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Applications of Optically Active Aryl Cyanohydrins in the Synthesis of α-Hydroxy Aldehydes, α-Hydroxy Ketones and β-Hydroxy Amines*

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Abstract

Cyanohydrins, prepared in high optical purity from aryl aldehydes, have been converted into α-hydroxy aldehydes, α-hydroxy ketones and β-hydroxy amines without any racemization and frequently with good stereoselectivity for the *erythro*-diastereoisomer (>90%) at the newly introduced stereogenic centre.

Introduction

Cyanohydrins are a well established source of several important classes of compounds such as α-hydroxy ketones[1,2] and β-amino alcohols.[3,4] Acyloins in turn are important precursors for a wide variety of heterocycles[5] and carboxylic acid derivatives,[6] while β-amino alcohols are useful precursors for several heterocyclic systems.[7] Optically active aryl cyanohydrins of high enantiomeric purity are readily prepared on a multigram scale by a number of methods. The enzyme D-oxynitrilase can be used to prepare (*R*)-cyanohydrins of very high

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enantiomeric purity.[8] The 'Inoue peptide' system[9–11] and the alkoxytitanium(IV) catalyst system[12] can be used to prepare cyanohydrins with high enantiomeric excess (e.e.) (≥80%) of either the (*R*)- or (*S*)-enantiomer.

In this paper we demonstrate that these optically active cyanohydrins can be converted into a range of useful products without loss of optical activity.

Results and Discussion

Cyanohydrins

Optically active cyanohydrins from aryl aldehydes were prepared by the method described previously by us.[9,10] Most of the work was carried out by using benzaldehyde cyanohydrin of *c.* 80% e.e. with the (*R*)-enantiomer predominating, and (*R*) 4-methoxybenzaldehyde cyanohydrin which had been recrystallized to enantiomeric purity.[10] However, materials derived from racemic cyanohydrins[13] were used to evaluate the diastereoselection that could be achieved in the preparation of β-amino alcohols and 1,2-diols.

O-Protection of the cyanohydrins mainly involved the use of trimethylsilyl derivatives which can be formed without significant racemization.[14] The ethoxyethyl protecting group was used in a limited number of experiments. It was found that higher yields of the protected cyanohydrins were obtained if trifluoroacetic acid was used instead of hydrochloric acid as recommended by the original workers.[15]

Preparation of β-Amino Alcohols

The simplest route to β-amino alcohols involves direct reduction with lithium aluminium hydride of the unprotected cyanohydrin. This method was exemplified by a preparation (Scheme 1) of the β-blocker pronethalol (3). The cyanohydrin from 2-naphthaldehyde was obtained with 70% e.e., the (*R*)-enantiomer predominating. Reduction with lithium aluminium hydride followed by reaction with acetone and hydrogen over platinum gave pronethalol with the (*R*)-enantiomer in excess, e.e. 66%. Thus little racemization had occurred during the two steps.

[8] Becker, W., Freund, H., and Pfeil, E., *Angew, Chem. Int. Ed. Engl.*, 1965, **4**, 1079; Effenberger, F., Ziegler, T., and Förster, S., *Angew. Chem., Int. Ed. Engl.*, 1987, **26**, 458; Becker, W., and Pfeil, E., *J. Am. Chem. Soc.*, 1966, **88**, 4299.

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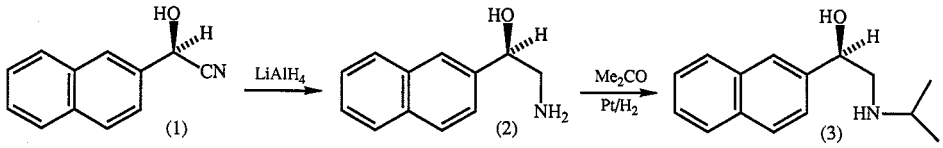
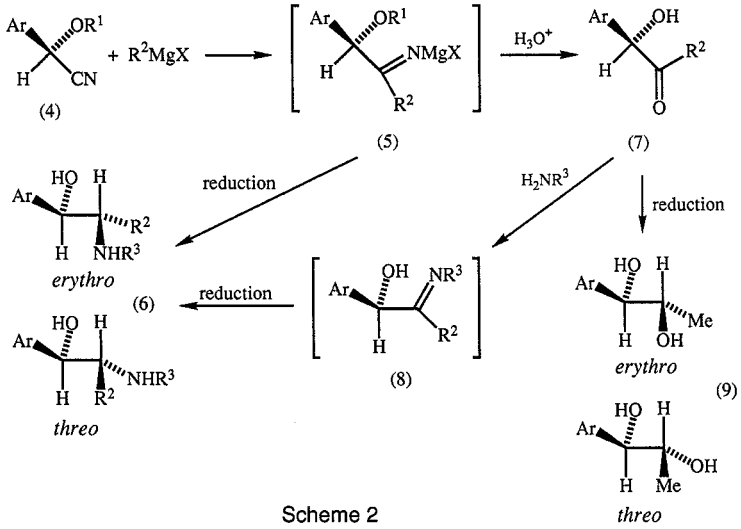


Scheme 1

Preparation of β-amino alcohols related to ephedrine involves the introduction of a second chiral centre at the carbon atom bearing the amino group. We have explored the use of reagents which lead to good diastereoselectivity in the reduction of magnesium imines (5) and also imines (8) prepared from hydroxy ketones (7) (see Scheme 2).



Scheme 2

The magnesium imines were prepared by reactions of the *O*-protected cyanohydrins with Grignard reagents.[1] A range of reagents and experimental conditions was used, and these together with the resulting diastereoisomeric ratios are summarized in Table 1.

All reductions with borohydride reagents gave a preference for the *erythro*-diastereoisomers of the amino alcohols (6) in agreement with the model transition state discussed previously.[3] Use of zinc borohydride in place of sodium borohydride led to a significant improvement in the *erythro* diastereoselectivity (compare entries 3 and 4 with 1 and 2, 9 and 10 with 7 and 8, 14 with 13, and 16 with 15). Reactions at −76° gave no significant improvement in diastereoselection over reactions carried out at ambient temperature (compare entries 1 and 2, 3 and 4, 7 and 8, and 9 and 10). The ratios were found to be insensitive to the substitution pattern in the phenyl ring (compare entires 4, 10 and 12). Surprisingly, work reported by previous workers suggests that the diastereoselectivity is sensitive to temperature and the pattern of ring substitution but not to the replacement of sodium borohydride by zinc borohydride.[3] This work involved only a limited number of examples but the

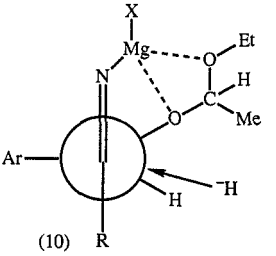
authors suggest that the lack of improvement on using zinc borohydride in their work is due to the fact that the magnesium atom is already heavily chelated to the silyloxy group. We thus prepared the ethoxyethyl-protected cyanohydrin which offers further opportunities for chelation of the magnesium atom to the protecting group [see (10)]. Reduction of this compound with sodium borohydride at −76° gave better stereoselection than for reduction of the silyloxy compound under similar conditions (compare entries 2 and 5). However, further significant improvement was observed on using zinc borohydride (entry 6); this suggests that chelation of zinc to the oxygen atoms in the protecting group is important.

Table 1. Reduction of some *O*-protected magnesium imines (5)

Temperature −76°C, unless otherwise stated. All reactions were carried out in ether and gave yields better than 70%. The results are of two or more experiments. Isomer ratios varied ≤±3% in individual experiments. All new compounds gave satisfactory microanalyses

Entry	Ar	R^1	R^2	Reagent	*erythro/threo*[A]
1[B]	Ph	$SiMe_3$	Me	$NaBH_4$	68/32
2	Ph	$SiMe_3$	Me	$NaBH_4$	69/31
3[B]	Ph	$SiMe_3$	Me	$Zn(BH_4)_2$	79/21
4	Ph	$SiMe_3$	Me	$Zn(BH_4)_2$	83/17
5	Ph	CHMeOEt	Me	$NaBH_4$	81/19
6	Ph	CHMeOEt	Me	$Zn(BH_4)_2$	88/12
7[B]	4-$MeOC_6H_4$	$SiMe_3$	Me	$NaBH_4$	77/23
8	4-$MeOC_6H_4$	$SiMe_3$	Me	$NaBH_4$	76/24
9[B]	4-$MeOC_6H_4$	$SiMe_3$	Me	$Zn(BH_4)_2$	83/17
10	4-$MeOC_6H_4$	$SiMe_3$	Me	$Zn(BH_4)_2$	85/15[C]
11	3,4-$(MeO)_2C_6H_3$	$SiMe_3$	Me	$NaBH_4$	79/21
12	3,4-$(MeO)_2C_6H_3$	$SiMe_3$	Me	$Zn(BH_4)_2$	86/14[C]
13	Ph	$SiMe_3$	Ph	$NaBH_4$	88/12[C]
14	Ph	$SiMe_3$	Ph	$Zn(BH_4)_2$	100/0
15	4-$MeOC_6H_4$	$SiMe_3$	Ph	$NaBH_4$	89/11[C]
16	4-$MeOC_6H_4$	$SiMe_3$	Ph	$Zn(BH_4)_2$	100/0

[A] Ratio determined by ^1H n.m.r. (300 MHz).
[B] Room temperature.
[C] Recrystallization of a sample of this material from toluene/light petroleum afforded the pure *erythro*-isomer (^1H n.m.r.).



(10)

Reductions of the magnesium imines derived from benzoin derivatives (5; R^2 = Ph) all gave higher stereoselectives than of the corresponding methyl derivatives (5; R^2 = Me) (see entries 13–16) in agreement with greater conformational rigidity in the transition states (10) for reductions of these compounds with more bulky substituents.

Several of the *erythro* β-amino alcohols are obtained isomerically pure by recrystallization. When optically active starting cyanohydrin was used the final *erythro* amino alcohols were obtained with the same degree of optical purity which shows that no racemization occurred during the reaction sequence. Thus, for example when the amino alcohol (6; Ar = Ph, R^2 = Me, R^3 = H) was prepared from benzaldehyde cyanohydrin, $[\alpha]_D$ +34·4° (*c*, 5·3 in benzene), e.e. 83% (*R*), it was shown to have $[\alpha]_D^{21}$ −12·8° (*c*, 1·12 in $CHCl_3$) corresponding to an e.e. value of about 90% based on a literature value of $[\alpha]_D$ −14·4° (*c*, 1·0 in $CHCl_3$).[16] Thus the diastereoisomerically pure *erythro* amino alcohols (6; Ar = 4-$MeOC_6H_4$, R^2 = Me and Ph, R^3 = H) prepared from enantiomerically pure 4-methoxybenzaldehyde cyanohydrin[10] were assumed also to be enantiomerically pure.

