# Competitive inhibition of aristolochene synthase by phenyl-substituted farnesyl diphosphates: evidence of active site plasticity†

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Analogues of farnesyl diphosphate (FPP, **1**) containing phenyl substituents in place of methyl groups have been prepared in syntheses that feature use of a Suzuki–Miyaura reaction as a key step. These analogues were found not to act as substrates of the sesquiterpene cyclase aristolochene synthase from *Penicillium roqueforti* (AS). However, they were potent competitive inhibitors of AS with $K_I$-values ranging from 0.8 to 1.2 μM. These results indicate that the diphosphate group contributes the largest part to the binding of the substrate to AS and that the active sites of terpene synthases are sufficiently flexible to accommodate even substrate analogues with large substituents suggesting a potential way for the generation of non-natural terpenoids. Molecular mechanics simulations of the enzyme bound inhibitors suggested that small changes in orientations of active site residues and subtle alterations of the conformation of the backbones of the inhibitors are sufficient to accommodate the phenyl-farnesyl-diphosphates.

## Introduction

Terpenoids are the largest group of natural products with immense diversity in their structure and function.[1] There has been significant interest in terpenoids as antifungal, antibacterial and anticancer agents for the treatment of human disease with multibillion-dollar sales worldwide. Despite their enormous structural variety, all terpenes are derived from simple linear precursors such as geranyl diphosphate (GPP), farnesyl diphosphate (FPP), and geranyl geranyl diphosphate (GGPP). Cyclisation of GPP to monoterpenes, FPP to sesquiterpenes and GGPP to diterpenes is accomplished by terpene synthases. These enzymes, many of which share the mainly α-helical class I terpene fold, serve as high fidelity templates that subtly channel conformation and stereochemistry during the cyclisation reactions and are key to the generation of the wide diversity in structure and stereochemistry found in terpenoids (Fig. 1). They bind their respective substrates together with the obligatory $Mg^{2+}$-cofactor, catalyse the loss of the diphosphate group and chaperone the reaction intermediates along complex reaction pathways; often with exquisite specificity. Terpene synthases catalyse highly regio- and stereospecific cyclisations, hydride

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† Electronic supplementary information (ESI) available: General experimental procedures and protocols for diphosphorylation of target alcohols. Enzyme preparation, purification and kinetic characterisation of inhibitors as well as plots of [*I*] *versus* apparent $K_M$ for FPP turnover by AS in the presence of **19**, **29**, and **36**. See DOI: 10.1039/b713301b

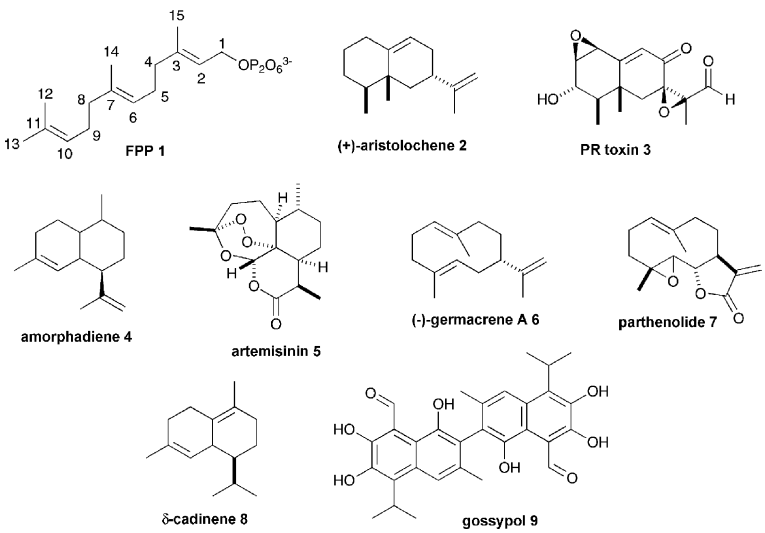
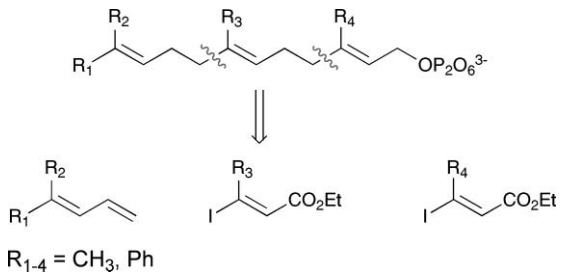



**Fig. 1** Structure of FPP (**1**) and some examples of the complexity of natural products derived from it. The parent sesquiterpenes such as **2**, **4**, **6** and **8** may be further transformed by downstream metabolic processes into a diverse set of sesquiterpenoids such as PR toxin (**3**), artemisinin (**5**), parthenolide (**7**), and gossypol (**9**).

and methyl transfers as well as deprotonation reactions while at the same time excluding solvent from the active site to prevent premature quenching by water of the extremely reactive cationic reaction intermediates. The majority of the characterised terpene synthases form only one or a few products; however, there are some enzymes that form a variety of products from a single substrate. The δ-selinene and γ-humulene synathases from *Abies grandis* (the grand fir) produce 34 and 52 sesquiterpenes, respectively.[2,3]

Clearly the exact arrangement of the amino acid residues in the active site of individual terpene cyclases within a common protein fold is crucial for the outcome of the reaction. Site directed replacement of amino acids in and around the active site of several terpene synthases has indicated that the product distribution can often be altered.[4–13] While these experiments indicated the high adaptability of these enzymes, the products generated by the mutant enzymes were always known natural terpenoids. However, the plasticity of terpene synthases suggests that they have the potential for the generation of novel "unnatural" terpenes from unnatural prenyl-diphosphate analogues. While biosynthetic restrictions imply that all prenyl-diphosphates carry methyl substituents only, a synthetic approach to analogues of the substituents of terpene cyclases currently allows the introduction of a wide variety of substituents.

To test whether the active sites of terpene synthases can accommodate alternate substrates we report here syntheses of the FPP analogues containing phenyl substituents in place of the methyl groups on C3 and C11 (Scheme 1). While (2*E*,6*E*,10*E*)-3,7-dimethyl-11-phenyldodeca-2,6,10-trien-1-yl diphosphate (**19**), (2*E*,6*E*,10*Z*)-3,7-dimethyl-11-phenyldodeca-2,6,10-trien-1-yl diphosphate (**29**) and (2*Z*,6*E*)-7,11-dimethyl-3-phenyldodeca-2,6,10-trien-1-yl diphosphate (**36**) were not converted to products by AS from *Penicillium roqueforti*, all three FPP analogues acted as potent competitive inhibitors indicating that they bound to the active site of this sesquiterpene cyclase in a fashion similar to the natural substrate, thereby highlighting the enormous plasticity of these enzymes and their potential for the production of novel terpenoid analogues that might have superior properties for many applications including the treatment of human disease.




**Scheme 1**

## Results

In order to explore the plasticity of terpene cyclases and to investigate their potential for the synthesis of non-natural terpenoid analogues from modified prenyl diphosphates, we have synthesised three FPP analogues in which the methyl groups on C3 and C11 were replaced by phenyl substituents. The general structure of these analogues is shown in Scheme 1 along with the retrosynthetic disconnection used here. Previous syntheses of analogues of farnesol concentrated on modification of the C15 methyl group[14–18] and to some extent the C14[19] with little attention to the C12 and C13 methyl groups of FPP. These syntheses have largely used the elegant and robust chain extension methodology of Weiler and Sum as a key step.[20] For the syntheses of the compounds required here, a synthesis allowing changes to all the methyl groups of FPP was required and it seemed that a disconnection that exploits the oligomeric nature of FPP would be both appropriate and efficient. Hence two series of monomers were envisaged with one group being composed of 1,3-dienes representing the C-terminal end of the farnesyl group and the other set comprising various *E*-crotonyl iodides. The key forward reaction to connect these two monomers would involve transformation of the terminal alkenyl group with a hindered borane such as 9-BBN followed by Suzuki–Miyaura coupling with the appropriate iodide.[21–25]

### Synthesis of *E*- and *Z*-11-phenyl farnesyl diphosphate analogues

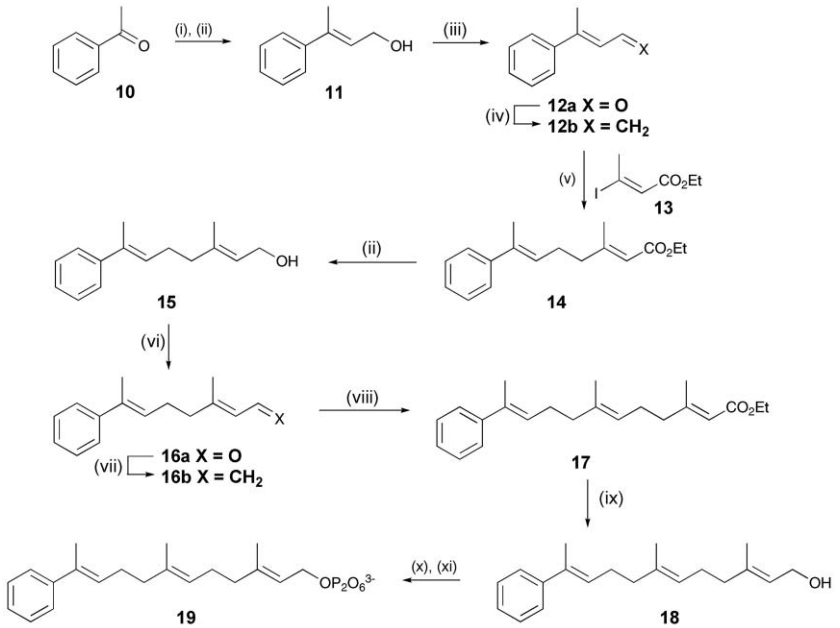
Both of these compounds were prepared using novel Suzuki–Miyaura coupling methodology. The synthesis of the *E*-11-phenyl FPP analogue **19** is shown in Scheme 2. The C-terminal 1,3-diene, compound **12b**, was prepared from acetophenone **10** in four steps. Horner–Emmons modification using triethyl phosphonoacetate and sodium hydride followed by DIBAL-H reduction yielded the *E*-cinnamyl alcohol **11**, then oxidation using PCC and then a Wittig reaction using methyltriphenylphosphonium bromide gave the required *E*-phenyl diene **12b**. This compound was then hydroborated using crystalline 9-BBN and immediately coupled to iodide **13** using $PdCl_2$dppf as catalyst, triphenylarsine as co-ligand and aqueous sodium hydroxide as base.[24] The *E*-phenyl-geranyl ester product **14** was isolated in 59% yield under these conditions. Ester **14** was then homologated to a new 1,3-diene derivative **16b** in a very similar manner to the preparation of **12b** and a second Suzuki coupling to iodide **13** under identical conditions gave the farnesyl ester analogue **17** in 54% yield for the coupling step. Ester **17** was then transformed into the diphosphate **19** by DIBAL-H reduction, bromination of the resulting alcohol and diphosphorylation using the methodology of Poulter *et al*.[26]

