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A concise procedure for the preparation of enantiopure 3-alkylpiperidines

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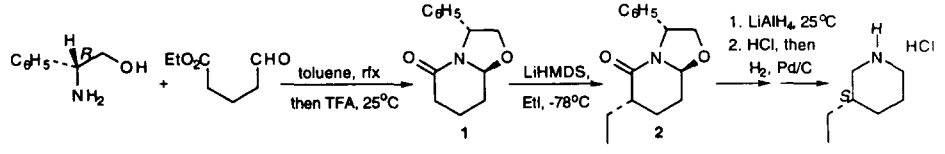
Abstract: Reaction of (*R*)-phenylglycinol with racemic methyl 4-formylhexanoate takes place with a remarkable stereoselectivity to give two diastereomeric 6-ethyloxazolopiperidones (9:1 ratio) in 76% overall yield. After $LiAlH_4$ reduction and catalytic hydrogenation, the major isomer was converted to (*S*)-3-ethylpiperidine. © 1997 Elsevier Science Ltd

The interest of enantiopure 3-alkylpiperidines lies in the fact that this moiety is present in a large number of alkaloids.[1] In particular, most of the secologanin-derived alkaloids, such as monoterpenoid indole alkaloids[2] and some isoquinoline alkaloids (the emetine group) incorporate a 3-ethylpiperidine unit.

In the context of our studies on the synthesis of enantiopure piperidine derivatives,[3] in previous papers we reported the stereoselective alkylation of oxazolopiperidone **1**,[3b,d] which is now accessible in 73% overall yield from (*R*)-phenylglycinol and ethyl 5-oxopentanoate.[4] Reduction of the lactam carbonyl group of the alkylated product **2** with simultaneous reductive cleavage of the oxazolidine ring, followed by hydrogenolysis, ultimately led to (*S*)-3-ethylpiperidine[3d] (Scheme 1).



Scheme 1.

We report here a simpler procedure for the enantioselective preparation of 3-alkylpiperidines,[5] based on an asymmetric transformation of racemic aldehyde ester **3**.[6] Thus, treatment of (*R*)-phenylglycinol with an equimolecular amount of **3** stereoselectively led, in a single synthetic step, to the ethyl substituted oxazolopiperidone **4a** in 68% yield. Minor amounts (8% yield) of the diastereomeric oxazolopiperidone **4b** were also formed.[7] The configuration of the stereogenic centre at the piperidine 3-position in the major isomer **4a** was unambiguously established by $LiAlH_4$ reduction to the known[3d] enantiopure 3-ethylpiperidine **5a** (Scheme 2). Similarly, the minor epimer **4b** was converted to the piperidine derivative **5b** and then to (*R*)-3-ethylpiperidine. However, as both enantiomers of phenylglycinol are commercially available, from the synthetic standpoint (*R*)-3-ethylpiperidine would be more conveniently prepared from the *S* enantiomer of phenylglycinol.

The above asymmetric transformation,[8] which involves the epimerization of the stereogenic centre adjacent to the formyl group, can be rationalized by considering that the four initially formed oxazolidines (two *cis* and two *trans*)[9] are in equilibrium via the corresponding imines/enamines[10] and that irreversible lactamization occurs faster from the *cis*-oxazolidine that leads to an oxazolopiperidone bearing an equatorial ethyl group (Scheme 3). The minor oxazolopiperidone **4b** would result from cyclization of a *trans*-oxazolidine, also via a transition state with an equatorial ethyl group.

