Direct and enantiospecific *ortho*-benzylation of phenols by the Mitsunobu reaction

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***ortho*-Substituted phenol derivatives with high optical purity have been obtained directly by Mitsunobu reaction between an appropriate phenol and an optically active benzyl alcohol. In this reaction, the chemical yield was well balanced with the optical purity of the *ortho*-substituted compound when 5 equiv. of phenol was allowed to react with 1 equiv. of alcohol in a solvent such as dichloroethane or toluene. In addition, it was confirmed by an X-ray analysis of the product that stereochemical inversion of the asymmetric centre took place in this reaction, as well as the usual Mitsunobu reaction. This reaction is useful in the preparation of optically active phenol derivatives possessing a diarylmethane moiety.**

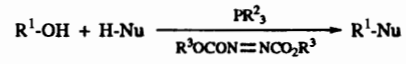
The Mitsunobu reaction, wherein alcohols (R-OH) and acidic compounds (H-Nu) are condensed using the redox couple of a triaryl- or trialkyl-phosphine and a dialkyl azodicarboxylate (Scheme 1),[1] proceeds with stereochemical inversion by an S_N2 mechanism. Accordingly, the Mitsunobu reaction is both a convenient and very powerful tool for stereochemical control in organic synthesis.

Many types of bond formation such as carbon–oxygen, carbon–nitrogen, carbon–sulfur and carbon–halogen are effected by the Mitsunobu reaction, although carbon–carbon bond formation is limited on account of the relative low acidity of the carbon nucleophile. Thus, formation of carbon–carbon bonds by the Mitsunobu reaction has been carried out successfully only in the case of highly active methylene compounds or in an intramolecular reaction.[2]

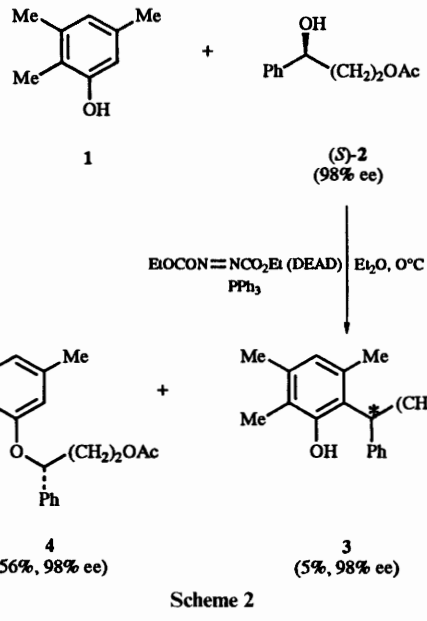
In the Mitsunobu reaction of equimolar proportions of 2,3,5-trimethylphenol **1** and (*S*)-1-acetoxy-3-phenylpropan-3-ol (*S*)-**2** in diethyl ether we found formation of an *ortho*-alkylated compound, 3-(2-hydroxy-3,4,6-trimethylphenyl)-3-phenylpropyl acetate **3** (5%) in addition to the major product, the *O*-alkylated compound 3-phenyl-3-(2,3,5-trimethylphenoxy)-propyl acetate **4** (Scheme 2). Interestingly, the enantiomeric excess of **3** (98% ee) was equivalent to the ees of the alcohol (*S*)-**2** and the ether **4**. Additionally, the *ortho*-alkylated product **3** was produced directly and not by rearrangement of **4**; this was established by the fact that **4** failed to undergo rearrangement to **3** under the Mitsunobu conditions and, further, the ee of **3** was greater than that obtained by a rearrangement under acidic conditions.† This is the first example of stereospecific *ortho*-alkylation of phenols under Mitsunobu reaction conditions. Since the stereochemical control of the newly constructed tertiary carbon in the highly hindered system is useful for the synthesis of optically active phenol derivatives, we have investigated the reaction conditions in order to optimize the chemical yield and optical purity of the *ortho*-alkylated product.

Phenol derivatives which have a diarylmethyl moiety can be synthesized by the Friedel–Crafts alkylation of phenols with α-substituted benzyl alcohols in good yield.

† Treatment of the phenol ether with 1 equiv. of CF_3SO_3H at −78 °C gave *ortho* benzylated product with *ca.* 10% racemization.



Scheme 1



Scheme 2

However, since the preparation of optically active derivatives is very difficult by this method, highly stereocontrolled *ortho*-benzylation of phenols has potential for the synthesis of enantiomers of phenol derivatives which are orally active nonprostanoid thromboxane A_2 (TXA_2) receptor antagonists.[3]

Here, we report that the Mitsunobu reaction of phenols with optically active benzyl alcohol produces *ortho*-alkylated product with high optical purity.

