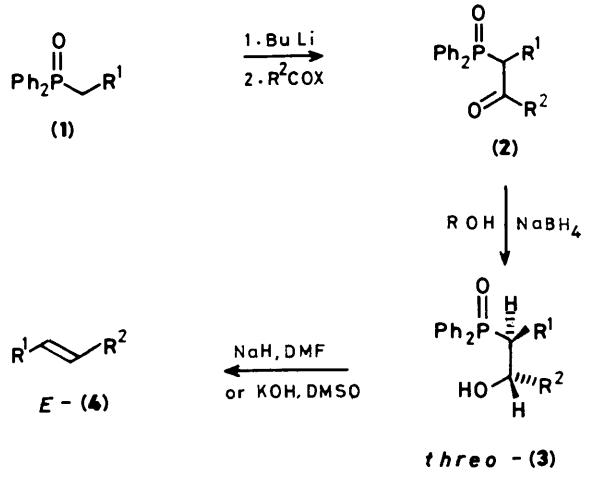
Applications of the Stereochemically-Controlled Horner-Wittig Reaction: Synthesis of Feniculin, (*E*)-Non-6-en-1-ol, a Pheromone of the Mediterranean Fruit Fly, (*E*)- and (*Z*)-Dec-5-en-1-ol, Tri-substituted Alkenes, and (*Z*)-α-Bisabolene

Antony D. Buss, Nicholas Greeves, Ralph Mason, and Stuart Warren *
University Chemical Laboratories, Lensfield Road, Cambridge, CB2 1EW

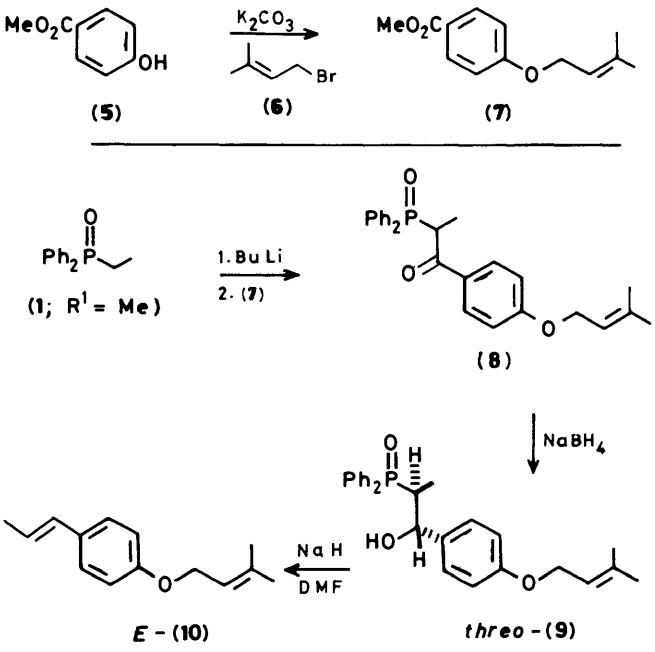
Stereoselective reduction of the appropriate α-diphenylphosphinoyl ketone or addition of the lithium derivative of an alkyl diphenylphosphine oxide to an aldehyde or a ketone gives Horner-Wittig intermediates and hence the title compounds.

The Horner-Wittig reaction[1] between lithium derivatives of alkyl diphenylphosphine oxides (**1**) and aldehydes is *erythro* selective[2,3] and provides a synthesis of *Z*-alkenes, while reduction of the corresponding α-diphenylphosphinoyl ketones (**2**) is *threo* selective[3,4] and gives *E*-alkenes by elimination of $Ph_2PO_2^-$ from the intermediates (**3**) (Scheme 1). Separation of the crystalline *erythro* and *threo* intermediates (**3**) by chromatography or crystallisation is usually easier than separation of the geometrical isomers of the final products. High stereoselectivity in the reduction of ketones (**2**) results if the larger substituent is placed on the ketone [R^2 in (**2**)] rather than next to the Ph_2PO group, in agreement with the predictions of the Felkin model.[3] We report the synthesis of four alkenes by these methods, and their extension to the synthesis of tribustituted alkenes.



Scheme 1.

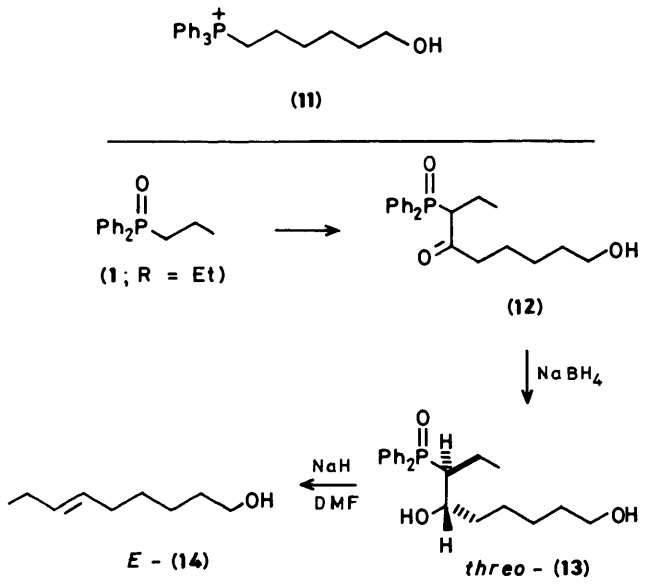
Feniculin (**10**), a constituent of fennel and star anise,[5] has been synthesized by alkylation[5,6] from naturally occurring anethole, which already contains the *E* double bond. To gain the higher stereoselectivity in reduction and stereospecificity of $Ph_2PO_2^-$ elimination,[3] we placed the large aryl group next to the carbonyl group and the small alkyl group next to the phosphine oxide in the ketone (**8**). Reduction of the ketone (**8**) gave an 11:1 selectivity in favour of *threo*-(**9**). Separation by column chromatography gave pure *threo*-(**9**) (74%) and a small amount (7%) of the *erythro* isomer. Elimination of $Ph_2PO_2^-$ gave (*E*)-feniculin (**10**) showing $\nu_{max.}$ 960 cm^{-1} (out-of-plane deformation for *E*-CH=CH) and J_{HH} 15 Hz across the double bond (Scheme 2). The stereoselectivity resembles that found with other alkoxy-aryl ketones.



Scheme 2.

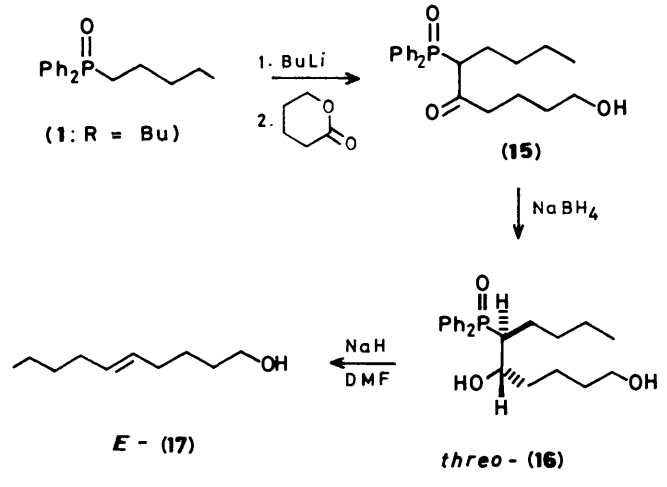
Two of the remaining targets are unsaturated alcohols. (*E*)-Non-6-en-1-ol (**14**) is a pheromone of the Mediterranean Fruit Fly,[7] and has been synthesized from dihydropyran in eight steps (unspecified yield) and from propanal in four steps (40—50%).[8] A Wittig reaction between the phosphonium salt (**11**) and propanal gave[9] 91% of a 75:25 *Z*:*E* mixture which was improved by radical isomerisation, chromatographic separation of the epoxides and stereospecific removal of oxygen to give pure *E*-(**14**). Schlosser's modification[10] of the Wittig reaction with the same phosphonium salt gave 74% of a 99:1 *E*:*Z* mixture. We preferred not to place the longer hydroxypentyl chain next to the Ph_2PO group both for higher stereoselectivity and because the ketone (**12**) could easily be made by acylation[11] of the lithium derivative of (**1**; R^1 = Et) with a lactone. Reduction of the ketone (**12**) gave 85% *threo* alcohol-(**13**) and 15% *erythro*-(**13**), easily separated by flash column chromatography.[12] Elimination of $Ph_2PO_2^-$ from *threo*-(**13**) required two equivalents of NaH and gave a very high yield of the pure pheromone *E*-(**14**): the *Z*-isomer was not detected by g.l.c. (Scheme 3).

(*E*)-Dec-5-en-1-ol (**17**) and its acetate are pheromones of the peach twig borer moth and other insects.[13] It has been synthesized by routes in which the geometry of the double bond

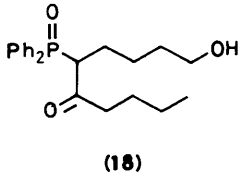


Scheme 3.

is fixed by the opening of tetrahydropyrans,[14] by reduction of a triple bond,[15] base-catalysed elimination of HI,[16] and by a Claisen rearrangement.[17] The Wittig reaction between pentyl triphenylphosphonium bromide and ^{2}H-hydroxytetrahydropyran is 93% *Z*-selective,[15,18] although Schlosser's modification[10] would no doubt be *E*-selective. Either ketone, (**15**) or (**18**), for the Horner-Wittig route could be used in this case as the two side-chains are roughly equal in size, but we preferred the ketone (**15**) as it can be made by acylation with a lactone and there is some evidence[19] for low stereoselectivity with functional groups in the upper side chain [R^1 in (**2**)]. The stereoselectivity of reduction of the ketone (**15**) was less (75:25) than that of ketone (**12**) (85:15) but *threo*-(**16**) was still isolated in 68% yield. Elimination again gave pure *E*-alcohol (**17**) (Scheme 4). The separation also gave 14% *erythro*-(**16**) which

