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Synthesis of Enantiomerically Pure 2,2-Disubstituted-2-Amino-ethanols by Dissolving Metal Reduction of α,α -Disubstituted Amino Acid Amides

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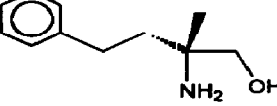
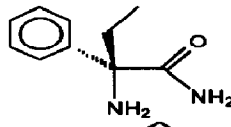
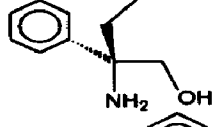
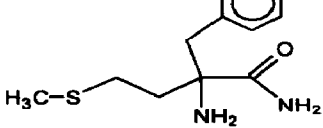
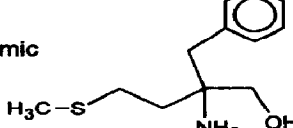
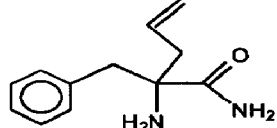
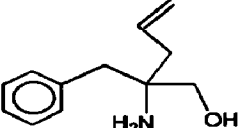
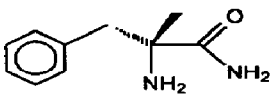
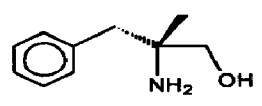
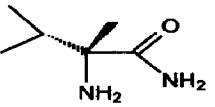
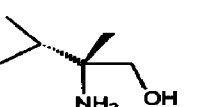
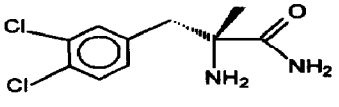
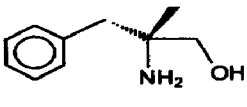
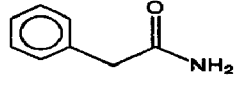
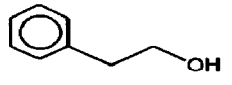
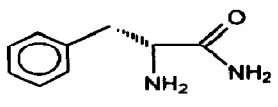
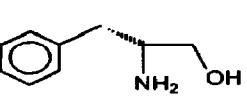
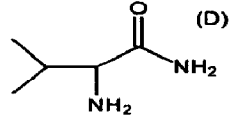
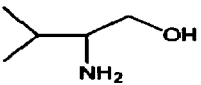
Abstract: Enantiomerically pure 2,2-disubstituted 2-amino-ethanols are prepared in 65 - 99% yield by reduction of α,α -disubstituted amino acid amides using liquid sodium metal in refluxing 1-propanol.

Chiral amino alcohols are versatile starting materials in asymmetric synthesis¹ and for the synthesis of biologically active compounds². In general the 2-substituted 2-amino-ethanols are readily prepared by reduction of amino acids or their corresponding esters by LiAlH_4 , BH_3 , or NaBH_4 either in combination with a protic or a Lewis acid^{3,4}. 2,2-Disubstituted 2-amino-ethanols are less frequently mentioned in literature despite the fact these amino alcohols too, are of interest for new pharmaceuticals like Fedotozine tartrate⁵ and Cericlamine hydrochloride⁶.

We wish to report here our results on the synthesis of this type of amino alcohol by a new method, namely by reduction of enantiomerically pure amino acid amides using liquid sodium metal in refluxing alcohols. Mono- and disubstituted amino acid amides are readily available in high enantiomeric excesses by enzymatic methods⁷.

In the course of our studies on chiral 1,2-diamines from amino acid amides our attention was drawn to a recent article by Chatterjee *et al*⁸. In the reduction of amides using sodium, amines were isolated as the sole product. The formation of mixtures of alcohols and amines has also been described however⁹. We used liquid sodium metal in refluxing 1-propanol for the reduction of amino acid amides but to our surprise no 1,2-diamine was formed and only amino alcohols were isolated¹⁰.

Table 1

substrate	e.e. ^a	product	yield	e.e. ^a
	> 98 %		99 %	> 98 %
	> 98 %		98 %	> 98 %
	racemic		99 % ^b	-
	racemic		99 %	-
	> 99.6 %		96 % ^c	> 99.6 %
	> 95 %		95 % ^d	> 95 %
	> 99.6 %		65 % ^e	> 99.6 %
	-		78 %	-
	> 98 %		80 %	11 %
	racemic		40 %	-

Notes: a. Enantiomeric excesses were determined by ¹H NMR (using trifluoroanthrylethanol) or by HPLC (ref 13); b. 6-8 eq. of sodium in 1-propanol containing 4 % of water were used; c. 82 % yield after bulb-to-bulb distillation (110-115 °C/0.1 Torr.); d. due to high solubility this compound was isolated via its Schiff base with benzaldehyde (ref 14); e. 17 eq. of sodium were used.

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