A Facile General Route to Enantiomeric 1-(4-Hydroxyphenyl)alkanols, and an Improved Synthesis of 4-Vinylphenol

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Optically pure 1-(4-hydroxyphenyl)alkanols, the phenolic hydroxy groups of which are protected, have been obtained by an improved resolution procedure. Since subsequent deprotection of these is accompanied by complete elimination to the phenolic styrenes, an efficient synthesis of 4-vinylphenol from the racemic protected alcohols by simultaneous deprotection and elimination at 0 °C has been developed.

The target chiral 1-(4-hydroxyphenyl)alkanols have been prepared by treatment of the *O*-protected 4-hydroxyphenyl alkyl ketone with the enantiomers of chlorodiisopinocampheylborane at 0 °C, when asymmetric reduction and simultaneous deprotection gives the enantiomeric diols in >99.7% e.e. and high chemical yield.

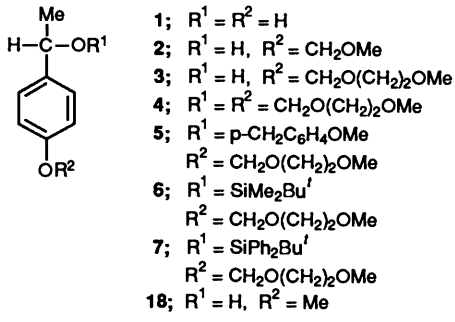
para-Alkylphenols such as *p*-cresol and 4-ethylphenol, which occur widely in foods and alcoholic beverages,[1] are detoxified by the enzyme *p*-cresol methylhydroxylase[2] to form 1-(4-hydroxyphenyl)alkanols such as 4-hydroxybenzyl alcohol[3] and (*S*)-1-(4-hydroxyphenyl)ethanol **1**.[4,5]

Optically active **1** has not been reported in the literature. Classical resolution methods use the hydrogen phthalate ester of the alcohol,[6] requiring prior protection of the phenolic hydroxy moiety by a formaldehyde acetal protecting group such as the methoxymethyl[7] (MOM) or Corey's 2-methoxyethoxymethyl[8] (MEM) unit. Reaction of 4-hydroxyacetophenone **8** with dimethoxymethane gave the protected 4-(methoxymethoxy)acetophenone **9** (84%), reduced quantitatively to 1-(4-methoxymethoxyphenyl)ethanol **2**. Acylation with phthalic anhydride in benzene–pyridine yielded 63% of the hydrogen phthalate, while the use of *N*,*N*-dimethylformamide (DMF)–imidazole raised the yield to 88%. The addition of (*R*)-(+)-1-phenylethylamine caused the quantitative precipitation of the *R*,*R*-salt in less than 1 min. The *S*,*S* salt was obtained in analogous fashion from (*S*)-(−)-1-phenylethylamine. The free acids (*R*)-(−)-1-(4-methoxymethoxyphenyl)ethyl hydrogen phthalate and its *S*-(+)-enantiomer racemized slowly at 5 °C, and were therefore either hydrolysed immediately or stored at −78 °C.

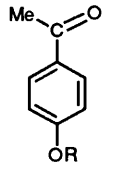
Hydrolysis using either $LiBH_4$ in THF (tetrahydrofuran), sodium in 96% ethanol, or sodium hydroxide in 77% ethanol gave 1-(4-methoxymethoxyphenyl)ethanol **2** in 90% yield, with the last affording the highest optical purity (96% e.e.) as shown by HPLC analysis of the ester formed with (*S*)-(−)-α-methoxy-α-trifluoromethylphenylacetic acid (MTPA).[9]

In an analogous manner, the ketone **8** was coupled with 2-methoxyethoxymethyl chloride[8] to give the protected acetophenone **10**, reduced quantitatively to the alcohol **3**, and converted into the hydrogen phthalate. Resolution as above again occurred within 1 min giving the pure *R*,*R*- and *S*,*S*-salts after one crystallization. The free *R*- and *S*-hydrogen phthalates were liberated using oxalic acid, and were immediately hydrolysed[10] (sodium in 96% ethanol) giving quantitative yields of the *R*- and *S*-alcohols **3** in optically pure form.

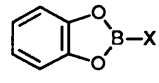
Cleavage of the MEM and MOM protecting groups has been reported[8] using $ZnBr_2$ or $TiCl_4$, but others have found[11–14] this reaction to be slow. In our hands, the protected ketone **10** required 5 weeks for quantitative cleavage to **8**, using 5 mol equiv. of $ZnBr_2$. This result, together with concern for elimination catalysed by coordination of the $ZnBr_2$ with the benzylic hydroxy group in **1**–**3**, led us to abandon the use of these reagents.



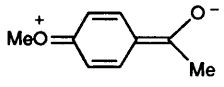
1; $R^1 = R^2 = H$
2; $R^1 = H$, $R^2 = CH_2OMe$
3; $R^1 = H$, $R^2 = CH_2O(CH_2)_2OMe$
4; $R^1 = R^2 = CH_2O(CH_2)_2OMe$
5; $R^1 = p\text{-}CH_2C_6H_4OMe$, $R^2 = CH_2O(CH_2)_2OMe$
6; $R^1 = SiMe_2Bu^t$, $R^2 = CH_2O(CH_2)_2OMe$
7; $R^1 = SiPh_2Bu^t$, $R^2 = CH_2O(CH_2)_2OMe$
18; $R^1 = H$, $R^2 = Me$



8; R = H
9; R = CH_2OMe
10; R = $CH_2O(CH_2)_2OMe$



11; X = Cl
12; X = Br



17

The use of dimethyl- and diphenyl-boron bromide for the rapid cleavage of MEM and MOM ethers of alcohols has been reported,[13] but in our hands these reagents were inert towards phenolic MEM ethers. Thus the MEM ether of 4-ethylphenol was recovered unchanged even after refluxing with 3 mol equiv. of diphenylboron bromide for 32.5 h. This is presumably due to the reduced nucleophilicity of the lone pair of electrons on the phenolic oxygen atom of the protected phenol, and its resultant inability to attack the coordinated boron reagent in the postulated mechanism.[13]

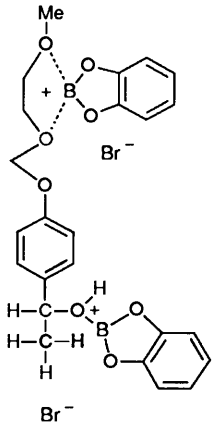
The catechol boron halides (2-halogeno-1,3,2-benzodioxaboroles) **11** and **12** have been recently reported[15] for the mild cleavage of aliphatic MEM ethers. We found that 1.1 mole equiv. of **12** cleaved the MEM ether of 4-ethylphenol in 15 min (room temp.) while the corresponding chloride **11** required 3 h.