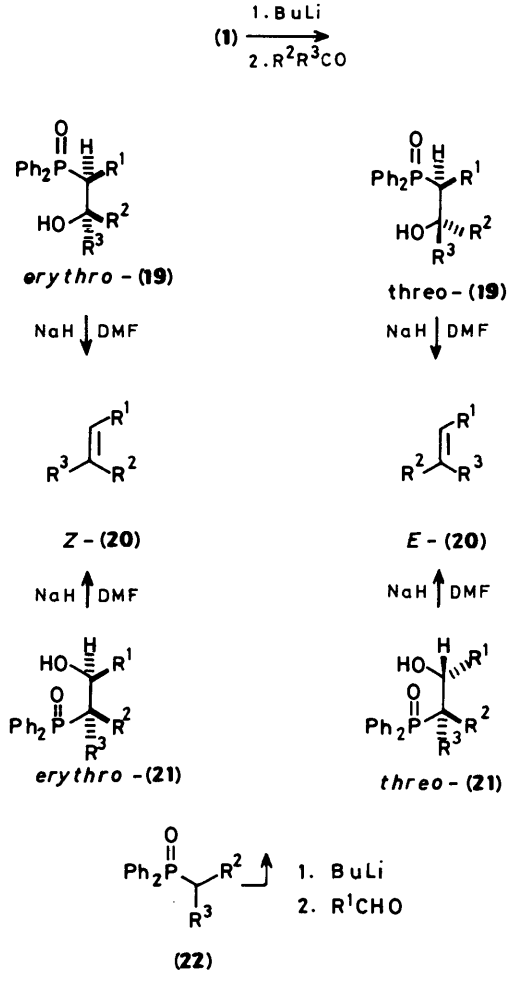


Scheme 4.



gave *Z*-(**17**) on elimination: the acetate of *Z*-(**17**) is a pheromone of the male turnip moth.[13] Each unsaturated alcohol *E*- or *Z*-(**17**) was free from the other.

Tri-Substituted Alkenes.—The synthesis of olefins with three substituents on the double bond presents special problems of geometrical control. Faulkner's 1971 review[20] and the many approaches to *Cecropia* juvenile hormone[21] gave some solutions, more recently extended by carbometallation of acetylenes[22] and metal (Pd,Ni) catalysed reactions of vinyl halides,[23] sulphides,[24] triflates,[25] and silyl enol ethers.[26] The Wittig approach rarely produces much stereoselectivity. Bestmann[27] achieved reasonable selectivity with salt-free ylides and Still[28] had some spectacular (200:1) results in the special case of allyl ether synthesis from ylides and α-alkoxyketones. In most cases, the problem is the separation of geometrical isomers of the final product. Although our Horner-Wittig approach has not achieved high stereoselectivity, separation of the diastereoisomeric intermediates (**19**) or (**21**) and stereospecific elimination of $Ph_2PO_2^-$ are usually successful,[29] giving pure *E*- or *Z*-alkenes (Scheme 5).



Scheme 5.

Route (a). Addition of Lithium Derivatives of Primary Alkyl Phosphine Oxides (**1**) *to Ketones.*—We have reported examples of this route with functional groups on the phosphine oxide in the α (PhS,[30] MeO[31]), β (R_2N),[32] and γ (ketal)[33] positions (Table 1, entries a—f). In general, stereoselectivity is poor, and often favours *threo*-(**19**) and hence *E*-(**20**). Unfunctionalised

Table 1. Adducts (**19**) of primary alkyl phosphine oxides (**1**) and ketones

Entry	R^1	R^2	R^3	Yield (**19**) (%)	*erythro*: *threo*	Isolated yields of single isomers (%) *erythro*-(**19**)	*Z*-(**20**)	*threo*-(**19**)	*E*-(**20**)	Ref.
a	PhS	Ph	Me	*a*	14:86[a]		90[b]		90[b]	30
b	MeO	Ph	Me	89	50:50	11		25		31
c	$-CH_2(CH_2)_3CH_2$	Pr	Me	36	28:74	7	88	29	87	32
d	$-CH_2(CH_2)_3CH_2$	Pr^i	Me	47	20:80	12	86	35	91	32
e	$-CH_2CH_2C(Me)O(CH_2)_2O$	Et	Me	77	50:50[c]	39	73	38	81	33
f	$-CH_2CH_2C(Me)O(CH_2)_2O$	Pr^i	Me	62	53:47[c]	29	82	33	67	33
g	Me	4-MeC_6H_4	Me	83	35:65[c]	29		54		*d*
h	$PhCH_2$	Et	Me	79	53:47[c]	39	89[e]	42	87	*d*
i	$MeCH_2CH{=}C(Me)_2$	$-CH(CH_2)_2CH(Me){=}CHCH_2$	Me	57	98:7	53[f]	91	4[f]	83	*d*

[a] Intermediates (**19**) not isolated, ratio deduced from ratio of alkenes. [b] Not separated: mixture of vinyl sulphides converted directly to ketone. [c] Stereochemistry not definitely assigned. [d] This work. [e] *E*-Isomer. [f] Mixture of diastereoisomer at a third chiral centre.

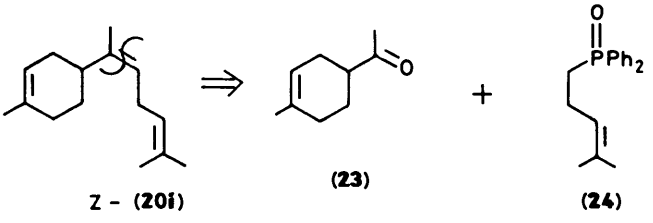
phosphine oxides gave some problems. Adduct (**19g**) and adducts (**19**; R^1 = Ph, R^2 = Et, R^3 = Me), and (**19**; R^1 = Me, R^2 = $PhCH_2$, R^3 = Me) underwent mostly reverse Horner-Wittig reactions on treatment with NaH to give ketone R^2R^3CO and only a trace of alkene. The adduct (**19h**) was separated into diastereoisomers, but both gave *E*-3,4-dimethyl-1-phenylpent-2-ene on elimination, presumably by reversion to starting materials.[34] An adduct (**19**; R^1 = Ph, R^2 = Et, R^3 = Me) of benzyl diphenylphosphine oxide gave a mixture of olefins directly in poor yield. However, this approach did give a good stereochemically-controlled synthesis of α-bisabolene; and additions of several functionalised phosphine oxides to symmetrical ketones give good yields of trisubstituted alkenes.[32,33]

Synthesis of α-Bisabolene.—The α-bisabolene in oil of *Opopanax* is the *Z*-isomer and has more desirable perfumery qualities ('green and flowery') than the *E*-isomer ('woody-herbal with a green subnote . . . rather fatty').[35] Disconnection of the central tri-substituted double bond[36] suggests a synthesis from the Diels-Alder adduct (**23**) and the phosphine oxide (**24**). A Wittig reaction between the same ketone (**23**) and the phosphonium salt corresponding to (**24**) gave a 25% yield of α-bisabolene in a 97:3 *Z*:*E* ratio (Scheme 6).

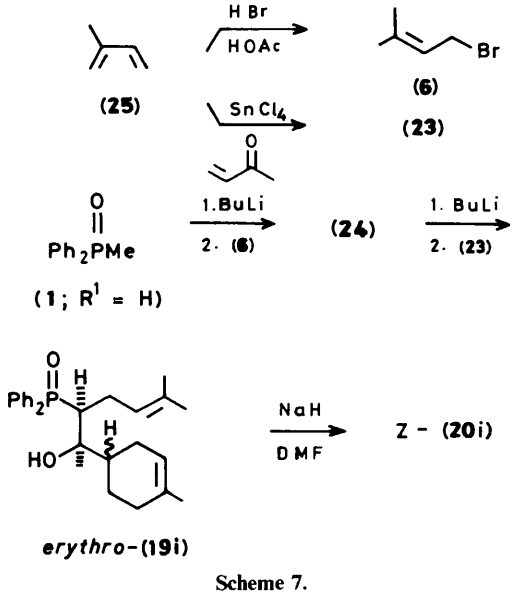
The Diels–Alder reaction giving the ketone (**23**) from isoprene (**25**) is regiospecific if Lewis acid catalysis is used.[37] Isoprene (**25**) was also the starting material for the phosphine oxide (**24**) *via* alkylation of (**1**; R^1 = H) with 3-methylbut-2-enyl bromide[38] (**6**). The Horner-Wittig reaction between the lithium derivative of (**24**) and the ketone (**23**) gave a mixture of all four diastereoisomers of the adduct (**19i**), separated by flash column chromatography into a crystalline pair (53%) and an oily pair (4%). Elimination of $Ph_2PO_2^-$ from the crystalline pair gave pure (*Z*)-α-bisabolene and, from the oily pair, pure (*E*)-α-bisabolene (Scheme 7). The stereochemistry was assigned by comparison of the 400 MHz ^{1}H n.m.r. spectra.[35] The crystalline pair of alcohols must both be *erythro*-(**19i**) and the oily pair *threo*, and the chromatographic separation operated only on the functionalised chiral centres and ignored the minor chiral centre on the ring. G.l.c. and i.r. analysis showed that each isomer of α-bisabolene was free from the other but that both contained a trace of the ketone (**23**), undetectable by n.m.r., presumably derived from reversal of the Horner-Wittig reaction.[34]

Route (b). Addition of Lithium Derivatives of Secondary Alkyl Phosphine Oxides (**22**) *to Aldehydes.*—We had previously made dienes[39,40] (entries a, b; Table 2), vinyl sulphides[30,41] (entries c, d), and unsaturated ketals[33,42] (entries e, f) by this route observing little stereoselectivity except in the vinyl sulphide (**20d**) where reversible addition probably favours[41] *threo*-(**21d**). Nevertheless, pure single isomers *E*-(**20**) or *Z*-(**20**) can be obtained in most cases. We have now studied adduct (**21g**) to investigate the selectivity of the direct Horner-Wittig reaction and the reduction route [*cf.* (**2**) to (**3**)] in this simple trisubstituted system.

The secondary alkyl phosphine oxide [**22**; R^1 = $Ph(CH_2)_2$, R^2 = Me] gave a good yield of adducts (**21g**) with low stereoselectivity in favour of *threo*-(**21g**). Separation was easy and pure samples (g.l.c.) of each alkene were formed in very



Scheme 6.

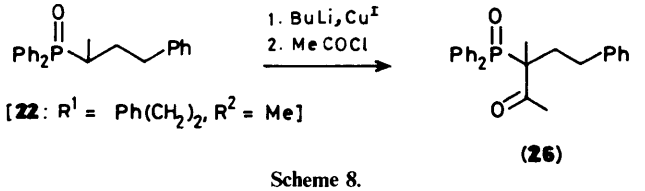


Scheme 7.