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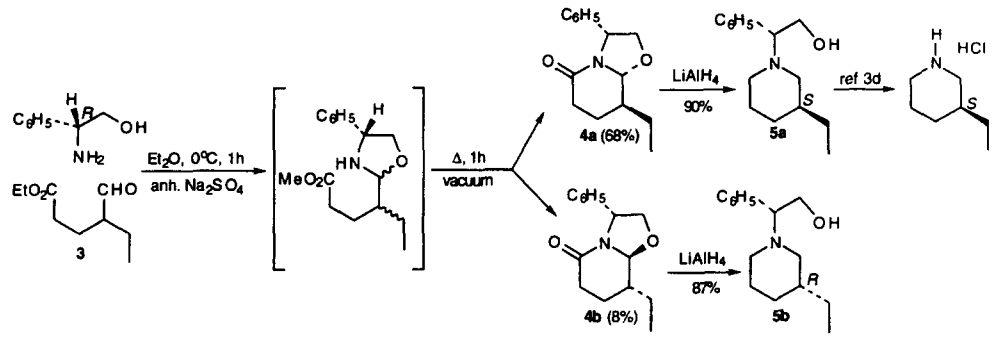

Scheme 2.

Scheme 3.

The extension of this procedure to the enantioselective synthesis of pharmacologically active 3-arylpiperidines (*e.g.*, preclamol), which are not accessible by alkylation of **1**, is currently under investigation.

Experimental section

General

Melting points were determined in a capillary tube on a Büchi apparatus and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were recorded on a Varian Gemini-200 instrument (200 and 50.3 MHz, respectively) or in a Varian Gemini-300 instrument (300 and 75 MHz, respectively). Chemical shifts are expressed in parts per million (δ) relative to internal Me_4Si. IR spectra were recorded on a Nicolet 205 FT-IR spectrophotometer. Optical rotations were measured on Perkin–Elmer 241 polarimeter using a 1 dm cell with a total volume of 1 ml. Flash chromatography was carried out on SiO_2 (silica gel 60, SDS, 0.040–0.060 mm). All reactions were carried out under nitrogen or argon atmosphere. Drying of organic extracts during the work-up of reactions was performed over anhydrous Na_2SO_4. Microanalyses were performed on a Carlo Erba 1106 analyzer by the Centro de Investigación y Desarrollo (CSIC), Barcelona.

(3R,8S,8aR)-8-Ethyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5H-oxazolo[3,2-a]pyridine ***4a*** *and its diastereomer 3R,8R,8aS* ***4b***

A mixture of racemic ester aldehyde **3** (3.86 g, 24.4 mmol), (*R*)-phenylglycinol (3.35 g, 24.4 mmol), and Na_2SO_4 (13.5 g, 95 mmol) in Et_2O (80 ml) was stirred at 0°C for 1 h. The resulting suspension was filtered, and the filtrate was concentrated under reduced pressure. The residue was heated at 80–100°C for 1 h under vacuum (10–15 mm Hg). Column chromatography (SiO_2 previously washed with 8:2 Et_3N–AcOEt; AcOEt as eluent)[11] of the residue successively afforded oxazolopiperidones **4b** (490 mg, 8%) and **4a** (4.1 g, 68%). **4a**: $[\alpha]_D^{22}$ −23.5 (*c* 1.0, EtOH); IR (KBr) 1655 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.05 (t, *J*=7.4 Hz, 3H, CH_3), 1.41 (m, 2H, H-7, CH_2), 1.82 (m, 2H, H-8, CH_2), 2.05 (m, 1H, H-7), 2.30 (ddd, *J*=18.0, 11.2, 7.0 Hz, 1H, H-6), 2.42 (ddd, *J*=18.0, 7.2, 2.5 Hz, 1H, H-6), 4.00 (d, *J*=9.0 Hz, 1H, H-2), 4.13 (dd, *J*=9.0, 6.7 Hz, 1H, H-2), 4.52 (d, *J*=8.8 Hz, 1H, H-8a), 4.92 (d, *J*=6.7 Hz, 1H, H-3), 7.28 (m, 5H, Ar); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 10.8 (CH_3), 23.6 (C-7), 24.0 (CH_2), 31.2 (C-6), 40.6 (C-8), 58.8 (C-3), 73.6 (C-2), 92.4 (C-8a), 126.1 (C-*o*), 127.2 (C-*p*), 128.3

