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Potential Routes to Flavan-3-ols, Part 2: The Mitsunobu Reactions of *para*-Oxygenated Benzylic Alcohols[1,2]

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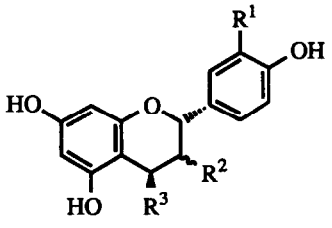
Abstract: Under Mitsunobu reaction conditions *para*-methoxy benzylic alcohols give substantially racemic products, whereas *para*-pivaloyloxy and *para*-acetoxy benzylic alcohols give products resulting from inversion.

Introduction

There are many reports in the literature regarding extracts of plants which contain flavan-3-ols being used as natural remedies for various human ailments. Extracts of various *Cistus* species contain many different flavan-3-ols and these extracts have been used as traditional medicines.[4] (+)-Afzelechin (1) is found in the fern *Polypodium glycyrrhiza* D.C.Eaton (Polypodiaceae), extracts of which are used by the indigenous people of the Pacific north-west of North America as a medicinal agent.[5] (-)-Epiafzelechin (2) exhibits *in vitro* antifibrinolytic activity[6] and (+)-catechin (3) produces a marked decrease in the serum triglyceride levels in rats with hyperlipidemia[7] and has been shown to possess antimicrobial and immunostimulating activity.[8] It is also used in the treatment of liver diseases.[9] One of the more interesting biological activities of this class of compound and the report that stimulated our interest in this field was the recent discovery that (-)-epicatechin (4) and procyanidin B_2 (5) mediate DNA strand scission at micro molar concentrations.[10]



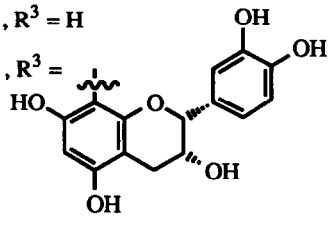
(1) $R^1 = H$, R^2 =  OH , $R^3 = H$

(2) $R^1 = H$, R^2 =  OH , $R^3 = H$

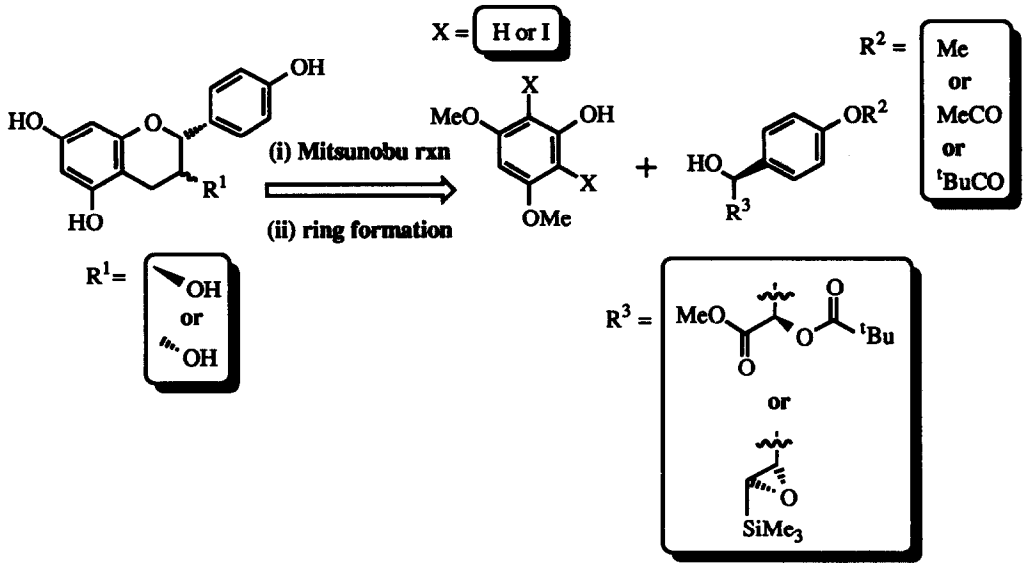
(3) $R^1 = OH$, R^2 =  OH , $R^3 = H$

(4) $R^1 = OH$, R^2 =  OH , $R^3 = H$

(5) $R^1 = OH$, R^2 = OH , R^3 =



The number of asymmetric syntheses of flavan-3-ols is very limited with most work focusing on the cyclisation of optically enriched chalcone epoxides.[11,12] We have been interested for some time in developing a general asymmetric synthesis of flavan-3-ols and one of our approaches is illustrated in the retrosynthetic analysis of (+)-afzelechin (1) and (-)-epiafzelechin (2) (Scheme 1). The two problems we envisaged were the stereoselective formation of the aryl ether bond by the Mitsunobu reaction[13,14] of a phenol and an appropriately substituted benzylic alcohol and cyclisation of this aryl ether to give the desired benzopyran ring.



Scheme 1: Retrosynthetic analysis of flavan-3-ols

This paper examines the influence of the *para*-substituent (R^2O) on the stereoselectivity of these Mitsunobu reactions and presents some initial attempts at ring formation reactions.

Results and Discussion

Synthesis of starting materials for the Mitsunobu reactions

(i) Regioselective acylation of 1,2 diols.

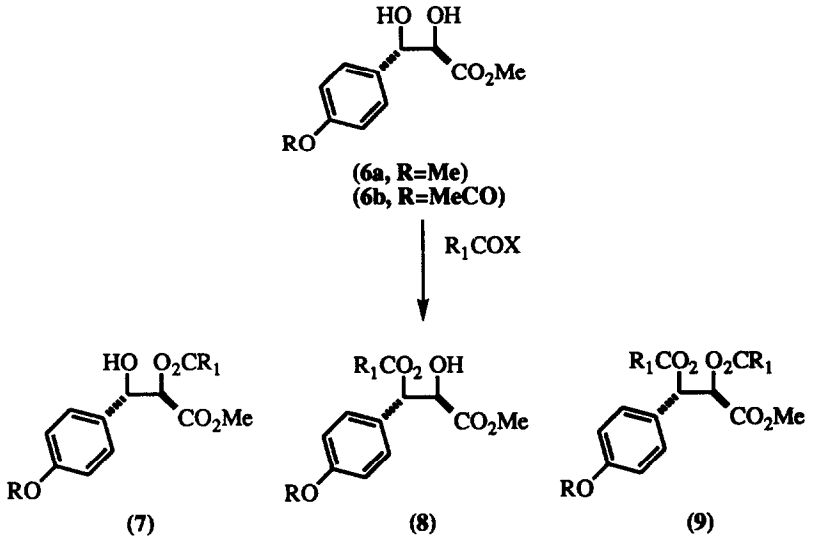
The regioselective sulphonation of 1,2-dihydroxy esters with arylsulphonyl chlorides is now well established.[15,16] It has been shown to give the product arising from sulphonation of the hydroxy group alpha to the ester, with no beta sulphonated product being detected. We planned to extend on this work and investigate the regioselective acylation of diols derived from the dihydroxylation of cinnamates and the results are summarised in table 1

Initial reactions examined the acylation of the diol (6a, R=Me)[1,17] with 4-nitrobenzoyl chloride. A pyridine solution of the diol (6a, R=Me) was treated with one equivalent of 4-nitrobenzoyl chloride at 0°. The crude ^1H n.m.r. spectrum indicated predominant acylation of the hydroxy group alpha to the ester of diol (6a, R=Me) (table 1, entry 1). The assignment of the two regioisomers (7a, R=Me, R^1= 4-nitrophenyl) and (8a, R=Me, R^1= 4-nitrophenyl) in the crude ^1H n.m.r. spectrum was determined from calculated chemical shifts[18] of the methine protons in each regioisomer. The crude reaction product was an oil and the desired benzoate (7a, R=Me, R^1= 4-nitrophenyl) could not be obtained pure by crystallisation of the crude reaction mixture. Column chromatography on silica gel separated the benzoates (7a, R=Me, R^1= 4-nitrophenyl) and (8a, R=Me, R^1= 4-nitrophenyl) from the starting diol (6a, R=Me) and the diacylated product (9a, R=Me, R^1= 4-nitrophenyl) but caused transacylation to occur resulting in a 1:1 mixture of the benzoates (7a, R=Me, R^1= 4-nitrophenyl) and (8a, R=Me, R^1= 4-nitrophenyl) as a yellow oil.

Yamada has used 3-pivaloylthiazolidine-2-thione to selectively acylate primary hydroxyl groups over secondary under both basic[19] and thermal[20] conditions. 3-Pivaloylthiazolidine-2-thione was shown to be

regioselectively superior to pivaloyl chloride for the acylations studied. When the diol (6a, R=Me) and 1.1 equivalents of 3-pivaloylthiazolidine-2-thione in THF were treated with 1.1 equivalents of NaH as a suspension in THF the regioisomeric hydroxy esters (7b, R=Me, R^1= ^{t}Bu) and (8b, R=Me, R^1= ^{t}Bu) were formed in a ratio of 27:66 (table 1, entry 2). The poor regioselectivity is probably a result of transacylation under the strongly basic reaction conditions.

When the diol (6a, R=Me) in pyridine was treated with one equivalent of pivaloyl chloride at low temperature and allowed to stir at 0° for 2 days, the hydroxy ester (7b, R=Me, R^1= ^{t}Bu) was formed in 98% yield (table 1, entry 3). The ^{1}H n.m.r. spectrum showed the presence of the desired hydroxy ester (7b, R=Me, R^1= ^{t}Bu) with no detectable amounts of either the starting diol (6a, R=Me), diacylated material (9b, R=Me, R^1= ^{t}Bu) or the regioisomeric hydroxy ester (8b, R=Me, R^1= ^{t}Bu). Crystallisation gave pure hydroxy ester (7b, R=Me, R^1= ^{t}Bu) as a colourless solid. Similarly when the diol (6b, R=MeCO) was treated with pivaloyl chloride the hydroxy ester (7c, R=MeCO, R^1= ^{t}Bu) was obtained as colourless crystalline solid in 98% yield (table 1, entry 4).