α-Hydroxy Ketones

Hydrolysis of the magnesium imines (5) gave the hydroxy ketones (7). Reaction of optically pure (*R*) 4-methoxybenzaldehyde cyanohydrin with methylmagnesium iodide gave, after hydrolysis, (*R*)-(−)-1-hydroxy-1-(4-methoxyphenyl)propan-2-one (7; Ar = 4-$MeOC_6H_4$, R^2 = Me) of >96% e.e. Similarly (*R*)-(−)-4-methoxybenzoin (7; Ar = 4-$MeOC_6H_4$, R^2 = Ph) was obtained by reaction with phenylmagnesium bromide. Benzoin (7; Ar = Ph, R^2 = Ph) and 1-hydroxy-1-phenylpropan-2-one (7; Ar = Ph, R^2 = Me) were prepared with e.e. >80% (*R*) from benzaldehyde cyanohydrin of e.e. 83% (*R*).

N-Substituted β-Amino Alcohols

1-Hydroxy-1-phenylpropan-2-one was converted into imines (8; Ar = Ph, R^2 = Me) by reactions with methylamine and benzylamine. The imines were reduced *'in situ'* with sodium and zinc borohydrides, and the ratios of resulting diastereoisomers are summarized in Table 2.

As with reductions of magnesium imines (see Table 1), zinc borohydride gave higher *erythro* selectivities than sodium borohydride (compare entries

Table 2. Reductions of imines (8; Ar = Ph, R^2 = Me) derived from 1-hydroxy-1-phenylpropan-2-one

Yields were better than 75% for all the reactions

Entry	R^3	Reagent	Conditions	*erythro/threo*
17	Me	$NaBH_4$	MeOH, 10°	70/30
18	Me	$NaBH_4$	ether, 10°	76/24
19	Me	$NaBH_4$	ether, −76°	82/18
20	Me	$Zn(BH_4)_2$	ether, 10°	91/9
21	Me	$Zn(BH_4)_2$	ether, −76°	97/3
22	CH_2Ph	$NaBH_4$	ether, −76°	80/20
23	CH_2Ph	$Zn(BH_4)_2$	ether, 10°	83/17
24	CH_2Ph	$Zn(BH_4)_2$	ether, −76°	86/14

[16] Stefanovsky, J. N., Spassov, S. L., Kurter, B. J., Balla, M., and Otvos, L., *Chem. Ber.*, 1969, **102**, 717.

20 and 18, 21 and 19, and 24 and 22). The benzyl imines gave slightly lower selectivities than the methyl imines under similar reaction conditions. When 1-hydro-1-phenylpropan-2-one, e.e. 80% (*R*), was reacted with methylamine and reduced with zinc borohydride, ephedrine (6; Ar = Ph, $R^2 = R^3 = Me$) was obtained without loss of optical activity. It should be noted that (*R*) benzaldehyde cyanohydrin of very high optical purity can be obtained by the use of enzymic catalysis.[8]

1,2-Diols

Reductions of 1-hydroxy-1-phenylpropan-2-one (7; Ar = Ph, $R^2 = Me$) or its 1-*O*-trimethylsilyl derivative with borohydride gave predominantly the *erythro*-diols (9). Again *erythro* selectivity was improved by the use of zinc borohydride at low temperature (see Table 3). These selectives are better or equal to those obtained with aluminium hydride derivatives bearing bulky substituents.[17]

Table 3. Reduction of 1-hydroxy-1-phenylpropan-2-one (7; Ar = Ph, R^2 = Me) in ether

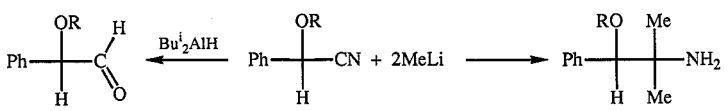
Yields were better than 90% for all the reactions

Entry	Reducing agent	Conditions	*erythro/threo*[A]
25	$NaBH_4$	room temperature	70/30
26	$Zn(BH_4)_2$	room temperature	81/19
27	$Zn(BH_4)_2$	room temperature	85/15[B]
28	$Zn(BH_4)_2$	−76°C	87/13

[A] Ratio determined from ^1H n.m.r. spectra of the acetonide derivatives.
[B] Reaction of the 1-*O*-trimethylsilyl derivative of 1-hydroxy-1-phenylpropan-2-one.

β,β-Dimethyl β-Amino Alcohols

Silyl-protected benzaldehyde cyanohydrin enriched in the (*S*)-enantiomer (e.e. 82%) was reacted (Scheme 3) with methyllithium under conditions described by Amouroux and Axiotis.[18] The amine (13; R = $SiMe_3$) was obtained in good yield (68%) with $[\alpha]_D^{21}$ +39·7° ($CHCl_3$). The enantiomeric excess of this compound was not determined. It is not possible to selectively add one methyl group to the nitrile group by this method and thus it cannot be used in a direct synthesis of ephedrine.



(11) (12) (13) Scheme 3

α-Alkoxy Phenylacetaldehydes (11)

α-Alkoxy aldehydes are frequently unstable compounds and often need to be used without purification.[15] They are of significant interest as synthetic

[17] Bowlus, S. B., and Katzenellenbogen, J. A., *J. Org. Chem.*, 1974, **39**, 3309.
[18] Amouroux, R., and Axiotis, G. P., *Synthesis*, 1981, 270.

intermediates[19] and thus the preparation of these compounds by direct reduction of the protected cyanohydrins was studied. Reduction (Scheme 3) of the *O*-t-butyldimethylsilyl (12; R = Bu^tMe_2Si) and *O*-ethoxyethyl (12; R = CHMeOEt) derivatives of benzaldehyde cyanohydrin with diisobutylaluminium hydride at −76° gave the alkoxy aldehydes (11) in acceptable yields (60 and 74%). The t-butyldimethylsilyloxy aldehyde was also prepared by reduction of a sample of the corresponding 2-*O*-silyl derivative of optically pure methyl (*R*)-2-hydroxy-2-phenylacetate. The optical rotation of the semicarbazide of the products prepared from the optically pure phenylacetate was $[\alpha]_D$ +81·7° whereas that prepared from the nitrile (e.e. 68%) was $[\alpha]_D$ +66·8°. Thus it is probable that no loss of optical activity occurs under the reaction conditions although the enantiomeric purity of the compounds was not directly established. Similarly, reduction of the 2-*O*-ethoxyethyl derivative of (*R*)-2-hydroxy-2-phenylacetate gave the aldehyde (11; R = CHMeOEt). The optical rotation of the two samples again suggested that no racemization had occurred. The methoxy-substituted compound was also shown to reduce smoothly to the aldehyde (11; R = Me) without loss of activity.

Experimental

General

General conditions were as described previously.[9]

4-Methoxybenzaldehyde, 3,4-dimethoxybenzaldehyde, and methyl (*R*)-2-hydroxy-2-phenylacetate were purchased from Aldrich Chemical Company. Zinc borohydride was prepared by the method of Gensler *et al.*[20]

Enantiomeric excesses for cyanohydrins and alcohols were determined by reaction with (*R*)- or (*S*)-cyhalothrin acid as described previously.[10]

2-Hydroxy-2-(2-naphthyl)acetonitrile (1)

Reaction of 2-naphthaldehyde with hydrogen cyanide in the presence of (*S,S*)-cyclo(phenylalanylhistidyl)[10] gave the cyanohydrin (1) as a yellow solid (83%), m.p. 87–104° (from ether/light petroleum), $[\alpha]_D^{19}$ +21·2° (*c*, 0·654 in $CHCl_3$). ν_{max} (Nujol) 3420s, 2250w cm^{-1}. ^1H n.m.r. δ (90 MHz) 2·65, br s, 1H, OH; 5·72, s, 1H, CH; 7·5–7·7, m, 3H, ArH; 7·8–8·0, m, 4H, ArH.

The enantiomeric excess was shown to be 70% by esterification with (+)-cyhalothrin acid.[10] (*R*)-(+)-Cyhalothrin ester: ^1H n.m.r. δ (300 MHz) (1′*R*,2*R*,3′*R*)-isomer 1·33, s, 3H, CH_3; 1·35, s, 3H, CH_3; 1·97, d, *J* 8·3 Hz, 1H, H1′; 2·24, br t, *J* 8·3 Hz, 1H, H3′; 6·53, s, 1H, CH; 6·84, br d, *J* 9·0 Hz, 1H, H1″; 7·5–7·7, m, 3H, ArH; 7·8–8·0, m, 4H, ArH; (1′*R*,2*S*,3′*R*)-isomer 1·22, s, 3H, CH_3; 1·28, s, 3H, CH_3; 2·06, d, *J* 8·3 Hz, 1H, H1′; 2·24, br t, *J* 8·3 Hz, 1H, H3′; 6·59, s, 1H, CH; 6·84, br d, *J* 9·0 Hz, 1H, H1″; 7·5–7·7, m, 3H, ArH; 7·8–8·0, m, 4H, ArH.

2-Amino-1-(2-naphthyl)ethanol (2)

A solution of 2-hydroxy-2-(2-naphthyl)acetonitrile (1) (0·37 g, 2 mmol) {$[\alpha]_D^{21}$ +21·2° (*c*, 0·654 in $CHCl_3$); e.e. 70%} in dry ether (3 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (0·17 g, 4·5 mmol) in ether (10 ml). The mixture was heated under reflux for 2 h and then cooled to 4°. Water (1 ml), 10% sodium hydroxide solution (2 ml), and water (2 ml) were successively added to the cooled mixture. The ether was decanted,

[19] Vinson, W. A., Prickett, K. S., Sphahic, B., and Ortiz de Montellano, P. R., *J. Org. Chem.*, 1983, **48**, 4661.

[20] Gensler, W. J., Johnson, F., and Sloan, A. D. B., *J. Am. Chem. Soc.*, 1960, **82**, 6074.

and the granular inorganic residue washed several times with more ether. The combined ether solutions were washed with water, dried ($MgSO_4$), and concentrated under vacuum to give 2-amino-1-(2-naphthyl)ethanol (2) as a white solid (0·33 g, 87%). Recrystallization of this material from ether afforded a powder, m.p. 115–118° (lit.[3] 118°), $[\alpha]_D^{20}$ −23·8° (*c*, 0·322 in EtOH). ν_{max} (Nujol) 3400–2200s(br), 3350m, 3280m, 1600m, 1070m, 820m, 740m cm^{-1}. ^1H n.m.r. δ [90 MHz; $CDCl_3/(CD_3)_2SO$] 2·3–3·3, 5H, CH_2, NH_2, OH; 4·79, m, 1H, CH; 7·4–7·6, m, 3H, ArH; 7·7–7·9, m, 4H, ArH.

