Tetrahedron Vol. 41, No. 18, pp. 3825 to 3836, 1985
Printed in Great Britain.

0040-4020/85 $3.00 + .00
Pergamon Press Ltd.

WITTIG AND HORNER-WITTIG COUPLING REACTIONS OF 2-SUBSTITUTED CYCLIC ETHERS AND THEIR APPLICATION TO SPIROKETAL SYNTHESIS

Steven V Ley*, Barry Lygo, Helen M. Organ and Anne Wonnacott.

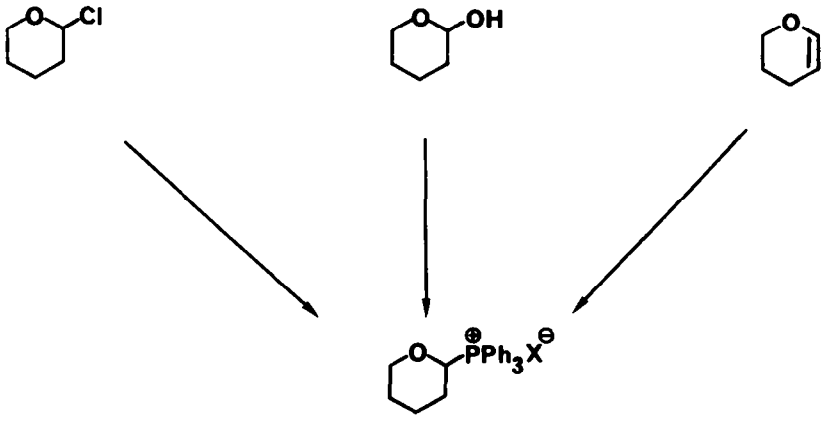
Department of Chemistry, Imperial College, London SW7 2AY, England.

(*Received in UK* 10 *April* 1985)

Abstract: Wittig and Horner-Wittig coupling reactions of tetrahydropyran or tetrahydrofuran 2-triphenylphosphonium salts or 2-diphenylphosphine oxides with aldehydes and lactols affords good yields of the corresponding enol ethers. In selected examples these enol ether products may be further converted to spiroketals some of which are natural pheromones derived from Dacus oleae and Paravespula vulgaris.

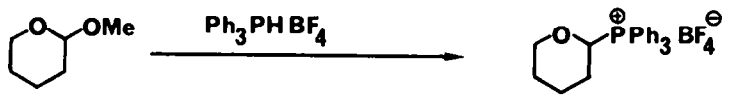
The preparation of enol ethers using Wittig related procedures is of course well known and is an important synthetic transformation.[1]
Remarkably however, the use of phosphoranes or diphenylphosphinoxy carbanions at the 2-position of cyclic ethers has not been exploited.[2]
In view of the developing interest, for natural product synthesis, in being able to form new carbon-carbon bonds at this position, we have undertaken a more detailed study of these potentially very versatile systems.[3,4]

The preparation of the initially required tetrahydro-2H-pyran-2-yl triphenylphosphonium salt (1) by reaction of PPh_3 with the corresponding anomeric chloride resulted in a poor chemical yield, probably due to the instability of the starting material. However this problem was overcome by using conditions which formed the anomeric chloride in situ, either by treating the lactol with PPh_3 in benzene with gaseous hydrogen chloride for 5 h which gave the salt in 85% yield, or alternatively by reacting 2,3-dihydropyran under the same conditions give the salt in 90% yield. (Scheme 1)



Scheme 1

Owing to the fact that the phosphonium chloride (1) could not be purified to acceptable microanalytical levels alternative methods to more stable salts were investigated. For example, when the same starting materials were subjected to gaseous hydrogen bromide under the previous conditions, the pure phosphonium salt (2) was obtained in 80% yield. Although the best procedure involved treating 2-methoxy tetrahydropyran with triphenylphosphonium tetrafluoroborate in acetonitrile for 4 h which gave the salt (3) in essentially quantitative yield. (Scheme 2) In this case compound (3) was easily purified by recrystallisation and appeared much more stable to heat than the corresponding chloride or bromide.



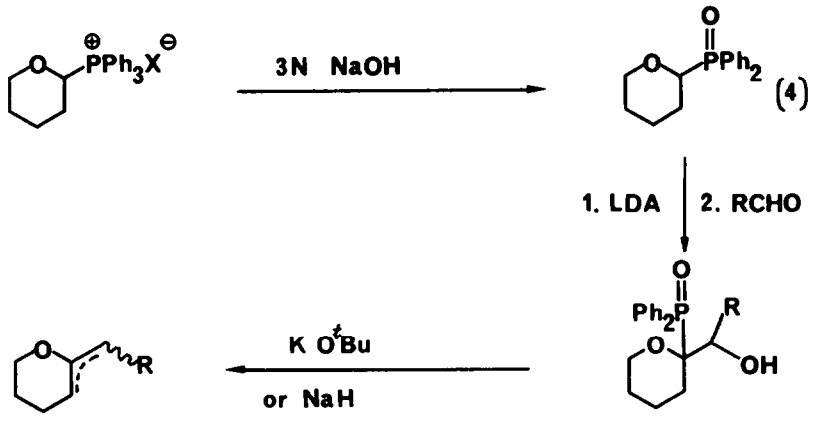
(3)

Scheme 2

The phosphonium chloride and bromide salts were readily deprotonated with n-butyllithium in THF at -10°C over 30 min to generate the deep red phosphorane although subsequent Wittig coupling reactions of the phosphorane with either aldehydes or lactols afforded only low yields of product (Table 1). This was probably due to other by-products being formed which were derived from ring opening of the tetrahydropyran unit. It is also possible that the reaction with n-butyllithium at -10°C leads to some decomposition of the salt. Attempts to improve the reaction by adding HMPA as a cosolvent were not successful. On the other hand results using the phosphonium tetrafluoroborate salt (3) where much better. Generation of the phosphorane by treating the salt (3) with n-butyllithium at -78°C and quenching with an aldehyde or lactol at this temperature, gave after work-up, the desired enol ethers in good yields (Table 1). Elimination of the triphenylphosphine oxide during these reactions was rapid as the mixture was warmed to room temperature and gave a mixture of three possible isomers (E, Z and endo) which were not separable by chromatography but could be identified by their NMR data.

Since it was known that phosphoranes with a β-oxygen substituent are thermally unstable and do not react particularly well in the Wittig reaction,[5] the use of phosphine oxide anions [Horner-Wittig couplings] have been recommended in some cases.[1c] This modification has also been applied to this work.

The triphenylphosphonium salt (1) was first converted to the corresponding diphenylphosphine oxide (4) by treatment with aqueous sodium hydroxide at reflux in 80% yield. Subsequent deprotonation of the diphenylphosphine oxide was achieved with lithium diisopropyl amide at -78°C, to form a deep red anion which reacted rapidly with the aldehyde or lactol. Treatment of the crude phosphine oxide adduct with either potassium t-butoxide in tetrahydrofuran at room temperature for 1 h or sodium hydride in dimethylformamide for 2 h at 50°C, resulted in the elimination of the diphenylphosphinic acid to give the coupled product again as a mixture of isomers (E, Z and endo) as in the previous Wittig method (Table 1) (Scheme 3).