Table 2. Adducts (**21**) of secondary alkyl phosphine oxides (**22**) and aldehydes

Entry	R^1	R^2	R^3	Yield (**21**) (%)	*erythro*: *threo*	Isolated yields of single isomers (%) *erythro*-(**21**)	*Z*-(**20**)	*threo*-(**21**)	*E*-(**20**)	Ref.
a	$-CH(CH_2)_2CH(Me)=CHCH_2$	Me	Me	79[a]	63:27	50	80	29	80	39
b	$Me_2C=CMe$	Me	Me	58[a]	43:57	25	70	33	80	40
c	PhS	Et	Ph	*b*	43:57		93[b]		93[b]	30
d	MeS	Et	Ph	90[a]	20:80	18	92	72	100	41
e	$-CH_2C(Me)O(CH_2)_2O$	Me	Pr	55[a]	67:33	38	76	17		42
f	$CH_2CH_2C(Me)O(CH_2)_2O$	Me	Ph	72[a]	49:51	35[c]		37[c]		33
g	$(CH_2)_2Ph$	Me	Me	81[a]	47:53	38	92	43	93	*d*

[a] Isolated only as separated diastereoisomers. [b] Alkene formed directly as mixture: ratio from n.m.r. [c] Stereochemistry not definitely assigned. [d] This work.



Scheme 8.

good yield. The alternative route,[3] the reduction of the ketone (**26**), gave a ratio of 67:33 in favour of *threo*-(**21g**) (Scheme 8).

Conclusions

Either route to tri-substituted alkenes usually gives single isomers of the alkene after separation of the diastereoisomers of the intermediate (**19**) or (**21**), but each case must be taken separately, and high stereoselectivity is not observed.

Experimental

M.p.s were determined on a Buchi 510 melting point apparatus or a Kofler hot stage, and are uncorrected. ^1H N.m.r. spectra were recorded on a Varian Associates EM 390 spectrometer at 90 MHz and on Bruker WH-250 and WH-400 spectrometers at 250 and 400 MHz. ^{13}C N.m.r. spectra were recorded at 62.8 MHz on a Bruker WH-250 spectrometer. Chemical shifts are given in p.p.m. downfield from tetramethylsilane. Mass spectra were recorded on A.E.I.-Kratos MS902 and MS30 spectrometers. High resolution mass spectra employed a DS50S data system. I.r. spectra were recorded on a Perkin-Elmer 297 spectrometer. Preparative t.l.c. was run on silica gel GF_{254} (1 mm) plates, t.l.c. was run on Merck Kieselgel 60 F_{254} plates. Column chromatography was performed on Merck Kieselgel 60 70-230 mesh and flash chromatography on Merck Kieselgel 60 230-400 mesh. H.p.l.c. was carried out using a 50 cm × 1 cm steel column packed with Lichrosorb SI60 silica, pressurised by an Altex 110A pump. Dry THF was freshly distilled from potassium using benzophenone radical as an indicator in a recycling still. Micro-analyses were carried out by technical staff at the University Chemical Laboratory, Cambridge. All solvents were distilled before use.

Methyl 4-(3-*Methylbut*-2-*enyloxy*)*benzoate* (**7**) was prepared from methyl *p*-hydroxybenzoate, 1-bromo-3-methylbut-2-ene (**6**), potassium iodide, and anhydrous potassium carbonate and had m.p. 43—44.5 °C (from hexane, lit.,[43] 45—46 °C).

2-*Diphenylphosphinoyl*-1-[4-(3-*methylbut*-2-*enyloxy*)]*phenyl*-*propan*-1-*one* (**8**).—Acylation of ethyl diphenylphosphine oxide[3] (226 mg, 0.98 mmol) by the above ester (220 mg, 1 mmol) gave the *ketone* (**8**) (250 mg, 61%) as needles, m.p. 115—115.5 °C, R_F(EtOAc) 0.4, $\nu_{max.}$(Nujol) 1 662 (C=O), 1 640 (C=C), 1 600 (aryl), 1 440 (Ph–P), 1 240 (P=O), and 840 cm^{-1} (*p*-disubstituted Ar); $\delta_H(CDCl_3)$ 7.9 (4 H, m, ArH), 7.88 (2 H, d, *J* 8 Hz, ArH), 7.53 (6 H, m, ArH), 6.86 (2 H, d, *J* 8 Hz, ArH), 5.53 (1 H, t, *J* 8 Hz, =C*H*CH_2), 4.55 (3 H, m, CH_2 and PC*H*Me), 1.83 (3 H, s, =CMe), 1.80 (3 H, s, =CMe), and 1.57 (3 H, dd, J_{HP} 16, J_{HMe} 8 Hz, PCH*Me*) (Found: M^+, 418.1700. $C_{26}H_{27}O_3P$ requires *M*, 418.4703); *m*/*z* 418 (5%, M^+) and 350 (100, $M - C_5H_8$).

2-*Diphenylphosphinoyl*-1-[4-(3-*methylbut*-2-*enyloxy*)]*phenyl*-*propan*-1-*ol* (**9**).—Reduction of the above ketone (2.8 g, 5.5 mmol) with sodium borohydride[3] gave a yellow oil (2.3 g) separated by column chromatography on silica eluting with EtOAc to give the threo-*alcohol* (**9**) (1.7 g, 74%), m.p. 95.5—97 °C (from EtOAc–hexane), R_F(EtOAc) 0.8, $\nu_{max.}$(Nujol) 3 220 (OH), 1 600 (aryl), 1 230 (P=O), and 830 cm^{-1} (*p*-disubstituted Ar); $\delta_H(CDCl_3)$ 7.90 (4 H, m, ArH), 7.63 (6 H, br s, ArH), 7.33 (2 H, d, *J* 7.5 Hz, ArH), 6.92 (2 H, d, *J* 7.5 Hz, ArH), 5.56 (1 H, t, *J* 6 Hz, =C*H*CH_2), 4.86 (1 H, t, $J_{HH} = J_{HOH}$ = 7.5 Hz, C*H*OH), 4.54 (2 H, d, *J* 6 Hz, =CHC*H*$_2$), 4.0 (1 H, br s, exchanges with D_2O, OH), 3.0 (1 H, m, PC*H*Me), 1.84 (3 H, s, =CMe), 1.80 (3 H, s, =CMe), and 0.80 (3 H, dd, J_{HH} 6, J_{HP} 16.5 Hz, PCH*Me*); *m*/*z* 420 (30%, M^+) and 352 (100, $M - C_5H_8$), and the *erythro*-alcohol (**9**) (160 mg); $\delta_H(CDCl_3)$ 7.7—8.2 (4 H, m, *o*-PhP), 7.4—7.7 (6 H, m, PhP), 7.25 (2 H, d, *J* 8 Hz, Ar), 6.87 (2 H, d, *J* 8 Hz, Ar), 5.47 (1 H, br t, *J* 6 Hz, OCH_2CH=), 5.24 (1 H, d, *J* 9 Hz, C*H*OH), 4.48 (2 H, d, *J* 6 Hz, OCH_2CH=), 2.53 (1 H, quint, *J* 7 Hz, PC*H*Me), 1.78 (3 H, s, Me), 1.71 (3 H, s, Me), and 1.01 (3 H, dd, J_{PH} 16, J_{HH} 7 Hz, PCH*Me*).

(E)-1-[4-(3-*Methylbut*-2-*enyloxy*)*phenyl*]*prop*-1-*ene*, *Feniculin* (**10**).—A stirred solution of sodium hydride (60 mg, 50% dispersion in oil) and the above *threo*-alcohol (514 mg) in dry DMF was heated to 50 °C for 30 min. The cooled solution was poured into water and extracted with ether. The extracts were washed with water, dried ($MgSO_4$), and the solvent was evaporated under reduced pressure. The yellow oil was distilled (Kugelrohr) to give feniculin (175 mg, 71%), b.p. 109—120 °C/0.1—0.15 mmHg, R_F(EtOAc) 0.7, $\nu_{max.}$ (liquid film) 960 (out-of-plane def. for *trans* CH=CH), 840 (*p*-disubstituted aryl), and 790 cm^{-1} (CH=CMe_2); $\delta_H(CDCl_3)$ 7.32 (2 H, d, *J* 8 Hz, ArH), 6.90 (2 H, d, *J* 8 Hz, ArH), 6.49 (1 H, d, *J* 15 Hz, ArC*H*=CH), 6.08 (1 H, dq, J_{HH} 15, J_{HMe} 6 Hz, ArCH=C*H*Me), 5.56 (1 H, t, *J* 7 Hz, =C*H*CH_2), 4.54 (2 H, d, *J* 7 Hz, =CHC*H*$_2$), 1.88 (3 H, d, J_{HMe} 6 Hz, =CH*Me*), 1.84 (3 H, s, =CMe), and 1.78 (3 H, s, =CMe) (Found: M^+, 202.1357. $C_{14}H_{18}O$ requires *M*,

202.1358); *m/z* 202 (10%, M^+) and 134 (100, $M - C_5H_8$), $\lambda_{max.}$(EtOH) 271, 259, 251, and 206 nm.

3-*Diphenylphosphinoyl*-9-*hydroxynonan*-4-*one* (**12**).—Butyllithium (6.7 ml, 1.5M in hexane) was added dropwise from a syringe to a stirred solution of diphenylpropylphosphine oxide (**1**; R^1 = Et) (2.44 g, 0.1 mol) in dry THF (30 ml) at 0 °C. After 15 min the red reaction solution was cooled to −78 °C (acetone–dry ice) and ε-caprolactone (1.14 g, 0.01 mol) was added dropwise from a syringe. The temperature was maintained at −78 °C for 10 min and the reaction was quenched by adding a saturated aqueous solution of ammonium chloride (20 ml). The reaction mixture was allowed to warm to room temperature before the THF was evaporated under reduced pressure. The aqueous residues were extracted with dichloromethane (3 × 30 ml) and the combined organic extracts were dried ($MgSO_4$) and evaporated to dryness to give the *hydroxy ketone* as needles (2.9 g, 81.0%), m.p. 89—91 °C (from EtOAc–Et_2O) (Found: C, 70.1; H, 7.7; P, 8.6. M^+, 358.1688. $C_{21}H_{27}O_3P$ requires C, 70.3; H, 7.6; P, 8.7%. *M*, 358.1698), R_F(EtOAc) 0.2, $\nu_{max.}$ 3 300 (OH), 1 705 (C=O), 1 440 (P–Ph), 1.85, and 1 195 cm^{-1}; $\delta_H(CDCl_3)$ 7.9—7.1 (10 H, m, Ph_2PO), 3.7—3.2 (3 H, m, C*H*P and CH_2OH), 2.7 (1 H, s, OH), 2.4 (2 H, t, *J ca.* 6 Hz, $COCH_2$), 2.2—1.1 [8 H, m, $(CH_2)_3CH_2OH$ and CH_2Me], and 0.85 (3 H, t, *J* 7 Hz, Me); *m/z* 358 (10%), 244 (56%, Ph_2POPr), 229 [82%, $Ph_2PO(CH_2)_2^+$], 202 (92%, Ph_2POH), and 201 (100%, Ph_2PO^+).