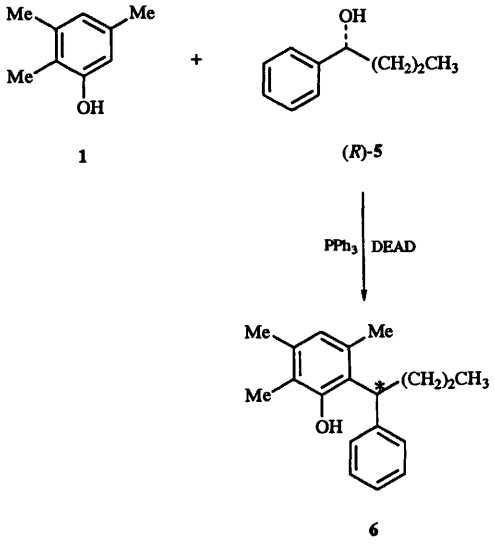
Results and discussion

In order to optimize the yield and ee of the *ortho*-alkylated product formed in the Mitsunobu reaction of 2,3,5-trimethylphenol **1** and (*R*)-1-phenylbutan-1-ol (*R*)-**5** (Scheme 3) we varied

Table 1 *ortho*-Benzylation of **1** by the Mitsunobu reaction

Run	Solvent	[1]/[7]	Temp./ °C	Yield of **6** (%)	Optical yield of **6** (% ee)[a]
1	$Cl(CH_2)_2Cl$	1	10	16	96
2	$Cl(CH_2)_2Cl$	3	10	36	95
3	$Cl(CH_2)_2Cl$	5	10	37	94
4	$Cl(CH_2)_2Cl$	10	10	40	92
5	$Cl(CH_2)_2Cl$	5	20	36	89
6	$Cl(CH_2)_2Cl$	5	40	35	91
7	$Cl(CH_2)_2Cl$	5	60	33	89
8	CH_2Cl_2	5	10	42	94
9	Toluene	1	25	19	99
10	Toluene	5	25	40	99
11	Xylene	5	25	40	99
12	Et_2O	1	10	7	>99
13	Et_2O	5	10	26	99
14	THF	5	10	30	96

[a] Enantiomeric excesses were determined by chiral HPLC with Daicel Chiralcel ODR.



Scheme 3

the reaction solvent, the reaction temperature and the alkyl group in the diazocarboxylate in a series of experiments. Table 1 shows the yields and ees of the *ortho*-alkylated product **6** obtained by HPLC analysis with a chiral column (CHIRALCEL ODR). The optical purity of (*R*)-**5** was >99% ee.

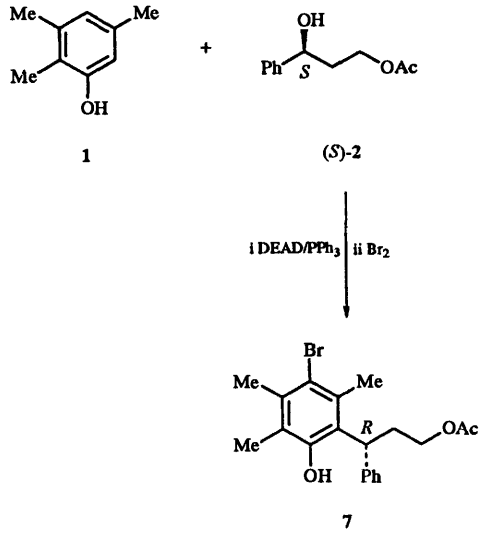
With increasing amounts of phenol **1** in reactions using 1,2-dichloroethane (runs 1–4) as a solvent, the chemical yield of **6** also increased; thus, the yields of **6** were 16, 36, 38 and 40% for molar ratios of **1** to (*R*)-**5** of 1, 3, 5, and 10, respectively. Concurrently, optical yield of **6** decreased from 96 to 92% ee. Similar increases in the yield of **6** were obtained for reactions in toluene (runs 9, 10) and diethyl ether (runs 12, 13). Reactions with 5 equiv. of the phenol **1** were carried out in different solvents. Thus, relatively good yields (*ca.* 40%) were obtained using 1,2-dichloroethane (run 3), dichloromethane (run 8), toluene (run 10) and xylene (run 11) as solvent, while **6** was obtained in relatively low yield (26–30%) in diethyl ether and tetrahydrofuran (THF) (runs 13, 14). The optical purity of the product was low in reactions carried out in 1,2-dichloroethane (run 3, 94% ee) and dichloromethane (run 8, 94% ee), compared with that obtained in other solvents (runs 10, 11, 13, 99% ee); a reaction in THF gave a moderate result (96% ee).

The yield and enantiomeric excess of **6** decreased in reactions in 1,2-dichloroethane (runs 3, 5–7) with increasing reaction temperature (from 10 to 60 °C). The best result was obtained at 10 °C; reactions at temperatures < 10 °C, were impracticable since **1** was then not completely soluble in the solvent. For the same reason, the best result for reactions in toluene was at 25 °C (40%, 99% ee).

Table 2 Effects of alkyl groups in $ROCON{=}NCO_2R$

Run	R in $ROCON{=}NCO_2R$	Yield of **6** (%)	Optical yield of **6** (% ee)[a]
1	Me	40	93
2	Et	37	94
3	Pr^i	42	93
4	Bu	52	83

[a] Enantiomeric excesses were determined by chiral HPLC with Daicel Chiralcel ODR.



