Use of the Wadsworth–Emmons reaction for preparing hindered vinyl ethers and related 1,2-dioxetanes

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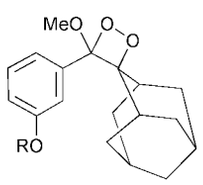
Arylaldehyde acetals can be reacted with trimethyl phosphite to produce the corresponding dimethyl α-methoxybenzylphosphonates, themselves used in a Wadsworth–Emmons reaction with adamantanone to produce hindered methyl vinyl ethers. These vinyl ethers are useful in the preparation of chemiluminescent 1,2-dioxetanes. The scope of the reaction has been explored.

Hindered dioxetanes of the type **1** are commercially exploited



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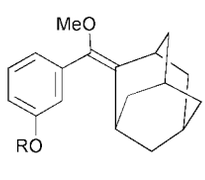

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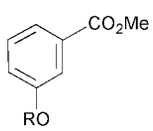

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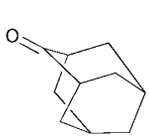

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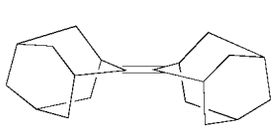

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in chemiluminescent assays.[1] Adamantylidene derivatives are particularly popular although other alkylidene groups have also been recommended.[2] The protected phenol derivatives are relatively stable compounds that can be stored for months at low temperatures, whereas the corresponding phenolate anions, by comparison, rapidly collapse with liberation of light. The protecting groups (R in **1**) are selected to be sensitive to enzymic removal, hence allowing the reagents to be used in biochemical assay systems of the enzyme-linked type.[3]

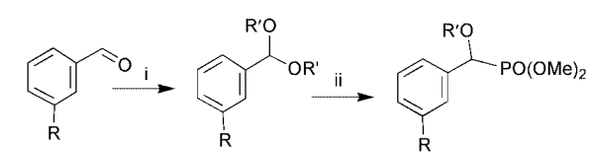
Results and discussion

In a programme aimed at extending the range of enzymes that can be used in biochemical assays,[4] we needed a versatile route to the parent vinyl ethers, *e.g.* **2**, from which the dioxetanes **1** are prepared. Apart from descriptions in patents,[5] published experimental details for preparing such systems are sparse[6] and mainly utilise mixed McMurray type couplings of a ketone with an ester, for example of a methyl ester, such as **3**, with a ketone, such as **4**. Such mixed couplings are generally inefficient, the major product being the coupled ketone, in this case the bi(adamantylidene) **5**, with only low yields of the required, mixed product **2**. In our hands, using a range of titanium catalysts and reaction conditions, the yields of the required vinyl ethers, such as **2**, were always low and variable. Furthermore, the lower-valent titanium catalysts recommended are not universally available from chemical suppliers.

Herein we describe an efficient, alternative route to the required vinyl ethers which utilises the Wadsworth–Emmons reaction (also known as the Horner–Emmons or Wittig–Horner reaction).[7]

The reagents required are an α-alkoxyphosphonate, to be coupled to a ketone such as adamantanone **4**. The common route to the α-alkoxy phosphonates is through a Michaelis–Arbusov substitution of an α-haloether with a trialkyl phosphite. However, α-haloethers are difficult to handle, being labile alkylating agents, and they are also difficult to prepare from an arylaldehyde using an alcohol and the hydrogen halide acid.[8]

Reaction of an arylaldehyde dialkyl acetal with a trialkyl phosphite in the presence of a Lewis acid, such as boron trifluoride, has been reported as a superior method, avoiding the need to produce the α-haloether.[9] Initially we used trimethylsilyl chloride as a mild Lewis acid. Thus benzaldehyde **6** (Scheme 1) was converted to its dimethyl acetal **9** and reacted with trimethyl phosphite, using trimethylsilyl chloride as the catalyst,

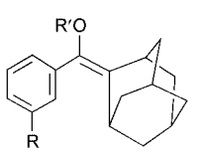


6 R = H
7 R = $PhCH_2O$
8 R = $PhCO_2$

9 R = H, R′ = Me
10 R = $PhCH_2O$, R′ = Me
11 R = $PhCO_2$, R′ = Me
12 R = $PhCO_2$, R′ = Et

13 R = H, R′ = Me
14 R = $PhCH_2O$, R′ = Me
15 R = $PhCO_2$, R′ = Me
16 R = $PhCO_2$, R′ = Et

iii



17 R = H, R′ = Me
18 R = $PhCH_2O$, R′ = Me
19 R = HO, R′ = Me
20 R = $PhCO_2$, R′ = Me
21 R = HO, R′ = Et

Scheme 1 *Reagents*: i, $CH_3C(OR)_2CH_3$, tosic acid; ii, $TiCl_4$–$P(OMe)_3$; iii, Li(*i*-Pr_2)N, THF, then **4**.

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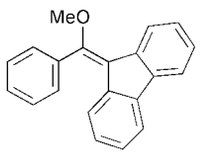
to produce the dimethyl α-methoxylbenzylphosphonate **13** in good yield (70%). Presumably the mechanism involves attack by the trimethyl phosphite on the intermediate carbocation, followed by demethylation of the intermediate phosphonium species by the chloride anion, to produce methyl chloride and the product phosphonate. Coupling of the latter with adamantanone, using lithium diisopropylamide as base, afforded the corresponding vinyl ether **17** in good yield. The reaction is general and use of fluorenone, for example gave a high yield of the corresponding alkene **22**.



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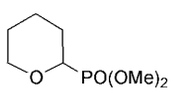
Direct use of 3-hydroxybenzaldehyde in the preparation of an acetal was not possible since polymerisation occurred. In seeking a suitable protecting group we prepared the benzyl and benzoyl derivatives, **7** and **8**, respectively, each readily converted into the corresponding dimethyl acetals **10** and **11**, using 2,2-dimethoxypropane and toluene-4-sulfonic acid as catalyst, and thence their α-methoxy phosphonates, **14** and **15**. The diethyl acetal **12** also reacted smoothly under these conditions to give the corresponding ethoxy phosphonate **16**, demonstrating the generality of the method.

