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Synthesis and antimicrobial evaluation of farnesyl diphosphate mimetics

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Abstract

The synthesis and first antimicrobial evaluation of farnesyl diphosphate mimetics are described. Several analogues (**10**, **12**, **13**, and **20**) are inhibitors of *Candida albicans*, *Shizosaccharomyces pombe*, and *Saccharomyces cerevisiae*. The activities of analogues **10**, **12**, and **13**, which contain a ω -phenyl moiety and a diphosphate isostere, are not attributable to inhibition of sterol biosynthesis via squalene synthase. Two geranyl phenylsulphones (**14** and **15**) are potent inhibitors of *Escherichia coli*. Analogue **15** exhibits potent activity towards *Salmonella typhimurium* and *Pseudomonas aeruginosa* (MIC=2 μ g/mL) and represents the first type of semi-synthetic terpenoid allylic sulphone active against these bacteria.

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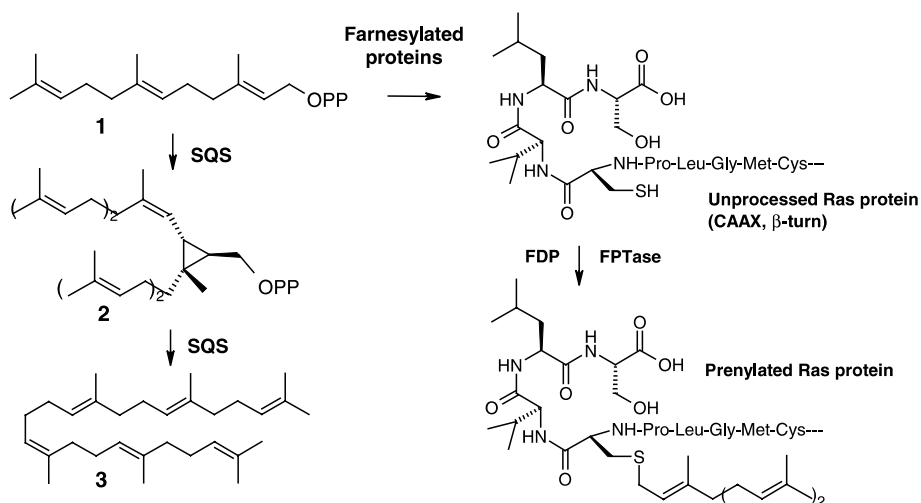
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1. Introduction

The synthesis and biological evaluation of farnesyl diphosphate (FDP) mimetics has received notable attention, mainly as FDP is used as a substrate by both *Squalene synthase* [1] (SQS) and *farnesyl-protein transferase* [2] (FPTase). SQS is a membrane-bound enzyme located in the cholesterol biosynthetic pathway which catalyses the reductive dimerisation of two molecules of FDP via presqualene diphosphate (**2**) to squalene (**3**) (Scheme 1). Compounds that inhibit SQS reduce the formation of cholesterol, a substance implicated in the development of Atherosclerosis [1]. FPTase catalyses the farnesylation of the thiol group of cysteine located at the forth amino acid (CAAX) position from the C-terminal of several small G-proteins. Amongst them is the protein *ras*, which is involved in growth regulatory signal transduction [2]. Mutated *ras* genes have been frequently found in various human malignancies and play a role in human tumour growth. Hence, inhibition of FPTase is highly desirable, as the oncogenic activity of mutated *ras* is dependant on the farnesylation by FPTase [3].

As part of an ongoing project into finding active antimicrobial agents, we were particularly drawn to FDP mimetics, as they show diverse biological activity when simple structural changes are made [3,4]. The antimicrobial activities of FDP mimetics remains an area unexplored, even though potent agents that target sterol biosynthesis or related biosynthetic pathways would be ideal targets that merit investigation. FDP mimetics are synthetically easily accessible and therefore the construction of a wide range of structurally diverse FDP mimetics are available for anti-fungal evaluation.

From the extensive published works in this area we considered a farnesyl mimic and diphosphate isostere essential for inhibitory activity [3]. Several hydrophobic mimics of



Scheme 1. FDP (**1**) is converted into squalene (**3**) by SQS and utilised by FPTase in the S-prenylation process.

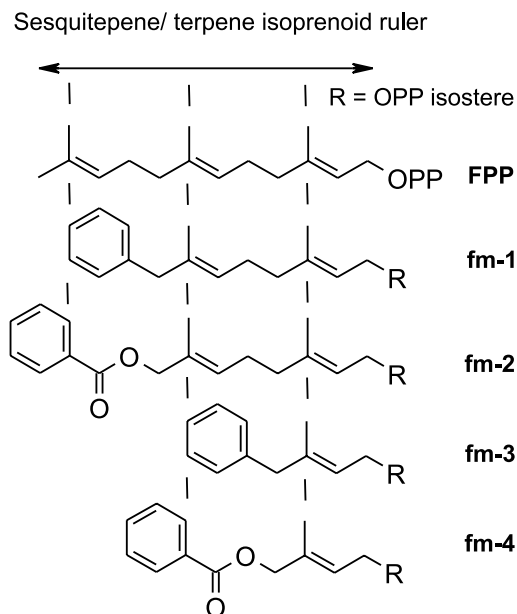


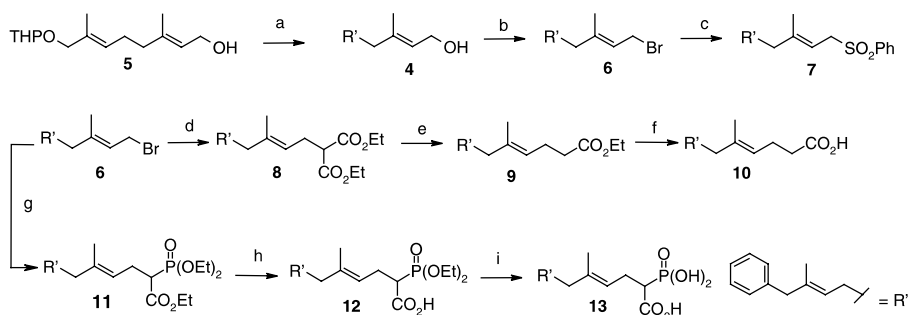
Fig. 1. Molecular ruler hypothesis for isoprenoid specificity.

the farnesyl chain are well preceded [3–5]. The X-ray co-crystal structure of FPTase and FDP demonstrates the elongated orientation of the farnesyl chain within the enzyme active site [6]. A “molecular ruler” hypothesis for isoprenoid substrate specificity has been proposed, where the depth of the hydrophobic binding cavity acts as a ruler in discriminating between isoprenoids of different lengths [6] (Fig. 1).

We were particularly drawn to the farnesyl mimics **fm-1** and **fm-2**, developed by Wiemer [4a] and Distefano [5], respectively (Fig. 1). Based on the molecular ruler hypothesis it was envisaged that the smaller farnesyl mimics, such as **fm-3** or **fm-4**, might be less specific towards SQS or FPTase. An ideal diphosphate isostere would be one that shares electronic and steric similarities with the diphosphate moiety [7]. Such isosteres include bisphosphonic acids, mixed phosphonic/carboxyl acids, and dicarboxyl acid moieties. We envisaged that an unusual isostere would be a sulphonyl moiety ($-\text{SO}_2\text{R}$), which may act as a less polar variant of diphosphate or as a pro-drug, where on hydrolysis the sulphonic acid (a known phosphonate isostere) is released.

2. Results and discussion

The synthetic routes to the **fm-1** derivatives are shown in Scheme 2. Alcohol **4** was synthesised in five steps from commercially available geraniol in 69% overall yield using the method of Wiemer [4a]. The key step in this route was THPO-displacement of **5** with PhMgBr under copper(I) iodide catalysis, proceeding in 82% yield.