2-(Isopropylamino)-1-(2-naphthyl)ethanol (Pronethalol) (3)

A mixture of 2-amino-1-(2-naphthyl)ethanol (2) (0·3 g, 1·6 mmol), ethanol (10 ml), acetone (10 ml) and platinum(IV) dioxide (50 mg) was stirred under hydrogen at room temperature and pressure for 16 h. The mixture was filtered and the filtrate concentrated to give a white solid (0·24 g). This solid was recrystallized from ethyl acetate/light petroleum to yield 2-(isopropylamino)-1-(2-naphthyl)ethanol (3) as a powder (0·15 g, 41%), m.p. 93–95° [lit.[21] racemic 106°; lit.[22] (*R*) 102°, (*S*) 108–109°] $[\alpha]_D^{21}$ −18·7° (*c*, 0·402 in EtOH) [lit.[23] (*R*) $[\alpha]_D^{20}$ −17·3° (*c*, 0·98 in EtOH), (*S*) $[\alpha]_D^{21}$ +28·4° (*c*, 0·99 in EtOH)]. ν_{max} (Nujol) 3600–2200s(br), 1600w, 1170m, 1075m, 1060m, 890m, 820m, 745m, 735m cm^{-1}. ^1H n.m.r. δ (90 MHz; $CDCl_3/D_2O$) 1·07, d, *J* 6·2 Hz, 6H, 2×CH_3; 2·6–3·1, m, 3H, C**H**$(CH_3)_2$, CH_2; 4·85, m, 1H, **CH**CH_2; 7·4–7·5, m, 3H, ArH; 7·8–7·9, m, 4H, ArH.

2-Hydroxy-2-phenylacetonitrile (4; Ar = Ph, R^1 = H)

To an efficiently stirred solution of benzaldehyde (20 ml, 0·198 mol) in toluene (85 ml) at 15° were added (*S,S*)-cyclo(phenylanalylhistidyl) (600 mg, 2·0 mmol) and hydrogen cyanide (20 ml, 500 mmol). The resulting mixture was stirred at −15° for 26 h and then poured into an equal volume of ether. The precipitated peptide catalyst was removed by filtration, and the ether/toluene filtrate was evaporated to give a pale yellow oil (24·6 g). This material was shown to be cyanohydrin (87%) and aldehyde (13%) by ^1H n.m.r. $[\alpha]_D^{21}$ (corrected for chemical conversion) +34.4° (*c*, 5·3 in C_6H_6). Enantiomeric excess was established as 83% by esterification with (*R*)-cyhalothrin acid. ν_{max} (film) 3400s(br) 2250w cm^{-1}. ^1H n.m.r. δ (300 MHz) 4·03, br s, 1H, OH, 5·50, s, 1H, CH; 7·35–7·61, complex multiplet, 5H, ArH. Massspectrum *m/z* 133 (M, 23%), 132 (15), 116 (9), 115 (12), 106 (76), 105 (90), 79 (12), 78 (20), 77 (100), 52 (11), 51 (49), 50 (22).

(*R*)-(+)-Cyhalothrin ester: ^1H n.m.r. δ (300 MHz) (1′*R*,2*R*,3′*R*)-isomer 1·34, s, 3H, CH_3; 1·35, s, 3H, CH_3; 2·04, d, *J* 8·4 Hz, 1H, H1′; 2·24, br t, *J* 8·4 Hz, 1H, H3′; 6·38, s, 1H, CH; 6·84, dd, *J* 9·2, 0·8 Hz, 1H, H1″; 7·45–7·55, m, 5H, ArH; (1′*R*,2*S*,3′*R*)-isomer 1·23, s, 3H, CH_3; 1·29, s, 3H, CH_3; 2·04, d, *J* 8·4 Hz, 1H, H1′; 2·24, br t, *J* 8·4 Hz, 1H, H3′; 6·43, s, 1H, CH; 6·84, dd, *J* 9·2, 0·8 Hz, 1H, H1″; 7·45–7·55, m, 5H, ArH.

The racemic cyanohydrin was prepared as an oil (yield 96%) by the method of Vogel.[13] The cyhalothrin ester of this material showed two baseline-resolved peaks of equal intensity, one for each diastereomeric ester (at 300 MHz).

2-Phenyl-2-(trimethylsilyloxy)acetonitrile (4; Ar = Ph, R^1 = $SiMe_3$)

Trimethylsilyl chloride (21·1 ml, 0·17 mol), imidazole (14·2 g, 0·28 mol) and a catalytic amount of 4-dimethylaminopyridine were added successively to a stirred solution of (*R*)-2-hydroxy-2-phenylacetonitrile [87% by mass, e.e. 83% (*R*), 20·7 g of the mixture] in dry ether (200 ml) under an atmosphere of nitrogen. Stirring was continued overnight and water was added; the ether layer was separated, washed again with water, and saturated sodium metabisufite, and dried ($MgSO_4$). Evaporation of the solvent afforded 2-phenyl-2-(trimethylsilyloxy)acetonitrile as a pale yellow oil in a quantitative yield, $[\alpha]_D^{20}$ +25·9° (*c*, 2·486 in $CHCl_3$), b.p. 95° (oven)/0·1 mm Hg (lit.[24] 253–254°). ν_{max} (film) 2960m, 1490m,

[21] Howe, R., Growther, A. F., Stephenson, J. S., Rao, B. S., and Smith, L. H., *J. Med. Chem.*, 1968, **11**, 1000.
[22] ICI Australia provided data.
[23] ICI Ltd, Belg. Pat. 622,487 (1963) (*Chem. Abstr.*, 1964, **60**, 478e).
[24] Neef, H., and Müller, R., *J. Prakt. Chem.*, 1973, **315**, 367.

1450m, 1260s, 1195m, 1110s, 1095s, 1070s, 870s, 830s, 750m, 700 cm^{-1}. ^1H n.m.r. δ (200 MHz) 0·21, s, 9H, $Si(CH_3)_3$; 5·35, s, 1H, CH; 7·2–7·4, m, 5H, ArH. Mass spectrum *m/z* 205 (M, 40%), 191 (100), 116 (61), 106 (12), 105 (51), 89 (30), 84 (98), 77 (20), 73 (24).

This compound was also prepared from 2-hydroxy-2-phenylacetonitrile enriched with the (*S*)-isomer [e.e. 82% (*S*)] in good yield (82%), $[\alpha]_D^{20}$ −25·4° (*c*, 5·39 in $CHCl_3$).

The racemic material was also prepared as an oil in good yield (88%), the above method being used.

2-(t-Butyldimethylsilyloxy)-2-phenylacetonitrile (4; Ar = Ph, R^1 = $SiBu^tMe_2$)

Imidazole (1·0 g, 15 mmol) was added to a stirred solution of crude 2-hydroxy-2-phenylacetonitrile [79% by mass, e.e. 68% (*R*); 1·70 g, 10 mmol] and t-butyldimethylsilyl chloride (2·00 g, 13 mmol), and the mixture protected from moisture with a drying tube ($CaCl_2$). The white suspension was stirred at ambient temperature overnight. Water was added; and organic phase was separated and washed with 1 M hydrochloric acid, saturated sodium hydrogen sulfite solution (to remove aldehyde impurities present in the starting α-hydroxy nitrile), saturated sodium hydrogen carbonate solution, and water. After drying ($MgSO_4$), the solution was concentrated under vacuum to afford a clear liquid. Purification by flash chromatography (benzene) gave 2-(t-butyldimethylsilyloxy)-2-phenylacetonitrile (2·06 g, 83%) (Found: C, 67·7; H, 8·5. Calc. for $C_{14}H_{21}NOSi$: C, 68·0; H, 8·6%). $[\alpha]_D^{20}$ +20·9° (*c*, 0·880 in C_6H_6) {lit.[14] $[\alpha]_D^{20}$ +16° (*c*, 1·0 in $CHCl_3$)}. ν_{max} (film) 2940s, 2910s, 2870m, 2240w, 1600w, 1495s, 1470m, 1460m, 1450m, 1255s, 1195s, 1115s, 1100s, 1070s, 940m, 845s, 780s, 740m, 700s, 675m cm^{-1}. ^1H n.m.r. δ (300 MHz) 0·15, s, 3H, CH_3; 0·23, s, 3H, CH_3; 0·94, s, 9H, $C(CH_3)_3$; 5·52, s, 1H, CH; 7·30–7·50, m, 5H, ArH. Mass spectrum *m/z* 232 (M−CH_3, 2%), 192 (5), 191 (16), 190 (100), 116 (14), 84 (23).

2-(1-Ethoxyethoxy)-2-phenylacetonitrile (4; Ar = Ph, R^1 = CHMeOEt)

Method 1.—Trifluoroacetic acid (0·3 ml) was added to a stirred solution of 2-hydroxy-2-phenylacetonitrile [71% by mass, e.e. 85% (*R*); 1·31 g, 7·0 mmol] and ethyl vinyl ether (2·0 ml, 20 mmol) in dry methylene chloride (30 ml) kept at 0–5°. The mixture was allowed to warm to room temperature and was stirred overnight before being washed with saturated sodium hydrogen carbonate solution, saturated sodium metabisulfite solution, and finally water. The organic solution was then dried (Na_2SO_4) and evaporated to afford 2-(1-ethoxyethoxy)-2-phenylacetonitrile as a clear liquid (1·29 g, 90%), $[\alpha]_D^{20}$ +51·3° (*c*, 0·599 in $CHCl_3$). ν_{max} (film) 2250w, 1500m, 1445s, 1390s, 1145s, 1115s, 1085s, 1055s, 1030s, 955s, 935s, 885s, 760s, 700s cm^{-1}. ^1H n.m.r. showed two isomers: δ (300 MHz) 1·22, t, *J* 7·0 Hz, 3H, CH_2CH_3; 1·25, t, *J* 7·0 Hz, 3H, CH_2CH_3; 1·41, d, *J* 5·4 Hz, 3H, $CHCH_3$; 1·47, d, *J* 5·4 Hz, 3H, $CHCH_3$; 3·5–3·8, m, 4H, 2×CH_2; 4·91, q, *J* 5·4 Hz, 1H, OCHO; 5·11, q, *J* 5·4 Hz, 1H, OCHO; 5·42, s, 1H, CHCN; 5·54, s, 1H, CHCN; 7·4–7·6, m, 10H, ArH. Mass spectrum *m/z* 160 (2%), 159 (16), 133 (4), 117 (17), 116 (100), 105 (15), 89 (13), 77 (12), 73 (72). These spectroscopic data are in agreement with those reported in the literature for the ethoxyethoxyacetonitrile.[15] If necessary this material could be purified by flash chromatography (benzene). However, in most cases the crude product was of sufficient purity to be used without further purification.