These trimethylsilyl chloride-catalysed phosphonation reactions proceeded slowly, taking several days to complete. During this time a considerable amount of competing rearrangement, of the trimethyl phosphite into dimethyl methylphosphonate, co-occurred.[10] Alternative Lewis acids were therefore tried, amongst which titanium tetrachloride proved to be better.[11] With $TiCl_4$ the reaction went rapidly, within a few hours at low temperatures, and the isolation of the product phosphonate was simpler. The reaction was also general and, for example, 2-methoxytetrahydropyran could be reacted with trimethyl phosphite using $TiCl_4$, to give the corresponding phosphonate **23** in high yield.



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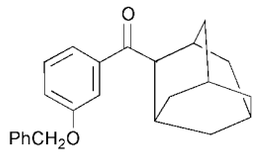
Subsequent treatment of the phosphonates **14** to **16** to the Wadsworth–Emmons coupling with adamantanone proceeded smoothly in every case, except that, whereas the benzyl protecting group remained intact, to give the vinyl ether **18**, the benzoyl group was removed during reaction and the isolated products were the corresponding phenols **19** and **21**. The yield of the phenol could be improved by using a further equivalent of base during the olefination step. Benzoylation of the phenol **19** gave the benzoate ester **20** but only a very small amount of this ester could be detected by TLC, in the crude product from the olefination reaction. That this method gave relatively good olefin yields, by coupling the relatively hindered phosphonate anions with the hindered adamantanone, can possibly be explained by the fact that the α-methoxy group imparts to the conjugate base supernucleophilic properties by the α-effect.[12]

As expected, the vinyl ethers were unstable to acid, rapidly forming the ketones, *e.g.* the benzyl ether **18** produced ketone **24**. Ketone **24** is hindered and *C*-alkylation of the enolate would not be expected to proceed with ease. An attempt was made to *O*-alkylate the enolate anion, produced by treatment of the ketone **24** with lithium diisopropylamide, using methyl iodide as alkylating agent. A small amount of the methyl vinyl ether **18** was formed but attempts to introduce other *O*-alkyl groups by this direct alkylation method failed.



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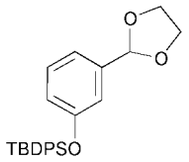

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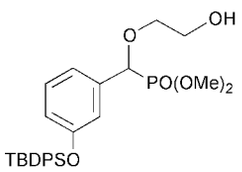

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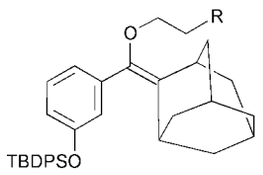
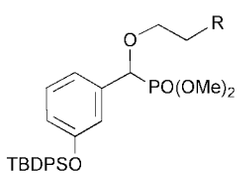


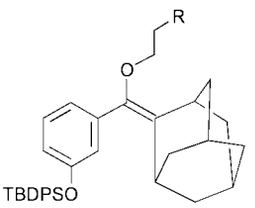
27 R = OH

28 R = OTosyl

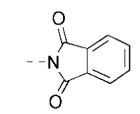


29 R = *N*-phthalimide

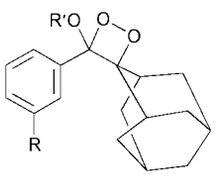
30 R = NH_2



31 R =



32 R = NH_2



33 R = H, R′ = Me

34 R = OH, R′ = Me

35 R = OH, R′ = Et

The reaction of trimethyl phosphite with the ethylene acetal of the *tert*-butyldiphenylsilyl[13] protected phenol, **25**, using titanium tetrachloride as catalyst, produced the 2-hydroxyethoxy phosphonate **26**. Attempts to use this in the Wadsworth–Emmons reaction with adamantanone, using an excess of base to protect the alcohol group as its alkoxide anion, failed to produce any of the desired alkene **27** or of the corresponding ethylene acetal, expected by intramolecular cyclisation during work-up. However, when the reaction mixture was treated with toluene-4-sulfonyl chloride prior to work-up, a moderate yield of the tosylated alcohol **28** could be obtained. Efforts to use this derivative to conjugate to fluorophores are in hand and will be reported elsewhere.

The alcohol **26** was also used to prepared other derivatives containing a potential linker function. Thus reaction with phthalimide under Mitsunobu conditions,[14] afforded the phthalimide **29** and this could be converted to the corresponding amine, **30**. Wadsworth–Emmons reactions on the last two compounds with adamantanone were attempted but in neither case were the desired compounds, **30** and **31** respectively, obtained.

Dioxetane formation from the vinyl ethers, produced as described above, followed literature methods.[2,15] For example, using Methylene Blue as the sensitiser, the vinyl ethers **17**, **19** and **21** afforded the corresponding dioxetanes, **33**, **34** and **35** in yields >90%. On appropriate decomposition these dioxetanes

showed chemiluminescence. Thus on treatment of the phenol **35** with base an emission with a peak at λ_{em} 450 nm was observed, identical to that produced from the fluorescence spectrum of ethyl 3-hydroxybenzoate under similar basic conditions.

Experimental

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Solvents were generally dried and distilled before use, using recommended methods.[16] Petroleum ether refers to the fraction of boiling range 40–60 °C; THF refers to tetrahydrofuran and brine to a saturated solution of sodium chloride. Reaction solvents were generally dried over anhydrous sodium sulfate, the solutions filtered and then removed under reduced pressure using a rotary evaporator. Thin layer chromatography (TLC) was carried out on Whatman 0.25 mm GF60A silica plates and column chromatography used Sorbisil silica, particle size in the range 50–300 μm. Solvent ratios are in volumes used prior to mixing. Infrared spectra were recorded on a Perkin-Elmer System 2000 FTIR spectrometer, either as films or as KBr discs. ^{1}H NMR spectra were obtained on either AC300 or AC360 instruments at 300 and 360 MHz respectively, using $CDCl_3$ as solvent, unless otherwise specified, and using tetramethylsilane as internal reference. Mass spectra were generally recorded either under electron impact (EI) or chemical ionisation (CI) modes, the latter with ammonia as carrier gas. Microanalyses were carried out by MEDAC Ltd, Englefield Green, Surrey.

