Asymmetric Synthesis of Optically Active *threo*- and *erythro*-Pyrrolidinylbenzyl Alcohol by the Highly Stereospecific Arylation of (*S*)-Proline and the Subsequent Highly Diastereoselective Reduction of the α-Amino Ketone

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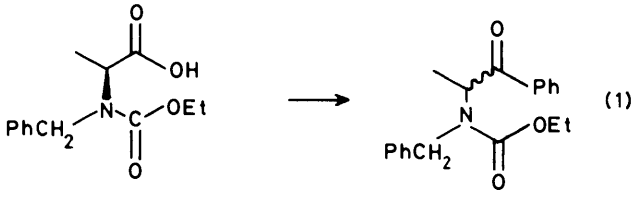
Optically active α-amino phenyl ketones in 92—94% enantiomeric excess (e.e.) were obtained from the stereospecific arylation of (*S*)-proline or its derivatives by Friedel–Crafts reaction or by Grignard reaction. The subsequent complementary diastereoselective reductions of the α-amino ketone afforded respectively (*S*)- and (*R*)-α-[(*S*)-pyrrolidin-2-yl]benzyl alcohol in 93—100% e.e. and in 100% diastereoisomeric excess. The stereochemical course of the reduction of the α-amino ketone is discussed.

Optically active α-amino ketones are important synthetic intermediates. Transformation of the easily available and optically pure α-amino acids into these ketones may become an efficient synthetic route. Rapoport reported the synthesis of optically active α-amino ketones by arylation of *N*-protected *primary* α-amino acids.[1] However, in the reaction of *N*-protected *secondary* amino acids considerable racemization occurred [equation (1)].[1] On the other hand, in the arylation of



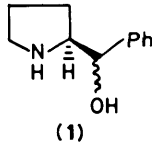
(1)

(*S*)-*N*-methoxycarbonylproline, the corresponding pure phenyl ketone was not isolated.[2] Nordlander *et al.* very recently reported the arylation of (*S*)-*N*-trifluoroacetylproline by the Friedel–Crafts reaction.[3]

Amino alcohols have various pharmacological activities, and these activities are often different for different enantiomers. In many asymmetric syntheses, optically active amino alcohols have been utilized as chiral auxiliaries.[4] Therefore, diastereoselective reduction of α-amino ketones to the corresponding α-amino alcohols is an important synthetic goal.[5–7] However, only very few amino alcohols have hitherto been synthesized in enantiomerically and in diastereoisomerically pure form.[5]

α-[(*S*)-Pyrrolidin-2-yl]benzyl alcohol (**1**) has pharmacological activity.[8a,c] Although a few reports have appeared on the synthesis of alcohol (**1**), asymmetric synthesis of optically active (**1**) has not been reported.[8]

We now report stereospecific arylation of (*S*)-proline and its derivatives by organometallic reaction and by Friedel–Crafts reaction. The subsequent diastereoselective reduction of the α-amino ketone afforded (*S*)-α-[(*S*)-pyrrolidin-2-yl]benzyl alcohol (**1a**) and its (*R*)-epimer (**1b**).[9]



(1)

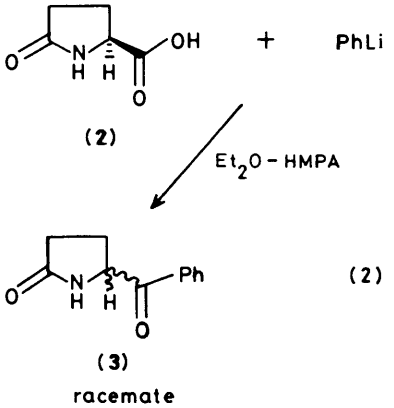
Table 1. Synthesis of ketones (**3**) by arylation of acids (**2**) with phenyllithium in the presence of HMPA

Entry	Solvent	Molar ratio[b]	Temperature (°C)	(3) Yield (%)
1	Et_2O	3.0	−40—room temp.	0[c]
2	Et_2O–HMPA[a]	3.0	−40—room temp.	41
3	Et_2O–HMPA[a]	3.0	−40—0	38
4	Et_2O–HMPA[a]	3.5	−40—0	53

[a] Et_2O:HMPA = 3.5:1 (v/v). [b] Ratio of PhLi:(**2**). [c] Desired ketone was not detected by t.l.c. analysis.

Results and Discussion

Attempted Arylation of (S)-*Pyroglutamic Acid* (*5-Oxopyrrolidine-2-carboxylic Acid*).—We chose (*S*)-pyroglutamic acid (**2**) as an *N*-protected amino acid. Our first attempt to synthesize the ketone was performed by the direct arylation of (*S*)-pyroglutamic acid (**2**) with phenyl-lithium. To a solution of the acid (**2**) in ether–hexamethylphosphoric triamide (HMPA), at −40 °C was added phenyl-lithium (3 equiv.) in ether. Then the mixture was allowed to warm to room temperature. Phenyl ketone (**3**) was isolated in 40—55% yield. Results are summarized in Table 1. Unfortunately, however, nearly complete racemization occurred during the reaction, and the ketone (**3**) obtained was racemic [equation (2)].



(2)

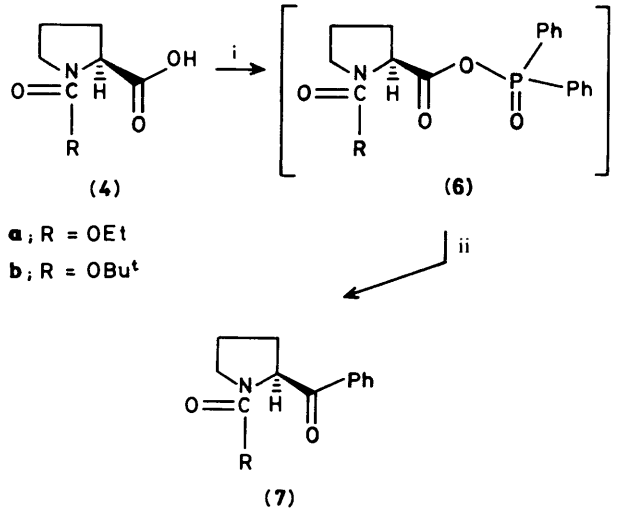
Arylation of the Mixed Anhydride with Grignard Reagent.—A Grignard reagent was examined in the arylation of the mixed anhydride of our *N*-protected proline.[10] Mixed anhydrides (**6**) were prepared from an (*S*)-*N*-protected proline (**4**), diphenyl-

