

Asymmetric Synthesis with Chiral Hydrogenolysable Amines. Cyclic β -Enamino Ester Reduction A Diastereoselective Route to 2,3-Disubstituted Pyrrolidines

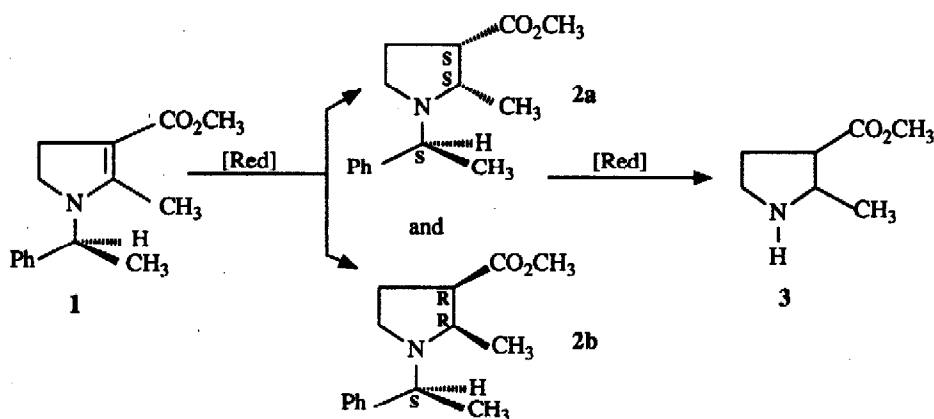
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Abstract : Cyclic β -enamino esters prepared from chiral α -methylbenzylamines are catalytically reduced with high a diastereoisomeric excess.

Homochiral pyrrolidines present some insecticidal properties¹, and in our continuing study towards the synthesis of such five-membered ring heterocycles, we report preliminary results concerning a diastereoselective reduction of cyclic β -enamino esters **1** which have been obtained by condensation of primary amines with activated cyclopropane². Hydrogenolysable cheap (S)- α -methylbenzylamine³ has been choosen to realise such a transformation, then reductive conditions permit the formation of 2,3-disubstituted pyrrolidine **3**.

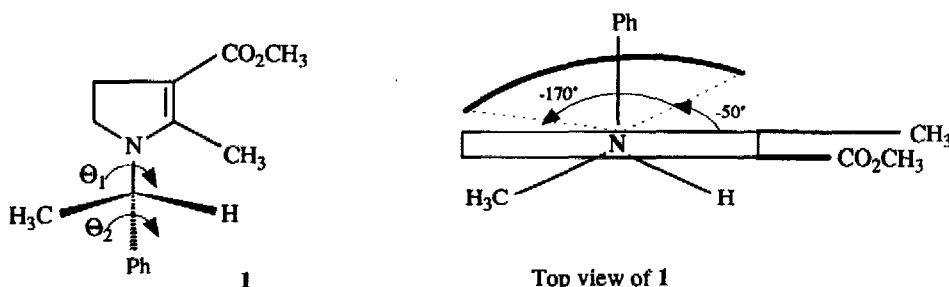


Methyl 2-acetylcyclopropanecarboxylate and chiral amine were refluxed in toluene with azeotropic distillation and gave after distillation the dihydropyrrole **1** in 74% yield [b.p./0.05: 135°C; [α]_D²⁰ = +40 (c=1.96, EtOH)]. Dihydropyrrole reduction over Raney Nickel (W-7) or PtO₂ (1 bar) gave after distillation (b.p./0.05: 135°C) the two *cis*-diastereoisomers **2a** and **2b** with a high diastereoisomeric excess (90%) as

measured by g.c. Recrystallization in hexane led to pyrrolidine **2a** in 90% yield [m.p. 62°C, $[\alpha]_D^{20} = -28$ ($c=2.03$, EtOH)]⁴. The absolute configuration of compound **2a** has been fully established by X-ray diffraction method and these result permits to conclude that (S)-methylbenzylamine leads to a (S,S,S) diastereoisomer **2a**.

Molecular Mechanics calculations, aimed at the determination of the most stable conformer of compound **1** (absolute configuration S) were undertaken. Rotation around the N-C* (Θ_1) and the C*-Ph (Θ_2) bonds gave a three dimensional (E, Θ_1, Θ_2) graph. Its two dimensional projection on the E, Θ_1 plane gave a curve with a single minimum instead of the expected curve with three minima situated 120° apart. The minimum was very wide with a width of 120° (between -50° and -170°) for a depth of 2 kcal.mol⁻¹. The bottom of the curve was rather flat with a minimum between -80 and -120°. The energy barrier was around 10 kcal.mol⁻¹.

As a consequence only one conformer is present. The rear face of the molecule is severely crowded by the phenyl ring, explaining the stereochemical course of the hydrogenation reaction.



Finally (2S,3S)-disubstituted pyrrolidine **3** has been easily obtained in 80% yield by debenzylolation with catalytic hydrogenation on Pd-C (10%) [b.p./0.05mm Hg 40°C, $[\alpha]_D^{20} = -4$ ($c=2.2$, EtOH)]⁵.

In conclusion, chiral methylbenzylamines are very efficient amines for asymmetric reduction of rigid β -enamino esters into 2,3-disubstituted dihydropyrroles.

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References

1. Cassier, P.; Lemaire, M.; Clément, J.L.; Basselier, J.J.; Lange, C.; Célérier, J.P.; Lhommet, G. *French Patent* FR2, 563, 696; *Chem. Abstr.* **1986**, *104*, p202330j.
2. Célérier, J.P.; Haddad, M.; Jacoby, D.; Lhommet, G. *Tetrahedron Lett.* **1987**, *28*, 6597-6600.
3. Marx, E.; El Bouz, M.; Célérier, J.P.; Lhommet, G. *Tetrahedron Lett.*, Asymmetric Synthesis with Chiral Hydrogenolysable Amine, preceding paper.
4. Satisfactory IR, ¹H and ¹³C-NMR, and microanalyses were obtained for all new compounds. NMR data for **2a** : ¹H-NMR (200 MHz, CDCl₃) δ 0.80 (d, J=6.8 Hz, 3H); 1.35 (d, J=6.8 Hz, 3H); 1.80-2.00 (m, 1H); 2.10-2.30 (m, 1H); 2.40-2.60 (m, 1H); 2.60-2.80 (m, 1H); 3.00-3.20 (m, 1H); 3.40-3.60 (m, 2H); 3.70 (s, 3H); 7.10-7.40 (m, 5H). ¹³C-NMR (50 Hz, CDCl₃) δ 12.5, 20.9, 24.9, 47.5, 48.8, 51.5, 57.0, 60.8, 126.9, 127.4, 128.2, 145.3, 173.7.
5. The enantiomer has been prepared from the commercially available (R)- α -methylbenzylamine.