Preparation of aldehyde dimethyl acetals

The aromatic aldehyde (0.4 mol) was dissolved in 2,2-dimethoxypropane (100 cm^3) and a few crystals of toluene-4-sulfonic acid (dried over phosphorus pentaoxide) added. The solution was gently heated to 70 °C for several hours, distilling off product acetone until no more formed. The solution was cooled, poured into aqueous sodium hydrogen carbonate solution and extracted with dichloromethane, washing with water (×2) before drying and removing the solvent. The residue was vacuum distilled to give the required acetal.

In this manner the following acetals were prepared:

Benzaldehyde dimethyl acetal 9. 84%, colourless oil, bp 59–61 °C/3 Torr (lit.[17] 59–61 °C/18 Torr); δ_H 3.32 (6 H, s, *Me*O), 5.38 (1 H, s, ArC*H*), 7.28–7.38 (5 H, m, aromatic).

3-Benzyloxybenzaldehyde dimethyl acetal 10. 82%, pale yellow oil, bp 165–168 °C/1 Torr; ν_{max} 3018, 2926, 2836, 1588, 1244, 1168, 766, 688 cm^{-1}; δ_H 3.32 (6 H, s, CH_3O), 5.07 (2 H, s, $PhCH_2$), 5.35 (1 H, s, ArC*H*), 6.43–6.92 (9 H, m, aromatic); *m*/*z* (EI) 259 (MH^+), 258 (M^+), 227, 167, 91. Found: $M^{+\bullet}$ 258.3165; $C_{16}H_{18}O_3$ requires 258.3164.

3-Benzoyloxybenzaldehyde dimethyl acetal 11. Isolated as a pale yellow oil by flash chromatography through silica gel (5% ethyl acetate–light petroleum) and used without further purification (95%); ν_{max}(film) 2858, 1737, 1202, 1035, 760, 708 cm^{-1}; δ_H 3.33 (6 H, s, *Me*O), 5.40 (1 H, s, ArC*H*), 7.18 (1 H, d, *J* 8 Hz, ArH), 7.21 (1 H, s, ArH), 7.37–7.62 (5 H, m, ArH), 8.20 (2 H, d, *J* 8 Hz, ArH); *m*/*z* (EI) 273 (MH^+), 272 (M^+), 167, 105. Found: $M^{+\bullet}$ 272.3001. $C_{16}H_{16}O_4$ requires 272.3000.

3-Benzoyloxybenzaldehyde diethyl acetal 12. A mixture of 3-benzoyloxybenzaldehyde[18] (5.3 g, 23.4 mmol) and ethanol (90 cm^3) in toluene (120 cm^3) containing a few crystals of dried toluene-4-sulfonic acid, was heated to reflux, removing the water side product *via* a Dean–Stark condenser. After 4 h the solution was washed with saturated aqueous sodium hydrogen carbonate solution, then brine, the organic layer dried over anhydrous sodium sulfate, with some added decolourising charcoal, filtered and the solvent removed under reduced pressure to afford the *title compound* as a pale yellow oil (6.26 g, 89%); bp 162–164 °C/3 Torr; ν_{max}(film) 2975, 2882, 1739, 1451, 1263, 1229, 1062, 1080, 1025, 779, 707 cm^{-1}; δ_H 1.23 (6 H, t, *J* 7 Hz, CH_3), 3.56 (4 H, q, *J* 7 Hz, OCH_2), 5.58 [1 H, s, $CH(O)_2$], 7.18–7.64 (9 H, m, ArH); *m*/*z* (CI), 318 (MNH_4^+), 288. Found: MNH_4^+ 318.1705. $C_{19}H_{24}O_4{\cdot}NH_4$ requires 318.1705.

Dimethyl 1-methoxy-1-phenylmethylphosphonate 13

The acetal **9** (38 g, 0.25 mol, bp 59–61 °C/3 Torr), trimethyl phosphite (redistilled, 30.5 cm^3, 0.26 mol) and trimethylsilyl chloride (46.2 g, 0.42 mol) were stirred under N_2 for 68 h. The resulting yellow oil was carefully poured into aqueous sodium hydrogen carbonate solution, extracted into dichloromethane and washed with water before drying and work-up. The residual oil was vacuum distilled to produce the *title compound* (40.1 g, 70%), bp 124 °C/1 Torr (lit.[8b] 111–113 °C/0.3 Torr); ν_{max}(film) 2954, 1258, 1186, 1034, 777, 712 cm^{-1}; δ_H 3.38 (3 H, s, *Me*O), 3.68 (6 H, m, *Me*OP), 4.5 (1 H, d, *J* 17 Hz), 7.36–7.45 (5 H, m, aromatic); *m*/*z* 230 (3.6%, $M^{+\bullet}$), 229 (27), 122 (50), 121 (100). Found: M^+ 230.2001. $C_{10}H_{15}O_4P$ requires 230.1999.

Dimethyl 1-methoxy-1-(3-benzyloxyphenyl)methylphosphonate 14

A mixture of the acetal **10** (2 g, 7.8 mmol), trimethyl phosphite (1.58 g, 12.6 mmol) and trimethylsilyl chloride (2 cm^3, 16 mmol) were stirred under a dry N_2 atmosphere at room temperature for 80 h. The resulting yellow oil was poured into aqueous sodium hydrogen carbonate solution and extracted into dichloromethane. The extract was washed with water (2 × 25 cm^3), dried and the solvent removed before distilling the residue under reduced pressure to afford the *title phosphonate* (1.77 g, 68%) as a pale yellow, viscous oil, bp 230–232 °C/3 Torr; ν_{max}(film) 2954, 2826, 1599, 1452, 1259, 1182, 1153, 1032, 740, 696 cm^{-1}; δ_H 3.37 (3 H, s, *Me*O), 3.63–3.71 (6 H, m, *Me*OP), 4.5 (1 H, d, *J* 18 Hz, C*H*P), 5.08 (2 H, s, CH_2Ar), 6.95–7.45 (9 H, m, ArH). Found: M^+ 336.3237. $C_{17}H_{21}O_5P$ requires 336.3237.

