ASYMMETRIC SYNTHESIS OF 1-METHYL-2-(2-HYDROXYETHYL)PYRROLIDINE

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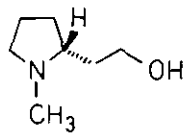
Abstract - An asymmetric synthesis of 1-methyl-2-(2-hydroxyethyl) pyrrolidine based on optically active 1-phenylethylamine is described.

The R(+)-enantiomer of 1-methyl-2-(2-hydroxyethyl)pyrrolidine 1 is an important intermediate in the synthesis of the antihistaminic drug Clemastine [1] :



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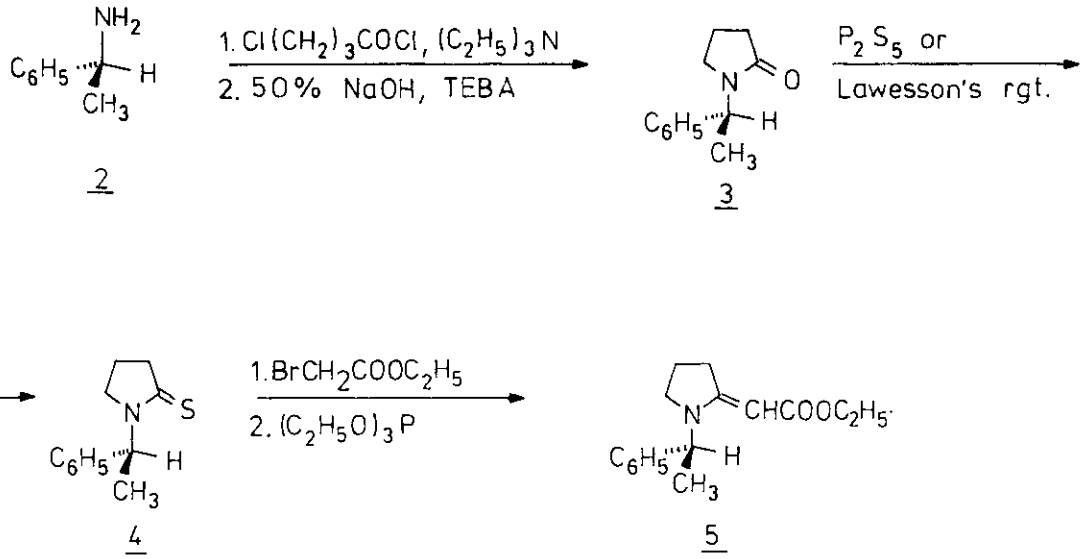
A number of syntheses of the optically active forms of this aminoalcohol have been described, mainly in the patent literature. Most of them rely upon resolution either of a racemic mixture of 1 and its enantiomer or of some of its synthetic precursors [2]. Other routes start with optically active proline or pyroglutamic acid, which are converted stereospecifically into 1 or its enantiomer [3]. However, the absolute configuration of 1 correlates with that of the unnatural enantiomers of these compounds, which are relatively expensive. To our knowledge, no asymmetric synthesis of the title compound has been published until now. In this communication we wish to report the first asymmetric synthesis of 1-methyl-2-(2-hydroxyethyl) pyrrolidine, which is based on the easily available optically active 1-phenylethylamine and which could be useful in the preparation of other optically active pyrrolidine derivatives.

The key inthermediate in our synthesis is 1-/1'-(S)-phenylethyl/-2-/ethoxycarbonylmethylidene/pyrrolidine 5, which was obtained in 61% overall yield as shown in Scheme 1.

Scheme 1



Optically active 1-(S)-phenylethylamine 2 was acylated with 4-chlorobutyryl chloride in CH_2Cl_2 and the resulting amide was cyclized without isolation under phase-transfer conditions with 50% NaOH in the presence of benzyltriethylammonium chloride (TEBA) to give 3 [4]. Conversion of this pyrrolidinone to its thioanalog 4 could be carried out either with P_2S_5 in CS_2 or with Lawesson's reagent [5] in boiling toluene. S - Alkylation of 4 with ethyl bromoacetate was completed in a few hours at room temperature in CH_3CN and the resulting salt was subjected to the sulfide contraction reaction [6] using $(C_2H_5O)_3P$ and $(C_2H_5)_3N$ in CH_2Cl_2 to give the desired enaminoester 5 [7].

