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STUDIES IN MARINE CEMBRANOLIDE SYNTHESIS: A SYNTHESIS OF 2,3,5-TRISUBSTITUTED FURAN INTERMEDIATES FOR LOPHOTOXIN AND PUKALIDE

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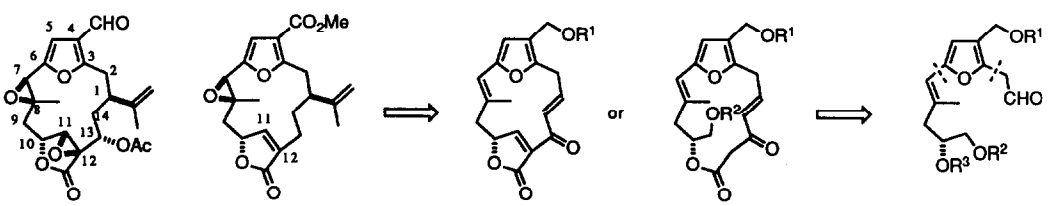
Summary: Pd(0)-catalysed coupling between various furyl zinc or tin compounds and vinyl iodides is demonstrated to be a versatile method for the synthesis of 2,3-dialkyl-5-alkenylfurans like **3**, as potential precursors of the ring system of lophotoxin and pukalide. A possible cyclisation substrate was successfully prepared by glycol cleavage, **21** → **24**, when alcohol oxidation failed.

Lophotoxin, isolated from several species of the Pacific sea whip *Lophogorgia*,[1] is a potent neurotoxin that irreversibly blocks nicotinic acetylcholinergic neurotransmission in autonomic ganglia causing paralysis and asphyxiation.[2] Together with close structural analogues,[3] it offers considerable potential as a selective neuropharmacological probe for characterising the nicotinic acetylcholine receptor.[2] Lophotoxin shares the same furanocembranolide skeleton and stereochemical features as the structurally simpler marine diterpenoids pukalide[4] and 11β,12β-epoxypukalide,[5] although the absolute configuration remains uncertain. Little is known about the chemistry[1] and conformational preferences of these tricyclic systems and only a limited amount of synthetic work has been reported.[6,7] Their high level of oxygenation and the close proximity of sensitive functional groups provide a significant synthetic challenge.

Scheme 1



In our approach, we propose to rely on macrocyclic stereocontrol[8] in addition reactions at C_1, C_7, C_8, C_{11}, and C_{12} to the basic ring system, as outlined in the retrosynthetic analysis in **Scheme 1**. This strategy is much simpler and more flexible than an alternative approach involving the careful construction and coupling of enantiomerically pure segments. Firstly, these ring systems will have few low energy conformations due to the

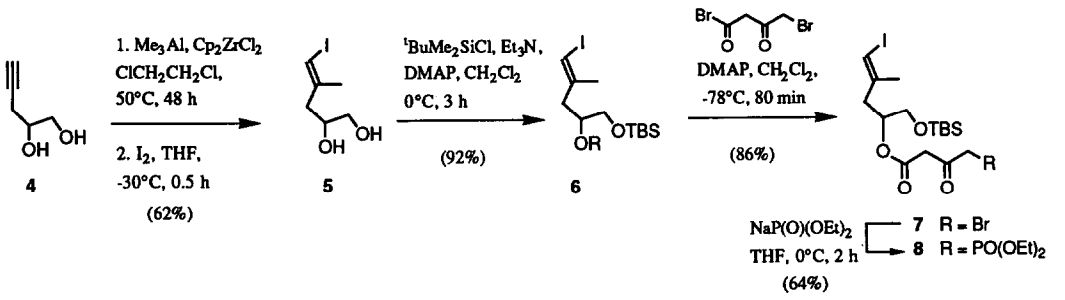
rigidity imparted by the furan, γ-lactone, and double bond(s), such that highly stereoselective reactions are likely. Secondly, the introduction of sensitive functionality, like the epoxide groups, is postponed to the closing stages of the synthesis. If we remove the epoxides at $C_{7,8}$ and $C_{11,12}$ and consider the acetoxy group at C_{13} to arise from reduction of a ketone and the isopropenyl group at C_1 to come from a conjugate addition reaction, we get back to **1** (or **2**) as a possible common synthetic intermediate for lophotoxin, 11β,12β-epoxypukalide and pukalide.

We now report our results for the construction of 2,3,5-trisubstituted furans like **3**, as potential precursors of the required ring system, by elaboration of 3-furanmethanol.

Results and Discussion

We first prepared the vinyl iodide **5** in racemic form starting from the adduct **4** of lithium acetylide and glycidol (**Scheme 2**). For an enantioselective synthesis, the use of (*R*)- or (*S*)-glycidol[9] should provide a single enantiomer of **5**. Carbometallation[10] by trimethylaluminium of the alkyne **4**, in the presence of zirconocene dichloride (0.2 equiv.) in 1,2-dichloroethane (50°C, 48 h), was followed by iodination of the intermediate vinyl alane to give the iodide **5** in 62% yield. The primary hydroxyl group was then selectively protected as its *tert*-butyldimethylsilyl ether to give **6**, R = H. It was found to be important to carry out these two reactions in this order, as the carbometallation step is very sluggish and gives only low yields (≤30%) on **4** when various ether protecting groups are attached (*e.g.* TBS, Bn, or ^{t}BuPh$_2$Si). Similar difficulties have been described by Tius.[7c] Acylation of the secondary hydroxyl group of **5** gave the esters **6**, R = Ac (Ac_2O, DMAP, CH_2Cl_2; 99%) and R = $COCH_2COMe$ (diketene, DMAP, Et_2O; 71%),[11] as model substrates for the subsequent Pd(0) coupling reactions. A more elaborate intermediate, the β-ketophosphonate **8**, was obtained *via* **7** by acylation of **6**, R = H, with the bromine adduct of diketene followed by bromide displacement with sodium diethylphosphite.

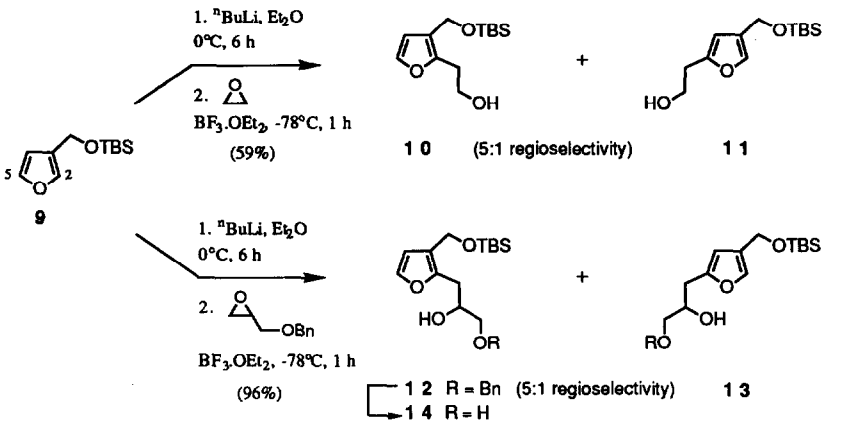
Scheme 2



To prepare a suitable 2,3-disubstituted furan substrate for the coupling reactions, the regioselective lithiation and alkylation of hydroxyl protected 3-furanmethanol was examined (**Scheme 3**). Using the *tert*-butyldimethylsilyl ether derivative **9** and *n*-butyl lithium (Et_2O, 20°C, 6 h), we obtained 5:1 regioselectivity for substitution at the 2 over the 5 position of the furan in boron trifluoride etherate promoted epoxide opening reactions. Using epoxides as electrophiles, we were unable to obtain the very high regioselectivity which has been reported for lithiation/silylation of **9**.[12] In this way, we prepared the alcohol **10** from ethylene oxide, as well as the