Preparation of the *Z*-11-phenyl FPP analogue was achieved in much the same fashion (Scheme 3). Preparation of the initial *Z*-1,3-diene **23b** was a little more complex because Horner–Emmons or Wittig modification of acetophenone **10** will only yield a small amount of the *Z*-ester **21**. It was therefore made by Suzuki–Miyaura coupling of phenylboronic acid to *Z*-crotonyl iodide **20**, which was an intermediate in the preparation of **13**.[27] Hence treatment of **20** with phenylboronic acid in the presence of $Pd(OAc)_2$, triphenylarsine and $K_3PO_4$ in toluene at 90 °C yielded ester **21** in 44% yield after chromatography.[28] This ester was then transformed into the 1,3-diene **23b** and then to the *Z*-11-phenyl FPP analogue **29** using almost identical chemistry as used for the preparation of **19**. The two crucial Suzuki–Miyaura coupling steps took place in approximately 40% yield in each case.

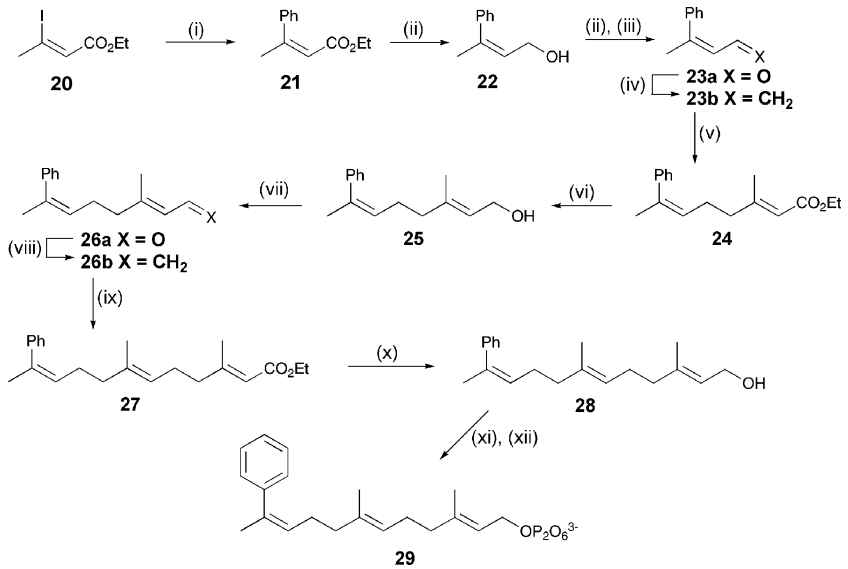
### Synthesis of 3-phenyl farnesyl diphosphate 36

For the synthesis of **36** the chain extension methodology of Weiler and Sum was found most effective (Scheme 4).[20] Hence geraniol **30** was transformed into geranyl bromide and then treated with




**Scheme 2** Synthesis of the *E*-11-phenylfarnesyl diphosphate derivative **19**. *Reagents and conditions:* (i) triethylphosphonoacetate, NaH, DME, 61%; (ii) DIBAL-H, THF, −78 °C, 96%; (iii) PCC, $CH_2Cl_2$, 56%; (iv) $CH_3PPh_3Br$, *n*-BuLi, THF, 94%; (v) 9-BBN, THF then **13**, $PdCl_2$dppf, NaOH, $AsPh_3$, THF, 50 °C, 59%; (vi) TPAP, NMO, $CH_3CN$, 89%; (vii) $CH_3PPh_3Br$, *n*-BuLi, THF, 81%; (viii) 9-BBN, THF then **13**, $PdCl_2$dppf, NaOH, $AsPh_3$, THF, 50 °C, 54%; (ix) DIBAL-H, THF, −78 °C, 86%; (x) $NEt_3$, MsCl, −45 °C then LiBr; (xi) $(Bu_4N)_3HP_2O_7$, $CH_3CN$ then cation exchange $Bu_4N^+/NH_4^+$, 31%.

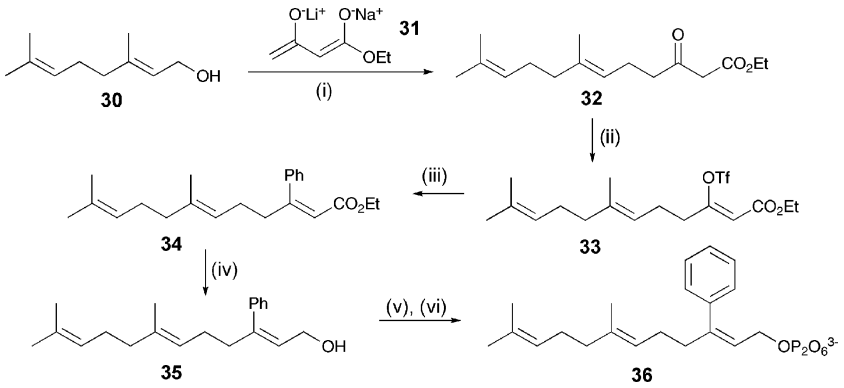



**Scheme 3** Synthesis of *Z*-11-phenylfarnesyl diphosphate **29**. *Reagents and conditions:* (i) $PhB(OH)_2$, $Pd(OAc)_2$, $AsPh_3$, $K_3PO_4$, toluene, 90 °C, 44%; (ii) DIBAL-H, THF, −78 °C, 99%; (iii) oxalyl chloride, DMSO, $CH_2Cl_2$ −78 °C then $NEt_3$, 88%; (iv) $CH_3PPh_3Br$, *n*-BuLi, THF, 76%; (v) 9-BBN, THF then **13**, $PdCl_2$dppf, NaOH, $AsPh_3$, THF, 50 °C, 41%; (vi) DIBAL-H, THF. −78 °C, 91%; (vii) TPAP, NMO, $CH_3CN$, 87%; (viii) $CH_3PPh_3Br$, *n*-BuLi, THF, 86%; (ix) 9-BBN, THF then **13**, $PdCl_2$dppf, NaOH, $AsPh_3$, THF, 50 °C, 40%; (x) DIBAL-H, THF, −78 °C, 77%; (xi) $NEt_3$, MsCl, −45 °C then LiBr; (xii) $(Bu_4N)_3HP_2O_7$, $CH_3CN$ then cation exchange $Bu_4N^+/NH_4^+$, 36%.

the dienolate **31** derived from ethyl acetoacetate[20] giving the β-ketoester **32** in 92% yield. This was then treated with triflic anhydride and KHMDS at −78 °C in THF to give the *Z*-enol triflate compound **33** in 51% yield.[16] This compound underwent a Suzuki–Miyaura cross-coupling reaction with phenylboronic acid to give **34** in 66% yield. Derivatisation of this compound to the diphosphate analogue **36** was achieved in the usual manner.[26]

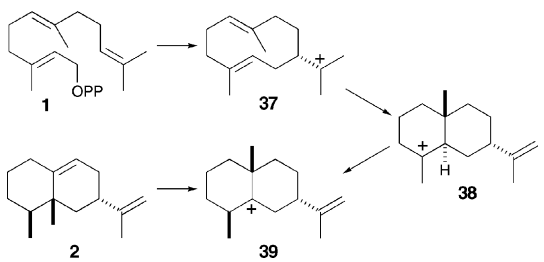
## Studies of the kinetics of AS-catalysis in the presence of 19, 29 and 36

To test whether the active site of terpene synthases could accommodate the size increases resulting from the replacement of a methyl with a phenyl group, the farnesyl diphosphate analogues **19**, **29** and **36** were tested as substrates for and as inhibitors of




**Scheme 4** Synthesis of 3-phenylfarnesyl diphosphate **36**. *Reagents and conditions:* (i) $NEt_3$, MsCl, THF, −45 °C then LiBr, then **31**, 92%; (ii) KHMDS, $(CF_3SO_2)_2O$, THF, −78 °C, 51%; (iii) $PhB(OH)_2$, $AsPh_3$, $Pd(OAc)_2$, $Ag_2O$, THF, Δ, 66%; (iv) DIBAL-H, THF, −78 °C, 85%; (v) $NEt_3$, MsCl, −45 °C then LiBr; (vi) $(Bu_4N)_3HP_2O_7$, $CH_3CN$ then cation exchange $Bu_4N^+/NH_4^+$, 31%.

aristolochene synthase. AS is a $Mg^{2+}$ dependent sesquiterpene cyclase that catalyses the conversion of FPP to (+)-aristolochene (**2**), which in the fungus is further transformed to produce a family of toxins that includes PR toxin (**3**) (Fig. 1).[29–31] The catalytic mechanism for the formation of **2** in the active site of AS has been studied extensively by classical substrate labelling studies as well as by analysing the reaction products generated from substrate analogues and by enzyme mutants.[9–11,32,33] The reaction proceeds through the intermediate eudesmane cation (**38**), the positive charge of which is stabilised through interaction with the indole ring of Trp 334 of AS. Hydride and methyl shifts followed by site-specific deprotonation generate the bicyclic product (Scheme 5).