These reagents appeared attractive because of the possibility that during cleavage of *e.g.* the MEM-protected alcohol **2**, the introduction of a second mole equiv. of the catechol reagent **12** in presence of a tertiary base would bring about[16] the protection of the secondary alcohol group by formation of its boron ester, with subsequent mild aqueous hydrolysis to regenerate the hydroxy function.

It was necessary to determine which *tert*-amines could be employed as proton scavengers in this step without inhibiting the effectiveness of the boron reagents. Excess of triethylamine was found to inhibit the reactivity of the reagents **11** and **12** towards MEM ethers of phenols. Thus, while the MEM ether of 4-ethylphenol was cleaved in 30 min with 1.4 mol equiv. of both **12** and triethylamine, an increase in triethylamine to 30 mol equiv. led to only 30% cleavage in the same time. No cleavage was observed in 3 h with 2 mol equiv. of **11** containing 20 mol equiv. of triethylamine, and none was found when the MOM ether **3** was treated with 4 mol equiv. of **11** and 14 mol equiv. of triethylamine even after 38 h.

We next examined the possible use of pyridine bases to protect the sensitive secondary hydroxy group of **3**, while allowing the efficient cleavage of the MEM ether. Pyridine is known[15] to form stable 1:1 complexes with both **11** and **12**. As expected, 2-methylpyridine was also found to inhibit the catechol reagents totally. However, the MEM ether of 4-ethylphenol was completely cleaved in 4 h when treated with 2 mol equiv. of **11** and 20 mol equiv. of the more hindered 2,6-dimethylpyridine. Having shown that 2,6-dimethylpyridine did not inhibit the reagent, we treated the MEM-protected alcohol **3** with 4 mol equiv. of 2,6-dimethylpyridine for 10 h. HPLC analysis showed that elimination had occurred to give 4-vinylphenol as the major product, with only a trace of the desired **1**. Similarly, the hindered base *N*,*N*-diisopropylethylamine (25 mol equiv.) did not inhibit the cleavage of the MEM ether of 4-ethylphenol by 1.25 mol equiv. of **12**, but when the MEM-protected alcohol **3** was treated with either **11** or **12**, containing up to 30 mol equiv. of diisopropylethylamine, only 4-vinylphenol was produced, in 51–59% yield.

These results indicate that while unhindered bases inhibited the boron reagent, hindered tertiary bases were unable to protect the hydroxy from elimination, being too sterically hindered to abstract the proton from the benzylic oxygen atom as it attacks the electrophilic boron of the reagent **11** or **12** and acquires electropositive character in the complex **13**.



13

In order to test whether elimination could be prevented in this system, a series of ethers, **4**–**7**, of the MEM-protected alcohol **3** were prepared and treated with the reagents **11** and **12** in the presence of 1 mol equiv. of diisopropylethylamine as a proton sponge. The bis-MEM ether **4** gave only 4-vinylphenol. The 4-methoxybenzyl ether **5** was made in the expectation that coordination of the benzylic ether oxygen atom with the boron of the reagent would be followed by a preferential attack of the halide on the primary 4-methoxybenzylic carbon to form 4-methoxybenzyl halide, leaving the alcohol **1** protected as the catechol borate ester. However, treatment of **5** with **11** or **12** afforded only catechol, 4-methoxybenzyl alcohol, and 4-vinylphenol. Similarly, the *tert*-butyldimethylsilyl and *tert*-butyldiphenylsilyl ethers **6** and **7** also gave only 4-vinylphenol with **11** or **12**. The reactivity of the system **13** is therefore controlled by the thermodynamic driving force leading to elimination to the conjugated styrene.

Although 4-vinylphenol was first reported as a natural product[17] in 1945, it was not recognized for some time that vinylphenols are widely produced[18,19] microbiologically from phenolic acids, and that *e.g.* *p*-hydroxycinnamic acid is decarboxylated to 4-vinylphenol by *Aerobacter* due to the presence of a nonoxidative decarboxylase.[20] Vinylphenols are now known to be common food constituents, responsible for the smoky aroma of many foods.[1,21] Early attempts to synthesize 4-vinylphenol led only to polymeric materials[22,23] and the literature contains only a single report of its preparation[24] in a 4-step synthesis from 4-hydroxybenzaldehyde in 34% overall yield. The present preparation therefore represents an improved synthesis of this compound.

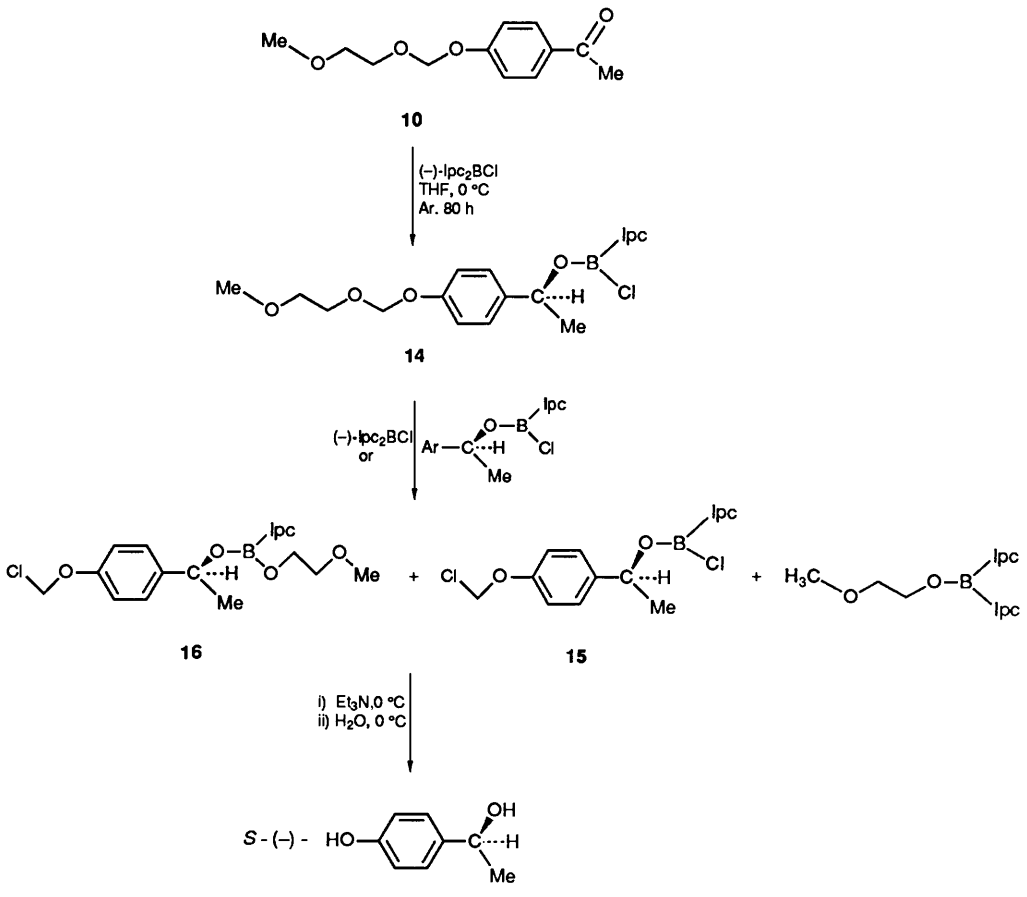
From the above results it became clear that the use of a boron halide reagent R^1R^2BCl (while extremely efficient for the deprotection of the phenolic MEM protecting group) on the alcohol **3** would inevitably result in 1,2-elimination to the styrene because of the electropositive character of the protonated oxygen atom in the complex **13**. To protect the benzylic alcohol as a neutral boron ester **14** would require the generation of **14** from the precursor acetophenone **10** by a chiral chlorodialkylborane reducing agent. Such a reagent was available in the recently reported chlorodiisopinocampheylborane (Ipc_2BCl) introduced[25,26] as a chiral reducing agent for aromatic prochiral ketones. Reduction of the ketone is accomplished[26] by β-elimination of a hydride ion with the formation of an alkyl chloroborane complex of the product alcohol (Scheme 1).