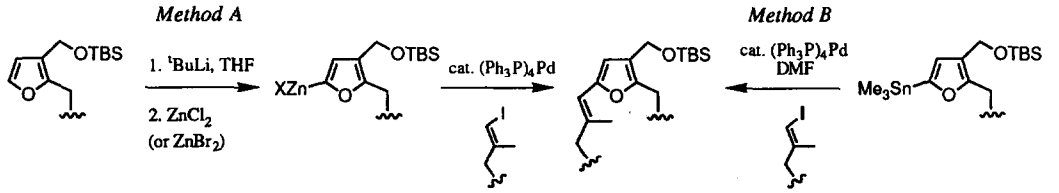
diol **14** after debenzylation (Li, NH_3, THF, -78°C, 2 min; 72%) of the benzylglycidol adduct **12**. If the Lewis acid was omitted the regioselectivity dropped (**10**:**11**, **12**:**13** = *ca* 2:1) and the yield was much poorer.

Scheme 3



We anticipated that a Pd(0)-catalysed coupling reaction between a furyl zinc intermediate and a vinyl iodide, *i.e.* method A in **Scheme 4**, would provide a useful entry into the required 2,3,5-trisubstituted furan systems for lophotoxin and pukalide.[7c,13,14] Alternatively, the Pd(0)-catalysed coupling of the corresponding furyl stannane compound and a vinyl iodide, *i.e.* method B, might also be useful.[15] In practice, both proved to be effective, as shown by the results in the **Table**. In method A, the furan substrate (**10**, **14**, or **15**) was first lithiated in THF by addition of an appropriate number of equivalents of *tert*-butyl lithium (1.2-3.6 equiv.; -78°C, 1 h), then transmetallated by addition of zinc halide (1.2-3.6 equiv.; -78 → 20°C, 0.5 h), followed by slow addition to a THF solution of the appropriate vinyl iodide (**6**, R = Ac, or **8**) containing $(Ph_3P)_4Pd$ (2-4 mol%). In method B, the furyl stannane substrate (**16** or **17**) and the vinyl iodide (**6**, R = $COCH_2COMe$, or **18**) were stirred together with $(Ph_3P)_4Pd$ (8 mol %) in dry DMF at 20°C under argon for 16 h.

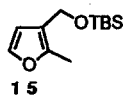
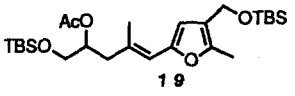
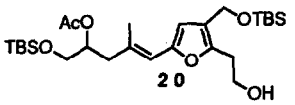
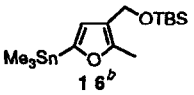
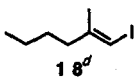
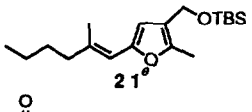
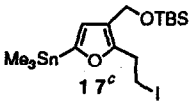
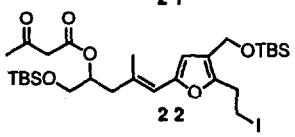
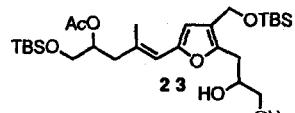
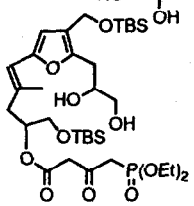
Scheme 4



Method A is effective in coupling di- and trimetallated derivatives of hydroxylated furans (entries 2, 5, and 6) with various vinyl iodides, even including those with relatively acidic hydrogens as in **8**. This led to the formation of the 2,3,5-trisubstituted furans **19**, **20**, **23**, and **24** in 46-89% yield. In two cases, we prepared the 5-

furyl stannane derivatives, **16** and **17**, by quenching an intermediate organolithium with trimethylstannyl chloride. The corresponding Pd(0)-catalysed reaction with a vinyl iodide (entries 3 and 4) then led to the coupled products **21** and **22** in 58 and 35% yield, respectively.

Table $(Ph_3P)_4Pd$ catalysed coupling reactions for the synthesis of 2,3-dialkyl-5-alkenyl furans.

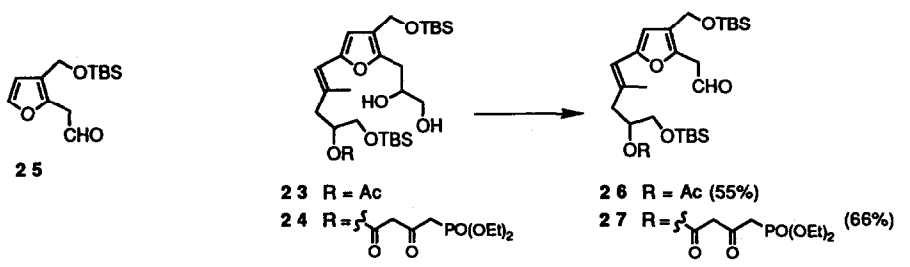
entry	furan	vinyl iodide	method	coupled product	yield[a]
1	 **15**	**6**, R = Ac	*A*	 **19**	79%
2	**10**	**6**, R = Ac	*A*	 **20**	89%
3	 **16**[b]	 **18**[d]	*B*	 **21**[e]	58%
4	 **17**[c]	6, R = $COCH_2COMe$	*B*	 **22**	35%
5	**14**	**6**, R = Ac	*A*	 **23**	57%
6	**14**	**8**	*A*	 **24**	46%

[a] Isolated yield based on vinyl iodide; the furan component was generally used in excess. [b] Prepared from **15** (^tBuLi, THF, -78→0°C, 3 h; Me_3SnCl; 85%). [c] Prepared from **10** (i. ^tBuLi, THF, -78→0°C, 3 h; Me_3SnCl. ii. TsCl, Et_3N, DMAP, CH_2Cl_2. iii. NaI, Me_2CO). [d] Prepared from 1-hexyne (ref. 11). [e] The *bis*-furan dimer from self-coupling of **16** was also isolated in 34% yield.