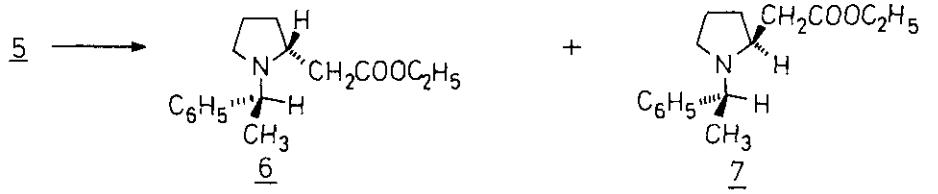
Next the reduction of the prochiral double bond in 5 was studied using different reducing agents and conditions. A summary of the results of this reduction is given in Table 1.

The highest diastereoselectivity was achieved using the 9-BBN-KCN complex [8], but the catalytic reduction using Pt/C as a catalyst also showed relatively high selectivity. The results in the latter case were better when a less polar hexane/ethyl acetate mixture was used as a solvent rather than pure ethyl acetate (ds = 66%). In all cases the main diastereomer formed had the R - configuration at C2 in the pyrrolidine ring, which was established by its conversion to R(+)-1-methyl-2-(2-hydroxyethyl)pyrrolidine (see below).

In order to obtain 1-methyl-2-(2-hydroxyethyl)pyrrolidine of high enantiomeric purity it was important to find a way of enhancing the diastereomeric ratio 6/7 and if possible to obtain pure 6. We found a simple solution to this problem when we attempted preparation of the picrate of the 6/7 mixture. We noticed that the precipitated picrate [9] consisted only of one diastereomer and after conversion to the free base it was shown to be pure 6 [10]. The yield of diastereomerically

Table 1

Diastereoselectivity (ds) of the reduction of enaminoester 5 to 6 and 7 with different reagents (ratio 6/7 given in brackets)

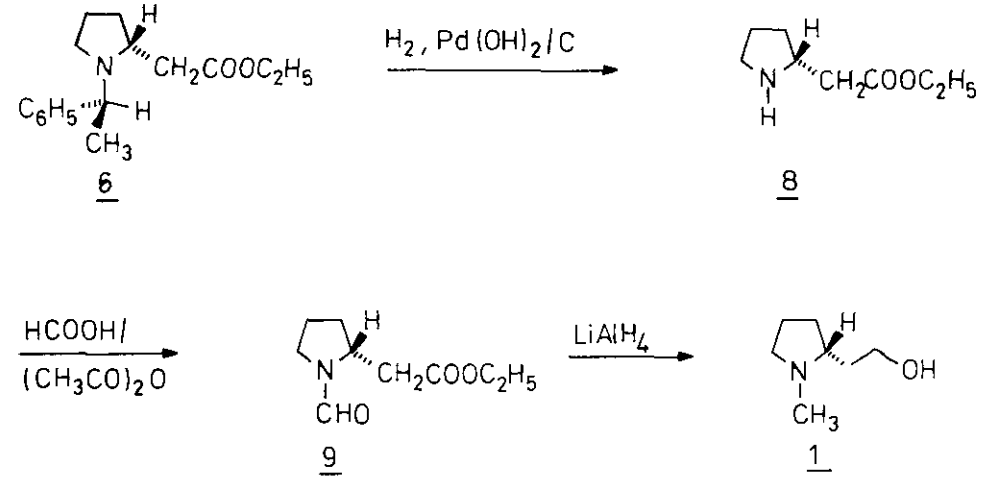


1. $NaBH_4$ / CH_3COOH / THF / 0°C	54 % (77/23)
2. $NaCNBH_3$ / CH_3OH / 0°C	40 % (70/30)
3. $NaCNBH_3$ / THF / 0°C	56 % (78/22)
4. $(C_4H_9)_4NCNBH_3$ / CH_2Cl_2 / 20°C	56 % (78/22)
5. 9-BBN-KCN / THF / 0°C	84 % (92/ 8)
6. H_2 (10 bar) / 5% Pt/C / C_6H_{14} / $CH_3COOC_2H_5$	74 % (87/13)

pure 6 was approximately equal to the diastereoselectivity of the reaction by which the corresponding mixture had been obtained. Thus, from a 78/22 mixture of 6 and 7 the yield of pure 6 was 52%. No crystalline picrate resulted from an equimolar mixture of these diastereomers.