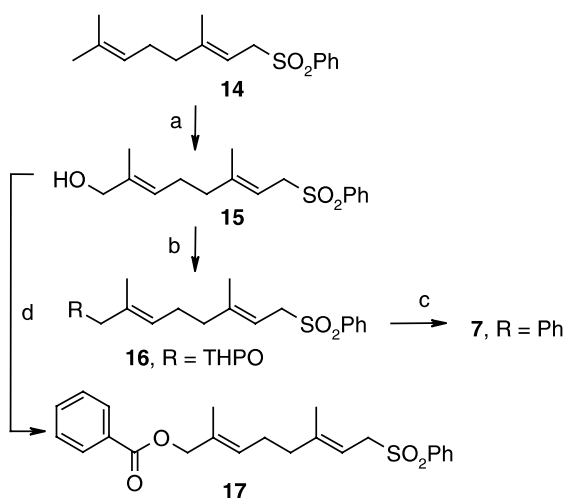
a. CuI, PhMgBr, THF, 50°C. b. NBS-DMS or PBr₃. c. PhSO₂Na⁺, DMF. d. NaH, DEM, THF. e. NaCl, H₂O-DMF, reflux. f. NaOH, EtOH, reflux. g. NaH, triethylphosphonoacetate, THF. h. NaOH, EtOH, reflux. c. i). TMSBr, collidine. ii). NaOH

Scheme 2. Synthetic Routes to **fm-1** derivatives.

Bromination of **4** with NBS-DMS [8] or PBr₃ affords **6**, which is taken as crude for reaction with benzenesulphinic acid sodium salt in DMF, providing the **fm-1** sulphone target **7** in 81% overall yield from **4**. PBr₃ is the brominating reagent of choice on scaling up the synthesis of **6**. Alkylation of **6** using the anions of diethyl malonate and triethyl phosphonoacetate was possible (generated in situ using NaH in THF) to give **8** and **11** in 60% and 44% yields, respectively. Compound **8** was decarboxylated under neutral conditions using NaCl in moist DMF, which proceeded in 63% yield. Ester **9** was then hydrolysed using ethanolic NaOH at reflux to give acid **10** in 85% yield. Selective hydrolysis of **11** using ethanolic NaOH at reflux gave acid **12** in 88% yield. Conversion of **12**–**13** using TMSBr in collidine was somewhat cumbersome in that hydrolysis with NaOH took over 22 days, affording **13** in 58% yield. The synthesis of **fm-2** derivatives was approached via two routes (Schemes 3 and 4).

E-Selective SeO₂ oxidation of **14**, followed by NaBH₄ reduction, gave alcohol **15** in 80% yield (Note. We obtained 90% yield on 1.3 mmol scale) [9]. Alcohol **15** was protected using 3,4-dihydro-2*H*-pyran (DHP) catalysed by TsOH, yielding the tetrahydropyranyl ether **16** in essentially quantitative yield (98%). The tetrahydropyranyl ether (THPO–) generates a reactive centre allowing S_N2 Grignard coupling using RMgBr under CuI catalysed conditions [4a]. Tetrahydropyranyl ether **16** reacts with PhMgBr (10 eqv) and CuI (5 eqv) to give **7** in 21% yield. Reducing the Grignard reagent to 5 equivalents, CuI to 1 equivalent and increasing the dilution (3-fold) gave **7** in 42% yield. The **fm-2** target **17** was synthesised via standard benzoylation of **15** (57% yield).

The **fm-2** alcohol **20** was synthesised according to the procedure of Distefano and coworkers **19** [5] (Scheme 4). In short, compound **18** [9] was converted to **19** via esterification with benzoyle chloride in 38% yield under standard conditions (Compound **19** is unstable). Selective hydrolysis of **19** using NH₄OH in methanol proceeded to give free alcohol **20** in 42% yield. It was also possible to synthesise **17** from **20**, by conversion to the light-sensitive bromide **21** using PBr₃ or NBS-DMS, followed by S_N2 displacement using benzenesulphinic acid sodium salt in DMF to give **17** in 77% yield.



- a. i). SeO_2 (5mol%), T-HYDROTM (3eqv.), CH_2Cl_2 ,
 ii). NaBH_4 -MeOH, 0°C . b. DHP, TsOH, CH_2Cl_2 .
 c. PhMgBr , CuI, THF, 50°C . d. PhCOCl , Pyr., DMAP.

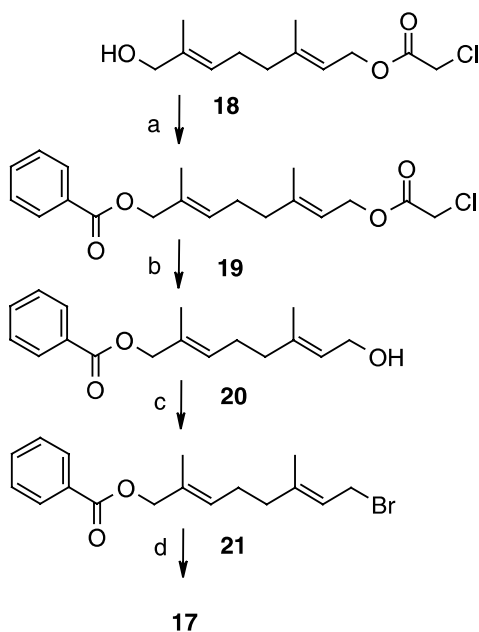
Scheme 3. Synthetic route A to **fm-2** derivatives.

3. Biological results

The target and intermediate test compounds were passed through a general antimicrobial screen [10]. Three yeasts (*Candida albicans*, *Shizosaccharomyces pombe*, and *Saccharomyces cerevisiae*, Table 1) and three bacteria (*Bacillus subtilis*, *Escherichia coli*, and *Staphylococcus aureus*, Table 2) were chosen to evaluate the effectiveness of the test compounds. All compounds were tested at a concentration of $200\text{ }\mu\text{g/mL}$ in triplicate. The activities of compounds **4**, **7–15**, **17**, **20**, **23**, **24**, and the control Squalastatin **S1** [11] (Fig. 2) were screened against the yeasts shown in Table 1.

The test compounds exhibit quite diverse activities. Free alcohol **4** is a modest inhibitor of *S. pombe* and *S. cerevisiae*. Incorporation of a diphosphate bioisostere results in enhanced activity. For example, compounds **10**, **12**, and **13** were all active against the three yeasts. The free phosphonic acid **13** was, as expected, more potent than the protected ester derivative **12**. Free carboxylic acid **10** surprisingly showed similar activity to the protected ester derivative **9**. This is presumably due to the presence of an esterase enzyme capable of hydrolysing **9** to the active acid **10** in vitro.

The control, squalastatin **S1** [11], exhibited no activity towards any of the bacteria. Therefore, **S1** is either unable to cross the bacterial cell wall, or all of the bacteria species screened are non-dependant on SQS and ultimately sterol biosynthesis [12]. Several of the compounds (**4**, **7**, **10**, **13**, **14**, **15**, and **20**) were active against Gram-positive *B. subtilis*, although only compounds **10** and **20** were inhibitors of *S. aureus* (Gram-positive) (Table 2). Compound **10** was also a modest inhibitor of *E. coli*



a. PhCOCl, Pyr., DMAP. b. NH_4Cl , MeOH.
c. NBS-DMS, THF, 0°C or PBr_3 , Et_2O , 0°C .
d. PhSO_2Na^+ , DMF

Scheme 4. Synthetic route B to **fm-2** derivatives.