Table 2. Synthesis of ketones (7) from acids (4) by mixed anhydride method

Compound (4)			Yield (%)	
Entry	Solvent	Temp. (°C)	Product (7)	By-product[a]
1 (4b)	THF	−74—room temp.	(7b) 69	19
2 (4b)	Et_2O	−74—room temp.	(7b) 72	*d*
3 (4a)	THF	−74—room temp.	(7a) 75	15
4[b] (4a)	Et_2O–THF	−78	(7a) 34	58[c]

[a] Triphenylphosphine oxide unless otherwise noted. [b] Pivaloyl chloride was used instead of diphenylphosphinoyl chloride (5). [c] Phenyl t-butyl ketone. [d] Yield not determined.

phosphinoyl chloride (5),[11] and triethylamine in dichloromethane. The mixed anhydride (6a) prepared from (*S*)-*N*-ethoxycarbonylproline (4a) with (5) was treated with phenylmagnesium bromide (1 equiv.) at −72 °C. Then the mixture was gradually warmed to room temperature and the reaction was quenched with phosphate buffer solution and 1M-hydrochloric acid. Phenyl ketone (7a) was obtained in 72% yield and in 93% enantiomeric excess (e.e.) as the result of a small amount of racemization during the reaction. Results (Scheme 1) are summarized in Table 2. When the mixed anhydride prepared from pivaloyl chloride[12] instead of diphenylphosphinoyl chloride (5) was treated with PhMgBr, the desired ketone (7a) and phenyl t-butyl ketone were obtained in 34 and 58% yield respectively. The lack of regioselectivity of the Grignard reagent toward the two carbonyl groups in this mixed anhydride may be explained by the fact that the difference of the steric hindrance of the carbon atoms adjacent to the two carbonyl groups is that between carbons which are secondary *vs.* tertiary.*

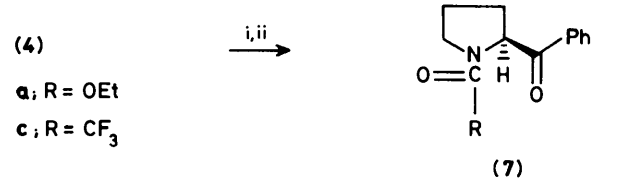


Scheme 1. *Reagents:* i, $Ph_2P(O)Cl$ (5), Et_3N, CH_2Cl_2; ii, PhMgBr

It was also found that the mixed anhydride method was applicable to the synthesis of the ketone (7b) with the acid-sensitive functional group. Thus, (*S*)-*N*-t-butoxycarbonylproline (4b) was converted into the mixed anhydride (6b) using the acid chloride (5). Subsequent reaction with PhMgBr afforded the corresponding phenyl ketone (7b) in 72% yield in optically active form {$[\alpha]_D$ −62.1° (*c* 1.02 in $CHCl_3$)}. This ketone (7b) may not be prepared by Friedel–Crafts reaction because the t-butoxycarbonyl group is easily deprotected under the acidic conditions.†

Arylation by Friedel–Crafts Reaction.—Arylation of an *N*-protected proline by Friedel–Crafts reaction was next examined. (*S*)-*N*-Ethoxycarbonylproline (4a) was converted into the corresponding acyl chloride with oxalyl chloride using a catalytic amount of dimethylformamide (DMF) in dichloromethane; the acid chloride was, without purification, treated with benzene in the presence of aluminium chloride. Then the reaction mixture was poured into a mixture of phosphate buffer solution and crushed ice while saturated aq. $NaHCO_3$ was added in order to maintain pH in the range 4—7. The desired phenyl ketone (7a) was obtained in 67% yield and in 94% e.e. as the result of a small amount of racemization {$[\alpha]_D$ −41.2° (*c* 1.02 in $CHCl_3$). Determination of the e.e. will be discussed later on.} On the other hand, when the reaction was quenched with 1M-HCl and the mixture stirred for 2 h, the e.e. of the ketone (7a) dropped considerably to 76% {$[\alpha]_D$ −34.2° (*c* 1.12 in $CHCl_3$)}. This racemization probably occurred *via* acid-catalysed enolization of the ketone (7a). It should be noted that the arylation of (*S*)-*N*-methoxycarbonylprolyl chloride with benzene and aluminium chloride does not proceed smoothly and that the obtained ketone (30—35%) was contaminated by an unknown by-product.[2]

Following a recently reported procedure, optically active phenyl ketone (7c)[3] was synthesized from (*S*)-*N*-trifluoroacetylproline (4c) (Scheme 2). However, loss of the trifluoroacetyl group occurred during the subsequent reduction of ketone (7c) with potassium tri-s-butyl borohydride (K-selectride), and the amino alcohol (1), thus produced, had only low e.e. (35%). This racemization is thought to occur during the reduction since the starting amino ketone (7c) should be of high optical purity.[3] Thus trifluoroacetyl as a protective group in the nucleophilic reduction step of the ketone was not suitable since it is readily removed by the nucleophilic reducing reagent.‡



Scheme 2. *Reagents:* i, $(COCl)_2$, DMF; ii, $AlCl_3$, benzene

Synthesis of Compound (1b) *from* (S)-*Proline* (8).—Friedel–Crafts reaction of the unprotected acid chloride (9) of (*S*)-proline was examined. (*S*)-Proline (8) was converted into its acid chloride hydrochloride (9) by reaction with phosphorus pentachloride in dichloromethane. Subsequent reaction with benzene in the presence of $AlCl_3$ afforded the corresponding phenyl ketone hydrochloride (10). Since the free amino ketone of (10) was unstable, the hydrochloride was reduced directly with sodium borohydride. *erythro*-Amino alcohol (1b) was

* The regioselectivity between the two carbonyl groups of the mixed anhydride in the reaction of Grignard reagents was good when the difference in steric hindrance is due to primary *vs.* tertiary (or 2-substituted phenyl) groups. See ref. 12.

