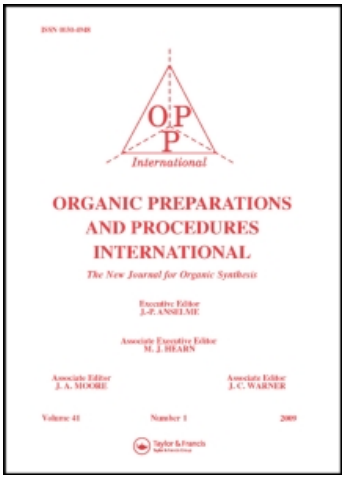

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SYNTHESES OF (S)-(-)-N-METHYLPROLINOL

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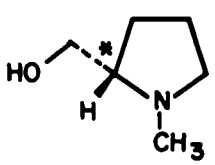
We required an efficient preparation of (S)-(-)-N-methylprolinol (I) as an intermediate in an optically active alkaloid synthesis in our laboratory.[1] This compound and related aminoalcohols are also of interest as precursors (both racemic and optically active) to azabicyclo[3.1.0]hexanes.[2] Previous approaches to functionalized pyrrolidine derivatives, from either L-proline or glutamic acid, have required a number of steps.[3] We now report two new syntheses of the optically active title compound, both of which comprise only two steps from commercially available L-proline.[4] One of these approaches is one step from commercially available L-prolinol,[4] which can also be obtained by the $LiAlH_4$ reduction of L-proline.[2c,e]

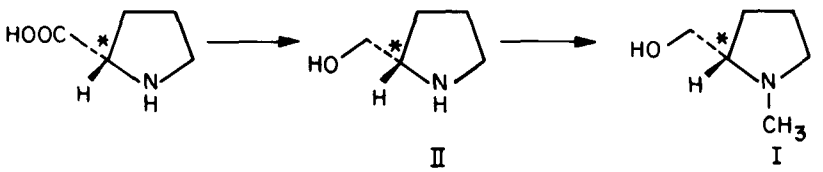


I

The initial approach to I (Scheme 1) involved the N-methylation of L-prolinol (II) with refluxing aqueous formaldehyde/formic acid (Eschweiler-Clarke method[5]). A low yield of impure I resulted. Reductive alkylation of L-prolinol (II) by the method of Borch,[6] utilizing $NaBH_4$

and aqueous formaldehyde in acetonitrile, provided a product mixture from which I could be distilled in 44% yield ($[\alpha]_D^{20}$ - 48°, methanol). A large quantity of a viscous pot residue remained.

Scheme 1

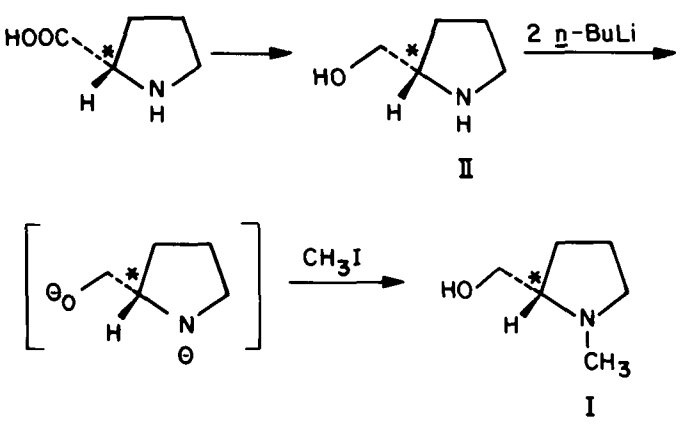


II I

Since the above standard methods were not fully satisfactory, two novel approaches were developed.

Treatment of L-prolinol (II) with two equivalents of n-butyllithium in THF at -70° generated the dianion. Addition of one equivalent of methyl iodide to the dianion cleanly afforded (S)-(-)-N-methylprolinol (I) in a 52% yield of distilled product ($[\alpha]_D^{20}$ -50°, methanol) (Scheme 2).