Scheme 1 *Reagent and conditions:* i, THF (1 mol dm^{-3}), −25 °C, 7 h

There is ample precedent in the literature for the use of dialkyl-and dioxy-chloroboranes for the cleavage of MOM and MEM groups[13,15,16] to the free phenol, and preliminary experiments showed that the MEM ether of 4-ethylphenol was indeed cleaved (70%) at 0 °C to the parent phenol by 1.2 mol equiv. of (+)-Ipc_2BCl in 43 h.

A time-course study of the asymmetric reduction of 4-methoxyacetophenone with (−)-Ipc_2BCl (1.2 mol equiv.) at 0 °C showed that 7 h were required for the reaction to go to 97% completion. Since the reduction of acetophenone by this reagent is reported[25] to require 7 h for completion at −25 °C, the 25 °C increase in temperature required for the 4-methoxy compound to react at a rate comparable to that of acetophenone is in agreement with the deactivated nature of the carbonyl group in the 4-methoxy compound due to the presence of resonance forms such as **17**.

Reduction of the MEM ether ketone **10** with 1.2 mol equiv. of (+)-Ipc_2BCl at 0 °C was followed by HPLC analysis of aliquots at hourly intervals. A steady decrease in the concentration of **10** and a corresponding increase in the concentration of the



Scheme 2

protected alcohol **3** were found, with a slower increase in the concentration of the target diol **1**. The concentration of **3** and **1** became equal after *ca.* 25 h and the concentration of **1** then continued to increase, and **3** to decrease, levelling off at *ca.* 70 h (a small amount of 4-hydroxyacetophenone **8** remained).

Isolation of the product diol by a modified procedure (see Experimental section) gave *R*-(+)-**1** in 65% yield. The optical purity of the crude product (96% e.e.) was raised to >99.7% e.e. by one crystallization; optical purity was determined by HPLC analysis of the (−)-MTPA esters of the *R*-4-methoxy derivative **18** obtained by diazomethane methylation of *R*-**1**. In the same way, reaction of **10** with (−)-Ipc_2BCl gave the enantiomer *S*-(−)-**1** of the same optical purity.

This is the first report of a one-pot asymmetric reduction of a carbonyl group and cleavage of an acetal protecting group with a 1 mol equiv. of Ipc_2BCl (Scheme 2). From kinetic data, reduction is by far the faster step, as indicated by the model experiments, and forms the chloroisopinocampheylborate ester **14** of the MEM-protected phenolic alcohol. The second step is then the (slower) removal of the MEM protecting group from this ester, either by a second molecule of the alkylchloroborate ester **14** or by some unused Ipc_2BCl reagent. Following the mechanism of Guindon[13,14] for cleavage of MEM ethers, the product of this cleavage will be the chloromethyl ether-protected phenolic alcohol **1**, either as its chloroisopinocampheylborate ester **15** or as its isopinocampheyl(methoxyethoxy)borate diester **16**. Both esters **15** and **16** are then hydrolysed to the product **1** by the addition of triethylamine and water at 0 °C.

In summary, this work describes a method for the efficient preparation of the optically pure 1-(4-hydroxyphenyl)alkanols by asymmetric reduction of the protected phenolic ketone with concurrent *in situ* deprotection at 0 °C. In addition, a simple route has been developed for the synthesis of 4-vinylphenol by a simultaneous deprotection–elimination sequence at 0 °C.

Experimental

M.p.s were measured on a Thomas–Hoover capillary m.p. apparatus and are uncorrected. ^1H NMR spectra were recorded on a Varian FT-80 spectrometer as solutions in $CDCl_3$ using TMS (tetramethylsilane) as internal reference. *J* Values are given in Hz. IR spectra were taken on a Nicolet 5DX FTIR instrument. Mass spectra were obtained on a Kratos MS-50 mass spectrometer. Optical rotations are given in 10^{-1} deg cm^2 g^{-1}. Elemental analyses were carried out by the Microanalytical Laboratory, University of California, Berkeley. HPLC analyses were performed on a Beckman 344 instrument.

4-*Methoxymethoxyacetophenone* **9**.—A mixture of 4-hydroxyacetophenone (50.6 g, 373 mmol), dimethoxymethane (138 g, 1.81 mol), toluene-4-sulphonic acid–water (407 mg, 2.14 mmol) and dichloromethane (800 cm^3) was heated at reflux, with removal of water by 3 Å molecular sieve (224 g) in a Soxhlet thimble, for 7 h. The pot was recharged with dichloromethane (200 cm^3) and the mixture was heated at reflux for 12 h, when the pot was again recharged with dimethoxymethane (85.9 g, 1.13 mol) and dichloromethane (400 cm^3). The mixture was heated at reflux for an additional 24 h, cooled to room temp., treated with triethylamine (3 cm^3), washed with NaOH (1 mol dm^{-3}; 5 × 200 cm^3), dried (Na_2SO_4), filtered and evaporated under reduced pressure to yield 4-*methoxymethoxyacetophenone* (56.0 g, 310 mmol, 84%): m.p. 32–34 °C; b.p. 87–89 °C (0.350 mmHg); δ_H 7.97, 7.86, 7.11, 7.00 (q, 4 H, *para*-substituted aromatic), 5.22 (s, 2 H, OCH_2O), 3.47 (s, 3 H, CH_3O) and 2.54 (s, 3 H, CH_3CO); ν(neat)/cm^{-1} 2959, 2910, 2828, 1672 (C=O),

1598, 1507, 1417, 1360, 1270, 1237, 1155, 1081, 982, 925 and 843 (Found: C, 66.45; H, 6.85. $C_{10}H_{12}O_3$ requires C, 66.65; H, 7.72%).