**Scheme 5** Proposed catalytic mechanism of AS from *P. roqueforti*.

The phenyl-FPPs **19**, **29** and **36** were incubated at a concentration of 200 μM with 100 nM aristolochene synthase at pH 7.5 in the presence of the essential cofactor $Mg^{2+}$ at 25 °C. The reaction rate for the conversion of 5 μM FPP was proportional to the concentration of AS at this concentration of enzyme.[5,11] Incubations were overlayed with pentane in order to extract potential products and to minimise product inhibition that is often observed with these enzymes due to the hydrophobic nature of the terpenoid products. The organic phase was concentrated carefully and the reaction products analysed by GC-MS. While the production of aristolochene from FPP was manifest by the strong GC signal and by its mass spectrum after only 16 hours, even prolonged incubation with **19**, **29** and **36** of up to 7 days did not indicate the formation of any products as judged by GC-MS analysis suggesting that these compounds were not substrates of AS.

Each compound was examined as an inhibitor of AS using a radiolabelled assay. Initially, $IC_{50}$ values were determined with FPP concentrations maintained at 1 μM (close to the $K_M$ of FPP).[5,29] The concentrations of the phenyl-FPP analogues were varied between 1 mM and 1 nM. **19**, **29** and **36** acted as inhibitors of AS with $IC_{50}$ values ranging from 1–5 μM. Therefore full $K_i$ determinations were performed in order to examine the mode of inhibition of these compounds. The Michaelis constant of FPP was determined both in the presence and absence of each inhibitor at various concentrations by use of a non-linear fit.‡ Double reciprocal plots for each set of fitted data indicated that the compounds were all reversible competitive inhibitors of AS (Fig. 2) and hence bound to the enzyme's active site in a way similar to that of the natural substrate. The $K_I$-values were determined as 0.8 ± 0.2, 1.2 ± 0.2 and 1.2 ± 0.1 μM for **19**, **29**, and **36**, respectively (see ESI†). No time dependent inactivation of the enzyme was observed when each inhibitor was preincubated with enzyme prior to the assay indicating that the inhibition was reversible in all three cases.

### Molecular mechanics simulations of inhibitor-bound AS

Each of the FPP-analogues **19**, **29** and **36** are characterised by the replacement of a methyl group by the much bulkier phenyl substituent. Despite the high structural similarities observed in sesquiterpene synthases, that suggest that these enzymes have evolved to facilitate subtle conformational changes of their common substrate through the positional reorganisation of only a limited number of active site residues, the observation that the phenyl-substituted farnesyl-diphosphates acted as potent competitive inhibitors of AS was somewhat surprising.

Each inhibitor was therefore docked to the active site of AS using the existing molecular model of **1** bound to AS[34] as a starting point. Energy minimisations of the docked structures were performed using the MMFF94 forcefield.[35] Amino acids within 6.5 Å of the inhibitor molecule were allowed to move while the co-ordinates of all other residues were fixed. Each inhibitor appeared to fit well into the active site of AS and only minor reorganisations of active site residues were necessary to avoid steric clashes through the introduction of the bulky phenyl substituents (Fig. 3). In

‡ Data were fitted using Systat Sigmaplot 10.0, 2007. Sigmaplot for Windows Version 10.0, Build 10.0.0.54, 2006, Systat Software Inc. 1735, Technology Drive, Ste 430, San Jose, CA 95110, USA. Molecular Operating Environment (MOE 2004.03) Chemical Computing Group, Inc., 1255 University St. Suite 1600, Montreal, Quebec, Canada. H3B 3 × 3.

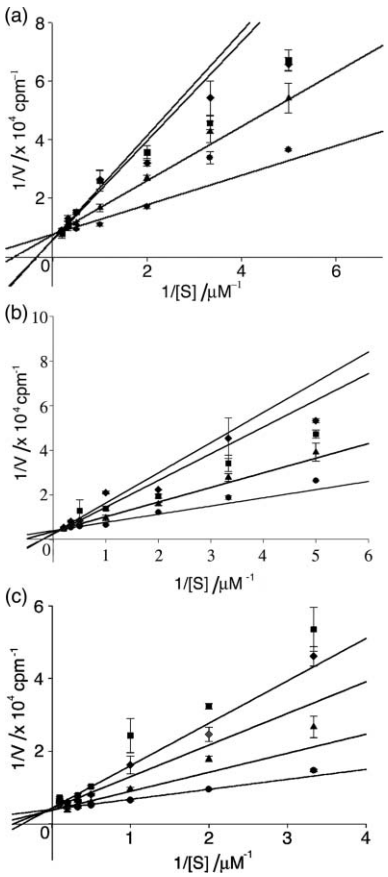



**Fig. 2** Double reciprocal plots of initial rates *versus* the concentration of substrate for AS catalysed turnover of FPP in the presence of **19**, **29** and **36** are shown on panels a, b and c for increasing concentrations of inhibitor (0 μM (●), 1 μM (▲), 2 μM (◆) and 3 μM (■)). Intersection of the lines on the *y*-axis indicate that each compound is a competitive inhibitor of AS. All assays were carried out at 37 °C and pH 7.5.

addition, some rearrangements of the inhibitors' prenyl-chains were observed relative to the conformation calculated for FPP. In the *E*-11-phenyl FPP analogue (**19**) an alteration in the orientation of the C7–C11 portion of the prenyl chain and a movement of the diphosphate group towards the Tyr 92 residue of AS was observed. This was accompanied by an approximate 90° rotation of the phenyl ring of Phe 112 and minor rotations of the rings of Phe 178 and Tyr 92. The indole ring of Trp 334 moved slightly away from the bound substrate analogue. The phenyl ring of **19** and that of Phe 178 appear to be in reasonably close proximity in this simulation.

The *Z*-11-phenyl FPP analogue (**29**) showed an entirely different set of movements. In this instance Trp 334 did not move at all. Most interestingly, there appears to be a possible π–π stacking arrangement between the phenyl ring of **29** and Phe 112 aided by a substantial movement of the side chain of Phe 112. In this case the overall fold of the prenyl chain was very similar to that observed for the substrate with a more modest movement of the diphosphate group relative to that observed for **19**. Again Phe 178 and Tyr 92 show small rotations upon binding of the analogue relative to their positions adopted upon binding of FPP.

The simulation of the binding of **36** indicated that the binding of this compound to FPP requires the least amount of active site

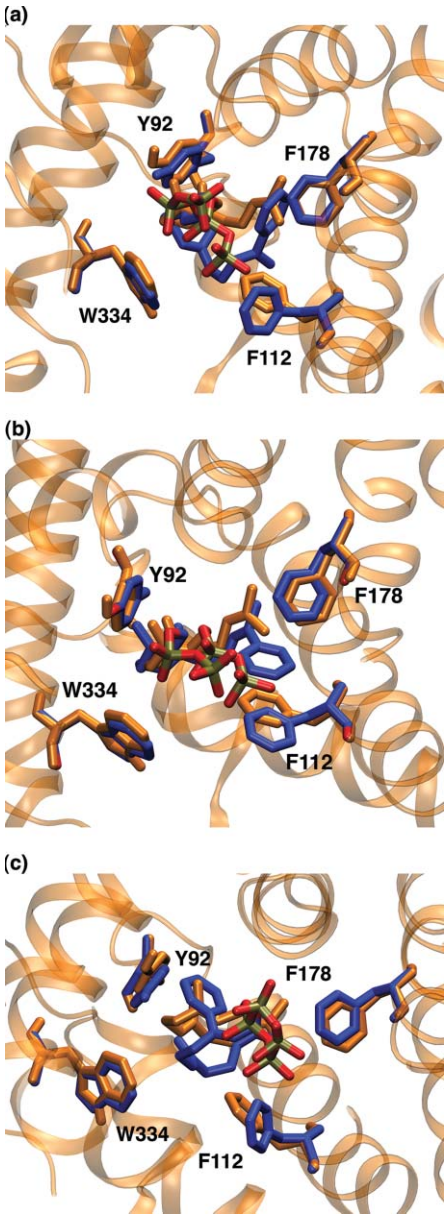



**Fig. 3** Sketches from molecular mechanics simulations of the active sites of AS complexed with (2*E*,6*E*,10*E*)-3,7-dimethyl-11-phenyldodeca-2,6,10-trien-1-yl diphosphate (**19**) (a), (2*E*,6*E*,10*Z*)-3,7-dimethyl-11-phenyldodeca-2,6,10-trien-1-yl diphosphate (**29**) (b) and (2*Z*,6*E*)-7,11-dimethyl-3-phenyldodeca-2,6,10-trien-1-yl diphosphate (**36**) (c). The substrate and the inhibitors as well as key amino acid residues are shown in gold for the original structure and in blue for the energy minimised structures of the inhibitor complexes of AS.

movement for the compounds in this study. Trp 334, Phe 178 and Tyr 92 displayed only minor rearrangements; the phenyl ring of Phe 178 was rotated by approximately 45° relative to its position in the substrate complex. The overall fold of the prenyl chain in the inhibitor complex was similar to that observed for the substrate with the exception of the C4–C7 portion of the chain where the apex of the phenyl group of **36** adopts an almost identical position to that of C3 of FPP, thereby forcing the C4–C7 chain downwards (Fig. 3) to accommodate the rest of the bulky phenyl residue in the active site.

## Discussion

Three analogues of farnesyl diphosphate have been prepared using novel methodology that involves a Suzuki–Miyaura cross-coupling reaction as a key step in the synthesis. These coupling reactions proceed in moderate to good yield. It should be possible to use this technology to prepare combinatorial libraries of FPP analogues in the future. Some members of such libraries may act as substrates for AS and other terpene cyclases thereby opening up the possibility of short economical routes to complex, synthetic unnatural analogues of terpenoids.

While the replacement of the methyl groups on C11 and C3 of FPP with phenyl substituents did not produce substrates for AS, compounds **19**, **29** and **36** proved to be potent competitive inhibitors of AS that acted in a reversible fashion. The most potent of these inhibitors was the *E*-11-phenyl-FPP analogue **19** with a $K_I$ of 0.8 μM, which is comparable to the $K_M$ of the natural substrate[5,9] and to the inhibitory constant of 12,13-difluoro-FPP.[36] Given the relatively size neutral substitutions in 12,13-difluoro-FPP, the tight binding of the phenyl substituted FPP analogues to AS clearly indicate the remarkable plasticity of this enzyme's active site. Furthermore, farnesyl thiodiphosphate, an analogue of FPP where the oxygen attached directly to the farnesyl chain was replaced by a sulfur, was a much more weakly bound inhibitor of this enzyme ($K_I$ = 10 μM) (Beyer and Allemann, unpublished). Replacing the oxygen with sulfur in the diphosphate group clearly reduces the binding energy more significantly than a change from a methyl to a phenyl group in the prenyl chain. The majority of the binding energy seems to stem from the interaction of the charged diphosphate group to the $Mg^{2+}$ binding site while the interaction of the aliphatic chain with the hydrophobic pocket of the active site contributes a smaller amount.