Table 1
Activity of FDP mimetics against yeasts^a

Compound	<i>C. albicans</i>	<i>S. pombe</i>	<i>S. cerevisiae</i>
4	na	8	11
7	9	11	10
8	11	11	12
9	na	14	19
10	13	17	20
11	11	7	9
12	10	11	16
13	19	18	20
14	13	15	12
15	7	14	16
17	9	10	nd
20	12	15	7
23	na	5	5
24	na	7	na
SI ^b	26	35	30

^a Zone of inhibition (values are means of three experiments). Na, not active and nd, not determined.

^b Control at 200 $\mu\text{g/mL}$.

Table 2
Activity of FDP mimetics against bacteria^a

Compound	<i>B. subtilis</i>	<i>E. coli</i>	<i>S. aureus</i>
4	10	na	na
7	7	na	na
8	na	na	na
9	na	na	na
10	25	14	30
13	15	na	na
14	7	15	na
15	12	42	na
17	na	na	na
20	15	8	6
S1^b	na	na	na

^a Zone of inhibition (values are means of three experiments). Na, not active.

^b Control at 200 µg/mL.

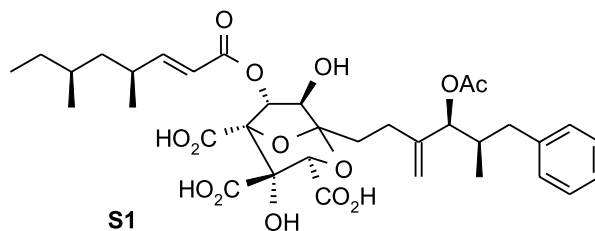


Fig. 2. Squalenstatin **S1**.

(Gram-negative) and is therefore non-selective towards Gram-positive or Gram-negative bacteria. Nevertheless, the activity of **10** is reliant on the presence of a free acid, as ethyl ester **9** was inactive against all of the bacteria screened.

Both phenyl sulphones **14** and **15** are active against *E. coli* (Gram-negative). The large zone of inhibition for **15** against *E. coli* is of notable attention (Fig. 3i). The minimum inhibitory concentration (MIC) for **15** was determined to be 1.5 µg/mL [13]. This result led to the additional screening of **15** (at varying concentrations)

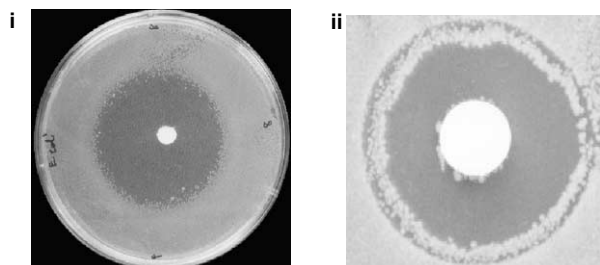


Fig. 3. (i) Inhibition zone of **15** (200 µg/mL) against *E. coli*. (ii) Inhibition zone of **15** (20 µg/mL) against *S. typhimurium*.

Table 3
Inhibition zones of **15** against bacteria^a

Bacteria	Concentration (μg)			
	200	20	2	0.2
<i>S. epidermidis</i>	na	na	na	na
<i>E. coli</i> 8110	19	7	na	na
<i>P. aeruginosa</i>	15	7	5	na
<i>S. typhimurium</i>	23	16	5	na
<i>Acinetobacter</i> sp.	na	na	na	na

^a Zone of inhibition (values are means of three experiments). Na, not active.

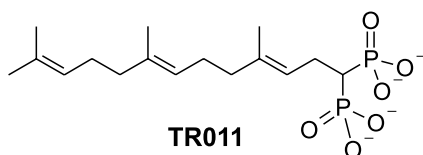


Fig. 4. Control FDP mimetic—**TR011**.

against several species of bacteria, including *Staphylococcus epidermidis*, *E. coli* 8110, *Pseudomonas aeruginosa*, *Salmonella typhimurium*, and *Acinetobacter* sp. (Table 3).

Compound **15** is active against three of the five bacteria tested, with inhibition observed for both *P. aeruginosa* and *S. typhimurium* at 2 μg/mL concentration. The MIC for **15** against *P. aeruginosa* and *S. typhimurium* were determined to be 2 μg/mL.

However, for *S. typhimurium* at 20 μg/mL, it was apparent within the inhibition zones that bacterial colonies had formed which were clearly not as sensitive to **15** compared to the others on the plate (Fig. 3ii). This seemingly resistant strain of reduced sensitivity to **15** is most likely to be a sub-type of *S. typhimurium*.

Preliminary efforts to determine the inhibition target(s) of the active compounds were focused on SQS activity using an assay previously developed [14]. Unfortunately we found that compounds **4**, **10**, **11**, and **12** were not inhibitors of this enzyme at 0.1 and 1 μM, respectively, whereas the controls Squalastatin **S1** and **TR011** [15] (Fig. 4) caused >90% inhibition at both concentrations.

Compounds **7**, **13**, and **17** caused minor inhibition (~20%) of SQS at 1 and 0.1 μM. At higher concentrations the inhibitory activity of the phenylsulphone **17** was reduced, and we attribute that to low water solubility and associated micelle formation.

4. Conclusions

In conclusion, we have constructed several FDP analogues, utilizing the synthetic methodology described by Wiemer and coworkers [4] for the introduction of a

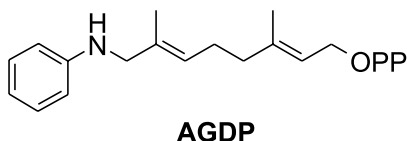


Fig. 5. The AGDP analogue described by Spielmann [16].

phenyl moiety at the ω -terminus, that incorporate an appropriate isostere of the diphosphate moiety. The FDP analogues exhibit promising antimicrobial activities and to the best of our knowledge are the first such results reported for any FDP analogues. The activity of compounds **9–13** was thought to be attributable to inhibition of SQS. However, the low SQS inhibition results suggest an alternative site of inhibition, possibly FPTase, when compared directly with the antimicrobial results. Our results correlate well with the 8-anilino geranyl diphosphate (AGDP) analogue recently reported by Spielmann and coworkers [16] (Fig. 5). AGDP is a poor SQS inhibitor ($IC_{50} = 1000 \mu M$) and good FPTase inhibitor ($IC_{50} = 0.5 \mu M$). Selectivity is an important objective when developing competitive FDP inhibitors as these compounds may interfere with other FDP utilizing enzymes. Thus there is a clear possibility that replacement of the terminal isoprene unit for a phenyl moiety increases the selectivity of these FDP analogues toward FPTase.

Phenyl sulphone **15** was an unexpected inhibitor of the yeasts and bacteria species, although its mode of inhibition may lie via inhibition of *Farnesyl synthase* (FSase), the enzyme preceding SQS within the sterol biosynthetic pathway, for which compound **15** shares closer electronic and structural similarity to geranyl diphosphate (GDP)—the substrate for FSase. Recently Świeżewska [17] presented results that show FSase is the main regulatory enzyme within ergosterol biosynthesis in *S. cerevisiae*, responding to the greatest extent to changes in internal and external environmental conditions when compared directly to SQS and 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) [18]. Inhibition of FSase may therefore represent an attractive target for future sterol biosynthesis inhibitors.

The biological activities of the active antimicrobial compounds reported here, against both FSase and FPTase, will be determined and reported in due course.