Method 2.—A mixture of 2-hydroxy-2-phenylacetonitrile [6·16 g, 0·046 mol; e.e. 82% (*S*)] and ethly vinyl ether (3·3 g, 0·046 mol) was treated with concentrated hydrochloric acid (0·47 ml), and the resulting mixture was stirred overnight at room temperature. Chloroform (50 ml) was added and the organic layer was washed with a dilute sodium bicarbonate solution followed by a saturated solution of sodium metabisulfite and then water. The organic layer was dried ($MgSO_4$) and evaporated to yield a clear liquid. Bulb-to-bulb distillation (90°/0·1 mm) afforded pure 2-(1-ethoxyethoxy)-2-phenylacetonitrile (7·5 g, 79%), $[\alpha]_D^{19}$ +49·1° (*c*, 1·631 in $CHCl_3$). This material had identical spectroscopic features to those reported above.

Racemic 2-(3,4-Dimethoxyphenyl)-2-hydroxyacetonitrile (4; Ar = 3,4-$(MeO)_2C_6H_3$, R^1 = H)

To a stirred solution of powdered sodium cyanide (3·1 g, 62·5 mmol) and 3,4-dimethoxybenzaldehyde (10·4 g, 62·5 mmol) in water (100 ml) was added a saturated solution of sodium metabisulfite [prepared by dissolving of sodium metabisulfite (31·2 g)

in water (42 ml) at 0°]. The solution was stirred for 40 min at 10° and extracted with dichloromethane. The combined organic extracts were dried ($MgSO_4$) and evaporated to give a pale yellow solid. Recrystallization of this material from dichloromethane/light petroleum afforded *2-(3,4-dimethoxyphenyl)-2-hydroxyacetonitrile* as a white powder (10·5 g, 86%), m.p. 110–112° (Found: C, 62·2; H, 5·9; N, 7·2. $C_{10}H_{11}NO_3$ requires C, 62·2; H, 5·7; N, 7·2%). ν_{max} (Nujol) 3440s(br), 1600m, 1510m, 1450s, 1260s, 1240s, 1140s, 1020s, 850s, 808m, 760s cm^{-1}. ^1H n.m.r. δ (300 MHz) 2·51, br s, 1H, OH; 3·94, s, 3H, OCH_3; 3·95, s, 3H, OCH_3; 5·53, s, 1H, CH, 6·9–7·5, m, 3H, ArH. Mass spectrum *m/z* 193 (M, 68%), 176 (39), 166 (100), 165 (54), 162 (27), 151 (17), 95 (28), 79 (16), 77 (25), 65 (13), 63 (12), 51 (21).

Racemic 2-(3,4-Dimethoxyphenyl)-2-(trimethylsilyloxy)acetonitrile (4; Ar = 3,4-(MeO)$_2$C$_6$H$_3$, R^1 = SiMe$_3$)

Trimethylsilyl chloride (0·94 ml, 7·45 mmol), imidazole (0·6 g, 8·7 mmol) and a catalytic amount of 4-dimethylaminopyridine were added successively to a stirrred solution of 2-(3,4-dimethoxyphenyl)-2-hydroxyacetonitrile (1·2 g, 6·21 mmol) in dry ether (30 ml) under an atmosphere of nitrogen. Stirring was continued overnight and water was added; the ether layer was separated, washed again with water, and dried ($MgSO_4$). Evaporation of the solvent afforded 2-(3,4-dimethoxyphenyl)-2-(trimethylsilyloxy)acetonitrile as a clear oil in quantitative yield. ν_{max} (film) 1600m, 1595s, 1500s, 1450s, 1410m, 1245s, 1142s, 1130s, 1070s, 1010s, 850s, 835s, 750m cm^{-1}. ^1H n.m.r. δ (200 MHz) 0·12, s, 9H, $OSiMe_3$; 3·88, s, 3H, OCH_3; 3·90, s, 3H, OCH_3; 5·42, s, 1H, CH; 6·85–7·11, m, 3H, ArH. Mass spectrum *m/z* 265 (M, 39%), 250 (24), 176 (100), 166 (28), 165 (17), 135 (43), 95 (10), 77 (10), 75 (13), 73 (26).

2-(4-Methoxyphenyl)-2-(trimethylsilyloxy)acetonitrile (4; Ar = 4-MeOC$_6$H$_4$, R^1 = SiMe$_3$)

Trimethylsilyl chloride (0·94 ml, 7·45 mmol), imidazole (0·6 g, 8·7 mmol) and a catalytic amount of 4-dimethylaminopyridine were added successively to a stirred solution of 2-hydroxy-2-(4-methoxyphenyl)acetonitrile (1·0 g, 6·21 mmol) in dry ether (35 ml) under an atmosphere of nitrogen. Stirring was continued overnight and water was added; the ether layer was separated and dried ($MgSO_4$). Evaporation of the solvent afforded 2-(4-methoxyphenyl)-2-(trimethylsilyloxy)acetonitrile as a clear oil in quantitative yield, $[\alpha]_D^{19}$ +23·1° (*c*, 0·2516 in $CHCl_3$) {lit.[14] $[\alpha]_D^{20}$ +22° (*c*, 1·0 in $CHCl_3$)}. ν_{max} (film) 1600s, 1510s, 1465m, 1308m, 1250s, 1200m, 1090s, 945m, 875m, 840s, 795m, 755m cm^{-1}. ^1H n.m.r. δ (200 MHz) 0·14, s, 9H, $OSiMe_3$; 3·79, s, 3H, OMe; 5·23, s, 1H, CH; 6·68, 6·73, 7·15 and 7·20, 4H, aromatic AA′BB′ system. Mass spectrum *m/z* 235 (M, 32%), 220 (51), 146 (100), 136 (13), 135 (27).

2-Amino-1-phenylpropan-1-ol (6; Ar = Ph, R^2 = Me, R^3 = H)

A solution of 2-phenyl-2-(trimethylsilyloxy)acetonitrile [0·41 g, 2 mmol; e.e. 82% (*S*)] in dry ether (3 ml) was added to a solution of methylmagnesium iodide (0·3 mmol) in ether (10 ml) under nitrogen. The mixture was stirred for 1 h at room temperature and then a suspension of sodium borohydride (0·1 g, 2·6 mmol) in ethanol (3 ml) was added dropwise. The mixture was stirred for 1 h and then 1 M hydrochloric acid (10 ml) added. After 30 min, the aqueous layer was separated and the organic layer extracted with more 1 M hydrochloric acid solution (3 ml). The combined acidic aqueous layers were made alkaline (pH 10) with 10% sodium hydroxide solution, then extractd with chloroform. The combined chloroform extracts were dried ($NaSO_4$) and evaporated to afford 2-amino-1-phenylpropan-1-ol as an oil (214 mg, 71%), $[\alpha]_D^{20}$ −2·0° (*c*, 0·20 in EtOH). ν_{max} (film) 3600–2400s(br) cm^{-1}. ^1H n.m.r. showed both isomers (*erythro/threo* 68 : 32): δ (300 MHz) *erythro* 0·92, d, *J* 6·5 Hz, 3H, CH_3; 2·62, br s, 3H, NH_2, OH; 3·06, m, 1H, H2; 4·45, d, *J* 4·7 Hz, 1H, H1; 7·27, m, 5H, ArH; *threo* 0·91, d, *J* 6·4 Hz, 3H, CH_3; 2·62, br s, 3H, NH_2, OH; 2·94, m, 1H, H2; 4·16, d, *J* 6·8 Hz, 1H, H1; 7·27, m, 5H, ArH. Mass spectrum *m/z* 152 (M, 5%), 132 (18), 118 (14), 117 (11), 107 (34), 105 (34), 105 (32), 91 (20), 85 (15), 84 (18), 79 (74), 78 (25), 77 (100), 52 (15), 51 (52). These spectroscopic data agree well with literature values.[25a]

[25] Buckingham. J., and Donaghy, S. M., (Eds) 'Dictionary of Organic Compounds' 5th Edn (*a*) Vol. 1, p. 315; (*b*) Vol. 3, p. 3223; (*c*) Vol. 5, p. 3728 (Chapman & Hall: London 1982).

Similar reactions with the (ethoxyethoxy)acetonitrile (4; Ar = Ph, R^1 = CHMeOEt) gave mixtures of *erythro*- and *threo*-2-amino-1-phenylpropan-1-ol as summarized in Table 1.

Racemic and Optically Active 2-Amino-1-(4-methoxyphenyl)propan-1-ol (6; Ar = 4-MeOC$_6$H$_4$, R^2 = Me, R^3 = H)

Reaction of the trimethylsilyl derivative of racemic 4-methoxybenzaldehyde cyanohydrin with methylmagnesium iodide followed by reduction with sodium borohydride and hydrolysis as described above afforded *2-amino-1-(4-methoxyphenyl)propan-1-ol* as a viscous oil (1·3 g, 75%) which solidified on standing, m.p. 98–101° (Found: C, 66·5; H, 8·7; N, 7·6. $C_{10}H_{15}NO_2$ requires C, 66·3; H, 8·3; N, 7·7%). ν_{max} (Nujol) 3140m(br), 1380m, 965m, 705s cm^{-1}. ^{1}H n.m.r. showed both isomers (*erythro/threo* 77 : 23): δ (300 MHz) *erythro* 0·84, d, *J* 6·65 Hz, 3H, CH_3; 2·35, br s, 3H, NH_2, OH; 3·94, m, 1H, H2; 3·77, s, 3H, OMe; 4·34, d, *J* 4·98, Hz, 1H, H1; 6·81, 6·85, 7·14 and 7·17, aromatic AA′BB′ system; *threo* 0·93, d, *J* 6·44 Hz, 3H, CH_3; 2·35, br s, 3H, NH_2, OH; 2·88, m, 1H, H2; 3·77, s, 3H, OMe; 4·07, d, *J* 7·29 Hz, 1H, H1; 6·81, 6·85, 7·14 and 7·17 aromatic AA′BB′ system. Mass spectrum *m/z* 181 (M, 8%), 138 (13), 137 (100), 136 (13), 135 (31), 109 (46), 94 (44), 92 (12), 78 (13), 77 (68), 66 (53), 65 (29), 64 (11), 63 (12), 51 (20).

A reduction of the protected cyanohydrin was carried out with zinc borohydride at–76° and gave *erythro*- and *threo*-isomers in ratio 85 : 15. Recrystallization of a sample of this material from toluene/light petroleum afforded a sample of the pure *erythro*-stereoisomer, m.p. 116–118°. A similar reaction procedure on a sample of optically pure (*R*)-cyanohydrin trimethylsilyl ether gave pure *erythro* (1*R*,2*S*)-2-amino-1-(4-methoxyphenyl)propan-1-ol, m.p. 97–100° $[\alpha]_D^{20}$ –7·13° (*c*, 0·56 in $CHCl_3$).