Dimethyl 1-methoxy-1-(3-benzoyloxyphenyl)methylphosphonate 15

The acetal **11** (13 g, 48 mmol) and trimethyl phosphite (7.8 cm^3, 66 mmol) in dichloromethane (90 cm^3) were cooled to −78 °C before adding titanium(IV) chloride (7.8 cm^3, 71 mmol), and the dark mixture was then stirred for 30 min before allowing it to warm to room temperature and stirring for a further 45 min. Aqueous methanol (2:1, 50 cm^3) was added and the mixture filtered before washing the organic filtrate with aqueous sodium hydrogen carbonate solution (50 cm^3) and brine (50 cm^3), dried, filtered and then evaporated under reduced pressure.The resultant light brown oil was purified by column chromatography through silica, using 2:1 acetone–light petroleum as eluant. The major, *title compound* crystallised as a colourless solid (12.2 g, 73%), mp 49–52 °C; ν_{max}(Nujol mull) 2898, 1734, 1234, 1027, 1002, 710 cm^{-1}; δ_H 3.43 (3 H, s, CH_3O), 3.72 (6 H, dd, *J* 7, 10 Hz, CH_3OP), 4.60 (1 H, d, *J* 15 Hz, CHP), 7.22 (1 H, d, *J* 8 Hz, ArH), 7.34 (1 H, s, ArH), 7.38–7.51 (4 H, m, ArH), 8.19 (2 H, d, *J* 7 Hz, ArH); δ_P 21.35; *m*/*z* (CI) 368 (MNH_4^+), 351 (MH^+), 241. Found: C, 58.1; H, 5.3. $C_{17}H_{19}O_6P$ requires C, 58.3; H, 5.5%.

Dimethyl 1-ethoxy-1-(3-benzoyloxyphenyl)methylphosphonate 16

This was prepared in a similar manner to the methoxy analogue **15**. The acetal **12** (6 g, 20 mmol) was reacted with trimethyl phosphite (3.6 cm^3, 30.6 mmol) using titanium(IV) chloride (3.6 cm^3, 33 mmol). Work-up afforded the the *title compound* as a viscous oil (4.87 g, 67%), ν_{max}(film) 2983, 2854, 1742, 1221, 1030, 802, 698 cm^{-1}; δ_H 1.24 (3 H, t, *J* 7 Hz, CH_3), 3.71 (2 H, dq,

J 1, 7 Hz), 4.70 (1 H, d, *J* 18 Hz, CHP), 7.18 (1H, d, *J* 8 Hz, ArH), 7.27 (1 H, s, ArH), 7.32–7.61 (5 H, m, ArH), 8.19 (2 H, d, *J*, 8 Hz, ArH); *m*/*z* (CI) 382 (MNH_4^+), 365 (MH^+), 255. Found: M^+ 382.1417. $C_{18}H_{21}O_6P{\cdot}NH_4^+$ requires 382.1420.

General method for the Wadsworth–Emmons reactions

The phosphonate (40 mmol) in THF (10 cm^3) was added dropwise to a stirred preformed solution of lithium diisopropylamide [prepared from diisopropylamine (9.2 cm^3, 64 mmol) and *n*-butyllithium (40 cm^3, 1.6 M solution in hexane, 64 mmol) in THF (50 cm^3) at −78 °C for 30 min] kept at −78 °C under a dry N_2 atmosphere. After stirring for 1 h, a solution of adamantanone (or, for **8**, fluorenone) (6.05 g, 40 mmol) in THF (10 cm^3) was slowly added, over 15 min, and the solution was allowed to warm to room temperature for 6 h. The reaction was quenched by pouring into 0.2 M phosphate buffer (at pH 7.0), rapidly followed by extraction into dichloromethane (100 cm^3), washing the extract with aqueous sodium hydrogen carbonate solution (100 cm^3), then brine (2 × 100 cm^3). After drying and removal of solvent the residue was purified by flash chromatography through silica gel (using solvents such as 5% ethyl acetate–petroleum ether) to afford the vinyl ether.

In this manner the following compounds were prepared.

1-(2-Adamantylidene)-1-methoxy-1-phenylmethane 17. 61%, mp 88–89 °C (from petroleum ether) (lit.[19] 92 °C), obtained from the phosphonate **13**; ν_{max}($CHCl_3$ film) 3030, 2900, 1658, 1580 cm^{-1}; δ_H 1.78–1.97 (12 H, m, adamantanyl-H), 2.61 (1 H, br s, adamantanyl-H), 3.28 (3 H, s, CH_3O), 7.26–7.36 (5 H, m, aromatic). Found: C, 85.0; H, 8.7. $C_{18}H_{22}O$ requires C, 85.0; H, 8.7%.

1-(Fluoren-9-ylidene)-1-methoxy-1-phenylmethane 22. 61%, mp 104 °C (from petroleum ether) (lit.[20] 110 °C) obtained from the phosphonate **13**; ν_{max}($CHCl_3$ film) 3018, 2920, 2864, 1689, 1610, 1420, 1272, 1098, 756 cm^{-1}; δ_H 3.65 (3 H, s, CH_3O), 6.21–8.35 (13 H, aromatic); *m*/*z* (EI) 284 (M^+). Found: C, 89.0; H, 5.7. $C_{21}H_{16}O$ requires C, 88.7; H, 5.7%.

1-(2-Adamantylidene)-1-methoxy-1-(3-benzyloxyphenyl)-methane 18. 64%, mp 75–77 °C (from petroleum ether), obtained from the phosphonate **14**; ν_{max}($CHCl_3$ film) 2908, 2847, 1578, 1454, 1288, 1239, 1097, 1081, 1027, 755, 697 cm^{-1}; δ_H 1.58–2.03 (12 H, m, adamantanyl-H), 2.62 (1 H, br s, adamantanyl-H), 3.24 (1 H, br s, adamantanyl-H), 3.28 (3 H, s, CH_3O), 5.06 (2 H, s, CH_2Ar), 6.89–7.44 (9 H, m, ArH); *m*/*z* (EI) 361 (MH^+), 360 (M^+), 345 ($M^+ - CH_3$), 91 ($C_7H_7^+$). Found: C, 83.4; H, 7.9. $C_{25}H_{28}O_2$ requires C, 83.3; H, 7.8%.