(C-*m*), 141.4 (C-*ipso*), 167.1 (C=O); m.p. 97–100°C (Et_2O–hexane). Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.80; N, 5.70. Found: C, 73.59; H, 7.89; N, 5.81. **4b**: $[\alpha]_D^{22}$ −103.5 (*c* 1.1, EtOH); IR (KBr) 1660 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.03 (t, *J*=7.4 Hz, 3H, CH_3), 1.37 (m, 1H, CH_2), 1.51 (m, 2H, H-7, CH_2), 1.80 (m, 1H, H-8), 1.96 (m, 1H, H-7), 2.36 (ddd, *J*=18.5, 11.3, 6.5 Hz, 1H, H-6), 2.57 (dd, *J*=18.0, 5.0 Hz, 1H, H-6), 3.74 (dd, *J*=9.0, 7.8 Hz, 1H, H-2), 4.47 (dd, *J*=9.0, 7.8 Hz, 1H, H-2), 4.67 (d, *J*=7.8 Hz, 1H, H-8a), 5.24 (t, *J*=7.8, 1H, H-3), 7.29 (m, 5H, Ar); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 10.9 (CH_3), 22.7 (CH_2), 24.5 (C-7), 31.3 (C-6), 41.1 (C-8), 58.1 (C-3), 72.3 (C-2), 92.6 (C-8a), 125.9 (C-*o*), 127.3 (C-*p*), 128.6 (C-*m*), 139.4 (C-*ipso*), 168.7 (C=O); m.p. 77–80°C (Et_2O). Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.80; N, 5.70. Found: C, 73.04; H, 7.81; N, 5.52.

(3S,αR)-3-Ethyl-1-(2-hydroxy-1-phenylethyl)piperidine ***5a***

$LiAlH_4$ (495 mg, 13.0 mmol) was added portionwise to a solution of oxazolopiperidone **4a** (1 g, 4.08 mmol) in anhydrous THF (57 ml), and the mixture was stirred at 25°C for 1 h. The excess hydride was destroyed by dropwise addition of 15% aqueous NaOH (30 ml) and H_2O (30 ml). The resulting suspension was filtered through a Celite pad, and the aqueous layer was extracted with AcOEt. The combined organic extracts were dried and concentrated, and the resulting oil was purified by column chromatography (AcOEt) to afford piperidine **5a** (856 mg, 90%): $[\alpha]_D^{22}$ −27.2 (*c* 0.5, EtOH). The NMR data of **5a** were identical to those reported for its enantiomer.[3d]

(3R,αR)-3-Ethyl-1-(2-hydroxy-1-phenylethyl)piperidine ***5b***

Operating as above, from oxazolopiperidone **4b** (70 mg, 0.28 mmol) and $LiAlH_4$ (34 mg, 0.89 mmol) in anhydrous THF (4 ml) was obtained pure piperidine **5b** (58 mg, 87%) after purification by column chromatography (AcOEt): $[\alpha]_D^{22}$ +15.1 (*c* 0.8, CH_2Cl_2); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.63 (m, 1H, H-4), 0.77 (t, *J*=7.3 Hz, 3H, CH_3), 1.07 (m, 2H, CH_2), 1.29 (m, 2H, H-3, H-2), 1.48–1.64 (m, 3H, H-4, 2H-5), 2.17 (td, *J*=11.0, 3.4 Hz, 1H, H-6), 2.65–2.73 (m, 2H, H-2, H-6), 3.27 (br s, 1H, OH), 3.52 (dd, *J*=10.0, 5.2 Hz, 1H, CH_2O), 3.60 (dd, *J*=10.0, 5.2 Hz, 1H, NCH), 3.92 (t, *J*=10.0 Hz, 1H, CH_2O), 7.10 (br d, *J*=7.0 Hz, 2H, Ar), 7.20–7.32 (m, 3H, Ar); ^{13}C-NMR ($CDCl_3$, 50.3 MHz) δ 11.4 (CH_3), 25.8 (C-5), 27.0 (CH_2), 30.5 (C-4), 38.2 (C-3), 52.5 (C-2), 53.0 (C-6), 59.8 (CH_2O), 70.0 (NCH), 127.7 (C-*p*), 128.0 (C-*m*), 128.9 (C-*o*), 135.4 (C-*ipso*). Anal. Calcd for $C_{15}H_{23}NO$: C, 77.20; H, 9.94; N, 6.00. Found: C, 77.20; H, 9.97; N, 6.00.