Reduction of the Hydroxy Ketone (**12**).—Sodium borohydride (135 mg, 3.56 mmol) was added in one portion to a stirred solution of the hydroxy ketone (**12**) (1.28 g, 3.56 mmol) in ethanol (20 ml). The reaction mixture was heated under reflux for 3 h, cooled to room temperature and a saturated aqueous solution of ammonium chloride (15 ml) was added. The ethanol was evaporated under reduced pressure and several drops of dilute HCl were added to the aqueous residues. After being diluted with brine (20 ml), the aqueous reaction mixture was extracted with dichloromethane (3 × 50 ml) and the combined organic extracts were dried ($MgSO_4$) and evaporated to dryness to give the product as a mixture of diastereoisomers which was separated by flash column chromatography (elution with acetone). The first *diastereoisomer* eluted was assigned the (6*RS*,7*SR*)-configuration *erythro* alcohol (**13**) (195 mg, 15.2%), R_F(EtOAc) 0.15; $\delta_H(CDCl_3)$ 7.9—7.1 (10 H, m, Ph_2PO), 4.0 (1 H, m, C*H*OH), 3.55 (2 H, br t, *J ca.* 6 Hz, CH_2OH), 3.15 (2 H, br s, 2 × OH), 2.5—1.1 [11 H, m, C*H*P, CH_2Me and $CH(CH_2)_4$], and 0.9 (3 H, t, *J* 7 Hz, Me). The second *diastereoisomer* eluted from the column was the (6*RS*,7*RS*)-alcohol *threo*-(**13**), needles (1.085 g, 84.8%), m.p. 114—116 °C (from EtOAc–light petroleum, b.p. 40—60 °C) (Found: C, 69.6; H, 8.1; P, 8.4. M^+, 360.1857. $C_{21}H_{29}O_3P$ requires C, 69.9; H, 8.5; P, 8.6%. *M*, 360.1854), R_F(EtOAc) 0.1, $\nu_{max.}$ 3 350 (OH), 1 440 (P–Ph), and 1 170 cm^{-1} (P=O); $\delta_H(CDCl_3)$ 8.0—7.25 (10 H, m, Ph_2PO), 4.0 (1 H, dm, C*H*OH), 3.7 (2 H, br s, 2 × OH), 3.5 (2 H, t, *J* 6 Hz, CH_2OH), 2.4 (1 H, m, CHP), 1.9—1.1 [10 H, m, CH_2Me and $CH(CH_2)_4$], and 0.9 (3 H, t, *J* 7 Hz, Me); *m/z* 360 (2%), 273 [100% $M - (CH_2)_5OH$], 244 (70%, Ph_2POPr), 229 [98%, $Ph_2PO(CH_2)_2^+$], 202 (85%, Ph_2POH), and 201 (98%, Ph_2PO^+).

(E)-*Non*-6-*en*-1-*ol* (**14**).—Sodium hydride (50 mg; 80% dispersion in oil, 1.67 mmol) was added in one portion to a stirred solution of the (6*RS*,7*RS*)-adduct *threo*-(**13**) (300 mg, 0.833 mmol) in dry DMF (20 ml). The clear reaction solution was warmed to 50 °C for 30 min by which time a white solid had precipitated from solution. The reaction mixture was cooled and the precipitate dissolved by the addition of water (25 ml). The mixture was diluted with brine (15 ml) and extracted with Et_2O (3 × 40 ml). The combined organic extracts were washed with water (3 × 40 ml), dried ($MgSO_4$), and evaporated under reduced pressure. Bulb-to-bulb distillation (Kugelrohr apparatus) gave the alkene (115 mg, 97.5%) as a unpleasant-smelling, colourless liquid, b.p. 92—94 °C/0.5 mmHg (lit.,[8] b.p. 83—87 °C/0.25 mmHg), R_F 0.7, $\nu_{max.}$ (liquid film) 3 340 (OH), 1 050 (CO), and 965 cm^{-1} (C=H out of plane def.); $\delta_H(CCl_4)$ 5.25 (2 H, m, CH=CH), 3.4 (2 H, t, *J* 5 Hz, CH_2OH), 3.25 (1 H, br s, OH), 1.85 (4 H, m, CH_2CH=CHCH_2), 1.25 (6 H, remaining CH_2), and 0.85 (3 H, t, *J* 7 Hz, Me); *m/z* 124 (10%, $M - H_2O$), 95 (57%), 82 (62), and 67 (100). The (*Z*)-isomer was not detected by g.l.c. (columns 2, 4, and 5).

6-*Diphenylphosphinoyl*-1-*hydroxydecan*-5-*one* (**15**).—Butyllithium (20.1 ml of a 1.5M solution in hexane), pentyldiphenylphosphine oxide[3] (8.16 g, 30 mmol) in dry THF (90 ml) under nitrogen at 0 °C, and δ-valerolactone (3.0 g, 30 mmol) gave the *hydroxy ketone* (**15**) (9.63 g, 86.3%) as needles (from EtOAc–hexane), m.p. 83—84 °C (Found: C, 70.8; H, 8.1; P, 8.1. M^+ 372.1860. $C_{22}H_{29}O_3P$ requires C, 70.9; H, 7.85; P, 8.3%. *M*, 372.1854); R_F(EtOAc) 0.14; $\nu_{max.}(CHCl_3)$ 3 340 (OH), 1 698 (C=O), 1 440 (Ph–P), 1 195, and 1 185 cm^{-1} (P=O); $\delta_H(CDCl_3)$ 90 MHz, 8.05—7.45 (10 H, m, Ph_2PO), 3.8—3.45 (1 H, m, CHP), 3.55 (2 H, t, *J* 7 Hz, CH_2OH), 2.58 (2 H, t, *J* 6 Hz, CH_2CO), 2.32 (1 H, s, OH), 2.4—1.9 (2 H, m, CH_2CHP), 1.9—1.0 [8 H, m, $(CH_2)_2$ and $(CH_2)_2$], and 0.8 (3 H, t, *J* 6 Hz, Me); *m/z* 372 (0.84%, M^+), 354 (0.6, $M - H_2O$), 272 (20, $Ph_2POPent$), 229 [62, $Ph_2PO(CH_2)_2$], 219 (25), 202 (100, Ph_2POH), and 201 (60, Ph_2PO).

6-*Diphenylphosphinoyldecane*-1,5-*diol* (**16**).—Sodium borohydride (1.0 g, 26.3 mmol) and the hydroxy ketone (**15**) (5.0 g, 13.4 mmol) under nitrogen in ethanol (75 ml) gave the product as a mixture of diastereoisomers, which were separated by fractional crystallisation from EtOAc–hexane. The first *diastereoisomer* to crystallise was assigned the (5*RS*,6*RS*)-configuration *threo*-(**16**) as needles (3.4 g, 67.6%), m.p. 145—146 °C (Found: C, 70.4; H, 8.5; P, 8.0. $C_{22}H_{31}O_3P$ requires C, 70.6; H, 8.35; P, 8.3%), R_F(EtOAc) 0.12, $\nu_{max.}(CHCl_3)$ 3 380 (OH), 1 440 (Ph–P), and 1 160 cm^{-1} (P=O); $\delta_H(CDCl_3$; 90 MHz) 8.1—7.4 (10 H, m, Ph_2PO), 4.0 (2 H, m, C*H*OH and OH), 3.55 (2 H, t, *J* 6 Hz, CH_2OH), 2.45 (2 H, m, C*H*P and OH), 2.0—0.9 [12 H, m, $(CH_2)_3$ and $(CH_2)_3$], and 0.75 (3 H, t, *J* 6 Hz, Me) (Found: $M^+ - H_2O$, 356.1901. $C_{22}H_{29}O_2P$ requires $M - H_2O$, 35.1905); *m/z* 356 (1.03%, $M - H_2O$), 301 [63, $M - (CH_2)_4OH$], 272 (30, $Ph_2POPent$), 229 [85, $Ph_2PO(CH_2)_2$], 202 (100, Ph_2POH), and 201 (73, Ph_2PO). The second *diastereoisomer* was obtained by column chromatography on silica eluting with EtOAc–MeOH (93:7) and was assigned the (5*RS*,6*SR*)-configuration *erythro*-(**16**) (0.704 g, 14%) as needles (EtOAc–hexane), m.p. 92—93 °C (Found: C, 70.5; H, 8.35; P, 8.3. $C_{22}H_{31}O_3P$ requires C, 70.6; H, 8.35; P, 8.3%), R_F(EtOAc) 0.18, $\nu_{max.}(CHCl_3)$ 3 400 (OH), 1 440 (PhP), and 1 170 cm^{-1} cm^{-1} (P=O); δ_H ($CDCl_3$; 90 MHz) 8.05—7.35 (10 H, m, Ph_2PO), 4.05 (1 H, m, C*H*OH), 3.9 (2 H, s, 2 × OH), 3.55 (2 H, t, *J* 6 Hz, CH_2OH), 2.2 (1 H, m, CHP), 2.1—0.9 [12 H, m, $(CH_2)_3$ and $(CH_2)_3$], and 0.65 (3 H, t, *J* 6 Hz, Me) (Found: $M^+ - H_2O$, 35.1916. $C_{22}H_{29}O_2P$ requires $M - H_2O$, 356.1905); *m/z* 356 (0.95%, $M - H_2O$), 301 [35, $M - (CH_2)_4OH$], 272 (50, $Ph_2POPent$), 229 [95, $Ph_2PO(CH_2)_2$], 202 (100, Ph_2POH), and 201 (80, Ph_2PO). The mixed residue (0.85 g) was analysed by h.p.l.c. with EtOAc–MeOH (20:1) as eluant and was found to contain 34% LR_F and 59% HR_F. Overall yield is 97.4% with 3:1 diastereoselectivity.