1-(2-Adamantylidene)-1-methoxy-1-(3-hydroxyphenyl)methane 19. 48%, mp 130–134 °C (lit.[5] 133–134 °C), obtained from the benzoate **15**, using 2.5 equiv. lithium diisopropylamide. The phenol showed ν_{max}($CHCl_3$ film) 3336, 2849, 1582, 1447, 1287, 1245, 1080, 872 cm^{-1}; δ_H 1.78–1.96 (12 H, m, adamantanyl-H), 2.64 1 H, br s, adamantanyl-H), 3.24 (1 H, br s, adamantanyl-H), 3.30 (3 H, s, CH_3O), 4.94 (1 H, br s, exch. D_2O, OH), 6.76 (1 H, d, *J* 8 Hz, ArH), 6.81 (1 H, s, ArH), 6.88 (1 H, d, *J* 8 Hz, ArH), 7.23 (1 H, t, *J* 8 Hz, ArH); *m*/*z* (EI) 270 (M^+). Found: C, 80.0; H, 8.2. $C_{18}H_{22}O_2$ requires C, 79.9; H, 8.25%.

A sample of the phenol **19** could be benzoylated, using benzoyl chloride in pyridine, to form, as a less polar material, the corresponding benzoate, which was not further characterised. Examination of the crude reaction mixture from a repeated Wadsworth–Emmons reaction using **15** as starting material, showed that only traces of this ester were formed amongst the products.

1-(2-Adamantylidene)-1-ethoxy-1-(3-hydroxyphenyl)methane 21. 56%, mp 109–111 °C (from methanol), obtained from the phosphonate **16**; ν_{max}($CHCl_3$ film) 3330 (OH), 2839, 1586, 1445, 1256, 1242, 1080, 790 cm^{-1}; δ_H 1.15 (3 H, t, *J* 7 Hz, CH_3CH_2), 1.72–2.17 (12 H, m, adamantanyl-H), 2.67 (1 H, br s, adamantanyl-H), 3.25 (1 H, br s, adamantanyl-H), 3.48 (2 H, q, *J* 7 Hz, CH_3CH_2), 5.72 (1 H, br s, exch. D_2O, OH), 6.75 (1 H, d, *J* 8 Hz, ArH), 6.83 (1 H, s, ArH), 6.85 (1 H, d, *J* 8 Hz, ArH), 7.19 (1 H, t, *J* 8 Hz, ArH); *m*/*z* (EI) 284 (M^+). Found: C, 80.5; H, 8.5; $C_{19}H_{24}O_2$ requires C, 80.2; H, 8.5%.

Dimethyl tetrahydropyran-2-ylphosphonate 23

A mixture of 2-methoxytetrahydropyran (5.5 g, 47 mmol) and trimethyl phosphite (7.8 cm^3, 66 mmol) in dichloromethane (90 cm^3) under argon, was cooled to −78 °C before adding titanium(IV) chloride (7.8 cm^3, 71 mmol, 1.5 equiv.) dropwise with stirring. After a further 30 min the mixture was allowed to warm to room temperature and was stirred for a further 45 min before adding aqueous methanol (2:1, 50 cm^3). The reaction mixture was filtered and the organic layer washed with saturated aqueous sodium hydrogen carbonate solution and then brine before drying, filtering and evaporation under reduced pressure. The resultant brown oil was purified by column chromatography, using 2:1 acetone–light petroleum as eluant, to afford the *title compound* as a pale yellow oil (6.62 g, 72%), bp 100–101 °C/0.2 Torr (lit.[21] 109–111 °C/0.3 Torr), ν_{max}(film) 2955, 1267, 1237, 1090, 1045, 1032, 927, 889, 840, 823 cm^{-1}; δ_H 1.49–1.57 (2 H, m), 1.62–1.71 (2 H, m), 1.74–1.89 (2 H, m), 3.45 (1 H, t, *J* 6 Hz, OCH), 3.77 (1 H, t, *J* 6 Hz, OCH), 3.79–3.84 (6 H, m, CH_3OP), 4.09 (1 H, m, CHO); *m*/*z* (CI) 212 (MNH_4^+), 195 (MH^+), 85. Found: $M^{+\bullet}$ 212.2049. $C_7H_{15}O_4P{\cdot}NH_4^+$ requires 212.2052.

3-(Benzyloxy)phenyl 2-adamantyl ketone 24

The vinyl ether **18** (55 mg, 0.16 mmol) was stirred in 1:1 v/v glacial acetic acid–conc. hydrochloric acid (2 cm^3) at room temperature for 10 min. Ether (10 cm^3) was added and the mixture washed with brine (2 × 10 cm^3) before drying, filtering and evaporation to dryness to yield the *title ketone* as an off-white solid (52 mg, 98%), mp 78–79 °C; ν_{max}($CHCl_3$ film) 3020, 2914, 1678, 1580, 1216, 1029, 752, 698 cm^{-1}; δ_H 1.54–2.09 (11 H, m, adamantanyl-H), 2.29 (2 H, m, adamantanyl-H), 3.39 (1 H, s, adamantanyl-H), 5.11 (2 H, s, CH_2), 7.14 (1 H, d, *J* 8 Hz, ArH), 7.34–7.45 (8 H, m, ArH); *m*/*z* (EI) 347 (MH^+), 346 (M^+), 255, 211, 91. Found: C, 83.0; H, 7.6; $C_{24}H_{26}O_2$ requires C, 83.2; H, 7.6%.

Methylation of the ketone 24

The ketone (69 mg, 0.2 mmol) was dissolved in THF (10 cm^3) under argon and cooled to −30 °C before adding a solution of freshly prepared lithium diisopropylamide (0.3 mmol) in THF (5 cm^3). The solution was stirred for 1 h before adding methyl iodide (43 mg, 0.3 mmol) and allowing the mixture to warm to room temperature, during 30 min, and then heating to a gentle reflux for a further 30 min. The solution was cooled, poured into dichloromethane (10 cm^3) and washed with brine (2 × 10 cm^3) before drying, filtering and evaporating to dryness. TLC indicated the presence of the methyl vinyl ether **18**. The crude product was chromatographed, using 5% ethyl acetate–light petroleum, to give the vinyl ether (7 mg, 10%), mp and mixed mp 75–77 °C.