Analysis of the X-ray crystal structure of AS indicates that the indole ring of Trp 334 is positioned close to C3 of FPP.[7,34] The GC-MS analysis of the sesquiterpenes produced by mutants of AS in which this residue was replaced by non aromatic amino acids indicated that the indole ring was involved in the stabilisation of the positive charge build up on C3 during formation of the eudesmane cation (**38**).[7] The tight binding of **36**, where the methyl group on C3 was replaced with a phenyl substitutent was therefore most interesting. No steric clash between the two aromatic groups appeared to prevent tight binding of the inhibitor. The precise geometry of binding of these compounds in the active site of AS is currently being studied by X-ray crystallography of the inhibitor complexes. However, our molecular modelling studies of AS bound to the **19**, **29** and **36** suggest possible binding modes for these competitive inhibitors. AS appears to be sufficiently flexible to accommodate the extra bulk of the phenyl groups in the active site. The reorganisation of the active site residues, which is accompanied by alteration of the conformation of the prenyl chain, does however lead to loss of catalytic activity. This may be a consequence of changes in the position of the diphosphate group in each simulation thereby preventing the initial diphosphate loss and hence cyclisation of FPP. In addition, the active site conformation of the prenyl chain has been shown to be critical for AS catalysis[6,36] and the rearrangement of the substrate analogue necessary to accommodate the phenyl ring, may lead to an unreactive conformation.

The results described here show that the active site geometry of terpene synthases is sufficiently flexible to accommodate substrate analogues even when these carry large pendant groups. The plasticity of the terpene cyclases appears not only to provide the framework for the combinatorial production of many natural terpenoids through subtle alterations in the composition of the active site during evolution but may also allow modifications of the active site residues by site directed or random mutagenesis *in vitro* or *in vivo* for the production of functional enzymes that convert FPP analogues to unnatural "terpenoids".

## Experimental

For general experimental procedures, final synthesis of diphosphates, enzyme preparation and purification and kinetic characterisation of inhibitors see ESI.†

### (*E*)-3-Phenylbut-2-en-1-ol (11)[37]

To a stirred solution of sodium hydride (4.40 g, 110 mmol) in anhydrous DME (200 $cm^3$) at room temperature under $N_2$, triethyl phosphonoacetate (21.8 $cm^3$, 110 mmol) and a solution of acetophenone (11.7 $cm^3$, 100 mmol) in anhydrous DME were sequentially added, dropwise. After 3 h, water (50 $cm^3$) was added and the organic layer was separated. The aqueous layer was extracted with diethyl ether (3 × 50 $cm^3$). The combined organic phases were washed with brine (50 $cm^3$), dried over $MgSO_4$, filtered and then concentrated under reduced pressure to give the intermediate ester as a pale yellow oil (11.6 g, 61%); TLC $R_f$ 0.39 (hexane–EtOAc = 9 : 1); HRMS ($ES^+$, $[M + H]^+$) found 191.1067, $C_{12}H_{15}O_2$ requires 191.1067; $\nu_{max}$(thin film)/$cm^{-1}$ 2980.1, 1713.0, 1628.4, 1576.4, 1494.0, 1446.0, 1365.9, 1343.8, 1272.6, 1171.3, 1044.1, 872.4, 766.9 and 694.9; $\delta_H$ (500 MHz, $C^2HCl_3$) 1.23 (3 H, t, *J* 7.5, $CH_3CH_2O$), 2.50 (3 H, d, *J* 1.5, $CH_3CPh$), 4.13 (2 H, q, *J* 7.5, $CH_3CH_2O$), 6.05 (1 H, q, *J* 1.5, PhC=CH) and 7.27–7.40 (5 H, m, Ar–H); $\delta_C$ (125 MHz, $C^2HCl_3$) 14.4 ($CH_3CH_2O$), 18.0 ($CH_3C$=CH), 59.8 ($CH_3CH_2O$), 117.2 (PhC=*C*H), 126.3, 128.4 and 129.0 (Ar–CH), 142.3 and 155.5 (quaternary C) and 166.9 (C=O); *m*/*z* ($ES^+$) 191.1 (100%, $[M + H]^+$).

The ester (9.08 g, 47.8 mmol) was dissolved in anhydrous THF (50 $cm^3$) and cooled to −78 °C (acetone–dry ice bath). To this stirred solution, under $N_2$, was added diisobutylaluminium hydride (1.0 M solution in hexanes, 152 $cm^3$, 152 mmol) dropwise over 10 min. This solution was stirred for 2 h at −78 °C then allowed to warm to 0 °C. Saturated potassium sodium tartrate solution (50 $cm^3$) and diethyl ether (50 $cm^3$) were added. The mixture was stirred at room temperature for another 30 min, and the organic layer was separated. The aqueous layer was extracted with diethyl ether (2 × 50 $cm^3$). The combined ethereal extracts were washed with brine (150 $cm^3$), dried over $MgSO_4$, filtered and then concentrated under reduced pressure. Purification by flash chromatography on silica gel with hexane and ethyl acetate (2 : 1) gave **11** as a light yellow oil (6.7 g, 96%); $R_f$ 0.27 (hexane–EtOAc = 2 : 1); HRMS: ($EI^+$, $M^+$) found 148.0890, $C_{10}H_{12}O$ requires 148.0888; $\nu_{max}$(thin film)/$cm^{-1}$ 3347.2, 2922.2, 2597.9, 1493.8, 1444.5, 1379.9, 1003.0, 758.1 and 696.1; $\delta_H$ (500 MHz, $C^2HCl_3$) 2.11 (3 H, s, $CH_3CPh$), 4.40 (2 H, d, *J* 6.5, $CH_2OH$), 6.01 (1 H, t, *J* 6.5, PhC=CH) and 7.28–7.45 (5 H, m, Ar–H); $\delta_C$ (125 MHz, $C^2HCl_3$) 16.1 ($CH_3CPh$), 60.0 ($CH_2OH$), 126.5

(PhC=*C*H), 125.8, 127.3 and 128.3 (Ar–CH) and 137.8 and 142.9 (quaternary C); *m/z* ($EI^+$) 148.1 (13%, $M^+$) and 115.1 (100).

**(*E*)-3-Phenylbut-2-enal (12a)**

Pyridinium chlorochromate (12.3 g, 56.0 mmol) was suspended in anhydrous $CH_2Cl_2$ (50 $cm^3$) then a solution of **11** (6.7 g, 45 mmol) in $CH_2Cl_2$ (50 $cm^3$) was added in one portion to the stirred suspension. After 4 h, dry diethyl ether (100 $cm^3$) was added and the supernatant liquid was decanted from the resulting black gum. The insoluble residue was washed with diethyl ether (100 $cm^3$) and became a black granular solid. The organic phases were combined, washed with brine (300 $cm^3$), dried over $MgSO_4$, filtered and then concentrated under reduced pressure to give **12a** as a yellow oil (3.7 g, 56%); $R_f$ 0.37 (hexane–EtOAc = 4 : 1); HRMS: ($EI^+$, $M^+$) found: 146.0730, $C_{10}H_{10}O$ requires 146.0732; $\nu_{max}$(thin film)/$cm^{-1}$ 1722.2, 1659.7, 1446.2, 1377.3, 1248.1, 1144.5, 865.5 and 758.6; $\delta_H$ (500 MHz, $C^2HCl_3$) 1.94 (3 H, d, *J* 1.0, C$H_3$CPh), 6.41 (1 H, dq, *J* 7.5, *J* 1.0, PhC=CH), 7.10–7.18 (5 H, m, Ar–H) and 10.05 (1 H, d, *J* 7.5, CHO); $\delta_C$ (125 MHz, $C^2HCl_3$) 15.5 (*C*$H_3$CPh), 127.4 (PhC=*C*H), 126.2, 128.5 and 129.5 (Ar–CH), 140.8 and 155.8 (quaternary C) and 189.8 (CHO). *m/z* ($EI^+$) 146.1 (46%, $M^+$) and 145.1 (100).

**(*E*)-Penta-2,4-dien-2-ylbenzene (12b)**

A stirred suspension of methyltriphenylphosphonium bromide (7.61 g, 21.3 mmol) in anhydrous THF (50 $cm^3$) was cooled to −78 °C then *n*-BuLi (2.5 M, 8.52 $cm^3$, 21.3 mmol) was added dropwise under argon. The reaction mixture was allowed to warm to 0 °C giving a clear deep yellow solution. After stirring at 0 °C for 30 min, the aldehyde **12a** (1.83 g, 12.6 mmol) was added dropwise and the complete reaction mixture was stirred for 16 h whilst slowly warming to room temperature. Water (20 $cm^3$) and diethyl ether (20 $cm^3$) were added and the organic layer was separated. The aqueous layer was extracted with diethyl ether (2 × 15 $cm^3$). The combined ethereal extracts were washed with water (2 × 20 $cm^3$) and brine (20 $cm^3$), dried over $MgSO_4$, filtered and then concentrated under reduced pressure. Purification by flash chromatography on silica gel with hexane and ethyl acetate (9 : 1) as eluent gave **12b** as a light yellow oil (1.70 g, 94%); $R_f$ 0.57 (hexane–EtOAc = 19 : 1); HRMS: ($EI^+$, $M^+$) found 144.0938, $C_{11}H_{12}$ requires 144.0939; $\nu_{max}$(thin film)/$cm^{-1}$ 3029.5, 2923.2, 1803.9, 1627.6, 1594.2, 1493.3, 1445.8, 1380.1, 1175.1, 1027.4, 985.3, 903.6, 759.8 and 694.8; $\delta_H$ (400 MHz, $C^2HCl_3$) 2.09 (3 H, s, C$H_3$CPh), 5.10 (1 H, d, *J* 10.0, CHCH=CH$_{trans}H_{cis}$), 5.22 (1 H, d, *J* 17.0, CHCH=C$H_{trans}$H$_{cis}$), 6.37 (1 H, d, *J* 11.0, C*H*CH=CH$_2$), 6.68 (1 H, dt, *J* 17.0, *J* 10.5, CHC*H*=CH$_2$) and 7.14–7.26 (5 H, m, Ar–H); $\delta_C$ (100 MHz, $C^2HCl_3$) 16.1 (*C*$H_3$CPh), 117.7 (CHCH=*C*H$_2$), 127.8 (*C*HCH=CH$_2$), 125.7, 127.2 and 128.3 (Ar–CH), 133.6 (CH*C*H=CH$_2$) and 136.8 and 143.0 (quaternary C); *m/z* ($EI^+$) 144.1 (35%, $M^+$) and 129.1 (100, $[M - CH_3]^+$).