(E)-*Dec*-5-*en*-1-*ol* [E-(**17**)].—Sodium hydride (70 mg, 1.46 mmol, 50% dispersion in oil) and the (5*RS*,6*RS*) diol *threo*-(**16**) (260 mg, 0.70 mmol) in dry DMF (20 ml) gave the alkene (104 mg, 95.9%) as an unpleasant-smelling clear liquid, b.p. 83—

85 °C/0.15 mmHg (lit.,[14] b.p. 100—120 °C/14 mmHg) (Found: C, 76.7; H, 13.0. M^+, 156.1526. $C_{10}H_{20}O$ requires C, 76.9; H, 12.9%; M, 156.1514), $\nu_{max.}$ (liquid film) 3 300 (OH), and 988 cm^{-1} (E – HC=CH def.); $\delta_H(CDCl_3)$ 5.6—5.15 (2 H, m, CH=CH), 3.6 (2 H, t, J 6 Hz, CH_2OH), 2.2 (1 H, s, OH), 1.95 (4 H, m, CH_2CH=$CHCH_2$), 1.5—1.1 [8 H, m, $(CH_2)_2$ and $(CH_2)_2$], and 0.87 (3 H, t, J 7 Hz, Me); m/z 156 (4%, M^+), 138 (18, $M - H_2O$), and 55 (100, C_4H_7). The Z-isomer was not detected by g.l.c. on a 15% Carbowax 20M on Chromosorb W column.

(*Z*)-*Dec-5-en-1-ol* [Z-(**17**)].—In a similar way, sodium hydride (40 mg), (5*RS*,6*SR*) diol *erythro*-(**16**) (150 mg) in DMF (10 ml) after 2 h at 50 °C, gave the alkene (61 mg, 97.5%) as an unpleasant-smelling clear liquid, b.p. 100—105 °C/0.2 mmHg (lit.,[14] b.p. 114—115 °C/14 mmHg), $\nu_{max.}(CHCl_3)$ 3 600 (OH), 1 600 (C=C), and 1 455 cm^{-1} (CH def.); $\delta_H(CDCl_3)$ 5.45—5.3 (2 H, m, CH=CH), 3.65 (2 H, t, J 6 Hz, CH_2OH), 2.05 (4 H, m, CH_2CH=$CHCH_2$), 1.7—1.2 [8 H, m, $(CH_2)_2$ and $(CH_2)_2$], 0.9 (3 H, t, J 6 Hz, Me) (Found: $M^+ - H$, 155.1429. $C_{10}H_{20}O$ requires $M - H$, 155.1436); m/z 155 (53%, $M - H$), and 98 (100, $M - C_4H_{10}$). The E-isomer was not detected by g.l.c. as above.

3-*Diphenylphosphinoyl*-2-(p-*tolyl*)*butan*-2-*ol* (**19g**).—Butyllithium (5.8 ml, 1.5M in hexane) ethyldiphenylphosphine oxide (2.0 g, 8.692 mmol) in dry THF (30 ml) and 4-methylacetophenone (1.17 g, 8.692 mmol) gave the adduct as a mixture of diastereoisomers which was separated by flash chromatography (elution with Et_2O–EtOAc, 4:1). The first *diastereoisomer* eluted from the column was obtained as needles (HR_F isomer) (1.71 g, 53.9%), m.p. 224—226 °C (from EtOAc) (Found: C, 75.5; H, 7.0; P, 8.5. $C_{23}H_{25}O_2$ requires C, 75.8; H, 6.9; P, 8.5%), R_F (Et_2O–EtOAc, 4:1) 0.5, $\nu_{max.}$ 3 380 (OH), 1 440 (P–Ph), and 1 160 cm^{-1} (P=O); $\delta_H(CDCl_3)$ 8.1—7.0 (14 H, m, Ph_2PO and Ar), 5.2 (1 H, br s, OH), 2.9 (1 H, dq, $J_{HMe} = J_{HP} = 7$ Hz, CHP), 2.3 (3 H, s, ArMe), 1.45 (3 H, s, Me), and 0.85 (3 H, dd, J_{HMe} 7, J_{MeP} 16 Hz, CH*Me*); m/z 230 (100%, Ph_2OEt) and 202 (40%, Ph_2POH). The second *diastereoisomer* eluted from the column was obtained as needles (LR_F isomer) (920 mg, 29.0%), m.p. 183—185 °C (from EtOAc) (Found: C, 75.7; H, 7.1; P, 8.6. $C_{23}H_{25}O_2P$ requires C, 75.8; H, 6.9; P, 8.5), R_F (Et_2O–EtOAc, 4:1) 0.4, $\nu_{max.}$ 3 360 (OH), 1 440 (P–Ph), and 1 170 cm^{-1} (P=O); $\delta_H(CDCl_3)$ 7.85—6.6 (14 H, m, Ph_2PO and ArH), 5.45 (1 H, br s, OH), 2.9 (1 H, dq, $J_{HMe} = J_{HP} = 8$ Hz, CHP), 2.1 (3 H, s, ArMe), 1.5 (3 H, s, Me), and 1.15 (3 H, dd, J_{HMe} 7, J_{MeP} 17 Hz, CH*Me*); m/z 230 (100%, Ph_2POEt) and 202 (34%, Ph_2POH).

2-*Diphenylphosphinoyl*-3-*methyl*-1-*phenylpentan*-3-*ol* (**19h**).—In the same way, butyl-lithium (6.7 ml, 1.5M in hexane) 2-phenylethyldiphenylphosphine oxide[44] (**1**; $R^1 = CH_2Ph$) (3.06 g, 0.01 mol) in dry THF (40 ml) and butan-2-one gave the adduct as a mixture of diastereoisomers which was separated by preparative h.p.l.c. (elution with Et_2O). The first *diastereoisomer* eluted from the column was obtained as needles (HR_F isomer) (1.617 g, 42.8%), m.p. 189—190 °C (from EtOAc) (Found: C, 76.3; H, 7.35; P, 8.50. $C_{24}H_{27}O_2P$ requires C, 76.1; H, 7.2; P, 8.2%), R_F(EtOAc) 0.5, $\nu_{max.}$ 3 330 (OH), 1 440 (P–Ph), and 1 150 cm^{-1} (P=O); $\delta_H(CDCl_3)$ 7.9—6.5 (15 H, m, 3 × Ph), 4.65 (1 H, s, OH), 3.2—2.7 (3 H, m, CHP and $PhCH_2$), 1.7 (2 H, q, J 7 Hz, CH_2Me), 1.2 (3 H, s, Me), and 0.8 (3 H, t, J 7 Hz, CH_2Me); m/z 360 (12%, $M - H_2O$), 349 (27%, M – Et), 306 [27%, $Ph_2PO(CH_2)_2Ph$], and 202 (100%, Ph_2POH). The second *diastereoisomer* eluted from the column was obtained as needles (LR_F isomer) (1.457 g, 38.5%), m.p. 158—159 °C (from EtOAc–light petroleum, b.p. 60—80 °C) (Found: C, 75.8; H, 7.2; P, 8.3), R_F(EtOAc) 0.5, $\nu_{max.}$ 3 420 (OH), 1 440 (P–Ph), and 1 180 cm^{-1} (P=O); $\delta_H(CDCl_3)$ 7.8—6.45 (15 H, m, 3 × Ph), 4.5 (1 H, br s, OH), 3.3—2.85 (3 H, m, CHP and $PhCH_2$), 1.75—1.2 (total 5 H, q overlain by s, CH_2Me and Me), and 0.8 (3 H, t, J 7 Hz, CH_2Me); m/z 360 (10%, $M - H_2O$), 349 (52%, M – Et), 306 [24%, $Ph_2PO(CH_2)_2Ph$], and 202 (100%, Ph_2POH).

Reaction of the HR_F *isomer* threo-(**19h**) *with Sodium Hydride*.—Sodium hydride (79 mg; 80% dispersion in oil, 2.64 mmol) was added in one portion to a stirred solution of the above HR_F isomer (500 mg, 1.32 mmol) in dry DMF (50 ml). The clear reaction solution was warmed to 50 °C for 3 h before cooling and adding water (20 ml). The mixture was then diluted with brine (40 ml) and extracted with Et_2O (3 × 30 ml). The combined organic extracts were washed with water (3 × 50 ml), dried over $MgSO_4$, and the solvent evaporated under reduced pressure. Bulb-to-bulb distillation (Kugelrohr apparatus) gave (E)-3-*methyl*-1-*phenylpent*-2-*ene* (*E*)-(**20h**) as a colourless liquid (185 mg, 87.3%), $\nu_{max.}$ (liquid film) 1 605, 1 495, and 1 450 (ArH), 935, and 700 cm^{-1}; $\delta_H(CDCl_3)$ 7.15 (5 H, m, Ph), 5.25 (1 H, br t, J 7 Hz, =CH), 3.3 (2 H, d, J 7 Hz, $PhCH_2$), 2.1 (2 H, q, J 8 Hz, CH_2Me), 1.7 (3 H, br s, =CMe), and 1.0 (3 H, t, J 8 Hz, CH_2Me). G.l.c. analysis (column 2) indicated that the product was a single isomer.

Reaction of the LR_F *isomer of* erythro-(**19h**) *with Sodium Hydride*.—In the same way, the LR_F isomer (500 mg, 1.32 mmol) and sodium hydride (79 mg; 80% dispersion in oil, 2.64 mmol) gave, after distillation, a colourless liquid (188 mg, 88.7%) with n.m.r., i.r., and g.l.c. data identical to those for (*E*)-3-methyl-1-phenylpent-2-ene [(*E*)-(**20h**)].