† The *N*-t-butoxycarbonyl group is easily removed by, *e.g.* 3M-HCl or $AlCl_3$ (G. L. Stahl, R. Walter, and C. W. Smith, *J. Org. Chem.*, 1978, **43**, 2285; T. Tsuji, T. Kataoka, M. Yoshioka, Y. Sendo, Y. Nishitani, S. Hirai, T. Maeda, and W. Nagata, *Tetrahedron Lett.*, 1979, 2793).

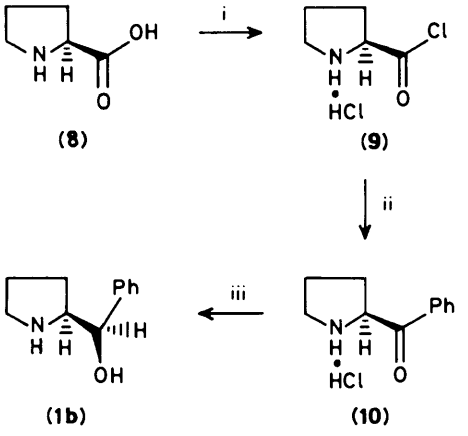
‡ The *N*-trifluoroacetyl group of proline is readily removed by sodium borohydride, a mild reducing agent, at 20 °C within a few minutes (F. Weygand and E. Frauendorfer, *Chem. Ber.*, 1970, **103**, 2437).

Table 3. Complementary diastereoselective reduction of ketone (**7a**) to alcohols (**11a**) and (**11b**)[a]

Entry	Reducing[b] agent	Product (**11a**):(**11b**)[c] (*threo*):(*erythro*)
1	$KBBu^s_3H$	100:0
2	$LiBBu^s_3H$	91:9
3	$NaBH_4$[d]	57:43
4	$LiAlH_4$	65:35
5	$AlBu^i_2H$	4:96
6	BH_3·THF	34:66
7	$SiMe_2PhH$[e]	38:62

[a] Unless otherwise noted, THF was used as solvent. [b] Molar ratio of reducing reagent to (**7a**) was 1.2—2.0:1. [c] Ratios were determined by ^1H n.m.r. spectroscopy and g.l.c.; see ref. 15. [d] Mixed solvent THF–MeOH (98:2, v/v) (see ref. 24). [e] Trifluoroacetic acid, see ref. 5.

predominantly formed {(**1a**):(**1b**) 6:94, 88% d.e., 92% e.e., determined by g.l.c. analysis of the corresponding α-methoxy-α-(trifluoromethyl)phenylacetyl (MTPA) amides, *vide infra*} in 55% overall yield from proline (**8**) (Scheme 3).



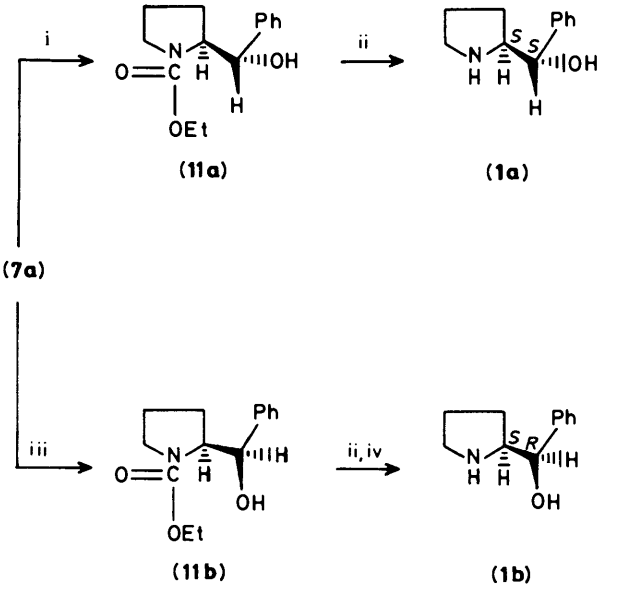
Scheme 3. *Reagents:* i, PCl_5; ii, $AlCl_3$, benzene; iii, $NaBH_4$

Diastereoselective Reduction of the α-Amino Ketones.—Diastereoselective reduction of 1-ethoxycarbonylpyrrolidin-2-yl phenyl ketone (**7a**) to the alcohols (**11**) was examined. Results are shown in Table 3. In the reduction of keto ester (**7a**), nucleophilic reducing reagents afforded *threo*-(**11**). Thus, reduction with potassium tri-s-butylborohydride (K-selectride) proceeded with 100% *threo*-selectivity to afford compound (**11a**). On the other hand, electrophilic reducing agents such as borane–tetrahydrofuran (THF) or di-isobutylaluminium hydride (DIBAL) showed the opposite selectivity and the *erythro*-alcohol (**11b**) was obtained (Scheme 4). The reduction, especially with DIBAL, proceeded with high diastereoselectivity (92% d.e.). The reversal of the sense of diastereoselectivity in the reduction by reagents of different types may be explained as follows. Cram's open-chain model[13] may be applied to the reduction with the nucleophilic reagents (see Figure 1). On the other hand, for the reductions using electrophilic reagents, Cram's chelation model[14] may be applied (see Figure 2). In both cases, the more stable conformations are considered to be (**13**) and (**14**) respectively judging from the steric repulsions between the phenyl group and the hydrogen atoms on the pyrrolidine ring. The hydride attack from the less hindered side produces respectively the

Table 4. Diastereoselectivities in the reduction of ketones (**3**)[a]

Entry	Reducing agent	Product[b] (**12a**):(**12b**) (*threo*):(*erythro*)
1	$NaBH_4$[c]	16:84
2	$NaBH_4$[d]	18:82
3	$Zn(BH_4)_2$	24:76
4	K-Selectride	21:79
5	$LiAlH_4$	20:80[f]
6	$LiAlH_4$[e]	24:76
7	$LiBH_4$	39:61
8	Red-Al	16:84
9	BH_3·THF	20:80

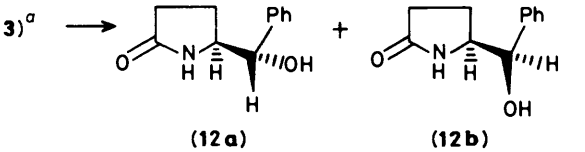
[a] Unless otherwise noted, THF was used as solvent. Molar ratio of reducing agent to ketone (**3**) was 2:1. Ratios were determined by ^1H n.m.r. spectroscopy. [b] Products were racemic. Only one enantiomer is shown. [c] Mixed solvent THF–MeOH (99:1, v/v) (see ref. 24). [d] Mixed solvent THF–MeOH (95:5, v/v) (see ref. 24). [e] Et_2O Was used as solvent. [f] At reflux temperature, (**3**) was reduced to (**1**).