Scheme 3

We have also studied the related Wittig and Horner-Wittig coupling reactions of the corresponding tetrahydrofuran derivatives. Treatment of 2,3-dihydrofuran with triphenylphosphine and gaseous hydrogen chloride gave the tetrahydrofuran-2-yl-triphenylphosphonium chloride (25) in 88% yield. As this salt could not be satisfactorily purified the deprotonation studies were not investigated. However, hydrolysis with aqueous sodium hydroxide at reflux gave the tetrahydrofuran- 2-yl diphenylphosphine oxide (26) in 82% yield. Deprotonation with lithium diisopropylamide at -78°C produced a deep red anion which could be quenched by various aldehydes and lactols. (Table 2)†

Other phosphine oxides were similarly studied, these included 5-methoxytetrahydrofuran-2-yl diphenylphosphine oxide, (27) prepared by adding chlorodiphenylphosphine to 2,5 dimethoxy tetrahydrofuran at 0°C in dichloromethane (67%) and 5-methoxy-tetrahydrofuran-2-yl diethoxy phosphine oxide (28) prepared by treating 2,5-methoxy tetrahydrofuran with diethylchloro-phosphite under the same conditions (48%).These salts carry additional functionality which could be usefully elaborated at a later stage in a synthetic scheme.

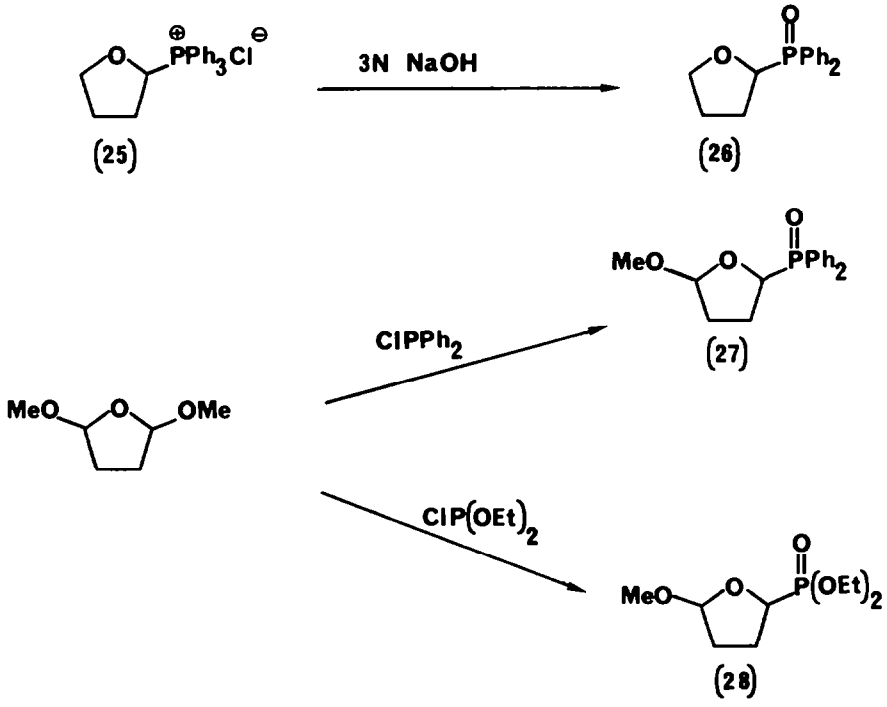
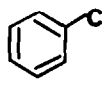
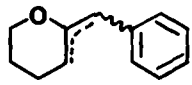
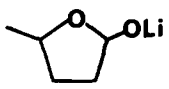
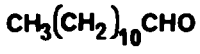
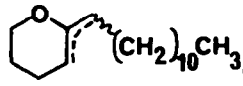
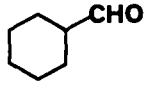
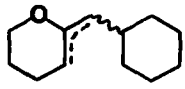
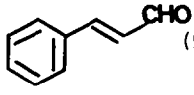
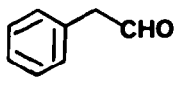
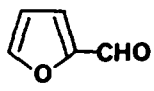
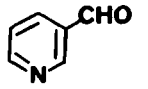
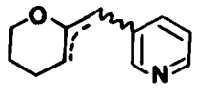
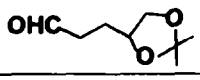
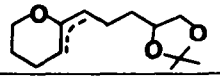
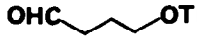
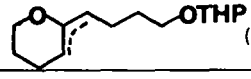
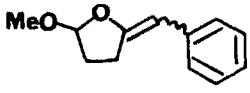


Table 1

Phosphonium salt/ Phosphine oxide	Aldehyde or Lactol	Product	Yield%
(1)	 (5)	 (15)	24*
(2)	(5)	(15)	31
(3)	(5)	(15)	79
(4)	(5)	(15)	76
(2)	 (6)	 (16)	12
(3)	(6)	(16)	33
(4)	(6)	(16)	59.5
(1)	 (7)	 (17)	0
(2)	(7)	(17)	0
(3)	(7)	(17)	40
(4)	(7)	(17)	71
(1)	 (8)	 (18)	0
(3)	(8)	(18)	53
(4)	(8)	(18)	68
(3)	 (9)	 (19)	0
(4)	(9)	(19)	78
(3)	 (10)	 (20)	0
(4)	(10)	(20)	68
(3)	 (11)	 (21)	60
(4)	(11)	(21)	41
(3)	 (12)	 (22)	41
(4)	(12)	(22)	64
(4)	 (13)	 (23)	65
(4)	 (14)	 (24)	62

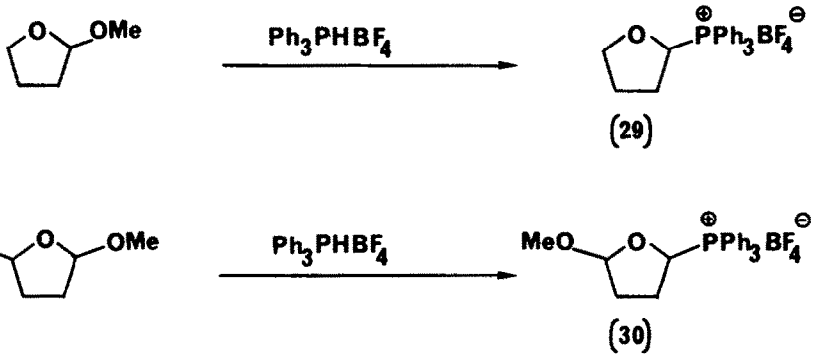
* All yields are of pure products, purified by Kugelrohr distillation