4-*Diphenylphosphinoyl*-3-*methyl*-1-*phenylpentan*-3-*ol*.—Ethyldiphenylphosphine oxide (2.3 g, 0.01 mmol), butyl-lithium (6.66 ml, 1.5M in hexane) and 4-phenylbutan-2-one (1.48 g, 0.01 mol) gave the *adduct* as a crystalline solid (3.2 g, 84.7%), m.p. 186—190 °C (from EtOAc–acetone), R_F(EtOAc) 0.45, $\nu_{max.}$ 3 340 (OH), 1 440 (P–Ph), and 1 175 cm^{-1} (P=O); $\delta_H(CDCl_3)$ 7.95—6.95 (15 H, m, 3 × Ph), 4.75 (1 H, s, OH), 3.0—2.4 (3 H, m, C*H*P and $PhCH_2$), 2.0—1.65 (2 H, m, CH_2), and 1.3—0.95 (total 6 H, s, overlain by dd, J_{HMe} 7, J_{MeP} 16 Hz, 2 × Me) (Found: M^+, 378.1757. $C_{24}H_{27}O_2P$ requires M, 378.1748); m/z 379 (3%, M + 1), 378 (14%), 273 [100%, $M - (CH_2)_2Ph$], 230 (82%, Ph_2POEt), and 202 (84%, Ph_2POH).

Diphenyl-3-*phenylpropylphosphine Oxide*.—The phosphonium salt method[3] gave the phosphine oxide (84%) as needles, m.p. 99—101 °C (from EtOAc–light petroleum, b.p. 60—80 °C) (lit.,[45] 102—103 °C) (Found: C, 78.8; H, 6.5; P, 10.0. M^+, 320.1312. Calc. for $C_{21}H_{21}OP$, C, 78.7; H, 6.6; P, 9.7%. M, 320.1330), R_F(EtOAc) 0.3, $\nu_{max.}$ 1 170 cm^{-1} (P=O); $\delta_H(CDCl_3)$ 7.85—7.0 (15 H, m, 3 × Ph), 2.7 (2 H, t, J 7 Hz, $PhCH_2$), and 2.45—1.75 (4 H, m, PCH_2CH_2), m/z 321 (5%, M + 1), 320 (20%), 216 (52%, Ph_2POMe), 215 (10%, $Ph_2POCH_2^+$), and 201 (12%, Ph_2PO^+).

(1-*Methyl*-3-*phenylpropyl*)*diphenylphosphine Oxide* [**22**; R^1 = $Ph(CH_2)_2$, R^2 = Me].—*Method A*. Butyl-lithium (6.7 ml, 1.5M in hexane) was added dropwise from a syringe to a stirred solution of diphenyl-3-phenylpropylphosphine oxide (3.2 g, 0.01 mol) in dry THF (20 ml) at 0 °C. After 30 min the red reaction solution was cooled to −78 °C and iodomethane (1.4 g, 0.01 mol) was added slowly from a syringe. The colourless reaction solution was allowed to warm to room temperature, water (20 ml) was added, and the THF was evaporated under reduced pressure. The aqueous residue was diluted with brine (15 ml) and extracted with dichloromethane. The combined organic extracts were dried ($MgSO_4$) and evaporated to give a white crystalline material. Purification by flash column chromatography (elution with EtOAc then acetone) gave the *phosphine*

oxide (2.9 g, 87.9%), m.p. 84—85 °C (from EtOAc–light petroleum, b.p. 40—60 °C) (Found: C, 79.0; H, 7.25; P, 9.4. M^+, 334.1469. $C_{22}H_{23}OP$ requires C, 79.0; H, 6.95; P, 9.3%. *M*, 334.1486), R_F(EtOAc) 0.3, $\nu_{max.}$ 1 440 (P–Ph) and 1 180 cm^{-1} (P=O); $\delta_H(CDCl_3)$ 7.85—6.9 (15 H, m, 3 × Ph), 3.0—1.6 (5 H, m, $CHCH_2CH_2$) and 1.2 (3 H, dd, J_{HMe} 7, J_{MeP} 17 Hz, Me); *m/z* 335 (3%, *M* + 1), 334 (17%), 230 (100%, Ph_2POEt), 202 (65%, Ph_2POH), and 201 (51%, Ph_2PO^+).

Method B. With TMEDA (1 equiv.), the same alkylation gave, after flash chromatography (eluting with EtOAc then acetone), 1,1-*dimethyl*-3-*phenylpropyl*)*diphenylphosphine oxide* (530 mg, 15.2%), m.p. 155—157 °C (from EtOAc–light petroleum, b.p. 60—80 °C) (Found: C, 79.5; H, 7.5; P, 8.8; M^+, 348.1630. $C_{23}H_{25}OP$ requires C, 79.3; H, 7.25; P, 8.9%; *M*, 348.1643), R_F(EtOAc) 0.35, $\nu_{max.}$ 1 440 (P–Ph) and 1 175 cm^{-1} (P=O); $\delta_H(CDCl_3)$ 8.15—7.85 (4 H, m, Ph_2PO *ortho*-protons), 7.6—7.35 (6 H, m, Ph_2PO *meta*- and *para*-protons), 7.3—6.9 (5 H, m, remaining Ph), 2.8—2.5 (2 H, m, $PhCH_2$), 2.1—1.7 (2 H, m, CH_2) and 1.3 (6 H, d, J_{MeP} 16 Hz, Me_2); *m/z* 349 (2%, *M* + 1), 348 (3%), 244 (82%, $Ph_2POCHMe_2$), and 202 (100%, Ph_2POH), and the *phosphine oxide* [**22**; R^1 = $Ph(CH_2)_2$, R^2 = Me) (2.53 g, 76.6).

Method C. Butyl-lithium (7.25 ml, 1.5M in hexane) was added dropwise from a syringe to a stirred solution of ethyldiphenylphosphine oxide (5.0 g, 21.73 mmol) and TMEDA (2.5 g, 21.73 mmol) in dry THF (40 ml) at 0 °C. After 30 min, 1-bromo-2-phenylethane (2.0 g, 10.86 mmol) was added slowly to the dark red solution; this caused immediate precipitation of a solid. The reaction mixture was stirred for 1 h at 0 °C and more butyllithium (7.25 ml, 1.5M in hexane) was added. After 15 min, 1-bromo-2-phenylethane (2.0 g, 10.86 mmol) was added slowly to the reaction mixture and the dark red suspension was allowed to warm to room temperature. After 3 h, water (25 ml) was added to the now yellow reaction mixture and the THF was evaporated under reduced pressure. The aqueous residue was diluted with brine and extracted with dichloromethane. The combined organic extracts were washed with 5% aqueous HCl, dried ($MgSO_4$), and evaporated to give a yellow oil. Purification by flash column chromatography gave the phosphine oxide [**22**; R^1 = $Ph(CH_2)_2$, R^2 = Me] (1.47 g, 20.1%, 80.3% based on recovered starting phosphine oxide).

4-*Diphenylphosphinoyl*-4-*methyl*-1-*phenylpentan*-3-*ol* (**21g**).—Butyl-lithium (3.0 ml, 1.5M in hexane), (1-methyl-3-phenylpropyl)diphenylphosphine oxide (1.5 g, 4.49 mmol), and acetaldehyde in dry THF (30 ml) gave the adduct as a crystalline mixture of diastereoisomers which was separated by flash column chromatography (elution with EtOAc). The first *diastereoisomer* to elute from the column was obtained as needles (HR_F isomer) (650 mg, 38.2%), m.p. 179—181 °C (from EtOAc–light petroleum, b.p. 60—80 °C) (Found: C, 75.9; H, 7.35; P, 8.0. M^+, 378.1763. $C_{24}H_{27}O_2P$ requires C, 76.1; H, 7.2; P, 8.2. *M*, 378.1749), R_F(EtOAc) 0.5, $\nu_{max.}$ 3 430 (OH),1 440 (P–Ph), and 1 180 cm^{-1} (P=O); $\delta_H(CDCl_3)$ 8.3—7.85 (4 H, m, Ph_2PO *ortho*-protons), 7.65—7.3 (6 H, m, Ph_2PO *meta*- and *para*-protons), 7.25—7.0 (3 H, m, ArH), 6.9—6.7 (2 H, m, ArH), 5.1 (1 H, br s, OH), 4.2 (1 H, m, $CHOH$), 2.7 (2 H, m, $PhCH_2$), 2.3—1.75 (2 H, m, remaining CH_2), and 1.3—1.0 (6 H, two overlapping doublets centred at *ca.* 1.15, J_{HMe} 6, J_{MeP} 17 Hz, 2 × Me); *m/z* 378 (4%), 243 [100%, $Ph_2PO(CH_2)_3^+$], 202 (33%, Ph_2POH), and 201 (26%, Ph_2PO^+). The second *diastereoisomer* eluted from the column was obtained as needles (LR_F isomer) 738 mg, 43.4%), m.p. 193—194 °C (from EtOAc–light petroleum, b.p. 60—80 °C) (Found: C, 75.9; H, 7.2; P, 8.2. M^+ 378.1763), R_F(EtOAc) 0.45, $\nu_{max.}$ 3 330 (OH), 1 440 (P–Ph), and 1 175 cm^{-1} (P=O); $\delta_H(CDCl_3)$ 8.15—7.8 (4 H, m, Ph_2PO *ortho*-protons), 7.6—7.35 (6 H, m, Ph_2PO *meta*- and *para*-protons), 7.25—7.05 (3 H, m, ArH), 7.0—6.8 (2 H, m, ArH), 4.5—4.1 (2 H, m, CHOH), 2.7—2.4 (2 H, m, $PhCH_2$), 2.2—1.6 (2 H, m, remaining CH_2), and 1.45—1.1 (6 H, two overlapping doublets at *ca.* 1.3 and 1.2, J_{HMe} *ca.* 7, J_{MeP} *ca.* 17 Hz, 2 × Me); *m/z* 378 (3%), 243 [100%, $Ph_2PO(CH_2)_3^+$], 202 (37%, Ph_2POH), and 201 (41%, Ph_2PO^+).