(7) (8) (9)

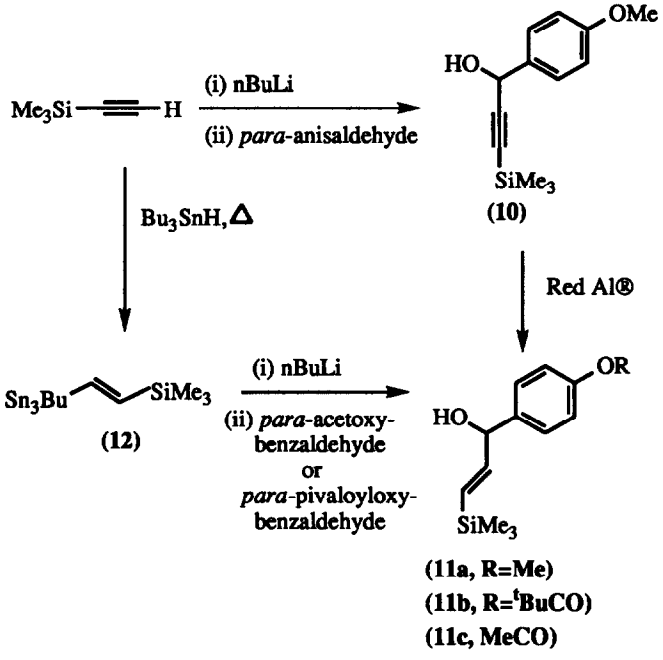
Entry	R	R^1	X	% (7)	% (8)	% (9)
1	Me	*p*-$O_2NC_6H_4$	Cl	75	4	4
2	Me	^{t}Bu	thiazolidine-2-thione	27	66	7
3	Me	^{t}Bu	Cl	>98	<2	<2
4	MeCO	^{t}Bu	Cl	>98	<2	<2

Table 1: Regioselective acylation of the diols (6a, R=Me) and (6b, R=MeCO)

(ii) Sharpless kinetic resolution of γ-trimethylsilyl allylic alcohols

Sato *et al* [21,22] have recently shown that the Sharpless kinetic resolution[23] of various gamma trimethylsilyl secondary allylic alcohols is particularly efficient with both the epoxy alcohol and the allylic alcohol being obtained in >95% e.e.. This methodology was applied to the synthesis of the allylic alcohols (11a, R=Me), (11b, R=^{t}BuCO) and (11c, R=MeCO). Trimethylsilylacetylene was treated with one equivalent

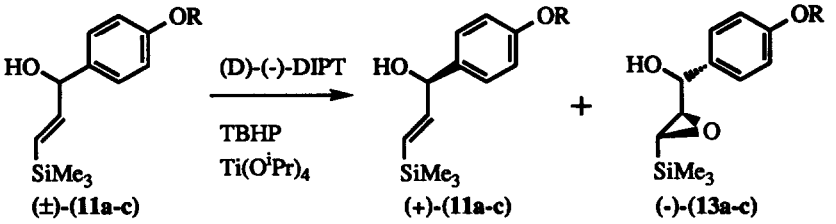
of methyl lithium and the resulting acetylide quenched with *para*-anisaldehyde to give the acetylenic alcohol (±)-(10) in quantitative yield. The acetylenic alcohol (±)-(10) was stereoselectively reduced with sodium bis(2-methoxyethoxy)aluminium hydride (Red Al®) to give the allylic alcohol (±)-(11a, R=Me) in high yield (>90%). The reduction was performed in THF at room temperature. Elevated temperatures led to more complex mixtures of products and lower isolated yields of the allylic alcohol (±)-(11a, R=Me). This methodology could not be applied to the synthesis of the allylic alcohols with the *para*-ester functionality (11b, R=^{t}BuCO) or (11c, R=MeCO) as the ester groups would also be reduced by Red Al®. An alternative route was based on treating trimethylsilylacetylene with tributyltin hydride to give the vinyl tin reagent (12).[24] Transmetallation with nBuLi and quenching of the vinyl lithium reagent[24] with either *para*-pivaloyloxybenzaldehyde[25] or *para*-acetoxybenzaldehyde[25] at -100° gave the allylic alcohols (11b, R=^{t}BuCO) and (11c, R=MeCO) respectively. Addition of the aldehydes at higher temperatures caused significant attack at the ester carbonyl.



Scheme 2: Synthesis of the allylic alcohols (11a, R=Me), (11b, R=^{t}BuCO and (11c, R=MeCO)

The racemic alcohols (±)-(11a-c) were treated with *tert*-butylhydroperoxide (TBHP) in the presence of (D)-(-)-diisopropyl tartrate (DIPT) and titanium *iso*-propoxide for 13.5 h at -20°. Work-up and column chromatography gave the optically pure allylic alcohols (+)-(11a-c) and the optically enriched epoxy alcohols (-)-(13a-c) and the results are summarised in table 2. The work-up differed from that reported by Sato[22] and was more in line with that described by the Sharpless group.[23] The key differences were that excess TBHP was reduced with ferrous sulphate rather than dimethyl sulphide. This was purely from the point of view of cost and ease of handling of materials. The excess DIPT was hydrolysed by aqueous NaOH prior to chromatography as it co-eluted with the epoxy alcohols (-)-(13a-c). Chromatography was conducted on silica gel, deactivated by the addition of triethylamine as the allylic alcohols, especially (+)-(11a, R=Me), seemed to be slightly unstable

on silica gel. The allylic alcohols (+)-(11a-c) could be retreated under the same conditions substituting (L)-(+)-DIPT for (D)-(-)-DIPT to give the silyl epoxide (+)-(13a-c) in quantitative yield. The absolute stereochemistry of the products of the resolution are based on that indicated from epoxidation of related systems.[23]



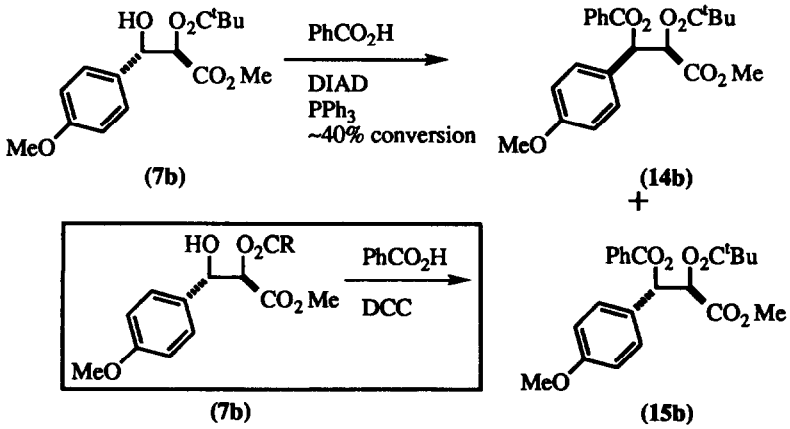
Entry	R	allylic alcohol (11) yield and e.e.		epoxy alcohol (13) yield and e.e.	
1	Me	25%	>99%	38%	90%
2	^{t}BuCO	45%	>99%	50%	90%
3	MeCO	35%	>99%	33%	>99%

Table 2: Kinetic resolution of the allylic alcohols (11a, R=Me), (11b, R=^{t}BuCO) and (11c, R=MeCO)

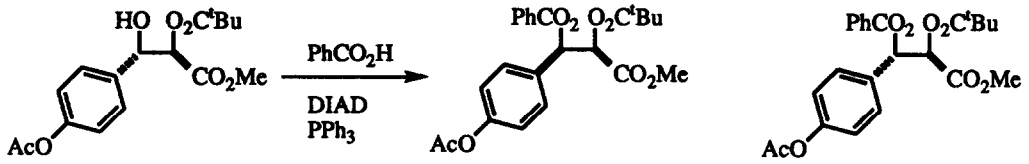
Mitsunobu reactions

With the hydroxy esters (7b, R=Me, R^1=^{t}Bu) and (7c, R=MeCO, R^1=^{t}Bu) and the epoxy alcohols (13a-c) in hand we turned our attention to the Mitsunobu reactions of these substrates.

The Mitsunobu reaction of the hydroxy ester (7b, R=Me, R^1=^{t}Bu) was first examined using benzoic acid as the nucleophile. The stereoselectivity of the reaction could be accurately determined as a sample of the benzoate (15b), the product arising from retention of configuration at the benzylic centre, could be synthesised by direct esterification of the hydroxy ester (7b) with benzoic acid. When a THF solution of the hydroxy ester (7b), benzoic acid and triphenylphosphine was treated with diisopropylazodicarboxylate (DIAD) and stirred overnight at ambient temperature, the crude ^{1}H n.m.r. spectrum showed a mixture of benzoates (14b) and (15b) in a ratio of 2:1 together with starting hydroxy ester (7b). Although this was an unexpected result the *para*-methoxy group must cause the phosphonium salt intermediate to have significant carbocation character and the benzoates (14b) and (15b) would result from an S_N1 type reaction.



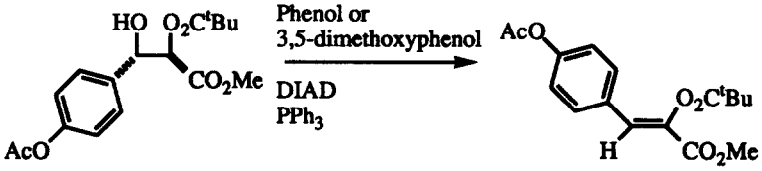
When the hydroxy ester (7c, R=MeCO, R^1= ^{t}Bu) and benzoic acid were treated under identical Mitsunobu reaction conditions the crude ^{1}H n.m.r. spectrum, while indicating a poor conversion (25%), showed the ratio of benzoate (14c) to (15c) to be >99:1.



(7c) (14c) **only product** (15c) **not detected**

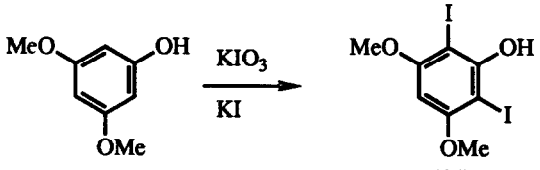
Having established that the Mitsunobu reaction of the hydroxy ester (7c) was stereoselective at the benzylic position, the reaction of hydroxy ester (7c) was investigated using various phenols as nucleophiles.

When the hydroxy ester (7c) was treated with phenol or 3,5-dimethoxyphenol under Mitsunobu reaction conditions only the enol pivalate (16) was isolated in 86% and 83% yields respectively. The enol pivalate (16) arises from elimination of H_2O from the hydroxy ester (7c).