Scheme 4. *Reagents and conditions:* i, K-Selectride, THF; ii, KOH–MeOH; iii, DIBAL, THF; iv, HCl–MeOH; recrystallization; NaOH

threo-isomer (**11a**) from (**13**) and the *erythro*-isomer (**11b**) from (**14**).*

On the other hand, in the reduction of 5-oxopyrrolidin-2-yl phenyl ketone (**3**) and the ketone (**10**), all of the nucleophilic and electrophilic reducing reagents showed *erythro*-selectivity to afford respectively compounds (**12b**) and (**1b**) as the predominant isomers [equation (3)]. Compound (**12b**) was



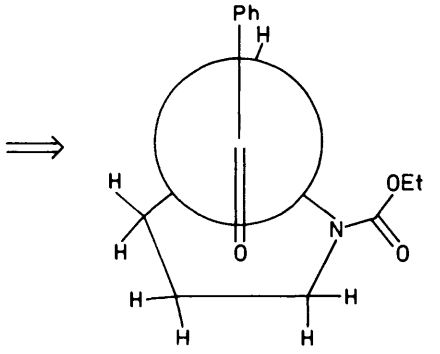
[a] Racemic (**3**) was used. Only one enantiomer of each diastereoisomer is shown

* Opposite diastereoselectivity was observed between nucleophilic and electrophilic reducing agents in the reduction of ketones (M. M. Midland and Y. C. Kwon, *J. Am. Chem. Soc.*, 1983, **105**, 3725; K.-Y. Ko, W. J. Frazee, and E. L. Eliel, *Tetrahedron*, 1984, **40**, 1333).

obtained predominantly from the chemoselective reduction of the ketone carbonyl of compound (**3**) at −90—0 °C. When (**3**) was reduced with $LiAlH_4$ in refluxing THF, both ketone and amide carbonyls were reduced to afford (**1b**) predominantly. The results are shown in Table 4. In these cases, metal atoms (B and Al) of the reducing reagents are considered to co-ordinate the nitrogen atom of the carbamoyl or imino groups after the reaction with a relatively acidic hydrogen atom. The stereochemical course may be explained by the chelation model. The formation of the cyclic intermediate (**15**) (see Figure 3) and the subsequent hydride attack on the carbonyl group from the less hindered side affords *erythro*-isomers.

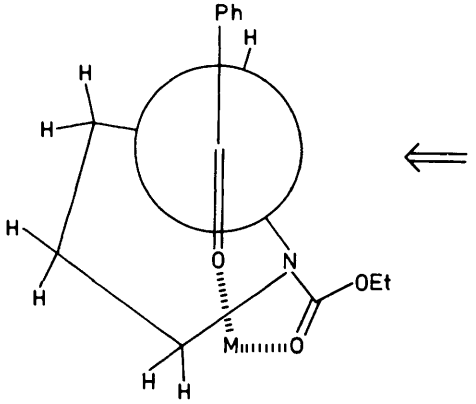
In the reductions using the same nucleophilic reagents, the opposite diastereoselectivities between the ketone (**7a**) and the compounds (**3**) and (**10**) were observed. The different diastereoselectivities may be attributed to the presence of a hydrogen atom in the carbamoyl and imino groups of compounds (**3**) and (**10**).*

Synthesis of (S)-α-[(S)-*Pyrrolidin-2-yl*]*benzyl Alcohol* (**1a**) *and its* (R)-*Epimer*.—Esters (**11a**) and (**11b**) (93—94% e.e.) were hydrolysed separately in methanolic KOH at reflux temperature for 4 h. Distillation under reduced pressure afforded respectively



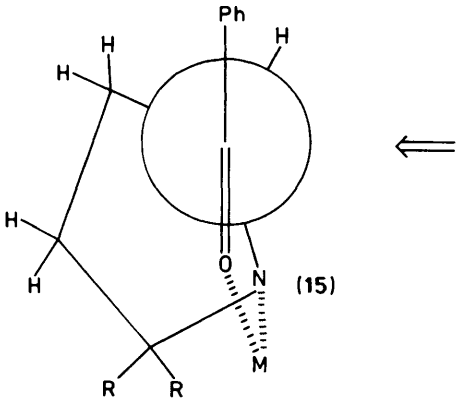
(13)

Figure 1.



(14)

Figure 2.



(15)

(10); R = H, (3); RR = O
M; Al, B or Li, Na

Figure 3.

compounds (**1a**) and (**1b**) in 85—87% yield. These products were converted into their hydrochlorides with methanolic hydrogen chloride (100% yield). The e.e.s of compounds (**1a**) and (**1b**) were each 93% at this stage, and (**1a**) was found to be diastereoisomerically pure. Compound (**1b**) was made enantiomerically and diastereoisomerically pure by recrystallization from acetonitrile–di-isopropyl ether. The configuration was assigned by comparison of ^1H n.m.r. spectra [benzylic methine proton: (**1a**), δ 4.3, *J* 7.0 Hz; (**1b**), δ 4.7, *J* 4.2 Hz] with that of the corresponding authentic *threo*-pseudoephedrine (δ 4.17, *J* 7.8 Hz) and the *erythro*-ephedrine (δ 4.72, *J* 4.0 Hz).[15]

Determination of E.e.s.—α-(Pyrrolidin-2-yl)benzyl alcohol (**1**) was converted into the corresponding MTPA amide[16] under Schotten–Baumann reaction conditions. Diastereoisomeric and enantiomeric excesses of compound (**1**) were analysed by g.l.c. after trimethylsilylation of the hydroxy group. The retention times for (±)-MTPA-amides of (**1**) were as follows: (**1a**), 42.6 and 44.4 min (SE-30, 25 m capillary column, column temp. 175 °C); (**1b**), 85.9 min and 88.2 min (OV-1, 50 m capillary column, column temp. 210 °C).