Our strategy for further elaboration of these highly substituted furans required access to an aldehyde at C_1 (lophotoxin numbering). With the simple furyl alcohol **10**, oxidation was only successful to any extent with a few reagents (PCC, PDC, or (i) NCS, PhSMe; (ii) Et_3N) and none of these gave >50% yield of the aldehyde **25** (**Scheme 5**). However, when these conditions were applied to the more substituted (and more acid-labile) furyl alcohol **20**, the oxidation reaction now failed to give any of aldehyde **26** at all. Fortunately, this problem was easily circumvented by periodate oxidative cleavage of the corresponding glycol, such that **25** was obtained in a much improved yield (90%) from **14** (H_5IO_6, Et_2O, 0°C, 20 min). Moreover, the glycol cleavage reactions **23** → **26**

(H_5IO_6, Et_2O, 0°C, 1 h; 55%) and **24** → **27** ($NaIO_4$, aq. MeOH, 20°C, 10 min; 66%) were also performed in reasonable yield.

Scheme 5



In conclusion, we find that Pd(0)-catalysed coupling is a versatile method for introducing the 5-alkenyl sidechain and that periodate glycol cleavage is a mild and effective method for obtaining the 2-formylmethyl sidechain in **3**. The macrocyclisation of some of these 2,3,5-trisubstituted furans, *e.g.* **22** and **27**, to set up the carbon skeleton of lophotoxin and pukalide is under study.

Experimental

NMR spectra were recorded on the following instruments: 400 (^1H) and 100.6 (^{13}C) MHz, Bruker WH400; 250 (^1H) and 63 (^{13}C) MHz, Bruker WM250. IR spectra were recorded on either a Perkin Elmer 297 or 1310 spectrophotometer. High resolution mass spectra were recorded on an AEI MS30, MS50 or MS90 instrument using electron impact (EI) or fast atom bombardment (FAB), or chemical ionisation (CI). Starting materials and reagents were used as supplied (Aldrich), unless otherwise stated. Dichloromethane, 1,2-dichloroethane, DMF, and triethylamine were distilled from calcium hydride; tetrahydrofuran THF was distilled from sodium wire/benzophenone; diethyl ether was distilled from lithium aluminium hydride.

(*E*)-1-Iodo-2-methyl-4-pentene-1,2-diol (5). To a stirred solution of zirconocene dichloride (0.235 g, 0.80 mmol) in dry 1,2-dichloroethane (5 ml) under argon was added a 2.0 M solution of trimethylaluminium in hexanes (2.71 ml, 5.42 mmol). A solution of 4-propyne-1,2-diol (0.181 g, 1.81 mmol) in dry 1,2-dichloroethane (2 ml) was added and the solution stirred at 50°C for 48 h. The reaction mixture was cooled to -35°C and a solution of iodine (0.713 g, 2.81 mmol) in dry THF (2 ml) was added over 10 min. After a further 30 min, the reaction mixture was poured into a saturated solution of sodium potassium tartrate (5 ml) and hexane (30 ml), stirred for 5 min and then extracted with ethyl acetate. The separated aqueous layer was saturated with sodium chloride and further extracted with ethyl acetate, the combined organic extracts were dried (Na_2SO_4) and evaporated *in vacuo*. Flash chromatography (EtOAc) gave* the diol **5** (0.254 g, 62%) as a colourless oil; R_f (MeOH-CH_2Cl_2, 1:9) 0.35; υ_{max} (film) 3 400, 3 060, 1 615; ^1H NMR δ ($CDCl_3$, 250 MHz) 6.01 (1H, s, CIH=C), 3.82 (1H, m, C*H*OH), 3.59 (1H, dd, *J*=11.3, 2.5 Hz, CH_aH_bOH), 3.39 (1H, dd, *J*=11.3, 7.1 Hz, CH_aH_bOH), 3.25 (2H, br s, OH), 2.39 (1H, dd, *J*=14.0, 7.4 Hz, CH_aH_b), 2.28 (1H, dd, *J*=14.0, 4.3 Hz, CH_aH_b), 1.86 (3H, br s, $C=CCH_3$); ^{13}C NMR δ ($CDCl_3$, 62.9 MHz) 144.2, 77.2, 69.5, 66.1, 43.2, 24.1; HRMS (EI) M^+ 241.9794, $C_6H_{11}IO_2$ requires 241.9804; m/e (EI) 242, 115, 61, 55. (*a 5% yield of 4-methyl-4-pentene-1,2-diol was also isolated)

(*E*)-5-Iodo-4-methyl-1-(t-butyldimethylsiloxy)-4-penten-2-ol (6, R = H). To a solution of DMAP (0.052 g, 0.426 mmol, 0.16 mmol) and triethylamine (1.5 ml, 10.78 mmol) in dry dichloromethane (25 ml), at 0°C under argon, was added a solution of **5** (0.660 g, 2.73 mmol) in dichloromethane (2 ml) and then a solution of t-butyldimethylsilyl chloride (0.682

g, 4.53 mmol). After stirring for 16 h, the reaction mixture was forced through a plug of silica with dichloromethane, and evaporated *in vacuo*. Flash chromatography (CH_2Cl_2) gave **6**, R = H, (0.820 g, 84%) as a colourless oil; R_f (CH_2Cl_2) 0.4; υ_{max} ($CHCl_3$) 3 560; ^1H NMR δ (250 MHz, $CDCl_3$) 5.97 (1H, s, ICH=C), 3.77 (2H, br m, CHOH), 3.56 (1H, dd, *J*=3.8, 10.2 Hz, OCH_aH_b), 2.32 (2H, d, *J*=6.5 Hz, CH_2), 1.86 (3H, s, $C=CCH_3$), 0.87 (9H, s, $C(CH_3)_3$), 0.05 (6H, s, $Si(CH_3)_2$); ^{13}C NMR δ (62.9 MHz, $CDCl_3$) 144.6, 76.9, 69.6, 66.4, 43.0, 25.8, 24.2, 18.2, -5.4; HRMS (CI) $(M+NH_4)^+$ 374.10197, $C_{12}H_{25}IO_2Si + NH_4$ requires 374.10110; m/e (EI) 281, 117.

(*E*)-1-Iodo-2-methyl-5-(t-butyldimethylsiloxy)-1-penten-4-yl acetate (6, R = Ac). To a solution of DMAP (0.91 g, 7.46 mmol) and **6**, R = H, (0.964 g, 2.708 mmol) in dry dichloromethane (30 ml) at 0°C was added acetic anhydride (0.30 ml, 3.18 mmol). After 80 min, the reaction mixture was poured into saturated ammonium chloride solution (30 ml) and extracted with dichloromethane. The combined organic extracts were dried ($MgSO_4$) and evaporated *in vacuo*. Flash chromatography (CH_2Cl_2) gave **6**, R = Ac, (1.067 g, 99%) as a colourless oil; R_f (CH_2Cl_2) 0.60; υ_{max} ($CHCl_3$) 1 735; ^1H NMR δ (250 MHz, $CDCl_3$) 5.97 (1H, s, CIH=C), 4.99 (1H, m, *CH*OAc), 3.60 (2H, d, *J*=6.0 Hz, CH_2O), 2.47 (2H, m, CH_2), 2.02 (3H, s, CH_3CO_2), 1.93 (3H, s, $C=CCH_3$), 0.88 (9H, s, $C(CH_3)_3$), 0.04 (6H, s, $Si(CH_3)_2$); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 170.3, 143.7, 77.6, 71.8, 63.7, 40.4, 25.8, 24.0, 21.1, 16.2, -5.4; HRMS (FAB, 3-nitrobenzyl alcohol) M^+ 399.0848, $C_{14}H_{28}IO_3Si$ requires 399.0848; m/e (EI) 341, 281, 207, 128, 117.