Scheme 4

The influence of the alkyl groups in diazocarboxylates on the yield and optical purity of **6**, was investigated by allowing 5 equiv. phenol **1** to react with the benzyl alcohol (*R*)-**5** in dichloroethane at 10 °C; the results are summarized in Table 2. Although there was no great difference in the results for the three alkyl groups Me, Et and Pr^i, the chemical yield increased in the reaction for the diazocarboxylate R = Bu^t, although the ee of **6** was lower.

From our study it was concluded that the reaction of 5 equiv. of the phenol **1** with the benzyl alcohol **6** in toluene at 25 °C in the presence of triphenylphosphine and diethyl azocarboxylate was the most efficient reaction for the preparation of optically active *ortho*-substituted phenols (40%, 99% ee).

To confirm the stereochemistry of this Mitsunobu reaction, the absolute configuration at the α-carbon of the *ortho*-alkylated phenol obtained in the reaction of 2,3,5-trimethylphenol **1** and 1-acetoxy-3-phenylpropan-3-ol (*S*)-**2** was established as follows. Treatment of 10 equiv. of compound **1** with (*S*)-**2** in 1,2-dichloroethane followed by bromination gave compound **7** (Scheme 4), the absolute configuration of which was determined to be *R* by X-ray crystallographic analysis (Fig. 1). It was, therefore, confirmed that stereochemical inversion of the asymmetric centre took place during the Mitsunobu reaction.

As shown in Tables 1 and 2, the amount of phenol and reaction solvent influenced the chemical yield and optical purity of the *ortho*-alkylated product, the reason for which is as follows. From a stereochemical point of view the mechanism for this reaction is thought to be the same as for a Mitsunobu reaction. The latter, proposed by Mitsunobu [1a] and applied to the alkylation of phenols, is shown in Fig. 2. In this, an active oxyphosphonium salt intermediate, formed by the reaction of a redox couple and an alcohol, undergoes an S_N2 reaction with anions present to produce inverted products and the phosphine oxide. In the case of a phenol, an ambident nucleophile, reaction on the phenol oxygen produces *O*-alkylated product,

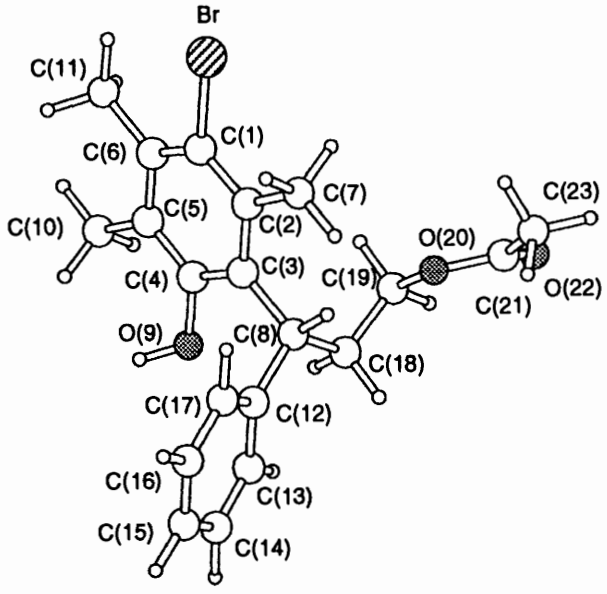


Fig. 1 Molecular structure of compound **7** as determined by X-ray crystallographic analysis

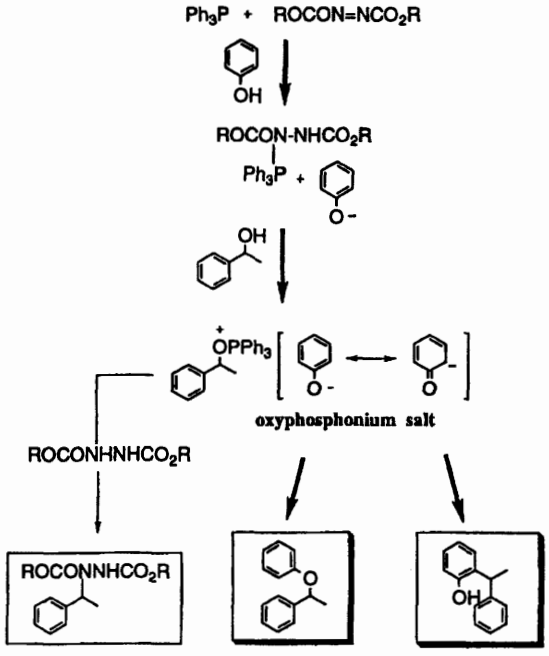
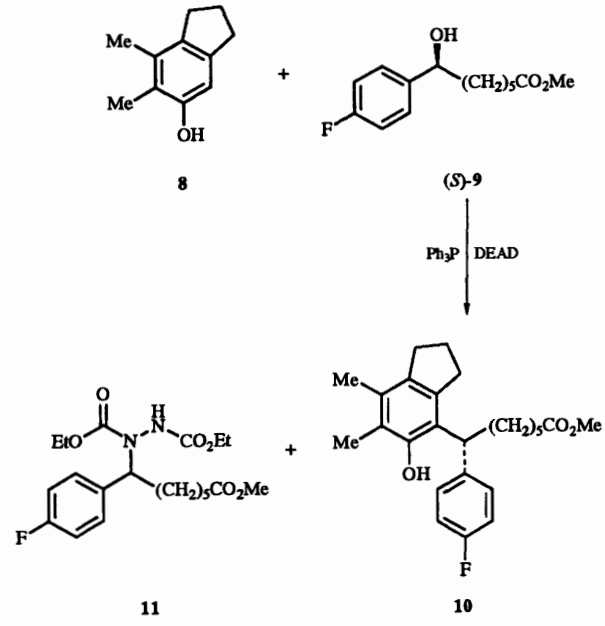


