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The Synthesis of Alkenes *via epi*-Phosphonium Species: 1. An *Anti*-Wittig Elimination

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Abstract: *Anti*-1,2-phosphinyl alcohols **11** and their corresponding *syn*-isomers upon treatment with phosphorus trichloride and triethylamine give *E* and *Z* alkenes respectively, by an *anti* elimination. This is in marked contrast to the *syn* Horner-Wittig elimination of the corresponding 1,2-phosphinoyl alcohols. The 1,2-phosphinyl alcohols **11** were prepared by the reduction of 1,2-phosphinoyl alcohols with cerium(III) chloride/lithium aluminium hydride. The *anti* elimination is explained by the formation of a transient *epi*-phosphonium species. An unexpected *E*-selective Horner-Wittig elimination during the cerium(III) chloride/lithium aluminium hydride reduction of a 1,2-phosphinoyl alcohol in which the diphenylphosphinoyl group is adjacent to an aryl group is described. This led to the synthesis of the antimitotic agent *E*-combretastatin A-4. An alternative synthesis of the 1,2-phosphinyl alcohols from the corresponding phosphine-borane complex is also described.

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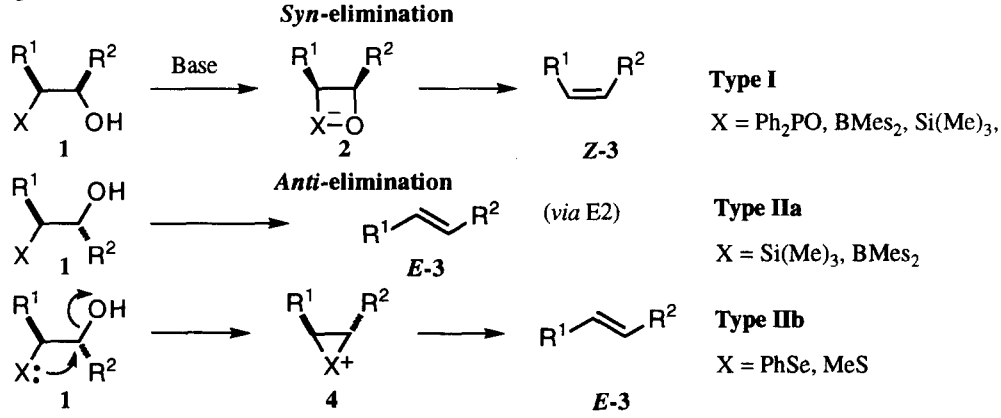
Keywords: alkenes; elimination reactions; phosphines; Wittig reaction.

β-Substituted alcohols bearing an adjacent functional group X are very useful intermediates for the synthesis of alkenes. Scheme 1 summarises several reported examples of stereoselective elimination of β-substituted alcohols. We classify the three types of reaction as Type I (*syn* elimination, under basic conditions, **1** → ***Z*-3**); Type IIa (*anti* elimination, **1** → ***E*-3**, *via* an E2 type mechanism); and Type IIb (*anti* elimination, **1** → ***E*-3**, *via* a transient three-membered ring **4**). When reactions exist that effectively allow the X and OH groups to be lost in both a *syn* and *anti* fashion both *E* and *Z* alkenes can be obtained separately from a common stereodefined starting material.



Scheme 1

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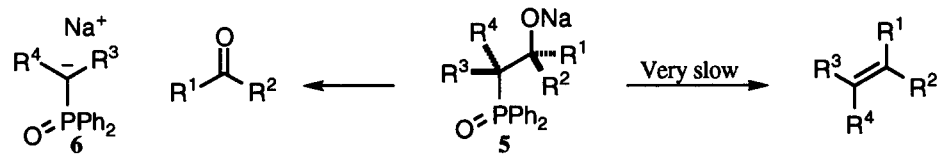
Some general features of these types of elimination are listed below.

Type I: This mode of elimination, which proceeds *via* a four membered-ring containing intermediate **2**, is possible if the group X is electrophilic and can stabilise a negative charge and the OH group is nucleophilic (i.e. utilising its natural polarity). Hence reactions of this type are often carried out under strongly basic conditions that form the alkoxide ion. [For example X = Ph_2PO[1], $BMes_2$[2], $Si(Me)_3$[3]]

Type IIa: The reaction is also possible if the X group is electrophilic and the OH has been activated to be a nucleofuge. [For example X = $Si(Me)_3$,[3] $BMes_2$[2]]

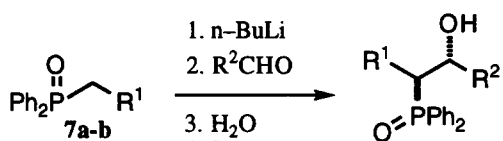
Type IIb: For this reaction pathway the OH group, or activated derivative, must be a good nucleofuge and the X group must be nucleophilic. [For example X = PhSe[4], MeS[5]]

Whilst the Wittig reaction, and its many variants, are perhaps the most important example of a type I reaction, until recently its counterpart type II reaction was unknown. As far as we are aware the only reported example of an *anti* elimination (type II) of a phosphorus containing species comes from our laboratories.[6] We now report the full details of that study. Our search for an *anti* elimination of 1,2-phosphinoyl alcohols was prompted by a need to make tri-substituted and tetra-substituted carbon–carbon double bonds. These types of alkene are generally not accessible using the Horner-Wittig reaction[7] since the intermediate alkoxide often undergoes a reverse aldol type reaction, expelling the α-phosphinyl anion (**5** → **6**)(scheme 2). We reasoned that this might not be a problem if we could find conditions for the elimination that did not require the use of a strong base. Our solution was to develop a type II reaction based on Horner-Wittig intermediates.



Scheme 2

The *anti* and *syn* alcohols **8a** and **8b** were prepared by the methods of Warren and co-workers[8,9] from substituted alkyldiphenylphosphine oxides **7a** and **7b**.[10,11] The *anti* isomers *anti*-**8a** and *anti*-**8b** are the major diastereoisomers from the reactions between the lithiated phosphine oxide **7a** and **7b** and benzaldehyde (scheme 3).[8] Separation of the *anti* diastereoisomers from the minor *syn* isomers was achieved either by column chromatography (silica gel) or by recrystallisation.

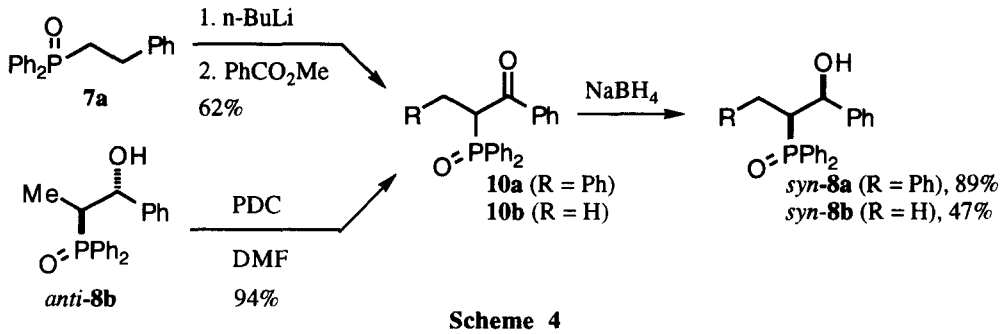


anti-**8a** $R^1 = PhCH_2$, R_2 = Ph, 62%, *anti:syn* 88:12.

anti-**8b** R^1 = Me, R_2 = Ph, 71%, *anti:syn* 85:15

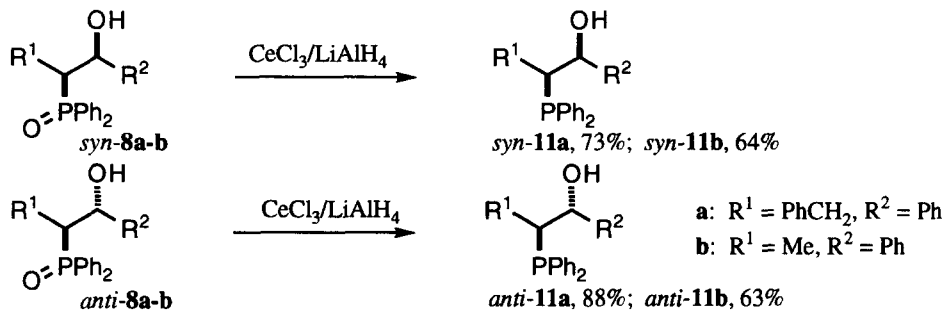
Scheme 3. The ratio of *anti/syn* measured by ^1H NMR of the crude reaction mixture.

The *syn* 1,2-phosphinoyl alcohols *syn*-**8a** and *syn*-**8b** were obtained by reduction of the β-ketophosphine oxides **10a** and **10b** respectively with sodium borohydride.[9] The sequential reaction of phenethyldiphenylphosphine oxide **7a** with n-butyllithium and methylbenzoate gave β-ketophosphine oxide **10a**,[12] which was reduced with sodium borohydride in methanol to give the *syn*-1,2-phosphinoyl alcohol *syn*-**8a** (scheme 4). The β-ketophosphine oxide **10b** was prepared by the oxidation of the *anti*-1,2-phosphinoyl alcohol *anti*-**8b** by pyridinium dichromate (PDC) in DMF. Reduction of this ketone with sodium borohydride in methanol (scheme 4) gave the alcohol *syn*-**8b**.



