Pergamon

Tetrahedron: Asymmetry, Vol. 7, No. 9, pp. 2501-2504, 1996

0957-4166/96 $15.00 + 0.00

PII: S0957-4166(96)00317-5

New Chiral Non-Racemic Piperidine-Derived Epoxy Lactams

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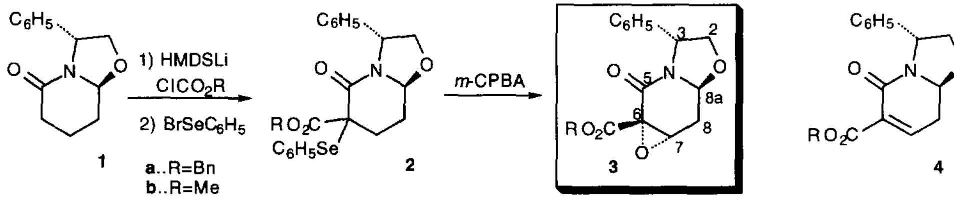
Abstract: The preparation of the chiral non-racemic epoxy lactams **3a** and **3b** from the respective oxazolopiperidones **1** and the conversion of **3b** to the enantiopure piperidine-derived α,β-epoxy alcohol **6** is reported. Copyright © 1996 Elsevier Science Ltd

Methods for the asymmetric synthesis of substituted piperidine derivatives, in particular involving the use of chiral non-racemic piperidine synthons, are receiving considerable attention[1] because of the presence of the piperidine ring in many naturally occurring and biologically active compounds.[2] In this context we have recently reported[3] the preparation of the chiral non-racemic oxazolopiperidone **1** (derived from *R*-phenylglycinol) as well as its enantiomer,[4] and have demonstrated the potential of these chiral synthons in the synthesis of a variety of enantiopure alkyl and dialkylpiperidines, including (-)-coniine (2-alkyl),[3] (-)-dihydropinidine (*cis*-2,6-dialkyl),[5] the indole alkaloid (+)-decarbomethoxytetrahydrosecodine (3-alkyl),[4] and the distomer of the antidepressant drug paroxetine (*trans*-3,4-dialkyl).[6,7]

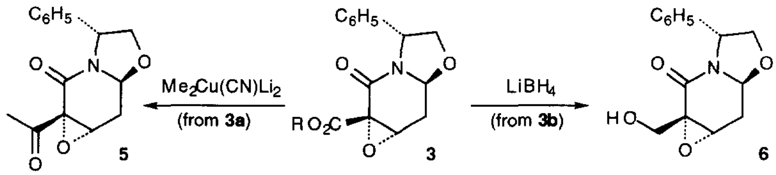
We present here the preparation of α,β-epoxy lactams **3a** and **3b**, which are new chiral, highly functionalized synthons derived from **1**, and their conversion to other functionalized piperidine-derived epoxides.[8] Epoxy lactams **3a**[9] and **3b**[10] were obtained in 58% and 80% overall yield,[11] respectively, by sequential treatment of bicyclic lactam **1** with lithium bis(trimethylsilyl)amide (2.2 equiv, -78°C), benzyl (or methyl) chloroformate (1.0 equiv, -78°C), and phenylselenyl bromide (1.4 equiv, -78°C), followed by oxidation of the resulting mixtures of diastereomeric selenides **2** with *m*-CPBA (6 equiv, -20°C → rt) (Scheme 1). Interestingly, when the oxidation of the intermediate selenides **2** was effected with ozone, the corresponding α,β-unsaturated lactams **4a** or **4b** were isolated in ≈65% overall yield from **1**.[5]



Scheme 1

Formation of epoxy lactams **3** can be rationalized by considering that the initially formed selenoxides spontaneously eliminate PhSeOH to give α,β-unsaturated lactams **4**, which undergo conjugate addition of *m*-CPBA with subsequent displacement of a benzoate anion from the resulting enolate.[12] In fact, treatment of **4a** with *m*-CPBA gave the epoxide **3a** in 65% yield. The configuration of the new stereogenic centers of **3** was deduced by NMR from the multiplicity and coupling constants of the H-8 protons and was confirmed by single crystal X-ray diffraction analysis of **3b**.[13] This configuration is consistent with the stereochemical course of the conjugate addition of cyanocuprates to the unsaturated lactam **4**.[5] It is worth mentioning that there are very few reports on the epoxidation of unsaturated lactams,[16] a process that has proved to be more difficult than anticipated.[17]