Fig. 2

whilst reaction at the *ortho*-position gives the *ortho*-alkylated product.‡

The amount of phenol used influences the chemical yield of *ortho*-alkylated product in two way. The first arises as a result of chelation of the phenoxide anion by the excess of phenol. An excess of phenol chelates phenoxide anion to shield the hydroxy group and inhibit the reaction on the oxygen atom and, consequently, the yield of *ortho*-alkylated product increases. It is known that *O*-alkylation is inhibited by a similar chelation effect in the alkylation of phenol using phenol as a solvent.[4] The second way is a result of side reactions being depressed. The Mitsunobu reaction of equimolar amounts of the phenol **8** with the alcohol (*S*)-**9** gave *ortho*-alkylated product **10** (9%) and DEAD adduct **11** (33%) (Scheme 5). The production of significant amounts of **11** might be the result of a small

‡ Reaction at the *para*-position of phenol gives a *para*-substituted product and a small amount of *para*-alkylated product.



Scheme 5

difference between the pK_a of the NH of hydrogenated DEAD and that of the phenol **9**. In this system, a large amount of phenol is favourable for the reaction of phenol and oxyphosphonium ion. In fact, no diethyl diazodicarboxylate (DEAD) adduct **11** was detected in the reaction of 5 equiv. of the phenol **8**.

The solvent effect influences both the ratio of *C* to *O* alkylation and the optical purity of the product. The chemical yields in Et_2O (26%) and THF (30%) were lower than those in other non-polar solvents (37–42%), since the former have a great potential for solvation of the hydroxy group of the phenol. Thus, by forming hydrogen bonds with phenol in the reaction system they inhibit the interaction between the excess of phenol and the oxygen of phenoxide anions and, consequently, the yields are relatively low.

The optical purity of products (see Table 1) were also affected by reaction solvent used. Although the Mitsunobu reaction proceeds by an S_N2 process, in this work there was some racemization. Thus, the ees were very high in Et_2O and aromatic hydrocarbons (toluene, xylene), and relatively low in dichloroethane and dichloromethane. For reactions carried out in the last two solvents, which have a relatively large dielectric factor (ε_r) [$Cl(CH_2)_2Cl$: ε_r = 10.36, CH_2Cl_2: ε_r = 9.08] and an ability to solvate cations, the oxyphosphonium ion is solvated, while the phenoxide anion is chelated by the excess of phenol. Racemization then tends to occur in the solvated ion pairs so formed. In contrast, in toluene and xylene (ε_r are 2.379 and 2.2699, respectively) the cation is less strongly solvated and reactions proceed without racemization. Differences in the ees for products obtained in Et_2O (99% ee) and THF (96% ee) may also reflect dielectric differences (Et_2O: ε_r = 4.335, THF: ε_r = 7.58).

To examine the effectiveness of *ortho*-benzylation of phenols in this modified Mitsunobu condition, three phenols (**12**–**14**) were allowed to react with benzyl alcohols. The results are summarized in Table 3. The reaction of the phenol **12**, which possesses no substituent at the 3-position, with (*S*)-**2** gave the desired *ortho*-benzylated product **15** (32%), with no *para*-benzylated product. The position of benzylation in **15** was determined by NOE measurements. This result indicated that phenols are regioselectively benzylated at the *ortho*-position in this reaction. The phenols **13** and **14** which have electron-withdrawing groups (Br, Ac) were benzylated to give the *ortho*-derivatives **7** and **16**, respectively, in a similar manner. In particular, the observation that the acetylphenol **14** reacted

Table 3 *ortho*-Benzylation of phenols

Phenol			Alcohol		*ortho*-Benzylated phenol		
	R^3	R^4	R^5			Yield (%)	$[\alpha]_D$
12	H	H	(*S*)-**2**	$(CH_2)OAc$	**15**	32	−19.3
13	Br	Me	(*S*)-**2**	$(CH_2)OAc$	**7**	34	+110.0
14	Ac	*Me*	(*R*)-**5**	$(CH_2)_2CH_3$	**16**	26	−126.8

to produce a benzylated phenol underlines the considerable reactivity of the phosphonium intermediates in the Mitsunobu reaction and the effectiveness of the *ortho*-benzylation of phenols under these conditions.