(RS)-1-(4-*Methoxymethoxyphenyl*)*ethanol* **2**.—4-Methoxymethoxyacetophenone (43.7 g, 242 mmol) in ethanol (95%; 380 cm^3) was slowly treated with $NaBH_4$ (9.67 g, 256 mmol) after which the mixture was stirred overnight. It was then quenched with water (100 cm^3) and the aqueous phase was saturated with NaCl. The layers were separated. The aqueous phase was extracted with ether. The ethanol was evaporated under reduced pressure and the residue was dissolved in the ether extract, which was dried (Na_2SO_4), filtered and evaporated under reduced pressure to yield (RS)-1-(4-*methoxymethoxyphenyl*)*ethanol* (43.8 g, 240 mmol, 99%); b.p. 79–81 °C (0.005 mmHg); δ_H 7.29, 7.18, 7.00, 6.89 (q, 4 H, *para*-substituted aromatic), 5.09 (s, 2 H, OCH_2O), 4.75 (q, 1 H, ArCH, *J* 6.5), 3.41 (s, 3 H, CH_3O), 2.86 (br s, 1 H, D_2O exch., OH) and 1.40 (d, 3 H, CH_3, *J* 6.5); ν(neat)/cm^{-1} 3394 (OH), 2968, 2927, 2894, 1614, 1507, 1228, 1196, 1155, 1081, 999, 925 and 835 (Found: C, 65.8; H, 7.75. $C_{10}H_{14}O_3$ requires C, 65.91; H, 7.74%).

(RS)-1-(4-*Methoxymethoxyphenyl*)*ethyl Hydrogen Phthalate*.—(*RS*)-1-(4-Methoxymethoxyphenyl)ethanol (5.40 g, 24.6 mmol) in dry DMF (5 cm^3) was slowly added to a solution of phthalic anhydride (4.38 g, 24.6 mmol) in dry DMF (8 cm^3) protected from atmospheric moisture and containing imidazole (2.03 g, 29.9 mmol). The reaction mixture was stirred at 95 °C for 1 h, cooled to room temp. and partitioned between ether (50 cm^3) and water (50 cm^3). The aqueous phase was adjusted to pH 2 with HCl (1 mol dm^{-3}) and the layers were separated; the aqueous phase was then extracted with ether (2 × 75 cm^3). The combined extracts were washed with saturated $NaHCO_3$ (2 × 40 cm^3) and the washings were adjusted to pH 2 with HCl (1 mol dm^{-3}) and extracted with ether (4 × 100 cm^3). The combined extracts were dried (Na_2SO_4), filtered and evaporated under reduced pressure to give a viscous oil which was dissolved in chloroform and filtered free from a trace of phthalic acid. Evaporation of the filtrate under reduced pressure yielded (RS)-1-(4-*methoxymethoxyphenyl*)*ethyl hydrogen phthalate* (8.61 g, 26.1 mmol, 88%) as a viscous oil which slowly crystallized: m.p. 94–96 °C (hexane–ethyl acetate); δ_H 11.16 (br s, 1 H, D_2O exch., CO_2H), 7.94–7.47 (m, 4 H, *ortho*-substituted aromatic) 7.41, 7.30, 5.05, 6.94 (q, 4 H, *para*-substituted aromatic), 6.11 (q, 1 H, ArCH, *J* 6.5), 5.11 (s, 2 H, OCH_2O), 3.42 (s, 3 H, CH_3O) and 1.64 (d, 3 H, CH_3, *J* 6.6); ν(neat)/cm^{-1} 3400, 3130, 3070, 2992, 2896, 2828, 2664, 2549, 1737 (C=O), 1516, 1286, 1212, 1154, 1081, 998, 835 and 774 (Found: C, 65.65; H, 5.45. $C_{18}H_{18}O_6$ requires C, 65.45; H, 5.49%).

(R)-(−)-1-(4-*Methoxymethoxyphenyl*)*ethyl Hydrogen Phthalate*.—A vigorously-stirred solution of (*RS*)-1-(4-methoxymethoxyphenyl)ethyl hydrogen phthalate (5.04 g, 15.3 mmol) in ether (80 cm^3) was treated with (*R*)-(+)-1-phenylethylamine (1.88 g, 15.5 mmol); and the salt, which precipitated within 1 min, was filtered off from solution by suction and washed with ether. The air-dried salt (3.44 g, 7.63 mmol, 100%) crystallized from ethanol as rosettes of needles; m.p. 145–146 °C; $[\alpha]_D^{25}$ +6.55 (*c* 2.61 EtOH) (Found: C, 68.9; H, 6.45; N, 3.1. $C_{26}H_{29}NO_6$ requires C, 69.16; H, 6.47; N, 3.10%).

A slurry of the dextrorotatory salt (2.93 g, 6.45 mmol) in water (75 cm^3) was cooled to 5 °C, adjusted to pH 2 with HCl (1 mol dm^{-3}) and extracted with ethyl acetate (3 × 75 cm^3). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated under reduced pressure to yield *R*-(−)-1-(4-methoxymethoxyphenyl)ethyl hydrogen phthalate as a viscous oil; $[\alpha]_D^{25}$ −15.1 (*c* 5.30 in EtOH). After 50 d at 5 °C the specific rotation had decreased to −13.2.

(S)-(+)-(4-*Methoxymethoxyphenyl*)*ethyl Hydrogen Phthalate*.—(*RS*)-1-(4-Methoxymethoxyphenyl)ethyl hydrogen phthalate in ether was treated with (*S*)-(−)-1-phenylethylamine in a manner analogous to that reported for the *R*-(+)-amine, to yield the laevorotatory salt as rosettes of needles; m.p. 144–145 °C; $[\alpha]_D^{25}$ −6.62 (*c* 2.52 in EtOH) (Found: C, 69.05; H, 6.45; N, 3.1. $C_{26}H_{29}NO_6$ requires C, 69.16; H, 6.47; N, 3.10%).

The free acid was liberated from the laevorotatory salt in a manner analogous to that reported for the dextrorotatory salt. *S*-(+)-1-(4-Methoxymethoxyphenyl)ethyl hydrogen phthalate was a colourless viscous oil; $[\alpha]_D^{25}$ +16.2 (*c* 5.04 in EtOH). The sample was stored at 5 °C, and in 16 d the specific rotation had decreased to +14.7.