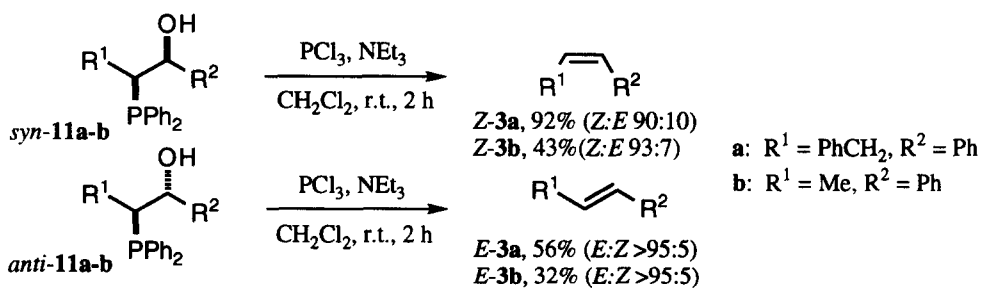
Scheme 4

With both the *syn* and *anti* diastereoisomers of the phosphinoyl alcohols **8** in hand we were now in a position to test our proposed *anti*-elimination reaction. First, the *syn*-1,2-phosphinoyl alcohol *syn*-**8a** was reduced with an excess of lithium aluminium hydride and cerium(III) chloride, under conditions developed by Imamoto and co-workers,[13,14] to produce the *syn*-1,2-phosphinyl alcohol *syn*-**11a** in good yield (scheme 5). Care had to be taken in handling the phosphines, since they proved susceptible to oxidation if left exposed to air. Indeed, these phosphines proved difficult to characterise fully, so were used without purification. The $CeCl_3$ probably activates phosphine oxides by co-ordination to the P=O functionality, so that the deoxygenation with lithium aluminium hydride proceeds readily. Imamoto has not commented upon a detailed mechanism of the reaction, but has shown that the reduction is very efficient. Indeed, when we carried out the reduction with lithium aluminium hydride by itself the reaction was problematic; we obtained many products, which were not isolated. Reduction of the three other phosphinoyl alcohols *syn*-**8a** and *anti*-**8a-b** worked equally well.



Scheme 5

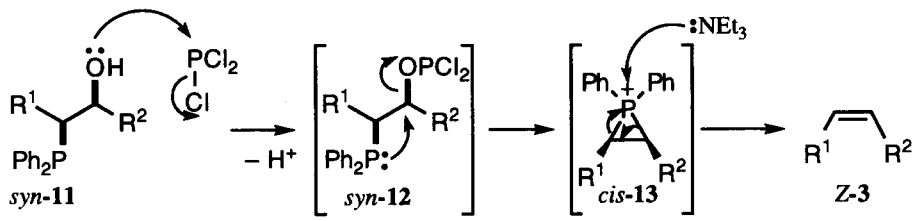
Having prepared the β–hydroxyphosphines *syn*-**11a** and *syn*-**11b** the next step required was the conversion of the hydroxyl group into a good leaving group in order to achieve the *anti*-elimination, thereby giving the *cis*-alkenes *Z*-**3a** and *Z*-**3b**. We chose phosphorus trichloride as a simple activating group. The *syn*-



Scheme 6

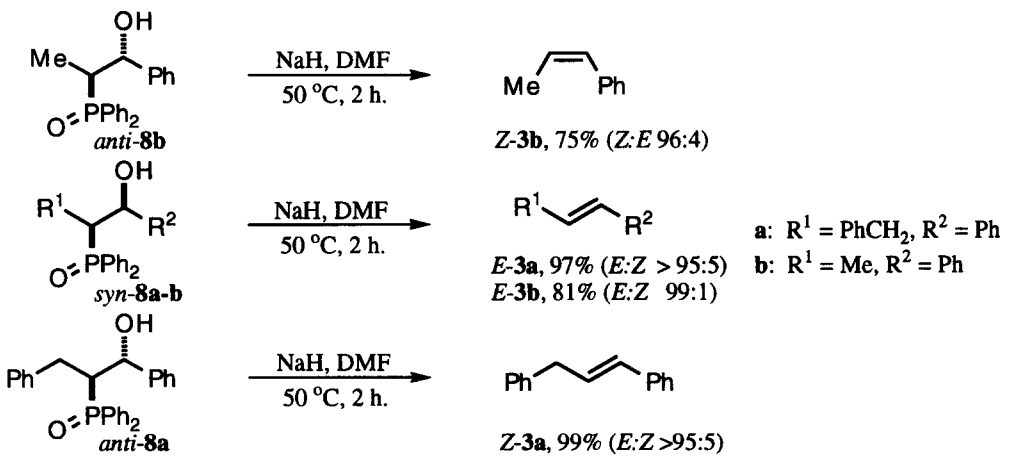
1,2-phosphinyl alcohols *syn*-**8a** and *syn*-**8b** were used crude from the $LiAlH_4/CeCl_3$ reaction and stirred with phosphorus trichloride and triethylamine. Much to our satisfaction we did observe alkene formation, and most importantly the stereochemistry was consistent with the *anti*-elimination of the phosphorus and OH groups (scheme 6) since the olefin was configured *cis*. In both cases the major product was the *cis* isomer as determined by ^1H nmr spectroscopic analysis of the crude and isolated product. In a similar fashion, the $LiAlH_4/CeCl_3$ reduction of the alcohols *anti*-**11a-b** followed by treatment of the intermediate phosphines gave alkenes, which this time were configured *trans*.

The proposed mechanism of the reaction of the *syn*-1,2–diphenylphosphinyl alcohol **11** to **3** is depicted in scheme 7. We believe that the reaction proceeds *via* the formation of a three-membered ring intermediate *cis*-**13**. This *epi*-phosphonium (phosphiranium) species undergoes nucleophile induced extrusion of the phosphorus atom, in a retro-cheleotropic type of process, to form the alkene. There is an alternative and plausible mechanism, in which the Ph_2P group is lost at the same time as the $OPCl_2$ group in an E2 fashion (i.e. a type IIa reaction). Evidence for the former mechanism *syn*-**11** → *Z*-**3** (scheme 7) will be presented in the following paper. Whilst phosphiranes[15] and phosphiranium salts[16] are known species, the process **13** → **3** has not been previously described.



Scheme 7

In order to both obtain authentic samples of the alkenes **3** and illustrate that our procedure is complementary to the Horner-Wittig reaction, we carried out the base promoted reactions of alcohols **8**. The *syn*-1,2-phosphinoyl alcohols *syn*-**8a** and *syn*-**8a** were reacted with sodium hydride in DMF at 50 °C, producing the *trans* alkenes *E*-**3a** and *E*-**3a** as expected. Elimination of *anti*-**8b** provided the *Z*-alkene *Z*-**3b**.

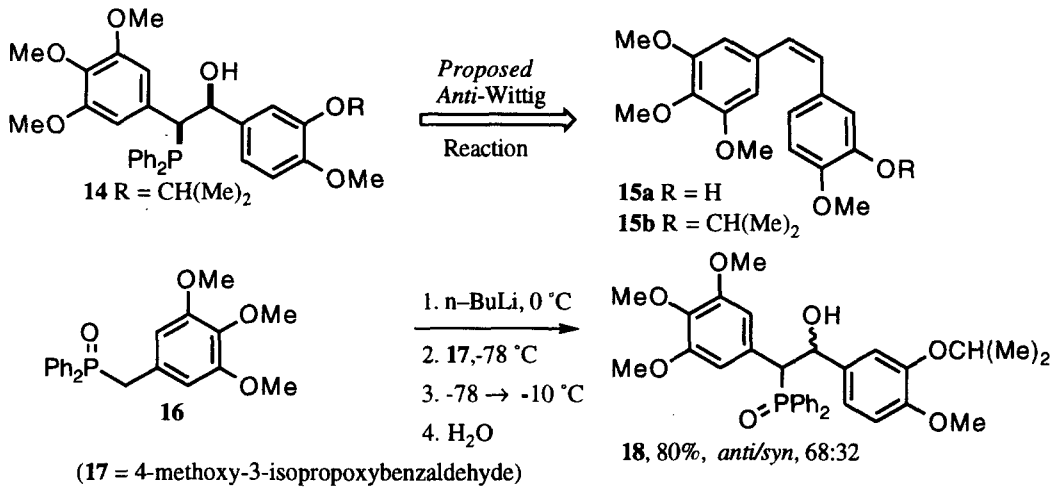


Scheme 8

However, when the *anti*-1,2-phosphinoyl alcohol *anti*-**8a** was treated with sodium hydride *E*-**3a** was obtained, rather than *Z*-**3a** as expected. It would seem that the alkene *Z*-**3a** is configurationally unstable under these basic conditions, even when only one equivalent of sodium hydride is used.[17] Treatment of the alkene *Z*-**3a** with sodium diphenylphosphinate, the basic by-product from the elimination, and also sodium hydride itself

had no effect upon the *Z*:*E* ratio. The likelihood that the alcohol *anti*-**8a** is converted into the *syn* isomer *syn*-**8a**, prior to elimination, is small since alkyldiphenylphosphinoyl alcohols of this type are stable. It is only when the anion of the phosphine oxide is stable (for example, when it is benzylic)[18,19] and the alkene is sterically compressed, that loss of stereospecificity is sometimes observed. We are not able to provide a convincing argument for why the *trans*-alkene *E*-**3a** is obtained from *anti*-**8a**. Nevertheless, the reaction was repeated several times, and on each occasion the *trans*-alkene was isolated.

We chose to apply our new reaction to the synthesis of *cis*-combretastatin A-4 *Z*-**15a**, a potent antimitotic[20] stilbene, isolated from the African bush willow, *Combretum caffrum*.[21] This structurally simple alkene shows exciting potential as an anticancer agent which displays potent and selective toxicity toward tumor vasculature.[22] The precursor required for the synthesis of *Z*-**15a** *via* the *anti*-Wittig reaction is the *syn*-1,2-phosphinyl alcohol **14** (scheme 9).



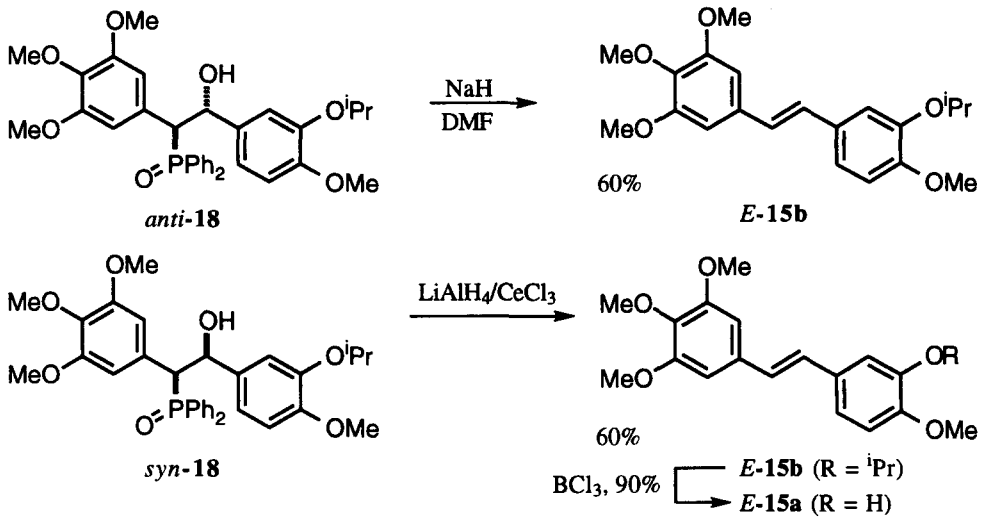
Scheme 9

The synthesis of 1,2-phosphinoyl alcohols in which the phosphorus group is benzylic is problematic; the lithium alkoxide first formed, after addition of the metallated phosphine oxide anion to the aldehyde, has a pronounced tendency to eliminate to give the alkene. However, Warren and co-workers[18] have shown that *anti* and *syn* 1,2-phosphinoyl alcohols, derived from benzyldiphenylphosphine oxide can be obtained when the reaction is quenched at 0 °C after warming from –78 °C. This technique was applied to the reaction between (3,4,5-trimethoxybenzyl)diphenylphosphine oxide **16** and the 4-methoxy-3-isopropoxybenzaldehyde **17**; quenching with water at 0 °C gave stilbene *E*-**15b** but at –10 °C gave the desired *syn* **18** and *anti*-**18** which were by separable column chromatography (silica gel, ethyl acetate).