5. Experimental

5.1. Antimicrobial assay

The determination of the antimicrobial activity of each compound was assessed using an established standard disc-plate method [10]. Sabourad's agar (Oxoid Products) was prepared according to the manufacturers instructions, and then dispensed in 20 mL amounts into glass universal bottles and these were autoclaved at 121 °C and 15 psi for 15 min. The molten agar was poured into agar plates (Sterilin). Each strain was inoculated into 10 mL of Sabourad's broth (prepared according to

manufacturers instructions) and incubated at the appropriate temperatures (25 °C for *S. pombe* and *S. cerevisiae*, 37 °C for *C. albicans* for 12 h). After incubation the resultant broth culture was diluted in sterile saline to produce a 1/100 dilution. Aseptically, a 0.1 mL aliquot of this dilution was pipetted onto the agar plate and carefully spread around the agar surface. A sterile 4 mm paper disc was placed on the centre of agar plate and then the test compound (20 µl of a 10, 1, 0.1, or 0.01 mg/mL in absolute ethanol or water with final concentrations of 200, 20, 2, 0.2 µg/mL, respectively) was inoculated onto the sterile paper disc. These plates were incubated at the appropriate temperatures (25 °C for *S. pombe* and *S. cerevisiae*, 37 °C for *C. albicans* for 24 h). To investigate the antimicrobial activity of the test compounds on the bacterial species an identical procedure to the yeast assay was adopted, however, nutrient agar (LAB M) and nutrient broth (LAB M) were the preferred growth media. Incubation of the bacterial species was conducted at 37 °C for 24 h.

5.2. *In vitro* SQS enzyme assay

The SQS screening was performed using an assay previously described [14]. Squalestatin **S1** [11] and **TR011** [15] were used as controls in this assay. The controls inhibited the enzyme by greater than 90% at both 0.1 and 1 µM.

5.3. General

Nuclear magnetic resonance (^1H and ^{13}C) spectra were recorded on a Jeol GNX 270 (at 270 and 67.8 MHz, respectively) spectrometer. Chemical shifts are reported in parts per million (δ) downfield from an internal tetramethylsilane reference. Coupling constants (J values) are reported in hertz (Hz), and spin multiplicities are indicated by the following symbols: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad). The relative proportion of solvents in mixed chromatography solvents refer to the volume/volume ratio. Triethylamine, hexane, and dichloromethane were dried over calcium hydride and distilled before use. All reaction solvents were distilled for purity. Diethyl ether and THF were distilled from sodium-benzophenone ketyl. Chloroform (400 mL) was washed with water (6×200 mL) (to remove ethanol), dried over MgSO_4 , and then distilled over P_2O_5 twice. All reactions were performed in an inert atmosphere created by a slight positive pressure of argon. GC spectra were recorded on a Finnigan 2000 series GC coupled to a Finnigan Trace MS, source Electron Impact (EI) 70 eV. GC Column: Restek Rtx-5MS Crossbond 5% diphenyl-95% dimethyl polysiloxane (15 m, 0.25 mmID, 0.25 µm df). GC Conditions: 60–310 °C, Rate 10 °/min. GC internal standard—octadecane.

8-Phenyl-3,7-dimethyl-2E,6E-octadien-1-ol (**4**). To a stirred suspension of magnesium turnings (washed with dry THF and dried at 80 °C) in dry THF (20 mL) under an atmosphere of argon was added a small crystal of iodine. Bromobenzene (2.47 g, 15.8 mmol, 10 eqv) in dry THF (5 mL) was added dropwise over 10 min. The mixture was then heated to 50 °C for 3 h with good stirring. The grey metallic solution was allowed to cool and then added slowly via cannula to a separate flask containing a stirred mixture of compound **5** (400 mg, 1.58 mmol, 1 eqv), copper(I) iodide

(1.49 g, 7.85 mmol, 5 eqv) in dry THF (10 mL) under a steady stream of argon. The resulting mixture was heated to 50 °C with good stirring for 4 h. The reaction was quenched by the addition of a sat. aq. NH_4Cl (50 mL) and extracted with ether (3×100 mL). The combined organic extracts were dried (MgSO_4) and concentrated in vacuo to afford a yellow oil. Purification by flash chromatography using ethyl acetate/hexane (2:3, v/v) gave the known *title compound* [4] as a pale yellow oil (294 mg, 81.4%). ^1H (270 MHz) (CDCl_3) δ 7.12–7.29 (5H, m, Ph–H), 5.29–5.33 (1H, t, J 6.9, C2–H), 5.20–5.29 (1H, t, J 7, C6–H), 4.08–4.10 (2H, d, J 6.9, C1–H₂), 3.26 (2H, s, C8–H₂), 2.03–2.20 (4H, m, C4–H₂, and C5–H₂), 1.65 (3H, s, C9–H₃), 1.52 (3H, s, C10–H₃), 1.35 (1H, br, C1–OH). ^{13}C NMR (67.8 MHz) (CDCl_3) δ 140.2, 138.8, 134.6, 128.6 (2C), 128 (2C), 127 (2C), 123.6, 59.1, 46.1, 39.4, 26.2, 16.1, 15.6. LRMS (EI) m/z 230 (M^+), 212, 199 ($\text{M}^+ - \text{CH}_2\text{OH}$), 185, 172, 157, 144, 117, 105, 91 (CH_2Ph), 81, 71, 55 (100%). HRMS (EI) m/z exact mass calculated for $\text{C}_{16}\text{H}_{22}\text{O}$ 230.16706; found 230.16652.

8-Phenyl-3,7-dimethyl-2E,6E-octadien-1-bromide (**6**). Compound **4** (202 mg, 0.87 mmol) in ether (3 mL) was stirred at 0 °C for 30 min, then PBr_3 (87.3 mg, 0.32 mmol, 0.36 eqv) in ether (1 mL) was added dropwise over 10 min in the absence of light. The reaction was stirred at 0 °C for 3 h. The mixture was poured onto crushed ice-water (10 mL) and extracted with ether (3×10 mL). The combined extracts were washed with 10% aq. NaHCO_3 (2×10 mL) and water (1×10 mL). The organic extract was dried (MgSO_4) and concentrated in vacuo to give a pale yellow oil, which was taken up in ether/hexane (5:1, v/v) and passed through a small column of silica (500 mg). Concentration in vacuo afforded the *title compound* as a pale yellow oil (233 mg, 90.5%). ν_{max} (neat)/ cm^{-1} 3058, 3024, 2974, 2920, 2854, 1948, 1878, 1805, 1655, 1601, 1493, 1450, 1384, 1076, 891, 732. ^1H (270 MHz) (CDCl_3) δ 7.14–7.34 (5H, m, Ph–H), 5.49–5.56 (1H, td, J 1.1, and 8.4, C2–H), 5.17–5.24 (1H, t, J 8.1, C6–H), 3.99–4.02 (2H, d, J 8.4, C1–H₂), 3.26 (2H, s, C8–H₂), 2.02–2.18 (4H, m, C4–H₂, and C5–H₂), 1.71 (3H, s, C9–H₃), 1.53 (3H, s, C10–H₃). LRMS (EI) m/z 294 ($\text{M}^+ ^{81}\text{Br}$) 1%, 292 ($\text{M}^+ ^{79}\text{Br}$) 1%, 279, 255, 213 ($\text{M}^+ - \text{Br}$), 145 (100%), 91, 81, 79, 49, 41. HRMS (EI) m/z exact mass calculated for $\text{C}_{16}\text{H}_{21} ^{79}\text{Br}$ 292.08266; found 292.08253.