Conclusions

Optically active α-amino ketones are synthesized by the stereospecific arylation of (*S*)-proline by (i) reaction of phenyl Grignard reagent with the mixed anhydride derived from (*S*)-*N*-protected proline and diphenylphosphinoyl chloride, and (ii) Friedel–Crafts reaction.

(*S*)-α-[(*S*)-Pyrrolidin-2-yl]benzyl alcohol (**1a**) and its (*R*)-epimer (**1b**) were synthesized with high diastereoselectivity by the reduction of (*S*)-1-ethoxycarbonylpyrrolidin-2-yl phenyl ketone (**7a**) with K-selectride or DIBAL respectively, or by the reduction of the hydrochloride of phenylpyrrolidin-2-yl ketone (**10**) with $NaBH_4$.

Experimental

M.p.s were measured with Yamato melting point apparatus MP-21 and are uncorrected. I.r. spectra, high-resolution mass spectra, and optical rotations were recorded respectively with a Hitachi 260-10 spectrophotometer, a Hitachi M-80 mass spectrometer, and a JASCO DIP-181 polarimeter. ^1H N.m.r. spectra (60 MHz) were recorded by using either a Varian EM-360A n.m.r. spectrometer or a JEOL JNM-PMX-60 n.m.r. spectrometer.

* In the reduction of amino ketone derivatives, secondary amido ketones and *N,N*-dialkylamino ketones and tertiary amido ketones are reduced in the opposite sense (S. Yamada and K. Koga, *Tetrahedron Lett.*, 1967, 1711; K. Koga and S. Yamada, *Chem. Pharm. Bull.*, 1972, **20**, 539).

Materials.—Ether, THF, and benzene were distilled from lithium aluminium hydride. Dichloromethane was purified by the literature procedure.[17] HMPA and methanol were stored over molecular sieves 4Å and 3Å respectively. Triethylamine and DMF were distilled from calcium hydride. The concentrations of organometallic reagents[18] and reducing agents[19] were determined by the respective literature procedure.

Diphenylphospinoyl chloride, K-selectride, lithium tri-s-butylborohydride (L-selectride), DIBAL, and dimethylphenylsilane were purchased from Aldrich Chemical Co. (*S*)-Pyroglutamic acid, (±)-pyroglutamic acid, and (±)-proline were purchased from Tokyo Kasei.

(S)-1-*Ethoxycarbonylproline* (**4a**).—To a stirred solution of (*S*)-proline (**8**) (23.03 g, 200 mmol) in 1M-NaOH (200 ml) at 0 °C was added ethyl chloroformate (23.8 ml, 250 mmol) in three portions during 1.5 h, with the addition of small portions of 1M-NaOH to maintain the pH of the mixture at 9—10. After being stirred for 1.5 h at room temperature, the mixture was washed with dichloromethane and was then acidified to pH 1 with 6M-HCl. The mixture was extracted with dichloromethane and the extract was dried over anhydrous sodium sulphate. The solvent was evaporated off under reduced pressure and the title product (**4a**) was obtained (32.27 g, 86%), m.p. 63.0—64.2 °C (lit.,[20] 62—63 °C); $[\alpha]_D^{26}$ −94.2° (*c* 1.08 in $CHCl_3$); δ($CDCl_3$) 1.05—1.53 (3 H), 1.70—2.55 (4 H), 3.27—3.80 (2 H), 3.85—4.57 (3 H), and 9.10 (1 H); $\nu_{max.}$ 3 425, 1 680, and 1 440 cm^{-1}.

(S)-1-*t-Butoxycarbonylproline* [**4b**).—To an ice-cooled solution of (*S*)-proline (**8**) (2.45 g, 21.3 mmol) in a mixture of 1,4-dioxane–water (30 ml; 2:1 v/v) and 1M-NaOH (20 ml) was added di-t-butyl dicarbonate ($Bu^tO{\cdot}CO{\cdot}O{\cdot}CO{\cdot}OBu^t$) (4.65 g, 21.3 mmol).[21] The reaction mixture was stirred for 30 min at this temperature, then stirred for 1.5 h at room temperature. Most of the dioxane was removed on a rotary evaporator. The residual mixture was washed with chloroform, acidified to pH 2 with 0.5M-citric acid, then extracted with ethyl acetate. The extract was washed with water and dried over anhydrous sodium sulphate. Removal of the solvent afforded the title compound (**4b**) (4.22 g, 94%), which was recrystallized from ethyl acetate–hexane (3.28 g, 73%), m.p. 133.5—135.0 °C (lit.,[22] 136—137 °C); $[\alpha]_D^{26}$ −61.0° (*c* 1.02 in AcOH) {lit., $[\alpha]_D^{25}$ −60.2° (*c* 2.01 in AcOH)}; δ($CDCl_3$) 1.45 (9 H), 1.65—2.45 (4 H), 3.20—3.65 (2 H), 4.00—4.40 (1 H), and 10.20 (1 H); $\nu_{max.}$ 1 740, 1 640, 1 425, and 1 220 cm^{-1}.