Under basic conditions (sodium hydride in DMF) the *syn*-phosphinoyl alcohol *syn*-**18** gave *E*-stilbene *E*-**15b** (scheme 10). This conversion of *syn*-**18** to the *E*-stilbene is probably occurring *via* decomposition to the parent starting materials (the sodium derivative of phosphine oxide **16** and benzaldehyde **17**) and subsequent recombination to the anions of both *anti* and *syn* **18** and finally elimination to *E*-stilbene **15b**.[23] Apparently the combined influence of unfavourable Ar–Ar eclipsing interactions in the *syn*-elimination pathway from *anti*-**18** and the relatively high acidity of phosphine oxide **16** conspire to favour the formation of *E*-**15b** from the *syn*-**18**. In other words, the rate of the Wittig elimination of *syn*-**18** is faster than that of *anti*-**18**.

The attempted *anti*-Wittig elimination route to *Z*-**15b** also highlights the problems of obtaining *Z*-stilbenes by the Horner-Wittig method. Reduction of the phosphine oxide *syn*-**18** with lithium aluminium hydride in the presence of cerium(III) chloride did not give the phosphine **14**. The product of the reaction was actually the *trans*-stilbene *E*-**15b** (scheme 10). In the light that the lithium alkoxide of **18** readily undergoes Wittig elimination to the alkene, it is not surprising that the attempted reduction also results in the production of

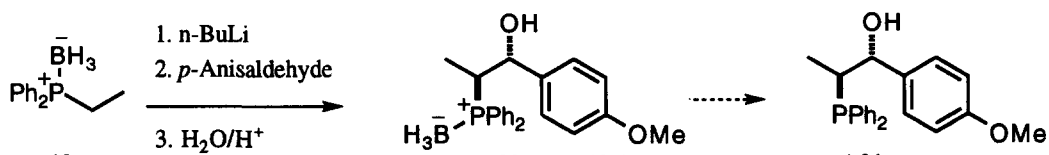
E-**15b**. Clearly the reduction of the P–O bond is occuring much slower than the deprotonation of the alcohol and subsequent Wittig reaction. Whilst the synthesis of *Z*-**15b** has not been achieved, it should be noted that the *trans* isomer is indeed active, though less so than the *cis* isomer.[24] The *anti*-Wittig and Horner-Wittig reactions are therefore not suited for the synthesis of *Z*-alkenes derived from benzylic phosphine oxides.



anti-**18** *E*-**15b** *syn*-**18** **15b** (R = ^{i}Pr) **15a** (R = H)

Scheme 10

To circumvent the problem of unwanted Horner–Wittig elimination during the reduction we chose to investigate an alternative strategy, utilising a protected phosphine from which we hoped the required 1,2-hydroxyphosphine could be released prior to the *anti*-elimination reaction. The protecting group we chose was the BH_3 group, since it forms well studied stable complexes with phosphines. In addition, recent disclosures from the group of Le Corre[25] had shown that anions of phosphine-borane complexes behave very much like phosphine oxides with aldehydes to give alkenes in a Horner–Wittig type reaction. Indeed, the P^+–BH_3^- unit being isoelectronic with P^+–O^- appears to show similar chemical reactivity. With this in mind we chose to see whether it would be possible to make the 1,2-phosphinyl alcohol *anti*-**21** from the precursor phosphine-borane *anti*-**20**, which itself would be made from the ethyldiphenylphosphine-borane **19**. The hydroxyphosphine–borane **20** was prepared by the addition of *p*-anisaldehyde to the anion, generated *via* addition of n-butyllithium to the phosphine-borane **19** (itself prepared by the sequential one-pot titanium(IV) isopropoxide/triethoxysilane reduction of ethyldiphenylphosphine oxide and treatment with borane·THF) followed by aqueous work-up (scheme 11).



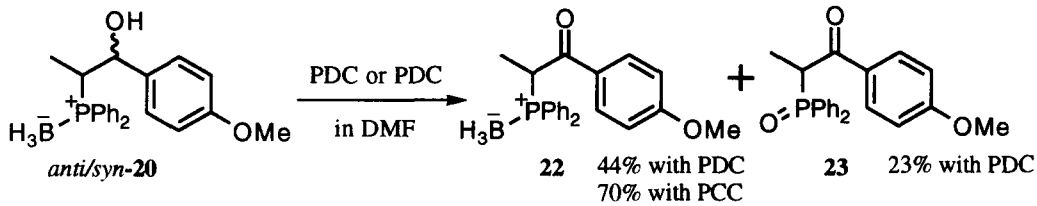
19 *anti*-**20** 48% *anti*-**21**

anti/syn, 60:40 (before separation)

Scheme 11

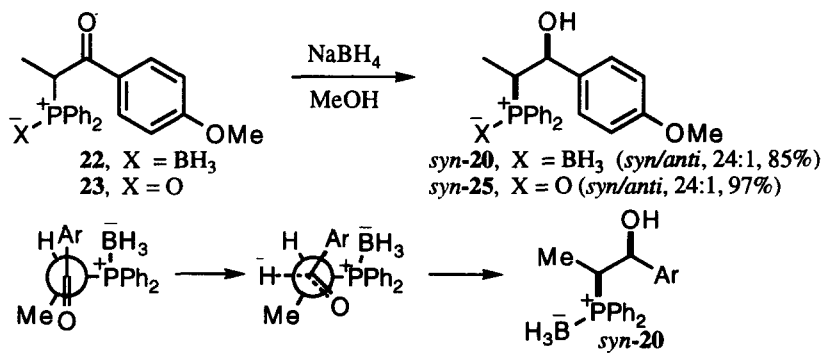
Similar reactions have been described by Imamoto and co-workers[26] and Le Corre and colleagues.[25] However, this is the first report of the diastereoselectivity in the reaction, which in this case is poor. The mixture of *anti* and *syn* diastereoisomers of 1,2-hydroxyphosphine-borane **20** can be readily separated by chromatography or alternatively can be oxidized directly to the ketone **22** in the hope that its diastereoselective reduction would be high. When the β-hydroxyphosphine-borane **20** was subjected to the usual oxidation

conditions (pyridinium dichromate in *N,N*-dimethylformamide)[1] we obtained two products, the required ketone **22** and the undesired ketone **23** (scheme 12). Pellon[27] did not observe oxidative cleavage of the P–B bond in the reaction of phosphine-borane complexes with pyridinium chlorochromate. When pyridinium chlorochromate was used the β-ketophosphine-borane **22** was obtained in good yield (70%).



Scheme 12

The reduction of ketophosphine–borane **22** with sodium borohydride in methanol gives predominantly the *syn*-β-hydroxyphosphine-borane **20** (scheme 13); from NMR analysis of the crude reaction mixture the ratio of *syn* to *anti* isomers was estimated to be 24:1. This selectivity is essentially the same as that observed for the corresponding phosphine oxides. The high stereoselectivity is in accord with the Felkin-Anh model. Addition of the hydride occurs to the conformation which has the largest group on the chiral centre at 90° to the C=O bond, allowing overlap of the lowest energy σ* (C^{α}–P) orbital with the *p* orbitals of the C=O π bond.[28] Addition of the hydride occurs *anti* to the large group from the least-hindered face of the carbonyl group to give the *syn* isomer *syn*-**20**.



Scheme 13

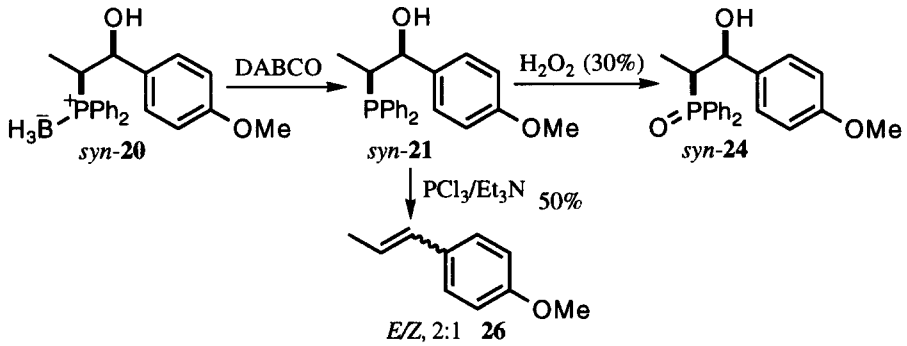
Table 1 summarises the *syn* selectivity we observed with other reducing reagents. All of the reducing reagents give a similarly high level of diastereoselectivity in favour of the expected[9] *syn*-adduct. The *syn:anti* ratio was calculated from the ^{1}H NMR integration of the methyl signals which appeared as double doublets at δ 0.80 ppm (*anti*) and δ 1.08 ppm (*syn*). The β-ketophosphine oxide **23** also gives a similar *syn* selectivity on reduction to β-hydroxyphosphine oxide **25** with sodium borohydride in methanol.

Table 7. Reduction of ketophosphine-borane **22** to *syn*-hydroxyphosphine-borane *syn*-**20**.

Reducing reagent/solvent	*syn/anti*	Yield (%)
$LiAlH_4$/THF	23.5:1[a]	85
DIBAL/CH_2Cl_2	24:1[a]	82
L-Selectride®/THF	34:1[b]	65
$NaBH_4/CeCl_3 \cdot 7H_2O$/MeOH	23:1[a]	77

a. Ratio of the *syn/anti* measured by ^{1}H NMR spectroscopy from the crude reaction mixture.;
b. Ratio measured by ^{1}H NMR spectroscopy after chromatography (which did not separate the stereoisomers). We were unable to measure the ratio directly from the crude product since the methyl signals were masked with by-products derived the L-selectride®.