3-(*tert*-Butyldiphenylsilyloxy)benzaldehyde ethylene acetal 25

A mixture of 3-hydroxybenzaldehyde (3 g, 24.6 mmol), *tert*-butyldiphenylsilyl chloride (6.4 cm^3, 24.6 mmol) and triethylamine (4 cm^3, 28.7 mmol, 1.16 equiv.) in dichloromethane (10 cm^3) was stirred at room temperature for 24 h. The solution was washed with 10 cm^3 portions of dilute hydrochloric acid (1 M), dilute sodium hydroxide (2 M, × 2) and water (×2) before drying, filtering and removal of solvent under reduced pressure. The crude oil produced was purified by flash column chromato-

graphy (1:1 acetone–light petroleum) to give the silylated phenol (8.56 g, 97%) as a viscous oil; ν_{max}(film) 2932, 2858, 1702, 1583, 1482, 1278, 833, 742, 701 cm^{-1}. Found: M$^+$ 360.1544. $C_{23}H_{24}O_2Si$ requires 360.1545.

A solution of the protected aldehyde (3.61 g, 10 mmol), ethylene glycol (1.5 cm^3, 2.7 equiv.) and a few crystals of dried toluene-4-sulfonic acid in toluene (30 cm^3) was heated to a gentle reflux, using a Dean–Stark apparatus to azeotrope off the water formed. After 2.5 h the solution was neutralised with a saturated aqueous sodium hydrogen carbonate solution, and the organic phase then washed with brine (2 × 30 cm^3), dried, filtered and the solvent removed under reduced pressure. The product pale orange oil was distilled to afford the *title acetal* (3.60 g, 89%) as a pale yellow oil, bp 244–246 °C/2 Torr; ν_{max}(film) 2932, 2859, 1589, 1486, 1283, 1113, 822, 742, 701 cm^{-1}; δ_H 1.11 [9 H, s, $(CH_3)_3C$], 4.00 (4 H, m, 2 × CH_2), 5.76 (1 H, s, ArCH), 6.76 (1 H, d, *J* 8 Hz, ArH), 6.98 (1 H, s, ArH), 6.99 (1 H, d, *J* 8 Hz, ArH), 7.05 (1 H, dd, *J* 7, 8 Hz), 7.34–7.42 (6 H, m, ArH), 7.70–7.74 (4 H, m, ArH); *m*/*z* (EI) 404 (M$^+$), 347 (M$^+$ − C_4H_9), 303. Found M$^+$ 404.1794. $C_{25}H_{28}O_3Si$ requires 404.1808.

Dimethyl 1-(3-*tert*-butyldiphenylsilyloxyphenyl)-1-(2-hydroxyethoxy)methylphosphonate 26

To a solution of the ethylene acetal **25** (2.25 g, 5.6 mmol) in dichloromethane (40 cm^3), under argon at −78 °C, was added, dropwise, titanium(IV) chloride (1 cm^3, 9.1 mmol). To the stirred solution was added trimethyl phosphite (1 cm^3, 8.5 mmol) and the solution stirred at −78 °C for a further 30 min prior to warming to room temperature and stirring for a further 45 min. The reaction was quenched by pouring into an excess of saturated aqueous sodium hydrogen carbonate solution and then extraction into ethyl acetate (4 × 50 cm^3). The organic extract was washed with brine, dried, filtered and evaporated under reduced pressure to afford a light brown oil. The crude product was purified by chromatography (2:1 acetone–light petroleum) to afford the *title compound* as a colourless oil (1.95 g, 68%); ν_{max}(film) 3408, 2956, 2858, 1600, 1483, 1277, 1113, 1038, 822, 742, 701 cm^{-1}; δ_H 1.09 [9 H, s, $(CH_3)_3C$], 2.70 (1 H, br s, D_2O exch., OH), 3.46 (2 H, t, *J* 4 Hz, CH_2O), 3.47, 3.49 (6 H, d, *J* 10 Hz, CH_3O), 3.61 (2 H, t, *J* 4 Hz, CH_2O), 4.53 (1 H, d, *J* 16 Hz, ArCH), 6.78 (1 H, d, *J* 8 Hz, ArH), 6.80 (1 H, s, ArH), 6.92 (1 H, d, *J* 8 Hz, ArH), 7.11 (1 H, t, *J* 8 Hz, ArH), 7.34–7.42 (6 H, m, ArH), 7.70–7.74 (4 H, m, ArH); *m*/*z* (EI) 514 (M$^+$), 457, 426. Found: M$^+$ 514.1930. $C_{27}H_{35}O_6PSi$ requires 514.1941.

Dimethyl 1-(3-*tert*-butyldiphenylsilyloxyphenyl)-1-(2-phthalimidoethoxy)methylphosphonate 29

A solution of the alcohol **26** (3.31 g, 6.5 mmol), triphenylphosphine (1.85 g, 7.1 mmol) and phthalimide (0.96 g, 6.5 mmol) in dry THF (35 cm^3) was cooled to 0 °C and diethyl azodicarboxylate (1.1 cm^3) added dropwise over 10 min. The mixture was stirred for a further 10 min before allowing to warm to room temperature for 1.5 h. The solvent was removed under reduced pressure and the crude oil obtained was chromatographed, using 2:1 ethyl acetate–light petroleum as eluant, to afford the *title compound* as a pale viscous oil (2.67 g, 70%); ν_{max} ($CHCl_3$ film) 2955, 2858, 1774, 1712, 1601, 1277, 1112, 1036, 823, 763, 722 cm^{-1}; δ_H 1.00 [9 H, s, $(CH_3)_3C$], 3.46 and 3.48 (6 H, d, *J* 10 Hz, 2 × CH_3O), 3.54 (2 H, t, *J* 4 Hz, CH_2), 3.75 (2 H, t, *J* 4 Hz, CH_2), 4.49 (1 H, d, *J* 15 Hz, CHP), 6.70 (1 H, d, *J* 8 Hz, ArH), 6.80 (1 H, s, ArH), 6.83 (1 H, d, *J* 8 Hz, ArH), 6.85 (1 H, dd, *J* 1, 8 Hz, ArH), 7.34–7.36 (6 H, m, ArH), 7.71 (6 H, m, ArH), 7.82 (2 H, m, ArH); *m*/*z* (CI) 644 (MH$^+$), 535, 454. Found: 643.7475. $C_{35}H_{38}NO_7PSi$ requires 643.7470.