**(2*E*,6*E*)-Ethyl 3-methyl-7-phenylocta-2,6-dienoate (14)**

A mixture of **12b** (1.45 g, 9.92 mmol) and 9-BBN (3.63 g, 14.9 mmol) dissolved in anhydrous THF (50 $cm^3$) was stirred at room temperature under $N_2$ until all the starting material had been consumed as judged by TLC (approx. 2 h). The iodide **13**[27] (2.38 g, 9.92 mmol), triphenylarsine (0.30 g, 0.99 mmol), $PdCl_2$dppf (0.37 g, 0.45 mmol) and aqueous NaOH (6.0 M. 9.92 $cm^3$, 39.7 mmol) were added in quick succession, the complete solution was then stirred at 50 °C for 15 h. After cooling to room temperature, aqueous hydrogen peroxide solution (30%, 15 $cm^3$) was carefully added and the solution was stirred for a further 30 min. Water (30 $cm^3$) and diethyl ether (30 $cm^3$) were added, and the organic layer was separated. The aqueous layer was extracted with diethyl ether (2 × 25 $cm^3$). The combined ethereal extracts were washed with water (2 × 20 $cm^3$) and brine (20 $cm^3$), dried over $MgSO_4$, filtered and then concentrated under reduced pressure. Purification by flash chromatography on silica gel with hexane and ethyl acetate gave **14** as a light yellow oil (1.51 g, 59%); $R_f$ 0.27 (hexane–EtOAc = 19 : 1); HRMS: ($ES^+$, $[M + NH_4]^+$) found 276.1959, $C_{17}H_{26}NO_2$ requires 276.1958; $\nu_{max}$(thin film)/$cm^{-1}$ 2978.8, 2930.2, 1714.9, 1647.6, 1493.8, 1444.3, 1381.4, 1327.6, 1272.3, 1222.8, 1146.1, 1098.9, 1049.6, 864.4, 757.9 and 696.4; $\delta_H$ (500 MHz, $C^2HCl_3$) 1.20 (3 H, t, *J* 7.0, C$H_3$CH$_2$O), 1.96 (3 H, d, *J* 1.0, C$H_3$C=CHCO$_2$Et), 2.13 (3 H, d, *J* 1.0, C$H_3$CPh), 2.19–2.32 (4 H, m, C$H_2$C$H_2$), 4.07 (2 H, q, *J* 7.0, CH$_3$C$H_2$O), 5.64 (2 H, m, 2 × C=CH) and 7.13–7.30 (5 H, m, Ar–H); $\delta_C$ (125 MHz, $C^2HCl_3$) 14.4 (*C*H$_3$CH$_2$O), 15.9 (*C*H$_3$C=CHCO), 18.9 (*C*H$_3$CPh), 26.8 and 40.6 (*C*H$_2$*C*H$_2$), 59.6 (CH$_3$*C*H$_2$O), 115.9 (C=*C*HCO), 126.66 (PhC=*C*H), 125.7, 126.73 and 128.2 (Ar–CH), 135.8, 144.7, 159.3 (quaternary C) and 166.9 (C=O); *m/z* ($CI^+$) 276.2 (100%, $[M + NH_4]^+$).

**(2*E*,6*E*)-3-Methyl-7-phenylocta-2,6-dien-1-ol (15)**

To a stirred solution of **14** (1.46 g, 5.67 mmol) in anhydrous THF (60 $cm^3$) at −78 °C (acetone–dry ice bath) was added diisobutylaluminium hydride (1.0 M solution in hexanes, 13.6 $cm^3$, 13.6 mmol) dropwise. The resulting mixture was stirred at −78 °C for 2 h and then allowed to warm to 0 °C at which time the reaction was judged complete by TLC analysis. Saturated potassium sodium tartrate solution (50 $cm^3$) and diethyl ether (50 $cm^3$) were added. The mixture was stirred at room temperature for another 30 min, and the organic layer was separated. The aqueous layer was extracted with diethyl ether (2 × 30 $cm^3$). The combined ethereal extracts were washed with brine (30 $cm^3$), dried over $MgSO_4$, filtered and then concentrated under reduced pressure. Purification by flash chromatography on silica gel with hexane and ethyl acetate (2 : 1) as eluent gave **15** as a light yellow oil (1.2 g, 96%); $R_f$ 0.27 (hexane–EtOAc = 2 : 1); HRMS: ($ES^+$, $[M + NH_4]^+$) found 234.1851, $C_{15}H_{24}NO$ requires 234.1852; $\nu_{max}$(thin film)/$cm^{-1}$ 3363.0, 2923.4, 1493.3, 1444.0, 999.4, 756.3 and 695.8; $\delta_H$ (500 MHz, $C^2HCl_3$) 1.65 (3 H, s, C$H_3$C=CHCH$_2$OH), 1.96 (3 H, d, *J* 0.9, CH$_3$CPh), 2.09–2.29 (4 H, m, C$H_2$C$H_2$), 4.09 (2 H, d, *J* 10.0, C$H_2$OH), 5.40 (1 H, tq, *J* 10.0, *J* 1.5, C*H*CH$_2$OH), 5.68 (1H, tq, *J* 7.0, *J* 1.5, C*H*CH$_2$CH$_2$) and 7.13–7.31 (5 H, m, Ar–H); $\delta_C$ (125 MHz, $C^2HCl_3$) 15.9 (*C*H$_3$C=CHCH$_2$OH), 16.4 (*C*H$_3$CPh), 27.1 and 39.2 (*C*H$_2$*C*H$_2$), 59.4 (CH$_2$OH), 123.7 (*C*HCH$_2$OH), 127.7 (PhC=*C*H), 125.6, 126.6 and 128.2 (Ar–CH) and 135.0, 139.4, 143.9 (quaternary C); *m/z* ($CI^+$) 234.2 (100%, $[M + NH_4]^+$).

**(2*E*,6*E*)-3-Methyl-7-phenylocta-2,6-dienal (16a)**

A mixture of **15** (0.98 g, 4.52 mmol), *N*-methylmorpholine-*N*-oxide (074 g, 6.33 mmol) and freshly activated powdered 4 Å

molecular sieves (0.35 g) in anhydrous acetonitrile (35 $cm^3$) was stirred for 10 min whereupon tetra-*n*-propylammonium perruthenate (81 mg, 0.23 mmol) was added. The reaction became warm and was then stirred at room temperature for 16 h. The mixture was filtered through a short pad of Celite® and the solvent was concentrated under reduced pressure. Purification by flash chromatography on silica gel with hexane and ethyl acetate (4 : 1) as eluent gave **16a** as a light yellow oil (0.86 g, 89%); $R_f$ 0.33 (hexane–EtOAc = 4 : 1); HRMS: ($EI^+$, $M^+$) found 214.1350, $C_{15}H_{18}O$ requires 214.1352; $\nu_{max}$(thin film)/$cm^{-1}$ 1672.0, 1493.5, 1443.9, 1193.1, 1124.0, 757.7 and 696.2; $\delta_H$ (500 MHz; $C_6{}^2H_6$) 1.62 (3 H, d, *J* 1.1, C$H_3$C=CHCHO), 1.92 (3 H, d, *J* 1.0, C$H_3$CPh), 1.86–2.10 (4 H, m, C$H_2$C$H_2$), 5.64 (1 H, tq, *J* 7.0, *J* 1.0, C=C*H*$CH_2CH_2$), 5.95 (1 H, dq, *J* 7.5, *J* 1.0, C*H*CHO), 7.21–7.44 (5 H, m, Ar–H) and 9.98 (1 H, d, *J* 7.5, CHO); $\delta_C$ (125 MHz; $C_6{}^2H_6$) 15.7 (*C*$H_3$CPh), 16.7 (*C*$H_3$C=CHCHO), 26.3 and 39.8 (*C*$H_2$*C*$H_2$), 126.3 (PhC=*C*H), 127.5 (*C*HCHO), 125.8, 127.0 and 128.4 (Ar–CH), 136.0, 143.8 and 160.9 (quaternary C) and 189.6 (CHO); *m*/*z* ($CI^+$) 232.2 (100%, $[M + NH_4]^+$).