The P–B bond of a phosphine-borane is relatively easy to cleave (a tertiary amine is often sufficiently nucleophilic to release a phosphine from the corresponding phosphine-borane complex). The *syn* 1,2-hydroxyphosphine **21** was obtained by treatment of the *syn* 1,2-hydroxyphosphine-borane complex **20** with 1,4-diazabicyclo[2.2.2]octane (DABCO™). The *syn* β-hydroxyphosphine **21** was first oxidised with hydrogen peroxide to the known[1] *syn*-1,2-phosphinoyl alcohol **24** (thereby proving its *syn* stereochemical relationship). Treatment of *syn*-**21** with phosphorus trichloride in the presence of triethylamine gave as expected alkene **26** (scheme 14); we believe the mechanism to be the same as before. The only thing worthy of comment is the marked lack of stereospecificity. The $OPCl_2$ group can be envisaged as leaving prior to attack by the diphenylphosphine, as the carbocation generated is resonance stabilised.



Scheme 14

In summary, we have presented the first example of a type IIb elimination reaction of a 1,2-phosphinyl alcohol. The *syn*-1,2-phosphinyl alcohol gives the *Z*-alkene, whilst the *anti*-isomer gives the *E*-alkene. Evidence for the proposed mechanism of the reaction is provided in the following paper.

Acknowledgements : We thank the Pakistan Ministry of Education for a scholarship (F.M.) and the Nuffield Foundation for financial support.

Experimental

200 MHz ^{1}H nmr spectra were recorded using a Brucker AC 200 nmr spectrometer whilst all 300 MHz ^{1}H and 75 MHz ^{13}C nmr spectra were recorded using a Brucker AC 300. The ^{13}C NMR spectra were recorded using Distortionless Enhancement by Polarisation Transfer, (DEPT), and both ^{1}H and ^{13}C spectra were recorded using $CHCl_3$ as an internal standard. Chemical ionisation, (CI), and electron impact, (EI), mass spectra were recorded using a Kratos MS25 mass spectrometer; fast atom bombardment, (FAB), mass spectra were recorded using a Kratos MS50 mass spectrometer, using a *meta*-nitrobenzyl-alcohol matrix. Accurate mass determinations were performed using a Kratos Concept IS mass spectrometer. Elemental analysis were performed using a Carlo-Ebra 1106 elemental analyser. Infra red spectra were recorded using a Phillips Analytical PU9625 pulsed-FT spectrometer. All melting points were determined using a Büchi 510 melting point apparatus and were not corrected. Kugelrühr distillation, where appropriate, was performed using a Büchi GKR-51 apparatus. Column chromatography was conducted using silica gel, 60 230-400 mesh, (Merck & Co.), and silica TLC was conducted on pre-coated aluminium sheets, (60 F_{254}), with a 0.2 mm thickness, (Aldrich Chemical Co.). Ether refers to diethyl ether which was distilled prior to use. Hexane used for column chromatography was also distilled prior to use. Anhydrous ether, anhydrous dichloromethane, anhydrous methanol and anhydrous *N,N*-dimethylformamide, (DMF), were obtained from the Aldrich Chemical Co. and used as supplied. Anhydrous toluene was distilled from sodium metal and stored, under nitrogen, in the presence of type 4Å molecular sieves. Anhydrous dimethyl sulfoxide was distilled, under reduced pressure, and stored, under nitrogen, in the presence of type 4Å molecular sieves. THF was distilled from sodium metal in the presence of benzophenone immediately prior to use.

(*1RS,2SR*)-1,3-Diphenyl-2-(diphenylphosphinoyl)propan-1-ol ***anti*-8a**.—To a stirred solution of phenethyldiphenylphosphine oxide **7a** (2.15 g, 7.0 mmol) in dry THF (35 cm^3) was added n-butyllithium (4.4 cm^3 of a 1.6 M solution in hexanes, 7.0 mmol) at 0 °C. After 30 min. the red solution was cooled to –78 °C and benzaldehyde (0.71 cm^3, 7.0 mmol) in THF (10 cm^3) was added dropwise maintaining the solution temperature at –78 °C. The pale yellow solution was allowed to warm to room temperature over *ca.* 2 h and water (50 cm^3) added. The THF was removed *in vacuo* and brine added. The mixture was extracted with dichloromethane (3 × 50 cm^3). The organic extracts were dried ($MgSO_4$) and evaporated *in vacuo* to give a mixture of *anti* and *syn* adducts (*anti/syn*, 88:12), which were separated by column chromatography (SiO_2, EtOAc/hexane 70:30, v/v) to give *anti*-1,3-diphenyl-2-(diphenylphosphinoyl)propan-1-ol **8a** (1.8 g, 62%), m.p. 186–188 °C (lit.,[29] m.p. 187–189 °C), R_f 0.47 (EtOAc/hexane 70:30); δ^1H (300 MHz, $CDCl_3$) 2.70–3.30 (3 H, m, CH_2CHP), 4.96 (1 H, s, OH), 5.35 (1 H, d, *J* 9.6 Hz, C*H*OH), 6.05–8.00 (20 H, m, 4 × Ph).

(*1RS,2SR*)-1-Phenyl-2-(diphenylphosphinoyl)propan-1-ol ***anti*-8b**.—In the same way as above, ethyldiphenylphosphine oxide **7b** (4 g, 17.4 mmol), n-butyllithium (10.9 cm^3 of a 1.6 M solution in hexanes, 17.4 mmol) and benzaldehyde (1.84 cm^3, 17.4 mmol) gave an oil containing two diastereoisomeric alcohols (*anti/syn*, 85:15), which were separated by chromatography (SiO_2, EtOAc) to give the phosphine oxide *anti*–**8b** (2.3 g, 71%) as white needles, m.p. 173-175 °C (lit.,[30] m.p. 169-171 °C), R_f 0.53 (EtOAc); Found: C, 75.1; H, 6.0; P. 9.2%. $C_{21}H_{21}O_2P$ requires C, 75.0; H, 6.3; P, 9.2%.

1,3-Diphenyl-2-(diphenylphosphinoyl)propan-1-one 10a.—To a stirred solution of phenethyldiphenylphosphine oxide **7a** (2.68 g, 8.7 mmol) in dry THF (40 cm^3) was added n-butyllithium (5.4 cm^3 of a 1.6 M solution in hexanes, 8.7 mmol) at 0 °C. After 30 min. the red solution was cooled to –78 °C and methyl benzoate (1.07 cm^3, 8.7 mmol) in dry THF (15 cm^3) was added dropwise. The mixture was allowed to warm to room temperature and stirred for 1 h. Water (20 cm^3) was added and the THF evaporated *in vacuo*. the residue was extracted with dichloromethane (3 × 100 cm^3). The organic extracts were dried ($MgSO_4$) and evaporated *in vacuo*. The product was recrystallised from EtOH/hexane (1:1, v/v), to give 1,3-diphenyl-2-(diphenylphosphinoyl)propan-1-one **10a** (2.2 g, 62%) as white needles, m.p. 201-202 °C (lit.,[31] 202–204 °C), R_f 0.53 (EtOAc); Found: C, 79.0; H, 5.6; P, 7.4. $C_{27}H_{23}O_2P$ requires C, 79.0; H, 5.6; P, 7.5%; δ^1H (300 MHz, $CDCl_3$) 3.24 (1 H, m, CH_aH_bPh), 3.53 (1 H, ddd, *J* 4.7, 11.5 and 13.8 Hz, CH_aH_bPh), 4.82 (1 H, ddd, *J* 2.6, 11.5 and 15.7 Hz, C*H*P), 7.06–7.95 (20 H, m, 4 × Ph).

1-Phenyl-2-(diphenylphosphinoyl)propan-1-one 10b.—To a solution of 1-phenyl-2-(diphenylphosphinoyl)propan-1-ol ***anti*-8b** (1.02 g, 3.03 mmol) in DMF (65 cm^3) was added pyridinium dichromate (5.71 g, 15.15 mmol). The reaction mixture was stirred overnight at room temperature. Water (50 cm^3) was added and the slurry extracted with dichloromethane (3 × 100 cm^3). The organic extracts were washed with water (2 × 100 cm^3), dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by recrystallisation from EtOAc, giving the ketone **10b** (950 mg, 94 %) as white solid, m.p. 155–156 °C (lit.,[31] 152–154 °C), R_f 0.30 (EtOAc); Found: C, 75.4; H, 5.7; P, 9.3. $C_{21}H_{19}O_2P$ requires C, 75.4; H, 5.7; P, 9.3%; δ^1H (200 MHz, $CDCl_3$) 1.56 (3 H, dd, *J* 7.0 and 16.0 Hz, CH_3), 4.37 (1 H, dq, *J* 7.0 and 15.0 Hz, CHP), 7.26–7.93 (15 H, m, 3 × Ph).

(*1RS,2RS*)-1,3-Diphenyl-2-(diphenylphosphinoyl)propan-1-ol ***syn*-8a**.—To a stirred solution of 1,3-diphenyl-2-(diphenylphosphinoyl)propan-1-one **10a** (1.62 g, 3.95 mmol) in ethanol (30 cm^3) was added a solution of sodium borohydride (0.60 g, 15.8 mmol) in ethanol (30 cm^3) at 0 °C. The mixture was allowed to warm to room temperature. After 1 h water (20 cm^3) was added and the mixture extracted with dichloromethane (3 × 50 cm^3). The extracts were dried ($MgSO_4$) and evaporated *in vacuo*. The crude mixture was recrystallised from EtOAc to give the phosphinoyl alcohol ***syn*-8a** (1.17 g, 72%) as white crystals, m.p. 164–168 °C, R_f 0.55 (EtOAc); Found: C, 78.9; H, 6.4; P, 7.4. $C_{27}H_{25}O_2P$ requires C, 78.6; H, 6.1; P, 7.5%; $\nu_{max.}$ (KBr)cm^{-1} 3320 (OH), 1440 (P–Ph), 1170 (P=O); δ^1H (300 MHz, $CDCl_3$) 2.72–2.84 (1 H, m, PhCH_aH_b), 2.95–3.13 (1

H, m, $PhCH_aH_b$), 3.16–3.20 (1 H, m, PCH), 4.96 (1 H, ddd, *J* 3.5, 8.5 and 24.3 Hz, PhC*H*OH), 5.70 (1 H, d, *J* 9.4 Hz, OH), 6.84–7.81 (20 H, m, 4 × Ph); $\delta^{13}C$ (75 MHz, $CDCl_3$) 32.8, 45.9 (d, J_{P-C} 66.2 Hz), 73.2, 125.9, 126.4, 126.8, 127.6, 128.0, 128.5, 128.6, 128.7, 130.0, 130.1, 130.6, 130.7, 130.9, 130.9, 131.4, 131.6, 131.7, 131.7, 132.7, 132.9, 139.1, 139.2, 142.2, 142.3; *m/z* (FAB), 847 (25%, 2 M + Na), 825 (20, 2 M + H), 435 (20, M + Na), 413 (79, M + H), 395 (36, M – OH), 201 (100, Ph_2PO).