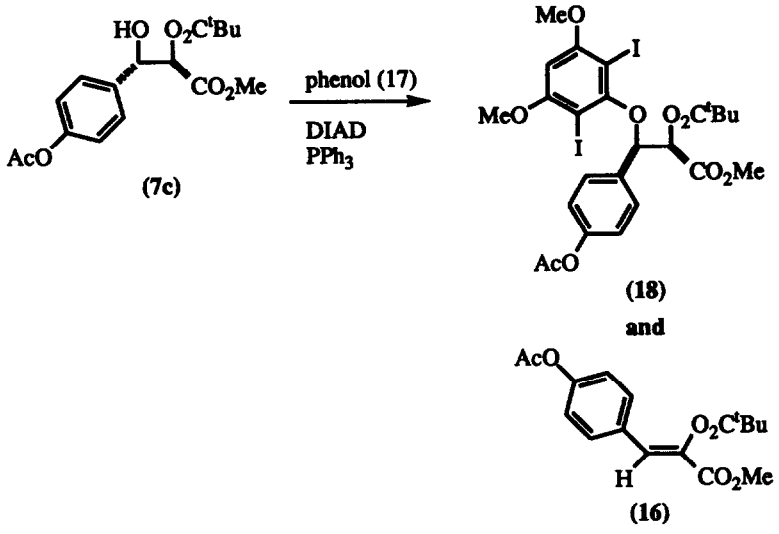
(7c) **(16) only product**

The stereochemistry of the double bond in the enol pivalate (16) was not determined.[26] The enol pivalate (16) has been drawn as the *cis*-isomer and the chemical shift of the olefin proton was 7.30 p.p.m.. The calculated[18] chemical shift of the olefinic proton in the *cis*-enol pivalate (16) is 7.17 p.p.m. compared with 6.83 p.p.m. for the *trans*-isomer. We felt that the base responsible for the elimination was the phenolate ion formed as the triphenylphosphine adds to the DIAD.[14] If the size of the phenol was increased then the rate for the reaction leading to the enol pivalate (16) would be reduced. A bulky phenol, with the same oxygenation pattern as 3,5 dimethoxyphenol, is the diiodophenol (17).[27] The phenol (17) was easily prepared by treating 3,5 dimethoxyphenol with KIO_3 and KI under the conditions developed by Weitl *et al*[28] to give the diiodophenol (17) as a crystalline solid.



(17)

The reaction of the hydroxy ester (7c) and the diiodophenol (17) was investigated under a variety of conditions to try and optimise the yield of the aryl ether (18) and minimise the occurrence of the enol pivalate (16). The results are summarised in table 3.



Entry	Solvent	Conditions	Ratio (18) to (16)	Yield (18) %	Yield (16) %
1	THF	18 h, ambient temperature	45:55	34	60
2	Toluene	1.2 equiv phenol (17).	40:60	30	45
3	CH_2Cl_2	as for entry (1).	70:30	48	30
4	CH_2Cl_2	Doubling Conc^n of reagents cf. entry (3)	70:30	47	32
5	CH_2Cl_2	Slow add^n of DIAD over 2 h	70:30	48	31
6	CH_2Cl_2	1 equiv of phenol (17).	70:30	47	31
7	CH_2Cl_2	1equiv phenol (17). 5 equiv PPh_3 and DIAD.	85:15	60	12

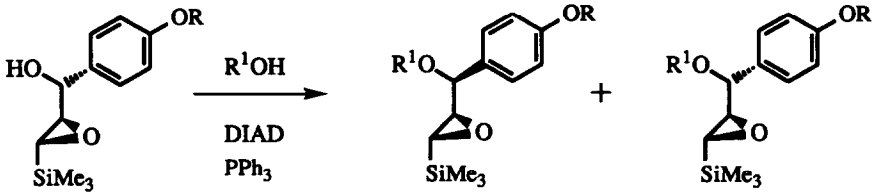
Table 3: Mitsunobu reaction of the hydroxy ester (7c) and the phenol (17)

The initial reactions were run in THF (entry 1, table 3) using 3 equivalents of the phenol (17) and the reactions were stirred overnight at ambient temperature. An excess of the phenol (17) was used to prevent anticipated coupling of two moles of the hydroxy ester (7c).[29] Some of the desired aryl ether (18) was isolated but the major product was the enol pivalate (16). Benzene has been shown to be a excellent solvent for the inversion of a hindered steroidal hydroxyl group under Mitsunobu reaction conditions.[30] It was felt that reactions in an aromatic solvent may accelerate the formation of the aryl ether (18) over the enol pivalate (16).

Toluene was substituted for benzene due to the reported health risks of benzene.[31] Only 1.2 equivalents of the phenol (17) were used in the reaction due to its poor solubility . Unfortunately the ratio of the aryl ether (18) to enol pivalate (16) was slightly inferior (entry 2, table 3) to reactions run in THF (entry 1, table 3). Walba *et al*[32] has shown that CH_2Cl_2 was superior to THF in the coupling of a hindered secondary alcohol and a phenol. When the reaction was run in CH_2Cl_2 (entry 3, table 3) the ratio of the aryl ether (18) to the enol pivalate (16) was improved and the isolated yield of the aryl ether (18) increased to ~50%. Doubling the initial concentration of the reagents (cf. entry 3) had no effect on the product ratio (entry 4, table 3). The addition of DIAD slowly to the reaction mixture (entry 5, table 3) did not affect the yield of the aryl ether (18) within experimental error. When the amount of the phenol (17) was reduced to one equivalent (entry 6, table 3) the product ratio and yield of the aryl ether (18) remained unchanged (cf. entry 3, table 3) and no evidence for products arising from the coupling of two moles of the hydroxy ester (7c) were detected. When the hydroxy ester (7c) and one equivalent of the phenol (17) were treated with five equivalents of DIAD and triphenylphosphine[34] the ratio of the aryl ether (19) to enol pivalate (16) increased to 85:15 and the isolated yield of the aryl ether (19) increased to 60% (entry 7, table 3). The reaction cost becomes high when using such an excess of DIAD and triphenylphosphine and the isolation of the aryl ether (18) by column chromatography becomes tedious due to the larger column required to avoid contamination of the product by the DIAD hydrazine.

Mitsunobu reaction of the epoxy alcohols (-)-(13a-c)

In an analogous result to the Mitsunobu reactions of the hydroxy ester (7b, R=Me, R^1= ^{t}Bu), when the epoxy alcohols (-)-(13a, R=Me) was treated with benzoic acid under Mitsunobu reaction conditions a 60:40 mixture of benzoates (19a, R=Me, R^1=$PhCO_2$) and (20a, R=Me, R^1=$PhCO_2$) was isolated in a combined yield of 86% (entry 1, table 4).[34] An authentic sample of the benzoate (20a) arising from retention of configuration at the benzylic position was synthesised by DCC promoted esterification of the epoxy alcohol (-)-(13a) with benzoic acid.



(-)-(13a-c) (19a-f) (20a-f)

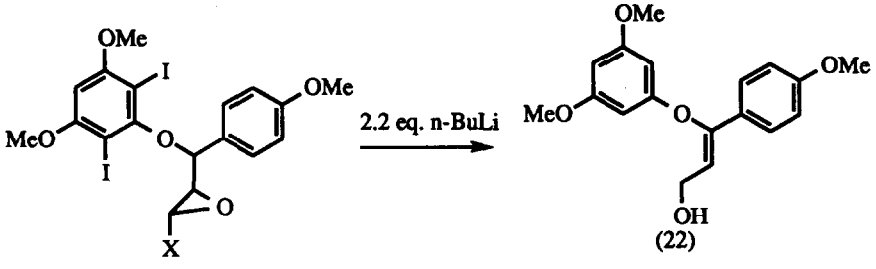
Entry	R	R^1OH	Ratio 19:20
1	Me	$PhCO_2H$	(19a):(20a), 60:40
2	^{t}BuCO	$PhCO_2H$	(19b):(20b), 96:4
3	MeCO	$PhCO_2H$	(19c):(20c), >98:2
4	Me	Phenol (17)	(19d):(20d), 50:50
5	^{t}BuCO	Phenol (17)	(19e):(20e), >98:2
6	MeCO	Phenol (17)	(19f):(20f), >98:2

Table 4: Mitsunobu reaction of the epoxy alcohols (-)-(13a, R=Me), (13b, R=^{t}BuCO) and (13c, R=MeCO)

As was noted for the Mitsunobu reactions of the hydroxy esters (7b) and (7c), replacing the *para*-methyl ether substituent with a less activating ester group gave essentially only the product of inversion of configuration at the benzylic centre. When the epoxy alcohols (-)-(13b) or (-)-(13c) were treated under identical conditions the benzoate (19b) and (19c), arising from inversion of configuration at the benzylic centre were by far the major products (entry 2 and 3, table 4). The small amount of the benzoate (20c) probably arises due to direct acylation of the epoxy alcohol (-)-(13c) by benzoic anhydride formed under the Mitsunobu reaction conditions. The phenomenon of the *para*-methoxy group causing racemisation was seen again when the nucleophile (R^1OH) was changed to the phenol (17) . Reaction of the epoxy alcohol (-)-(13a) with the phenol (17) again caused racemisation of the benzylic centre (entry 4, table 4) to give a 1:1 ratio of the two diastereoisomers (19d) and (20d). However reactions of the epoxy alcohol (-)-(13b) (entry 5) or (-)-(13c) (entry 6) led to only one diastereoisomer being isolated in very high yields. The aryl ethers (19e) and (19f) are thought to be the products of inversion of configuration at the benzylic centre in line with results when benzoic acid was used as a nucleophile (entries 1-3).

Application of this methodology to the synthesis of flavan-3-ols

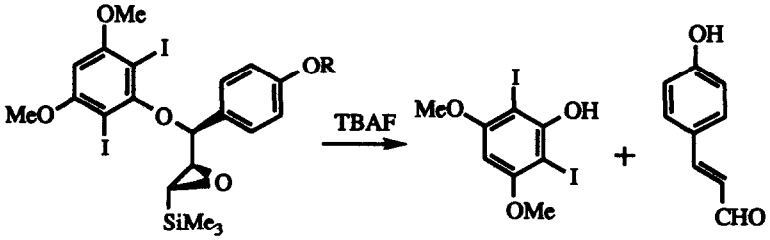
When the mixture of the aryl ethers (19d) and (20d) was recrystallised one diastereoisomer could be obtained pure. The relative stereochemistry of this aryl ether was not determined but when treated with tetrabutylammonium fluoride it gave a terminal epoxide (21) in quantitative yield. The epoxide (21) has been drawn without representing the relative configuration. It was planned to form the benzopyran ring by a Parham type cyclisation[35] of the terminal epoxide (21). However when the epoxide (21) was treated with 2.2 equivalents of n-BuLi at <-95° and allowed to warm to room temperature only the allylic alcohol (22), resulting from epoxide rearrangement, was isolated in 75% yield. Attempts at facilitating the opening of the epoxide by the addition of lewis acids, for example $MgBr_2$,[36] or the formation of aryl cuprates by the addition of $CuBr.SMe_2$ were not successful in eliminating the formation of the allylic alcohol (22) and no cyclised product was isolated. While the benzylic hydrogen of the epoxide (21) is not particularly acidic, once lithium halogen exchange occurs, the molecule must adopt a conformation that allows the abstraction of the proton via a five membered transition state.