Table 2

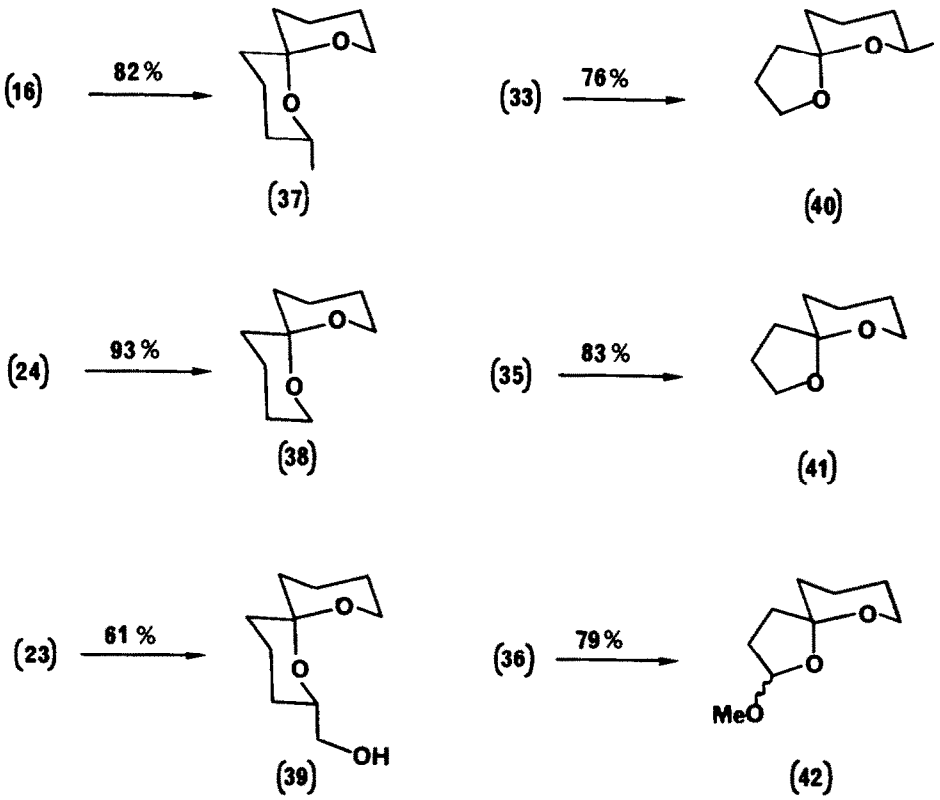
Phosphine oxide Phosphonium salt	Aldehyde or Lactol	Product	Yield%
(26)	(5)	 (31)	54
(29)	(5)	(31)	0
(27)	(5)	 (32)	60.5
(28)	(5)	(32)	51
(30)	(5)	(32)	0
(26)	(6)	 (33)	86
(27)	(6)	 (34)	0
(26)	(14)	 (35)	70
(29)	(14)	(35)	71
(27)	(14)	 (36)	37
(28)	(14)	(36)	32
(30)	(14)	(36)	65

As before the phosphine oxides were deprotonated at -78°C in THF using diisopropylamide and reacted with several aldehydes and lactols to give coupled products (Table 2). These enol ether products were extremely hydroscopic and are best used rapidly after preparation.

The phosphonium tetrafluoroborate salts (29) and (30) were also prepared and could be readily purified by recrystallisation. These salts too could be deprotonated and coupled to aldehydes and lactols to give a range of enol ether products. (Table 2) Attempted isolation of the enol ethers derived from condensation with benzaldehyde suggested that some ring opening of the tetrahydrofuran unit had also occurred.



A key objective behind the above study is that many of the enol ethers which have been prepared are useful precursors for spiroketal synthesis. The spiroketal functional group occurs in many natural products, ranging from simple insect pheromones to complex ionophore antibiotics. In the examples we have investigated the enol ethers (16) (24) (23) (33) (35) and (36) upon treatment with camphor sulphonic acid in methanol or dichloromethane gave excellent yields of the corresponding spirocyclic products (37)-(42) respectively.[6] The spiroketal (38) being identical to the natural pheromone derived from the olive fly Dacus oleae[7] while (40) was equivalent to the pheromone from the common wasp Paravespula vulgaris.[8] Enol ethers derived by these Wittig strategies should find many further applications in organic synthesis.



Experimental

^{1}H NMR spectra were obtained on Bruker WH-250, Jeol FX90Q and Varian EM-360A spectrometers in deuteriochloroform solutions with tetramethylsilane as internal standard. IR spectra were recorded on a Perkin-Elmer 983 G spectrophotometer as liquid films or chloroform solutions. Mass spectra were obtained on a VG Micromass 7070B instrument. Melting points were determined using a Kofler hot-stage apparatus and are uncorrected. Column chromatography was performed on MN-silica gel 60 230-400 mesh, under pressure. Light petroleum refers to the fraction boiling in the range 40°-60°C and ether to diethyl ether. Solutions were dried over anhydrous sodium sulphate, and solvents by standard methods.

Preparation of Tetrahydro-2-H-pyran-2-yl triphenyl phosphonium chloride (1) - (Method A)
2-Hydroxytetrahydropyran (128mg, 1.27mmol) was added dropwise to a solution of triphenylphosphine (334 mg, 1.27 mmol) in dry benzene (4 cm^3) at room temperature. Dry hydrogen chloride was bubbled through the solution for 3 h, and the solvent removed to give a white solid, which could be semi-purified from dichloromethane-ethyl acetate, to give tetrahydro-2H-pyran-2-yl triphenylphosphonium chloride (1) (413 mg, 85%) as a white amorphous solid, mp 113-116°C; IR ($CHCl_3$) 3369, 1439, 1113, and 691 cm^{-1}; NMR δ (90 MHz): 8.95 (3.5H, br. s, impurity), 8.00-7.55 (15H, m, Ar H), 6.15-5.85 (1H, m, H_2), 4.20-3.80 (2H, m, H_6), and 2.20-1.50 (6H, m); m/z (no M^+), 85.

Preparation of Tetrahydro-2H-pyran-2-yl triphenylphosphonium chloride (1) (Method B)
2,3-Dihydro-4H-pyran (40.0 g, 0.48 mol) was added dropwise to a solution of triphenylphosphine (120 g, 0.46 mol) in dry benzene (1l), and dry hydrogen chloride bubbled through the resulting solution at room temperature for 5 h. The solvent was removed under reduced pressure to give a solid, which could be semi-purified by recrystallisation from dichloromethane-ethyl acetate, to give tetrahydro-2H-pyran-2-yl triphenylphosphonium chloride (1) (158g, 90%) identical to the material prepared earlier.