(*1RS,2RS*)-1-Phenyl-2-(diphenylphosphinoyl)propan-1-ol *syn*-**8b**.—In a similar way as above, 1-phenyl-2-(diphenylphosphinoyl)propan-1-one **10b** (950 mg, 2.84 mmol) and sodium borohydride (566 mg, 14.97 mmol) gave the phosphinoyl alcohol *syn*-**8b** (450 mg, 47%) as cubes, m.p. 148–149 °C (lit.,[1] 145–146 °C), R_f 0.3 (EtOAc); Found: C, 74.9; H, 6.4; P, 9.0. $C_{21}H_{21}O_2P$ requires C, 75.0; H, 6.3; P, 9.2%; δ^1H (200 MHz, $CDCl_3$) 0.75 (3 H, dd, *J* 7.3 and 17.4 Hz, CH_3CH), 2.95 (1 H, m, CHP), 4.79 (1 H, m, C*H*Ph), 5.72 (1 H, s, OH), 7.18-7.84 (15 H, m, 3 × Ph).

(*1RS,2SR*)-1-Phenyl-2-(diphenylphosphinyl)propan-1-ol *anti*-**11b**.—Cerium(III) chloride heptahydrate (750 mg, 2 mmol) was heated at 150 °C (oil-bath temp.) on a high vacuum line for 2 h with stirring and allowed to cool to room temperature. Tetrahydrofuran (5 cm^3) was added and the slurry was stirred for 30 min. at room temperature. Lithium aluminium hydride (6 cm^3 of a 1 M solution in THF, 6 mmol) was added to the slurry at 0 °C and the mixture stirred for 1 h. *Anti*-1-phenyl-2-diphenylphosphinoyl alcohol **8b** (288 mg, 0.9 mmol) in THF (5 cm^3) was added to the mixture, which was stirred at room temperature for 2 h. Water (50 cm^3) was then added very carefully, followed by saturated aqueous ammonium chloride (25 cm^3) and the mixture extracted with ether (3 × 50 cm^3). The organic extracts were dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by chromatography (SiO_2, EtOAc/hexane, 1:1, v/v) to give the phosphinyl alcohol *anti*-**11b** (240 mg, 88%) as a colourless oil, R_f 0.74 (EtOAc); $\nu_{max.}$ (neat)cm^{-1} 3440 (OH), 1435 (P–Ph); δ^1H (200 MHz, $CDCl_3$) 0.91 (3 H, dd, *J* 13.6 and 7.0 Hz, CH_3CH), 2.73 (1 H, m, CHP), 4.82 (1 H, dd, *J* 4.7 and 6.9 Hz, C*H*OH), 7.26-7.78 (15 H, m, 3 × Ph); $\delta^{13}C$ (75 MHz, $CDCl_3$) 9.6 (d, J_{P-C} 16.8 Hz), 39.6 (d, J_{P-C} 11.6 Hz), 73.0 (d, J_{P-C}14.2 Hz), 125.8, 127.1, 128.4, 128.4, 128.5, 128.7, 128.8, 129.1, 129.2, 133.6, 133.8, 133.9, 134.1, 136.1, 136.3, 136.8, 143.1, 143.2; *m/z* (EI), 320 (24%, M^+), 262 (65), 230 (60), 202 (40), 136 (100), 107 (73), 77 (92). The phosphine was used without further purification.

(*1RS,2RS*)-1,3-Diphenyl-2-(diphenylphosphinyl)propan-1-ol *syn*-**11a**.—In the same way as above, cerium(III) chloride heptahydrate (750 mg, 2 mmol), lithium aluminium hydride (9 cm^3 of a 1 M solution in THF, 9 mmol) and 1,3-diphenyl-2-(diphenylphosphinoyl)propan-1-ol *syn*-**8a** (330 mg, 0.80 mmol) gave the phosphine *syn*-**11a** (239 mg, 75 %) as a colourless oil; δ^1H (300 MHz, $CDCl_3$) 2.82 (2 H, m, $PhCH_2$), 2.96 (1 H, m, $PhCH_2CH$), 4.82 (1 H, dd, *J* 8.6 and 1.2 Hz, PhC*H*OH), 6.98-7.47 (20 H, m, 4 × Ph). The phosphine, which was prone to oxidation, was used crude in the next reaction.

(*1RS,2RS*)-1-Phenyl-2-(diphenylphosphinyl)propan-1-ol *syn*-**11b**.—In the same way as above, cerium (III) chloride heptahydrate (750 mg, 2 mmol), lithium aluminium hydride (6 cm^3, 6 mmol) and *syn*-1-phenyl-2-(diphenylphosphinoyl)propan-1-ol *syn*-**8b** (333 mg, 0.99 mmol) gave the phosphine *syn*-**11b** (202 mg, 64%) as a colourless oil, R_f 0.43 (CH_2Cl_2); $\nu_{max.}$ (neat)cm^{-1} 3420 (OH), 1440 (P–Ph); δ^1H (200 MHz, $CDCl_3$) 0.71 (3 H, dd, *J* 7.1 and 10.0 Hz, CH_3CH), 2.63 (1 H, bs, OH), 2.83 (1 H, quintet, *J* 7.1 Hz, $CHCH_3$), 4.58 (1 H, t, *J* 7.2 Hz, PhC*H*), 7.25-7.78 (15 H, m, 3 × Ph); $\delta^{13}C$ (50 MHz, $CDCl_3$) 12.9, 39.0, 126.7, 127.5, 127.9, 128.0, 128.1, 128.2, 128.8, 132.1, 132.6, 134.1, 134.6. The phosphine, which was prone to oxidation, was used crude in the next reaction.

***E*-1,3-Diphenylprop-1-ene 3a**.—

Method A. To a solution of 1,3-diphenyl-2-(diphenylphosphinoyl)propan-1-ol *syn*-**8a** (378 mg, 0.78 mmol) in DMF (25 cm^3) was added sodium hydride (80 mg of 60 % dispersion in oil; 2 mmol). After 1 h stirring at 50 °C, water (20 cm^3) was added and the slurry extracted with ether (3 × 50 cm^3). The organic layer was washed

with water (2 × 50 cm^3), dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by chromatography (SiO_2, hexane) to give the alkene ***E*-3a** (0.12 g, 79%) as a colourless oil. The ratio of ***E*-3a**: ***Z*-3a** was 98:2 as determined from the ^1H NMR spectrum.

Method B. To a solution of *anti*-1,3-diphenyl-2-(diphenylphosphinoyl)propan-1-ol *anti*-**8a** (318 mg, 0.77 mmol) in dry DMF (15 cm^3) was added sodium hydride (55 mg of 60 % dispersion in oil, 2 mmol). After 1 h stirring at 50 °C water (20 cm^3) was added and the slurry extracted with ether (3 × 50 cm^3). The organic layer was washed with water (2 × 50 cm^3), dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by chromatography (SiO_2, hexane) to give the alkene ***E*-3a** as a colourless oil (81 mg, 54%). The ratio of ***E*-3a**: *Z*-**3a** was 98:2 as determined from the ^1H NMR spectrum.

Method C. To a stirred solution of phosphine *anti*-**11a** (170 mg, 0.43 mmol) in dry dichloromethane (5 cm^3) was added triethylamine (0.5 cm^3, 3.57 mmol) at 0 °C. Phosphorus trichloride (0.1 cm^3, 1.2 mmol) was added dropwise at this temperature. After 3 h water (20 cm^3) was added and the mixture extracted with dichloromethane (3 × 50 cm^3). The organic extracts were dried ($MgSO_4$), filtered and evaporated *in vacuo*. The residue was purified by chromatography (SiO_2, hexane) to give the alkene ***E*-3a** (45 mg, 56 %) as a colourless oil[32] R_f 0.74 (EtOAc); $\nu_{max.}$ (neat)cm^{-1} 1600 (Ph), 1495 (Ph), 970 (*trans* PhC=CR); δ^1H (300 MHz, $CDCl_3$) 3.64 (2 H, d, *J* 6.2 Hz, PhCH_2), 6.37 (1 H, dt, *J* 16.0 and 6.6 Hz, CH_2CH=CH), 6.47 (1 H, d, *J* 16.0 Hz, CH=C*H*Ph) 7.25-7.47 (10 H, m, 2 × Ph); $\delta^{13}C$ (75 MHz, $CDCl_3$) 40.0, 126.8, 127.8, 129.2, 129.3, 129.9, 131.7, 137.5, 140.2; *m/z* (EI), 194 (100%, M^+), 179 (36, M – Me), 115 (73), 91 (55, $PhCH_2$), 77 (30, Ph). The ratio of ***E*-3a**:***Z*-3a** was 98:2 as determined from the ^1H NMR spectrum.