In conclusion, *ortho*-substituted phenols with high optical purity have been obtained directly by the Mitsunobu reaction between an appropriate phenol and an optically active benzyl alcohol. The chemical yield was well balanced with the optical purity of the *ortho*-substituted product when 5 equiv. phenol were allowed to react with 1 equiv. of an alcohol in a solvent such as dichloroethane or toluene. This reaction is, moreover, useful for the stereocontrolled synthesis of phenol derivatives containing a diarylmethane moiety. The modified Mitsunobu reaction has been applied to the synthesis of phenol derivatives which possess potent TXA_2 receptor antagonistic activity [*e.g.* compound **17** (Fig. 3)].[5] An attempt to increase the yield of *ortho*-substituted product and to apply this reaction to other phenols and alcohols is now under investigation.

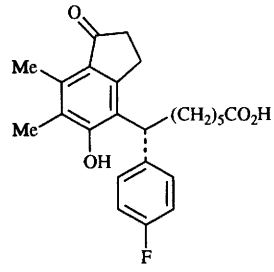


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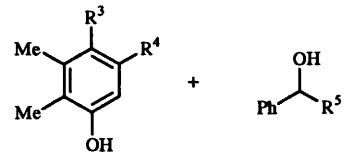
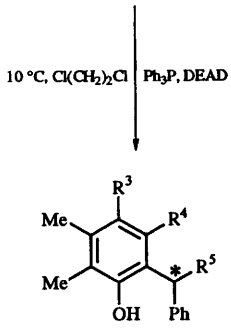
Fig. 3



12 $R^3 = H$, $R^4 = H$
13 $R^3 = Br$, $R^4 = Me$
14 $R^3 = Ac$, $R^4 = Me$

(*S*)-**2** $R^5 = (CH_2)_2OAc$
(*R*)-**5** $R^5 = (CH_2)_2CH_3$



15 $R^3 = H$, $R^4 = H$, $R^5 = (CH_2)_2OAc$
7 $R^3 = Br$, $R^4 = Me$, $R^5 = (CH_2)_2OAc$
16 $R^3 = Ac$, $R^4 = Me$, $R^5 = (CH_2)_2CH_3$

Experimental

IR spectra were taken on a HITACHI-215 spectrometer. Mass spectra were performed on a JEOL JMS-AX 505W spectrometer. ^1H NMR spectra were recorded on a JEOL JNM-GX400 FT NMR spectrometer at 400 MHz and a Varian Gemini 200 instrument at 200 MHz, and ^{13}C NMR spectra were recorded on a JEOL JNM-GX400 FT NMR spectrometer at 100 MHz with tetramethylsilane as an internal standard; signal patterns are indicated as s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and br = broad. Melting points were obtained with a Yanaco micro melting apparatus and the data are uncorrected. Optical rotations were recorded on a JASCO DIP-370 digital polarimeter and are recorded as 10^{-1} deg cm^2 g^{-1}. For thin-layer chromatography (TLC) analysis pre-coated silica gel plates (E. Merck 60 F254, 0.2 mm) were used. Solutions in organic solvents were dried over anhydrous $MgSO_4$. Column chromatography was carried out on silica gel (Wakogel C-300, particle size 45–75 μm) by the flash chromatography technique.

Mitsunobu reaction of 2,3,5-trimethylphenol 1 and 1-acetoxy-3-phenylpropan-3-ol (*S*)-2

Diethyl diazodicarboxylate (DEAD) (95%; 2.4 cm^3, 14.4 mmol) was added dropwise to a solution of compound (*S*)-**2** (2.8 g, 14.4 mmol), 2,3,5-trimethylphenol **1** (2.0 g, 14.4 mmol) and triphenylphosphine (3.8 g, 14.4 mmol) in diethyl ether (100 cm^3) at 0 °C. The mixture was stirred at 0 °C for 2 h after which it was filtered and evaporated under reduced pressure. The residue was chromatographed on silica gel with EtOAc–hexane (1:100–1:20) as eluent to yield (*R*)-3-phenyl-3-(2,3,5-trimethylphenoxy)propylacetate **3** (2.5 g, 56%) and (*R*)-3-(2-hydroxy-3,4,6-trimethylphenyl)-3-phenylpropyl acetate **4** (0.2 g, 5%).

Compound 3. A colourless oil (Found: C, 76.3; H, 7.5. Calc. for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74%); $[\alpha]_D^{20}$ +0.7 (*c* 0.76 in $CHCl_3$); $[\alpha]_{Hg435}^{20}$ −9.7 (*c* 0.76 in $CHCl_3$); 98% ee [CHIRALCEL OJ, hexane–EtOH (950:50), 0 °C]; ν_{max}(KBr)/cm^{-1} 2910, 1738, 1235 and 1100; δ_H(200 MHz; $CDCl_3$) 2.03 (3 H, s, COMe), 2.10–2.45 (2 H, m, $CHCH_2$), 2.12 (3 H, s, ArMe), 2.21 (3 H, s, ArMe), 2.23 (3 H, s, ArMe), 4.10–4.35 (2 H, m, CH_2CH_2), 5.23 (1 H, dd, *J* 5.0, 8.5, CH), 6.31 (1 H, s, ArH), 6.53 (1 H, s, ArH) and 7.20–7.38 (5 H, m, Ph); *m*/*z* 312 (M^+, 2), 177 (25), 136 (19), 117 (100) and 91 (5).