1-(2-Adamantylidene)-1-[2-(4-tolylsulfonyloxy)ethoxy]-1-(3-*tert*-butyldiphenylsilyloxyphenyl)methane 28

To a solution of diisopropylamine (2 cm^3, 14.3 mmol, 3 equiv.) and dry THF (30 cm^3) under argon at −78 °C was added a solution of *n*-butyllithium (1.6 mol dm^{-3}, 4.6 cm^3, in hexane) and stirring continued for 45 min. A solution of the alcohol **26** (1.9 g, 3.6 mmol) in dry THF (10 cm^3) was slowly added and stirring continued for a further 45 min. Adamantan-2-one (0.59 g, 3.93 mmol) in dry THF (120 cm^3) was added, the solution allowed to warm to room temperature and stirring continued for a further 3 h. Toluene-4-sulfonyl chloride (0.69 g, 3.6 mmol, 1.0 equiv.) in dry THF (10 cm^3) was added and the mixture stirred for a further 16 h. The reaction mixture was then poured into an excess of 0.1 mol dm^{-3} phosphate buffer at pH 7.0 and the product extracted into ether (2 × 100 cm^3). The ether extract was washed with brine before drying, filtering and evaporation under reduced pressure to give a viscous oil. This was purified by chromatography (1:10 acetonitrile–light petroleum) to afford the *title compound* as a white powdery solid (0.50 g, 20%), mp 95–97 °C; ν_{max}($CHCl_3$ film) 2924, 2853, 1597, 1360, 1283, 1257, 1113, 1097, 819, 737, 707 cm^{-1}; δ_H 1.09 [9 H, s, $(CH_3)_3C$], 1.37–1.86 (12 H, m, adamantanyl-H), 2.33 (1 H, br s, adamantanyl-H), 2.44 (3 H, s, CH_3Ar), 3.02 (1 H, s, adamantanyl-H), 3.26 (2 H, t, *J* 4 Hz, CH_2), 3.91 (2 H, t, *J* 4 Hz, CH_2), 6.52 (1 H, s, ArH), 6.75 (1 H, d, *J* 8 Hz, ArH), 6.77 (1 H, d, *J* 8 Hz, ArH), 7.07 (1 H, t, *J* 8 Hz), 7.30–7.39 (6 H, m, ArH), 7.40 (2 H, m, ArH), 7.69 (4 H, m, ArH), 7.76 (2 H, m, ArH); *m*/*z* (EI) 693 (M$^+$), 522. Found: C, 73.1; H, 7.2. $C_{42}H_{48}O_5SSi$ requires C, 72.8; H, 7.0%.

Dimethyl 1-(3-*tert*-butyldiphenylsilyloxyphenyl)-1-(2-aminoethoxy)methylphosphonate 30

To a solution of the phthalimide **29** (1.0 g, 1.7 mmol) in ethanol (10 cm^3) was added hydrazine hydrate (0.9 cm^3, 2.55 mmol, 1.5 equiv.). The mixture was stirred at 50 °C until the solution became turbid, after about 15 min. The slurry was poured into an excess of 2 M aqueous hydrochloric acid (20 cm^3) and the mixture heated at 100 °C on a steam bath for 10 min. The mixture was cooled and the solid phthalohydrazide that formed was removed by filtration. The filtrate was basified to pH 8, with the addition of 2 M aqueous sodium carbonate solution before extraction with ethyl acetate (2 × 25 cm^3), washing with brine, drying, filtering and evaporation to afford the *title compound* as a viscous pale yellow oil (0.523 g, 60%); ν_{max}(film) 3251, 2956, 2858, 1659, 1600, 1277, 1113, 1055, 822, 743, 703 cm^{-1}; δ_H 1.09 [9 H, s, $(CH_3)_3C$], 2.44 (2 H, br s, exch. D_2O, NH_2), 3.41–3.56 (8 H, m, CH_2 and CH_3O), 4.20 (2 H, t, *J* 4 Hz, CH_2), 4.47 (1 H, d, *J* 16 Hz, CHP), 6.67 (2 H, m, ArH), 6.92 (1 H, d, *J* 8 Hz, ArH), 7.1 (1 H, m, ArH), 7.32–7.43 (6 H, m, ArH), 7.65–7.72 (4 H, m, ArH); *m*/*z* (CI) 531 (MNH_4^+), 514 (MH$^+$), 483, 456, 404. Found: M$^+$ 531.6821. $C_{27}H_{36}NO_5PSi\cdot NH_4^+$ requires 531.6827.

4′-Methoxy-4′-phenylspiro[adamantane-2,3′-[1,2]dioxetane] 33

A solution of the vinyl ether **17** (0.30 g, 1.2 mmol) and Methylene Blue (1 mg) in dichloromethane, kept at room temperature, was irradiated with a water-cooled 400 W medium pressure Hg arc lamp whilst oxygen was bubbled through the solution. After 40 min, when no starting material remained, irradiation was stopped and the solution was passed through a plug of silica gel to remove the sensitizer, washing with more dichloromethane. Removal of solvent under reduced pressure afforded the *title peroxide* as a crystalline solid (0.32 g, 93%), mp 85–88 °C (lit.[22] 84–85 °C); δ_H 1.55–2.10 (12 H, m, adamantanyl-H), 2.17 (1 H, s, adamantanyl-H), 3.05 (1 H, s, adamantanyl-H), 3.22 (3 H, s, CH_3O), 7.42–7.46 (5 H, m, ArH).

4′-Methoxy-4′-(3-hydroxyphenyl)spiro[adamantane-2,3′-[1,2]dioxetane] 34

Prepared in a similar manner to compound **33**, but from the phenol **19** (0.214 g, 0.8 mmol). The product *peroxide* (0.22 g, 90%) showed mp 129–133 °C (decomp.) (lit.[5] 135 °C); δ_H 1.54–

1.99 (12 H, m, adamantanyl-H), 2.72 (1 H, s, adamantanyl-H), 3.22 (1 H, s, adamantanyl-H), 3.40 (3 H, s, CH_3O), 5.28 (1 H, br s, exch. D_2O, OH), 6.74–6.80 (2 H, m, ArH), 6.88 (1 H, d, *J* 8 Hz, ArH), 7.21 (1 H, m, ArH).