Z*-1,3-Diphenylprop-1-ene *Z*-3a**.—Cerium(III) chloride heptahydrate (0.75 g, 2 mmol) was heated at 150 °C (oil–bath temp.) on a high vacuum line for 2 h with stirring. The solid was cooled and dry THF (5 cm^3) was added and stirred for 30 minutes. Lithium aluminium hydride (9 cm^3 of a 1 M solution in THF, 9 mmol) was added at 0 °C and the mixture stirred for 1 h at room temperature. *Syn*-1,3-diphenyl-2-(diphenylphosphinoyl)-propan-1-ol **8a** (412 mg, 1 mmol) in dry THF (4 cm^3) was added and stirred at room temperature for 2 h, cooled to 0 °C and water (50 cm^3) was added very carefully. When the gas was no longer evolved ammonium chloride solution (1 M, 15 cm^3) was added and the mixture extracted with ether (3 × 25 cm^3). The organic extracts were dried ($MgSO_4$), and evaporated *in vacuo* to give a colourless oil. Purification by flash chromatography, eluting with EtOAc, gave 1,3-diphenyl-2-(diphenylphosphinyl)propan-1-ol *syn*-**11a** (239 mg, 75%). The crude phosphine *syn*-**11a** (239 mg, 0.6 mmol) in dry dichloromethane (5 cm^3) was added triethylamine (0.7 cm^3, 5.0 mmol) followed by phosphorus trichloride (0.1 cm^3, 1.2 mmol) at 0 °C. Water (20 cm^3) was added after 3 h stirring and the slurry extracted with dichloromethane (3 × 50 cm^3). The extracts were dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by chromatography (SiO_2, hexane) to give the 1,3-diphenylprop-1-ene *Z*-**3a** (107 mg, 92%) as a colourless oil,[32] R_f 0.71 (EtOAc); $\nu_{max.}$ (neat)cm^{-1} 1600 (C=C); δ^1H (300 MHz, $CDCl_3$) 3.67 (2 H, dd, *J* 7.5 and 1.5 Hz, PhCH_2), 5.89 (1 H, dt, *J* 11.5 and 7.5 Hz, $PhCH_2CH$), 6.58 (1 H, td, *J* 1.7 and 11.5 Hz, PhC*H*CH), 7.22–7.37 (10 H, m, 2 × Ph). The ratio of *Z*-**3a**:E*-3a** was 90:10 as determined by ^1H NMR spectroscopy.

Z*-1-Phenylprop-1-ene *Z*-3b**.—To a stirred solution of 1-phenyl-2-(diphenylphosphinoyl)propan-1-ol *syn*-**11b** (188 mg, 0.59 mmol) in dry dichloromethane (5 cm^3) was added triethylamine (0.7 cm^3, 5 mmol) followed by phosphorus trichloride (0.1 cm^3, 1.2 mmol) at 0 °C. After 3 h water (20 cm^3) was added and the mixture extracted with dichloromethane (3 × 50 cm^3). The organic extracts were dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, hexane) to give the 1-phenylprop-1-ene *Z*-**3b**[1] (30 mg, 43%) as an oil, R_f 0.67 (EtOAc); δ^1H (200 MHz, $CDCl_3$) 1.89 (3 H, dd, *J* 7.1 and 1.8 Hz, CH_3CH), 5.79 (1 H, qd, *J* 7.1 and 11.6 Hz, CH_3CH), 6.44 (1 H, dq, *J* 11.6 and 1.8 Hz, PhC*H*), 7.18–7.38 (5 H, m, Ph). The ratio of *Z*-**3b**:E*-3b** was 95:5 as determined by ^1H NMR spectroscopy.

***E*-1-Phenylprop-1-ene *E*-3b**.—In the same way as above, 1-phenyl-2-(diphenylphosphinoyl)propan-1-ol *anti*-**11b** (330 mg, 0.98 mmol) in dry dichloromethane (5 cm^3) and triethylamine (1 cm^3, 7.17 mmol) and

phosphorus trichloride (0.15 cm^3, 1.71 mmol) gave 1-phenylprop-1-ene *E*-**3b**[1] (32%); δ^1H (200 MHz, $CDCl_3$) 1.88 (3 H, dd, *J* 6.2 and 0.9 Hz, CH_3CH), 6.23 (1 H, qd, *J* 6.2 and 15.8 Hz, $CHCH_3$), 6.40 (1 H, dq, *J* 15.8 and 0.9 Hz, PhC*H*), 7.15–7.36 (5 H, m, Ph). The ratio of *E*-**3b**:*Z*-**3b** was 98:2 as determined by ^1H NMR spectroscopy.

3-Isopropoxy-4-methoxybenzaldehyde 17.—To a stirred solution of isovanillin (14.9 g, 97.8 mmol) in *N,N*-dimethylformamide (100 cm^3) was added potassium carbonate (27.03 g, 195.6 mmol) followed by 2-iodopropane (24.4 cm^3, 244.4 mmol) at room temperature under nitrogen. After 24 h water (100 cm^3) was added and the slurry extracted with chloroform (3 × 100 cm^3). The organic extracts were washed with water (4 × 100 cm^3), dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by column chromatography (SiO_2, hexane/EtOAc, 3:2, v/v) to give 3-isopropoxy-4-methoxybenzaldehyde[33] **17** (15.84 g, 82%) as an oil δ^1H (200 MHz, $CDCl_3$) 1.39 (6 H, d, *J* 6.0 Hz, $CH(Me)_2$), 3.93 (3 H, s, OMe), 4.64 (1 H, sept, *J* 6.0 Hz, C*H*(Me)$_2$), 6.97 (1 H, d, *J* 8.0 Hz, H-5), 7.41 (1 H, d, *J* 1.8 Hz, H-2), 7.44 (1 H, dd, *J* 1.8 and 8.0 Hz, H-6), 9.83 (1 H, s, ArC*H*O).

1-(3'-Isopropoxy-4'-methoxyphenyl)-2-[(3",4",5"-trimethoxyphenyl)diphenylphosphinoyl]-ethan-1-ol *anti*-**18** and *syn*-**18**.—To a stirred mixture of (3,4,5-trimethoxybenzyl)diphenylphosphine oxide **16** (4.13 g, 12.36 mmol) in THF (50 cm^3) was added n-butyllithium (5.2 cm^3 of a 2.5 M solution in hexane, 13.0 mmol) at 0 °C. After 30 min. the mixture was cooled to –78 °C and 3-isopropoxy-4-methoxybenzaldehyde **17** (2.39 g, 12.36 mmol) was added at this temperature. The reaction mixture was stirred for 2 h at –78 °C and slowly warmed to –10 °C and then quenched with water (100 cm^3) at –10 °C. The slurry was extracted with chloroform (3 × 50 cm^3). The organic extracts were dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was purified by column chromatography (SiO_2, EtOAc) to give the *anti* and *syn* isomers of phosphinoyl alcohol *anti*-**18** and *syn*-**18** (*anti/syn*, 68:32) which were separated by chromatography (SiO_2, EtOAc) and recrystallised from ethyl acetate to give *anti* (*1RS,2SR*) phosphinoyl alcohol *anti*-**18** (2.82 g, 40%) as an amorphous solid, m.p. 164–166 °C, R_f 0.58 (EtOAc) and *anti* (*1RS,2RS*) phosphinoyl alcohol *syn*-**18** (1.70 g, 24%) as an amorphous solid, m.p. 159–160 °C, R_f 0.46 (EtOAc).

For (*1RS,2SR*) *anti*-18: Found: C, 68.5; H, 6.6; P, 5.4. $C_{33}H_{37}O_7P$ requires C, 68.7; H, 6.5; P, 5.4%; $\nu_{max.}$ (KBr)cm^{-1} 3350 (OH), 1440 (P–Ph); δ^1H (200 MHz, $CDCl_3$) 1.06 [3 H, d, *J* 6.1 Hz, $CH(Me)_2$], 1.20 [3 H, d, *J* 6.1 Hz, $CH(Me)_2$], 3.48 (1 H, dd, *J* 8.2 and 2.1 Hz, C*H*POPh$_2$), 3.58 (6 H, s, 3",5"-*Me*OC$_6$H$_2$), 3.67 (3 H, s, *Me*OC$_6$H$_3$), 3.71 (3 H, s, *Me*OC$_6$H$_2$), 4.21 [1 H, sept, *J* 6.1 Hz, C*H*(Me)$_2$], 4.94 (1 H, bs, OH), 5.40 (1 H, d, *J* 6.9 Hz, C*H*OH), 6.39 (2 H, s, C$_6$H$_2$), 6.47–6.64 (3 H, m, C$_6$H$_3$), 7.15–7.96 (10 H, m, 2 × Ph); $\delta^{13}C$ (75 MHz, $CDCl_3$) 21.5, 22.1, 53.4 (d, J_{P-C} 50.4 Hz), 55.9, 60.5, 70.9, 72.3, 73.4, 108.6, 111.1, 113.8, 118.3, 127.6–137.0 (m), 146.6, 149.2, 152.2; *m/z* (FAB), 577 (8%, M + H), 559 (14, M – OH), 517 [94, M – CH(Me)$_2$], 382 [100, HOCH$_2$C$_6$H$_3$(OMe)OCH(Me)$_2$].

For (*1RS,2RS*) *syn*-18: $\nu_{max.}$ (KBr)cm^{-1} 3300 (OH), 2840 (OMe), 1440 (P–Ph), 1170 (P=O); δ^1H (200 MHz, $CDCl_3$) 1.17 [3 H, d, *J* 6.1 Hz, $CH(Me)_2$], 1.22 [3 H, d, *J* 6.1 Hz, $CH(Me)_2$], 3.47 (6 H, s, 3",5"-*Me*OC$_6$H$_2$), 3.67 (3 H, s, *Me*OC$_6$H$_2$), 3.72 (3 H, s, *Me*OC$_6$H$_3$), 3.80 (1 H, d, *J* 11.3 Hz, C*H*POPh$_2$), 4.30 [1 H, sept, *J* 6.1 Hz, C*H*(Me)$_2$], 5.38 (1 H, dd, *J* 7.3 and 1.9 Hz, C*H*OH), 5.75 (1 H, s, OH), 5.95 (2 H, s, C$_6$H$_2$), 6.67 (3 H, m, C$_6$H$_3$), 7.30–7.76 (10 H, m, 2 × Ph); $\delta^{13}C$ (75 MHz, $CDCl_3$) 21.8, 21.9, 55.5 (d, J_{P-C} 32.4 Hz), 55.6, 60.7, 71.2, 75.7, 102.2, 107.5, 111.2, 114.7, 119.5, 127.8–136.8 (m), 146.4, 149.5, 152.4; *m/z* (FAB), 599 (44%, M + Na), 577 (60, M + H), 559 (22), 517 [100, M – OCH(Me)$_2$], 382 [96, (OMe)$_3$C$_6$H$_2$CH$_2$POPh$_2$], 367 (58), 201 (78, Ph$_2$PO); Found: M + H, 577.2357. $C_{33}H_{38}O_7P$ requires M + H, 577.2355.