(S)-3-Ethylpiperidine

The hydrochloride formed from 700 mg (3 mmol) of piperidine **5a** was dissolved in anhydrous methanol (50 ml) and hydrogenated in the presence of Pd/C (75 mg) until the starting material was not observed by TLC. The mixture was filtered and the catalyst was washed with hot methanol (40 ml). The combined methanolic solutions were dried and concentrated under reduced pressure. The residue was washed with anhydrous Et_2O (2×40 ml) and then crystallized to give (*S*)-3-ethylpiperidine hydrochloride (341 mg, 76%): $[\alpha]_D^{22}$ −3.5 (*c* 1.0, EtOH); m.p. 161–162°C. For the free base: $[\alpha]_D^{22}$ −2.3 (*c* 0.68, EtOH); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.88 (t, *J*=7.4 Hz, 3H, CH_3), 0.97 (dddd, *J*=12.5, 12.5, 11.0, 4.0 Hz, 1H, H-4), 1.17 (m, 2H, CH_2), 1.29 (m, 1H, H-3), 1.42 (qt, *J*=12.5, 4.0 Hz, 1H, H-5), 1.64 (dm, *J*=12.5 Hz, 1H, H-5), 1.83 (dm, *J*=12.5 Hz, 1H, H-4), 1.88 (br s, 1H, NH), 2.20 (dd, *J*=11.9, 10.2 Hz, 1H, H-2), 2.51 (td, *J*=11.9, 2.8 Hz, H-6), 3.00 (m, 2H, H-2, H-6); ^{13}C-NMR ($CDCl_3$, 75 MHz,) δ 11.2 (CH_3), 26.7 (C-5), 27.2 (CH_2), 31.2 (C-4), 38.9 (C-3), 47.0 (C-6), 52.8 (C-2).

(R)-3-Ethylpiperidine

Operating as above, (*R*)-3-ethylpiperidine hydrochloride was obtained: $[\alpha]_D^{22}$ +3.2 (*c* 1.0, EtOH); m.p. 157–158°C. For the free base: $[\alpha]_D^{22}$ +2.0 (*c* 0.70, EtOH).

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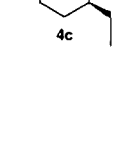
11. When SiO_2 was not previously washed with Et_3N, column chromatography afforded **4a**, **4b**, and the 3*R*,8*S*,8a*S* isomer **4c** in 45%, 18%, and 11% yields, respectively. **4c**: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.96 (t, *J*=7.4 Hz, 3H, CH_3), 1.20 (m, 1H, CH_2), 1.66 (m, 1H, CH_2), 1.80 (m, 1H, H-7), 1.90 (m, 1H, H-7), 2.18 (m, 1H, H-8), 2.36 (m, 2H, H-6), 3.77 (dd, *J*=8.8, 7.3 Hz, 1H, H-2), 4.42 (dd, *J*=8.8, 7.7, 1H, H-2), 5.09 (d, *J*=4.5 Hz, 1H, H-8a), 5.24 (t, *J*=7.4 Hz, 1H, H-3), 7.29 (m, 5H, Ar); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ11.3 (CH_3), 17.1 (CH_2), 20.4 (C-7), 27.9 (C-6), 36.8 (C-8), 58.2 (C-3), 72.1 (C-2), 90.1 (C-8a), 126.0 (C-*o*), 127.5 (C-*p*), 128.7 (C-*m*), 139.6 (C-*ipso*), 169.0 (C=O).



4c

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