TBAF → (19d) or (20d), X= $SiMe_3$
TBAF → (21) X= H

When the aryl ethers (19e) or (19f) were treated with tetrabutylammonium fluoride (TBAF) in THF, the ^1H n.m.r. spectrum of the crude reaction mixture indicated a mixture of the phenol (17) and *para*-hydroxycinnamaldehyde (23).[37] The expulsion of the phenol (17) probably arises from saponification of the

para-ester functionality of either (19e) or (19f) and quinone methide formation. Fluoride attack at the trimethylsilyl group leads to the formation of the unsaturated aldehyde.[38]



(19e, R=^{t}BuCO) **(17)** **(23)**
(19f, R=MeCO)

The Parham cyclisation of the aryl ether (18) was not successful, perhaps due to the number of electrophiles in close proximity in this molecule.

Conclusion

This work has shown that the nature of the *para*-substituent has a significant effect on the stereoselectivity of the Mitsunobu reaction of *para*-oxygenated benzylic alcohols. Methyl ethers lead to racemisation at the benzylic centre while the less activating *para*-ester functionality leads to complete inversion at the benzylic centre. In addition the regioselective acylation of cinnamate derived diols was achieve using pivaloyl chloride. This represents a useful method for distinguishing between the two hydroxy groups.

Current research is focused on the Parham cyclisation of the aryl ethers (19e) and (19f) which contain the silyl epoxide group. In intermolecular reactions, organocopper reagents have been shown to add exclusively at the carbon bearing the trimethylsilyl group.[39,40] We hope to extend this methodology to the intramolecular nucleophilic additions to silyl epoxides.

Experimental

General: Melting points were determined using a Gallenkamp MFB-595 melting point apparatus and are uncorrected. Kugelrohr (bulb to bulb) distillation temperatures are oven temperatures and serve only as a guide. Microanalyses were performed by the Australian Microanalytical Service, National Analytical Laboratories, Melbourne. Optical rotations were measured with a Perkin-Elmer 141 polarimeter (in a cell length 1dm) at a wavelength of 598 nm (sodium D line). Concentrations are expressed as c, (g/100 ml). The temperature of all rotations was 22±1°. Infra-red spectra were recorded using a Perkin-Elmer 1600 FTIR infra-red spectrometer (cm^{-1} scale) as paraffin (nujol) mulls of solids or as thin films of liquids between sodium chloride plates. Proton nuclear magnetic resonance (^{1}H n.m.r.) spectra were recorded at 200 MHz with a Bruker AC-200 spectrometer and at 300MHz with a bruker AM300 spectrometer. The ^{1}H n.m.r. spectra refer to deuterochloroform solutions with tetramethylsilane (TMS) as the internal standard (δ 0.00 p.p.m.) unless otherwise stated. Spectra of compounds containing a trimethylsilyl group were recorded in deuterochloroform solution in the absence of TMS and used the residual chloroform peak at 7.27p.p.m. as an internal standard. Carbon nuclear magnetic resonance (^{13}C n.m.r.) spectra were recorded at 50 MHz with a Bruker AC-200 spectrometer and refer to deuterochloroform solutions with TMS as the internal standard (δ 0.00 p.p.m.). Assignments were determined from *J*-Modulated Spin-Echo experiments for X-nuclei coupled to ^{1}H in order to determined the number of attached protons. Fluorine nuclear magnetic resonance (^{19}F n.m.r.) spectra were

recorded at 282 MHz with a Bruker AM-300 spectrometer and refer to deuterochloroform solutions with fluorotrichloromethane as the internal standard (δ 0.00 p.p.m.). Low resolution mass spectra were usually recorded on a VG TRIO-1 quadrupole mass spectrometer at 70eV with a source temperature of 180°C. Spectra recorded in C.I. mode were run on the same instrument using methane as the reagent gas. Accurate mass determinations were recorded on a VG Micromass 7070F spectrometer at high resolution by peak matching with an internal standard. All solvents were purified by literature procedures.[41] n-Butyl lithium , methyl lithium, tertrabutylammonium fluoride (1 M in THF), 2,2-dimethylpropanoyl chloride, (R)-Mosher's acid and diisopropylazodicarboxylate (DIAD) were purchased from Aldrich Chemicals. (-)- and (+)-Diisopropyl tartrate, *tert*-butylhydroperoxide (3 M in toluene) were purchased from Fluka AG. Methyl 2,3-dihydroxy-3-(4-acetoxyphenyl)propanoate (6b, R=MeCO) was prepared by Mr. Gary Day, Deparment of Chemistry, Monash University. The enantiomeric excess of the allylic alcohols (11a-c) and the epoxy alcohols (13a-c) were determined from the ^1H or ^{19}F n.m.r. spectrum of the derived (R)-Mosher's esters. The (R)-Mosher's esters were prepared by esterification with (R)-Mosher's acid using DCC or (R)-Mosher's acid chloride following the procedure of Ward.[42]

(1R*)-1-(4-Methoxyphenyl)-3-trimethylsilyl-2-propyn-1-ol (±)-(10): Trimethylsilylacetylene (0.96 ml, 6.80 mmol) was added to a solution of methyl lithium (3.28 ml, 1.6 M in diethyl ether, 5.23 mmol) in THF (6 ml) at 0°. The mixture was stirred for 1h at ambient temperature, cooled to -30°, treated with freshly distilled 4-methoxybenzaldehyde (712 mg, 5.23 mmol) and allowed to warm to ambient temperature. The reaction was quenched with an ice cold solution of saturated aqueous ammonium chloride and extracted with hexane (2 x 20 ml). The combined organic extracts were dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give the title alcohol (±)-(10) as a colourless liquid (1.22g, 100%) (Found: C, 66.5; H, 7.6. $C_{13}H_{18}SiO_2$ requires C, 66.7; H, 7.7%). υ_{max} (film): 3395bs, 2172m cm^{-1}. ^1H n.m.r. (200MHz): δ 0.21, s, 9H, Me_3Si; 3.82, s, 3H, MeO; 5.41, s, 1H, -CH-O; 6.91, d, *J* 8.6 Hz and 7.48, d, *J* 8.6 Hz, 4 x ArH. Mass spectrum *m/z* 234 (M^+, 58%), 219(35), 203(34), 191(46), 144(100), 135(49), 109(86), 73(82).

***E*-(1R*)-1-(4-Methoxyphenyl)-3-trimethylsilyl-2-propen-1-ol (11a, R=Me):** Sodium bis(2-methoxyethoxy)aluminium hydride (2.1 ml, 3.4 M in toluene, 7.2 mmol) was added to a solution of the acetylenic alcohol (±)-(10) (1.0 g, 4.3 mmol) in THF (5 ml) at 0°. The solution was allowed to warm to ambient temperature and stirred overnight. The reaction mixture was quenched with a saturated aqueous solution of sodium potassium tartrate (30 ml) and extracted with ether/light petroleum (1:1, 3 x 30 ml). The combined organic extracts were dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give a yellow oil. Distillation gave the allylic alcohol (±)-(11a, R=Me) as a colourless oil (946 mg, 93%), b.p. 150° (oven), 0.05mm. (Found: C, 66.2; H, 8.5. $C_{13}H_{20}SiO_2$ requires C, 66.1; H, 8.5). υ_{max} (film): 3374bs cm^{-1}. ^1H n.m.r. (200MHz): δ 0.09, s, 9H, Me_3Si; 2.03, d, 3.8 Hz, 1H, exchangable with D_2O; 3.81, s, 3H, MeO, 5.12-5.16, m, 1H, CH-O; 5.98, dd, 1.2 Hz, 18.6 Hz, 1H, Si-CH=; 6.21, dd, *J* 4.8 Hz, 18.6 Hz, 1H, =CH-C; 6.90, d, *J* 8.7 Hz and 7.26, d, *J* 8.7 Hz, 4 x ArH. Mass spectrum *m/z* 236 (M^+, 14%), 221(38), 146(73), 137(100), 75(47), 73(67).

4-(*E*-1-hydroxy-3-trimethylsilylprop-2-enyl)phenyl 2,2-dimethylpropanoate (±)-(11b, R=^{t}BuCO): n-Butylithium (2.3 ml, 2.5 M in hexane, 5.72 mmol) was added dropwise to a solution of *E*-1-trimethylsilyl-2-tri-n-butylstannylethylene (12) (2.23 g, 5.72 mmol) in THF (12 ml) at -78°. After 1 h at this temperature the reaction mixture was allowed to warm to -40° and stirred for 1 h. The reaction mixture was then cooled to -95°

and treated with freshly distilled *para*-pivaloyloxybenzaldehyde (1.17 g, 5.72 mmol) in THF (10 ml). After 3 h stirring at -78° the reaction mixture was quenched with saturated aqueous ammonium chloride (15 ml), the organic layer separated and the aqueous phase extracted with diethyl ether (3 x 10 ml). The combined organic extracts were dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give a colourless oil. Column chromatography (20% diethyl ether / light petroleum) gave the allylic alcohol (±)-(11b, R=^{t}BuCO) as a colourless solid (1.22g, 70%), m.p. 94-95° (Found: C, 66.5; H, 8.9. $C_{17}H_{26}O_3Si$ requires C, 66.7 H, 8.5%). υ_{max} (nujol): 3521s, 1733m cm^{-1}. ^1H n.m.r.(200MHz): δ 0.08, s, $SiMe_3$; 1.38, s, Me_3C; 5.18, d, *J* 5.0 Hz, CH-O; 5.98, dd, *J* 1.0, 18.6 Hz, Si-CH=C; 6.18, dd, *J* 5.0, 18.6 Hz, C=CH-C; 7.05, d, *J* 8.2 Hz and 7.37, d, *J* 8.2 Hz, 4 x ArH. Mass spectrum *m/z* 306 (M^+, 1%), 291(1), 221(50), 57(100).