Preparation of Tetrahydro-2H-pyran-2-yl triphenyl phosphonium bromide (2)
2,3-Dihydro-4H-pyran (27.0 g, 0.32 mol) was added dropwise to a solution of triphenylphosphine (83.8 g, 0.32 mol) in dry benzene (350 cm^3). Dry hydrogen bromide was bubbled through the resulting solution at room temperature for 5 h. The solvent was removed under reduced pressure and the product recrystallised from dichloromethane-ether to give tetrahydro-2H-pyran-2-yl triphenylphosphonium bromide (2) (109 g, 80%) as a white crystalline solid, mp 173-175°C; IR ($CHCl_3$) 3396, 1438, 1112, and 692 cm^{-1}; NMR δ (90 MHz): 8.15-7.60 (15H, m, ArH), 6.65-6.40 (1H, m, H_2), 4.40-3.90 (2H, m, H_6), and 2.50-1.40 (6H, m); m/z (FAB) 347 (M^+), 263, 85, 57 and 43. (Found: C, 64.44; H, 5.68; Br, 18.79; P, 6.83. $C_{23}H_{24}BrOP$ requires C, 64.65; H, 5.66; Br, 18.70; P, 7.25%).

General Procedure for the Wittig-Reaction of Tetrahydro-2H-pyran- 2-yl Triphenylphosphonium salts with aldehydes or lactols
The phosphonium salt was dissolved in dry THF at -10°C under argon. n-Butyllithium was added dropwise, the mixture stirred at -10°C for 30 min, then a THF solution of the aldehyde or lactol added and the solution warmed to room temperature. It was poured into saturated aqueous sodium chloride solution, and extracted with diethyl ether (3 X 10 cm^3). The ether extracts were dried and evaporated to give the crude adduct which was purified by Kugelrohr distillation.

Preparation of Enol Ethers (15).
To a solution of the anion of (1) (2.0 mmol) was added benzaldehyde (5) (0.204 cm^3, 2 mmol). Distillation after work up gave (15) (84 mg, 24%) as a mixture of three alkene isomers, bp. 110°C/0.3 mmHg; IR 2925, 1645, 1048, and 694 cm^{-1}; NMR δ (60 MHz): 7.60-6.93 (5H, m, ArH), 5.98 (0.5H, s, C=CHPh E isomer), 5.23 (0.25H, s, C=CHPh Z isomer), 4.41 (0.25H, t, J = 4Hz, C=CH endo), 3.87 (2H, m, OCH_2), 3.25 (0.5H, s, CH_2Ph endo), and 2.60-1.53 (5.5H, m). m/z 174 (M^+) 91, 90, 83 and 55 (Found: C, 82.66; H, 8.31; $C_{12}H_{14}O$ requires C, 82.72; H, 8.10%).

To a soluton of the anion of (2) (2.0 mmol) was added benzaldehyde (5) (0.204 cm^3, 2 mmol). Distillation after workup gave (15) (108 mg, 31%) identical to the material prepared above.

Preparation of Enol Ethers (16).
To a solution of the anion of (2) (2.0 mmol) was added the anion of 2-hydroxy 5-methyltetrahydrofuran (6) (0.204 g, 2.0 mmol) [generated from n-butyllithium at 0°C in THF] and after workup gave the adduct (16) (0.10 g, 12%) as a mixture of alkene isomers, bp 100°C/0.005 mmHg, IR 3400, 2928, 1625 and 1059 cm^{-1}; NMR δ (60 MHz): 4.87 (0.3H, t, J = 8Hz C=CH Z isomer), 4.42 (0.7H, t, J = 7 Hz, C=CH endo), 4.10-3.20 (3H, m) and 2.40-0.80 (14H, m); m/z 170 (M^+), 111, 98, 85 and 55, (Found M^+ 170.1305, $C_{10}H_{18}O_2$ requires 170.1307).

Preparation of Tetrahydro-2H-pyran-2-yl triphenylphosphonium tetrafluoroborate (3)
2-Methoxy tetrahydropyran (0.50 g, 4.3 mmol) was added dropwise to a solution of triphenylphosphonium tetrafluoroborate (1.50 g, 4.3 mmol) in dry acetonitrile (5 cm^3) at room temperature under argon, and stirred for 4 h. Removal of the solvent under reduced pressure gave tetrahydro-2H-pyran-2-yl triphenylphosphonium tetrafluoroborate (3), (1.87 g 100%) as a white crystalline solid, mp 171-173°C; IR ($CHCl_3$) 1321, 1056m and 690 cm^{-1}; NMR δ (90 MHz): 7.76 (15H, m, ArH), 5.61 (1H, m, H_2), 4.05 (2H, m, H_6), and 2.10-1.50 (6H, m): m/z (FAB) 347 (M^+), 263, 85 and 43 (Found: C, 63.51; H, 5.50; P, 7.57. $C_{23}H_{24}BF_4OP$ requires C, 63.62; H, 5.57; P, 7.13%).

General Procedure for the Wittig reaction of tetrahydro-2H-pyran- 2-yl triphenylphosphonium tetrafluoroborate (3) with aldehydes and lactols
The phosphonium salt (3) was suspended in dry THF at -78°C under argon, n-Butyllithium was added dropwise and the solution stirred at -78°C for 1 h, then the aldehyde or lactol in a THF solution added and the solution warmed to room temperature over 2 h, then poured into a saturated aqueous sodium chloride, and extracted with diethyl ether (3 x 10 cm^3). The ether extracts were dried and evaporated to give the crude adduct which was purified by Kugelrohr distillation.

Preparation of the Enol Ethers (15)
To a solution of the anion of (3) (0.87 g, 2 mmol) was added benzaldehyde (5) (0.204 cm^3, 2 mmol). Distillation gave (15) (280 mg, 79%) identical to that prepared above.

Preparation of the Enol Ethers (18)
To a solution of the anion of (3) (0.87 g, 2 mmol) was added cyclohexanecarboxaldehyde (8) (0.242 cm^3, 2.0 mmol). Distillation gave (18) (184 mg, 53%) as a mixture of three alkene isomers, bp 90°C/0.1 mmHg: IR 2925, 2850, 1676, 1067 and 1048 cm^{-1}; NMR δ (250 MHz): 4.74 (0.45 H, d, J = 9.8 Hz, C=CH E isomer), 4.41 (0.33 H, t J = 8.3 Hz, C=CH Z isomer), 4.05 (0.16 H, t, J = 6.25 Hz, C=CH endo), 3.85 (2H, m, OCH_2), 2.21 (0.32 H, m, CH_2 endo), 1.65-1.55 (6H, m), 1.36-1.12 (23 H, m), m/z 180 (M^+), 137, 96, 85, 83 and 55. (Found M^+ 180.1511, $C_{12}H_{20}O$ requires 180.1514).

Preparation of the Enol Ethers (17)
To a solution of the anion of (3) (0.87 g, 2 mmol) was added dodecanal (7) (0.442 cm^3, 2.0 mmol). Distillation gave (17) (203 mg, 40%) as a mixture of three alkene isomers, bp 120°C/0.1 mmHg; IR 2925, 2854, 1677, 1069 and 1047 cm^{-1}, NMR δ (250 MHz): 4.84 (0.5 H, t J = 8.3 Hz, C=CH E isomer), 4.41 (0.33H, t, J = 8.3 Hz, C=CH Z-isomer), 4.05 (0.16 H, t, J = 6.25 Hz, C=CH endo), 3.85 (2H, m, OCH_2), 2.21 (0.32 H, m, CH_2 endo) 1.65-1.55 (6H, m), 1.36-1.12 (23 H, m); m/z 252 (M^+), 167, 85 and 55. (Found M^+ 252.2448, $C_{17}H_{32}O$ requires 252.2453).