Epoxy lactams **3** expand the potential of oxazolopiperidones for the synthesis of diversely substituted piperidine derivatives in enantiomerically pure form. Both the α-oxy lactam and the epoxide moieties of **3** may allow the regio-, and stereocontrolled introduction of a variety of substituents on the lactam ring. Furthermore, and less predictably, some reactions can chemoselectively occur upon the ester group, the epoxy ring being unaffected. Thus, treatment of **3a** with the higher-order cyanocuprate $Me_2Cu(CN)Li_2$ (1.5 equiv, THF, -78°C, 5 min) led to the acetyl derivative **5**[18] in 53% yield, whereas reduction of **3b** with $LiBH_4$ (2.5 equiv, THF, rt, 1h) afforded α,β-epoxy alcohol **6**[19] in 47% yield (Scheme 2). The well-established synthetic utility of enantiopure α,β-epoxy alcohols[20] further enhances the interest of synthons **3** and **6** for the asymmetric synthesis of piperidine derivatives.



Scheme 2

Acknowledgment: Financial support from the DGICYT, Spain (project PB94-0214) and the "Comissionat per a Universitats i Recerca", Generalitat de Catalunya (Grants GRQ93-8036 and SGR95-00428 and a fellowship to N.Ll.) is gratefully acknowledged. Thanks are also due to the "Ministerio de Educación y Ciencia" for a fellowship to J. H.

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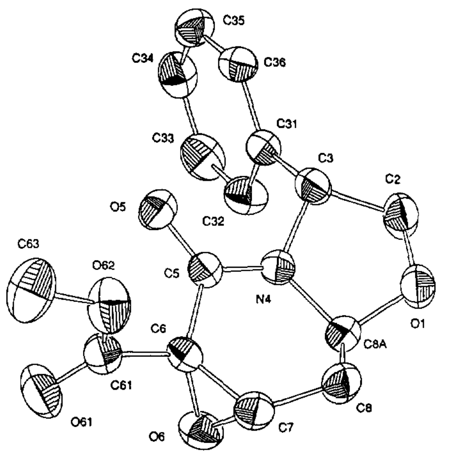
7. For other reports on the preparation of **1**, see: (a) Royer, J.; Husson, H.-P. *Heterocycles* **1993**, *36*, 1493. (b) Micouin, L.; Quirion, J.-C.; Husson, H.-P. *Synth. Commun.* **1996**, *26*, 1605.
8. For a review on the synthesis of chiral epoxides, see: Besse, P.; Veschambre, H. *Tetrahedron* **1994**, *50*, 8885.
9. **3a**: $[\alpha]^{22}_D$ -125.0 (c 1.0, EtOH). Mp 86-88°C (Et_2O-hexane). IR (film) 1750, 1673 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 2.08 (dd, J=14.5, 9.0 Hz, 1H, H-8); 2.97 (ddd, J=14.5, 5.0, 3.5 Hz, 1H, H-8); 3.75 (dd, J=9.0, 8.0 Hz, 1H, H-2); 3.77 (d, J=3.5 Hz, 1H, H-7); 4.43 (dd, J=9.0, 7.5 Hz, 1H, H-2); 5.16 (dd, J=9.0, 5.0 Hz, 1H, H-8a); 5.17 (t, J=7.5 Hz, 1H, H-3); 5.26 (s, 2H, $CH_2C_6H_5$); 7.20-7.40 (m, 10H, ArH). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 29.3 (C-8); 55.9 (C-7); 59.2 (C-3); 60.1 (C-6); 67.8 ($CH_2C_6H_5$); 72.8 (C-2); 84.4 (C-8a); 161.3 (C=O); 164.6 (C=O).
10. **3b**: $[\alpha]^{22}_D$ -135.9 (c 0.7, EtOH). Mp 149-150°C (THF). IR (KBr) 1749, 1670 cm^{-1} ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.09 (dd, J=14.5, 9.0 Hz, 1H, H-8); 3.00 (ddd, J=14.5, 5.0, 3.3 Hz, 1H, H-8); 3.77 (dd, J=9.0, 8.0 Hz, 1H, H-2); 3.80 (d, J=3.3 Hz, 1H, H-7); 3.82 (s, 3H, CH_3O); 4.44 (dd, J=9.0, 7.5 Hz, 1H, H-2); 5.14 (t, J=7.7 Hz, 1H, H-3); 5.17 (dd, J=9.0, 5.0 Hz, 1H, H-8a); 7.20-7.40 (m, 5H, C_6H_5). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 29.2 (C-8); 52.8 (CH_3O); 55.9 (C-7); 56.3 (C-6); 59.2 (C-3); 72.7 (C-2); 84.3 (C-8a); 126.1 (C-*o*); 127.9 (C-*p*); 128.7 (C-*m*); 137.7 (C-*ipso*); 161.3 (C=O); 165.0 (C=O).
11. All yields are from material purified by column chromatography. Satisfactory analytical and/or spectral data were obtained for all new compounds.
12. A similar mechanism has been proposed for the epoxidation of α,β-unsaturated ketones by hydroperoxide ion: House, H. O.; Ro, R. S. *J. Am. Chem. Soc.* **1958**, *80*, 2428.
13. Crystal structure of **3b**:



Crystal data: $C_{15}H_{15}NO_5$, orthorhombic, space group $P2_12_12_1$, a= 8.223(1) Å, b= 13.073(2) Å, c= 13.152(2) Å, V= 1413.8(4) Å^3, Z= 4, μ (MoKα)= 0.10 mm^{-1}, D_c= 1.36 g cm^{-3}. The experiment was done on an Enraf-Nonius CAD4 diffractometer using graphite monochromated MoKα radiation. A crystal of 0.51x0.39x0.14 mm was used for the data collection up to a resolution of 2θ= 60.8°. The structure was solved by direct methods (SHELXS 86)[14] after aplying Lorentz, polarization and absorption (em-pirical psi scan method) corrections to the 2430 independent reflections. Full matrix least-squares refinement (SHELXL 93)[15] using anisotropic thermal parametres for non-H atoms and a global isotropic temperature factor for the H-atoms (introduced at calculated positions) converged to a R factor of 0.102 (0.045 for reflection with $I>2\sigma(I)$). Maximum and minimum heights at the final difference Fourier synthesis were 0.29 and -0.21 e Å^{-3}. Complete data have been deposited at the Cambridge Crystallographic Data Centre.

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17. Woo, K.-C.; Jones, K. *Tetrahedron Lett.* **1991**, *32*, 6949.
18. **5**: IR (film) 1720, 1665 cm^{-1}. ^{1}H-NMR (CDCl$_3$, 300 MHz) δ 2.07 (dd, J=14.5, 9.0 Hz, 1H, H-8); 2.41 (s, 3H, CH$_3$); 3.00 (ddd, J=14.5, 5.0, 3.3 Hz, 1H, H-8); 3.65 (d, J=3.3 Hz, 1H, H-7); 3.76 (dd, J=9.2, 8.0 Hz, H-2); 4.46 (dd, J=9.2, 7.5 Hz, 1H, H-2); 5.16 (t, J=7.7 Hz, 1H, H-3); 5.19 (dd, J=9.0, 5.0 Hz, 1H, H-8a); 7.20-7.40 (m, 5H, C$_6$H$_5$). ^{13}C-NMR (CDCl$_3$, 75 MHz) δ 29.5 (C-8); 56.6 (C-7); 59.3 (C-3); 72.9 (C-2); 84.6 (C-8a); 126.1 (C-*o*); 128.1 (C-*p*); 129.0 (C-*m*); 137.9 (C-*ipso*); 162.5 (C=O); 199.6 (C=O).
19. **6**: $[\alpha]^{22}_D$ -84.9 (*c* 2.4, EtOH). Mp 122-126^{o}C (THF). IR (film) 3460, 1668 cm^{-1}; ^{1}H-NMR (CDCl$_3$, 300 MHz) δ 2.02 (dd, J=14.5, 9.0 Hz, 1H, H-8); 2.76 (br s, 1H, OH); 2.97 (ddd, J=14.5, 5.0, 3.3 Hz, 1H, H-8); 3.64 (d, J=3.3 Hz, 1H, H-7); 3.75 (dd, J=9.0, 8.0 Hz, 1H, H-2); 3.93 (d, J=13.0 Hz, 1H, CH$_2$O); 3.98 (d, J=13.0 Hz, 1H, CH$_2$O); 4.47 (dd, J=9.0, 7.5 Hz, 1H, H-2); 5.14 (t, J=7.7 Hz, 1H, H-3); 5.22 (dd, J=9.0, 5.0 Hz, 1H, H-8a); 7.20-7.40 (m, 5H, C$_6$H$_5$). ^{13}C-NMR (CDCl$_3$, 75 MHz) δ 29.5 (C-8); 54.9 (C-7); 56.7 (C-6); 59.1 (C-3); 61.1 (CH$_2$O); 73.0 (C-2); 84.9 (C-8a); 126.0 (C-*o*); 128.0 (C-*p*); 128.9 (C-*p*); 137.9 (C-*ipso*); 166.3 (C=O).
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(*Received in UK* 2 *July* 1996)