Racemic 2-Amino-1-(3,4-dimethoxyphenyl)propan-1-ol (6; Ar = 3,4-(MeO)$_2$C$_6$H$_3$, R^2 = Me, R^3 = H)

Reaction with MeMgX of the trimethylsilyl ether of the racemic cyanohydrin from 3,4-dimethoxybenzaldehyde, followed by reduction of the magnesium imine *'in situ'* by sodium borohydride at –76° and subsequent acid hydrolysis afforded a viscous oil (0·73 g, 82%) which solidified on standing to give the title compound, m.p. 110–130°. ν_{max} (Nujol) 3180m(br), 1600w, 1515m, 1445s, 1365m, 1240m, 1128m cm^{-1}. ^{1}H n.m.r. showed both isomers (*erythro/threo* 79 : 21): δ (300 MHz) *erythro* 0·98, d *J* 6·50 Hz, 3H, CH_3; 2·45, br s, 3H, NH_2, OH; 3·04, m, 1H, H2; 3·86, s, 6H, 2×OMe; 4·36, d, *J* 5·16, Hz; 1H, H1; 6·80–6·86, m, 3H, ArH; *threo* 0·89, d, *J* 6·48 Hz, 3H, CH_3; 2·45, br s, 3H, NH_2, OH; 2·94, m, 1H, H2; 3·86, s, 6H, 2×OMe; 4·10, d, *J* 6·91, Hz, 1H, H1; 6·8–6·86, m, 3H, ArH. Mass spectrum *m/z* 211 (M, 12%), 169 (10), 168 (100), 167 (69), 166 (22), 165 (22), 139 (93), 137 (15), 124 (28), 123 (11), 107 (17), 108 (27), 95 (15), 93 (10), 79 (12), 77 (22), 65 (21), 53 (21), 51 (14).

Recrystallization from toluene/light petroleum of a sample of material from a reduction with zinc borohydride at –76° (entry 12, Table 1) afforded the pure *erythro*-stereoisomer, m.p. 125–127°, whose ^{1}H n.m.r. spectroscopic data were in good agreement with literature data.[3]

Racemic and Optically Active 2-Amino-1-(4-methoxyphenyl)-2-phenylethanol (6; Ar = 4-MeOC$_6$H$_4$, R^2 = Ph, R^3 = H)

Reaction of the trimethylsilyl derivative of 4-methoxybenzaldehyde cyanohydrin with phenylmagnesium bromide followed by reduction of the magnesium imine with sodium borohydride at –76° and subsequent acid hydrolysis (entry 15, Table 1) afforded *2-amino-1-(4-methoxyphenyl)-2-phenylethanol* as a viscous oil (2·4 g, 78%) which solidified on standing, m.p. 112–115° (Found: C, 73·6; H, 7·2; N, 5·8. $C_{15}H_{18}O_2N$ requires C, 73·7; H, 7·4; N, 5·7%). ν_{max} (Nujol) 3180m(br) 1606w, 1510w, 1370m, 1245m, 1030m, 980m, 695m cm^{-1}. ^{1}H n.m.r. showed both isomers (*erythro/threo* 89 : 11): δ (300 MHz) *erythro* 2·89, br s, 3H, NH_2, OH; 3·78, s, 3H, OMe; 4·10, d, *J* 6·46 Hz, 1H, H2; 4·66, d, *J* 6·46 Hz, 1H, H1; 6·74, 6·77, 7·05 and 7·08, aromatic AA′BB′ system; 7·27, m, 5H, ArH; *threo* 2·89, br s, 3H, NH_2, OH; 3·75, s, 3H, OMe; 3·95, d, *J* 6·84 Hz, 1H, H2; 4·66, d, *J* 6·8 Hz, 1H, H1; 6·80,

6·84, 7·12 and 7·15, aromatic AA′BB′ system; 7·27, m, 5H, ArH. Mass spectrum *m/z* 244 (M, 0·3%), 107 (13), 106 (100), 79 (15), 77 (11).

Recrystallization of a sample of this material from toluene/light petroleum afforded the pure *erythro*-stereoisomer, m.p. 116–118°.

A similar reaction sequence on the trimethylsilyl derivative of the (*R*)-cyanohydrin and involving reduction with zinc borohydride at −76° (entry 16, Table 1) gave material which, after recrystallization from toluene/light petroleum, had m.p. 109–111°, $[\alpha]_D^{20}$ −8·8° (*c*, 1·44 in $CHCl_3$).

Racemic and Optically Active 2-Amino-1,2-diphenylethanol (6; Ar = R^2 = Ph, R^3 = H)

Reaction of the trimethylsilyl derivative of benzaldehyde cyanohydrin with phenylmagnesium bromide followed by reduction with sodium borohydride at −76° and subsequent hydrolysis gave a pale yellow solid (0·82 g, 77%), m.p. 155–157°. ν_{max} (Nujol) 3125m(br), 1600w, 1365m, 948m, 695s cm^{-1}. ^1H n.m.r. showed both isomers (*erthro/threo* 88 : 12): δ (200 MHz) *erythro* 1·9, br s, 3H, NH_2, OH; 4·17, d, *J* 6·36 Hz, 1H, H2; 4·75, d, *J* 6·30 Hz, 1H, H1; 7·27, m, 10H, ArH; *threo* 1·9, br s, 3H, NH_2, OH; 3·97, d, *J* 6·52 Hz, 1H, H2; 4·67, d, *J* 6·53 Hz, 1H, H1; 7·27, m, 10H, ArH. Mass spectrum *m/z* 106 (100%), 105 (42), 104 (67), 103 (25), 79 (18), 78 (17), 77 (51), 76 (12), 51 (25), 30 (12).

Recrystallization of a sample of this material from toluene/light petroleum afforded the pure *erythro*-stereoisomer, m.p. 162–165°, whose ^1H n.m.r. spectroscopic data agreed well with literature values.[16]

A similar reaction on material derived from benzaldehyde cyanohydrin, $[\alpha]_D^{20}$ +34·4° (*c*, 5·3 in benzene) {e.e. 83% (*R*)}, and involving reduction with zinc borohydride at −76° (entry 14, Table 1) gave pure *erythro*-isomer, m.p. 151–153°, $[\alpha]_D^{19}$ −12·8° (*c*, 1·12 in $CHCl_3$) {lit.[16] $[\alpha]_D$ −14·4° (*c*, 1·21 in $CHCl_3$) for the optically pure (1*R*,2*S*)-enantiomer}.

1-Hydroxy-1-phenylpropan-2-one (7; Ar = Ph, R^2 = Me)

A solution of (*R*)-2-phenyl-2-(trimethylsiloxy)acetonitrile [20 g, 0·098 mol; optical purity 83% (*R*)] in dry ether (80 ml) was added dropwise to a solution of methylmagnesium iodide (0·196 mol) in ether (140 ml). The resulting mixture was refluxed for 2 h, then cooled to −10°; 2M HCl was added slowly to decompose the imine. The ether layer was separated, washed with water, dried ($MgSO_4$) and evaporated to give pure hydroxy ketone as a yellow oil (12·6 g, 86%), $[\alpha]_D^{19}$ −148·3° (*c*, 1·82 in EtOH) (lit.[25b] $[\alpha]_D$ −157° in EtOH). Enantiomeric excess 80%, by esterification with cyhalothrin acid. ν_{max} (film) 3350s(br), 1700s, 1595w, 1485m, 1440m, 1345s, 1220m, 1160s, 1084s, 1020w, 962w, 840w, 744s, 680s cm^{-1}. ^1H n.m.r. δ (200 MHz) 2·48, s, 3H, CH_3; 4·22, s, 1H, OH; 5·50, s, 1H, CH; 7·3–7·4, m, 5H, ArH. Mass spectrum *m/z* 150 (M, 12%), 133 (17), 121 (55), 107 (98), 105 (75), 79 (100), 77 (93), 51 (32).

The above method was also used to prepare racemic 1-hydroxy-1-phenylpropan-2-one as a yellow oil in good yield (83%). The cyhalothrin ester of this material showed two baseline-resolved peaks at δ 5·97 and 5·99 of equal intensity for the α-CH proton, one for each diastomeric ester, in the ^1H n.m.r. spectrum (300 MHz).

1-Phenyl-1-(trimethylsilyloxy)propan-2-one

Trimethylsilyl chloride (1·86 ml, 14·6 mmol), imidazole (1·1 g, 15·9 mmol) and a catalytic amount of 4-dimethylaminopyridine were added successively to a stirred solution of 1-hydroxy-1-phenylpropan-2-one (7; Ar = Ph, R^2 = Me) (2·0 g, 13·3 mmol) in dry ether (35 ml) under an atmosphere of nitrogen. Stirring was continued overnight, and water was added; the ether layer was separated, washed again with water, and dried ($MgSO_4$). Evaporation of the solvent afforded the trimethylsilyl ether as an oil in quantitative yield. ν_{max} (film) 1700s, 1680m, 1485m, 1440m, 1340s, 1248s, 1210m, 1080s, 1095s, 1060s, 1020m, 870s, 835s, 740s, 695s cm^{-1}. ^1H n.m.r. δ (200 MHz) 0·12, s, OH, $SiMe_3$; 2·09, s, 3H, CH_3; 5·05, s, 1H, H1; 7·31, m, 5H, ArH. Mass spectrum *m/z* 222 (M, 0·9%), 180 (20), 179 (89), 134 (37), 121 (50), 116 (12), 107 (16), 105 (48), 73 (12), 77 (33), 75 (17), 73 (100), 51 (11).

(R)-(–)-1-Hydroxy-1-(4-methoxyphenyl)propan-2-one (7; Ar = 4-MeOC$_6$H$_4$, R^2 = Me)

Reaction of the trimethylsilyl derivative of the optically pure (*R*) 4-methoxybenzaldehyde cyanohydrin with methylmagnesium iodide followed by hydrolysis as described above afforded an oil (0·41 g, 83%), $[\alpha]_D^{18}$ –344° (*c*, 0·213 in $CHCl_3$) {lit.[14] $[\alpha]_D^{20}$ –343° (*c*, 1·0 in $CHCl_3$)}. ν_{max} (film) 3456m(br), 1678s, 1590s, 1511s, 1440m, 1306m, 1256s, 1175s, 1070s, 1031m, 974s, 828s, 753m, 691s, 591s cm^{-1}. ^{1}H n.m.r. δ (200 MHz) 2·03, s, 3H, CH_3; 3·75, s, 3H, OMe; 4·30, s, 1H, OH; 4·96, s, 1H, CH; 6·88, 6·92, 7·20 and 7·25, 4H, aromatic AA′BB′ system. Mass spectrum *m/z* 180 (M, 3%), 131 (10), 135 (100), 77 (11).