Preparation of Enol Ethers (21)
To a solution of the anion of (3) (0.87 g, 2.0 mmol) was added furfural (11) (0.166 cm^3, 2.0 mmol). Distillation gave (21) (203 mg 62%) as a mixture of three alkene isomers, bp 90°C/0.08 mmHg; IR 2943, 1663, 1493 and 1051 cm^{-1}, NMR δ (250 MHz): 7.35 (1H, m H_2), 6.32 (1H, m, H_4), 6.15 (1H, m, H_3), 5.85 (0.5 H, s, C=CH E-isomer), 5.45 (0.3 H, s, C=CH Z isomer), 4.60 (0.2 H, m, C=C endo), 4.0 (2H, m, OCH_2), 2.91 (0.4 H, m, CH_2 endo), 1.98-1.72 (5.6H, m); m/z 164 (M^+) 85, 81 and 55. (Found M^+ 164.0831. $C_{10}H_{12}O_2$ requires 164.0837).

Preparation of the Enol Ethers (22)
To a solution of the anion of (3) (0.87 g, 2.0 mmol) was added 3-Pyridinecarboxaldehyde (12) (0.188 cm^3, 2.0 mmol). Distillation gave (22) (140 mg, 41%) as a mixture of three alkene isomers, bp 90°C/0.03 mmHg: IR 2927, 1673, 1061 and 1047 cm^{-1}; NMR δ (250 MHz): 8.41 (1.6H, m, α-Pyr), 8.22 (0.4H, m, α-Pyr E-Isomer), 7.91 (0.4 H, dt, J = 10, 7.5 Hz, p-Pyr, E isomer), 7.48 (0.6 H, dt, J = 10, 7.5 Hz, p-Pyr endo iosmer), 7.1 (1H, m, m-Pyr), 5.23 (0.4 H, s, C=CH E isomer) 4.41 (0.6 H, t, J = 11 Hz, C=CH endo), 3.95-3.87 (2H, m, OCH_2), 3.2 (1.2 H, s, CH_2 endo), 2.3-1.72 (4.8 H, m); m/z 175 (M^+), 91,85 and 55 (Found M^+ 175.0994, $C_{11}H_{13}NO$ requires 175.0997).

Preparation of the Enol Ethers of (16)
To a solution of the anion of (3) (0.435 g, 1.0 mmol) was added the anion of 2-hydroxy-5-methyl-tetrahydrofuran [generated as previously]. The solution was stirred at room temperature for 5 h. Distillation gave (16) (56 mg, 33%) identical to that prepared earlier.

Preparation of Tetrahydro-2H-pyran-2-yl diphenyl phosphine oxide (4)
Phosphonium salt (1) (36.3 g, 94.9 mmol) was dissolved in 3N aqueous sodium hydroxide (180 cm^3, 540 mmol) and the resulting solution heated under reflux for 30 min. After cooling to room temperature, the mixture was extracted with chloroform (3 X 100 cm^3) and the organic extracts dried and evaporated, to give a solid which was recrystallised from dichloromethane--ethyl acetate to give tetrahydro- 2H-pyran-2-yl diphenylphosphine oxide (4) (23.0 g, 85%) as a white crystalline solid, mp 154°C, IR ($CHCl_3$) 2939, 1437, 1183 and 696 cm^{-1}; NMR δ (90 MHz): 8.10-7.70 (4H, m, ArH), 7.60-7.20 (6H, m, ArH), 4.40-3.90 (2H, m), 3.60-3.25 (1H, m) and 2.15-1.30 (6H, m): m/z (no M^+) 203, 202, 201, 155, 85, 77, and 47 (Found: C, 71.13; H, 6.70; P, 10.55; $C_{17}H_{19}O_2P$ requires C, 71.32; H, 6.69; P, 10.82%).

General Procedure for the Horner-Wittig Reaction of the Compound (4) with aldehydes and lactols
The phosphine oxide was dissolved in dry THF under argon and added to a stirred solution of lithium diisopropylamide [from diisopropylamine (1.1 eq.) and n-Butyllithium (1.1 eq.)] at -78°C in THF under argon. The anion was stirred for 1 h at -78°C, then a THF solution of the aldehyde or lactol was added and the solution warmed to room temperature. It was poured into saturated aqueous ammonium chloride solution, and extracted with chloroform (3 X 10 cm^3). The organic extracts were dried and evaporated to give the crude adduct. This was immediately dissolved in dry THF and a solution of potassium t-butoxide (1 eq) in THF added and stirred at room temperature for 1 h. The solvent was removed and the residue dissolved in dichloromethane, then extracted with diethylether, filtered through a celite pad and the solvent removed under reduced pressure to give the crude product which was purified by Kugelrohr distillation

Preparation of the Enol Ethers (15)
To a solution of the anion of (**4**) (1.40 g, 4.9 mmol) was added benzaldehyde (**5**) (0.50 cm^3 4.9 mmol). Distillation gave (**15**) (650 mg, 76%) identical to that prepared above.

Preparation of Enol Ethers (16)
To a solution of the anion of (**4**) (0.286 g, 1 mmol) was added the anion of 2-hydroxy, 5-methyl-tetrahydrofuran (**6**) (0.102 g, 1 mmol). Distillation gave the adduct (**16**) (101 mg, 59.5%), identical to that prepared above.

Preparation of Enol Ethers (17)
To a solution of the anion of (**4**) (0.286 g, 1 mmol) was added dodecanal (**7**) (0.221 cm^3, 1 mmol). Distillation gave the adduct (**17**) (178 mg, 71%) as above.

Preparation of Enol Ethers (18)
To a solution of the anion of (**4**) (0.286 g, 1 mmol) was added cyclohexane carboxaldehyde (0.121 cm^3, 1 mmol). Distillation gave (**18**) (122 mg, 68%) identical to that prepared above.

Preparation of Enol Ethers (19)
To a solution of the anion of (**4**) (0.286 g, 1mmol) was added cinnamylaldehyde (0.126 cm^3, 1 mmol). Distillation gave (**19**) (156 mg, 78%) as a mixture of six isomers, bp 130°C/0.08 mmHg; IR 2947, 1643, 1594, 1273 and 1044 cm^{-1}; NMR δ (250 MHz): 7.55-7.07 (5H, m, ArH), 6.72-6.58, 6.45-5.82, 5.25, 4.35 (3H, m, C=CH) 3.87-3.72 (2H, m, OCH_2), 2.56-2.22 and 1.87-1.54 (6H, m); m/z 200 (M^+), 116, 85, 77 and 55. (Found M^+ 200.1207, $C_{14}H_{16}O$ requires 200.1201).

