Tetrahedron Letters, Vol. 34, No. 10, pp. 1599-1600, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

Asymmetric Synthesis with Chiral Hydrogenolysable Amines. A Short Synthesis of (-) Isoretronecanol

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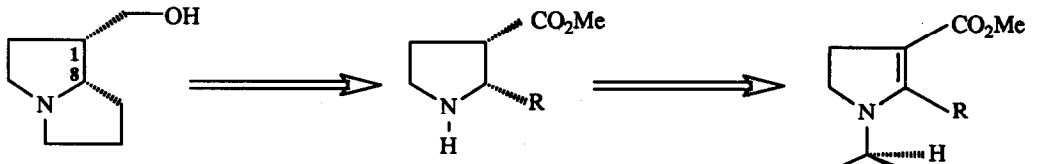
Abstract: Dihydropyrrole prepared from (S)-α-methylbenzylamine is reduced with high diastereomeric excess. A short non epimeric route to isoretronecanol is reported.

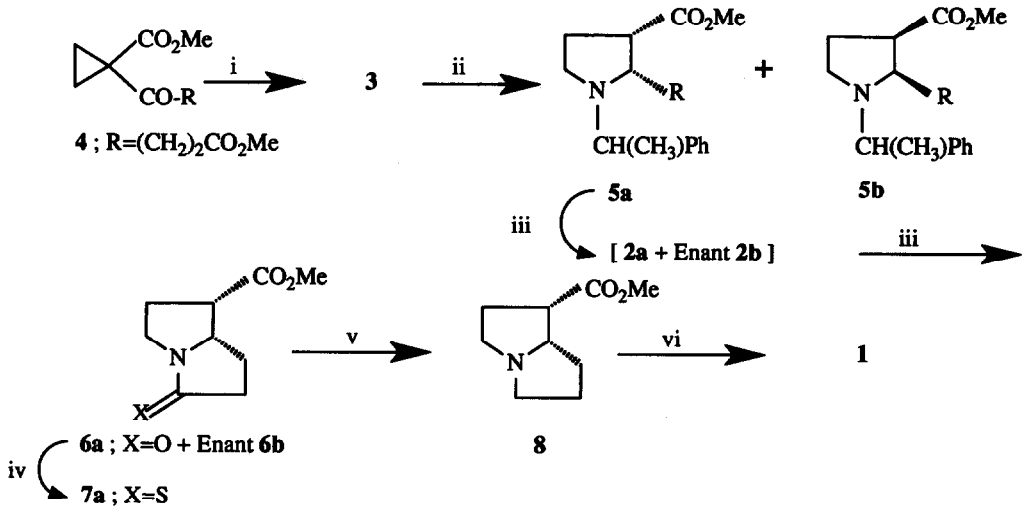
Necine bases have been widely studied due to their biological properties. Many racemic routes to the 1-hydroxymethyl pyrrolidines like isoretronecanol **1** have been reported[1] and a few enantioselective syntheses have been described using amino acids[2a-i] or sugars[2j]. Herein we report a preparation of (-) isoretronecanol using an unexpensive chiral source: the (S)-α-methylbenzylamine. Meanwhile we have recently shown[3] the high diastereoselective reduction of dihydropyrrole **3** (R=CH_3) which leads to the corresponding 2,3-disubstituted pyrrolidine **5a** (R=CH_3) with S,S absolute configurations. Our retrosynthetic approach is based on the synthesis of the suitable pyrrolidine **2** bearing an appropriate substituant permitting the formation of the second five membered ring.



1 (1S,8S) **2a**; R= $(CH_2)_2$-CO_2Me **3**

At room temperature, methyl 3-oxo-hexanedioate reacts with 1,2-dibromoethane in presence of anhydrous potassium carbonate in DMF leading to the cyclopropane derivative **4**[4]. Compound **4** and (S)-α-methylbenzylamine react in toluene refluxed with a water trap to obtain dihydropyrrole **3** (83% yield). Dihydropyrrole reduction over PtO_2 gives after distillation two *cis* diastereoisomers **5a** and **5b** with a high diastereomeric excess (90%) measured by g.l.c. (87% yield). Hydrogenolysis over Pd/C (10%) gives an enantiomeric mixture of pyrrolidines **2a** and **2b** which undergo a ring closure when heating in toluene at 90°C for 5h to give bicyclic compounds **6a** and **6b** with 90% yield after purification by flash chromatography. The optically pure thiolactam **7a** is isolated by lactam mixture transformation with Lawesson's reagent followed by recrystallization until constant specific rotation (three times in diethyl ether) [46% yield, m.p. 81°C, $[\alpha]^{20}_D$ -118 (c=0.9, EtOH)]. Thiolactam reduction[5] affords (-) chysine **8** in 77% yield [b.p./0.05 mm Hg 105°C, $[\alpha]^{20}_D$ -65 (c=2.16, $CHCl_3$)]. Finally, ester reduction without

epimerization using $LiAlH_4$ in THF at -80°C gives (-) isoretronecanol in 83% yield after distillation [b.p./0.05 mm Hg 180°C, $[\alpha]^{24}_D$ -77 (c=2.1, EtOH)].



Reaction conditions: i) (S)-α-methylbenzylamine, toluene, reflux; ii) H_2(1 bar)/PtO_2, MeOH; iii) H_2 (1 bar)/Pd-C (10%), MeOH then toluene (90°C), 5h; iv) Lawesson's reagent, toluene reflux; v) ICH_3, CH_2Cl_2 then $NaBH_4$, MeOH; vi) $LiAlH_4$, THF, (-80°C).

We report a short highly enantioselective synthesis of (-) isoretronecanol in six steps from activated cyclopropane with 20% overall yield. This general strategy is an easy route to the three other natural isomers: thrachelanthamidine diastereoisomer by epimerization[6] of the pivotal compound **8**, and (1R,8R)-lindelofidine or (1S,8R)-laburnine starting from (R)-α-methylbenzylamine.

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(Received in France 2 December 1992)