***E*-1-(3',4',5'-Trimethoxyphenyl)-2-(3"-isopropoxy-4"-methoxyphenyl)ethene *E*-15b.—From 16**: To a stirred solution of (3,4,5-trimethoxybenzyl)diphenylphosphine oxide **16** (197 mg, 0.59 mmol) in dry THF (10 cm^3) was added n-butyllithium (0.25 cm^3 of a 2.5 M solution in hexane, 0.62 mmol) at 0 °C. After 30 min. 3-isopropoxy-4-methoxybenzaldehyde **17** (114 mg, 0.59 mmol) was added and stirred overnight at room

temperature. Water (50 cm^3) was added and the mixture extracted with chloroform (3 × 25 cm^3). The organic extracts were dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was purified by column chromatography (SiO_2, CH_2Cl_2) to give alkene *E*-**15b** (154 mg, 73%).

From *anti*-**18**.—To a stirred solution of phosphinoyl alcohol *anti*-**18** (163 mg, 0.283 mmol) in dimethylformamide (10 cm^3) was added sodium hydride (23 mg of 60% dispersion in oil, 0.566 mmol) at room temperature. The reaction mixture was heated under reflux for 1 h and then allowed to cool to room temperature. Water (50 cm^3) was added and the mixture extracted with diethyl ether (3 × 50 cm^3). The organic extracts were washed with water (3 × 50 cm^3), dried ($MgSO_4$) and evaporated *in vacuo*. The residue was recrystallised from ethanol (3 cm^3) to give *trans* alkene *E*-**15b** (61 mg, 60%) as rods, m.p. 94–96 °C, R_f 0.69 (CH_2Cl_2); Found: C, 70.1; H, 7.6. $C_{21}H_{26}O_5$ requires C, 70.4; H, 7.3%; $\nu_{max.}$ (KBr)cm^{-1} 2840 (OMe), 980 (*trans* ArC=CAr); δ^1H (200 MHz, $CDCl_3$) 1.40 [6 H, d, *J* 6.1 Hz, CH(*Me*)$_2$], 3.86 (3 H, s, *Me*OAr), 3.87 (3 H, s, *Me*OAr), 3.91 (6 H, s, 3',5'-*Me*OC_6H_2), 4.54 [1 H, sept, *J* 6.1 Hz, *CH*(Me)$_2$], 6.71 (2 H, s, H-2',6'), 6.86 (1 H, d, *J* 16.2 Hz, CH=CH), 6.94 (1 H, d, *J* 16.2 Hz, CH=CH), 6.85–7.09 (3 H, m, H-2",5",6"); $\delta^{13}C$ (75 MHz, $CDCl_3$) 22.1, 55.9, 56.0, 60.9, 71.5, 103.2, 111.9, 113.6, 120.0, 126.5, 127.9, 130.1, 133.3, 137.5, 147.3, 150.3, 153.3; *m/z* (FAB), 358 (100%, M^+).

***E*–1-(3',4',5'-Trimethoxyphenyl)-2-(3"-hydroxy-4"-methoxyphenyl)ethene** (*trans*-combretastatin A-4) *E*-**15a**.—To a stirred solution of alkene *E*-**15b** (91 mg, 0.254 mmol) in dichloromethane (5 cm^3) was added boron trichloride (1.5 cm^3 of 1 M solution in hexane, 1.5 mmol) at –10 °C. The reaction mixture was maintained for 10 min. at this temperature. Water (50 cm^3) was added and the mixture was extracted with dichloromethane (3 × 25 cm^3). The organic extracts were washed with water (3 × 50 cm^3) and then dried ($MgSO_4$). The solvent was evaporated *in vacuo* and the residue purified by column chromatography (hexane/EtOAc, 1;1, v/v) to give *trans*-combretastatin A-4 *E*-**15a** (74 mg, 92%) as a crystalline solid m.p. 103–104 °C (lit.,[34] m.p. 103–104 °C), which had ^1H NMR data similar to that published.

Ethyldiphenylphosphine–borane 19.—To a stirred mixture of ethyldiphenylphosphine oxide (6.73 g, 29.26 mmol) and triethoxysilane (16.17 cm^3, 87.78 mmol) in dry THF (40 cm^3) was added titanium(IV) isopropoxide (1.0 cm^3, 3.4 mmol) at room temperature under nitrogen. The mixture was heated under reflux for 1 h and then cooled to room temperature. Borane-tetrahydrofuran complex (58.5 cm^3 of 1 M solution in THF, 58.5 mmol) was added and stirred for 48 h at room temperature. The solvent was removed *in vacuo* and the residue purified by column chromatography (SiO_2, hexane/EtOAc, 4:1, v/v) to give ethyldiphenylphosphine-borane[14] **19** (6.71 g, 100%) as a colourless oil, R_f 0.56 (hexane/EtOAc, 4:1, v/v); Found: C, 73.4; H, 8.2; P, 13.2; B, 4.7. $C_{14}H_{18}BP$ requires C, 73.7; H, 8.0; P, 13.6; B, 4.7%; $\nu_{max.}$ (neat)cm^{-1} 2380 (B–H), 1440 (P–Ph); δ^1H (200 MHz, $CDCl_3$) 1.14 (3 H, 3 H, dt, *J* 2.4 and 7.7 Hz, CH_2*Me*), 2.28 (2 H, dq, *J* 3.3 and 7.6 Hz, C*H*$_2$Me), 7.38–7.52 (6 H, m, Ph), 7.62–7.72 (4 H, m, Ph); $\delta^{13}C$ (75 MHz, $CDCl_3$) 7.1, 18.7 (d, $J_{P\text{-}C}$ 37.9 Hz), 128.8 (d, $J_{P\text{-}C}$ 7.5 Hz), 129.6, 131.1, 132.1 (d, $J_{P\text{-}C}$ 9.7 Hz); *m/z* (FAB), 227 (72%, M – H), 185 (25, Ph_2P), 137 (27),109 (100).

***(1RS,2SR)*-1-(4-Methoxyphenyl)-2-(diphenylphosphine-borane)-propan-1-ol** *anti*-**20**.—To a stirred solution of ethyldiphenylphosphine-borane **19** (6.71 g, 29.43 mmol) in dry THF (90 cm^3) was added n-butyllithium (13 cm^3 of 2.5 M solution in hexane, 32.37 mmol) at 0 °C. After 30 min. the mixture was cooled to –78 °C and *p*-anisaldehyde (4.0 g, 29.43 mmol) added at this temperature. The reaction mixture was stirred for 20 min. at this temperature and then at room temperature for 2 h. Water (100 ml) was added and the mixture was extracted with chloroform (3 × 100 cm^3). The organic extracts were dried ($MgSO_4$) and evaporated *in vacuo*. Separation of the diastereoisomers by chromatography (SiO_2, $CHCl_3$) gave diphenylphosphine-borane *anti*-**20** (5.61 g, 48%) as an amorphous solid, m.p. 111–112 °C, R_f 0.36 (hexane/EtOAc, 4:1, v/v); Found: C, 72.8; H, 6.8; P, 8.5. $C_{22}H_{26}BO_2P$ requires C, 72.5; H, 7.2; P, 8.5%; $\nu_{max.}$ (KBr)cm^{-1} 3600 (OH), 2840 (OMe), 2380 (B–H), 1440 (P–Ph); δ^1H (200 MHz, $CDCl_3$) 1.08 (3 H, dd, *J* 8.7 and 16 Hz, *Me*CHP), 2.87 (1 H, dq, *J* 7.4 and 0.3 Hz, Me*CH*P), 3.11 (1 H, d, *J* 1.9 Hz, OH), 3.78 (3 H, s, MeO), 5.04 (1 H, bd, *J* 7.4 Hz, C*H*OH),

6.86 (2 H, d, *J* 8.7, H-3',5'), 7.21 (2 H, d, *J* 8.7 Hz, H-2',6'), 7.28–8.00 (10 H, m, 2 × Ph); δ^{13}C (75 MHz, $CDCl_3$) 6.7, 37.6 (d, $J_{P\text{-}C}$ 32.5 Hz), 55.3, 70.1 (d, $J_{P\text{-}C}$ 4.5 Hz), 113.2, 126.7, 128.9 (d, $J_{P\text{-}C}$ 24.0 Hz), 129.1 (d, $J_{P\text{-}C}$ 22.5 Hz), 131.5 (d, $J_{P\text{-}C}$ 17.2 Hz), 132.5 (d, $J_{P\text{-}C}$ 4.5 Hz), 134.4 (d, $J_{P\text{-}C}$ 12.7 Hz), 158.8; *m/z* FAB, 365 (18%, M + H), 333 (M – OMe), 185 (100, Ph_2P).

1-(4'-Methoxyphenyl)-2-(diphenylphosphine-borane)propan-1-one 22.—To a stirred solution of phosphine-borane *syn/anti*-**20** (75 mg, 0.206 mmol) in dichloromethane (5 cm^3) was added pyridinium chlorochromate (220 mg, 1.03 mmol) at room temperature. After 12 h water (50 ml) was added and the mixture extracted with dichloromethane (3 × 25 cm^3). The extracts were washed with water (2 × 50 cm^3), dried ($MgSO_4$) and evaporated *in vacuo*. The residue was recrystallised from ethyl acetate to give ketophosphine-borane **22** (52 mg, 70%) as a crystalline solid, m.p. 115–116 °C, R_f 0.8 (CH_2Cl_2); Found: C, 72.6; H, 6.6; P, 8.5. $C_{22}H_{24}BO_2P$ requires C, 73.0; H, 6.7; P, 8.6%; $\nu_{max.}$ (KBr)cm^{-1} 2840 (OMe), 2380 (B–H), 1680 (C=O); δ^1H (200 MHz, $CDCl_3$) 1.51 (3 H, dd, *J* 8.5 and 15.7 Hz, CH*Me*), 3.83 (3 H, s, MeO), 4.52 (1 H, dq, *J* 8.7 and 16 Hz, C*H*Me), 6.80 (2 H, d, *J* 8.9 Hz, H-3',5'), 7.73 (2 H, d, *J* 8.8 Hz, H-2',6'), 7.27–8.01 (10 H, m, 2 × Ph); δ^{13}C (75 MHz, $CDCl_3$) 14.2, 39.4 (d, $J_{P\text{-}C}$ 27.7 Hz), 55.5, 113.7, 128.4, 128.5, 128.6, 130.9, 131.2, 131.5, 132.9, 133.0, 134.0, 134.2, 163.7, 196.8; *m/z* (FAB), 361 (100%, M – H), 185 (50, Ph_2P), 154 (72), 107 (20), 89 (38).