Preparation of the Enol Ethers (20)
To a solution of the anion of (**4**) (0.286 g, 1 mmol) was added phenylacetaldehyde (**10**) (0.120 g, 1.0 mmol). Distillation gave (**20**) (127 mg, 68%) as a mixture of isomers, bp 60°C/0.005 mmHg; IR 2939, 2861, 1676, 1087 and 1045 cm^{-1}; NMR δ (250 MHz): 7.28-7.15 (5H, m, ArH), 5.15 (0.4 H, t J = 9.1 Hz, C=CH E-isomer), 4.65 (0.4 H, t, J = 9.1 Hz, C=CH Z isomer), 4.45 (0.2 H, m, C=CH endo), 3.85 (2H, m, OCH_2), 2.35-2.15 (2.4 H, m, $-CH_2-$ E, Z and endo isomer), 1.85-1.7 (5.6H, m). m/z 188 (M^+), 104, 97, 91 and 55. (Found M^+ 188.1203, $C_{13}H_{16}O$ requires 188.1201)

Preparation of the Enol Ethers (21)
To a solution of the anion of (**4**) (0.286 g, 1 mmol) was added furfural (**11**) (0.083 cm^3, 1 mmol). Distillation gave (**21**) (67 mg, 41%) as prepared before.

Preparation of the Enol Ethers (22)
To a solution of the anion of (**4**) (0.286 g, 1 mmol) was added 3-pyridinecarboxaldehyde (**12**) (0.094 cm^3, 1 mmol). Distillation gave (**22**) (112 mg, 64%) as prepared before.

Preparation of Enol Ether (23)
To a solution of the anion of (**4**) (0.36 g, 1.25 mmol) was added (**13**) (0.198 g, 1.25 mmol). Distillation gave (**23**) (183 mg, 65%). This was converted directly to the spiroketal (**39**).

Preparation of Enol Ether (24)
To a solution of the anion of (**4**) (1.40 g, 4.9 mmol) was added 1-[(tetrahydro-2H-pyran-2-yl)oxy]-butanal (**14**) (0.84 g, 4.9 mmol). Distillation gave 2-[4'-(tetrahydro-2H-pyran-2-yl)oxy butan]--5,6- dihydro-4H-pyran (**24**) (0.73 g, 62%), bp. 120°C/0.04 mmHg; IR 2938, 1675, 1114 and 1050 cm^{-1}; NMR δ (250 MHz): 4.59 (1H, br. s OCHO), 4.08 (1H, t, J = 6.5 Hz, C=CH), 3.91-3.71 (4H, m) 3.57-3.37 (2H, m), 2.42 (1H, br. t), and 1.99-1.25 (15 H, m); m/z 240 (M^+), 155, 101, 98, 85 and 55. (Found: C, 70.11; H, 10.17. $C_{14}H_{24}O_3$ requires C, 69.96, H, 10.07%).

Preparation of Tetrahydrofuran-2-yl triphenylphosphonium chloride (25)
2,3-Dihydrofuran (20.0 g, 0.29 mmol) was added dropwise to a solution of triphenylphosphine (74.9 g, 0.29 mmol) in dry benzene (300 cm^3). Dry hydrogen chloride was bubbled through the solution for 3 h at room temperature. The solvent was removed under reduced pressure to give a solid, which could be semi-purified by dissolving in dichloromethane and trituration of the solution with ethyl acetate giving tetrahydrofuran-2-yl triphenylphosphonium chloride (**25**) (94 g, 88%) as a white amorphous solid, IR ($CHCl_3$) 3358, 1438, 1113, and 691 cm^{-1}; NMR δ (90 MHz): 8.90-8.30 (1.5 H, br. s. impurity), 8.00-7.50 (15 H, m, ArH), 6.50-6.15 (1H, m, H_2), 4.15-3.85 (1H, m), 3.70-3.45 (1H, m), 3.30-2.70 (1H, m) and 2.50-1.40 (3H, m); m/z (no M^+), 71.

Preparation of Tetrahydrofuran-2-yl diphenylphosphine oxide (26)
The phosphonium salt (**25**) (10.0 g, 27.1 mmol) was dissolved in 3N aqueous sodium hydroxide solution (60 cm^3, 180 mmol) and the solution was heated at reflux for 30 min. After cooling to room temperature, the mixture was extracted with chloroform (3 X 50cm^3) and the organic layers dried and evaporated to leave a solid. Recrystallisation from dichloromethane-ethyl acetate gave tetrahydrofuran-2-yl diphenylphosphine oxide (**26**) (6.1 g, 82%) as a white amorphous solid, mp 115°C; IR ($CHCl_3$) 1437, 1120 and 697 cm^{-1}; NMR δ (90 MHz): 8.10-7.70 (4H, m, ArH), 7.60-7.20 (6H, m, ArH), 4.70 (1H, q, J = 7 Hz, H_2), 4.00-3.50 (2H, m) and 2.45-1.50 (4H, m); m/z (no M^+), 202, 155, 77, 71 and 43 (Found: C, 70.50; H, 6.31; P 11.30. $C_{16}H_{17}O_2P$ requires C, 70.56; H, 6.29; P, 11.38%).

Preparation of Tetrahydrofuran-2-yl triphenylphosphonium tetrafluoroborate (29)
2-Methoxytetrahydrofuran (0.51 g, 5 mmol) was added dropwise to a solution of triphenylphosphonium tetrafluoroborate (1.75 g, 5 mmol) in dry acetonitrile (10 cm^3) at room temperature under argon and stirred for 4 h. Removal of the solvent under reduced pressure gave tetrahydro-2H-furan-2-yl triphenylphosphonium tetrafluoroborate (**29**), (1.89, 88%) as a white crystalline solid, mp 130°C; IR ($CHCl_3$) 1438, 1287, 1052, 665 cm^{-1}; NMR δ (250 MHz): 7.85-7.6 (15 H, m ArH), 5.85 (1H, dt J = 11.5 Hz, H_2), 3.95 (1H, m, H_5), 3.55 (1H, m, H_5), 2.87 (1H, m), 2.18-1.95 (2H, m), 1.65 (1H, m) m/z (no M^+), 333, 71 (Found: C, 62.67; H, 5.37. $C_{22}H_{22}BF_4OP$ requires C, 62.88; H, 5.27).

Preparation of 5-methoxy tetrahydrofuran-2-yl diphenylphosphine oxide (27)
Chlorodiphenylphosphine (1.795 cm^3, 10 mmol) was added dropwise to a solution of 2,5-dimethoxytetrahydrofuran (1.295 cm^3, 10 mmol) at 0°C in dry dichloromethane (3 cm^3) under argon. The reaction was left to warm to room temperature and stirred for 12 h. The solvent was removed under reduced pressure to give an oil which could be purified by dissolving in toluene and trituration of the solution with petroleum ether giving 5-methoxy tetrahydrofuran-2-yl diphenylphosphine oxide (**27**) (2.02 g, 67%) as a white amorphous solid, mp. 98°C IR ($CHCl_3$) 2862, 1442, 1298 cm^{-1}; NMR δ (250 MHz): 7.85 (4H, m ArH), 7.50 (6H, m, ArH), 5.05 (1H, d, J = 6.25 Hz H_5), 4.9 (1H, br. q, J = 8.3 Hz H_2), 3.35 and 3.10 (3H, s, OCH_3), 2.5-1.5 (4H, m); m/z 302 (M^+) 202, 101. (Found: C, 67.27; H, 6.26. $C_{17}H_{19}O_3P$ requires C, 67.54; H, 6.26%).