(S)-(−)-1-(*Methoxymethoxyphenyl*)*ethanol* S-**2**.—*S*-(+)-1-(4-Methoxymethoxyphenyl)ethyl hydrogen phthalate (1.17 g, 3.53 mmol) was dissolved in NaOH in 77% ethanol (1.15 mol dm^{-3}; 25 cm^3, 29 mmol) and the mixture was heated at reflux for 1 h. The hydrolysate was cooled to room temp., diluted with water (25 cm^3) and saturated with NaCl. The layers were separated and the aqueous phase was extracted with ether (2 × 50 cm^3). The ethanol was evaporated under reduced pressure and the residue was dissolved in the combined ether extracts, which were dried (Na_2SO_4), filtered and evaporated under reduced pressure to yield (*S*)-(−)-1-1(4-methoxymethoxyphenyl)ethanol (579 mg, 3.18 mmol, 90%): b.p. 81 °C (0.005 mmHg, Kugelrohr); $[\alpha]_D^{20}$ −33.8, $[\alpha]_D^{25}$ −33.2 (*c* 5.01 in EtOH); LC analysis of the *S*-(−)-MTPA ester indicated the product to be a mixture of 98% *S*(−)-isomer and 2% *R*-(+)-isomer. The ^1H NMR and IR (neat) spectra were identical to those recorded for the racemic alcohol (Found: C, 65.5; H, 7.9. $C_{10}H_{14}O_3$ requires C, 65.91; H, 7.74%).

(R)-(+)-1-(4-*Methoxymethoxyphenyl*)*ethanol* R-**2**.—*R*-(−)-1-(4-Methoxymethoxyphenyl)ethyl hydrogen phthalate (1.04 g, 3.14 mmol), in a solution of sodium (348 mg, 15.1 mmol) in 96% ethanol 7 cm^3, was heated on a steam-bath for several min to give a thick precipitate. The mixture was diluted with water (50 cm^3) and extracted with ether (3 × 50 cm^3), and the combined extracts were dried (Na_2SO_4), filtered and evaporated under reduced pressure to yield (R)-(+)-1-(4-*methoxymethoxyphenyl*)-*ethanol* (498 mg, 2.74 mmol, 87%); b.p. 81 °C (0.005 mmHg, Kugelrohr); $[\alpha]_D^{20}$ +31.7, $[\alpha]_D^{25}$ +31.1 (*c* 5.44 in EtOH); LC analysis of the *S*-(−)-MTPA ester indicated the product to be a mixture of 93.1% *R*-(−)-isomer and 6.9% *S*-(−)-isomer; the ^1H NMR and IR (neat) spectra were identical with those recorded for the racemic alcohol (Found: C, 65.6; H, 7.9. $C_{10}H_{14}O_3$ requires C, 65.91; H, 7.74%).

4-[(2-*Methoxyethoxy*)*methoxy*]*acetophenone* **10**.—A stirred solution of 4-hydroxyacetophenone (39.0 g, 287 mmol) in dry dichloromethane (410 cm^3), protected from atmospheric moisture and containing *N*,*N*-diisopropylethylamine (55.5 g, 429 mmol), was slowly treated with 2-methoxyethoxymethyl chloride (53.5 g, 429 mmol). After 4 h, the mixture was washed with water (2 × 300 cm^3), NaOH (1 mol dm^{-3}; 2 × 200 cm^3) and water (2 × 300 cm^3), dried (Na_2SO_4), filtered and evaporated under reduced pressure to yield 4-[(2-*methoxyethoxy*)*methoxy*]*acetophenone* (64.2 g, 287 mmol, 100%); b.p. 100–109 °C (0.005 mmHg); δ_H 7.97, 7.86, 7.11, 7.02 (q, 4 H, *para*-substituted aromatic), 5.31 (s, 2 H, OCH_2O), 3.87–3.47 (m, 4 H, OCH_2CH_2O) and 3.35 (s, 3 H, CH_3O); ν(neat)/cm^{-1} 2921, 2888, 2814, 1677 (C=O), 1603, 1509, 1416, 1362, 1275, 1235, 1175, 1108, 987 and 840 (Found: C, 63.95; H, 7.05. $C_{12}H_{16}O_4$ requires C, 64.27; H, 7.19%).

(RS)-1-[4-(2-*Methoxyethoxy*)*methoxyphenyl*]*ethanol* **3**.—4-[(2-*Methoxyethoxy*)*methoxy*]*acetophenone* (123 g, 548 mmol) in 95% ethanol (900 cm^3) was slowly treated with $NaBH_4$ (10.4 g, 274 mmol). The mixture was stirred overnight and quenched with water (300 cm^3). After the aqueous phase had been saturated with NaCl the layers were separated and the aqueous phase was extracted with ether. The ethanol was evaporated under reduced pressure and the residue was dissolved in the ether extract, which was dried (Na_2SO_4), filtered and evaporated under reduced pressure to yield (RS)-[4-(2-*methoxyethoxy*)*methoxyphenyl*]*ethanol* (122 g, 533 mmol, 97%); b.p. 120–125 °C (0.005 mmHg); δ_H 7.34, 7.23, 7.06, 6.95 (q, 4 H, *para*-substituted aromatic), 5.24 (s, 2 H, OCH_2O), 4.82, (q, 1 H, ArCH, *J* 6.5), 3.87–3.47 [m, 4 H, $O(CH_2)_2O$], 3.35 (s, 3 H, CH_3O), 2.13 (bs, 1 H, D_2O exch., OH) and 1.45 (d, 3 H, CH_3, *J* 6.4); ν(neat)/cm^{-1} 3418 (OH), 2973, 2926, 2842, 1611, 1509, 1219, 1091, 1004, 846 and 835 (Found: C, 63.6; H, 8.05. $C_{12}H_{18}O_4$ requires C, 63.70; H, 8.02%).

(RS)-2-(*Methoxyethoxy*)*methyl* 1-[4-(2-*Methoxyethoxy*)-*methoxyphenyl*]*ethyl Ether* **4**.—A stirred solution of (*RS*)-1-[4-(2-methoxyethoxy)methoxyphenyl]ethanol (2.52 g, 11.1 mmol) in dry dichloromethane (25 cm^3), protected from atmospheric moisture and containing *N*,*N*-diisopropylethylamine (2.16 g, 16.7 mmol), was slowly treated with 2-methoxyethoxymethyl chloride (2.08 g, 16.7 mmol) in dichloromethane (2 cm^3). After 24 h, the reaction mixture was washed with water (3 × 50 cm^3), NaOH (1 mol dm^{-3}; 3 × 50 cm^3) and water (3 × 50 cm^3), dried (Na_2SO_4), filtered and evaporated under reduced pressure to give the *ether* **4** (3.34 g, 10.8 mmol, 97%); b.p. 130–132 °C (0.020 mmHg); δ_H 7.31, 7.20, 7.05, 6.95 (q, 4 H, *para*-substituted aromatic), 5.25 (s, 2 H, OCH_2OPh), 4.86–4.53 (m, 3 H, $ArCHOCH_2O$), 3.88–3.44 [m, 8 H, $O(CH_2)_2O$], 3.37 (s, 6 H, CH_3O) and 1.44 (d, 3 H, CH_3, *J* 6.3); ν(neat)/cm^{-1} 2931, 2884, 1609, 1510, 1224, 1098, 1038, 1012 and 839; *m*/*z* (E1, 70 eV) (rel. int.) 314 (M^+, 0.3), 269 (5), 225 (12), 209 (9), 131 (9), 121 (11), 120 (9) and 84 (100) (Found: M^+, 314.1720. $C_{16}H_{26}O_6$ requires *M*, 314.1729).