### (2*E*,7*E*)-8-Phenyl-4-methyl-nona-1,3,7-triene (16b)

This compound was prepared from **16a** in a manner identical to that for the **12b**; purification by flash chromatography using hexane and ethyl acetate (9 : 1) as eluent gave **16b** as a light yellow oil (0.68 g, 81%); $R_f$ 0.68 (hexane–EtOAc = 9 : 1); HRMS: ($EI^+$, $M^+$) found 212.1559, $C_{16}H_{20}$ requires 212.1560; $\nu_{max}$(thin film)/$cm^{-1}$ 2919.4, 1649.7, 1597.7, 1493.5, 1443.8, 1379.7, 987.8, 896.6, 756.3 and 695.3; $\delta_H$ (500 MHz, $C^2HCl_3$) 1.73 (3 H, s, C$H_3$C=CHCH=$CH_2$), 1.92 (3 H, s, C$H_3$CPh), 2.11–2.29 (4 H, m, C$H_2$C$H_2$), 4.92 (1 H, d, *J* 10.0, CH=CH$CH_{trans}H_{cis}$), 5.02 (1 H, dd, *J* 17.0, *J* 1.5, CH=C$H_{trans}H_{cis}$), 5.68 (1 H, t, *J* 7.0, C=C*H*$CH_2CH_2$), 5.82 (1 H, d, *J* 11.0, C*H*CH=$CH_2$), 6.52 (1 H, dt, *J* 17.0, *J* 10.5, C*H*=$CH_2$) and 7.12–7.30 (5 H, m, Ar–H); $\delta_C$ (125 MHz, $C^2HCl_3$) 15.9 (*C*$H_3$CPh), 16.8 (*C*$H_3$C=CH$CH_2CH_2$), 27.3 and 39.6 (*C*$H_2$*C*$H_2$), 114.9 (CH=*C*$H_2$), 125.8 (*C*HCH=$CH_2$), 127.8 (PhC=*C*H), 125.7, 126.6 and 128.2 (Ar–CH), 133.4 (*C*H=$CH_2$) and 135.0, 139.1 and 143.9 (quaternary C); *m*/*z* ($CI^+$) 213.1 (100%, $[M + H]^+$).

### (2*E*,6*E*,10*E*)-Ethyl-3,7-dimethyl-11-phenyldodeca-2,6,10-trienoate (17)

This compound was prepared from **16b** in a manner identical to that for the ester **14**; purification by flash chromatography using hexane and ethyl acetate (25 : 1) as eluent gave **17** as a light yellow oil (0.56 g, 54%); $R_f$ 0.32 (hexane–EtOAc = 25 : 1); HRMS ($ES^+$, $[M + H]^+$) found 327.2320, $C_{22}H_{31}O_2$ requires 327.2319; $\nu_{max}$(thin film)/$cm^{-1}$ 2928.8, 1714.9, 1647.2, 1444.1, 1381.4, 1221.1, 1143.0, 757.1 and 695.9; $\delta_H$ (500 MHz, $C^2HCl_3$) 1.21 (3 H, t, *J* 6.5, C$H_3$$CH_2$O), 1.50, 1.58 and 1.96 (3 × 3 H, s, 3 × C$H_3$C=CH), 2.02–2.24 (8H, m, 2 × C$H_2$C$H_2$), 4.07 (2 H, q, *J* 6.5, $CH_3$C$H_2$O), 5.08 and 5.67 (2 H, m, 2 × C=C*H*$CH_2CH_2$), 5.60 (1 H, d, *J* 1.0, C*H*$CO_2$Et) and 7.13–7.30 (5 H, m, Ar–H); $\delta_C$ (125 MHz, $C^2HCl_3$) 14.4 (*C*$H_3$$CH_2$O), 15.8, 16.1 and 18.9 (3 × *C*$H_3$C=CH), 26.0, 27.4, 39.4 and 41.0 (2 × C$H_2$*C*$H_2$), 59.5 ($CH_3$*C*$H_2$O), 115.6 (*C*H$CO_2$Et), 123.3 and 128.1 (C=*C*H), 125.6, 127.0 and 128.2 (Ar–CH), 131.6, 135.8, 144.0 and 159.8 (quaternary C) and 166.9 (C=O); *m*/*z* ($CI^+$) 344.3 (100%, $[M + NH_4]^+$), 327.3 (65, $[M + H]^+$).

### (2*E*,6*E*,10*E*)-3,7-Dimethyl-11-phenyldodeca-2,6,10-trien-1-ol (18)

This compound was prepared from **17** in a manner identical to that for the alcohol **15**; purification by flash chromatography using hexane and ethyl acetate (2 : 1) as eluent gave **18** as a light yellow oil (0.41 g, 86%); $R_f$ 0.31 (hexane–EtOAc = 2 : 1); HRMS ($EI^+$, $M^+$) found 284.2141, $C_{20}H_{28}O$ requires 284.2140; $\nu_{max}$(thin film)/$cm^{-1}$ 3321.5, 2921.0, 1666.9, 1597.7, 1493.7, 1444.1, 1381.1, 1000.4, 846.3, 756.6 and 696.1; $\delta_H$ (500 MHz, $C^2HCl_3$) 1.57 (3 H, s, C$H_3$C=CH), 1.60 (3 H, s, C$H_3$C=CH$CH_2$OH), 1.96 (3 H, d, *J* 1.0, PhCC$H_3$), 1.97–2.25 (8 H, m, 2 × C$H_2$C$H_2$), 4.04 (2 H, d, *J* 7.0, C$H_2$OH), 5.08 (1 H, dt, *J* 7.0, *J* 1.0, $CH_3$C=C*H*), 5.33 (1 H, m, C=C*H*$CH_2$OH), 5.68 (1 H, dt, *J* 7.0, *J* 1.5, PhC=C*H*) and 7.12–7.30 (5 H, m, Ar–H); $\delta_C$ (125 MHz, $C^2HCl_3$) 15.8, 16.1 and 16.3 (3 × *C*$H_3$), 26.3, 27.4, 39.4 and 39.5 (2 × *C*$H_2$*C*$H_2$), 59.4 ($CH_2$OH), 123.4 (*C*H$CH_2$OH), 124.3 ($CH_3$C=*C*H) and 128.2 (PhC=*C*H), 125.6, 126.5 and 128.2 (Ar–CH) and 134.6, 135.0, 139.7 and 144.0 (quaternary C); *m*/*z* (EI+) 284.2 (1%, $M^+$), 131.1 (100), 266.2 (2, $[M - H_2O]^+$).

### (*Z*)-Ethyl 3-phenylbut-2-enoate (21)[27,28]

To a stirred solution of the iodide **20** (7.20 g, 30.0 mmol) in anhydrous toluene (100 $cm^3$) under $N_2$ was added palladium(II) acetate (0.34 g, 1.50 mmol), triphenylarsine (0.79 g, 3.00 mmol), tripotassium orthophosphate (19.1 g, 90.0 mmol) and phenylboronic acid (5.49 g, 45.0 mmol). The complete reaction mixture was then stirred at 90 °C for 6 h. Water (50 $cm^3$) and diethyl ether (50 $cm^3$) were added, and the organic layer was separated. The aqueous layer was extracted with diethyl ether (2 × 30 $cm^3$). The combined ethereal extracts were washed with water (2 × 30 $cm^3$) and brine (30 $cm^3$), dried over $MgSO_4$, filtered and then concentrated under reduced pressure. Purification by flash chromatography on silica gel with hexane and ethyl acetate (9 : 1) as eluent gave **21** as a light yellow oil (2.49 g, 44%); $R_f$ 0.30 (hexane–EtOAc = 9 : 1); HRMS ($ES^+$, $[M + H]^+$) found 191.1067, $C_{12}H_{15}O_2$ requires 191.1067; $\nu_{max}$ (thin film)/$cm^{-1}$ 2979.6, 1725.4, 1639.5, 1492.5, 1442.6, 1374.8, 1277.2, 1230.2, 1162.1, 1095.6, 1076.6, 1047.3, 867.6, 768.4 and 698.1 $cm^{-1}$; $\delta_H$ (500 MHz, $C^2HCl_3$) 1.14 (3 H, t, *J* 7.5, C$H_3$$CH_2$O), 2.23 (3 H, d, *J* 1.5, C$H_3$CPh), 4.05 (2 H, q, *J* 7.5, $CH_3$C$H_2$O), 6.05 (1 H, q, *J* 1.5, PhC=C*H*) and 7.26–7.42 (5 H, m, Ar–H); $\delta_C$ (125 MHz, $C^2HCl_3$) 14.0 (*C*$H_3$$CH_2$O), 27.2 (*C*$H_3$CPh), 59.8 ($CH_3$*C*$H_2$O), 117.8 (PhC=*C*H), 126.9, 127.8 and 127.9 (Ar–CH), 140.9 and 155.4 (quaternary C) and 165.9 (C=O); *m*/*z* ($CI^+$) 208.1 (100%, $[M + NH_4]^+$) and 191.0 (35%, $[M + H]^+$).

### (*Z*)-3-Phenylbut-2-ene-1-ol (22)

This compound was prepared from **21** in a manner identical to that for the alcohol **15**; purification by flash chromatography using hexane and ethyl acetate (2 : 1) as eluent gave **22** as a colourless oil (4.12 g, 99%); $R_f$ 0.26 (hexane–EtOAc = 2 : 1); HRMS ($CI^+$, $[M + NH_4]^+$) found 166.1229, $C_{10}H_{16}NO$ requires 166.1226; $\nu_{max}$ (thin film)/$cm^{-1}$ 3331.7, 3055.2, 2969.9, 1656.1, 1600.0, 1493.6, 1434.8, 1376.0, 1246.4, 1065.2, 1002.0, 764.1 and 700.8; $\delta_H$ (500 MHz, $C^2HCl_3$) 1.46 (1 H, b, OH), 2.02 (3 H, d, *J* 1.0, C$H_3$CPh), 3.99 (2 H, dd, *J* 7.0, *J* 1.0, C$H_2$OH), 5.64 (1 H, tq, *J* 7.0, *J* 1.5, PhC=C*H*) and 7.09–7.28 (5 H, m, Ar–H); $\delta_C$ (125 MHz, $C^2HCl_3$) 25.4 (*C*$H_3$CPh), 60.3 (*C*$H_2$OH), 126.1 (PhC=*C*H), 127.2, 127.8 and 128.2

(Ar–CH), 140.3 and 140.8 (quaternary C); *m/z* ($CI^+$) 166.1 (20%, $[M + NH_4]^+$), 148.1 (50, $M^+$) and 131.0 (100, $[M - OH]^+$).