Preparation of 5-methoxy tetrahydrofuran-2-yl diethoxyphosphine oxide (28)
Diethylchlorophosphite (0.714 ml, 5 mmol) was added dropwise to a stirred solution of 2,5-dimethoxytetrahydrofuran (0.65 ml, 5 mmol) at 0°C in dichloromethane under argon. The solution was stirred for 12 h at room temperature, concentrated and purified by Kugelrohr distillation to give (**28**) (0.475 g, 48%) as a colourless oil, bp 120°C/0.03 mmHg. IR 2862, 1252 and 1032 cm^{-1}; NMR δ (250 MHz):5.1 (1H, dd, J = 4.2 Hz, 16.6 Hz H_5), 4.3-4.2 (5H, m, $-OCH_2$, H_2) 3.3 (3H, d J = 4.2 Hz OCH_3), 2.3-1.9 (4H, m), 1.3 (6H, t, J = 6.94 Hz, $-CH_3$). m/z 237 (M^+), 207, 138, and 101. (Found: C, 45.41; H, 7.97; $C_9H_{18}O_5P$ requires C, 45.57; H, 7.65).

Preparation of 5-Methoxy-tetrahydro-2H-furan-2-yl triphenylphosphonium tetrafluoroborate (30)

2,5-dimethoxy tetrahydrofuran (0.648 cm^3 5 mmol) was added to triphenylphosphonium tetrafluoroborate (1.75 g, 5 mmol) in dry acetonitrile (10 cm^3) at room temperature under argon and stirred for 4 h. Removal of the solvent under reduced pressure gave 5-methoxy-tetrahydro-2H-furan-2-yl triphenylphosphonium tetrafluoroborate (**30**) (1.57 g, 68%) as a white amorphous solid mp 50°C; IR ($CHCl_3$) 2839, 1438, 1286, 1063, 665 cm^{-1}; NMR δ (250 MHz): 7.85-7.6 (15H, m, ArH), 6.05-5.85 (1H, m, H_2), 5.05 (1H, m, H_5) 3.35 (1.5H, s, OCH_3), 2.30-1.75 (4H, m). m/z (no M^+) 363, 101. (Found: C, 61.35; H, 5.43%. $C_{23}H_{24}BF_4O_2P$ requires C, 61.35; H, 5.37%).

Following the general Horner-Wittig procedure the following enol ethers were prepared.

Preparation of Enol Ethers (31)
To a solution of the anion of (**26**) (0.271 g, 1 mmol) was added benzaldehyde (0.102 cm^3, 1 mmol) stirring the resulting solution for 15 h at room temperature. Distillation gave (**31**) (86.5 mg, 54%) as a mixture of alkene isomers, bp: 80°C/0.02 mmHg, IR 3023, 2926, 1672, 1595, 1077 and 1028 cm^{-1}; NMR δ (250 MHz): 7.55-7.20 (5H, m, ArH), 5.23 (0.33 H, s, E or Z isomer), 4.65 (0.67, m, endo), 3.90- 3.75 (2H, m, OCH_2), 2.05-1.70 (4H, m); m/z 160 (M^+), 91, 77, and 71. (Found M^+ 160.0887, $C_{11}H_{12}O$ requires 160.0888).

Preparation of Enol Ethers (32)
To a solution of the anion of (**27**) (0.302 g, 1 mmol) was added benzaldehyde (0.102 cm^3, 1 mmol) and stirred for 15 h at room temperature. Distillation gave (**32**) (115 mg, 60.5%) as a mixture of alkene isomers, bp: 90°C/0.02 mmHg; IR 3383, 2926, 1674, 1599, 1025 and 695 cm^{-1}; NMR δ 7.55-7.20 (5H, m, ArH), 5.30 (0.5H, s, C=CH E or Z isomer), 4.72 (0.5H, s, C=CH endo), 4.41 (1H, m, $OCHOCH_2$), 3.35 (3H, s, OCH_3), 2.0-1.65 (4H, m); m/z 190 (M^+), 159, 91, 77 and 71. (Found: M^+ 190.1002, $C_{12}H_{14}O_2$ requires 190.0994).

Preparation of Enol Ethers (32)
To a solution of the anion of (**28**) (0.237 g, 1 mmol) was added benzaldehyde (0.102 cm^3, 1 mmol) and stirred for 15 h at room temperature. Distillation gave (**32**) (98 mg, 51%) as prepared previously.

In the following examples the enol ether was prepared following the general Wittig-Horner procedure and the crude product cyclised directly to the spiroketal.

Preparation of Enol Ether (33)
To a solution of the anion of (**26**) (3.09 g, 11.4 mmol) was added the anion of (**6**) (1.16 g, 11.4 mmol) and the reaction stirred over 15 h. Distillation gave (**33**) (1.53 g, 86%).

Preparation of Enol Ethers (35)
To a solution of the anion of (**26**) (0.271 g, 1 mmol) was added (**13**) (0.172 g, 1 mmol) and the reaction stirred over 15 h. Distillation gave (**35**) (159 mg, 70.3%) bp. 80°C/0.02 mmHg.

Preparation of Enol Ethers (36)
To a solution of the anion of (**27**) (0.302 g, 1 mmol) was added (**13**) (0.172 g, 1 mmol) and the reaction stirred over 15 h. Distillation gave (**36**) (96 mg, 37%) bp. 90°C/0.02 mmHg.

Preparation of Enol Ethers (36)
To a solution of the anion of (**28**) (0.237 g, 1 mmol) was added (**13**) (0.172 g, 1 mmol) and the reaction stirred over 15 h. Distillation gave (**36**) (83 mg, 32%) as prepared above.

Following the general procedure for Wittig type reactions.

Preparation of Enol Ethers (35)
To a solution of the anion of (**29**) (0.420 g, 1 mmol) was added (**13**) (0.172 g, 1 mmol) and the reaction stirred over 6 h. Distillation gave (**35**) (161 mg, 71%) as a mixture of ring open and ring closed products.

Preparation of Enol Ethers (36)
To a solution of the anion of (**30**) (0.69 g, 1.53 mmol) was added (**13**) (0.263 g, 1.53 mmol). Distillation gave (**36**) (166 mg, 65%) as a mixture of ring open and ring closed products.