RS-4-*Methoxybenzyl* 1-[4-(2-*Methoxyethoxy*)*methoxyphenyl*]*ethyl Ether* **5**.—(*RS*)-1-[4-(2-methoxyethoxy)methoxyphenyl]ethanol (3.89 g, 17.2 mmol) in dry THF (5 cm^3) was added, under nitrogen, to a stirred suspension of NaH (1.28 g, 53.2 mmol) in dry THF (50 cm^3). The mixture was heated at reflux for 2 h, cooled to room temp. and treated with 4-methoxybenzyl chloride (4.16 g, 26.6 mmol) in dry THF (5 cm^3). After the mixture had been heated at reflux for 24 h, it was cooled to room temperature and quenched by the slow addition of saturated brine (25 cm^3). The organic phase was dried ($MgSO_4$), filtered and evaporated under reduced pressure to give 7.18 g of material, purified by column chromatography on silica gel (hexane–ethyl acetate) to afford the *ether* **5** (3.42 g, 9.88 mmol, 57%); b.p. 190 °C (0.005 mmHg, Kugelrohr); δ_H(240) 7.28–6.84 (m, 8 H, ArH), 5.27 (s, 2 H, OCH_2O), 4.43 (q, 1 H, ArCH, *J* 6.4), 4.35 (d, 1 H, $ArCH_AH_B$, *J* 11.4), 4.20 (d, 1 H, $ArCH_AH_B$, *J* 11.4), 3.86–3.55 [m, 4 H, $O(CH_2)_2O$], 3.79 (s, 3 H, CH_3O), 3.38 (s, 3 H, CH_3O) and 1.43 (d, 3 H, CH_3, *J* 6.4); ν(neat)/cm^{-1} 2973, 2931, 2882, 1609, 1511, 1244, 1223, 1089, 1005 and 836 (Found: C, 69.3; H, 7.6. $C_{20}H_{26}O_5$ requires C, 69.34; H, 7.57%).

RS-tert-*Butyldimethylsilyl* 1-[4-(2-*Methoxyethoxy*)*methoxyphenyl*]*ethyl Ether* **6**.—(*RS*)-1-[4-(2-Methoxyethoxy)methoxyphenyl]ethanol (3.70 g, 16.4 mmol) in dry DMF (5 cm^3) was slowly added, under nitrogen, to a solution of *tert*-butyldimethylsilyl chloride (2.89 g, 19.2 mmol) in dry DMF (6 cm^3) containing imidazole (2.87 g, 42.1 mmol). The reaction mixture was stirred overnight, diluted with water (50 cm^3) and extracted with ether (4 × 100 cm^3). The combined extracts were dried (Na_2SO_4), filtered and evaporated under reduced pressure to give a residue containing DMF, which was removed by co-distillation with benzene under reduced pressure to give the *ether* **6** (5.48 g, 16.1 mmol, 98%); b.p. 115 °C (0.003 mmHg); δ_H 7.33, 7.22, 7.06, 6.95 (q, 4 H, *para*-substituted aromatic), 5.28 (s, 2 H, OCH_2O), 4.86 (q, 1 H, ArCH, *J* 6.3), 3.92–3.53 [m, 4 H, $O(CH_2)_2O$], 3.40 (s, 3 H, CH_3O), 1.41 (d, 3 H, CH_3, *J* 6.5), 0.93 [s, 9 H, $(CH_3)_3$], 0.08 (s, 3 H, CH_3Si-) and 0.00 (s, 3 H, CH_3Si); ν(neat)/cm^{-1} 2957, 2931, 2891, 2858, 1609, 1510, 1251, 1224, 1091, 1005, 959, 839 and 779 (Found: C, 63.6; H, 9.5. $C_{18}H_{32}O_4Si$ requires C, 63.48; H, 9.47%).

RS-tert-*Butyldiphenylsilyl* 1-[4-(2-*Methoxyethoxy*)*methoxyphenyl*]*ethyl Ether* **7**.—*RS*-1-[4-(2-Methoxyethoxy)methoxyphenyl]ethanol (3.94 g, 17.4 mmol) in dry DMF (4 cm^3) was slowly added, under nitrogen, to a solution of *tert*-butyldiphenylsilyl chloride (5.75 g, 21.0 mmol) in dry DMF (10 cm^3) containing imidazole (3.15 g, 48.2 mmol). The reaction mixture was stirred overnight, diluted with water (75 cm^3) and extracted with ether (4 × 100 cm^3). The combined extracts were washed with water (2 × 200 cm^3), dried (Na_2SO_4), filtered and evaporated under reduced pressure to yield 8.88 g of crude product. Purification by column chromatography on silica gel (hexane–benzene) afforded the *ether* **7** (7.68 g, 16.5 mmol, 95%); b.p. 180–200 °C (0.005 nmHg, Kugelrohr); δ_H 7.73–6.68 (m, 14 H, ArH), 5.24 (s, 2 H, OCH_2O), 4.80 (q, 1 H, ArCH, *J* 6.3), 3.36 (s, 3 H, CH_3O), 1.30 (d, 3 H, CH_3, *J* 6.3) and 1.05 [s, 9 H, $(CH_3)_3$]; ν(neat)/cm^{-1} 3070, 3050, 2964, 2931, 2898, 2858, 1609, 1510, 1430, 1224, 1111, 1005, 959, 832 and 706 (Found: C, 72.6; H, 7.9. $C_{28}H_{36}O_4Si$ requires C, 72.37; H, 7.81%).