(S)-1-*Trifluoroacetylproline* (**4c**).—To a mixture of (*S*)-proline (**8**) (8.645 g, 75.1 mmol) and ethyl trifluoroacetate (41.2 ml, 346 mmol) at 10 °C was added 1,1,3,3-tetramethylguanidine (14.2 ml, 113 mmol) during 10 min, and the mixture was stirred at room temperature for an additional 20 min. The excess of ethyl trifluoroacetate was removed on a rotary evaporator, water was added to the residue, and the mixture was acidified to pH 1 with 1M-HCl (20 ml) and 6M-HCl (15 ml). The mixture was extracted with ethyl acetate and the extract was dried over anhydrous sodium sulphate. Evaporation of the solvent afforded crude (*S*)-1-trifluoroacetylproline. The crude product was dissolved in Et_2O (95 ml) and dicyclohexylamine (18 ml, 90 mmol) was added to the stirred solution. The precipitate was collected by suction and washed with Et_2O. Recrystallization from propan-2-ol afforded the dicyclohexylamine salt (26.94 g). This salt was added to a stirred mixture of 3M-HCl (31 ml) and Et_2O (40 ml). The precipitate was filtered off by suction and was washed successively with 1M-HCl and Et_2O. The filtrate was extracted with Et_2O and the extract was washed with brine and dried over anhydrous sodium sulphate. Removal of solvent afforded the title compound (**4c**) (12.54 g, 79%), m.p. 53.8—55.0 °C (lit.,[23] 47—48 °C); $[\alpha]_D^{25}$ −65.19° (*c* 1.08 in PhH) {lit.,[23] $[\alpha]_D^{20}$ −60.9° (*c* 1 in PhH)}.

(±)-5-*Oxopyrrolidin-2-yl Phenyl Ketone* (**3**).—To a solution of (*S*)-pyroglutamic acid (**2**) (0.580 g, 4.49 mmol) In Et_2O (10.5 ml) containing HMPA (3 ml) at −40 °C was added phenyllithium (15.72 mmol). The mixture was gradually warmed to 0 °C, then the reaction was quenched with 1M-phosphoric acid. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The extract was dried over anhydrous sodium sulphate. After removal of most of the solvent on a rotary evaporator, HMPA was almost completely removed by bulb-to-bulb distillation (170 °C/3 mmHg). Purification of the residue by silica gel t.l.c. (ethyl acetate as developing solvent) afforded the *ketone* (**3**) (0.467 g, 53%), $[\alpha]_D$ 0 ° (*c* 1.08 in $CHCl_3$); δ($CDCl_3$) 1.90—2.90 (4 H), 4.95—5.30 (1 H), 6.30—6.65 (1 H), 7.35—7.60 (3 H), and 7.80—8.00 (2 H); $\nu_{max.}$ 3 200, 1 690, 1 260, and 700 cm^{-1} (Found: C, 69.9; H, 5.9; N, 7.4. $C_{11}H_{11}NO_2$ requires C, 69.82; H, 5.86; N, 7.40%).

(5S)-5-[(RS)-α-*Hydroxybenzyl*]*pyrrolidin-2-one* (**12**): *Table 4, Entry 1.*—To a suspension of sodium borohydride (0.013 g, 0.346 mmol) in THF–MeOH (99:1, v/v) (1 ml) at 0 °C was added a solution of the ketone (**3**) (0.065 g, 0.346 mmol) in THF–MeOH (99:1, v/v) (2 ml) during 5 min. After 2.5 h, 1M-HCl and water were added and most of organic solvent was evaporated off under reduced pressure. The aqueous layer was extracted with chloroform and the extract was dried over anhydrous sodium sulphate and evaporated under reduced pressure. Purification of the residue on silica gel t.l.c. (ethyl acetate as developing solvent) afforded a mixture of *threo* and *erythro* isomers of the title compound (**12**) (0.065 g, 99%), δ($CDCl_3$) 1.50—2.35 (4 H), 3.60—4.05 (2 H; 1 H exchangeable with D_2O), 4.33 [0.84 H, d, *J* 7.6 Hz for *erythro* isomer (**12b**)], 4.67 [0.16 H, d, *J* 3.8 Hz for *threo* isomer (**12a**)], 6.86 (1 H, exchangeable with D_2O), and 7.27 (5 H); $\nu_{max.}$ 3 280, 2 940, and 1 670 cm^{-1}.

[(S)-*Pyrrolidin-2-yl*]*benzyl Alcohol* (**1**) *by* $LiAlH_4$ *Reduction of* 5-*Oxopyrrolidin-2-yl Phenyl Ketone* (**3**): *Table 4, Entry 5.*—To a suspension of lithium aluminium hydride (0.163 g, 4.3 mmol) in THF (25 ml) at 0 °C was added 5-oxopyrrolidin-2-yl phenyl ketone (**3**) (0.406 g, 2.15 mmol). The mixture was refluxed for 2 h and cooled to room temperature. Water (0.18 ml), 10M-NaOH (0.07 ml) and water (0.07 ml) was successively added to the mixture, which was then stirred overnight at room temperature. The precipitate was filtered off through Celite and was washed with chloroform. The filtrate and washings were dried over sodium sulphate and evaporated under reduced pressure. The residue was distilled (180 °C/3 mmHg) (bulb-to-bulb) to afford the alcohol (**1**) (0.354 g, 93%). N.m.r. and i.r. spectra were identical with those described above. N.m.r. analysis showed the ratio of (**1a**) to (**1b**) was 20:80.

Ethyl (S)-2-*Benzoylpyrrolidine*-1-*carboxylate* (**7a**) *by Mixed Anhydride Method.*—Compound (**4a**) (0.189 g, 1.01 mmol) was treated with diphenylphosphinoyl chloride (**5**) (0.19 ml, 1.01 mmol) at 0 °C—room temperature in the presence of triethylamine (0.14 ml, 1.01 mmol) for 2 h to give the corresponding mixed anhydride. Ether was added to the mixture, which was then washed successively with water, saturated aq. $NaHCO_3$, and brine, and was dried over sodium sulphate. The organic layer was concentrated under reduced pressure, and the resulting oil was dissolved in THF (4 ml) and the solution was cooled to −72 °C. Phenylmagnesium bromide (1.01 mmol) was added and the mixture was gradually warmed to room temperature before being poured into a mixture of phosphate buffer and 1M-HCl at 0 °C. The aq. layer was extracted with chloroform. The combined organic layers were

washed successively with saturated aq. $NaHCO_3$ and brine and were dried over sodium sulphate. After evaporation of the organic solvent, purification on silica gel t.l.c. [ethyl acetate–hexane (1:2) as developing solvent] afforded the *keto ester* (**7a**) (0.165 g, 66%), $[\alpha]_D$ −41.2° (*c* 1.02 in $CHCl_3$); δ($CDCl_3$) 0.85—1.40 (3 H), 1.60—2.55 (4 H), 3.35—3.80 (2 H), 3.80—4.35 (2 H), 5.10—5.45 (1 H), 7.30—7.60 (3 H), and 7.70—8.10 (2 H); $\nu_{max.}$ 2 980 and 1 718 cm^{-1} [Found: M^+ (e.i.), 247.1194. $C_{14}H_{17}NO_3$ requires *M*, 247.1209].