**(*Z*)-3-Phenylbut-2-ene-1-al (23a)**

To a stirred solution of oxalyl chloride (2.69 $cm^3$, 31.3 mmol) in anhydrous $CH_2Cl_2$ (80 $cm^3$) at −78 °C under $N_2$, was added anhydrous dimethylsulfoxide (4.44 $cm^3$, 62.6 mmol). The reaction mixture was stirred for 5 min then a solution of **22** (3.85 g, 26.1 mmol) in $CH_2Cl_2$ was added over 5 min. Stirring was continued at −78 °C for an additional 15 min. Triethylamine (18.2 $cm^3$, 130 mmol) was added and the reaction mixture was stirred for 5 min and then allowed to warm to room temperature. Water (50 $cm^3$) was then added, and the organic layer was separated. The aqueous layer was extracted with $CH_2Cl_2$ (2 × 30 $cm^3$). The combined organic extracts were washed with water (2 × 30 $cm^3$) and brine (30 $cm^3$), dried over $MgSO_4$, filtered and then concentrated under reduced pressure. Purification by flash chromatography on silica gel with hexane and ethyl acetate (2 : 1) as eluent gave **23a** as a light yellow oil (3.36 g, 88%); $R_f$ 0.48 (hexane–EtOAc = 2 : 1); HRMS ($ES^+$, $[M - H]^+$) found 145.0645, $C_{10}H_9O$ requires 145.0648; $\nu_{max}$ (thin film)/$cm^{-1}$ 2357.8, 1668.3, 1614.1, 1433.3, 1388.2, 1136.6, 767.0 and 701.5; $\delta_H$ (500 MHz, $C^2HCl_3$) 1.81 (3 H, s, C*H*$_3$CPh), 6.09 (1 H, d, *J* 8.0, PhC=C*H*), 6.95–7.13 (5 H, m, Ar–H) and 9.71 (1 H, dd, *J* 8.0, *J* 3.5, CHO); $\delta_C$ (125 MHz, $C^2HCl_3$) 25.6 (*C*H$_3$CPh), 128.3, 128.4 and 128.7 (Ar–CH), 129.4 (PhC=*C*H), 138.5 and 160.1 (quaternary C) and 191.6 (CHO); *m/z* ($CI^+$) 164.1 (95%, $[M + NH_4]^+$), 161.1 (100%) and 146.1 (30%, $M^+$).

**(*Z*)-4-Phenyl-penta-1,3-diene (23b)**

This compound was prepared from **23a** in a manner identical to that for the diene **12b**; purification by flash chromatography using hexane and ethyl acetate (9 : 1) as eluent gave **23b** as a light yellow oil (1.80 g, 76%); $R_f$ 0.63 (hexane–EtOAc = 9 : 1); HRMS ($EI^+$, $M^+$) found 144.0938, $C_{11}H_{12}$ requires 144.0939; $\nu_{max}$ (thin film)/$cm^{-1}$ 3080.3, 2960.4, 2856.8, 1805.6, 1636.2, 1601.6, 1492.1, 1433.6, 1414.1, 1375.3, 1024.7, 995.6, 898.4, 766.1 and 700.2; $\delta_H$ (400 MHz, $C^2HCl_3$) 2.04 (3 H, s, C*H*$_3$CPh), 4.86 (1 H, d, *J* 10.0, CHCH=CH$_{trans}H_{cis}$), 5.08 (1 H, d, *J* 17.0, CHCH=C$H_{trans}$H$_{cis}$), 6.06 (1 H, d, *J* 11.0, C*H*CH=CH$_2$), 6.32 (1 H, dt, *J* 17.0, *J* 10.5, CHC*H*=CH$_2$) and 7.14–7.28 (5 H, m, Ar–H); $\delta_C$ (100 MHz, $C^2HCl_3$) 25.5 (*C*H$_3$CPh), 116.1 (CHCH=*C*H$_2$), 127.9 (*C*HCH=CH$_2$), 127.1, 128.1 and 128.3 (Ar–CH), 134.6 (CH*C*H=CH$_2$) and 139.5 and 141.5 (quaternary C); *m/z* ($EI^+$) 144.1 (35%, $M^+$), 129.1 (100, $[M - CH_3]^+$).

**(2*E*,6*Z*)-Ethyl 3-methyl-7-phenylocta-2,6-dienoate (24)**

This compound was prepared from **23b** in a manner identical to that for the ester **14**; the crude product was purified by flash chromatography using hexane and ethyl acetate (9 : 1) as eluent to give **24** as a light yellow oil (1.33 g, 41%); $R_f$ 0.35 (hexane–EtOAc = 9 : 1); HRMS ($ES^+$, $[M + H]^+$) found 259.1691, $C_{17}H_{23}O_2$ requires 259.1693; $\nu_{max}$ (thin film)/$cm^{-1}$ 2975.8, 2359.6, 1715.0, 1647.3, 1493.4, 1442.0, 1367.2, 1221.8, 1146.1, 1099.6, 1052.2, 865.4, 763.2 and 701.0; $\delta_H$ (500 MHz, $C^2HCl_3$) 1.18 (3 H, t, *J* 7.0, C*H*$_3$CH$_2$O), 1.95 (3 H, s, C*H*$_3$C=CHCO$_2$Et), 1.98 (3 H, d, *J* 1.0, C*H*$_3$CPh), 2.07 (4 H, m, C*H*$_2$C*H*$_2$), 4.07 (2 H, q, *J* 7.0, CH$_3$C*H*$_2$O), 5.32 (1 H, m, C=C*H*CH$_2$CH$_2$), 5.52 (1 H, d, *J* 0.5, C=C*H*CO$_2$Et) and 7.07–7.30 (5 H, m, Ar–H); $\delta_C$ (125 MHz, $C^2HCl_3$) 14.4 (*C*H$_3$CH$_2$O), 18.7 (*C*H$_3$CPh), 25.7 (*C*H$_3$C=CHCO$_2$Et), 26.9 and 41.2 (*C*H$_2$*C*H$_2$), 59.5 (CH$_3$*C*H$_2$O), 115.7 (C=*C*HCO$_2$Et), 125.8 (PhC=*C*H), 126.6, 127.9 and 128.2 (Ar–CH), 137.5, 141.8 and 159.4 (quaternary C) and 166.9 (C=O); *m/z* ($CI^+$) 276.2 (100%, $[M + NH_4]^+$), 259.2 (95, $[M + H]^+$).

**(2*E*,6*Z*)-3-Methyl-7-phenylocta-2,6-dien-1-ol (25)**

This compound was prepared from **24** in a manner identical to that for the alcohol **15**; purification by flash chromatography on silica gel using hexane and ethyl acetate (2 : 1) as eluent gave **25** light yellow oil (0.816 g, 91%); $R_f$ 0.31 (hexane–EtOAc = 2 : 1); HRMS ($ES^+$, $[M + NH_4]^+$) found 234.1850, $C_{15}H_{24}NO$ requires 234.1852; $\nu_{max}$ (thin film)/$cm^{-1}$ 3335.5, 2965.2, 2914.6, 1667.9, 1492.8, 1436.1, 1376.6, 999.9, 763.1 and 700.1; $\delta_H$ (500 MHz, $C^2HCl_3$) 1.22 (1 H, b, OH), 1.50 (3 H, s, C*H*$_3$C=CHCH$_2$OH), 1.95 (3 H, d, *J* 1.0, C*H*$_3$CPh), 1.97–2.04 (4 H, m, C*H*$_2$C*H*$_2$), 4.04 (2 H, d, *J* 7.0, C*H*$_2$OH), 5.28 (1 H, dt, *J* 7.0, *J* 1.0, C=C*H*CH$_2$OH), 5.36 (1 H, dt, *J* 7.0, *J* 1.5, C=C*H*CH$_2$CH$_2$) and 7.10–7.28 (5 H, m, Ar–H); $\delta_C$ (125 MHz, $C^2HCl_3$) 16.2 (*C*H$_3$C=CHCH$_2$OH), 25.6 (*C*H$_3$CPh), 27.3 and 39.8 (*C*H$_2$*C*H$_2$), 59.4 (CH$_2$OH), 123.5 (C=*C*HCH$_2$OH), 126.8 (PhC=*C*H), 126.5, 127.9 and 128.1 (Ar–CH) and 136.6, 139.5 and 142.1 (quaternary C); *m/z* ($CI^+$) 234.2 (100%, $[M + NH_4]^+$), 216.2 (80, $M^+$), 199.1 (40, $[M - OH]^+$).

**(2*E*,6*Z*)-3-Methyl-7-phenylocta-2,6-dienal (26a)**

This compound was prepared from **25** in a manner identical to that for the compound **16a**; purification by flash chromatography using hexane and ethyl acetate (2 : 1) as eluent to gave **26a** as a light yellow oil (0.86 g, 87%); $R_f$ 0.45 (hexane–EtOAc = 2 : 1); HRMS ($EI^+$, $M^+$) found 214.1352, $C_{15}H_{18}O$ requires 214.1358; $\nu_{max}$ (thin film)/$cm^{-1}$ 2912.7, 2851.7, 2360.2, 1672.8, 1630.3, 1492.6, 1439.9, 1379.2, 1193.2, 1124.0, 1025.8, 831.0, 764.1, 702.0 and 668.1; $\delta_H$ (500 MHz, $C^2HCl_3$) 1.49 (3 H, d, *J* 1.0, C*H*$_3$C=CHCHO), 1.85–2.08 (4 H, m, C*H*$_2$C*H*$_2$), 2.03 (3 H, d, *J* 1.0, C*H*$_3$CPh), 5.30 (1 H, td, *J* 7.0, *J* 1.0, C=C*H*CH$_2$CH$_2$), 5.85 (1 H, dd, *J* 8.0, *J* 1.0, C=C*H*CHO), 7.17–7.29 (5 H, m, Ar–H) and 9.91 (1 H, d, *J* 8.0, CHO); $\delta_C$ (125 MHz, $C^2HCl_3$) 16.4 (*C*H$_3$C=CHCHO), 25.5 (*C*H$_3$CPh), 26.7 and 40.4 (*C*H$_2$*C*H$_2$), 126.0 (PhC=*C*H), 127.6 (*C*H=CHO), 126.9, 127.9 and 128.3 (Ar–CH), 137.6, 141.8 and 160.8 (quaternary C) and 189.6 (CHO); *m/z* ($EI^+$) 214.1 (2%, $M^+$), 131.1 (100).