4-(*E*-1-Hydroxy-3-trimethylsilylprop-2-enyl)phenyl acetate (±)-(11c, R=MeCO): Substituting *para*-pivaloyloxybenzaldehyde for *para*-acetoxybenzaldehyde (870 mg, 5.3 mmol) and following the same procedure as is outline above, gave the allylic alcohol (±)-(11c, R=MeCO) as a colourless oil after column chromatography (20% diethyl ether / light petroleum) (1.12g, 80%) (Found: C, 63.4; H, 7.7. $C_{14}H_{20}O_3Si$ requires C, 63.6 H, 7.6%). υ_{max} (film): 3404s, 1763m cm^{-1}. ^1H n.m.r. (200MHz): δ 0.09, s, $SiMe_3$; 2.31, s, $MeCO_2$; 5.19, d, *J* 4.9 Hz, CH-O; 6.00, dd, *J* 1.1, 18.6 Hz, Si-CH=C; 6.19, dd, *J* 4.9, 18.6 Hz, C=CH-C; 7.08, d, *J* 8.7 Hz and 7.38, d, *J* 8.7 Hz, 4 x ArH. Mass spectrum *m/z* 264 (M^+, 2%), 222(20), 221(53), 205(42), 189(19), 133(16), 132(100), 123(50), 75(33), 73(67)

General Procedure for the kinetic resolution of the allylic alcohols (11a-c)

(D)-(-)-Diisopropyl tartrate (736 mg, 3.1 mmol) in CH_2Cl_2 (2 ml) was added to a solution of titanium isopropoxide (0.78 ml, 2.6 mmol) in CH_2Cl_2 (20 ml) while maintaining the temperature of the mixture below -20°. The solution was allowed to stir at this temperature for 10 min and then treated with a solution of the allylic alcohol (±)-(11) (2.62 mmol) in CH_2Cl_2 (2 ml). After a further 10 min stirring *tert*-butyl hydroperoxide (1.3 ml, 3 M in toluene, 3.9 mmol) was added dropwise and the solution was allowed to stand at -20° for 13.5 h. The reaction was quenched with the addition of a solution of ferrous sulphate heptahydrate (3.3 g, 12 mmol) and tartaric acid (5 g, 30 mmol) in water (50 ml) precooled to 0°.The two-phase solution was allowed to stir without external cooling for 10 min. The organic layer was separated and the aqueous layer extracted with dichloromethane (2 x 20 ml). The combined organic extracts were cooled to 0° and treated with a solution of sodium chloride (2.5 g) and sodium hydroxide (15 g) in water (50 ml) precooled to 0°. After 1 h of vigorous stirring at 0° the organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2 x 20 ml). The combined organic extracts were dried ($MgSO_4$), filtered and the solvent removed *in vacuo* . Column chromatography (SiO_2, 10% ether / light petroleum containing 2% v/v triethylamine) gave the (1S)-allylic alcohol (+)-(11) and the (1R, 2R, 3R)-epoxy alcohol (-)-(13).

(1S)-allylic alcohol (+)-(11a, R=Me): Yield=25%. Colourless oil. $[\alpha]_D$ = +8.0 (c=1, $CHCl_3$). When the (1S)-allylic alcohol (+)-(11) was subjected to the kinetic resolution conditions described above, replacing (D)-DIPT with (L)-DIPT the epoxy alcohol (+)-(13) was isolated in quantitative yield. Esterification with (R)-Mosher's acid / DCC gave the Mosher's ester, which by ^1H n.m.r. and ^{19}F n.m.r. spectroscopy showed none of the major diastereoisomer reported below.

(1R, 2R, 3R)-epoxy alcohol (-)-(13a, R=Me): Yield=38%. Colourless solid, m.p. 68-70°. $[\alpha]_D$ = -21.1 (c=1, $CHCl_3$). E.e 90%. ^1H n.m.r. (200 MHz): δ 0.05, s, $SiMe_3$; 2.22, d, *J* 2.0 Hz, (exchangeable), OH; 2.58, d, *J* 3.6 Hz, CH-$SiMe_3$; 3.04, dd, *J* 3.1, 3.6 Hz, CH-C-$SiMe_3$; 3.82, s, MeO; 4.88, dd, *J* 2.0, 3.1 Hz, CH-OH; 6.91, d, *J*

8.6 Hz and 7.30, d, *J* 8.6 Hz, 4 x ArH. (R)-Mosher's ester: Major diastereoisomer ^{1}H n.m.r. (300 MHz): δ 0.05, s, $SiMe_3$; 2.33, d, *J* 3.5 Hz, CH-$SiMe_3$; 3.12, dd, *J* 3.5, 4.3 Hz, CH-C-$SiMe_3$; 3.54, d, *J* 1.2 Hz, MeO (Mosher's acid); 3.82, s, MeOAr; 5.97, d, *J* 4.3 Hz, CH-O_2C; 6.86, d, *J* 8. Hz and 7.23, d, *J* 8.8 Hz, 4 x ArH, 7.29-7.46, m, 5H, ArH. ^{19}F n.m.r. (282 MHz): δ -72.08. Diagnostic peak for the minor diastereoisomer: ^{19}F n.m.r. (282 MHz): δ -72.00.

(1S)-allylic alcohol (+)-(11b, R=^{t}BuCO): Yield=45%. Colourless solid, m.p. 94-95°. $[\alpha]_D$ = +3.3 (c=1, $CHCl_3$). E.e. >99%. (R)-Mosher's ester :^{1}H n.m.r. (300 MHz): δ 0.03, s, $SiMe_3$; 1.37, s, Me_3C; 3.47, d, *J*1.2 Hz, MeO; 5.86, dd, *J* 1.0, 18.7 Hz, Si-CH=C; 6.02, dd, *J* 4.7, 18.7 Hz, C=CH-C; 6.49, d, *J* 4.7 Hz, CH-O_2C; 7.07, d, *J* 8.6 Hz, 2 x ArH; 7.35-7.43, m, 7H, 7 x ArH. The diagnostic peak in ^{1}H n.m.r. of the (R)-Mosher's ester of the (1R)-allylic alcohol was the resonance for the methoxy group in the Mosher's ester: δ 3.55, d, *J* 2 Hz, MeO.

(1R, 2R, 3R)-epoxy alcohol (-)-(13b, R=^{t}BuCO): Yield=50%. Colourless solid, m.p. 73.5-74.5°. $[\alpha]_D$ = -27.1 (c=1, $CHCl_3$). E.e. 86%. (Found: C, 63.2; H, 8.5. $C_{17}H_{26}O_4Si$ requires C, 63.4 H, 8.1%). υ_{max} (nujol): 3448s , 1756m cm^{-1}. ^{1}H n.m.r. (200 MHz): δ 0.04, s, $SiMe_3$; 1.36, s, Me_3C; 2.28, d, *J* 1.9 Hz, exchangable, OH; 2.56, d, *J* 3.8 Hz, C-CH-Si; 3.06, dd *J* 3.0, 3.8 Hz, C-CH-C; 4.91, d, *J* 3.0 Hz, CH-O; 7.07, d*J* 8.6 Hz, 2 x ArH; 7.39, d, 8.6 Hz, 2 x ArH. (R)-Mosher's ester, major diastereoisomer: ^{1}H n.m.r. (300 MHz): δ 0.05, s, $SiMe_3$; 1.37, s, Me_3C; 2.32 , d, *J* 3.4 Hz, Si-CH-C; 3.12, dd, *J* 3.4, 4.4 Hz, C-CH-C; 3.56, s, MeO; 6.00, d, *J* 4.4 Hz, CH-O; 7.05, d, *J* 8.6 Hz, 2 x ArH; 7.30, d, *J* 8.6 Hz, 2 x ArH; 7.33-7.46, m, 5 x ArH. Minor Diastereoisomer: ^{1}H n.m.r. (300 MHz): δ 0.02, s, $SiMe_3$; 1.37, s, Me_3C; 2.20, d, *J* 3.4 Hz, Si-CH-; 3.05, dd, *J* 3.4, 4.6 Hz, C-CH-C; 3.47, s, MeO; 6.00, d, *J* 4.6 Hz, CH-O_2C; 7.10, d, *J* 8.6 Hz, 2 x ArH; 7.36-7.48, m, 7 x ArH.

(1S)-allylic alcohol (+)-(11c, R=MeCO): Yield, 35%. Colourless oil. $[\alpha]_D$ = +3.0 (c=1.1, $CHCl_3$). E.e >99%. (R)-Mosher's ester : ^{1}H n.m.r.(300 MHz): δ 0.03, s, $SiMe_3$; 2.30, s, $MeCO_2$; 3.47, d, *J* 1.2 Hz, MeO; 5.88, dd, *J* 0.7, 18.7 Hz, Si-CH=C; 6.03, dd, *J* 4.6, 18.7 Hz, C=CH-C; 6.47, d, *J* 4.7 Hz, CH-O_2C; 7.09, d, *J* 8.6 Hz, 2 x ArH; 7.29-7.44, m, 7H, 7 x ArH. The diagnostic peak in ^{1}H n.m.r. of the (R)-Mosher's ester of the (1R)-allylic alcohol was the resonance for the methoxy group in the Mosher's ester: δ 3.54, d, *J* 1.2 Hz, MeO.

(1R, 2R, 3R)-epoxy alcohol (-)-(13c, R=MeCO): Yield, 33%. Colourless oil. $[\alpha]_D$ = -22.8 (c=1, $CHCl_3$). E.e >99%. (Found: C, 59.9; H, 7.4. $C_{14}H_{20}O_4Si$ requires C, 60.0 H, 7.1%.). υ_{max} (nujol): 3442s, 1760m cm^{-1} . ^{1}H n.m.r.(200 MHz): δ 0.04, s, $SiMe_3$; 2.31, s, $MeCO_2$; 2.55, d, *J* 3.6 Hz, C-CH-Si; 3.06, dd *J* 3.3, 3.6 Hz, C-CH-C; 4.90, d, *J* 3.3 Hz, CH-O; 7.11, d*J* 8.3 Hz, 2 x ArH; 7.40, d, 8.3 Hz, 2 x ArH. Mass spectrum: *m/z* 280 (M^+, < 1%), 238(1), 148(37), 123(100), 121(50), 107(30), 75(33), 73(41). (R)-Mosher's ester (major diastereoisomer): ^{1}H n.m.r.(200 MHz): δ 0.02, s, $SiMe_3$; 2.29, s, $MeCO_2$; 2.31 , d, *J* 3.4 Hz, Si-CH-C; 3.09, dd, *J* 3.4, 4.6 Hz, C-CH-C; 3.54, s, MeO; 5.95, d, *J* 4.6 Hz, CH-O_2C; 7.05, d, *J* 8.7 Hz, 2 x ArH; 7.29-7.49, m, 7 x ArH. (R)-Mosher's ester (minor diastereoisomer): ^{1}H n.m.r.(200 MHz): δ 0.00, s, $SiMe_3$; 2.20, d, *J* 3.4 Hz, Si-CH-C; 2.30, s, $MeCO_2$; 3.04, dd, *J* 3.4, 4.8 Hz, C-CH-C; 3.46 s, MeO; 5.97, d, *J* 4.8 Hz, CH-O_2C; 7.11, d, *J* 8.7 Hz, 2 x ArH; 7.32-7.59, m, 7 x ArH.

Methyl (2R*,3S*) 3-hydroxy-3-(4-methoxyphenyl)-2-[(4-nitrobenzoyl)oxy]propanoate (7a, R=Me, R^1=4-nitrophenyl) and methyl (2R*,3S*) 2-hydroxy-3-(4-methoxyphenyl)-3-[(4-nitrobenzoyl)oxy]propanoate (8a, R=Me, R^1=4-nitrophenyl): 4-Nitrobenzoyl chloride (816 mg, 4.4 mmol) in CH_2Cl_2 (10 ml) was added dropwise to a solution of diol (6a, R=Me) (1.00 g, 4.4 mmol) in pyridine (15 ml) at 0° and stirred overnight at -2°. The reaction mixture was quenched with ice/water (20 ml) and extracted with ethyl acetate (3 x 20 ml).