(*E*)-1-Iodo-2-methyl-5-(t-butyldimethylsiloxy)-1-penten-4-yl 3-oxo-1-butanoate (6, R = $COCH_2COMe$). To a stirred solution of the vinyl iodide **6**, R = H, (0.539 g, 1.514 mmol) and freshly distilled diketene (0.13 ml, 1.66 mmol) in dry ether (20 ml), at -23°C under argon, was added a solution of DMAP (0.003 g, 0.025 mmol) in ether (1 ml). After 16 h, the reaction mixture was forced through a plug of silica with dichloromethane, and evaporated *in vacuo*. Flash chromatography (CH_2Cl_2-hexane, 1:1) gave **6** , R = $COCH_2COMe$ (0.470 g, 71%) as a colourless oil; R_f (CH_2Cl_2-hexane, 1:1) 0.25; υ_{max} ($CHCl_3$) 3 400, 1 740, 1 700, 1 620; ^1H NMR δ (250 MHz, $CDCl_3$) 5.97 (1H, br s, CIH=C), 5.05 (1H, m, CHO), 3.60 (2H, d, *J*=4.9 Hz, CH_2O), 3.38 (2H, s, $C(O)CH_2C(O)$), 2.46 (2H, m, CH_2), 2.23 (3H, s, $C(O)CH_3$), 1.84 (3H, s, $C=CCH_3$), 0.85 (9H, s, $C(CH_3)_3$), 0.02 (6H, s, $Si(CH_3)_2$); ^{13}C NMR δ (100 MHz, $CDCl_3$) 200.1, 166.4, 143.3, 77.9, 72.8, 63.5, 50.1, 40.2, 30.0, 25.7, 23.9, 18.1, -5.5; HRMS (FAB, 3-nitrobenzyl alcohol) M^++H 441.0988, $C_{16}H_{30}IO_4Si$+H requires 441.0968; m/e (EI) 383, 281, 207, 59.

(*E*)-1-Iodo-2-methyl-5-(t-butyldimethylsiloxy)-1-propen-4-yl-4-bromo-3-oxo-1-butanoate (7). To a stirred solution of diketene (0.17 ml, 2.17 mmol) in dry carbon tetrachloride (5 ml), at 0°C under argon, was added bromine (0.11 ml, 2.14 mmol). After 15 min, this mixture was added to a stirred solution of DMAP (0.100 g, 0.82 mmol) and the vinyl iodide **6**, R = H, (0.186 g, 0.522 mmol) in dry dichloromethane (10 ml) at -78°C. After 1 h, a further amount of DMAP (0.100 g, 0.82 mmol) was added. After 20 min, the reaction mixture was poured into a saturated solution of ammonium chloride (20 ml) and extracted with dichloromethane. The combined organic extracts were dried ($MgSO_4$) and evaporated *in vacuo*. Flash chromatography (CH_2Cl_2) gave **7** (0.232 g, 86%) as a colourless oil; R_f (CH_2Cl_2) 0.70; υ_{max} ($CHCl_3$) 1 735, 1 710; ^1H NMR δ (250 MHz, $CDCl_3$) 11.89 (< 1H, s, enol OH), 5.99 (1H, s, CIH=C), 5.24 (< 1H, s, enol form C=CH), rest of enol form signals ignored, 5.08 (1H, m, CHO), 4.03 (2H, s, CH_2Br), 3.66 (2H, s, $C(O)CH_2C(O)$), 3.63 (2H, d, *J*=4.9 Hz, CH_2O), 2.49 (2H, m, CH_2), 1.86 (3H, s, $C=CCH_3$), 0.87 (9H, s, $C(CH_3)_3$), 0.04 (6H, s, $Si(CH_3)_2$); ^{13}C NMR δ (100 MHz, $CDCl_3$) 194.2, 165.9, 143.3, 78.1, 73.3, 63.5, 46.0, 40.2, 33.8, 25.7, 23.9, 18.2, -5.5; HRMS (FAB, 3-nitrobenzyl alcohol) M^++H 519.0116, $C_{16}H_{28}BrIO_4Si$+H requires 519.0066; m/e (EI) 463, 461, 383, 299, 239, 237, 195, 193, 117.

(*E*)-1-Iodo-2-methyl-5-(t-butyldimethylsilyloxy)-1-penten-4-yl 3-oxo-4-(diethoxyphosphinyl)-1-butanoate (8). To a stirred solution of **7** (0.220 g, 0.424 mmol) in dry THF, at 0°C under argon, was added a 0.52 M solution of sodium diethyl phosphite (2.5 ml, 1.30 mmol) in THF (made by heating diethyl phosphite and 2 equiv of sodium metal in THF under reflux for 2 h.). After 2 h, the reaction mixture was poured into a saturated solution of ammonium chloride (20 ml) and extracted with ether. The combined organic extracts were dried ($MgSO_4$) and evaporated *in vacuo*. Flash chromatography (CH_2Cl_2-MeOH, 97:3) gave **8** (0.157 g, 64%) as a colourless oil; R_f (EtOAc) 0.6; υ_{max} ($CHCl_3$) 1 740, 1 720, 1 620, 1 250; ^1H NMR δ (250 MHz, $CDCl_3$) 12.10 (< 1H, s, enol OH), rest of enol form signals ignored, 5.98 (1H, s, CIH=C), 5.03 (1H, m, CHO), 4.14 (4H, m, OCH_2CH_3), 3.63 (2H, s, $C(O)CH_2C(O)$), 3.62 (2H, m, CH_2O), 3.23 (2H, d, *J*=22.7 Hz, CH_2P), 2.49 (2H, m, CH_2CH), 1.85 (3H, s, $C=CCH_3$), 1.32 (6H, t, *J*=7.0 Hz, OCH_2CH_3), 0.86 (9H, s, $C(CH_3)_3$), 0.03 (6H, s, $Si(CH_3)_2$); ^{13}C NMR δ (100 MHz, $CDCl_3$) 194.1, 166.1, 143.4, 78.0, 73.1, 63.4, 62.8, 49.7, 42.6 (d, *J*=126.7 Hz, CH_2P),

40.2, 25.8, 24.0, 18.2, 16.3, -5.5; HRMS (FAB, 3-nitrobenzyl alcohol) M^++H 577.1256, $C_{20}H_{38}IO_7PSi$+H requires 577.1249; m/e (EI) 519, 221.