Ethyl 10-phenyl-4E,8E-ethoxycarbonyl-5,9-dimethyl-decadienoate (**8**). A 60% dispersion of NaH in oil (20.4 mg, 0.54 mmol, 1.05 eqv) was washed with dry THF (5 mL) and decanted. Dry THF (5 mL) was added via cannula and then diethyl malonate (0.41 g, 2.26 mmol, 5 eqv) in dry THF (5 mL) was added slowly via cannula at 0 °C over 30 min. The mixture was allowed to warm to ambient temperature over 2 h. Compound **6** (0.15 g, 0.51 mmol) in dry THF (2 mL) was added via cannula over 30 min, and then the mixture was stirred at ambient temperature overnight. The reaction was quenched by the addition of sat. NH_4Cl (10 mL), and extracted with ether (3×20 mL). The combined extracts were washed with water (2×30 mL), dried (MgSO_4), and concentrated in vacuo to give a yellow oil. Purification by flash chromatography using ethyl acetate/hexane (1:5, v/v) gave the *title compound* as a clear oil (113 mg, 59.5%). ν_{max} (neat)/ cm^{-1} 3058, 2983, 2935, 1737, 1601, 1450, 1369, 1269, 1150, 1037, 860, 737, 702. ^1H NMR (270 MHz) (CDCl_3) δ 7.14–7.30 (5H, m, Ph–H), 5.18–5.23 (1H, td, J 1.1, and 7.9, C4–H), 5.07–5.13 (1H, td, J 1.1, and

7.9, C8–H), 4.14–4.22 (4H, m, CO₂C–H₂x2), 3.31–3.26 (1H, t, *J* 7.7, C2–H), 3.26 (2H, s, C10–H₂), 2.58–2.63 (2H, dd, *J* 7.7, and 7.9, C3–H₂), 2.01–2.14 (4H, m, C6–H₂, and C7–H₂), 1.64 (3H, s, C11–H₃), 1.52 (3H, s, C12–H₃), 1.25–1.31 (6H, m, CO₂CH₂C–H₃x2). ¹³C NMR (67.8 MHz) (CDCl₃) δ 169.2, 140.4, 138.2, 134.5, 128.8, 128.1, 126.1, 125.8, 118.9, 61.2, 52.3, 46.2, 39.6, 27.5, 26.5, 16.1, 15.7, 14.0. LRMS (EI) *m/z* 372 (M⁺), 327 (M⁺ – OCH₂CH₃), 226, 159, 91 (CH₂ Ph), 77 (Ph). Found: C, 74.29; H, 9.07, C₂₃H₃₂O₄ requires C, 74.16; H, 8.66.

Ethyl 10-phenyl-4E,8E-5,9-dimethyl-decadienoate (**9**). Under an argon atmosphere compound **8** (51 mg, 0.14 mmol), NaCl (18.9 mg, 0.33 mmol, 2.35 eqv), water (50 μL), and *N,N'*-dimethylformamide (2 mL) were placed under reflux for 20 h. The mixture was diluted with water (5 mL) and extracted with ether (3 × 5 mL). The combined extracts were washed with water (2 × 8 mL), dried (MgSO₄), and concentrated in vacuo to yield a brown oil. Purification by flash chromatography using ethyl acetate/hexane (1:19, v/v) gave the *title compound* (19.2 mg, 46.7%, 62.8% based on recovered starting material) followed by unreacted starting material (13.1 mg). ¹H NMR (270 MHz) (CDCl₃) δ 7.15–7.30 (5H, m, Ph–H), 5.19–5.24 (1H, td, *J* 0.7, and 6.4, C4–H), 5.07–5.14 (1H, m, C8–H), 4.08–4.16 (2H, q, *J* 7.2, CO₂C–H₂), 3.26 (2H, s, C10–H₂), 2.27–2.36 (4H, m, C2–H₂, and C3–H₂), 2.00–2.17 (4H, m, C6–H₂, and C7–H₂), 1.62 (3H, s, C11–H₃), 1.52 (3H, s, C12–H₃), 1.23–1.28 (3H, t, *J* 7.2, CO₂CH₂C–H₃). ¹³C NMR (67.8 MHz) (CDCl₃) δ 173.4, 140.5, 136.4, 134.4, 128.8 (2C), 128.2 (2C), 126.3, 125.9, 122.6, 60.2, 46.3, 39.6, 34.6, 30.4, 26.6, 16.1, 15.9. LRMS (EI) *m/z* 301 (M⁺ + 1), 300 (M⁺), 255 (M⁺ – OCH₂CH₃), 209 (M⁺ – CH₂Ph), 181, 145, 117, 91 (CH₂Ph), 67. HRMS (EI) *m/z* exact mass calculated for C₂₀H₂₈O₂ 300.20893; found 300.20819.

10-Phenyl-4E,8E-5,9-dimethyl-decadienoic acid (**10**). Compound **9** (0.4 g, 1.3 mmol) in ethanol (5 mL) and water (5 mL) was stirred at ambient temperature. Crushed KOH pellets (0.75 g, 13.3 mmol, 10 eqv) were added slowly, and then the mixture was refluxed overnight. The mixture was acidified with 2.0 M aq. HCl (20 mL) and extracted with ether (3 × 30 mL). The organic extracts were combined and washed with water (2 × 40 mL), dried (MgSO₄), and concentrated in vacuo to give a pale yellow oil. Purification by flash chromatography using ethyl acetate/hexane (2:3, v/v) gave the *title compound* as a clear oil (0.30 g, 85.2%). ¹H NMR (270 MHz) (CDCl₃) δ 11.10–12.00 (1H, br, C1–OH), 7.14–7.30 (5H, m, Ph–H), 5.18–5.24 (1H, td, *J* 0.7, and 7.0, C4–H), 5.09–5.14 (1H, m, C8–H), 3.26 (2H, s, C10–H₂), 2.28–2.38 (4H, br m, C2–H₂, and C3–H₂), 2.00–2.16 (4H, m, C6–H₂, and C7–H₂), 1.62 (3H, s, C11–H₃), 1.52 (3H, s, C12–H₃). ¹³C NMR (67.8 MHz) (CDCl₃) δ 179.5, 140.5, 136.8, 134.5, 128.8 (2C), 128.2 (2C), 126.2, 125.9, 122.2, 110.3, 46.2, 39.5, 34.2, 26.5, 23.3, 15.9, 15.8. LRMS (EI) *m/z* 272 (M⁺), 195 (M⁺ – Ph), 181 (M⁺ – CH₂Ph), 165, 112, 91 (CH₂Ph), 77 (Ph). HRMS (EI) *m/z* exact mass calculated for C₁₈H₂₄O₂ 272.17763; found 272.17665.

Ethyl 2-(diethoxyphosphinyl)-10-phenyl-5,9-dimethyl-4E,8E-decadienoate (**11**). To a solution of NaH (46.7 mg, 1.2 mmol, 1.2 eqv, 60% dispersion in oil, washed with dry THF (5 mL) removed via cannula) in dry THF (7 mL) was added triethylphosphonoacetate (0.29 g, 1.33 mmol, 1.3 eqv) in dry THF (3 mL) via cannula. After 30 min the mixture was cooled to 0 °C and transferred via cannula over 30 min to a mixture of bromide **6** (0.3 g, 1.02 mmol, 1 eqv) in dry THF (8 mL). The resulting

mixture was allowed to warm slowly to ambient temperature. After 18 h the reaction was quenched by addition of water (20 mL). The mixture was extracted with ethyl acetate (4×20 mL), combined, dried (MgSO_4), and concentrated in vacuo to give an orange oil. Purification by flash chromatography using ethyl acetate/hexane (1:1, v/v) gave the *title compound* as a clear oil (196 mg, 44.1%). ^1H NMR (270 MHz) (CDCl_3) δ 7.13–7.30 (5H, m, Ph–H), 5.18–2.23 (1H, td, J 1.1, and 6.3, C4–H), 5.05–5.10 (1H, t, J 6.8, C8–H), 4.09–4.23 (6H, m, $\text{POC-H}_2\text{x2}$, and $\text{CO}_2\text{C-H}_2$), 3.26 (2H, s, C10–H₂), 2.88–3.01 (1H, ddd, J 4.0, 11.0, and 26.6, C2–H), 2.47–2.78 (2H, m, C3–H₂), 1.99–2.11 (4H, m, C6–H₂, and C7–H₂), 1.64 (3H, s, C11–H₃), 1.51 (3H, s, C12–H₃), 1.23–1.37 (9H, m, $\text{POCH}_2\text{C-H}_3\text{x2}$, and $\text{CO}_2\text{CH}_2\text{C-H}_3$). ^{13}C NMR (67.8 MHz) (CDCl_3) δ 168.9, 140.5, 138.0, 134.6, 128.2, 127.9, 126.1, 125.9, 120.7, 120.5, 62.7, 62.6, 62.5, 47.2, 45.3, 39.6, 26.6, 25.8, 25.7, 16.5, 16.4, 16.1, 15.8, 14.2. FAB LRMS: 459.3 ($\text{M} + \text{Na}$)⁺, 437.3 ($\text{M} + 1$, 100%)⁺, 391.3 ($\text{M} - \text{CH}_3\text{CH}_2\text{O}$), 293.2, 291.2, 247.1, 224.1, 197.1, 179.1, 157.1, 151, 145.1, 129.1, 117.1. FAB HRMS: m/z exact mass calculated for $\text{C}_{24}\text{H}_{37}\text{NaO}_5$ 459.2276; found 459.2273. Found: C, 65.11; H, 8.67; P, 6.90, $\text{C}_{24}\text{H}_{37}\text{O}_5\text{P}$ requires C, 66.04; H, 8.54; P, 7.10.