Optically Active 2-(1-Ethoxyethoxy)-1,2-diphenylethanone, and 2-Hydroxy-1,2-diphenylethanone [(–)-Benzoin] (7; Ar = R^2 = Ph)

A solution of optically active 2-(2-ethoxyethoxy)-2-phenylacetonitrile {1·0 g, 4·90 mmol; 85% (*R*)} in diethyl ether (15 ml) was added dropwise under nitrogen to phenylmagnesium iodide [prepared from phenyl iodide (0·74 g, 3·59 mmol) and magnesium turnings (0·16 g, 6·62 mmol)] in ether (20 ml). The resulting mixture was refluxed for 1 h and then stirred overnight at room temperature. A citric acid solution (10%) was added and the mixture stirred for 2 h; the ether layer was separated, washed with dilute bicarbonate, dried (Na_2SO_4) and evaporated to yield a pale yellow oil. Column chromatography (silica, benzene eluent) afforded the pure protected benzoin (1·24 g, 90%), $[\alpha]_D$ +31° (*c*, 1·413 in $CHCl_3$). ν_{max} (film) 1680s, 1600m, 1045m, 1178m, 1130s, 1080s, 1050s, 1024m, 975m, 700s cm^{-1}. ^{1}H n.m.r. δ (200 MHz) 1·07 and 1·09, two overlapping triplets, *J* 7·04 Hz, 3H, diastereomeric CH_3; 1·33 and 1·35, two overlapping doublets, *J* 5·28 Hz, 3H, CH_3; 3·34–3·68, m, 2H, CH_2; 4·77–4·98, two overlapping quartets, 1H, CH; 5·95 and 6·03, two singlets, benzylic, 1H, CH; 7·12–7·54, m, 10H, ArH. Mass spectrum *m/z* 105 (12%), 73 (100).

The protected benzoin (0·8 g, 2·8 mmol) was dissolved in chloroform (10 ml), and treated with 2M sulfuric acid. The resulting solution was stirred overnight at room temperature. The chloroform layer was separated, and washed with a saturated solution of sodium bicarbonate, dried (Na_2SO_4) and evaporated to give a viscous oil which slowly crystallized, $[\alpha]_D$ –77° (*c*, 0·356 in Me_2CO). This material was recrystallized from ethanol to give a white solid (0·49 g, 82%), m.p. 123–126° (lit.[26] 133–34°), $[\alpha]_D$ –93·2° (*c*, 0·988 in Me_2CO) suggesting e.e. of 79% {lit.[26] (*R*) $[\alpha]_D$ –118° (*c*, 1·2, in Me_2CO)}. ν_{max} (Nujol) 3350m(br), 1675s, 1595w, 1378m, 700s cm^{-1}. ^{1}H n.m.r. δ (300 MHz) 4·52, br s, 1H, OH; 5·95, s, 1H, CH; 7·26–7·56, m, 10H, ArH. Mass spectrum *m/z* 212 (M, 0·9%), 107 (63), 105 (100), 79 (36), 77 (62), 51 (25).

A similar reaction with the optically active *O*-trimethylsilyl protected cyanohydrin [e.e. 83% (*R*)] afforded (*R*)-(–)-benzoin in a good yield (73%) without any loss of optical purity.

(R)-(–)-2-Hydroxy-2-(4-methoxyphenyl)-1-phenylethanone (7; Ar = 4-MeOC$_6$H$_4$, R^2 = Ph)

Reaction of the trimethylsilyl derivative of the optically pure (*R*) 4-methoxybenzaldehyde cyanohydrin with phenylmagnesium bromide followed by hydrolysis afforded a solid. Recrystallization from ethanol afforded the pure benzoin, (0·22 g, 71%), m.p. 99–102° (lit.[27] 102–103°) $[\alpha]_D^{18}$ –69° (*c*, 6·2143 in Me_2CO) {lit.[27] $[\alpha]_D^{25}$ –73° (*c*, 1 in Me_2CO)}. ν_{max} (Nujol) 3455m, 1678s, 1600s, 1511s, 1450m, 1306m, 1256s, 1175s, 1070m, 1031m, 974s, 828m, 753m, 591m cm^{-1}. ^{1}H n.m.r. δ (200 MHz) 3·74, s, 3H, OMe; 4·4, s, 1H, OH; 6·86, s, 1H, CH; 6·85, 7·22, 7·27 and 7·37, 4H, aromatic AA′BB′ system; 7·4–7·71 and 7·87–7·92, 5H, ArH. Mass spectrum *m/z* 242 (M, 6%), 154 (15), 137 (46), 135 (100), 109 (13), 77 (38).

2-Methylamino-1-phenylpropan-1-ol (Ephedrine) (6; Ar = Ph, R^2 = R^3 = Me)

Procedure 1.—Dry methylamine gas was bubbled through a stirred and cooled (0°) solution of (*R*)-1-hydroxy-1-phenylpropan-2-one [e.e. 80% (*R*); 1·0 g, 6·6 mmol] in dry ether (35 ml) for 5 min. The resulting pale yellow solution was stirred for 30 min, and then treated with an ethanolic solution of sodium borohydride (0·5 g, 13·3 mmol; in 8 ml of ethanol). The mixture was then stirred at 10° and allowed to warm to room temperature, after which time

[26] Hopper, I. V., and Wilson, F. J., *J. Chem. Soc.*, 1928, 2483.
[27] Kenyon, J., and Patel, R. L., *J. Chem. Soc. C*, 1966, 97.

the excess methylamine was blown off under a stream of nitrogen. The solution was acidified with 1 M hydrochloric acid; the aqueous mixture was extracted twice with ether, basified with 2 M sodium hydroxide solution, and extracted again with ether. The combined extracts were washed, dried ($MgSO_4$) and evaporated to give a pale yellow semisolid (0·88 g, 79%), $[\alpha]_D^{20}$ −3·8° (*c*, 0·927 in EtOH). ν_{max} (film) 3400s(br), 1600w, 1365s, 1330m, 1280w, 1038m, 905w, 740s, 695s cm^{-1}. ^1H n.m.r. showed both isomers (*erythro/threo* 76 : 24). δ (200 MHz) *etythro* 0·84, d, *J* 6·5 Hz, 3H, CH_3; 2·56, s, 3H, NCH_3; 2·72–2·84, m, 1H, C**H**CH_3; 4·75, d, *J* 3·87 Hz, 1H, benzylic H; 7·31, s, 5H, ArH; *threo* 0·94, d, *J* 6·4 Hz, 3H, CH_3; 2·45, s, 3H, NCH_3; 2·55–2·81, m, 1H, C**H**CH_3; 4·19, d, *J* 8·2 Hz, 1H, benzylic H; 7·34, s, 5H, ArH. No NH or OH signals were observed. Mass spectrum *m/z* 166 (M, 4%), 120 (19), 150 (15), 79 (25), 78 (13), 75 (50), 59 (36), 58 (100), 56 (26), 51 (28). The ^1H n.m.r. spectroscopic data agree well with the literature.[28]

Procedure 2.—1-Hydroxy-1-phenylpropan-2-one [e.e. 80% (*R*)] was reacted with dry methylamine gas in anhydrous ether at 0°, and subsequently treated with an ethereal solution of zinc borohydride at −76° for 1 h. Workup as described above afforded a viscous oil which slowly crystallized as rosettes of fine needles. This solid was dissolved in a minimum amount of ether, and treated with dry hydrogen chloride gas at 0°. The resulting hydrochloride salt was collected by filtration and washed with anhydrous ether. The salt was dissolved in water, and basified with 2 M sodium hydroxide solution, and the solution extracted once again with ether (3×). The combined extracts were washed, dried (Na_2SO_4) and evaporated to give a hygroscopic solid as fine elongated needles, $[\alpha]_D^{19}$ −5·1° (*c*, 1 in EtOH) {lit.[25c] $[\alpha]_D^{19}$ −6·3° (*c*, 1 in EtOH)}; this material was shown to be the pure (1*R*,2*S*)-isomer with an e.e. of 80% (*R*).

Racemic 2-Benzylamino-1-phenylpropan-1-ol (6; Ar = Ph, R^2 = Me, R^3 = CH_2Ph)

Dry benzylamine (0·44 ml, 4·0 mmol) was added to a stirred and cooled (0°) solution of 1-hydroxy-1-phenylpropan-2-one (0·5 g, 3·3 mmol) in dry ether (25 ml). The resulting pale yellow solution was stirred for 40 min at 0°, cooled to −76° and then treated with an ethereal suspension of sodium borohydride (0·25 g, 6·6 mmol). The mixture was stirred at −76° for 3 h and then acidified with 1 M hydrochloric acid. The aqueous layer was separated, extracted twice with ether, basified with 2 M sodium hydroxide, and extracted again with ether. The combined washed and dried ($MgSO_4$) extracts were evaporated to give a pale yellow oil (0·631 g, 79%). ν_{max} (film) 3240m(br), 1600w, 1485m, 1448m, 740m, 700s cm^{-1}. ^1H n.m.r. showed both isomers (*erythro/threo* 80 : 20): δ (300 MHz) *erythro* 0·85, d, *J* 6·48 Hz, CH_3; 2·10, br s, 2H, NH, OH; 2·99, m, 1H, H2; 3·87, s, 2H, CH_2; 4·76, d, *J* 4·0 Hz, 1H, H1; 7·3, m, 10H, ArH; *threo* 0·85, d, *J* 6·40 Hz, CH_3; 2·10, br s, 2H, NH, OH; 2·79, m, 1H, H2; 3·84, s, 2H, CH_2; 4·21, d, *J* 8·20 Hz, 1H, H1; 7·3, m, 10H, ArH. Mass spectrum *m/z* 241 (M, 0·4%), 134 (57), 91 (100).

1-Phenylpropane-1,2-diol (9; Ar = Ph)

To a stirred solution of 1-hydroxy-1-phenylpropan-2-one {0.5 g, 3·32 mmol; e.e. 80% (*R*)} in absolute ethanol (15 ml) was added a solution of sodium borohydride {125 mg, 3·32 mmol, in absolute ethanol (3 ml)} at room temperature. The mixture was stirred at room temperature for 2 h and then a 1 M hydrochloric acid solution was added to quench the reaction. The aqueous mixture was extracted with ether; the combined ethereal extracts were washed, dried ($MgSO_4$) and evaporated to give a viscous yellow oil (0·45 g, 95%), $[\alpha]_D^{21}$ −18·0° (*c*, 0·545 in $CHCl_3$). ν_{max} (film) 3360s(br), 1600w, 1480m, 1440s, 1365m, 1120m, 1070m, 1035m, 1010m, 920w, 750s, 690s, cm^{-1}. ^1H n.m.r. showed both isomers (*erythro/threo* 60 : 40): δ (200 MHz) *erythro* 0·97, d, *J* 6·0 Hz, 3H, CH_3; 3·4, br s, 2H, 2×OH; 3·86–3·94, m, 1H, HOC**H**CH_3; 4·62, d, *J* 3·9 Hz, 1H, ArC**H**OH; 7·30, s, 4H, ArH; *threo* 1·0, d, *J* 6·3 Hz, 3H, CH_3; 3·4, br s, 2H, 2×OH; 3·90–3·94, m, 1H, HOC**H**CH_3; 4·27, d, *J* 7·62 Hz, 1H, ArC**H**OH; 7·30, s, 4H, ArH. Mass spectrum *m/z* 134 (M−H_2O, 0·8%), 108 (88), 107 (88), 105 (25), 104 (15), 79 (100), 77 (48), 51 (18). The ^1H n.m.r. spectroscopic data agree well with the literature, but to determine the *erythro/threo* ratio more accurately the reduction product was converted directly into the acetonides (see below).