2-[3-(t-Butyldimethylsiloxymethyl)-2-furanyl]-1-ethanol (10). To a stirred solution of **9** (0.205 g, 0.967 mmol) in dry ether (10 ml), at room temperature under argon, was added a 1.6 M solution of n-butyllithium in hexanes (0.65 ml, 1.04 mmol). After 6 h, the reaction mixture was cooled to -78°C and ethylene oxide (0.060 ml, 1.203 mmol) was added using a cooled syringe, followed by boron trifluoride etherate (0.13 ml, 1.09 mmol). After 1 h, the reaction mixture was poured into ammonium chloride solution (20 ml) and extracted with ether. The combined organic extracts were dried ($MgSO_4$) and evaporated *in vacuo*. Flash chromatography (CH_2Cl_2-MeOH, 99:1) gave returned starting material **9** (0.037 g, 18%), **10** (0.100 g, 40%) and the isomeric product **11** (0.021 g, 8%); the combined yield of **10** and **11** was 58% allowing for recovered **9**. **10** had R_f (CH_2Cl_2) 0.1; υ_{max} (film) 3 660, 3 400; ^{1}H NMR δ (250 MHz, $CDCl_3$) 7.26 (1H, d, *J*=1.9 Hz, OC*H*=CH), 6.30 (1H, d, *J*=1.9 Hz, OCH=C*H*), 4.51 (2H, s, C=CCH_2O), 3.79 (2H, t, *J*=5.8 Hz, OCH_2CH_2), 2.90 (2H, t, *J*=5.8 Hz, OCH_2CH_2), 2.2 (1H, br s, OH), 0.90 (9H, s, C(CH_3)$_3$), 0.09 (6H, s, Si(CH_3)$_2$); ^{13}C NMR δ (100 MHz, $CDCl_3$) 149.6, 140.6, 120.5, 111.1, 60.8, 56.8, 30.0, 25.7, 18.2, -5.4; HRMS (CI) M+NH_4^+ 274.18384, $C_{13}H_{24}O_3Si$+NH_4 requires 274.18384; m/e (EI) 199, 169. When the reaction was carried out in the absence of BF_3.OEt_2 at 0°C for 16 h, the product composition was **10** (33%) and **11** (15%), with recovered **9** (17%).

1-Benzyloxy-3-[3-(t-butyldimethylsiloxymethyl)-2-furanyl]-2-propanol (12). To a stirred solution of **9** (0.443 g, 2.09 mmol) in dry ether (20 ml), at room temperature under argon, was added a 1.6 M solution of n-butyllithium in hexanes (1.5 ml, 2.40 mmol). After 6 h, a solution of **25** (0.439 g, 2.68 mmol) was added at -78°C, followed by boron trifluoride etherate (0.34 ml, 2.76 mmol). After 1 h, the reaction mixture was poured into ammonium chloride solution (20 ml) and extracted with ether. The combined organic extracts were dried ($MgSO_4$) and evaporated *in vacuo*. Flash chromatography (EtOAc-pet ether 30-40, 1:4) gave returned starting material **9** (0.222 g, 50%), **12** (0.312 g, 40%) and the isomeric product **13** (0.065 g, 8%); the combined yield of **12** and **13** was 96% allowing for recovered **9**. **12** had R_f (EtOAc-pet ether 30/40, 1:4) 0.3; υ_{max} ($CHCl_3$) 3 450, 3 600, 1 100; ^{1}H NMR δ (250 MHz, $CDCl_3$) 7.36-7.28 (5H, m, C_6H_5), 7.27 (1H, d, *J*=1.8 Hz, OC*H*=CH), 6.32 (1H, d, *J*=1.8 Hz, OCH=C*H*), 4.56 (2H, s, CH_2Ph), 4.53 (2H, s, OC=CCH_2O), 4.05 (1H, br s, OH), 3.47-3.43 (3H, m, C*H*(OH)CH_2O), 2.94-2.79 (2H, m, C*H*OH), 0.91 (9H, s, C(CH_3)$_3$), 0.10 (6H, s, Si(CH_3)$_2$); ^{13}C NMR δ (100 MHz, $CDCl_3$) 148.5, 140.8, 138.0, 128.3, 127.7, 127.6, 121.0, 111.1, 73.5, 73.3, 69.2, 57.0, 31.0, 25.9, 18.3, -5.5; HRMS (EI) M^+ 376.2064 $C_{21}H_{32}O_4Si$ requires 376.2070; m/e (EI) 376, 319, 91. When the reaction was carried out in the absence of boron trifluoride diethyl etherate at 0°C for 16 h, the product composition was **12** (23%) and **13** (13%), with recovered **9** (55%).

3-[3-(t-Butyldimethylsiloxymethyl)-2-furanyl]-1,2-propanediol (14). To a mixture of liquid ammonia (50 ml) and dry THF (50 ml), at -78°C under argon, was added lithium shot (0.948 g, 135 mmol). After stirring vigorously for 3 h, a solution of **12** (4.43 g, 11.78 mmol) in THF (5 ml) was added, followed after 2 min by the addition of solid triethylamine hydrochloride until the dark blue colour dissipated. The reaction mixture was then allowed to warm up and the ammonia boiled off. Water (100 ml) and ether (200 ml) were then added and the separated aqueous layer was extracted with ether. The combined organic extracts were dried ($MgSO_4$) and evaporated *in vacuo*. Flash chromatography (CH_2Cl_2-Et_2O, 7:3) gave **14** (2.429 g, 72%) as a colourless oil; R_f (CH_2Cl_2-Et_2O, 7:3) 0.25; υ_{max} ($CHCl_3$) 3 600, 3 450, 1 080; ^{1}H NMR δ (250 MHz, $CDCl_3$) 7.23 (1H, d, *J*=1.9 Hz, OC*H*=CH), 6.25 (1H, d, *J*=1.9 Hz, OCH=C*H*), 4.48 (2H, s, OCH=CCH_2O), 3.88 (1H, m, C*H*OH), 3.53 (1H, dd, *J*=11.4, 3.5 Hz, C$H_a$$H_b$OH), 3.39 (1H, dd, *J*=11.4, 6.0 Hz, C$H_a$$H_b$OH), 3.30 (2H, br s, OH), 2.81 (2H, d, *J*=6.3 Hz, ArCH_2CHOH), 0.87 (9H, s, C(CH_3)$_3$), 0.07 (6H, s, Si(CH_3)$_2$); ^{13}C NMR δ (100 MHz, $CDCl_3$) 149.1, 140.9, 120.6, 111.2, 70.7, 65.5, 57.1, 30.6, 25.9, 16.4, -5.2; HRMS (EI) M^+ 286.1607 $C_{14}H_{26}O_4Si$ requires 286.1600; m/e (EI) 286, 285, 268, 229, 211, 155, 154, 137, 117.