Compound 4. A colourless oil (Found: C, 76.8; H, 7.8. Calc. for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74%); $[\alpha]_D^{28}$ +144.4 (*c* 1.0 in $CHCl_3$); 98% ee [CHIRALCEL OJ, hexane–EtOH (950:50), RT]; ν_{max}(KBr)/cm^{-1} 3375, 1710 and 1268; δ_H(200 MHz; $CDCl_3$) 2.02 (6 H, s, ArMe, COMe), 2.20 (3 H, s, ArMe), 2.33 (3 H, s, ArMe), 2.40–2.71 (2 H, m, $CHCH_2$), 3.84–3.99 (1 H, m, CH_2CHH), 4.04–4.20 (1 H, m, CH_2CHH), 4.51 (1 H, s, OH), 4.55 (1 H, dd, *J* 6.0, 10.0, CH), 6.63 (1 H, s, ArH) and 7.12–7.35 (5 H, m, Ph); *m*/*z* 312 (M^+, 19), 252 (100), 237 (46), 225 (36) and 175 (18).

Mitsunobu reaction of 2,3,5-trimethylphenol 1 and (*R*)-1-phenylbutan-1-ol (*R*)-5, typical procedure

DEAD (95%; 0.90 cm^3, 5.5 mmol) in 1,2-dichloroethane (5 cm^3) was added dropwise to a solution of **1** (2.3 g, 16.5 mmol), (*R*)-**5** (0.5 g, 3.3 mmol) and PPh_3 (1.3 g, 5.0 mmol) in 1,2-dichloroethane (20 cm^3). The mixture was stirred for 1 h, after which it was filtered and evaporated under reduced pressure. The residue was chromatographed on silica gel with hexane as eluent to yield 1-(2-hydroxy-3,4,6-trimethylphenyl)-1-phenylbutane **6** (0.33 g, 37%) as a colourless oil (Found: C, 85.1; H, 9.2. Calc. for $C_{19}H_{24}O$: C, 85.02; H, 9.01%); 94% ee [DAICEL CHIRALCEL ODR, H_2O–MeCN (25:75), RT]; ν_{max}(neat)/cm^{-1} 3525, 2975 and 1452; δ_H(200 MHz; $CDCl_3$) 0.95 (3 H, t, *J* 7.0, Me), 1.10–1.52 (m, 2 H, $CHCH_2$), 1.79–2.42 (m, 2 H, CH_2CH_2), 2.02 (3 H, s,

ArMe), 2.21 (3 H, s, ArMe), 2.36 (3 H, s, ArMe), 4.41 (1 H, dd, *J* 6.0, 9.5, CH), 4.54 (1 H, s, OH), 6.63 (1 H, s, ArH) and 7.15–7.46 (5 H, m, Ph); *m/z* 268 (M^+, 27), 225 (100), 211 (8) and 165 (4).

(*R*)-3-(2-Hydroxy-3,4,6-trimethylphenyl)-3-phenylpropyl acetate 4

DEAD (95%; 2.5 cm^3, 15.9 mmol) was added dropwise to a solution of 2,3,5-trimethylphenol **1** (13.6 g, 0.10 mol), (*S*)-3-hydroxy-3-phenylpropyl acetate (*S*)-**2** (1.94 g, 10 mmol) and PPh_3 (3.90 g, 15.0 mmol) in 1,2-dichloroethane (60 cm^3) at 20 °C. The mixture was stirred at 20 °C for 6 h after which it was evaporated under reduced pressure. The residue was chromatographed on silica gel with EtOAc–hexane (1:20) as eluent to yield compound **4** (0.94 g, 30%) as a colourless oil, 98% ee [CHIRALCEL OJ, hexane–EtOH (950:50), RT].