[28] Lovgren, K., and Nilsson, J. L. G., *Acta Pharm. Suec.*, 1977, **14**, 30.

The racemic diol was also prepared, by the above method, as an oil (96%) (*erythro/threo* 60 : 40).

2,2,4-Trimethyl-5-phenyldioxolan

A solution of the optically active diol (9; Ar = Ph) (1·0 g, 6·6 mmol) in 2,2-dimethoxypropane (10 ml) containing a catalytic amount of 4-toluenesulfonic acid was stirred at room temperature under an atmosphere of nitrogen. Triethylamine was then added to the solution and the mixture evaporated to dryness. The residue was taken up into ether, dried ($MgSO_4$) and evaporated to give a yellow oil (1·14 g, 90%). ν_{max} (film) 1600s, 1490m, 1425s, 1370s, 1237s, 1210s, 1160s, 1090s, 1038s, 1020s, 970w, 935w, 855s, 800w, 745s, 695s cm^{-1}. ^1H n.m.r. showed both isomers (*cis/trans* 60 : 40): δ (200 MHz) *cis* 0·81, d, *J* 6·5 Hz, 3H, CH_3; 1·49, s, 3H, CCH_3; 1·66, s, 3H, CCH_3; 4·55–4·60, m, 1H, H4; 5·21, d, *J* 6·8 Hz, H5; 7·31, m, 3H, ArH; *trans* 1·26, d, *J* 6·0 Hz, 3H, CH_3; 3·87–3·91, m, 1H, H4; 4·50, d, *J* 8·61 Hz, H5; 7·38, m, 5H, ArH. Mass spectrum *m/z* 192 (M, 5%), 177 (16), 162 (22), 161 (15), 149 (15), 148 (100), 147 (35), 135 (23), 134 (21), 133 (30), 121 (16), 120 (22), 119 (45), 117 (13), 107 (22), 105 (67), 104 (40), 91 (70), 90 (37), 89 (16), 73 (18), 38 (50), 31 (14). The ^1H n.m.r. spectroscopic data agree well with literature data.[29]

Optically Active 2-Methyl-1-phenyl-1-(trimethylsilyloxy)propan-2-amine (13; R = $SiMe_3$)

The alkylation of 2-phenyl-2-(trimethylsilyloxy)acetontrile with methyllithium was carried out according to the procedure of Amouroux and Axiotis.[18] Methyllithium (1·4 M in ether; 1·8 ml, 2·5 mmol) was added under nitrogen by syringe to a stirred solution of 2-phenyl-2-(trimethylsilyloxy)acetonitrile (0·2 g, 1 mmol), $[\alpha]_D^{21}$ −25·4° (*c*, 5·39 in $CHCl_3$), in dry ether (5 ml). The solution was stirred for 5 h at room temperature, then cooled in an ice bath, and quenched with saturated ammonium chloride solution (7 ml). The mixture was rapidly extracted with ether (4×15 ml); the combined extracts were washed with saturated sodium chloride solution, and dried ($MgSO_4$). Concentration of the dried extracts gave an orange oil which was purfied by Kugelrohr distillation to give 2-methyl-1-phenyl-1-(trimethylsilyloxy)propan-2-amine as a clear liquid (0·16 g, 68%), b.p. 140° (oven)/5 mm (lit.[18] 78°/1 mm), $[\alpha]_D^{21}$ +39·7° (*c*, 3·14 in $CHCl_3$). ν_{max} (film) 2960s, 1255s, 1090s, 885s, 845s, 735m, 705s cm^{-1}. ^1H n.m.r. δ (90 MHz) −0·01, s, 9H, $Si(CH_3)_3$; 0·95, s, 3H, CH_3; 1·10, s, 3H, CH_3; 1·90, br s, 2H, NH_2; 4·38, s, 1H, CH; 7·29, br s, 5H, ArH.

Methyl (R)*-2-(1-Ethoxyethoxy)-2-phenylacetate*

Optically pure methyl (*R*)-2-hydroxy-2-phenylacetate (3·32 g, 20 mmol) was dissolved in dry methylene chloride (25 ml), and chilled to −5°. Trifluoroacetic acid (0·1 ml) was added to the stirred solution followed by the dropwise addition of ethyl vinyl ether (2·7 ml, 28 mmol). The mixture was stirred at −5° for 24 h, then washed with saturated sodium hydrogen carbonate solution and water, and dried (Na_2SO_4). Concentration of the dried organic solution under reduced pressure gave a clear liquid (4·43 g, 93%). Kugelrohr distillation of a sample gave pure *methyl 2-(1-ethoxyethoxy)-2-phenylacetate*, b.p. 180° (oven)/4 mm (Found: C, 64·9, H, 7·7. $C_{13}H_{18}O_4$ requires C, 65·5; H, 7·6%). $[\alpha]_D^{21}$ −82·5° (*c*, 0·818 in $CHCl_3$). ν_{max} (film) 1750s, 1600w, 1210s, 1170s, 1135s, 1085s, 1060s, 735s, 700s cm^{-1}. ^1H n.m.r. showed two diastereoisomers in equal proportions: δ (300 MHz) isomer A 1·14, t, *J* 7·0 Hz, 3H, CH_2CH_3; 1·36, d, *J* 5·4 Hz, 3H, $CHCH_3$; 3·44, dq, *J* 9·4, 7·0 Hz, 1H, CH_2; 3·63, dq, *J* 9·4, 7·0 Hz, 1H, CH_2; 3·71, s, 3H, $COOCH_3$; 4·94, q, *J* 5·4 Hz, 1H, $CHCH_3$; 5·26, s, 1H, H2; 7·3–7·5, m, 5H, ArH; Isomer B 1·14, t, *J* 7·0 Hz, 3H, CH_2CH_3; 1·37, d, *J* 5·4 Hz, 3H $CHCH_3$; 3·4–3·7, m, 2H, CH_2; 3·71, s, 3H, $COOCH_3$; 4·78, q, *J* 5·4 Hz, 1H, $CHCH_3$; 5·20, s, 1H, H2; 7·3–7·5, m, 5H, ArH. Mass spectrum *m/z* 179 ($M-COOCH_3$, 6%), 149 (14), 121 (6), 107 (8), 77 (8), 73 (100).

(R)*-2-(1-Ethoxyethoxy)-2-phenylacetaldehyde (11; R = OCHMeOEt)*

Method 1.—Optically pure methyl (*R*)-2-(1-ethoxyethoxy)-2-phenylacetate (2·38 g, 10 mmol) in ether (35 ml) at −78° was treated with diisobutylaluminium hydride (1 M in hexane; 15 ml,

[29] Hanzlic, R. P., and Leinwetter, M., *J. Org. Chem.*, 1978, **43**, 438.

15 mmol) for 1·5 h. The crude product (2·25 g) was isolated in ether, and purified by flash chromatography (benzene followed by chloroform) to afford (*R*)-2-(1-ethoxyethoxy)-2-phenylacetaldehyde as a clear liquid (1·60 g, 77%), $[\alpha]_D^{18}$ −43·7° (*c*, 0·27 in $CHCl_3$). ν_{max} (film) 1730s, 1600w, 1130s, 1080s, 1050s, 1020s, 755m, 705s cm^{-1}. ^1H n.m.r. showed two diastereoisomers in equal proportion: δ (300 MHz) 1·13, t, *J* 7·2 Hz, 3H, CH_2CH_3; 1·14, t, *J* 7·1 Hz, 3H, CH_2CH_3; 1·36, d, *J* 5·3 Hz, 3H, $CHCH_3$; 1·41, d, *J* 5·4 Hz, 3H, $CHCH_3$; 3·4–3·7, m, 4H, 2×CH_2CH_3; 4·80, q, *J* 5·3 Hz, 1H, $CHCH_3$; 4·98, d, *J* 2·0 Hz, 1H, CHCHO; 4·99, q, *J* 5·4 Hz, 1H, $CHCH_3$; 5·08, d, *J* 2·0 Hz, 1H, CHCHO; 7·3–7·4, br s, 10H, ArH; 9·58, d, *J* 2·0 Hz, 2H, 2×CHO. Mass spectrum *m/z* 179 (M−CHO, 2%), 119 (12), 107 (10), 105 (21), 91 (10), 77 (19), 73 (100).

Method 2.—A solution of optically active 2-(1-ethoxyethoxy)-2-phenylacetonitrile [1·2 g, 5·8 mmol; e.e. 83% (*R*)] in toluene (20 ml) was cooled to −76°, and 1 M diisobutylaluminium hydride in toluene (6·2 ml, 6·2 mmol) was added. The mixture was stirred at −72° for 30 min and then at −30° for 2 h, and finally at room temperature for 1 h. Sulfuric acid (15 ml, 0·5 M) was added and the mixture stirred for 45 min, and then extracted with chloroform. The combined organic extracts were dried (Na_2SO_4) and evaporated to yield an oil (0·91 g, 74%), $[\alpha]_D^{20}$ −34·3° (*c*, 0·237 in $CHCl_3$). This material had identical spectroscopic features to those reported above.

Methyl (R)- *and* (S)-*2-(t-Butyldimethylsilyloxy)-2-phenylacetate*

Imidazole (1·80 g, 26 mmol) was added to a stirred solution of methyl (*R*)-2-hydroxy-2-phenylacetate (3·32 g, 20 mmol) and t-butyldimethylsilyl chloride (3·50 g, 23 mmol) in dry dimethylformamide (20 ml) following the procedure of Hoffman and Weidmann.[30] The solution was protected from moisture and stirred at room temperature for 15 h. Water was then added and the mixture extracted with light petroleum (5×). The combined extracts were washed with sodium chloride, saturated 1 M hydrochloric acid, and saturated sodium hydrogen carbonate solution, then dried (Na_2SO_4) and evaporated under reduced pressure to give a clear liquid. Flash chromatography of the crude product with benzene as the eluent gave *methyl* (R)-*2-(t-butyldimethylsilyloxy)-2-phenylacetate* (5·47 g, 98%). This product was purifed by bulb-to-bulb distillation, b.p. 100° (oven)/0·05 mm (Found: C, 64·0; H, 8·3. $C_{15}H_{24}O_3Si$ requires C, 64·2; H, 8·6%). $[\alpha]_D^{20}$ −46·9° (*c*, 0·458 in $CHCl_3$). ν_{max} (film) 2940s, 2920s, 2880m, 2850s, 1760s, 1600w, 1495m, 1470m, 1460m, 1455m, 1360m, 1255s, 1210s, 1195s, 1170s, 1130s, 1075s, 1010m, 865s, 840s, 780s, 750s, 700s, 670m cm^{-1}. ^1H n.m.r. δ (300 MHz), 0·04, s, 3H, CH_3; 0·11, s, 3H, CH_3; 0·92, s, 9H, $C(CH_3)_3$; 3·69, s, 3H, OCH_3; 5·24, s, 1H, CH; 7·3–7·4, m, 3H, ArH; 7·45–7·50, m, 2H, ArH. Mass spectrum *m/z* 265 (M−CH_3, 1%), 224 (10), 23 (60), 221 (19), 195 (35), 90 (10), 89 (100), 73 (42), 59 (23).