2-Methyl-3-(t-butyldimethylsiloxymethyl)-5-(trimethylstannyl)-furan (16). To a stirred solution of the furan **15** (0.165 g, 0.730 mmol) in dry THF (10 ml), at -78°C under argon, was added a 1.7 M solution of t-butyllithium (0.5 ml, 0.85 mmol). After 3 h, the reaction mixture was warmed to room temperature for 20 min. After recooling to -78°C, a solution of trimethyltin chloride (0.173 g, 0.868 mmol) in THF was added. After warming to room temperature, the reaction mixture was quickly forced through a short column of silica with dichloromethane (*NB* protodestannylation occurs on prolonged contact with silica gel) and evaporated *in vacuo* to give **16** (0.243 g, 85%) as a colourless oil; υ_{max} ($CHCl_3$) 1 620; ^{1}H NMR δ (250 MHz, $CDCl_3$) 6.50 (1H, s, C=CH), 4.50 (2H, s, CH_2O), 2.29 (3H, s, C=CCH_3), 0.92 (9H, s,

$C(CH_3)_3$), 0.29 (9H, s, $Sn(CH_3)_3$), 0.09 (6H, s, $Si(CH_3)_2$); ^{13}C NMR δ (100 MHz, $CDCl_3$) 157.5, 152.9, 122.6, 119.0, 57.4, 26.0, 18.5, 12.0, -5.2, -9.2; m/e (EI) 390, 388, 333, 331.

(*E*)-1-[5-(2-Hydroxyethyl)-4-(t-butyldimethylsiloxymethyl)-2-furanyl]-2-methyl-5-(t-butyldimethylsiloxy)-1-propen-4-yl acetate (20), *Method A*. To the furan alcohol **10** (0.212 g, 0.828 mmol) in dry THF (5 ml) at -78°C was added a 1.7 M solution of t-butyllithium in pentane (1.2 ml, 2.04 mmol). After 1h, a solution of anhydrous zinc bromide (0.516 g, 2.293 mmol) in dry THF (1.4 ml) was added and the reaction mixture was warmed to room temperature. The resulting solution was added slowly over 2 h (syringe pump) to a solution of the vinyl iodide **6**, R = Ac, (0.085 g, 0.214 mmol) and $Pd(PPh_3)_4$ (0.036 g, 0.031 mmol) in dry THF (5 ml) at room temperature. After 4 h, the reaction mixture was poured into a saturated solution of ammonium chloride (10 ml) and extracted with dichloromethane. The combined organic extracts were dried ($MgSO_4$) and evaporated *in vacuo*. Flash chromatography (CH_2Cl_2-Et_2O, 4:1) gave **20** (0.100 g, 89%) as a colourless oil; R_f (CH_2Cl_2-Et_2O, 4:1) 0.6; υ_{max} ($CHCl_3$) 3 600, 3 420, 1 730, 1 620; ^1H NMR δ (250 MHz, $CDCl_3$) 6.10 (1H, s, OC=CH), 6.01 (1H, br s, C*H*=CCH$_3$), 5.06 (1H, m, C*H*OAc), 4.48 (2H, s, ArCH_2O), 3.78 (2H, m, CH_2OH), 3.64 (2H, d, *J*=4.9 Hz, CH_2OSi), 2.88 (2H, t, *J*=5.9 Hz, CH_2CH_2OH), 2.53 (1H, m, OH), 2.43 (1H, dd, *J*=13.7, 5.7 Hz, CH_aH_bCHOAc), 2.33 (1H, dd, *J*=13.7, 7.6 Hz, CH_aH_bCHOAc), 2.00 (3H, s, CH_3CO_2), 1.97 (3H, s, CH=CCH_3), 0.89 (9H, s, C$(CH_3)_3$), 0.88 (9H, s, C$(CH_3)_3$), 0.09 (6H, s, $Si(CH_3)_2$), 0.04 (6H, s, $Si(CH_3)_2$); ^{13}C NMR δ (100 MHz, $CDCl_3$) 170.5, 151.5, 148.2, 133.1, 122.3, 116.7, 109.8, 72.8, 63.9, 61.0, 57.1, 41.7, 30.3, 25.9, 25.6, 21.2, 18.8, 18.4, 18.2, -5.2, -5.4; HRMS (EI) M^+ 526.3138, $C_{27}H_{50}O_6Si_2$ requires 526.3146; m/e (EI) 526, 466, 409, 277, 203.

(*E*)-2-Methyl-1-[5-methyl-4-(t-butyldimethylsiloxymethyl)-2-furanyl]-1-hexene (21), *Method B*. To a stirred solution of **16** (0.0275 g, 0.0707 mmol) and **18** (0.0175 g, 0.0781 mmol) under argon in DMF (1 ml), under argon at 20°C, was added $Pd(PPh_3)_4$ (0.0073 g, 0.0063 mmol). After 16 h, the reaction mixture was forced through a plug of silica with dichloromethane and evaporated *in vacuo*. Flash chromatography (CH_2Cl_2-hexane, 1:4) gave **21** (0.0133 g, 58%) as a colourless oil (the *bis*-furan dimer from self-coupling of **16** was also isolated in 34% yield); R_f (CH_2Cl_2) 0.8; υ_{max} ($CHCl_3$) 1 650, 1 625; ^1H NMR δ (250 MHz, $CDCl_3$) 6.17 (1H, s, OC=CH), 6.03 (1H, s, CH_3C=C*H*), 4.54 (2H, s, CH_2O), 2.31 (3H, s, OC(CH_3)=C), 2.18 (2H, t, *J*=7.0 Hz, $CH_2{}^nPr$), 1.99 (3H, s, C=CCH_3), 1.50 (2H, m, CH_2CH_2Et), 1.37 (2H, m, CH_2CH_3), 0.95 (9H, s, C$(CH_3)_3$), 0.94 (3H, t, CH_2CH_3), 0.12 (6H, s, $Si(CH_3)_2$); ^{13}C NMR δ (100 MHz, $CDCl_3$) 151.3, 146.0, 137.7, 120.6, 113.9, 108.8, 57.4, 40.4, 30.2, 26.0, 22.4, 18.5, 18.3, 14.0, 11.9, -5.1; HRMS (FAB, 3-nitrobenzyl alcohol) M^+ 322.2302, $C_{19}H_{34}O_2Si$ requires 322.2328; m/e (EI) 322, 265, 191, 57.

(*E*)-2-Methyl-1-[5-methyl-4-(t-butyldimethylsiloxymethyl)-2-furanyl]-5-(t-butyldimethylsiloxy)-1-penten-4-yl acetate (19). Coupling of **15** and **6**, R = Ac, by Method A (1.2 equiv. ^{t}BuLi, $ZnBr_2$) gave **19** (0.069 g, 79%) as a light yellow oil; R_f (CH_2Cl_2) 0.4; υ_{max} ($CHCl_3$) 1 735, 1 260; ^1H NMR δ (250 MHz, $CDCl_3$) 6.12 (1H, s, OC=CH), 6.00 (1H, s, ArC*H*=C), 5.07 (1H, s, C*H*OAc), 4.47 (2H, s, ArCH_2O), 3.64 (2H, d, *J*=4.8 Hz, CH_2O), 2.32 (2H, m, CH_2CHOAc), 2.24 (3H, s, OC(CH_3)=C), 2.00 (3H, s, CH_3CO_2), 1.97 (3H, s, C=C$(CH_3)CH_2$), 0.90 (9H, s, C$(CH_3)_3$), 0.88 (9H, s, C$(CH_3)_3$), 0.07 (6H, s, $Si(CH_3)_2$), 0.04 (6H, s, $Si(CH_3)_2$); ^{13}C NMR δ (100 MHz, $CDCl_3$) 170.4, 150.8, 146.5, 132.0, 120.6, 117.0, 109.5, 72.7, 63.9, 57.2, 41.8, 25.9, 25.7, 21.1, 18.6, 18.4, 18.2, 11.8, -5.3, -5.5; HRMS (EI) M^+ 496.3085, $C_{26}H_{48}O_5Si_2$ requires 496.3040; m/e (EI) 496, 439, 436, 379.