(*R*)-3-(3-Bromo-6-hydroxy-2,4,5-trimethylphenyl)-3-phenylpropyl acetate 7

A solution of Br_2 (0.15 cm^3) in AcOH (2 cm^3) was added dropwise to a solution of (*R*)-3-(2-hydroxy-3,4,6-trimethylphenyl)-3-phenylpropyl acetate **4** (0.90 g) in AcOH (10 cm^3) at room temperature. The mixture was stirred at room temperature for 30 min after which the reaction was quenched by addition of ice to the mixture which was then extracted with EtOAc. The extract was washed successively with saturated aqueous $NaHCO_3$, water and brine, dried and evaporated. The residue was chromatographed on silica gel with EtOAc–hexane (1:10–1:5) as eluent to yield compound **7** (1.05 g, 93%), which was recrystallized from EtOAc; mp 67–68 °C (Found: C, 61.4; H, 6.0; Br, 20.3. Calc. for $C_{20}H_{23}BrO_3$: C, 61.39; H, 5.92; Br, 20.42%); $[\alpha]_D^{28}$ +182.7 (*c* 1.00 in $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3340, 1710, 1283, 1260 and 1232; δ_H(200 MHz; $CDCl_3$) 2.03 (3 H, s, Me), 2.13 (3 H, s, Me), 2.28–2.73 (2 H, m, CH_2O), 2.40 (3 H, s, Me), 2.51 (3 H, s, Me), 3.80–3.96 (1 H, m, CHC*H*), 4.07–4.22 (1 H, m, CHC*H*), 4.58 (1 H, s, OH), 4.73 (1 H, dd, *J* 5.0, 10.0, CH) and 7.17–7.38 (5 H, m, ArH); *m/z* 392 (M^+ + 2, 15), 390 (M^+, 13), 332 (100), 330 (99), 316 (11), 315 (13), 303 (23), 251 (17) and 236 (24).

***N*-Alkylated product 11 from compounds 8 and (*S*)-9**

A solution of DEAD (95%; 0.33 cm^3, 2.1 mmol) in Et_2O (3 cm^3) was added dropwise to a solution of 6,7-dimethylindan-5-ol **8** (0.19 g, 1.2 mmol), (*S*)-methyl 7-(4-fluorophenyl)heptan-7-ol (*S*)-**9** (0.3 g, 1.2 mmol) and PPh_3 (0.46 g, 1.8 mol) in Et_2O (15 cm^3) at 25 °C. The mixture was stirred for 1 h after which it was filtered and evaporated under reduced pressure. The residue was chromatographed on silica gel with EtOAc–hexane (1:100–1:8) as eluent to yield methyl 7-(4-fluorophenyl)-7-(5-hydroxy-6,7-dimethylindan-5-yl)heptanoate **10** (0.04 g, 9%) and compound **11** (0.16 g, 33%).

Compound 10. A colourless oil (Found: C, 75.6; H, 7.7. Calc. for $C_{25}H_{31}FO_3$: C, 75.35; H, 7.84%); ν_{max}(neat)/cm^{-1} 3455, 2935, 1742, 1725, 1505, 1219 and 1168; δ_H(200 MHz; $CDCl_3$) 1.14–1.46 (4 H, m), 1.52–1.68 (2 H, m), 1.92–2.32 (6 H, m), 2.08 (3 H, s, ArMe), 2.16 (3 H, s, ArMe), 2.68–3.03 (4 H, m), 3.65 (3 H, s, CO_2Me), 4.23 (1 H, apparent t, *J* 8.5 CH), 4.40 (1 H, s, OH), 6.89–7.02 (2 H, m, ArH) and 7.23–7.35 (2 H, m, ArH); *m/z* 398 (M^+, 3), 237 (2), 205 (7), 187 (13), 162 (100), 147 (16) and 109 (26).

***N*-Alkylated DEAD 11.** A colourless oil (Found: M^+, 412.2014. Calc. for $C_{20}H_{29}FN_2O_6$: *M*, 412.2010); ν_{max}(neat)/cm^{-1} 3294, 2981, 2937, 1736, 1714, 1605, 1510 and 1414; δ_H(200 MHz; $CDCl_3$) 1.10–2.18 [8 H, m, CH(CH_2)$_4$], 1.25 (6 H, t, *J* 7.0, CH_2CH_3), 2.28 (2 H, t, *J* 7.5, CH_2CO_2Me), 3.65 (3 H, s, CO_2Me), 4.00–4.30 (4 H, m, CH_2CH_3), 5.23 (1 H, apparent t, *J* 6.0, CH), 6.22 (1 H, br s, NH), 6.92–7.06 (2 H, m, ArH) and 7.23–7.37 (2 H, m, ArH); *m/z* 412 (M^+, 0.7), 381 (2.5), 236 (89), 205 (57), 187 (60) and 109 (100).