2-(*Diethoxyphosphinyl*)-10-phenyl-5,9-dimethyl-4*E*,8*E*-decadienoic acid (**12**). Compound **11** (143 mg, 0.33 mmol) and 2 M aq. NaOH (0.6 mL, 1.3 mmol) in ethanol (10 mL) were refluxed for 4 h. The mixture was allowed to cool to ambient temperature and acidified with 1 M aq. HCl (5 mL). The mixture was extracted with ethyl acetate (4×20 mL), and the combined extracts were washed with water (2×5 mL), dried (MgSO_4), and concentrated in vacuo to give a yellow oil. Flash chromatography using methanol/ethyl acetate (1:19, v/v) gave the *title compound* as a yellow oil (0.19 g, 88.1%). ^1H NMR (270 MHz) (CDCl_3) δ 7.13–7.29 (5H, m, Ph–H), 5.13–5.23 (2H, m, C4–H, and C8–H), 4.12–4.23 (4H, q, J 7.0, $\text{POC-H}_2\text{x2}$), 3.26 (2H, s, C10–H₂), 2.93–3.06 (1H, m, C2–H), 2.43–2.70 (2H, m, C3–H₂), 1.97–2.15 (4H, m, C6–H₂, and C7–H₂), 1.61 (3H, s, C11–H₃), 1.51 (3H, s, C12–H₃), 1.28–1.33 (6H, t, J 7.0, $\text{POCH}_2\text{C-H}_3$). LRMS (EI) m/z 409 ($\text{M}^+ + 1$), 391 ($\text{M}^+ - \text{OH}$), 345, 305, 224, 179 ($\text{PO}(\text{OEt})_2\text{CHCO}$), 144, 117, 91 (CH_2Ph), and 67. FAB LRMS: m/z mass calculated for $\text{C}_{22}\text{H}_{33}\text{O}_5\text{P}$ 408.48; 431.2 ($\text{M} + \text{Na}$)⁺, 391.2 ($\text{M} - \text{OH}$)⁺, 247.1, 237.1, 191.1, 179.1 ($\text{PO}(\text{OEt})_2\text{CHCO}$), 165.1, 145.1 ($\text{C}_{11}\text{H}_{13}$), 129.1 ($\text{C}_{10}\text{H}_{10}$), 117.1 (C_9H_{10}), 105.1 (C_8H_7).

2-(*Phosphono*)-10-phenyl-5,9-dimethyl-4*E*,8*E*-decadienoic acid (**13**). To a stirred mixture of the acid **12** (134 mg, 0.33 mmol) and collidine (0.2 mL, ~ 5 eqv) in CH_2Cl_2 (6 mL) at 0 °C was added trimethylsilyl bromide (0.2 mL, ~ 5 eqv). The mixture was stirred at 0 °C for 30 min and then warmed to ambient temperature and stirring was continued overnight. Toluene (8 mL) was added and the mixture was then concentrated in vacuo to remove all the volatile components. A solution of 0.5 M aq. NaOH (5.5 mL) was added and the resulting clear solution was stirred for 22 days, after which time all the starting material had been consumed as adjudged by TLC. The reaction mixture was acidified with 2 M aq. HCl until pH 1, extracted with ethyl acetate (4×20 mL), and the combined organic extracts were dried (MgSO_4) and concentrated in vacuo affording the *title compound* as a yellow oil (67.6 mg, 58.4%). The oil was dried under in vacuo at 0.1 mm Hg for 10 h at 40 °C to ensure complete removal of toluene. ^1H NMR (270 MHz) (D_2O) δ Selected 7.14–7.32

(5H, m, Ph), 5.10–5.21 (2H, m, C4–H, and C8–H), 3.25 (2H, s, C10–H₂), 2.32–2.78 (3H, m, C2–H, and C3–H₂), 1.910–2.09 (4H, m, C6–H₂, and C7–H₂), 1.63 (3H, s, C11–H₃), 1.58 (3H, s, C12–H₃). ³¹P NMR (109.36 MHz) (D₂O) δ 22.3 (1P, s, PO(OH)₂). LRMS (ESI) m/z 353 and 352 (M⁺) 100%.

8-Phenyl-3,7-dimethyl-2E,6E-octadien-1-phenyl sulphone (7). Compound **6** (195 mg, 0.66 mmol) in dry *N,N'*-dimethylformamide (5 mL) was stirred at 0 °C. The sodium salt of benzenesulphonic acid (115 mg, 0.7 mmol, 1.01 eqv) was added in small portions over 20 min. The mixture was stirred at 0 °C for 1 h and then at ambient temperature overnight. The mixture was diluted with ether (30 mL) and washed with water (3 \times 20 mL). The organic extract was dried (MgSO₄) and concentrated in vacuo to give a light brown oil. Purification by flash chromatography using ethyl acetate/hexane (3:7, v/v) gave the title compound as a yellow oil (209 mg, 88.9%). ¹H NMR (270 MHz) (CDCl₃) δ 7.85–7.87 (2H, dd, *J* 1.5, and 8.4, SO₂Ph–C2'–H, C6'–H), 7.45–7.65 (3H, m, SO₂Ph–C3'–H, C4'–H, C5'–H), 7.13–7.41 (5H, m, Ph), 5.14–5.27 (2H, m, C2–H, and C6–H), 3.78–3.81 (2H, d, *J* 8.06, C1–H₂), 3.26 (2H, s, C8–H₂), 1.99–2.12 (4H, m, C4–H₂, and C5–H₂), 1.51 (3H, s, C9–H₃), 1.31 (3H, s, C10–H₃). ¹³C NMR (67.8 MHz) (CDCl₃) δ 146.1, 140.2, 133.1, 128.9, 128.8, 128.5, 128.2, 125.9, 125.319, 56.1, 46.1, 39.6, 26.2, 16.1, 15.8. LRMS (EI) m/z 354 (M⁺), 229 (100%), 213 (M⁺ – SO₂Ph), 197, 183, 171, 155 (CH₂SO₂Ph). Found: C, 74.22; H, 7.31, C₂₂H₂₆O₂S requires C, 74.54; H, 7.39.