(RS)-1-[4-(2-*Methoxyethoxy*)*methoxyphenyl*]*ethyl Hydrogen Phthalate*.—(*RS*)-1-[4-(2-Methoxyethoxy)methoxyphenyl]ethanol (24.8 g, 110 mmol) in dry DMF (25 cm^3) was slowly added to a solution of phthalic anhydride (16.3 g, 110 mmol) in dry DMF (75 cm^3) protected from atmospheric moisture and containing imidazole (7.47 g, 110 mmol). The mixture was stirred for 2 h at 100 °C, cooled to room temp. and worked up as described above for compound **5** to yield the *title compound* (29.8 g, 79.5 mmol, 72%) as a viscous oil: δ_H 10.21 (br s, 1 H, D_2O exch., CO_2H), 7.93–7.44 (m, 4 H, *ortho*-substituted aromatic), 7.40, 7.29, 7.07, 6.96 (q, 4 H, *para*-substituted aromatic), 6.10 (q, 1 H, ArCH, *J* 6.6), 5.21 (s, 2 H, OCH_2O), 3.85–3.44 [m, 4 H, $O(CH_2)_2O$], 3.35 (s, 3 H, CH_3O) and 1.64 (d, 3 H, CH_3, *J* 6.6); ν(neat)/cm^{-1} 3543, 3353, 3128, 3072, 2981, 2931, 2896, 2826, 2636, 2538, 1729 (C=O), 1511, 1286, 1223, 1124, 1103, 1075, 1005, 836 and 752 (Found: C, 63.95; H, 6.0. $C_{20}H_{22}O_7$ requires C, 64.16; H, 5.92%). The *methyl ester* was prepared from the free acid with diazomethane, *m*/*z* (EI, 70 eV) (rel. int.) 388 (M^+, 58), 225 (56), 209 (41), 208 (30), 163 (100), 149 (27) and 120 (66) (Found: M^+, 388.1517. $C_{21}H_{24}O_7$ requires *M*, 388.1520).

(S)-1-[4-(2-*Methoxyethoxy*)*methoxyphenyl*]*ethyl Hydrogen Phthalate*.—A vigorously-stirred solution of *RS*-1-[4-(2-methoxyethoxy)methoxyphenyl)]ethyl hydrogen phthalate (18.6 g, 49.6 mmol) in ether (300 cm^3) was treated with (*S*)-(−)-1-phenylethylamine (6.02 g, 49.7 mmol), and the salt, which precipitated within 1 min, was filtered off from solution by suction and washed with ether. The air-dried salt crystallized from methyl acetate as rosettes of needles (8.12 g, 16.4 mmol, 66%); m.p. 141–143 °C; $[\alpha]_D^{25}$ −6.10 (*c* 2.92 in EtOH) (Found: C, 67.65; H, 6.65; N, 2.85. $C_{23}H_{33}NO_7$ requires C, 67.86; H, 6.71; N, 2.83%).

The laevorotatory salt (32.5 g, 65.7 mmol) was suspended in water (700 cm^3) at 5 °C and the rapidly-stirred mixture was slowly treated with oxalic acid·$2H_2O$ (8.29 g, 65.8 mmol) in water (160 cm^3). The aqueous phase was saturated with NaCl

and extracted with ether (3 × 700 cm^3), and the combined extracts were dried (Na_2SO_4), filtered and evaporated under reduced pressure to yield the *title compound* as a viscous oil which was either hydrolysed immediately or stored at −78 °C.

R-1-[4-(2-*Methoxyethoxy*)*methoxyphenyl*]*ethyl Hydrogen Phthalate*.—The ether solution containing the ether-soluble fraction (150 cm^3) from the treatment of (*RS*)-1-[4-(2-methoxyethoxy)methoxyphenyl]ethyl hydrogen phthalate in ether with (*S*)-(−)-1-phenylethylamine was washed with ice-cold HCl (0.2 mol dm^{-3}; 125 cm^3) and brine (2 × 125 cm^3) to remove the amine and dried ($MgSO_4$). The stirred filtrate was treated with *R*-(+)-1-phenylethylamine (6.02 g, 49.7 mmol) and the precipitated salt was filtered off from solution by suction and washed with ether. The air-dried salt was crystallized from methyl acetate to yield the *salt* as rosettes of needles (7.92 g, 16.0 mmol, 65%); m.p. 141–143 °C; $[\alpha]_D^{25}$ +6.1 (*c* 2.82 in EtOH) (Found: C, 67.65; H, 6.6; N, 2.85. $C_{28}H_{33}NO_7$ requires C, 67.86; H, 6.71; N, 2.83%). The free acid was liberated from the salt in a manner analogous to that employed for the laevorotatory salt and was either hydrolysed immediately or stored at −78 °C.

(S)-(−)-1-[4-(2-*Methoxyethoxy*)*methoxyphenyl*]*ethanol* S-**3**.—The hydrogen phthalate liberated from the laevorotatory salt above (65.7 mmol) was dissolved in a solution of sodium (7.45 g, 324 mmol) in 96% ethanol (130 cm^3), and the mixture was heated on a steam-bath for several min to give a thick precipitate. The hydrolysate was diluted with water (750 cm^3), saturated with NaCl and extracted with ether (4 × 600 cm^3). The combined extracts were dried (Na_2SO_4), filtered and evaporated under reduced pressure to yield the *alcohol* S-**3** (14.8 g, 65.4 mmol, 100%), b.p. 120–125 °C (0.005 mmHg); d_4^{20} 1.108; $[\alpha]_D^{20}$ −37.44 (neat); CD $[\Theta]_{290}$ 0, $[\Theta]_{280}$ −275, $[\Theta]_{275}$ −143sh, $[\Theta]_{240}$ 0, $[\Theta]_{232}$ +326 (*c* = 2.20, EtOH); HPLC analysis of the *S*-(−)-MTPA ester of the alcohol (t_R 35.1 min) showed no trace of the *R*-(+)-isomer; the ^1H NMR and IR (neat) spectra were identical when those recorded for the racemic alcohol (Found: C, 63.45; H, 8.05. $C_{12}H_{18}O_4$ requires C, 63.70; H, 8.02%).

(R)-(+)-1-[4-(2-*Methoxyethoxy*)*methoxyphenyl*]*ethanol* R-**3**.—The phthalate liberated from the dextrorotatory salt above was hydrolysed in a manner analogous to that employed for the *S*-compound to yield the *alcohol* R-**3**, b.p. 120–125 °C (0.005 mmHg); d_4^{20} 1.108; $[\alpha]_D^{20}$ +37.2 (neat); HPLC analysis of the *S*(−)-MTPA ester of the alcohol (t_R 34.0 min) showed no trace of the *S*-(−)-isomer. The ^1H NMR and IR (neat) spectra were identical with those recorded for the racemic alcohol (Found: C, 63.6; H, 8.15. $C_{12}H_{18}O_4$ requires C, 63.70; H, 8.02%).

