Highly Stereospecific Arylation of (*S*)-Proline and Complementary Highly Diastereoselective Reduction of the α-Amino Ketone. Asymmetric Synthesis of (1*S*,2′*S*)- and (1*R*,2′*S*)-Phenyl(2′-pyrrolidinyl)methanol

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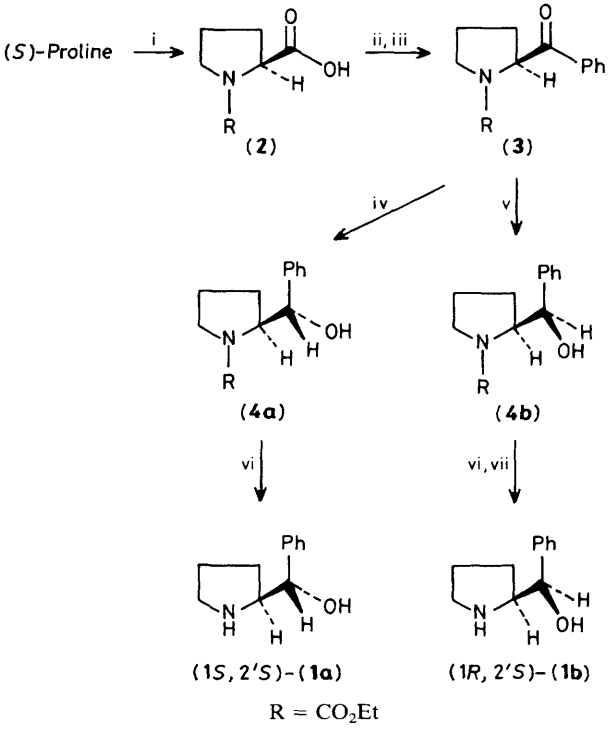
Both optically active *threo*- and *erythro*-phenyl(2′-pyrrolidinyl)methanol (93—100% enantiomeric excess, 100% diastereoisomeric excess) were synthesised from (*S*)-proline by a stereospecific arylation and the subsequent complementary diastereoselective reduction of the α-amino ketone.

Chiral amino alcohols show various kinds of pharmacological activity. It is recognised that receptor centres are in many cases very stereoselective towards these compounds. However, most of the diastereoisomeric amino alcohols utilised are racemic pairs, and only a limited number of optically active ones are known.[1] Additionally optically active amino alcohols can be employed in asymmetric synthesis of optically active compounds.[2]

Phenyl(2′-pyrrolidinyl)methanol (**1**) has biological activity,[3a] but has so far been prepared and utilised only as a racemate.[3] Stereospecific arylation of (*S*)-proline leading to formation of the aryl ketone and the subsequent diastereoselective reduction of the α-amino aryl ketone may be key steps in achieving an asymmetric synthesis of (**1**). Although arylation of *primary* amino acids has been reported, the method is not applicable to *secondary* amino acids such as proline.[4] Moreover, Friedel–Crafts reaction of the acid chloride of *N*-methoxycarbonylproline is sluggish and the product is not isolable because of contamination by impurities.[5] On the other hand, very few reports have appeared on complementary highly diastereoselective reduction of α-amino ketones.[1,6] We report here an asymmetric synthesis of optically active (1*S*,2′*S*)-(**1a**) and (1*R*,2′*S*)-(**1b**) in high diastereoisomeric excess (d.e.) and in high enantiomeric excess (e.e.) *via* highly stereospecific arylation of (*S*)-proline followed by highly diastereoselective reduction of the α-amino aryl ketone (**2**).

It was found, after many experiments, that phenyl Grignard reaction of the mixed anhydride of (*S*)-*N*-ethoxycarbonylproline (**2**)[7] with diphenylphosphinoyl chloride[8] was effective for the stereospecific arylation. The corresponding optically active (2′*S*)-phenyl pyrrolidinyl ketone (**3**) was obtained in 74% yield and in 93% e.e. as a result of a small amount of racemisation during the stereospecific arylation of (**2**) [e.e. was determined as for (**1**)] {$[\alpha]_D$ −41.2° (*c* 1.02, $CHCl_3$)}.[9]† The results of the diastereoselective reduction of (**3**) to (**4**) are summarised in Table 1. Nucleophilic reducing agents such as potassium tri-sec-butylborohydride (K-selectride) afforded (1*S*,2′*S*)-(**4a**) (*threo* isomer) in 97% yield {(**4a**) : (**4b**) = 100 : 0, entry 1}. Surprisingly, on the other hand electrophilic reducing agents such as di-isobutylaluminium hydride (DIBAL) afforded (1*R*,2′*S*)-(**4b**)(*erythro* isomer) in 46% yield {(**4a**) : (**4b**) = 4 : 96, entry 5}. Thus either diastereoisomer could be obtained from the same *N*-protected α-chiral-α-amino ketone by using appropriate reducing agents. Removal of the ethoxycarbonyl group of (**4a**) and (**4b**) in methanolic KOH afforded (**1a**) and (**1b**) respectively in 85—87% yield. The configuration was assigned by comparing ^{1}H n.m.r. data {benzylic methine proton: (**1a**), δ 4.3, *J* 7.0 Hz; (**1b**), δ 4.7, *J* 4.2 Hz} with those for the corresponding



Scheme 1. *Reagents:* i, $ClCO_2Et$; ii, Ph_2POCl, Et_3N, CH_2Cl_2; iii, PhMgBr, tetrahydrofuran (THF); iv, K-Selectride, THF; v, DIBAL, THF; vi, KOH–MeOH; vii, HCl–MeOH, recrystallisation, NaOH.

Table 1. Complementary diastereoselective reduction of (**3**) to (**4a**) and (**4b**).[a]

Entry	Reducing agent[b]	(**4a**) : (**4b**)[c] (*threo*) : (*erythro*)
1	KBu^s_3BH	100 : 0
2	$LiBu^s_3BH$	91 : 9
3	$NaBH_4$[d]	57 : 43
4	$LiAlH_4$	65 : 35
5	Bu^i_2AlH	4 : 96
6	BH_3·THF	34 : 66
7	Me_2PhSiH[e]	38 : 62

[a] Unless otherwise noted, tetrahydrofuran (THF) was used as solvent. [b] Molar ratio of reducing agent to (**3**) was 1.2—2.0. [c] Ratios were determined by ^{1}H n.m.r. spectroscopy and g.l.c., *cf.* ref. 10. [d] Mixed solvent of THF–MeOH (98 : 2, v/v) was used, see ref. 11. [e] Trifluoroacetic acid was used. See ref. 6.

† Satisfactory results were obtained for all new compounds from n.m.r. and i.r. spectroscopy and elemental (and/or high resolution mass spectrometric) analyses.

threo-pseudoephedrine (δ 4.17, *J* 7.8 Hz) and *erythro*-ephedrine (δ 4.72, *J* 4.0 Hz).[10] (1*S*,2′*S*)-(**1a**) (*threo* isomer) was obtained from K-selectride reduction in 93% e.e. and 100% d.e.‡ {$[\alpha]_D^{27}$ +51.8° (*c* 0.95, MeOH), as hydrochloride}. (1*R*,2′*S*)-(**1b**) obtained from DIBAL reduction in 93% e.e. and 92% d.e. was converted into the corresponding hydrochloride in quantitative yield and recrystallised from MeCN–Pr^i_2O to afford the diastereoisomerically pure *erythro* isomer: 100% e.e., 100% d.e. {$[\alpha]_D^{26}$ −56.9° (*c* 0.97, MeOH), as hydrochloride; m.p. 153.5—155.0 °C}.

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