3,7-Dimethyl-2E,6-octadien-1-phenyl sulphone (14). Geranyl bromide (8.69 g, 40.06 mmol) in dry *N,N'*-dimethylformamide (20 mL) was added dropwise to a stirred suspension of the sodium salt of benzenesulphonic acid (6.57 g, 40.06 mmol) in dry *N,N'*-dimethylformamide (20 mL) at 0 °C over 1 h. The reaction mixture was left to stir at 0 °C for a further 2 h and warmed to ambient temperature and stirred overnight. The reaction mixture was poured into ice-water (200 mL) and extracted with ether (5 \times 100 mL). The combined organic extracts were washed with water (5 \times 250 mL), dried (MgSO₄), and concentrated in vacuo to yield a yellow oil (10.16 g, 91.2%). Purification by flash chromatography using ethyl acetate/hexane (1:4, v/v) afforded the known *title compound* [19] as a light yellow oil (8.13 g, 72%). Purification by distillation in vacuo (15 mm Hg) resulted in rapid decomposition of the product. ν_{\max} (neat)/cm^{–1} 3062, 2967, 2922, 2857, 1972, 1903, 1819, 1678, 1585, 1447, 1405, 1386, 1307, 1150, 1086, 899. ¹H NMR (270 MHz) (CDCl₃) δ 7.85–7.88 (2H, m, C2'–H, and C6'–H), 7.61–7.66 (1H, m, C4'–H), 7.50–7.55 (2H, dd, *J* 7.2, and 7.2, C3'–H, and C5'–H), 5.16–5.22 (1H, t, *J* 8.0, C2–H), 5.01–5.06 (1H, m, C6–H), 3.79–3.82 (2H, d, *J* 8.0, C1–H₂), 1.99–2.08 (4H, m, C4–H₂, and C5–H₂), 1.69 (3H, s, C10–H₃), 1.59 (3H, s, C8–H), 1.32 (3H, s, C9–H). LRMS (EI) m/z 278.4 (M⁺), 155.1 (PhSO₂Ph), 137 (M⁺ – SO₂Ph) (100%), 141 (SO₂Ph), 121.1, 81, 77 (Ph).

8-Hydroxy-3,7-dimethyl-2E,6E-octadien-1-phenyl-sulphone (15). Compound **14** (5 g, 18 mmol) was reacted with *tert*-butyl hydroperoxide (6.13 mL, 44.9 mmol, 2.5 eqv) and SeO₂ (99.7 mg, 0.89 mmol, 5 mol%). A standard work-up gave a crude oil that was reduced using NaBH₄ (0.68 g, 17.9 mmol, 1 eqv) over 30 min at 0 °C. Standard work-up gave an oil. Purification by flash chromatography using ethyl acetate/hexane (3:7, v/v) gave the known *title compound* [9] as a viscous yellow oil (4.25 g, 80.3%). ν_{\max} (neat)/cm^{–1} 3064, 2978, 2931, 2875, 1979, 1907, 1819, 1680,

1585, 1244, 1196, 1149, 1089. ^1H NMR (270 MHz) (CDCl_3) δ 7.85–7.89 (2H, dd, J 1.5, and 7.0, C2'-H and C6'-H), 7.62–7.65 (1H, dd, J 1.5, and 7.0, C4'-H), 7.52–7.58 (2H, m, C3'-H and C5'-H), 5.31–5.36 (1H, m, C2-H), 5.16–5.22 (1H, td, J 1.1, and 8.05, C6-H), 3.99 (2H, s, C8-H₂), 3.79–3.82 (2H, d, J 8.05, C1-H₂), 2.08–2.16 (4H, m, C4-H₂, and C5-H₂), 1.65 (3H, s, C9-H₃), 1.37 (3H, s, C10-H₃). ^{13}C NMR (67.8 MHz) (CDCl_3) δ 145.9, 138.9, 135.5, 133.5, 128.9 (2C), 128.3 (2C), 124.5, 110.4, 68.5, 55.9, 39.1, 25.4, 16.1, 13.6. LRMS (EI) m/z 294.1 (M^+), 281.1 ($\text{M}^+ - \text{OH}$), 155.9 ($\text{CH}_2\text{SO}_2\text{Ph}$), 153.1 ($\text{M}^+ - \text{SO}_2\text{Ph}$), 119, 107.1, 93 (100%), 77 (Ph). HRMS (EI) m/z exact mass calculated for $\text{C}_{16}\text{H}_{22}\text{O}_3\text{S}$ 294.12896; found 294.12837.

8-[(2'-Tetrahydropyranyl)-oxy]-3,7-dimethyl-2E,6E-octadi-en-1-phenyl-sulphone (**16**). To compound **15** (2 g, 6.80 mmol) in dry CH_2Cl_2 (20 mL) was added toluene-sulphonic acid (64 mg, 0.34 mmol, 5 mol%). The mixture was allowed to stir at 0°C for 30 min, and then dihydropyran (1.14 g, 13.6 mmol, 2 eqv) in dry CH_2Cl_2 (5 mL) was added slowly over 30 min. The mixture was stirred at ambient temperature overnight. The solvent was removed in vacuo and the residue taken up in ether (50 mL), washed successively with 10% aq. NaHCO_3 (2 \times 30 mL) and water (3 \times 30 mL). The combined organic extracts were dried (MgSO_4) and concentrated in vacuo to yield a brown oil. Purification by flash chromatography using ethyl acetate/hexane (3:7, v/v) gave the known title compound [**20**] as a pale yellow oil (2.52 g, 97.9%). ν_{max} (neat)/ cm^{-1} 3060, 2923, 2868, 1978, 1902, 1815, 1722, 1685, 1599, 1446, 1241, 1149, 1078, 976, 869. ^1H NMR (270 MHz) (CDCl_3) δ 7.86–7.88 (2H, d, J 8.05, C2'-H, and C6'-H), 7.61–7.67 (1H, dd, J 2.13, and 8.05, C4'-H), 7.50–7.56 (2H, t, J 8.05, C3'-H, and C5'-H), 5.34–5.38 (1H, m, C2-H), 5.17–5.23 (1H, t, J 7.9, C6-H), 4.58–4.61 (1H, t, J 6.59, THP-C1'-H), 4.08–4.12 (1H, d, J 11.7, THP-C6'*ax*-H), 3.75–3.92 (4H, m, C1-H₂, and C8-H₂), 3.47–3.55 (1H, m, THP-C6'*eq*-H), 2.01–2.08 (4H, m, C4-H₂, and C5-H₂), 1.45–1.87 (9H, br m, THP-C3'-C4'-C5'-3H₂, and C10-H₃), 1.32 (3H, s, C9-H₃). Found: C, 66.67; H, 8.17, $\text{C}_{21}\text{H}_{30}\text{O}_4\text{S}$ requires C, 66.63; H, 7.99. LRMS (EI) m/z 396 (M^+) 30%, 312 (100%), 294, 277, 135, 118, 102, 85. HRMS (EI) m/z exact mass calculated for ($^+\text{NH}_4$ enhanced) $\text{C}_{21}\text{H}_{34}\text{NO}_4\text{S}$ 396.22085; found 396.22076.

8-Phenyl-3,7-dimethyl-2E,6E-octadien-1-phenyl sulphone (**7**) using CuI/PhMgBr . Compound **16** (0.5 g, 1.32 mmol) was reacted with a 3.0 M solution of PhMgBr in ether (4.4 mL, 13.22 mmol, 10 eqv) catalysed by CuI (1.26 g, 6.61 mmol, 5 eqv). The usual work-up afforded a mixture of products. Purification by flash chromatography using ether/hexane (1:4, v/v) afforded known (4b) 1,8-diphenyl-3,7-dimethyl-2E,6E-octa-diene and biphenyl (172 mg, 45% approx.), followed by the title compound as a yellow oil (98.6 mg, 21.1%). TLC; ^1H . Data for 1,8-diphenyl-3,7-dimethyl-2E,6E-octa-diene **85** and biphenyl ^1H NMR (270 MHz) (CDCl_3) in accordance with the ^1H data reported by Wiemer (4b): Selected δ 7.10–7.59 (\sim 10H, m, Ph-H_x2), 5.33–5.37 (1H, m, C2-H), 5.21–5.25 (1H, m, C6-H), 3.30–3.34 (2H, d, J 7.3, C1-H₂), 3.26 (2H, s, C8-H₂), 2.08–2.17 (4H, m, C5-H₂, and C6-H₂), 1.70 (3H, s, C9-H₃), 1.51 (3H, s, C10-H₃).