(Z)-3-*Methyl*-5-*phenylpent*-2-*ene*.—Sodium hydride (16 mg; 80% dispersion in oil, 0.529 mmol) was added in one portion to a stirred solution of the HR_F isomer of adduct (**21g**) (200 mg, 0.529 mmol) in dry DMF (15 ml). The clear reaction solution was warmed to 50 °C for 30 min before cooling and adding water (25 ml). The mixture was then diluted with brine (15 ml) and extracted with Et_2O (3 × 40 ml). The combined organic extracts were washed with water (3 × 40 ml), dried ($MgSO_4$), and the solvent evaporated under reduced pressure. Bulb-to-bulb distillation (Kugelrohr apparatus) gave the alkene as a colourless liquid (78 mg, 91.8%), $\nu_{max.}$ (liquid film) 1 610 and 1 500 (aryl), 1 455, 1 380, 750, and 700 cm^{-1}; $\delta_H(CCl_4)$ 7.1 (5 H, br s, Ph), 5.1 (1 H, q, *J* 7 Hz, =CH), 2.75—2.45 (2 H, m, $PhCH_2$), 2.35—2.1 (2 H, m, remaining CH_2), 1.65 (3 H, narrow m, CH=C*Me*), and 1.4 (3 H, broadened d, *J* 7 Hz, CH*Me*). Nuclear Overhauser experiments showed the product to be the *Z*-isomer. The *E*-isomer was not detected by g.l.c.

(E)-3-*Methyl*-5-*phenylpent*-2-*ene*. In the same way, the LR_F isomer of adduct (**21g**) (200 mg, 0.529 mmol) and sodium hydride (16 mg; 80% dispersion in oil, 0.529 mmol) gave, after distillation, the alkene as a colourless liquid (798 mg, 92.9%), $\nu_{max.}$ (liquid film) 1 605 and 1 500 (aryl), 1 455, 1 380, 750, and 700 cm^{-1}; $\delta_H(CCl_4)$ 7.1 (5 H, br s, Ph), 5.15 (1 H, q, *J* 7 Hz, =CH), 2.75—2.45 (2 H, m, $PhCH_2$), 2.34—2.05 (2 H, m, remaining CH_2), and 1.65—1.4 (total 6 H, s, at 1.55 overlain by d, *J ca.* 8 Hz, 2 × Me). Nuclear Overhauser experiments showed the product to be the *E*-isomer. The *Z*-isomer was not detected by g.l.c.

3-*Diphenylphosphinoyl*-3-*methyl*-5-*phenylpentan*-2-*one* (**26**).—Butyl-lithium (1.34 ml, 1.5M in hexane) was added from a syringe to a stirred solution of (1-methyl-3-phenylpropyl)diphenylphosphine oxide (670 mg, 2.0 mmol) in dry THF (20 ml) at 0 °C. After 30 min the dark red solution was cooled to − 60 °C and added dropwise, using a double-ended needle, to a stirred suspension of copper(I) iodide (382 mg, 2.0 mmol) in dry THF (20 ml) also at − 60 °C. After being stirred at − 35 °C for 2 h, the dark green reaction mixture was cooled to − 50 °C and freshly distilled acetyl chloride (157 mg, 2.0 mmol) was added dropwise from a syringe. The reaction solution was stirred a further 1.5 h and allowed to warm to room temperature overnight. Water (20 ml) was added to the pale yellow solution and the THF was evaporated under reduced pressure. The aqueous residue was stirred with brine (30 ml) and dichloromethane (50 ml), and filtered through Hyflo. The aqueous phase was separated and extracted with dichloromethane (3 × 50 ml); the combined organic phases were dried ($MgSO_4$) and evaporated to give the crude product. Purification by flash column chromatography (eluting with EtOAc) gave the *ketone* as needles (480 mg, 63.7%), m.p. 97—100 °C (from Et_2O–light petroleum, b.p. 60—80 °C) (Found: C, 76.7; H, 6.75; P, 8.2. M^+, 376.1581. $C_{24}H_{25}O_2P$ requires C, 76.5; H, 6.7; P, 8.2%. *M*, 376.1592), R_F(EtOAc) 0.5, $\nu_{max.}$ 1 700 (C=O), 1 440 (P–Ph), and 1 180 cm^{-1} (P=O); $\delta_H(CDCl_3)$ 8.05—7.0 (15 H, m, 3 × Ph), 2.85—2.35 (2 H, m, $PhCH_2$), 2.2 (3 H, s, COMe), 2.15—1.8 (2 H, m, remaining CH_2), and 1.5 (3 H, d, *J* 16 Hz, PCMe); *m/z* 377 (4%, *M* + 1), 376 (2%), 272 (30%, *M* − C_8H_8), and 201 (100%, Ph_2PO^+).

Reduction of 3-*Diphenylphosphinoyl*-3-*methyl*-5-*phenylpentan*-2-*one* (**26**).—Sodium borohydride (11 mg, 0.266 mmol)

reduction of the ketone (**26**) (100 mg, 0.266 mmol) gave the adduct as a mixture of diastereoisomers (99 mg, 98.0%). N.m.r. analysis showed the product was a 66:33 mixture of LR_F and HR_F adducts.

(4-*Methylpent*-3-*enyl*)*diphenylphosphine oxide* (**24**).—Butyllithium (25 ml, 1.5M in hexane) was added dropwise from a syringe to a stirred suspension of methyldiphenylphosphine oxide (8.0 g, 0.037 mol) in dry Et_2O (110 ml). After 30 min the pale yellow suspension was cooled to −78 °C and 1-bromo-3-methylbut-2-ene (5.5 g, 0.037 mol) in dry Et_2O (10 ml) was added dropwise. The reaction mixture was allowed to warm to 20 °C and water (120 ml) was added. The aqueous phase was separated and extracted with dichloromethane (3 × 100 ml). The combined organic extracts were dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. Purification by flash column chromatography (elution with EtOAc) gave two products; the first to be eluted from the column was the dialkylated product, 4-*methyl*-1-[(2-*methylbut*-2-*enyl*)*pent*-3-*enyl*]*diphenylphosphine oxide* (1.3 g, 10.0%), m.p. 130—131 °C (from Et_2O) (Found: C, 78.3; H, 8.35; P, 8.9. M^+, 352.1953. $C_{23}H_{29}OP$ requires C, 78.3; H, 8.3; P, 8.8%; *M*, 352.1956), R_F(EtOAc) 0.55, $\nu_{max.}$ 1 440 (P–Ph) and 1 180 cm^{-1} (P=O); $\delta_H(CDCl_3)$ 7.95—7.7 (4 H, m, Ph_2PO *ortho*-protons), 7.5—7.3 (5 H, m, Ph_2PO *meta*- and *para*-protons), 5.05 (2 H, m, 2 × =CH), 2.3 [5 H, m, $PCH(CH_2)_2$], 1.55 (5 H, s, 2 × Me), and 1.45 (6 H, s, 2 × Me); *m/z* 353 (5%, $M + 1$), 352 (15%), 283 (36%, $M - C_5H_9$), and 202 (100%, Ph_2POH). The second compound eluted from the column was the *phosphine oxide* (**21**) (7.1 g, 67.6%), m.p. 68—69 °C (from Et_2O–light petroleum, b.p. 40—60 °C) (Found: C, 76.2; H, 7.5; P, 10.9. M^+, 284.1340. $C_{18}H_{21}OP$ requires C, 76.0; H, 7.5; P, 10.9%. *M*, 284.1330), R_F(EtOAc) 0.45, $\nu_{max.}$ 1 445 (P–Ph) and 1 185 cm^{-1} (P=O); $\delta_H(CDCl_3)$ 7.85—7.3 (10 H, m, Ph_2PO), 5.1 (1 H, m, =CH), 2.3 (4 H, m, 2 × CH_2), 1.65 (3 H, s, Me), and 1.55 (3 H, s, Me); *m/z* 284 (39%), 215 (41%, $Ph_2POCH_2^+$), and 202 (100%, Ph_2POH).

Methyl 4-*Methylcyclohex*-3-*enyl Ketone* (**23**).[17]—Methyl vinyl ketone (20 g, 0.285 mol) isoprene (23.3 g, 0.342 mol) and anhydrous stannic chloride (13.4 g, 0.051 mol) in dry toluene (100 ml) gave, after distillation, a colourless liquid (29 g, b.p. 92 °C/20 mmHg) which was treated with semicarbazide hydrochloride and then hydrolysed by the method of Manjarrez, Rios, and Guzman.[46] Redistillation gave the ketone (**20**) as a colourless liquid (27.9 g, 70.8%), b.p. 91—92 °C/20 mmHg (lit.,[46] b.p. 45—47 °C/0.5 mmHg); R_F 0.8, $\nu_{max.}$ (liquid film) 1 710 (C=O) and 800 cm^{-1} (=C–H); $\delta_H(CDCl_3)$ 5.4 (1 H, m, =CH), 2.65—2.4 (1 H, m, ring CH), 2.25—1.9 (total 9 H, m overlain by s at 2.2, ring CH_2 and COMe), and 1.7 (3 H, br s, ring Me).

3-*Diphenylphosphinoyl*-2-(4-*methylcyclohex*-3-*enyl*)-6-*methylhept*-5-*en*-2-*ol* (**19i**).—Butyl-lithium (4.7 ml, 1.5M in hexane) was added dropwise from a syringe to a stirred solution of the phosphine oxide (**24**) (2.0 g, 7.037 mmol) in dry THF (30 ml) at 0 °C. After 30 min the dark red reaction solution was cooled to −78 °C (acetone–dry ice) and a solution of the ketone (**20**) (975 mg, 7.037 mmol) in dry THF (10 ml) was added from a syringe. The rate of addition was such that the internal solution temperature was maintained at −78 °C. The pale yellow solution was allowed to warm to room temperature (over *ca.* 2 h) and water (10 ml) was added. The THF was removed under reduced pressure and the aqueous residue was diluted with brine (30 ml) and extracted with dichloromethane (3 × 30 ml). The combined organic extracts were dried ($MgSO_4$) and evaporated to give the adduct (**19i**) as a mixture of diastereoisomers. Two pairs of diastereoisomers were separated by flash column chromatography (elution with EtOAc then acetone); the first pair of *diastereoisomers* (HR_F) eluted from the column was obtained as a white amorphous solid (1.6 g, 53.3%). A sample was recrystallised from EtOAc–light petroleum, b.p. 60—80 °C, to give the (2*RS*,3*SR*)-adduct as needles, m.p. 174—177 °C (Found: C, 76.6; H, 8.3; P, 7.7. M^+, 422.2373. $C_{27}H_{35}O_2P$ requires C, 76.6; H, 8.35; P, 7.3%. *M*, 422.2375), R_F(EtOAc) 0.6, $\nu_{max.}$ 3 470 (OH), 1 440 (P–Ph), and 1 170 cm^{-1} (P=O); $\delta_H(CDCl_3)$ 8.05—7.6 (4 H, m, Ph_2PO *ortho*-protons), 7.55—7.25 (6 H, m, Ph_2PO *meta*- and *para*-protons), 5.4 (1 H, m, ring =CH), 4.9 (1 H, br t, *J ca.* 6 Hz, remaining =CH), 4.3 (1 H, br s, OH), 2.85—2.4 (2 H, m, ring CH and PCH), 2.35—1.75 (8 H, m, 4 × CH_2), 1.6 and 1.55 (6 H, 2 × s, $=CHMe_2$), 1.15 (3 H, s, ring Me), and 1.05 (3 H, s, Me); *m/z* 423 (9%, $M + 1$), 422 (26%), 327 (68%, $M - C_7H_{11}$), and 202 (100%, Ph_2POH). The second pair of *diastereoisomers* (LR_F) eluted from the column was obtained as an impure oil (123 mg, 4.1%); R_F (EtOAc) 0.55; $\delta_H(CDCl_3)$ 7.95—7.3 (10 H, m, Ph_2PO), 5.4 (1 H, m, ring =CH), 5.3—4.85 (2 H, m, OH and remaining =CH), 2.6—1.85 (m, CH_2) and 1.8—1.2 (multiple singlets, Me) (Found: M^+, 422.2361); *m/z* 423 (4%, $M + 1$), 422 (11%), 307 (100), and 202 (40%, Ph_2POH).