Preparation of 2-Methyl-1,7-dioxaspiro[5,5]undecane (37)
The compound (**16**) (138 mg, 0.81 mmol) was dissolved in dry dichloromethane (2 cm^3) containing camphor sulphonic acid (2 mg), and the resulting solution stirred overnight. After passing through a silica pad (to remove the CSA), the solvent was evaporated to give 2-methyl-1,7--dioxaspiro[5,5]undecane (**37**) (113 mg, 82%). IR 2932 and 1058 cm^{-1}. NMR δ (90 MHz): 3.8-3.55 (3H, m, OCH_2), 1.92-1.35 (12 H, m), 1.15 (3H, d J = 6.3 Hz, CH_3) m/z 170 (M^+), 101, 85. (Found: M^+ 170.1303, $C_{10}H_{18}O_2$ requires 170.1307).

Preparation of 1,7-Dioxaspiro[5,5]undecane (38)
Compound (**24**) (0.49 g, 2.0 mmol) was dissolved in dry methanol (3 cm^3) with camphor sulphonic acid (2 mg), and the solution stirred at room temperature for 5 h. Removal of the solvent under reduced pressure followed by Kugelrohr distillation of the crude product gave 1,7-dioxaspiro[5,5]undecane (**38**) (0.29 g, 93%) as a colourless oil, bp 100°C at 28 mmHg, IR 2940, 1171, 1045 and 984 cm^{-1}; NMR δ (250 MHz): 3.77-3.55 (4H, m, OCH_2), 1.95-1.73 (2H, m) and 1.68-1.36 (10H, m); m/z 156 (M^+), 101, 100, 98, 83, 55 and 41 and was identical to the natural product.

E-2-Hydroxymethyl-1,7-dioxaspiro[5.5]undecane (39)
The enol ether (**23**) (0.14 g, 0.65 mmol) was added to a solution of CSA (2 mg) in methanol and stirred at room temperature for 6 h. The residue was purified by chromatography to give (**39**) (70 mg, 61%) as a colourless oil; IR 3430, 2930, 1045 and 990 cm^{-1}; NMR δ (250 MHz): 3.82-3.47 (5H, m), 2.21 (1H, br s. OH) 1.99-1.74 (2H, m), and 1.69-1.18 (10H, m); m/z 186 (M^+), 155, 111, 101 and 55 (Found: C, 64.49; H, 9.68; $C_{10}H_{18}O_3$ requires C, 64.34; H, 9.94).

(E)-7-methyl-1,6-dioxaspiro[4,5]decane (40)
The enol ether (**33**) (1.53 g, 9.8 mmol) was dissolved in dry dichloromethane containing CSA (5 mg) and stirred at room temperature for 5 h. Removal of solvent and Kugelrohr distillation gave (**40**) (1.16 g, 76%) as a colourless oil; IR 2940 and 1050 cm^{-1}; NMR δ (250 MHz): 3.92-3.60 (3H, m), 2.07-1.21 (10H, m) and 1.11 (3H, d, J = 6.3 Hz Me); m/z 156 (M^+), 141 and 97, which was identical with the natural product.

1,6-dioxaspiro[4.5]decane (41)
The enol ether (**35**) (159 mg, 0.70 mmol) was dissolved in dry dichloromethane containing CSA and stirred overnight. Removal of solvent and purification by chromatography gave (**41**) (83 mg, 83%) as a pale yellow oil; IR 2940, 1079 and 1035 cm^{-1}, NMR δ (250 MHz): 3.95-3.35 (4H, m, OCH_2), 2.05-1.45 (10H, m). m/z 142 (M^+) 85, 71 and 55. (Found: M^+ 142.0996 $C_8H_{14}O_4$ requires 142.0994).

(E)-2-methoxy,1,6-dioxaspiro[4.5]decane (42)
The enol ether (**36**) (96 mg, 0.375 mmol) was dissolved in dry dichloromethane containg CSA and stirred overnight. Purification by chromatography gave (**42**) (51 mg, 79%) as a colourless oil; IR 2927, 1452, 1369 and 1065 cm^{-1}; NMR δ (250 MHz): 4.50 (1H, m, OCH OCH_3), 3.95-3.55 (2H, m, OCH_2), 3.35 (3H, s, OCH_3), 1.95-1.45 (10H, m); m/z 172 (M^+), 141, 101, 85 and 71. (Found M^+ 172.1094, $C_9H_{16}O_3$ requires 172.1099).

Achnowledgement

We thank the SERC, Pfizer Central Research (CASE award to HMO); and the Wolfson Foundation for financial support and Dr. Bernard Banks (Pfizer U.K.) for useful discussions.

Footnotes

The enol ethers generated are labile and rapidly add water to give hemiethers, consequently they should be used soon after preparation.

References

1. (a) 'Organophosphorous Reagents in Organic Synthesis', Edited by J.I.G. Cadogan, Academic Press, 1979.
   (b) A. van der Gen, A.V. Henzen and T.A.M. van Schaik, Tetrahedron Lett., 1983, 24, 1303.
   (c) S. Warren, C. Earnshaw and C.J. Wallis, J. Chem. Soc., Perkin I, 1979, 3099.
   (d) E. Zbiral, Tetrahedron Lett., 1965, 20, 1483.
   (e) C. Reichardt and E. Würthwein, Synthesis, 1973, 604.
   (f) S.G. Levine, J. Am. Chem. Soc., 1958, 80, 6150.
   (g) G. Wittig and E. Knauss, Angew Chem., 1959, 71, 127.
   (h) D.R. Coulson, Tetrahedron Lett., 1964, 45, 3323.
   (i) E.J. Corey and M.A. Tius, Tetrahedron Lett., 1980, 21, 3535.
   (j) A.F. Kluge and I.S. Cloudsdale, J. Org. Chem., 1979, 44, 4847.
   (k) H. Schulde, Tetrahedron, 1975, 31, 89.
   (l) A.F. Kluge, Tetrahedron Lett., 1978, 39, 3629.
   (m) M. Schlosser and H.B. Tuong, Chimia, 1976, 30, 197.
2. (a) A. Miller, Mehran Maleki and O.W. Lever Jr., Tetrahedron Lett., 1981, 22, 365.
   (b) H. Gross, G. Engelhardt, J. Freiberg, W. Bürger and B. Costisella, Ann., 1967, 707, 35.
   (c) C.G. Kruse, E.K. Poels and A. van der Gen, J. Org. Chem., 1979, 44, 2911.
3. S.V. Ley and B. Lygo, Tetrahedron Lett., 1984, 25, 113; J. Godoy, S.V. Ley and B. Lygo, J. Chem. Soc., Chem. Commun., 1984, 1381.
4. J.R. Falck, C. Mioskowski, J.B. Ousset and Y.-L. Yang, Tetrahedron Lett., 1984, 25, 5903.
5. G. Lavielle and D. Reisdorf, Compt. rend., 1971, 272C, 100, G. Wittig, W. Boll and K.-H. Kruck, Chem. Ber., 1962, 95, 2514.
6. P. Deslongchamps, 'Stereoelectronic Effects in Organic Chemistry', Pergamon Press, Oxford, 1983.
7. R. Baker, R.H. Herbert and A.H. Parton, J. Chem. Soc., Chem. Commun., 1982, 601.
8. W. Francke, G. Hindorf and W. Reith, Angew. Chem. Int. Ed. Engl., 1978, 17, 862.