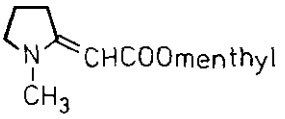
The conversion of pure 6 into the desired 1-methyl-2-(2-hydroxyethyl)pyrrolidine 1 was carried out as shown in Scheme 2.

Scheme 2



The debenzylation of 6 proceeded quantitatively in the presence of $Pd(OH)_2/C$ (Pearlman's catalyst) at about 8 bar H_2 in ethanol. The product 8 was formylated using the mixed formic/acetic anhydride and the resulting N - formyl derivative reduced with $LiAlH_4$ to give 1 in 80% yield based on pure 6. The purity of 1 after distillation was 95% as shown by GC and its enantiomeric purity , based on comparison of its specific rotation with the literature values was 100% [11] . A more reliable criterion for the enantiomeric purity of the product obtained by us is the diastereomeric purity of 6, which is easily determined by capillary gas chromatography (assuming that the starting phenylethylamine is 100% enantiomerically pure and that no racemization takes place during the conversion of 6 to 1). Because the diastereomeric purity of 6 was shown to be 96% [10], we assume that the enantiomeric purity (ee) of 1 obtained by us is also about 96%.

We have also prepared two other optically active enaminoesters, 10 and 11, starting from menthol and R(+) - 1 -phenylglycinol, respectively :



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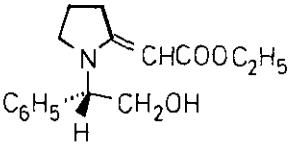

11

The reduction of the double bond in 10 using $NaCNBH_3$ in THF was totally unselective, whereas under the same conditions 11 was reduced with about 10% diastereoselectivity. Because of these disappointing results we have not further investigated the reductions of these two compounds.

In conclusion, we have successfully accomplished the first asymmetric synthesis of 1-methyl-2-(2-hydroxyethyl)pyrrolidine. Our route suffers from the disadvantage that the chiral auxiliary is destroyed during the synthesis. Nevertheless, we believe that this route to 1 (or its enantiomer) is more efficient than the routes described previously because of the high overall yield and the availability of the starting optically active amine. Compound 6 could also find applications to the synthesis of other C2-chiral pyrrolidine derivatives.

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7. 5 : mp. 64-66°C (hexane), $/\alpha/_D$ -290.2° (c = 0.68, $CHCl_3$);
   ^{1}H NMR (250 MHz, $CDCl_3$, TMS) : 1.25 t,3H; 1.55 d,2H; 1.90 m,2H; 3.09 m,2H; 3.30 m,2H; 4.09 q,2H; 4.70 s,1H; 4.90 q,1H; 7.30 m,5H.
   IR (KBr) : 1673, 1593 cm^{-1}.
   MS (70 eV) m/z 259 (73%, M^+), 105 (100%, $C_6H_5CHCH_3^+$).
8. J. E. Wrobel and B. Ganem, Tetrahedron Lett., 1981, 22, 3447.
9. Picrate of 6 : mp. 100-101°C; $/\alpha/_D$ -5.6° (c = 0.56, CH_3OH).
10. Capillary gas chromatography of the product at this stage showed 98% of 6 and 2% of 7. 100% pure 6 could be obtained by one recrystallization of the picrate from ethanol,in general, however, we have worked with this 98/2 mixture, which is referred to as " diastereomerically pure 6 " in the text.
11. Specific rotation data of 1 : $/\alpha/_D$ + 58.4° (c = 1.0, CH_3COCH_3), ref. [1] : $/\alpha/_D$ + 58.4° (c = 1.0, CH_3COCH_3).

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