(*Z*)-α-*Bisabolene* (**20i**).—Sodium hydride (14 mg; 80% dispersion in oil, 0.473 mmol) was added in one portion to a stirred solution of the HR_F pair of isomers of adduct (**24**) (200 mg, 0.473 mmol) in dry DMF (25 ml). The clear reaction solution was stirred at 70 °C for 1 h, cooled, and water (25 ml) was added. The mixture was diluted with brine (15 ml) and extracted with Et_2O (3 × 30 ml). The combined organic extracts were washed with water (3 × 30 ml), dried ($MgSO_4$) and the solvent evaporated under reduced pressure. Bulb-to-bulb distillation (Kugelrohr apparatus) gave (*Z*)-α-bisabolene (**19i**) as a colourless liquid (88 mg, 90.7%) possessing a green and flowery odour and giving an n.m.r. spectrum (400 MHz) identical to that described in the literature for the (*Z*)-isomer.[35] I.r. and g.l.c. (column 1) analysis showed the product to contain a trace of the ketone (**23**), but the (*E*)-isomer was not detected.

(*E*)-α-*Bisabolene* (**20i**).—Powdered potassium hydroxide (14 mg; 85% KOH, 0.206 mmol) was added in one portion to a stirred solution of the LR_F isomers of adduct (**19i**) (87 mg, 0.206 mmol) in dry DMSO (5 ml). The reaction solution was stirred for 1 h at 50 °C, cooled and water (10 ml) was added. The mixture was diluted with brine (10 ml) and extracted with Et_2O (3 × 15 ml). The combined organic extracts were washed with water (3 × 15 ml), dried ($MgSO_4$) and the solvent evaporated under reduced pressure. Bulb-to-bulb distillation (Kugelrohr apparatus) gave (*E*)-α-bisabolene as a colourless liquid (35 mg, 83.3%) possessing a woody-herbal odour and giving an n.m.r. spectrum (400 MHz) identical to that described in the literature for the (*E*)-isomer.[35] G.l.c. analysis (column 1) showed the product to contain a trace of the ketone (**23**), but the (*Z*)-isomer was not detected.

Acknowledgements

We thank the S.E.R.C. for grants, Glaxo Group Research (Ware) for CASE awards (to A. D. B. and N. G.), and Dr. Barry Price and Dr. Eric Collington for many helpful discussions.

References

1 L. Horner, H. Hoffmann, H.-G. Wippel, and G. Klahre, *Chem. Ber.*, 1959, **92**, 2499; L. Horner, H. Hoffmann, W. Klink, H. Ertel, and V. G. Toscano, *ibid.*, 1962, **95**, 581.
2 A. D. Buss and S. Warren, *J. Chem. Soc., Chem. Commun.*, 1981, 100; *Tetrahedron Lett.*, 1983, **24**, 3931.
3 A. D. Buss and S. Warren, *J. Chem. Soc., Perkin Trans. 1*, 1985, 2307.
4 A. D. Buss, R. Mason, and S. Warren, *Tetrahedron Lett.*, 1983, **24**, 5293.

5 H. M. Okely and M. F. Grundon, *J. Chem. Soc., Perkin Trans. 1*, 1981, 897.
6 E. Späth and J. Bruck, *Chem. Ber.*, 1938, **71**, 2708.
7 M. Jacobson, K. Ohinata, D. L. Chambers, W. A. Jones, and M. S. Fujimoto, *J. Med. Chem.*, 1973, **16**, 248; M. Jacobson, I. Keiser, D. L. Chambers, D. H. Miyashita, and C. Harding, *ibid.*, 1971, **14**, 236.
8 G. Jones, M. A. Acquadro, and M. A. Carmody, *J. Chem. Soc., Chem. Commun.*, 1975, 206.
9 A. G. Martinez and M. O. Ruiz, *Synthesis*, 1983, 663.
10 M. Schlosser, H. B. Tuong, and B. Schaub, *Tetrahedron Lett.*, 1985, **26**, 311.
11 R. S. Torr and S. Warren, *J. Chem. Soc. Pak.*, 1979, **1**, 15.
12 W. C. Still, M. Kahn, and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923.
13 R. Baker and D. A. Evans, *Annu. Rep. Prog. Chem., Sect. B, Org. Chem.*, 1975, **72**, 347; R. Baker and J. W. S. Bradshaw, *ibid.*, 1979, **76**, 404.
14 H. J. Bestmann, K. H. Koschatzky, W. Schätzke, J. Süss, and O. Vostrosvsky, *Liebigs Ann. Chem.*, 1981, 1705.
15 G. Ohloff, C. Vial, F. Näf, and M. Pawlak, *Helv. Chem. Acta*, 1977, **60**, 1161.
16 H. Yu, B. Zang, and X. Han, *Kunchong Zhishi*, 1983, **20**, 105 (*Chem. Abstr.*, 1983, **99**, 175425).
17 O. P. Vig, M. L. Sharma, M. Gakhar, and N. Malik, *Ind. J. Chem., Sect. B*, 1980, **19**, 755.
18 H. J. Bestmann and K. Li, *Tetrahedron Lett.*, 1981, **22**, 4941.
19 A. D. Buss, N. Greeves, D. Levin, P. Wallace, and S. Warren, *Tetrahedron Lett.*, 1984, **25**, 357.
20 D. J. Faulkner, *Synthesis*, 1971, 175.
21 C. H. Heathcock in 'The Total Synthesis of Natural Products,' ed. J. ApSimon, Wiley, New York, 1973, vol. 2, pp. 207—222; 1983, vol. 5, pp. 11—17.
22 A. Marfat, P. R. McGuirk, and P. Helquist, *J. Org. Chem.*, 1979, **44**, 3888; J. R. Normant and A. Alexakis, *Synthesis*, 1981, 841; G. Zweifel and J. A. Miller, *Org. React.*, 1984, **32**, 375.
23 N. Jabri, A. Alexakis, and J. R. Normant, *Tetrahedron Lett.*, 1981, **22**, 959.
24 H. Takei, H. Sugimura, M. Miura, and H. Okamura, *Chem. Lett.*, 1980, 1209.
25 J. E. McMurry and W. J. Scott, *Tetrahedron Lett.*, 1980, **21**, 4313.
26 T. Hayashi, Y. Katsuro, and M. Kumada, *Tetrahedron Lett.*, 1980, **21**, 3915.
27 H. J. Bestmann and A. Bomhard, *Angew. Chem., Int. Ed. Engl.*, 1982, **21**, 545.
28 C. Sreekumar, K. P. Darst, and W. C. Still, *J. Org. Chem.*, 1980, **45**, 4260.
29 Preliminary communication: A. D. Buss and S. Warren, *Tetrahedron Lett.*, 1983, **24**, 111.
30 J. I. Grayson and S. Warren, *J. Chem. Soc., Perkin Trans. 1*, 1977, 2263.
31 C. Earnshaw, C. J. Wallis, and S. Warren, *J. Chem. Soc., Perkin Trans. 1*, 1979, 3099.
32 D. J. Cavalla and S. Warren, *Tetrahedron Lett.*, 1982, **23**, 4505; 1983, **24**, 295.
33 C. A. Cornish and S. Warren, *J. Chem. Soc., Perkin Trans. 1*, 1985, 2585.
34 A. D. Buss, S. Warren, J. S. Leake, and G. H. Whitham, *J. Chem. Soc., Perkin Trans. 1*, 1983, 2215.
35 F. Delay and G. Ohloff, *Helv. Chim. Acta*, 1979, **62**, 369.
36 S. Warren, 'Organic Synthesis. The Disconnection Approach,' Wiley, Chichester, 1982, p. 348.
37 E. F. Lutz and G. M. Bailey, *J. Am. Chem. Soc.*, 1964, **86**, 3899.
38 H. Staudinger, W. Kreis, and W. Schilt, *Helv. Chim. Acta*, 1922, **5**, 743 (*Chem. Abstr.*, 1923, **17**, 2974).
39 A. H. Davidson and S. Warren, *J. Chem. Soc., Perkin Trans. 1*, 1976, 639.
40 A. H. Davidson, I. Fleming, J. I. Grayson, A. Pearce, R. L. Snowden, and S. Warren, *J. Chem. Soc., Perkin Trans. 1*, 1977, 550.
41 C. Earnshaw, J. I. Grayson, and S. Warren, *J. Chem. Soc., Perkin Trans. 1*, 1979, 1506.
42 C. Earnshaw, R. S. Torr, and S. Warren, *J. Chem. Soc., Perkin Trans. 1*, 1983, 2893.
43 V. Petrow, *J. Med. Chem.*, 1977, **20**, 781.
44 J. I. Grayson, H. K. Norrish, and S. Warren, *J. Chem. Soc., Perkin Trans. 1*, 1976, 2556.
45 J. R. Shutt and S. Trippett, *J. Chem. Soc. C*, 1969, 2038.
46 A. Manjarrez, T. Ríos, and A. Guzmán, *Tetrahedron*, 1964, **20**, 333.

Received 11*th September* 1986; *Paper* 6/1815