4′-Ethoxy-4′-(3-hydroxyphenyl)spiro[adamantane-2,3′-[1,2]-dioxetane] 35

Prepared in a similar manner to compound **33**, but from the phenol **21** (0.25 g, 0.88 mmol). The *title peroxide* was obtained as a white solid (0.22 g, 90%), mp 125–127 °C (decomp.); δ_H 1.20 (3 H, t, *J* 7 Hz, CH_3), 1.54–1.99 (12 H, m, adamantanyl-H), 2.72 (1 H, s, adamantanyl-H), 3.22 (1 H, s, adamantanyl-H), 3.54 (2 H, q, *J* 7 Hz, CH_2), 5.28 (1 H, br s, exch. D_2O, HO), 6.74–6.80 (2 H, m, ArH), 6.88 (1 H, d, *J* 8 Hz, ArH), 7.21 (1 H, m, ArH).

This dioxetane was further characterised by its base catalysed decomposition. Thus a solution of the dioxetane (28 mg, 0.1 mmol) in dimethyl sulfoxide (1 cm^3) was treated with *tert*-butylammonium hydroxide (0.2 mmol) at room temperature for 15 min. Water (5 cm^3) was added and the solution neutralised with glacial acetic acid before extracting into ether. The organic layer showed just two major components identified by TLC comparison with authentic samples as adamantanone and ethyl 3-hydroxybenzoate. The latter was isolated (11 mg, 66%) and showed mp and mixed mp 71–73 °C.

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References

1 A. K. Campbell, *Chemiluminescence*, Ellis Horwood Ltd, Chichester, 1988.
2 K. R. Kopecky and C. Mumford, *Can. J. Chem.*, 1969, **47**, 709; K. R. Kopecky, *Synthesis of 1,2-Dioxetanes*, in *Chemical and Biological Generation of Excited States*, ed. W. Adam and G. Cilento, Academic Press, London, 1982, p. 85 ff.
3 F. Kohen, M. Pazzagli, M. Serio, J. de Boever and D. Vandekerckhove, *Chemiluminescence and Bioluminescence Immunoassay*, in *Alternative Immunoassays*, ed. W. P. Collins, J. Wiley and Sons, Chichester, 1985, pp. 103–119; G. H. Thorpe, I. Bronstein, L. J. Kricka, B. Edwards and J. C. Voyta, *Clin. Chem.*, 1989, **35**, 2319; I. Bronstein, *Chemiluminescent 1,2-Dioxetane-based Enzyme Substrates and their Applications*, in *Luminescent Immunoassays and Molecular Applications*, ed. K. van Dyke and R. van Dyke, CRC Press Inc., Boca Raton, 1990, 255.
4 C. A. Roeschlaub, PhD thesis, University of Surrey, 2000.
5 A. P. Schaap and H. Akhaven-Tafti, EP 0254051A2 (1988), *Chem. Abstr.*, 1991, **114**, 181726g.
6 A. Fürstner, A. Hupperts, A. Ptock and E. Janssen, *J. Org. Chem.*, 1994, **59**, 5215; A. Fürstner and A. Hupperts, *J. Am. Chem. Soc.*, 1995, **117**, 4468; A. Fürstner and B. Bogdanovic, *Angew. Chem.*, *Int. Ed. Engl.*, 1996, **35**, 2442.
7 L. Horner, H. Hoffmann and H. G. Wippel, *Chem. Ber.*, 1958, **91**, 61; L. Horner, H. Hoffmann, H. G. Wippel and G. Klahre, *Chem. Ber.*, 1959, **92**, 2499; W. S. Wadsworth and W. D. Emmons, *J. Am. Chem. Soc.*, 1961, **83**, 1733; J. Boutagy and R. Thomas, *Chem. Rev.*, 1974, **74**, 87.
8 (*a*) F. Straus and H. Heinz, *Annalen*, 1932, 191; (*b*) F. Klages and E. Mullbauer, *Annalen*, 1959, 1818; (*c*) E. Schumann and F.-F. Grabley, *Annalen*, 1977, 88.
9 D. Burkhouse and H. Zimmer, *Synthesis*, 1984, **4**, 330.
10 A. Michaelis and R. Kaehne, *Ber. Dtsch. Chem. Ges.*, 1898, **31**, 1048; A. E. Arbusov, *J. Russ. Phys. Chem. Soc.*, 1906, **38**, 68; S. R. Landauer and H. N. Rydon, *J. Chem. Soc.*, 1953, 2224.
11 T. Yokomatsu, T. Yamagushi, K. Matsumoto and S. Shibuya, *Tetrahedron*, 1996, **52**, 11725.
12 R. F. Hudson, *Angew. Chem.*, *Int. Ed. Engl.*, 1973, **12**, 36.
13 S. Hanessian and P. Lavallee, *Can. J. Chem.*, 1975, **53**, 2975; M. Lalonde and T. H. Chan, *Synthesis*, 1985, 817.
14 O. Mitsunobu, *Synthesis*, 1981, 1.
15 J. H. Wieringa, J. Strating, H. Wynberg and W. Adam, *Tetrahedron Lett.*, 1972, 169.
16 W. L. F. Armarego and D. D. Perrin, *Purification of Laboratory Chemicals*, Butterworth Heinemann, Oxford, 4th edn., 1996.
17 J. Tateiwa, H. Honiuchi and S. Uemura, *J. Org. Chem.*, 1995, **60**, 4039.
18 A. Russell and S. F. Clark, *J. Am. Chem. Soc.*, 1935, **61**, 2651.
19 V. R. Bodipudi and W. J. Le Noble, *J. Org. Chem.*, 1994, **59**, 3265.
20 R. Perz and J. Boyer, *Bull. Soc. Chim. Fr.*, 1970, 262.
21 J. Thien, M. Gunter and H. Paulsen, *Chem. Ber.*, 1975, **108**, 2279.
22 L. Lopez and L. Triosi, *Tetrahedron*, 1992, **48**, 7321.