The combined organic extracts were washed with saturated aqueous copper sulphate (2 x 20 ml), H_2O (20 ml) and brine (20 ml), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give a yellow oil (1.43 g). ^1H n.m.r. indicated 17% starting diol (6a, R=Me), 4% diacylated material (9a, R=Me, R^1=4-nitrophenyl) and 79% of a mixture of the regio-isomeric benzoates (7a, R=Me, R^1=4-nitrophenyl) and (8a, R=Me, R^1=4-nitrophenyl) in a ratio of 95:5. Column chromatography (30% ethyl acetate / light petroleum) gave a 1:1 mixture of the benzoates (7a, R=Me, R^1=4-nitrophenyl) and (8a, R=Me, R^1=4-nitrophenyl) as a yellow foam (1.14 g, 69%) (Found: C, 57.7; H, 4.7; N, 3.7. $C_{20}H_{20}O_7$ requires C, 57.6; H, 4.5; N, 3.7%). υ_{max} (nujol) 3492s, 1732m cm^{-1}. Mass spectrum *m/z* 375(M^+, <1%), 286(20), 208(20), 167(23), 151(30), 150(100), 137(52), 121(90), 120(28), 104(23), 91(25), 77(46), 65(57). **Benzoate (7a, R=Me, R^1=4-nitrophenyl):** ^1H n.m.r. (200 MHz): δ 2.58, d, *J* 5.3 Hz, (exchangeable), OH; 3.77, s, and 3.79, s, 2 x MeO; 5.34, dd, *J* 3.9, 5.3 Hz, Ar-CH; 5.47, d, *J* 3.9 Hz, CH-CO_2; 6.89, d, *J* 8.8 Hz and 7.37, d, *J* 8.8 Hz, 4 x ArH; 8.20, d, *J* 9.1 Hz and 8.30, d, *J* 9.1 Hz, 4 x ArH. **Benzoate (8a, R=Me, R^1=4-nitrophenyl):** ^1H n.m.r. (200 MHz): (diagnostic peaks only) δ 3.12, d, *J* 6.9 Hz, (exchangeable), OH; 4.53, dd, *J* 3.1, 6.9 Hz, CH-CO_2; 6.25, d, *J* 3.1 Hz, Ar-CH.

Synthesis of methyl (2R* ,3S*) -2-(2',2'-dimethylpropanoyl)oxy-3-hydroxy-3-(4-methoxyphenyl)propanoate (7b, R=Me, R^1=^{t}Bu) and methyl (2R* ,3S*) -3-(2',2'-dimethylpropanoyl)oxy-2-hydroxy-3-(4-methoxyphenyl)propanoate (8b, R=Me, R^1=^{t}Bu): Sodium hydride (97 mg, 2.4 mmol) in THF (3 ml) was added to a solution of the diol (6a, R=Me) (500 mg, 2.2 mmol) and 3-propanoyl-1,3-thiazolidine-2-thione (491 mg, 2.4 mmol) in THF (20 ml) at ambient temperature. The reaction mixture was quenched with saturated aqueous ammonium chloride (10 ml), the organic phase separated and the aqueous phase extracted with CH_2Cl_2 (3 x 10 ml). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (2 x 10 ml of 1M), H_2O (20 ml) and brine (20 ml), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give a yellow oil. ^1H n.m.r. spectroscopy indicated a mixture of hydroxy esters (8b, R=Me, R^1=^{t}Bu) and (7b, R=Me, R^1=^{t}Bu) in a ratio of 70:30. Spectroscopic data is given below

Synthesis of methyl (2R* ,3S*) -2-(2',2'-dimethylpropanoyl)oxy-3-hydroxy-3-(4-methoxyphenyl) propanoate (7b, R=Me, R^1=^{t}Bu): 2,2-Dimethylpropanoyl chloride (0.30 ml, 2.2 mmol) in CH_2Cl_2 (2 ml) was added dropwise to a solution of the diol (6a, R=Me) (500 mg, 2.2 mmol) in pyridine (8 ml) at 0° and stirred for two days at this temperature. The reaction mixture was quenched with ice/water (5 ml) and extracted with ethyl acetate (3 x 10 ml). The combined organic extracts were washed with saturated aqueous copper sulphate (2 x 10 ml), H_2O (20 ml) and brine (20 ml), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give the title alcohol (7b, R=Me, R^1=^{t}Bu) as a colourless solid (680mg, 98%), m.p. 71-72° (Found: C, 61.8; H, 7.0. $C_{16}H_{22}O_6$ requires C, 61.9; H, 7.1%). υ_{max} (nujol) 3472s, 1757m, 1711m cm^{-1}. ^1H n.m.r. (200 MHz): δ 1.18, s, Me_3C; 3.73, s, and 3.80, s, 2 x MeO; 5.17, d, *J* 3.5 Hz, CH-CO_2; 5.23, d, *J* 3.5 Hz, Ar-CH; 6.88, d, *J* 8.8 Hz and 7.30, d, *J* 8.8 Hz, 4 x ArH. Mass spectrum: *m/z* 310(M^+, <1%), 292(1), 221(5), 208(10), 176(12), 148(15), 137(100), 121(23), 57(58). **Methyl (2R* ,3S*) -3-(2',2'-dimethylpropanoyl)oxy-2-hydroxy-3-(4-methoxyphenyl)propanoate (8b, R=Me, R^1=^{t}Bu)** : ^1H n.m.r. (200 MHz): (diagnostic peaks only) δ 1.21, s, Me_3C; 4.37, d, *J* 2.8 Hz, CH-CO_2; 6.00, d, *J* 2.8 Hz, Ar-CH.

Methyl (2R* ,3S*)-2-(2',2'-dimethylpropanoyl)oxy-3-hydroxy-3-(4-acetoxyphenyl)propanoate (7c, R=MeCO, R^1=^{t}Bu): Following a similar procedure to that detailed above the diol (6b, R=MeCO) was acylated with 2,2-dimethylpropanoyl chloride to give the title hydroxy ester (7c, R=MeCO, R_1=^{t}Bu) as a colourless solid (98% yield). m.p. 128-129°. (Found: C, 60.1; H, 6.7; $C_{17}H_{22}O_7$ requires C, 60.4; H, 6.5%). υ_{max} (nujol):

1751m, 1723m cm^{-1}. ^1H n.m.r. (200 MHz): δ 1.16, s, Me_3C; 2.30, s, MeCO; 2.56, d, *J* 6.3 Hz, (exchangeable), OH; 3.75, s, MeO_2C; 5.23, d, *J* 3.3 Hz, CH-CO_2; 5.29, dd, *J* 3.3, 6.3 Hz, Ar-CH; 7.09, d, *J* 8.7 Hz and 7.41, d, *J* 8.7 Hz, 4 x ArH. Mass spectrum: *m/z* 338(M^+, <1%), 249(3), 194(10), 174(8), 165(11), 123(30), 85(30), 57(100).

General procedure for all Mitsunobu reactions

Diisopropyl azodicarboxylate (0.17 ml, 0.88 mmol) was added dropwise to a stirred solution of the alcohols (7b), (7c) or (-)-(13a-c) (0.8 mmol), the nucleophile (either benzoic acid or one of the indicated phenols) and triphenylphosphine (231 mg, 0.88 mmol) in an appropriate solvent (15 ml) at ambient temperature. The reaction mixture was stirred overnight at ambient temperature and then quenched with water (10 ml) and extracted with CH_2Cl_2 (3 x 20 ml). The combined organic extracts were dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give a yellow oil. The diastereoselectivity of the reaction was determined from the ^1H n.m.r. spectrum of the crude reaction product. Column chromatography (10% ether / CH_2Cl_2) gave analytically pure products.

(1S, 2R, 3R) and (1R, 2R, 3R) 1-(4-Methoxyphenyl)-3-trimethylsilyl-2,3,-epoxypropanyl benzoate (19a, R=Me, R^1=$PhCO_2$) and (20b, R=Me, R^1=$PhCO_2$): Yield 86%. Ratio (19a) to (20b)=60:40. Solvent=THF, nucleophile=benzoic acid. Colourless oil. (Found: C, 67.4; H, 6.5. $C_{20}H_{24}O_4Si$ requires C, 67.4; H, 6.7%). υ_{max} (film): 1722s cm^{-1}. ^1H n.m.r. (200 MHz): mixture of (19a) and (20a) δ 0.02, s, $SiMe_3$; 0.06, s, $SiMe_3$; 2.25, d, *J* 3.4 Hz, 1H, Si-CH-C; 2.31, d, *J* 3.6 Hz, 1H, Si-CH-C; 3.21, dd, *J* 3.4, 4.0 Hz, Si-C-CH-C; 3.28, dd, *J* 3.6, 6.3 Hz, 1H, Si-C-CH-C; 3.80, s, MeO; 3.81, s, MeO; 5.75, d, *J* 6.3 Hz, 1H, CH-O_2C; 6.04, d, *J* 4.0 Hz, 1H, CH-O_2C; 6.86-6.95, m, 4 x ArH; 7.35-7.61, m, 10 x ArH; 8.05-8.15, m, 4 x ArH. Mass spectrum *m/z* 356 (M^+, 0.1%), 235(17), 179(12), 161(19), 135(21), 105(100), 73(60). An aliquot of epoxy alcohol (-)-(13a, R=Me) was esterified with benzoic acid using DCC to give the (1R, 2R, 3R)-benzoate (20b, R=Me, R_1=$PhCO_2$). ^1H n.m.r. (200 MHz): δ 0.06, s, $SiMe_3$; 2.25, d, *J* 3.4 Hz, 1H, Si-CH-C; 3.21, dd, *J* 3.4, 4.0 Hz, Si-C-CH-C; 3.81, s, MeO; 6.04, d, *J* 4.0 Hz, 1H, CH-O2C; 6.92, d, *J* 8.8 Hz, 2x ArH; 7.35-7.61, m, 5 x ArH; 8.06-8.17, m, 2 x ArH.