t-Butyl (S)-2-*Benzoylpyrrolidine*-1-*carboxylate* (**7b**) *by Mixed Anhydride Method.*—This keto ester was prepared from acid (**4b**) in the same manner as described above except for the use of citric acid instead of hydrochloric acid. The *title compound* (**7b**) (69%) had m.p. 97.5—98.4 °C; $[\alpha]_D^{21}$ −63.05° (*c* 1.02 in $CHCl_3$); δ($CDCl_3$) 1.05—1.67 (9 H), 1.70—2.55 (4 H), 3.35—3.80 (2 H), 5.00—5.45 (1 H), 7.20—7.60 (3 H), and 7.75—8.05 (2 H) [Found: M^+ (e.i.), 275.1534. $C_{16}H_{21}NO_3$ requires *M*, 275.1522].

Ethyl (S)-2-*Benzoylpyrrolidine*-1-*carboxylate* (**7a**) *by Friedel–Crafts Reaction.*—To a solution of (*S*)-1-ethoxycarbonylproline (**4a**) (0.562 g, 3 mmol) in dichloromethane (9 ml) at 0 °C were added DMF (0.1 ml) and oxalyl chloride (0.275 ml, 3.15 ml). The stirred reaction mixture was allowed to warm to room temperature during 2.0 h, and was then diluted with both dichloromethane (4.5 ml) and benzene (37.5 ml) and cooled in ice–salt-bath. Aluminium chloride (0.84 g, 6.3 mmol) was added in one portion and the stirred mixture was allowed to warm to room temperature overnight. The solution was poured into a mixture of phosphate buffer and crushed ice with simultaneous addition of saturated aq. sodium hydrogencarbonate to maintain pH within the range 4—7. The organic layer was separated, washed successively with cold 1M-HCl, water, saturated aq. sodium hydrogencarbonate, and brine, and dried over sodium sulphate. After evaporation of the solvent under reduced pressure, the oil was purified on silica gel t.l.c. [ethyl acetate–hexane (1:2) as developing solvent] to afford the *keto ester* (**7a**) (0.465 g, 63%), $[\alpha]_D^{25}$ −41.6° (*c* 0.99 in $CHCl_3$) [Found: M^+ (e.i.), 247.1221. $C_{14}H_{17}NO_3$ requires *M*, 247.1209]. N.m.r. and i.r. spectra were identical with those described above.

Phenyl (S)-1-*Trifluoroacetylpyrrolidin*-2-*yl Ketone* (**7c**) *by Friedel–Crafts Reaction.*—This ketone was prepared from the acid (**4c**) according to the literature procedure, and was recrystallized from benzene–hexane. Compound (**7c**) (84%) had m.p. 105—106 °C (lit.,[3b] 102—104 °C); $[\alpha]_D^{19}$ −83.3° (*c* 1.01 in $CHCl_3$); δ($CDCl_3$) 1.70—2.75 (4 H), 3.55—4.05 (2 H), 5.35—5.75 (1 H), 7.25—7.60 (3 H), and 7.75—8.05 (2 H); $\nu_{max.}$ 1 710, 1 685, 1 230, 1 205, 1 180, 1 140, and 705 cm^{-1}.

Ethyl (S)-2-[(S)-α-*Hydroxybenzyl*]*pyrrolidine*-1-*carboxylate* (**11a**).—A solution of K-Selectride (2 mmol) in THF was added to a THF solution of the ketone (**7a**) (0.247 g, 1 mmol) at −78 °C. The mixture was stirred for 6 h and was then warmed to room temperature. The reaction was quenched with water. Then 35% H_2O_2 (1 ml) was carefully added to the ice-cooled mixture, which was stirred for 3 h at room temperature. Sodium sulphate was added to decompose the excess of H_2O_2. The mixture was acidified with 3M-HCl, dried over sodium sulphate, and concentrated under reduced pressure. Purification on alumina t.l.c. (1,2-dichloroethane as developing solvent) gave *threo*-alcohol (**11a**) (0.239 g, 97%). ^1H N.m.r. and g.l.c. (SE-30, 25 m capillary column, column temp. 140 °C) analysis showed that the *threo*:*erythro* ratio was 100:0 {the retention times for isomers (**11a**) and (**11b**) were 56.0 and 54.2 min respectively}. threo-*Alcohol* (**11a**) had δ($CDCl_3$) 1.3 (3 H), 1.4—1.8 (4 H), 3.15—3.80 (2 H), 4.0—4.4 (3 H), 4.63 (1 H, *J* 8.0 Hz), 5.46 (1 H), and 7.25 (5 H); $\nu_{max.}$ 3 450, 2 980, 1 680, and 1 425 cm^{-1} [Found: M^+ (e.i.), 249.1386. $C_{14}H_{19}NO_3$ requires *M*, 249.1366].

Ethyl (S)-2-[(R)-α-*Hydroxybenzyl*]*pyrrolidine*-1-*carboxylate* (**11b**).—To a THF (2.5 ml) solution of the keto ester (**7a**) (0.198 g, 0.8 mmol) cooled at −78 °C was added a solution of DIBAL (1.6 mmol) in THF (1.6 ml). After being stirred for 10 h, the reaction mixture was quenched with both water (2 ml) and methanol (2 ml) and was stirred overnight at room temperature. The mixture was acidified with 3M-HCl and the same work-up procedure as above gave *erythro*-alcohol (**11b**) (0.092 g, 46%). G.l.c. and ^1H n.m.r. analyses showed that the *threo*:*erythro* ratio [(**11a**):(**11b**)] was 4:96. erythro-*Alcohol* (**11b**) had δ($CDCl_3$) 1.0—2.15 (7 H), 2.95—3.65 (2 H), 3.65—4.40 (3 H), 4.67 (0.04 H, for *threo* isomer), 5.05 (0.96 H, for *erythro* isomer), and 7.2 (5 H); $\nu_{max.}$ 3 440, 2 980, 1 690, 1 425, and 1 390 cm^{-1} [Found: *M* (e.i.), 249.1381].