Mitsunobu reactions listed in Table 3: typical procedure

A solution of DEAD (95%; 1.1 cm^3, 6.8 mmol) in dichloroethane (10 cm^3) was added dropwise to a solution of the phenol **12** (3.0 g, 24.6 mmol), (*S*)-**2** (0.6 g, 4.9 mmol) and PPh_3 (1.6 g, 6.2 mmol) in dichloroethane (12 cm^3) at 10 °C. The mixture was stirred for 1 h after which it was filtered and evaporated under reduced pressure. The residue was chromatographed on silica gel to yield (*R*)-3-(2-hydroxy-3,4-dimethylphenyl)-3-phenylpropyl acetate **15** (0.3 g, 32%) as a colourless oil (Found: M^+, 298.1565. Calc. for $C_{19}H_{22}O_3$: *M*, 298.1565); ν_{max}(neat)/cm^{-1} 3500, 2950, 1730, 1712, 1450 and 1360; δ_H(400 MHz; $CDCl_3$) 2.02 (3 H, s, Me), 2.09 (3 H, s, Me), 2.23 (3 H, s, Me), 2.24–2.42 (2 H, m, CHCH_2), 4.05 (2 H, dt, *J* 1.0, 6.6, CH_2O), 4.29 (1 H, apparent t, *J* 8.0, CH), 4.74 (1 H, s, OH), 6.76 (1 H, d, *J* 8.0, ArH), 6.98 (1 H, d, *J* 8.0, ArH) and 7.08–7.40 (5 H, m, ArH); δ_C(100 MHz; $CDCl_3$) 11.63 (Me), 19.92 (Me), 20.90 (Me), 33.38 (CH_2), 41.00 (CH), 62.83 (CH_2), 122.04 (Ar), 122.69 (Ar), 124.44 (Ar), 126.52 (Ar), 127.17 (Ar), 127.79 (Ar), 128.63 (Ar), 136.00 (Ar), 143.26 (Ar), 151.39 (Ar) and 170.99 (CO); *m/z* 298 (M^+, 35), 238 (100), 223 (86), 211 (78) and 196 (13).

(*R*)-3-(3-Bromo-6-hydroxy-2,4,5-trimethylphenyl)-3-phenylpropyl acetate 7. A colourless oil $[\alpha]_D^{20}$ +110.0 (*c* 0.759 in $CHCl_3$).

(*S*)-1-(3-Acetyl-6-hydroxy-2,4,5-trimethylphenyl)-1-phenylbutane 16. A colourless oil (Found: C, 80.8; H, 8.5. Calc. for $C_{21}H_{26}O_2$: C, 81.25; H, 8.44%); $[\alpha]_D^{20}$ −126.8 (*c* 0.56 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 3500, 2950 and 1680; δ_H(200 MHz; $CDCl_3$) 0.95 (3 H, t, *J* 7.5, CH_2CH_3), 1.1–1.65 [4 H, m, $(CH_2)_2$], 2.02 (3 H, s, Me), 2.11 (3 H, s, Me), 2.26 (3 H, s, Me), 2.48 (3 H, s, Me), 4.46 (1 H, dd, *J* 6.0, 9.0, CH), 4.68 (1 H, s, OH) and 7.18–7.38 (5 H, m, ArH); *m/z* 310 (M^+, 62), 295 (46), 267 (100), 223 (9) and 163 (9) [Found (HRMS): *m/z* 310.1931. Calc. for $C_{21}H_{26}O_2$: 310.1933].

X-Ray crystallographic analysis of (*R*)-3-(3-bromo-6-hydroxy-2,4,5-trimethylphenyl)-3-phenylpropyl acetate 7

A colourless plate (0.30 × 0.25 × 0.08 mm) obtained from hexane–ethyl acetate solution was used.

Crystal data. $C_{20}H_{23}BrO_3$, *M* = 391.31; triclinic, space group *P*1, *a* = 9.404(1), *b* = 9.509(1), *c* = 6.273(1) Å, α = 93.70(1), β = 106.62(1), γ = 62.89(1)°, *V* = 477.0(1) Å^3, *Z* = 1, D_X = 1.362 g cm^{-3}, μ(Cu-Kα) = 33.47 cm^{-1}. Cell dimensions were determined by 25 reflections whose 2θ angles were in the range of 79–80.

Data collection and processing

RIGAKU AFC5R diffractometer, graphite-monochromated Cu-Kα radiation (1.5418 Å), ω/2θ scan mode, scan speed 32.0° min^{-1}, 1406 unique reflections and their Friedel mates measured ($3.0 \leqslant 2\theta \leqslant 120.0°$), 1373 reflections measured ($F \geqslant 3\sigma$). Ψ Scan absorption correction [8] was applied.

Structure analysis and refinement

The structure was solved by fragment search and phase refinement procedures implemented in the program DIRDIF in TEXSAN software package. A model of hexa-substituted benzene including a bromine atom was used as a known fragment. Positions and anisotropic thermal parameters of non-hydrogen atoms were refined by full-matrix least-squares method. We put hydrogen atoms at idealized positions [*d*(C-H) = 1.09 Å] with isotropic thermal parameters of their parent atoms. Hydrogens were not refined but they were allowed to ride on their parent atoms during refinement. The final *R* value was 0.041 for *R* configuration and 0.044 for *S* configuration when dispersion corrections were incorporated for atomic scattering factors (Br, O and C). For further confirmation of the *R* configuration, the structure was re-refined without dispersion correction and structure factors were calculated again with

dispersion corrections. Sixteen Friedel pairs which satisfy $|F_c| \geqslant 10.0$ and $||F_c(+)| - |F_c(-)|| \geqslant 1.5$ were selected. All the relations between $F_c(+)$ and $F_c(-)$ in the list are consistent with the corresponding $F_o(+)$ and $F_o(-)$.

Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.§

§ For details of the system, see Instructions for Authors (1996), *J. Chem. Soc., Perkin Trans. 1*, 1996, Issue 1.

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