(1S, 2R, 3R)- and (1R, 2R, 3R)-1-(2,6-diiodo-3,5-dimethoxyphenoxy)-1-(4-methoxyphenyl)-3-trimethylsilyl-2,3-epoxypropane (19d, R=Me, R^1=2,6-diiodo-3,5-dimethoxypheny) and (20d, R=Me, R^1=2,6-diiodo-3,5-dimethoxypheny): Yield 65%. Ratio (19d) to (20d)=1:1. Solvent=THF, nucleophile=2,6-diiodo-3,5-dimethoxyphenol. Colourless oil. (Found: C, 39.0; H, 4.4. $C_{21}H_{26}I_2O_5Si$ requires C, 39.4; H, 4.1%). υ_{max} (nujol): 1613s cm^{-1}. ^1H n.m.r. (200 MHz): δ -0.1, s, $SiMe_3$; -0.06, s, $SiMe_3$; 1.75, d, *J* 3.3 Hz, 1H, Si-CH-C; 2.01, d, *J* 3.6 Hz, 1H, Si-CH-C; 3.52, dd, *J* 3.3, 8.8 Hz, Si-C-CH-C; 3.71, dd, *J* 3.6, 7.5 Hz, 1H, Si-C-CH-C; 3.84, s, MeO; 3.91, s, 3 x MeO; 3.92, s, 2 x MeO; 5.15, m, 2H, 2 x CH-O; 6.26, s, 2H, 2 x ArH; 6.96, m, 4 x ArH; 7.58, d, *J* 8.8 Hz; 7.72, d, *J* 8.8 Hz, 2 x ArH. Mass spectrum: *m/z* 640 (M^+, 0.1%), 406(16), 280(17), 235(100), 161(68). Trituration from ether gave one diastereoisomer as a colourless solid. ^1H n.m.r. (200MHz): δ -0.06, s, $SiMe_3$; 2.01, d, *J* 3.6 Hz, 1H, Si-CH-C; 3.71, dd, *J* 3.6, 7.5 Hz, 1H, Si-C-CH-C; 3.84, s, MeO; 3.91, s, 2 x MeO; 5.13, d, *J* 7.5 Hz, CH-O; 6.26, s, 1 x ArH; 6.95, d, *J* 8.8 Hz and 7.58, d, *J* 8.8 Hz, 4 x ArH.

Synthesis of (1S, 2R, 3R) and (1R, 2R, 3R) -4-(1-benzoyloxy-2, 3-epoxy-3-trimethylsilylpropanyl]phenyl 2,2-dimethylpropanoate (19b, R=^{t}BuCO, R^1=$PhCO_2$) and (20b, R=^{t}BuCO, R^1=$PhCO_2$): Yield 61%. Ratio (19b) to (20b)=96:4. Solvent=THF, nucleophile=benzoic acid. Colourless oil. (Found: C, 67.7; H, 7.3. $C_{24}H_{30}O_5Si$ requires C, 67.6; H, 7.0%). υ_{max} (film): 1722m, 1744m cm^{-1}. ^1H n.m.r. (200 MHz) (major isomer): δ 0.04, s, $SiMe_3$; 1.35, s, Me_3C; 2.34, d, J 3.5 Hz, Si-CH-C; 3.28, dd, J 3.5, 6.2 Hz, C-CH-C; 5.82, d, J

6.2 Hz, 1H, CH-O_2C; 7.08, d, *J* 8.6 Hz, 2x ArH; 7.42-7.62, m, 5 x ArH; 8.10-8.15, m, 2 x ArH. Mass spectrum (c.i.) *m/z* 427(M^++1, <1%), 321(3), 305(50), 231(20), 221(22), 179(36), 123(88), 105(78), 85(250), 57(100). A sample of the minor diastereoisomer (20b, R=^{t}BuCO, R_1=$PhCO_2$) was prepared by esterification of the epoxy alcohol (-)-(13b, R=^{t}BuCO) with benzoic acid using DCC. ^{1}H n.m.r.(200 MHz): δ 0.06, s, $SiMe_3$; 1.22, s, Me_3C; 2.25, d, *J* 3.5 Hz, Si-CH-C; 3.22, dd, *J* 3.5, 4.1 Hz, C-CH-C; 6.08, d, *J* 4.1 Hz, 1H, CH-O_2C; 7.08, d, *J* 8.6 Hz, 2x ArH; 7.39-7.58, m, 5 x ArH; 8.03-8.10, m, 2 x ArH.

(1S, 2R, 3R)-4-[1-(3,5-dimethoxy-2,6-diiodophenoxy)-2, 3-epoxy-3-trimethylsilylpropanyl]phenyl 2,2-dimethylpropaoate (-)-(19e, R=^{t}BuCO, R^1=3,5-dimethoxy-2,6-diiodophenyl): Yield 59%. Ratio (19e) to (20e)=>99:1. Solvent=THF, nucleophile=2,6-diiodo-3,5-dimethoxyphenol. Yellow foam. $[\alpha]_D$ = -53.3° (c=1, $CHCl_3$). (Found: C, 42.6; H, 4.7 $C_{25}H_{32}I_2O_6Si$ requires C, 42.3; H, 4.5%). υ_{max} (nujol): 1751 cm^{-1}. ^{1}H n.m.r. (200 MHz): δ -0.04, s, $SiMe_3$; 1.38, s, Me_3C; 2.06, d, *J* 3.6 Hz, C-CH-Si; 3.68, dd *J* 3.6, 7.6 Hz, C-CH-C; 3.91, s, 2 x MeO; 5.16, d, *J* 7.6 Hz, CH-O; 6.27, s, ArH; 7.12, d, *J* 8.5 Hz, 2 x ArH; 7.66, d, *J* 8.5 Hz, 2 x ArH. Mass spectrum *m/z* 710(M^+, <1%), 406(2), 383(1), 336(1), 305(24), 147(20), 57(100).

Synthesis of (1S, 2R, 3R)-4-(1-benzoyloxy-2, 3-epoxy-3-trimethylsilylpropanyl]phenyl acetate (19c, R=MeCO, R^1=$PhCO_2$): Yield 81%. Ratio (19c) to (20c)=>99:1. Solvent=THF, nucleophile=benzoic acid. Colourless solid, m.p. 94-95°. $[\alpha]_D$ = -10.3 (c=0.8, $CHCl_3$). υ_{max} (nujol): 1723s, 1761m cm^{-1}. ^{1}H n.m.r. (200 MHz): δ 0.04, s, $SiMe_3$; 2.31, s, $MeCO_2$; 2.34, d, J 3.5 Hz, Si-CH-C; 3.28, dd, J 3.5, 6.1 Hz, C-CH-C; 5.83, d, J 6.1 Hz, 1H, CH-O2C; 7.12, d, *J* 8.5 Hz, 2x ArH; 7.31-7.59, m, 5 x ArH; 8.10-8.14, m, 2 x ArH. Mass spectrum *m/z* 341(1%), 279(5), 263(5), 237(4), 221(22), 220(19), 179(18), 105(100), 77(39), 73(44). A sample of the (1R, 2R, 3R) benzoate (20c, R=MeCO, R^1=$PhCO_2$) was prepared by esterification of the epoxy alcohol (-)-(13c, R=MeCO) with benzoic acid using DCC. ^{1}H n.m.r.(200 MHz): δ 0.06, s, $SiMe_3$; 2.27, d, *J* 3.5 Hz, Si-CH-C; 2.30, s, $MeCO_2$; 3.22, dd, J 3.5, 4.3 Hz, C-CH-C; 6.06, d, J 4.3 Hz, 1H, CH-O2C; 7.12, d, *J* 8.7 Hz, 2x ArH; 7.41-7.59, m, 5 x ArH; 8.06-8.11, m, 2 x ArH.

(1S, 2R, 3R)-4-[1-(3,5-dimethoxy-2,6-diiodophenoxy)-2,3-epoxy-3-trimethylsilylpropanyl]phenyl acetate (-)-(19f, R=MeCO, R^1=3,5-dimethoxy-2,6-diiodophenyl): Yield 83%. Ratio (19f) to (20f)=>99:1. Solvent=THF, nucleophile=2,6-diiodo-3,5-dimethoxyphenol. Yellow oil. $\alpha]_D$ = -50.9 (c=1, $CHCl_3$). (Found: C, 39.5; H, 3.8. $C_{22}H_{26}I_2O_6Si$ requires C, 39.5; H, 3.9%). υ_{max} (film): 1765m cm^{-1}. ^{1}H n.m.r. (200 MHz): δ -0.05, s, $SiMe_3$; 2.05, d, *J* 3.6 Hz, C-CH-Si; 2.32, s, $MeCO_2$, 3.69, dd *J* 3.6, 7.6 Hz, C-CH-C; 3.91, s, 2 x MeO; 5.17, d, *J* 8.2 Hz, CH-O; 6.27, s, ArH; 7.16, d, *J* 8.7 Hz and 7.67, d, *J* 8.7 Hz, 4 x ArH. Mass spectrum *m/z* 668 (M^+, <1%), 406(17), 263(52), 221(32), 193(50), 147(48), 75(43), 73(100).

Methyl (2R*, 3R*) and(2R*, 3S*)-2-(2',2'-dimethylpropanoyl)oxy-3-benzoyloxy-3-(4-methoxyphenyl)propanoate (14b, R=Me, R^1=^{t}Bu) and (15b, R=Me, R^1=^{t}Bu): Yield 37% at 40% conversion. Ratio (14b) to (15b)=2:1. Solvent=THF, nucleophile=benzoic acid. Colourless oil. (Found: C, 66.9; H, 6.3%. $C_{23}H_{26}O_7$ requires C, 66.7; H, 6.3%). υ_{max} (film): 1732m cm^{-1}. Mass spectrum (c.i.): *m/z* 414(M^++1, <1%), 294(15), 293(100), 261(16), 241(16), 209(12), 193(14), 161(10, 135(11), 123(11), 105(57), 85(42), 57(41). (14, R=Me, R^1=^{t}Bu): ^{1}H n.m.r. (200 MHz): δ 1.19, s, Me_3C; 3.70, s, MeO_2C; 3.80, s, MeO-Ar; 5.52, d, *J* 5.6 Hz, CH-CO_2; 6.39, d, *J* 5.6 Hz, Ar-CH; 6.89, d, *J* 8.8 Hz, 2 x ArH; 7.38-7.58, m, 5 x ArH; 8.03-8.10, m, 2 x ArH. A sample of the alcohol (7b, R=Me, R^1=^{t}Bu) was esterified with benzoic acid using DCC/DMAP to give the benzoate (15b, R=Me, R^1=^{t}Bu). ^{1}H n.m.r. (200 MHz): δ 1.21, s, Me_3C; 3.66, s,

MeO_2C; 3.79, s, MeO-Ar; 5.38, d, *J* 4.3 Hz, CH-CO_2; 6.45, d, *J* 4.3 Hz, Ar-CH; 6.87, d, *J* 8.8 Hz, 2 x ArH; 7.38-7.58, m, 5 x ArH; 8.03-8.10, m, 2 x ArH.