Hydrolysis of Hydroxy Esters (**11a**) *and* (**11b**) *to Alcohols* (**1a**) *and* (**1b**).—A solution of a hydroxy ester (**11a**) or (**11b**) (1 mmol) in methanolic KOH [0.134 g, 2.4 mmol in MeOH (3 ml) and water (1 ml)] was refluxed for 4 h, and was then cooled to room temperature and evaporated to dryness. The residue was diluted with water, and was acidified with phosphoric acid, then was washed with ether. The mixture was made alkaline with aq. NaOH, and the mixture was extracted with chloroform. The extract was dried over anhydrous sodium sulphate and was evaporated under reduced pressure. Distillation of the residue under reduced pressure by bulb-to-bulb method (180 °C/3 mmHg, bath temperature) afforded the corresponding product (**1a**) or (**1b**) respectively in 85—87% yield. Each product was converted into its hydrochloride with methanolic hydrogen chloride (100% yield). The e.e. of the hydrochloride of either compound (**1a**) or (**1b**) was 93% at this stage and the former was diastereoisomerically pure. Recrystallization of (**1b**) hydrochloric from acetonitrile–di-isopropyl ether gave optically and diastereomerically pure product.

Compound (**1a**) $[\alpha]_D^{27}$ + 51.8° (*c* 0.95 in MeOH), as hydrochloride, 93% e.e. and 100% d.e. δ($CDCl_3$) 1.35—2.0 (4 H), 2.75—3.05 (2 H), 3.05—3.35 (1 H), 3.50 (2 H), 4.3 (1 H, *J* 7.0 Hz), and 7.25 (5 H); $\nu_{max.}$ 3 320, 2 880, and 705 cm^{-1} (hydrochloride: Found: C, 62.1; H, 7.6; N, 6.5. $C_{11}H_{16}ClNO$ requires C, 61.82; H, 7.55; N, 6.55%).

Compound (**1b**) $[\alpha]_D^{26}$ −56.9° (*c* 0.97 in MeOH), as hydrochloride, m.p. 153.5—155.0 °C, 100% e.e., 100% d.e. δ($CDCl_3$) 1.2—1.9 (4 H), 2.6—3.1 (2 H), 3.1—3.4 (1 H), 3.6 (2 H), 4.7 (1 H, *J* 4.2 Hz), and 7.2 (5 H); $\nu_{max.}$ 3 280, 2 875, 1 430, and 705 cm^{-1} (hydrochloride: Found: C, 61.6; H, 7.6; N, 6.4%).

α-(*Pyrrolidin*-2-*yl*)*benzyl Alcohol* (**1b**) *from* (S)-*Proline* (**8**).—To a suspension of phosphorus pentachloride (1.206 g, 5.79 mmol) in dichloromethane (17 ml) at 0 °C was added (*S*)-proline (**8**) (0.667 g, 5.79 mmol) and the mixture was stirred for 2 h. After evaporation of the solvent, the residue was dried at room temperature/2 mmHg for 1 h. To the residue were added benzene (17 ml) and aluminium chloride (2.316 g, 17.37 mmol). The mixture was heated at 60 °C for 4 h, cooled to room temperature, then poured into a mixture of 1M-HCl and crushed ice. The aqueous phase was separated and washed with ethyl acetate, then neutralized with sodium carbonate. The precipitate was filtered off (suction) and washed with ethyl acetate, and the combined filtrate and washings were extracted with dichloromethane. The combined extracts were dried over anhydrous sodium sulphate. After filtration of the extracts to remove sodium sulphate, methanolic hydrogen chloride was added to the filtrate and the solvent was evaporated off under reduced pressure. The residue was dissolved in ethanol and

cooled in an ice-bath. To the solution was added sodium borohydride in a few portions during 30 min, and the mixture was stirred overnight then quenched with 3M-HCl. Most of the ethanol was evaporated off and the aqueous layer was washed with ethyl acetate and then made alkaline with conc. NaOH (to pH 12) and extracted with dichloromethane. The extract was dried over anhydrous sodium sulphate and concentrated under reduced pressure. Distillation (170 °C/3 mmHg) of the residue afforded the alcohols (**1a**) and (**1b**) (94:6) (92% e.e.) in 55% yield. N.m.r. and i.r. spectra were identical with those described above.

Determination of E.e.s of Alcohols (**1a**) *and* (**1b**) *by G.l.c. Analysis of* MTPA-*amides*.—To a dichloromethane (0.3 ml) solution of MTPA chloride[16] (0.031 g, 0.12 mmol) were added the hydrochloride of alcohol (**1a**) or (**1b**) (0.012 g, 0.055 mmol) and 1M-NaOH (0.3 ml) and the mixture was stirred for 2 h at room temperature. After the addition of sodium sulphate to the mixture, inorganic materials were filtered off and the organic layer was evaporated under reduced pressure. Purification on silica gel t.l.c. (chloroform as developing solvent) afforded the MTPA-amide of (**1**) (0.0215 g, 97%). The product was analysed by g.l.c. after being heated with 1-(trimethylsilyl)imidazole. Retention times for (±)-MTPA-amides of (**1**) were as follows. (**1a**), 42.6 and 44.4 min (SE-30, 25 m capillary column, column temp. 175 °C); (**1b**), 85.9 and 88.2 min (OV-1, 50 m capillary column, column temp. 210 °C).

Note added in proof. In Figure 1, (**13**) may be orientated so that the benzoyl carbonyl is against the *N*-ethoxycarbonyl group. The hydride attack from the less hindered side produces the same *threo*-isomer (**1a**) as Figure 1.

Acknowledgements.
We thank Mr. Ken-ichi Sakama for technical assistance.

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Received 2*nd June* 1986; *Paper* 6/1095