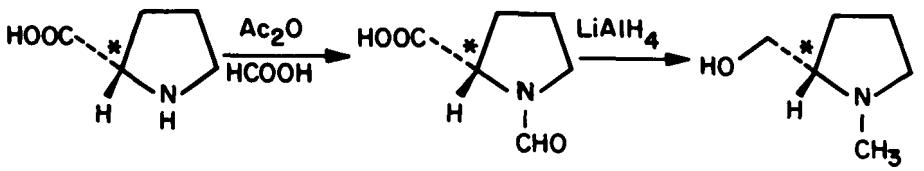
Scheme 2



II I

Alternatively, treatment of L-proline with Ac_2O/HCOOH yielded crude (S)-(-)-N-formylproline (III) which in turn, was reduced with $LiAlH_4$ in refluxing THF to I in 57% overall yield from L-proline (Scheme 3). The specific rotation of I obtained by this procedure, was identical to that obtained by the L-prolinol dianion method (Scheme 2).

Scheme 3



III I

It should be noted that although I was also obtained in 44% yield as described earlier by the method of Borch and Hassid,[6] the purity (as evidenced by the specific rotation) was lower than that obtained by either the dianion (Scheme 2) or formamide reduction (Scheme 3) approaches.

The fact that (S)-(-)-N-methylprolinol (I) is obtained with the same optical rotation and in high purity (as observed by gas chromatographic and spectral analyses) by either route would indicate a high degree of optical purity.

EXPERIMENTAL

(S)-(-)-N-Methylprolinol (I).

A. Dianion Procedure. - To a solution of 5.0 g (0.05 mol) of L-prolinol (Aldrich) in 75 ml of dry THF, under nitrogen, was gradually added 43.5 ml (0.1 mol) of 2.3 M n-butyllithium in hexane such that the temperature did not rise above -20°. The yellow solution was stirred at -70° for 30

min; this was followed by the addition of 3.39 ml (7.74 g, 0.055 mol) of methyl iodide over 10 min. The resultant white mixture was stirred at -70° for 5 min and allowed to warm to room temperature wherein the white precipitate dissolved. The solution was stirred overnight at room temperature and quenched with 10 ml of water. The organic layer was separated and the aqueous layer was extracted with methylene chloride (2x50 ml). The organic layers were combined, dried with $MgSO_4$, and evaporated to provide a mobile, yellow oil. Bulb-to-bulb distillation [oven temp 45-55° (0.2 torr)] yielded 2.97 g (52%) of I, a clear, colorless oil: $[\alpha]_D^{20}$ -51° (c 5.35, methanol); picrate, mp. 172-174°; ^{1}H-NMR ($CDCl_3$) δ 1.5-2.0 (m, 4), 2.13-2.75 (m, 2), 2.36 (s, 3), 2.93-3.25 (m, 1), 3.53 (br s, variable, 1), 3.54 (d ABq, J = 2.5 Hz, $\Delta\nu_{AB}$ = 13 Hz, 2); IR (film) 3325, 1450, 1020 cm^{-1}.

Anal. Calcd. for $C_{12}H_{16}N_4O_8$ (picrate): C, 41.86; H, 4.68; N, 16.28. Found: C, 41.95; H, 4.62; 16.18.

B. Formamide Reduction Procedure. - To a solution of 5.0 g (0.0434 mol) of L-proline (Aldrich) in 92 ml of 97% formic acid, maintained at 5-10°, was slowly added 30 ml of acetic anhydride. The solution was stirred for 2 hrs at room temperature followed by the addition of 35 ml of ice-cold water. Evaporation of the mixture afforded (S)-(-)-N-formylproline {$[\alpha]_D^{20}$ -105° (c 2.89, methanol)}, a clear, viscous, pale-yellow oil, utilized directly in the next step. A solution of the (S)-(-)-N-formylproline in 20 ml of THF was added to a slurry of 8.23 g (0.217 mol) of $LiAlH_4$ in 125 ml of THF under a nitrogen atmosphere. The addition was regulated such that a gentle reflux was maintained. After the addition was complete, the mixture was refluxed for 48 hrs. After cooling, the mixture was carefully treated with 8.3 ml of water, followed by 8.3 ml of 15% aq. NaOH, and finally 25 ml of water. The white mixture was filtered and the filtrate dried with $MgSO_4$ and evaporated to an oil. Bulb to bulb

distillation [oven temp 40-55° (0.15 torr)] afforded 2.82 g of I (57% overall yield from L-proline). The specific rotation was identical with that in part A.

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