1-(4'-Methoxyphenyl)-2-(diphenylphosphinoyl)propan-1-one 23.—To a stirred solution of phosphine-borane alcohol *anti/syn*-**20** (292 mg, 0.802 mmol) in DMF (10 cm^3) was added pyridinium dichromate (1.395 g, 4.01 mmol) at room temperature. After stirring overnight at this temperature water (50 cm^3) was added and the mixture extracted with ethyl acetate. The organic extracts were washed with water (2 × 100 cm^3) and dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was purified by column chromatography (SiO_2, hexane/EtOAc, 1:1, v/v) to give **22** and **23** which were recrystallised from (EtOAc/hexane, 9:1, v/v) and ethyl acetate respectively gave [1-(4'-methoxyphenyl)-2-(diphenylphosphine-borane)propan-1-one **22** (483 mg, 44%) as a crystalline solid and 1-(4'-methoxy phenyl)-2-(diphenylphosphinoyl)propan-1-one **23** (258 mg, 23%) as needles, m.p. 160–162 °C (lit.,[13] m.p. 157–159 °C), R_f 0.61 (EtOAc); Found: C, 72.8; H, 5.5; P, 8.3. $C_{22}H_{21}O_3P$ requires C, 72.5; H, 5.8; P, 8.5%; $\nu_{max.}$ (KBr)cm^{-1} 2850 (OMe), 1660 (C=O), 1440 (P–Ph), 1180 (P=O); δ^1H (300 MHz, $CDCl_3$) 1.53 (3 H, dd, *J* 7.1 and 16.1 Hz, CH*Me*), 3.80 (3 H, s, MeO), 4.52 (1 H, dq, *J* 7.1 and 15.5 Hz, C*H*Me), 6.80 (2 H, d, *J* 8.8 Hz, H-3',5'), 7.84 (2 H, d, *J* 8.8 Hz, H-2',6'), 7.33–7.92 (10 H, m, 2 × Ph); δ^{13}C (75 MHz, $CDCl_3$) 13.1, 45.5 (d, $J_{P\text{-}C}$ 60.0 Hz), 55.5, 113.6, 128.4, 128.4, 128.5, 129.9, 130.0, 130.5, 131.2, 131.4, 131.6, 131.9, 132.0, 132.0, 163.6, 196.3; *m/z* (FAB), 365 (100%, M + H), 201 (80, Ph_2PO).

(*1RS,2RS*)-1-(4'-Methoxyphenyl)-2-(diphenylphosphine-borane)-propan-1-ol *syn*-**20**.
Method A: To a stirred solution of ketone **22** (483 mg, 1.33 mmol) in methanol (80 cm^3) was added sodium borohydride (330 mg, 8.68 mmol) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 2 h. Water (100 cm^3) was added and the mixture was extracted with dichloromethane (3 × 50 ml). The extracts were washed with water (2 × 50 cm^3) and dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue purified by column chromatography (SiO_2, CH_2Cl_2) to give the phosphine-borane *syn*-**20** (410 mg, 85%) as an amorphous solid.
Method B: To a stirred solution of ketone **22** (14 mg, 0.039 mmol) in dry THF (2 cm^3) was added lithium aluminium hydride (0.05 cm^3, 1M solution in THF, 0.05 mmol) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 1 h. A similar work-up gave the alcohol *syn*-**20** (12 mg, 85%).
Method C: To a stirred solution of ketone **22** (18 mg, 0.05 mmol) in dry dichloromethane (2 cm^3) was added diisobutylaluminium hydride (0.07 cm^3, 1 M solution in CH_2Cl_2, 0.07 mmol) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 1 h. A similar work-up gave the alcohol *syn*-**20** (15 mg, 82%).
Method D: To a stirred solution of ketone **22** (20 mg, 0.05 mg, 0.55 mmol) in dry THF (5 cm^3) was added L-(tri-*sec*-butylboron) hydride (0.07 cm^3, 1 M solution in THF, 0.07 mmol) at –78 °C. The mixture was stirred

for 30 min. at –78 °C and for 30 min. at room temperature. A similar work-up gave the alcohol *syn*-**20** (13 mg, 65%).

Method E: To a stirred mixture of sodium borohydride (21 mg, 0.55 mmol) and cerium(III) chloride heptahydrate (20 mg, 0.055 mmol) in methanol (4 cm^3) was added ketone **22** (20 mg, 0.055 mmol) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 16 h. A similar work-up gave the alcohol *syn*-**20** (15 mg, 75%), R_f 0.29 (hexane/EtOAc, 4:1, v/v); Found: C, 72.8; H, 7.4; B, 2.8. $C_{22}H_{26}BO_2P$ requires C, 72.5; H, 7.2; B, 3.0%; $\nu_{max.}$ (KBr)cm^{-1} 3500 (OH), 2830 (OMe), 2380 (B–H), 1440 (P–Ph); δ^1H (300 MHz, $CDCl_3$) 0.71 (3 H, dd, *J* 8.5 and 15.7 Hz, *Me*CHP), 2.41 (1 H, d, *J* 3.9 Hz, OH), 3.06 (1 H, dquin, J_{HP} 9.8 and $J_{HMe} = J_{HH}$ = 7.3 Hz, C*H*Me), 3.80 (3 H, s, MeO), 4.80–4.87 (1 H, m, C*H*OH), 6.86 (2 H, d, *J* 8.7 Hz, H-3',5'), 7.29 (2 H, d, *J* 8.7 Hz, H-2',6'), 7.37–7.96 (10 H, m, 2 × Ph); $\delta^{13}C$ (75 MHz, $CDCl_3$) 13.1, 36.7 (d, $J_{P\text{-}C}$ 32.8 Hz), 55.2, 113.7, 127.9, 128.4 (d, $J_{P\text{-}C}$ 9.7 Hz), 130.7 (d, $J_{P\text{-}C}$ 7.5 Hz), 132.2 (d, $J_{P\text{-}C}$ 9 Hz), 132.8 (d, $J_{P\text{-}C}$ 8.2 Hz), 134.3 (d, $J_{P\text{-}C}$ 9.7 Hz), 159.3; *m/z* (FAB), 363 (32%, M – H), 333 (100, M – OMe), 185 (90, Ph_2P).

(*1RS,2RS*)-1-(4'-Methoxyphenyl)-2-(diphenylphosphinyl)propan-1-ol *threo*-**21**.—A mixture of alcohol *syn*-**20** (270 mg, 0.74 mmol) and 1,4-diazabicyclo[2.2.2]octane (DABCO™)(1.35 g, 12.05 mmol) in anhydrous dichloromethane (5 cm^3) was stirred at room temperature for 3 days. Separation of the mixture by column chromatography (SiO_2, CH_2Cl_2) gave the β–hydroxyphosphine *syn*-**21** (204 mg, 79%) as a colourless oil, R_f 0.61 (CH_2Cl_2); δ^1H (300 MHz, $CDCl_3$) 0.71 (3 H, dd, *J* 10.1 Hz, CH*Me*), 2.1 (1 H, bs, OH), 2.81 (1 H, quint, *J* 6.8 Hz, C*H*Me), 3.79 (3 H, s, MeO), 4.54 (1 H, dd, *J* 8 and 6.8 Hz, C*H*OH), 6.85 (2 H, d, *J* 8.7 Hz, H-3',5'), 7.25 (2 H, d, *J* 8.7 Hz, H-2',6'), 7.27–7.62 (10 H, m, 2 × Ph).

(*1RS,2RS*)-1-(4'-Methoxyphenyl)-2-(diphenylphosphinoyl)propan-1-ol *syn*-**24**.

Method A: To a solution of phosphinyl alcohol *syn*-**21** (57 mg, 0.163 mmol) in methanol/water (10 cm^3, 1:1, v/v) was added hydrogen peroxide 30% (5 cm^3) carefully at room temperature. The homogenous mixture was left overnight at room temperature. Water was added (50 cm^3) and the mixture extracted with chloroform (3 × 25 ml). The extracts were dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by column chromatography (SiO_2, EtOAc) to give phosphinoyl alcohol *syn*-**24** (58 mg, 97%).

Method B: To a stirred solution of ketone **23** (36 mg, 0.11 mmol) in ethanol (5 cm^3) was added sodium borohydride (41 mg, 1.1 mmol) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 1 h. After addition of water (25 cm^3) the slurry was extracted with chloroform (3 × 25 cm^3). The extracts were washed with dilute HCl (10 cm^3) and then with water (2 × 25 cm^3). The extracts were dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by column chromatography (SiO_2, EtOAc) to give phosphinoyl alcohol *syn*-**24** (33 mg, 91%) as a crystalline solid, m.p. 150–151 °C (lit.,[1] m.p. 149–150 °C).

***E/Z*-1-(4'-Methoxyphenyl)prop-1-ene** *E/Z*-**26**.—To a stirred solution of phosphinyl alcohol *syn*-**21** (132 mg, 0.528 mmol) in dry dichloromethane (5 cm^3) was added triethylamine (0.32 ml, 3.17 mmol) followed by phosphorus trichloride (0.09 cm^3, 1.06 mmol) at 0 °C. After 3 h water (50 cm^3) was added and the slurry extracted with dichloromethane (3 × 25 cm^3). The extracts were dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by column chromatography (SiO_2, hexane) to give inseparable mixture of *cis* and *trans* 1-(4-methoxyphenyl)prop-1-ene[1] *E/Z*-**26** (*E/Z*, 2:1)(39 mg, 50%) as a colourless oil. R_f 0.28 (hexane); δ^1H (300 MHz, $CDCl_3$) **for *E*:** 1.86 (3 H, dd, *J* 1.6 and 6.5 Hz, CH*Me*), 3.80 (3 H, s, MeO), 6.09 (1 H, dq, *J* 6.6 and 15.7 Hz, CH=CH), 6.33 (1 H, d, *J* 15.7 Hz, CH=CH), 6.83 (2 H, d, *J* 8.7 Hz, H-3',5'), 7.26 (2 H, d, *J* 8.7 Hz, H-2',6'); **for *Z*:** 1.89 (3 H, dd, *J* 1.8 and 7.2 Hz, CH*Me*), 3.82 (3 H, s, MeO), 5.70 (1 H, dq, *J* 7.2 and 11.6 Hz, CH=CH), 6.37 (1 H, d, *J* 11.6 Hz, CH=CH), 6.88 (2 H, d, *J* 8.7 Hz, H-3',5'), 7.25 (2 H, d, *J* 8.7 Hz, H-2',6').

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