Methyl (2R* ,3R*) -2-(2',2'-dimethylpropanoyl)oxy-3-benzoyloxy-3-(4-acetoxyphenyl)propanoate (14, R=MeCO, R^1=^{t}Bu): Yield 20% at 25% conversion. Ratio (14c) to (15c)=>99:1. Solvent=THF, nucleophile=benzoic acid. Colourless oil. υ_{max} (film): 1766m, 1731m cm^{-1}. ^{1}H n.m.r. (200 MHz): δ 1.19, s, Me_3C; 2.28, s, MeCO; 3.67, s, MeO_2C; 5.39, d, *J* 4.0 Hz, CH-CO_2; 6.53, d, *J* 4.0 Hz, Ar-CH; 7.09, d, *J* 8.7 Hz, 2 x ArH; 7.37-7.65, m, 5 x ArH; 8.05-8.19, m, 2 x ArH. Mass spectrum (c.i.): *m/z* 411(M^+-31, <1%), 321(53), 237(13), 123(100), 105(60). A sample of the alcohol (7c, R=MeCO, R^1=^{t}Bu) was esterified with benzoic acid using DCC/DMAP to give the benzoate (15c, R=MeCO, R^1=^{t}Bu). ^{1}H n.m.r. (200 MHz) (diagnostic peaks): δ 5.23, d, *J* 3.4 Hz, CH-CO_2; 6.44, d, *J* 3.4 Hz, Ar-CH.

Methyl Z-3-(4-acetoxyphenyl)-2-(2',2'-dimethylpropanoyl)oxy-2-propenoate (16): When the Mitsunobu reaction of the hydroxy ester (7c, R=MeCO, R^1=BuCO) was run using either phenol or 3,5-dimethoxyphenol as the nucleophile only the enol pivalate (16) was isolated in 86% and 83% yield respectively as a colourless solid, m.p. 76-78°. Accurate mass determination found 320.125±0.003, $C_{17}H_{20}O_6$ requires 320.126. υ_{max} (nujol): 1754m, 1722m, 1655m cm^{-1}. ^{1}H n.m.r. (200 MHz): δ 1.37, s, Me_3C; 2.31, s, MeCO; 3.83, s, MeO_2C; 7.11, d, *J* 8.7 Hz, 2 x ArH; 7.30, s, =CH-; 7.60, d, *J* 8.7 Hz, 2 x ArH. ^{13}C n.m.r. (50 MHz): 21.02, Me_3-; 26.91, CH_3CO; 38.92, CMe_3; 52.44, CO_2CH_3; 121.74, ArH; 126.01, olefinic CH; 129.70, quat. olefinic carbon; 131.16, ArH; 137.24 and 151.34, 2 x quat. carbons; 162.90, 169.00 and 175.98, 3 x carbonyl

Methyl (2R* ,3R*)-3-(2,6-diiodo-3,5-dimethoxyphenoxy)-2-(2',2'-dimethylpropanoyl)oxy-3-(4-acetoxyphenyl)propanoate (18, R=MeCO, R^1Bu) and methyl Z-3-(4-acetoxyphenyl)-2-(2',2'-dimethylpropanoyl)oxy-2-propenoate (16).

(i) Solvent=THF, nucleophile=2,6-diiodo-3,5-dimethoxyphenol (3 equivalents). Ratio (18) to (16)=45:55. Yield (18) 34%. Yield (16) 60%. Methyl (2R*, 3R*)-3-(2,6-diiodo-3,5-dimethoxyphenoxy)-2-(2',2'-dimethylpropanoyl)oxy-3-(4-acetoxyphenyl)propanoate (18, R=MeCO, R_1=Bu): Yield 34% . Colourless solid, m.p. 166-167° (Found: C, 41.7; H, 3.9. $C_{25}H_{28}I_2O_9$ requires C, 41.3; H, 3.9%.). υ_{max} (nujol): 1764m, 1727m cm^{-1}. ^{1}H n.m.r. (200 MHz): δ 1.20, s, Me_3C; 2.28, s, MeCO; 3.67, s, MeO_2C; 3.89, s, 2 x MeO-Ar; 5.69, d, *J* 3.7 Hz, CH-CO_2; 6.04, d, *J* 3.7 Hz, Ar-CH; 6.23, s, 1 x ArH; 7.06, d, *J* 8.7 Hz and 7.50, d, *J* 8.7 Hz, 4 x ArH.

(ii) Solvent=toluene, nucleophile=2,6-diiodo-3,5-dimethoxphenol (1.2 equivalents). Ratio (18) to (16)=40:60. Yield (18) 30%. Yield (16) 45%.

(iii) Solvent= CH_2Cl_2, nucleophile=2,6-diiodo-3,5-dimethoxyphenol. Ratio (18) to (16)=70:30. Yield (18) 48%. Yield (16) 30%.

(iv) Solvent= CH_2Cl_2 at double the concentration of reagents cf entry (iii), nucleophile=2,6-diiodo-3,5-dimethoxyphenol. Ratio (18) to (16)=70:30.

(v) Solvent= CH_2Cl_2 slow addition of DIAD, nucleophile=2,6-diiodo-3,5-dimethoxyphenol. Ratio (18) to (16)=70:30.

(vi) Solvent= CH_2Cl_2 , one equivalent of nucleophile=2,6-diiodo-3,5-dimethoxyphenol. Ratio (18) to (16)=70:30.

(vii) Solvent= CH_2Cl_2, one equivalent of nucleophile=2,6-diiodo-3,5-dimethoxyphenol. 5 equivalent DIAD. and PPh_3. Ratio (18) to (16)=85:15. The isolated yield of the aryl ether (18) increased to (260 mg, 60%).

(1R*, 2S*)- or (1S*, 2S*)-1-(2,6-diiodo-3,5-dimethoxyphenoxy)-1-(4-methoxyphenyl)-2,3-epoxypropane (21): Tetrabutylammonium fluoride (0.61 ml, 1 M in tetrahydrofuran, 0.61 mmol) was added to a solution of the aryl ether (19d or 20d, R=Me, R^1=2,6-diiodo-3,5-dimethoxyphenyl) (200 mg, 0.31 mmol) in tetrahydrofuran (8 ml) at ambient temperature and the reaction was allowed to stir overnight. The reaction was quenched with saturated aqueous ammonium chloride (5 ml) and extracted with ether (3 x 10 ml). The combined organic extracts were dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give the title terminal epoxide (21) as a colourless solid (178 mg, 99%) (Found: C, 38.2; H, 3.5. $C_{18}H_{18}I_2O_5$ requires C, 38.0; H, 3.2%). υ_{max} (nujol): 1615m cm^{-1}. ^1H n.m.r.(200 MHz): δ 2.49, dd, *J* 2.7, 4.8 Hz, C-HCH; 2.70, m, C-HCH; 3.82, m, 1H, C-CH-C; 3.84, s, 3H, MeO; 3.92, s, 2 x MeO; 5.17, d, *J* 7.7 Hz, CH-CH-O; 6.27, d, *J* 8.7 Hz and 6.97, d, *J* 8.7 Hz, 4 x ArH. Mass spectrum *m/z* 568 (M^+, 0.1%), 538(0.2), 278(3), 263(4), 235(3), 163(100), 135(35).

3-(3,5-dimethoxyphenoxy)-3-(4-methoxyphenyl)prop-2-en-1-ol (22)

(i) Reaction with n-BuLi : n-Butyl lithium (0.36 ml, 1.6 M in hexane, 0.58 mmol) was added to a solution of terminal epoxides (21) (145 mg, 0.26 mmol) in THF (10 ml) at <95°. The solution was allowed to warm to ambient temperature over 2 h and stirred for an additional 3 h at this temperature. The reaction was quenched with a saturated solution of aqueous ammonium chloride (5 ml) and extracted with CH_2Cl_2 (2 x 10 ml). The combined organic extracts were dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give a yellow oil. Preparative t.l.c. (50% ethyl acetate / light petroleum) gave the title alcohol (22) as a yellow oil (117 mg, 73%). υ_{max} (film): 3396s, 1656m cm^{-1}. ^1H n.m.r. (200 MHz): δ 3.70, s, 2 x MeO; 3.76, s, MeO; 4.31, d, *J* 6.8 Hz, CH_2-O; 5.91, t, *J* 6.8 Hz, C=CH-C; 6.07, d, *J* 2.2 Hz, 1 x ArH; 6.13, d, *J* 2.2 Hz, 2 x ArH; 6.80, d, *J* 8.9 Hz, 2 x ArH; 7.42, d, *J* 8.9 Hz, 2 x ArH. ^{13}C n.m.r. (50 MHz): δ 55.17, MeO; 55.24, 2 x MeO; 57.51, CH_2-O; 93.85, 1 x phloroglucinol ArH; 94.49, 2 x phloroglucinol ArH; 113.96, 2 x ArH; 114.11, =CH-C; 126.87, =CH-OAr; 126.96, 2 x ArH; 150.45, 159.10, 159.88, 161.48, 4 x quaternary aromatics. Mass spectrum *m/z* 316 (M^+, 3%), 298(30), 285(50), 163(55), 135(85), 133(100), 77(45), 55(60).

(ii) Reaction with n-BuLi and $MgBr_2$: The reaction was repeated as above except after the addition of the n-BuLi the reaction was treated with four equivalents of anhydrous magnesium bromide at -78°. After warming to ambient temperature and work up only the alcohol (22) was isolated in 75% yield.

(iii) Reaction with n-BuLi and CuBr.Me_2S: The reaction was repeated as above except after the addition of the n-BuLi the reaction was treated with two and a half equivalents of copper(I) bromide dimethyl sulphide at <95°. After warming to ambient temperature and work up only the alcohol (22) was isolated in 60% yield.

Desilylation of (1S, 2R, 3R)-4-[1-(3,5-dimethoxy-2,6-diiodophenoxy)-2, 3-epoxy-3-trimethylsilylpropanyl]phenyl 2,2-dimethylpropanoate (19e, R=^{t}Bu, R^1=2,6-diiodo-3,5-dimethoxyphenyl): Tetrabutylammonium fluoride (0.80 ml, 1 M in THF, 0.80 mmol) was added dropwise to a solution of the aryl ether (19e) (280 mg, 0.40 mmol) in THF (4 ml) at 0°. The reaction mixture was then allowed to warm to ambient temperature and stirred overnight. The reaction was quenched with saturated aqueous ammonium chloride (5 ml) and extracted with ether (3 x 10 ml). The combined organic extracts were dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give a slightly yellow solid (200 mg). ^1H n.m.r. spectroscopy analysis revealed a 1:1 mixture of 2,6-diiodo-3,5-dimethoxyphenol (17) and *E*-4-hydroxycinnamaldehyde (23).[38]

Desilylation of (1S, 2R, 3R)-4-[1-(3,5-dimethoxy-2,6-diiodophenoxy)-2, 3-epoxy-3-trimethylsilylpropanyl]phenyl acetate (19f, R=MeCO, R^1=2,6-diiodo-3,5-dimethoxyphenyl): The aryl ether (-)-(19f) was treated with tetrabutylammonium fluoride as described above to give a 1:1 mixture of 2,6-diiodo-3,5-dimethoxyphenol (17) and *E*-4-hydroxycinnamaldehyde (23).[38]

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