1H and ^{13}C NMR spectra of compounds **2**, **4**, **7a**, **11**, **12**, **16**, **19**, and **24** and complete X-ray crystallographic data for **3** and **20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) A similar stereoselectivity was observed in the NIS-promoted iodination of a phenylglycinol-derived 1,4-dihydropyridine: Lavilla, R.; Coll, O.; Nicolas, M.; Sufi, B. A.; Torrents, J.; Bosch, J. *Eur. J. Org. Chem.* **1999**, 2997.

(17) For previous enantioselective syntheses of 3-hydroxypiperidine, see: (a) Huh, N.; Thompson, C. M. *Tetrahedron* **1995**, *51*, 5935. (b) Monterde, M. I.; Nazabadioko, S.; Rebolledo, F.; Brieva, R.; Gotor, V. *Tetrahedron: Asymmetry* **1999**, *10*, 3449 and references therein.

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(19) For previous syntheses, see: (a) Bernotas, R. C.; Papandreou, G.; Urbach, J.; Ganem, B. *Tetrahedron Lett.* **1990**, *31*, 3393. (b) Legler, G.; Stütz, A. E.; Immich, H. *Carbohydr. Res.* **1995**, *272*, 17. (c) Godskesen, M.; Lundt, I.; Madsen, R.; Winchester, B. *Bioorg. Med. Chem.* **1996**, *4*, 1857.

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(21) For a previous synthesis, see: Chen, L.; Dumas, P.; Wong, C.-H. *J. Am. Chem. Soc.* **1992**, *114*, 741.