(*E*)-1-[5-(2-Iodoethyl)-4-(t-butyldimethylsiloxymethyl)-2-furanyl]-2-methyl-5-(t-butyldimethylsiloxy)-1-penten-4-yl 3-oxo-1-butanoate (22). Coupling of **17** and **6**, R = $COCH_2COMe$, by Method B gave **22** (0.0143 g, 35%) as a yellow oil; R_f (CH_2Cl_2) 0.4; υ_{max} ($CHCl_3$) 3 400, 1 740, 1 720; ^1H NMR δ (250 MHz, $CDCl_3$) 6.12 (1H, s, ArC*H*=C), 6.00 (1H, br s, OC=CH), 5.13 (1H, m, CHO), 4.50 (2H, s, ArCH_2O), 3.67 (2H, d, *J*=5.0 Hz, CH_2O), 3.39 (2H, s, $C(O)CH_2C(O)$), 3.32 and 3.20 (4H, 2xm, CH_2CH_2I), 2.41 (2H, m, CH_2CHO), 2.19 (3H, s, $C(O)CH_3$), 1.97 (3H, s, C=CCH_3), 0.90 (9H, s, C$(CH_3)_3$), 0.88 (9H, s, C$(CH_3)_3$), 0.08 (6H, s, $Si(CH_3)_2$), 0.04 (6H, s, $Si(CH_3)_2$); HRMS (EI) M^+- $CH_3C(O)CH_2C(O)$) 594.2092, $C_{25}H_{47}IO_4Si_2$ requires 594.2058; m/e (EI) 594, 576, 519, 387.

(*E*)-1-[5-(2,3-Dihydroxypropan-1-yl)-4-(t-butyldimethylsilyloxymethyl)-2-furanyl]-2-methyl-5-(t-butyldimethylsilyloxy)-1-penten-4-yl acetate (23). Coupling of **14** and **6**, R = Ac, by Method A (3.6 equiv. ^{t}BuLi, $ZnCl_2$) gave **23** (57%) as a colourless oil; R_f (CH_2Cl_2-Et_2O, 7:3) 0.3; υ_{max} ($CHCl_3$) 3 620, 3 450, 1 750, 1 260; ^1H NMR δ (250 MHz, $CDCl_3$) 6.07 (1H, s, ArCH=C), 6.01 (1H, s, OC=CH), 5.05 (1H, m, C*H*OAc), 4.48 (2H, s, ArCH_2O), 3.92 (1H, m, C*H*OH), 3.64 (2H, d, *J*=4.9 Hz, CH(OAc)CH_2), 3.57 (1H, m, CH_aH_bOH), 3.48 (1H, m, CH_aH_bOH), 3.08 (1H, br s, OH), 2.86 (2H, d, *J*=6.2 Hz, ArCH_2CHOH), 2.60 (1H, br s, OH), 2.38 (2H, m, C=C(CH_3)CH_2), 2.00 (3H, s, $C(O)CH_3$), 1.96 (3H, s, C=CCH_3), 0.90 (9H,

s, $C(CH_3)_3$), 0.87 (9H, s, $C(CH_3)_3$), 0.11 (6H, s, $Si(CH_3)_2$), 0.03 (6H, s, $Si(CH_3)_2$); ^{13}C NMR δ (100 MHz, $CDCl_3$) 170.5, 151.6, 147.7, 133.4, 122.2, 116.7, 109.7, 72.7, 70.5, 65.6, 63.9, 57.2, 41.8, 30.8, 25.9, 25.8, 21.1, 18.8, 18.4, 18.2, -5.2, -5.4; HRMS (EI) M^+ 556.3257, $C_{28}H_{52}O_7Si_2$ requires 556.3251; m/e (EI) 556, 496, 424.

(*E*)-1-[5-(2,3-Dihydroxypropan-1-yl)-4-(t-butyldimethylsiloxymethyl)-2-furanyl]-2-methyl-5-(t-butyldimethylsiloxy)-1-penten-4-yl 3-oxo-4-(diethoxyphosphinyl)-1-butanoate (24). Coupling of **14** and **8** by Method A (3.6 equiv. ^tBuLi, $ZnCl_2$) gave **24** (0.213 g, 46%) as a pale yellow oil; R_f (CH_2Cl_2-MeOH, 9:1) 0.55; υ_{max} ($CHCl_3$) 3 400, 1 750, 1 730, 1 710, 1 695, 1 260; ^1H NMR δ (250 MHz, $CDCl_3$) 6.10 (1H, s, ArC*H*=C), 5.98 (1H, s, OC=CH), 5.11 (1H, m, CHOC(O)), 4.49 (2H, s, $ArCH_2O$), 4.09 (4H, dq, *J* ~7.0 Hz, OCH_2CH_3), 3.93 (1H, m, CHOH), 3.65 (2H, d, *J*=5.1 Hz, CH_2O), 3.63 (1H, m, CH_aH_bOH), 3.59 (2H, s, $C(O)CH_2C(O)$), 3.46 (1H, m, CH_aH_bOH), 3.17 (2H, d, *J*=22.7 Hz, CH_2P), 2.83 (2H, d, *J*=6.2 Hz, $ArCH_2$), 2.44 (1H, d, *J*=13.8, 4.7 Hz, $C=C(CH_3)CH_aH_b$), 2.33 (1H, d, *J*=13.8, 8.5 Hz, $C=C(CH_3)CH_aH_b$), 1.95 (3H, s, $C=CCH_3$), 1.31 (6H, t, *J*=7.0 Hz, OCH_2CH_3), 0.89 (9H, s, $C(CH_3)_3$), 0.87 (9H, s, $C(CH_3)_3$), 0.09 (6H, s, $Si(CH_3)_2$), 0.03 (6H, s, $Si(CH_3)_2$); ^{13}C NMR δ (100 MHz, $CDCl_3$) 194.0, 166.0, 151.2, 147.4, 132.5, 122.3, 117.1, 109.7, 73.8, 70.5, 65.7, 63.8, 62.8, 57.1, 49.8, 41.9 (d, *J*=125.0 Hz, CH_2P), 41.8, 30.7, 25.8, 25.7, 18.6, 18.3, 18.1, 16.2, -5.3, -5.5; HRMS (EI) M^+ 734.3650, $C_{34}H_{63}O_{11}PSi_2$ requires 734.3646; m/e (EI) 734, 733, 717, 602.