4-*Vinylphenol*.—(*RS*)-1-[4-(2-Methoxyethoxy)-methoxyphenyl]ethanol **3** (236 mg, 1.04 mmol), in dry dichloromethane (2 cm^3) containing *N*,*N*-diisopropylethylamine (4.08 g, 31.6 mmol), was cooled to 0 °C and slowly treated, under nitrogen, with a solution of 2-bromo-1,3,2-benzodioxaborole (0.2 mol dm^{-3}; 15 cm^{-3}, 3.0 mmol) in dry dichloromethane. The reaction mixture was stirred for 3 h, quenched with water (25 cm^3) and stirred for an additional 15 min. The aqueous phase was adjusted to pH 7 with 1 mol dm^{-3} H_3PO_4, saturated with NaCl, separated from the organic phase and extracted with ether (2 × 40 cm^3). The combined organic phases were dried (Na_2SO_4), filtered and evaporated under reduced pressure to give a viscous oil which was chromatographed on silica gel (dichloromethane) to yield 94 mg of product; this on sublimation (50 °C, 0.35 mmHg) gave the pure phenol (74 mg, 59%) as white needles; m.p. 70–71 °C (lit.,[24] m.p. 71–72 °C); $\delta_H([^2H_6]$-DMSO) 9.50 (s, 1 H, D_2O exch., ArOH), 7.33, 7.23, 6.78, 6.67 (q, 4 H, *para*-substituted aromatic), 6.82, 6.71 (partially buried beneath the resonances at 6.78 and 6.67), 6.58, 6.44 (dd, 1 H, H of vinylic double bond), 5.57 (dd, 1 H, terminal methylene H *trans* to H_1, *J* 1.2, 17.6 and 5.03 (dd, 1 H, terminal methylene H *cis* to H_1, *J* 1.2, 10.9); ν(KBr)/cm^{-1} 3376 (OH), 1609, 1510, 1257, 1111, 992, 899 and 839.

This conversion was also accomplished in 51% yield employing the chloro analogue of the catechol reagent, 2-chloro-1,3,2-benzodioxaborole.[15]

(R)-(+)-1-(4-*Hydroxyphenyl*)*ethanol* R-**1**.—4-[2-(Methoxyethoxy)methoxy]acetophenone (8.88 g, 39.6 mmol) in dry THF (18 cm^3) was slowly added, under nitrogen, to a solution of (+)-chlorodiisopinocampheylborane (15.2 g, 47.4 mmol) in dry THF (26 cm^3), at 0 °C. The reaction mixture was stirred for 72 h and quenched by the slow addition of triethylamine (7.20 g, 71.3 mmol) and water (40 cm^3). The aqueous phase was saturated with NaCl, separated from the organic phase and extracted with ether (3 × 50 cm^3). The combined organic phases were dried (Na_2SO_4), filtered and evaporated under reduced pressure to give a mixture of product and (−)-α-pinene. The mixture was dissolved in ether (120 cm^3) and extracted with NaOH (1 mol dm^{-3}; 6 × 40 cm^3), and the combined extracts were washed with ether (3 × 150 cm^3), cooled to 5 °C and titrated to pH 7 with HCl (1 mol dm^{-3}; 240 cm^3).* The aqueous phase was saturated with NaCl and extracted with ethyl acetate (3 × 400 cm^3). The combined extracts were dried (Na_2SO_4), filtered and evaporated under reduced pressure. After purification by column chromatography on silica gel (hexane–ethyl acetate), the *alcohol* R-**1** (3.58 g, 25.9 mmol, 65%) had m.p. 157–158 °C (colourless, rhombic–prismatic plates); mixed m.p. with *S*-(−)-isomer: 136–138 °C; $[\alpha]_D^{20}$ +47.5, $[\alpha]_{578}^{20}$ +49.7, $[\alpha]_{546}^{20}$ 56.9, $[\alpha]_{436}^{20}$ +101.0 and $[\alpha]_{365}^{20}$ +168.5 (*c* 5.06 in EtOH). A sample of the recrystallized product was methylated with diazomethane, and HPLC analysis of the *S*-(−)-MTPA ester indicated the product to be >99.8% *R*-(+)-isomer; $\delta_H([^2H_6]$-$Me_2CO)$ 8.16 (bs, 1 H, D_2O exch., ArOH), 7.26, 7.15, 6.82, 6.71 (q, 4 H, *para*-substituted aromatic), 4.75 (q, 1 H, ArCH, *J* 6.2), 4.08 (bs, 1 H, D_2O exch., OH) and 1.36 (d, 3 H, CH_3, *J* 6.4); ν(KBr)/cm^{-1} 3396 (OH), 3310, 2971, 2924, 2825, 2692, 2612, 2499, 1895, 1616, 1596, 1516, 1463, 1238, 1078, 1072, 1012, 899 and 832 (Found: C, 69.8; H, 7.45. $C_8H_{10}O_2$ requires C, 69.54; H, 7.30%).

(S)-(−)-1-(4-*Hydroxyphenyl*)*ethanol* S-**1**.—4-[2-(Methoxyethoxy)methoxyacetophenone was reduced with (−)-chlorodiisopinocampheylborane in dry THF, in a manner analogous to the preceding experiment, to yield the *alcohol* S-**1**, m.p. 157–159 °C (colourless, rhombic–prismatic plates); mixed melt with the *R*-(+)-isomer: 136–138 °C; $[\alpha]_D^{20}$ −47.5, $[\alpha]_{578}^{20}$ −49.5, $[\alpha]_{546}^{20}$ −56.9, $[\alpha]_{436}^{20}$ −101.0 and $[\alpha]_{365}^{20}$ −168.4 (*c* 4.98 in EtOH); CD $[\Theta]_{300}$ 0°, $[\Theta]_{285}$ −433°, $[\Theta]_{278}$ −506°, $[\Theta]_{271}$ −433°, $[\Theta]_{250}$ 0°, $[\Theta]_{238}$ +263°; HPLC analysis of the *S*-(−)-MTPA ester of the *p*-methoxycarbinol indicated the product to be >99.7% *S*-(−)-isomer; $\delta_H([^2H_6]$-$Me_2CO)$ 8.15 (s, 1 H, D_2O exch., ArOH), 7.25, 7.15, 6.82, 6.71 (q, 4 H, *para*-substituted aromatic), 4.90–4.61 (m, 1 H, ArCH), 4.04 (d, 1 H, D_2O exch., OH, *J* 4.0) and 1.36 (d, 3 H, CH_3, *J* 6.4); the IR (KBr) spectrum was identical with that recorded for the *R*-(+)-isomer (Found: C, 69.7; H, 7.4. $C_8H_{10}O_2$ requires C, 69.54; H, 7.30%).

A dimorphic crystalline form of this material crystallized from hexane–ethyl acetate as jagged needles: m.p. 115–118 °C; $[\alpha]_D^{20}$ −47.8, $[\alpha]_{578}^{20}$ −49.9, $[\alpha]_{546}^{20}$ −57.2, $[\alpha]_{436}^{20}$ − 101.5 and $[\alpha]_{365}^{20}$ −169.3 (*c* 5.12 in EtOH); HPLC analysis of the *S*-(−)-MTPA ester of the *p*-methoxycarbinol indicated the

* Titration to pH < 4 resulted in a product of reduced enantiomeric purity.

product to be >99.7% *S*-(−)-isomer; the ^{1}H NMR and IR (KBr) spectra were identical to those recorded for the other crystal form (Found: C, 69.6; H, 7.35. $C_8H_{10}O_2$ requires C, 69.54; H, 7.30%).

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