8-Hydroxy-3,7-dimethyl-2E,6E-octadien-1-chloroacetate (**18**). Following a standard SeO_2 oxidation procedure, compound **18** (1.5 g, 6.51 mmol) was reacted with

SeO₂ (72.2 mg, 0.65 mmol, 10 mol%), *tert*-butyl hydroperoxide (3 mL, 23.4 mmol, 3.6 eqv) and benzoic acid (79.4 mg, 0.65 mmol, 10 mol%) in CH₂Cl₂ (20 mL). The usual work-up yielded a pale yellow oil. Purification by flash chromatography using ether/hexane (3:7, v/v) yielded the known title compound (**5**) as a colourless oil (0.69 g, 42.8%). ν_{\max} (neat)/cm⁻¹ 3386, 2979, 2933, 1741, 1672, 1450, 1414, 1385, 1363, 1246, 1194, 845, 787, 7480. ¹H NMR (270 MHz) (CDCl₃) δ 5.33–5.40 (2H, m, C2–H, and C6–H), 4.69–4.72 (2H, d, *J* 7.33, C1–H₂), 4.06 (2H, s, C12–H₂), 3.99 (2H, s, C8–H₂), 2.06–2.19 (4H, m, C4–H₂, and C5–H₂), 1.73 (3H, s, C9–H₃), 1.66 (3H, s, C10–H₃). ¹³C NMR (67.8 MHz) (CDCl₃) 167.6, 142.9, 135.4, 125.2, 118.1, 68.7, 63.2, 41.9, 38.9, 25.7, 16.8, 13.9.

8-Benzoxo-3,7-dimethyl-2E,6E-octadien-1-ol (**20**). Following a standard procedure, compound **18** (0.43 g, 1.74 mmol) was reacted with benzoyl chloride (0.37 g, 2.62 mmol, 1.5 eqv) in pyridine (5 mL) and DMAP (25 mg, 10 mol%). The mixture was left to stir for 24 h. The usual work-up gave a brown oil. Purification by flash chromatography using ether/hexane (3:2, v/v) gave a yellow oil (232 mg, 38.1%). Unstable chloroacetate **19** (0.22 g, 0.63 mmol) was hydrolysed with 0.1 M NH₄OH (3 mL) in aqueous methanol (9:1, v/v). The mixture was stirred for 1 h, and methanol was then removed in vacuo. The residue was dissolved in ether (30 mL) and washed with water (2 × 15 mL), dried (MgSO₄), and concentrated in vacuo to give an oil. Purification by flash chromatography using ethyl acetate/hexane (1:4, v/v) gave the known *title compound* [**5**] as a clear oil (72.4 mg, 42.1%). ¹H NMR (270 MHz) (CDCl₃) δ 8.04–8.12 (2H, m, C2'–H, and C6'–H), 7.53–7.61 (1H, m, C4'–H), 7.41–7.50 (2H, m, C3'–H, and C5'–H), 5.50–5.55 (1H, t, *J* 6.8, C2–H), 5.39–5.50 (1H, m, C6–H), 4.71 (2H, s, C8–H₂), 4.14–4.16 (2H, d, *J* 6.8, C1–H₂), 2.18–2.27 (2H, m, C5–H₂), 2.07–2.15 (2H, m, C4–H₂), 1.74 (3H, s, C9–H₃), 1.68 (3H, s, C10–H₃), 1.38 (1H, br, C1–OH). ¹³C NMR (67.8 MHz) (CDCl₃) δ 166.5, 138.9, 133.6, 132.9, 130.4, 130.1, 129.6, 128.8, 128.5, 128.4, 124.0, 70.5, 59.4, 38.9, 25.9, 16.2, 14.0. For complete characterisation this compound was converted to 8-benzoxo-3,7-dimethyl-2E,6E-octadien-1-acetate, using pyridine (10 mL), DMAP (10 mg, cat.), and acetic anhydride: Standard work-up and flash chromatography using ethyl acetate/hexane (1:10, v/v) to provide 68.2 mg (86.6%) of a clear oil. δ^1 H (CDCl₃) 8.25–8.28 (2H, m, C2'–H, and C6'–H), 8.14–8.18 (1H, m, C4'–H), 7.51–7.69 (2H, m, C3'–H, and C5'–H), 5.61–5.66 (1H, td, *J* 1.1, and 14.66, C2–H), 5.44–5.49 (1H, td, *J* 1.1, and 15.39, C6–H), 4.81 (2H, s, C8–H₂), 4.68–4.70 (2H, d, *J* 6.96, C1–H₂), 2.28–2.36 (2H, m, C5–H₂), 2.18–2.24 (2H, m, C4–H₂), 2.15 (3H, s, C12–H₃), 1.84 (3H, s, C9–H₃), 1.82 (3H, s, C10–H₃). LRMS (CI) *m/z* 334 (M + NH₄), 257, 196, 135 (100), 105. HRMS (EI) *m/z* exact mass calculated for (⁺NH₄ enhanced) C₁₉ H₂₈ NO₄ 334.20183; found 334.20155.

8-Benzoxo-3,7-dimethyl-2E,6E-octadien-1-phenyl sulphone (**17**) via bromide (**21**). Compound **20** (200 mg, 0.73 mmol) in dry CH₂Cl₂ (5 mL) was reacted with NBS (195 mg, 1.1 mmol, 1.5 eqv) and DMS (81.5 mg, 1.31 mmol, 1.8 eqv). The usual work-up afforded crude **21**, which was used without further purification. Crude **21** was taken up in *N,N'*-dimethylformamide (5 mL) and stirred for 30 min at 0 °C. The sodium salt of benzenesulphonic acid (126 mg, 0.77 mmol, 1.05 eqv) in *N,N'*-dimethylformamide (5 mL) was added slowly over 20 min and stirred for 1 h at 0 °C, and

then at ambient temperature overnight. The usual work-up gave a yellow oil. Purification by flash chromatography using ethyl acetate/hexane (1:3, v/v) gave the title compound as a yellow oil (223 mg, 77.4%). ν_{\max} (neat)/ cm^{-1} 3064, 2982, 2935, 1756, 1686, 1583, 1449, 1272, 1030, 939, 748, 707. ^1H NMR (270 MHz) (CDCl_3) δ 8.04–8.13 (2H, m, C2'–H, and C6'–H), 7.86–7.88 (2H, d, J 6.6, C2''–H, and C6''–H), 7.41–7.66 (6H, m, C3'–H, C4'–H, C5'–H, C3''–H, C4''–H, and C5''–H), 5.44–5.49 (1H, t, J 8.1, C2–H), 5.18–5.24 (1H, t, J 7.7, C6–H), 4.70 (2H, s, C8–H₂), 3.79–3.82 (2H, d, J 8.1, C1–H₂), 2.06–2.17 (4H, m, C4–H₂, and C5–H₂), 1.72 (3H, s, C9–H₃), 1.34 (3H, s, C10–H₃). FAB LRMS: m/z 421.2 ($\text{M} + \text{Na}$)⁺, 399.2 ($\text{M} + 1$)⁺, 278.1 ($\text{M} - \text{PhCO}_2 + 1$), 277.1 ($\text{M} - \text{PhCO}_2$), 189.1, 143, 135.1 (PhCO_2CH_2 , 100%), 133.1, 121.1 (PhCO_2), 105 (PhCO). FAB HRMS: m/z exact mass calculated for $\text{C}_{23}\text{H}_{26}\text{NaSO}_4$ 421.1450; found 421.1450. Found: C, 68.61; H, 6.68; S, 7.83, $\text{C}_{23}\text{H}_{26}\text{O}_4\text{S}$ requires C, 69.32; H, 6.58; S, 7.83.

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