2-[3-(t-Butyldimethylsilyloxymethyl)-2-furanyl]-ethanal (25). To a suspension of periodic acid (1.023 g, 4.587 mmol) in dry ether at 0°C was added a solution of **14** (0.169 g, 0.591 mmol) in ether (2 ml). After 20 min, the reaction mixture was diluted with dichloromethane (20 ml) and forced through a plug of silica to give **25** (0.135 g, 90%) as a colourless oil; R_f (CH_2Cl_2) 0.45; υ_{max} ($CHCl_3$) 2 860, 1 730; ^1H NMR δ (250 MHz, $CDCl_3$) 9.67 (1H, t, *J*=2.2 Hz, CHO), 7.33 (1H, d, *J*=1.9 Hz, OC*H*=CH), 6.34 (1H, d, *J*=1.9 Hz, OCH=C*H*), 4.55 (2H, s, CH_2O), 3.73 (1H, d, *J*=2.2 Hz, CH_2), 0.89 (9H, s, $C(CH_3)_3$), 0.07 (6H, s, $Si(CH_3)_2$); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 197.3, 142.6, 122.7, 111.1, 57.4, 41.7, 25.9, 18.3, -5.3; HRMS (FAB, 3-nitrobenzyl alcohol) M^+-H 253.1246, $C_{13}H_{22}O_3Si$-H requires 253.1260; m/e (EI) 239, 197, 124, 75.

(*E*)-2-Methyl-1-[5-(2-oxethan-1-yl)-4-(t-butyldimethylsiloxymethyl)-2-furanyl]-5-(t-butyldimethylsiloxy)-1-penten-4-yl acetate (26). To a stirred suspension of periodic acid (0.198 g, 0.888 mmol) in dry ether (10 ml), at 0°C under argon, was added a solution of the diol **23** (0.0288 g, 0.052 mmol) in ether (1 ml). After 1 h, the reaction mixture was diluted with dichloromethane and forced through a plug of silica. Evaporation *in vacuo* gave **26** (0.0150 g, 55%) as a colourless oil; R_f (CH_2Cl_2) 0.3; υ_{max} ($CHCl_3$) 1 750, 1 740, 1 260; ^1H NMR δ (250 MHz, $CDCl_3$) 9.67 (1H, t, *J*=2.2 Hz, CHO), 6.14 (1H, s, OC=CH), 6.02 (1H, s, C*H*=CCH$_3$), 5.05 (1H, m, C*H*OAc), 4.53 (2H, s, $ArCH_2O$), 3.71 (2H, d, *J*=2.2 Hz, CH_2CHO), 3.64 (2H, d, *J*=5.0 Hz, $CH(OAc)CH_2O$), 2.44 (1H, dd, *J*=13.8, 5.8 Hz, $C=C(CH_3)CH_aH_b$), 2.34 (1H, dd, *J*=13.8, 7.6 Hz, $C=C(CH_3)CH_aH_b$), 2.01 (3H, s, $C(O)CH_3$), 1.97 (3H, br s, $C=CCH_3$), 0.89 (9H, s, $C(CH_3)_3$), 0.88 (9H, s, $C(CH_3)_3$), 0.07 (6H, s, $Si(CH_3)_2$), 0.04 (6H, s, $Si(CH_3)_2$); ^{13}C NMR δ (100 MHz, $CDCl_3$) 197.1, 170.5, 152.6, 140.8, 134.0, 124.2, 116.7, 109.4, 72.7, 63.9, 57.4, 41.8, 29.7, 25.9, 25.8, 21.1, 18.8, 18.3, 18.2, -5.3, -5.4; HRMS (EI) M^+ 524.2975, $C_{27}H_{48}O_6Si_2$ requires 524.2989; m/e (EI) 524, 467, 407, 275.

(*E*)-2-Methyl-1-[5-(2-oxethan-1-yl)-4-(t-butyldimethylsilyloxymethyl)-2-furanyl]-5-(t-butyldimethylsilyloxy)-1-penten-4-yl 3-oxo-4-(diethoxyphosphinyl)-1-butanoate (27). To a solution of sodium periodate (0.020 g, 0.094 mmol) in methanol (1.5 ml) and water (0.7 ml) was added a solution of **24** (0.046, 0.0644 mmol) in methanol (0.2 ml). After 10 min, a yellow gum had formed on the side of the flask. Water (1 ml) was added and the liquid layer removed. The remaining organic material was washed with water and then freeze dried to constant mass to give **27** (0.030 g, 66%); R_f (CH_2Cl_2-^{i}PrOH, 24:1) 0.25; υ_{max} ($CHCl_3$) 2 840, 1 720 (br), 1 600, 1 220; ^1H NMR δ (250 MHz, $CDCl_3$) 9.67 (1H, t, *J*=1.8 Hz, CHO), 6.14 (1H, s, OC=CH), 6.00 (1H, s, ArC*H*=C), 5.10 (1H, m, CHOC(O)), 4.52 (2H, s, $ArCH_2O$), 4.11 (4H, m, OCH_2CH_3), 3.71 (2H, d, *J*=1.8 Hz, CH_2CHO), 3.65 (2H, d, *J*=5.1 Hz, $CHCH_2OTBS$), 3.62 (2H, s, $C(O)CH_2C(O)$), 3.20 (2H, d, *J*=22.7 Hz, CH_2P), 1.96 (3H, s, $C=CCH_3$), 1.30 (6H, t, *J*=7.0 Hz, OCH_2CH_3), 0.88 (9H, s, $C(CH_3)_3$), 0.87 (9H, s, $C(CH_3)_3$), 0.06 (6H, s, $Si(CH_3)_2$), 0.03 (6H, s, $Si(CH_3)_2$); ^{13}C NMR δ (100 MHz, $CDCl_3$) 197.1, 194.1, 166.1, 152.4, 140.9, 133.4, 124.2, 116.9, 109.5, 74.0, 63.6, 62.7, 57.4, 49.7, 42.3 (d, *J*=135.2 Hz, CH_2P), 41.8, 34.6, 25.9, 25.8, 18.7, 18.3, 18.1, 16.2, -5.4, -5.5; HRMS (EI) M^+ 702.3408, $C_{33}H_{59}O_{10}PSi_2$ requires 702.3384; m/e (EI) 702, 683, 482, 479.

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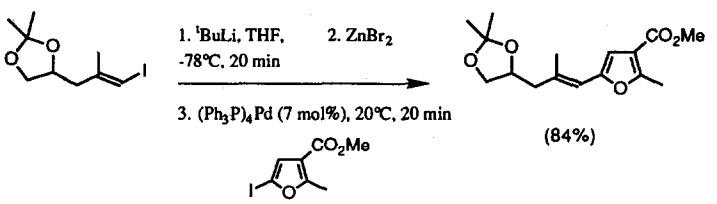
(14) We have also successfully carried out Pd(0)-catalysed coupling reactions with reversed polarity, *e.g.* forming the vinyl zinc species from the vinyl iodide and coupling with the furyl iodide (I. Paterson and M. Gardner, unpublished results), *e.g.*:



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