Methyl (*S*)-2-(t-butyldimethylsilyloxy)-2-phenylacetate, yield 85%, $[\alpha]_D^{21}$ +44·9° (*c*, 0·96 in $CHCl_3$), was prepared in an analogous manner.

(R)- *and* (S)-*2-(t-Butyldimethylsilyloxy)-2-phenylacetaldehyde (11; R = $SiMe_2Bu^t$)*

Diisobutylaluminium hydride (1 M in hexane; 15·0 ml, 15 mmol) was added, under nitrogen, to a stirred solution of methyl (*S*)-2-(t-butyldimethylsiloxy)-2-phenylacetate (2·80 g, 10 mmol) in dry ether (30 ml) maintained at −78°. The solution was stirred for 2·5 h at this temperature, then quenched with methanol (2 ml). A saturated solution of Rochelle salt (60 ml) was added and the mixture stirred at 20° for 1 h. The layers were separated and the aqueous layer was extracted with more ether. The combined organic phases were washed with saturated sodium hydrogen carbonate solution and water, then dried ($MgSO_4$), and concentrated to yield a clear oil (2·46 g). This oil was subjected to flash chromatography (benzene) to afford (*S*)-2-(t-butyldimethylsilyloxy)-2-phenylacetaldehyde as an oil (2·16 g, 86%), $[\alpha]_D^{19}$ −5·3° (*c*, 0·488 in $CHCl_3$). ν_{max} (film) 2940s, 2920s, 2870m, 2850s, 2800w, 1600w, 1475m, 1465m, 1455m, 1260s, 1120s, 1105s, 1075m, 865s, 840s, 785s, 700s cm^{-1}. ^1H n.m.r. δ (300 MHz) 0·04, s, 3H, CH_3; 0·12, s, 3H, CH_3; 0·95, s, 9H, $C(CH_3)_3$; 5·01, d, *J* 2·1 Hz, 1H, H2; 7·3–7·4, m, 5H, ArH; 9·51, d, *J* 2·1 Hz, 1H, CHO. Mass spectrum *m/z* 221 (M−CHO, 46%), 193 (38), 179 (37), 135 (18), 105 (40), 77 (33), 75 (79), 73 (100).

[30] Hoffman, R. W., and Weidmann, U., *Chem. Ber.*, 1985, **118**, 3966.

A small sample of the (*S*) aldehyde was converted into its *semicarbazide derivative* (98% yield) by standard methods. This material was recrystallized from ether/light petroleum as very fine matted needles, m.p. 195·5–197° (Found: C, 58·8; H, 7·9; N, 1·4. $C_{15}H_{25}N_3O_2Si$ requires C, 58·6; H, 8·2; N, 13·7%). $[\alpha]_D^{19}$ −77·5° (*c*, 0·64 in $CHCl_3$). ν_{max} (Nujol) 3440s, 3400–2800m(vbr), 1705s, 1580s, 1460s, 1105s, 1070m, 860m, 840s, 780s, 705m cm^{-1}. ^1H n.m.r. δ (300 MHz) 0·06, s, 3H, CH_3; 0·09, s, 3H, CH_3; 0·92, s, 9H, $C(CH_3)_3$; 5·26, d, *J* 6·5 Hz, 1H, H2; 6·93, d, *J* 6·5 Hz, 1H, H1; 7·30, m, 1H, H4′; 7·36, d, *J* 4·4 Hz, 4H, ArH; 8·06, br s, 1H, NH. The $CONH_2$ protons were not observed in the ^1H n.m.r. spectrum. Mass spectrum *m/z* 307 (M, 0·1%), 275 (0·1), 250 (14), 190 (15), 117 (78), 103 (13), 77 (16), 75 (100), 74 (18), 73 (22).

(*R*)-2-(t-Butyldimethylsilyloxy)-2-phenylacetaldehyde was also prepared as described above in 90% yield. Its semicarbazide derivative was recrystallized from ether/light petroleum as a mat of fine white needles, m.p. 194–196°, $[\alpha]_D^{20}$ +81·7° (*c*, 0·12 in $CHCl_3$).

In addition, the above procedure was used to reduce 2-(t-butyldimethylsiloxy)-2-phenylacetonitrile, optical purity 68%, to the aldehyde in a moderate yield (58%). The semicarbazide derivative was prepared from this material in excellent yield (90%), m.p. 194°, $[\alpha]_D^{18}$ +66·8° (*c*, 0·38 in $CHCl_3$).

(R), (S) *and Racemic Methyl 2-Methoxy-2-phenylacetates*

A mixture of freshly prepared silver oxide (9·3 g, 40 mmol) and optically pure (*R*)-2-hydroxy-2-phenylacetic acid (3·0 g, 20 mmol) was added in portions to methyl iodide (15 ml), with stirring and cooling as described by McKenzie.[31] The mixture was then heated under reflux for 1 h, diluted with ether, and filtered; the filtrate was concentrated to yield methyl (*R*)-2-methoxy-2-phenylacetate as a clear liquid (3·36 g, 100%), $[\alpha]_D^{20}$ −90·0° (*c*, 0·56 in Me_2CO) {lit.[30] $[\alpha]_D^{24}$ −89·1° (*c*, 1·111 in Me_2CO)}. ν_{max} (film) 1750s, 1600w, 1195s, 1110s, 730s, 700s cm^{-1}. ^1H n.m.r. δ (60 MHz) 3·39, s, 3H, OCH_3; 3·68, s, 3H, $COOCH_3$; 4·74, s, 1H, CH; 7·37, br s, 5H, ArH.

Also prepared as described above were methyl (*S*)-2-methoxy-2-phenylacetate (98%), $[\alpha]_D^{20}$ +86·0° (*c*, 0·81 in Me_2CO) {lit.[32] $[\alpha]_D^{23}$ +88·7° (*c*, 1·070 in Me_2CO)}, and racemic methyl 2-methoxy-2-phenylacetate (100%).

(R), (S) *and Racemic 2-Methoxy-2-phenylacetaldehydes (11; R = Me)*

A solution of methyl (*R*)-2-methoxy-2-phenylacetate (1·80 g, 10 mmol) in dry ether (30 ml) was cooled to −78° and a solution of diisobutylaluminium hydride (1 M in hexane; 15 ml, 15 mmol) was added by syringe under nitrogen. The mixture was stirred for 3 h at this temperature and then the excess diisobutylaluminium hydride destroyed by the addition of methanol (5 ml). After stirring for 15 min, the cooling bath was removed, a saturated solution of Rochelle salt (50 ml) was added, and the mixture stirred at room temperature for a further 20 min. The resulting clear mixture was extracted twice with ether; the combined extracts were washed with water, dried ($MgSO_4$) and concentrated to afford (*R*)-2-methoxy-2-phenylacetaldehyde as a clear oil (1·42 g, 95%), $[\alpha]_D^{19}$ −89·9° (*c*, 1·29 in $CHCl_3$) (lit.[31] $[\alpha]_D$ −54·6° in $CHCl_3$). ν_{max} (film) 2810m, 1735s, 1600w, 1495m, 1455m, 1200m, 1110s, 755m, 705s cm^{-1}. ^1H n.m.r. δ (300 MHz) 3·45, s, 3H, OCH_3; 4·65, d, *J* 1·7 Hz, 1H, H2; 7·2–7·4, m, 5H, ArH; 9·59, d, *J* 1·7 Hz, 1H, CHO. Mass spectrum *m/z* 150 (M, 0·5%), 121 (100), 105 (10), 91 (14), 77 (28).

In view of the sensitive nature of the above alkoxy aldehyde, purification was not attempted, and the aldehyde was used as a crude product. As confirmation of its identity, a small amount of the crude product (0·3 g, 2 mmol) was reduced with lithium aluminium hydride (0·1 g, 2·6 mmol) under standard conditions (ether, reflux, 1·5 h) to give the pure (*R*) alcohol (0·24 g, 79%) after bulb-to-bulb distillation, b.p. 65° (oven)/0·10 mm, $[\alpha]_D^{23}$ −119·2° (*c*, 0·224 in Me_2CO) (lit.[33] $[\alpha]_D^{25}$ −131° in Me_2CO).

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Lithium aluminium hydride reduction of methyl (*R*)-2-methoxy-2-phenylacetate gave another sample of the (*R*) alcohol, b.p. 82–83°/3mm (lit.[34] 82–85°/3 mm), $[\alpha]_D^{19}$ −130·7°, $[\alpha]_D^{28}$ −127·4° (*c*, 0·508 in EtOH) {lit.[35] $[\alpha]_D$ −127·0° (*c*, 6·4 in EtOH)}. ν_{max} (film) 3380s(br), 1600w, 1115s, 1065s, 760s, 705s cm^{-1}. ^1H n.m.r. δ (300 MHz) 2·48, br s, 1H, OH; 3·31, s, 3H, OCH_3; 3·61, dd, $J_{1A,1B}$ 11·7, $J_{1A,2}$ 4·0 Hz, 1H, H1A; 3·68, dd, $J_{1A,1B}$ 11·7, $J_{1B,2}$ 8·2 Hz, 1H, H1B; 4·31, dd, $J_{1A,2}$ 4·0, $J_{1B,2}$ 8·2 Hz, 1H, H2; 7·3–7·4, m, 5H, ArH.

Also prepared as described above were racemic 2-methoxy-2-phenylacetaldehyde [93% (crude)], and (*S*)-2-methoxy-2-phenyl acetaldehyde [100% (crude)], $[\alpha]_D^{19}$ +83·5° (*c*, 1·59 in $CHCl_3$) (lit.[32] $[\alpha]_D^{17}$ +83·2° in $CHCl_3$). From the latter crude material was obtained the pure (*S*) alcohol (89%), b.p. 60° (oven)/0·05 mm, $[\alpha]_D^{23}$ +119·7° (*c*, 0·95 in Me_2CO) (lit.[33] $[\alpha]_D^{25}$ +132° in Me_2CO).

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