**(3*E*,7*Z*)-4-Methyl-8-phenyl-nona-1,3,7-triene (26b)**

This compound was prepared from **26a** in a manner identical to that for the diene **12b**; purification by flash chromatography using hexane and ethyl acetate (2 : 1) as eluent gave **26b** as a light yellow oil (0.48 g, 86%); $R_f$ 0.62 (hexane–EtOAc = 9 : 1); HRMS ($ES^+$, $[M + H]^+$) found 212.1569, $C_{16}H_{20}$ requires 212.1565; $\nu_{max}$(thin film)/$cm^{-1}$ 2964.8, 2358.3, 1649.8, 1598.9, 1493.0, 1436.5, 1378.1, 985.7, 896.9, 761.8 and 700.0; $\delta_H$ (500 MHz, $C^2HCl_3$) 1.70 (3 H, s, C*H*$_3$C=CHCH=CH$_2$), 2.07 (3 H, s, C*H*$_3$CPh), 2.08–2.17 (4 H, m, C*H*$_2$C*H*$_2$), 5.00 (1 H, dd, *J* 10.0, *J* 1.5, CH=C$H_{cis}$H$_{trans}$), 5.10 (1 H, dd, *J* 17.0, *J* 2.0, CH=CH$_{cis}H_{trans}$), 5.46 (1 H, td, *J* 7.0, *J* 1.5, C=C*H*CH$_2$CH$_2$), 5.83 (1 H, dd, *J* 11.0, *J* 0.5, C*H*CH=CH$_2$), 6.59 (1 H, dt, *J* 17.0, *J* 10.5, CHC*H*=CH$_2$) and 7.21–7.39 (5 H,

m, Ar–H); $\delta_C$ (125 MHz, $C^2HCl_3$) 16.6 ($CH_3C{=}CHCH_2$), 25.6 ($CH_3CPh$), 27.4 and 40.1 ($CH_2CH_2$), 114.7 ($CHCH{=}CH_2$), 125.6 ($CHCH{=}CH_2$), 126.9 ($PhC{=}CH$), 126.5, 128.0 and 128.2 (Ar–CH), 133.4 ($CH{=}CH_2$) and 136.6, 139.1 and 142.1 (quaternary C); *m/z* ($EI^+$) 212.2 (5%, $M^+$), 131.1 (100) and 91.1 (40).

### (2*E*,6*E*,10*Z*)-Ethyl-3,7-dimethyl-11-phenyldodeca-2,6,10-trienoate (27)

This compound was prepared from **26b** in a manner identical to that for the ester **14**; purification by flash chromatography using hexane and ethyl acetate (19 : 1) gave **27** as a light yellow oil (0.29 g, 40%); $R_f$ 0.33 (hexane–EtOAc = 19 : 1); HRMS ($ES^+$, $[M + H]^+$) found 327.2318, $C_{22}H_{31}O_2$ requires 327.2319; $\nu_{max}$ (thin film)/$cm^{-1}$ 2926.3, 1715.4, 1647.5, 1442.7, 1366.5, 1221.5, 1144.3, 1053.9, 865.3, 762.0 and 700.5; $\delta_H$ (500 MHz, $C^2HCl_3$) 1.20 (3 H, t, *J* 7.0, $OCH_2CH_3$), 1.43 (3 H, s, $CH_3C{=}CH$), 1.95 (3 H, d, *J* 1.0, $CH_3C{=}CH$), 2.08 (3 H, d, *J* 1.0, $CH_3C{=}CHCO_2Et$), 1.91–2.11 (8 H, m, 2 × $CH_2CH_2$), 4.06 (2 H, q, *J* 7.0, $OCH_2CH_3$), 4.97 (1 H, b, $C{=}CHCH_2CH_2$), 5.35 (1 H, dt, *J* 7.0, *J* 1.0, $C{=}CHCH_2CH_2$), 5.58 (1 H, s, $C{=}CHCO_2Et$) and 7.09–7.30 (5 H, m, Ar–H); $\delta_C$ (125 MHz, $C^2HCl_3$) 14.4 ($OCH_2CH_3$), 16.0 ($CH_3C{=}CH$), 18.9 ($CH_3C{=}CHCO_2Et$), 25.6 ($CH_3C{=}CH$), 26.0, 27.5, 39.9 and 41.0 (2 × $CH_2CH_2$), 59.5 ($OCH_2CH_3$), 115.6 ($C{=}CHCO_2Et$), 123.1 and 127.2 (2 × $C{=}CHCH_2CH_2$), 126.4, 127.6 and 128.0 (Ar–CH), 135.7, 136.2, 142.1 and 159.9 (quaternary C) and 166.9 (C=O); *m/z* ($CI^+$) 344.3 (100%, $[M + NH_4]^+$) and 327.3 (50, $[M + H]^+$).

### (2*E*,6*E*,10*Z*)-3,7-Dimethyl-11-phenyldodeca-2,6,10-trien-1-ol (28)

This compound was prepared in a manner identical to that for the alcohol **15**; purification by flash chromatography using hexane and ethyl acetate (2 : 1) as eluent gave **28** as a light yellow oil (0.12 g, 77%); $R_f$ 0.26 (hexane–EtOAc = 2 : 1); HRMS ($ES^+$, $[M + NH_4]^+$) found 302.2477, $C_{20}H_{32}NO$ requires 302.2478; $\nu_{max}$ (thin film)/$cm^{-1}$ 3344.4, 2919.3, 1666.0, 1597.4, 1493.4, 1443.8, 1381.2, 998.9, 756.6 and 696.0; $\delta_H$ (500 MHz, $C^2HCl_3$) 1.23 (1 H, b, OH), 1.43 (3 H, s, $CH_3C{=}CH$), 1.60 (3 H, s, $CH_3C{=}CH$), 1.95 (3 H, d, *J* 1.0, $CH_3C{=}CH$), 1.91–2.06 (8 H, m, 2 × $CH_2CH_2$), 4.07 (2 H, d, *J* 7.0, $CH_2OH$), 4.99 (1 H, td, *J* 7.0, *J* 1.0, $C{=}CH$), 5.33 (2 H, m, 2 × $C{=}CH$) and 7.10–7.30 (5 H, m, Ar–H); $\delta_C$ (125 MHz, $C^2HCl_3$) 16.0, 16.3 and 25.6 (3 × $CH_3$), 26.3, 27.6, 39.5 and 40.0 (2 × $CH_2CH_2$), 59.4 ($CH_2OH$), 123.3, 124.0 and 127.3 (3 × $C{=}CH$), 126.4, 128.0 and 128.0 (Ar–CH) and 135.0, 136.1, 139.8 and 142.2 (quaternary C); *m/z* ($CI^+$) 302.3 (100%, $[M + NH_4]^+$), 284.3 (55, $M^+$).

### (*E*)-Ethyl 7,11-dimethyl-3-oxododeca-6,10-dienoate (32)[20,38]

To a stirred solution of geraniol (2.60 $cm^3$ g, 15.0 mmol) and triethylamine (4.20 $cm^3$, 30.0 mmol) in anhydrous THF (100 $cm^3$) at −45 °C under $N_2$ was added methanesulfonyl chloride (1.50 $cm^3$, 19.5 mmol). The resulting milky mixture was stirred at −45 °C for 45 min then a solution of lithium bromide (5.20 g, 60.0 mmol) in THF (10 $cm^3$) was added *via* a cannula at −45 °C. The suspension was allowed to warm to 0 °C and stirred for an additional 1 h before cold water (30 $cm^3$) and hexane (30 $cm^3$) were added to quench the reaction. The two layers were separated, and the aqueous layer was extracted with hexane (2 × 20 $cm^3$). The combined organic layers were washed with saturated $NaHCO_3$ solution (20 $cm^3$) and then brine (20 $cm^3$), dried over $Na_2SO_4$ and filtered. Concentration of the solvent gave the intermediate bromide as a light yellow oil, which was used without further purification.

To a stirred suspension of NaH (60% dispersion in mineral oil, 1.20 g, 49.5 mmol) in anhydrous THF (100 $cm^3$) was added ethyl acetoacetate (5.73 $cm^3$, 45.0 mmol) dropwise at 0 °C. After 10 min, *n*-BuLi (2.2 M, 21.5 $cm^3$, 47.3 mmol) was added slowly over 3 min, during which time the colourless solution gradually turned yellow. This was stirred for an additional 10 min at 0 °C, as a solution of the bromide in THF (5 $cm^3$) was added. The clear solution turned to a cloudy yellow suspension. After stirring for 30 min at 0 °C, hydrochloric acid (3 M, 10.0 $cm^3$) was added followed by water (30 $cm^3$) and diethyl ether (30 $cm^3$) then the organic layer was separated. The aqueous layer was extracted with diethyl ether (2 × 20 $cm^3$). The combined ethereal extracts were washed with water (2 × 20 $cm^3$) and brine (20 $cm^3$), dried over $MgSO_4$ then filtered and concentrated under reduced pressure. Purification by flash chromatography on silica gel with hexane and ethyl acetate (4 : 1) as eluent gave **32** as a pale yellow oil (3.61 g, 92%); $R_f$ 0.45 (hexane–EtOAc = 2 : 1); HRMS ($ES^+$, $[M + H]^+$) found 267.1954, $C_{16}H_{27}O_3$ requires 267.1954; $\nu_{max}$ (thin film)/$cm^{-1}$ 2968.0, 2918.6, 1746.5, 1717.2, 1648.9, 1445.8, 1409.9, 1367.4, 1313.3, 1235.8, 1177.2, 1035.9 and 839.8; $\delta_H$ (500 MHz, $C^2HCl_3$) 1.30 (3 H, t, *J* 7.0, $CH_3CH_2O$), 1.61 (3 H, s, $CH_3C{=}CH$), 1.63 (3 H, s, $CH_3C{=}CH$), 1.69 (3 H, s, $CH_3C{=}CH$), 1.98 (4 H, m, $(CH_3)_2C{=}CHCH_2CH_2$), 2.30 (2 H, q, *J* 7.5, $CH_2CH_2C{=}O$), 2.59 (2 H, t, *J* 7.5, $CH_2CH_2C{=}O$), 3.45 (2 H, s, $COCH_2CO$), 4.20 (2 H, q, *J* 7.0, $OCH_2CH_3$) and 5.09 (2 H, dt, *J* 1.0, *J* 7.0, 2 × $C{=}CH$); $\delta_C$ (125 MHz, $C^2HCl_3$) 14.1 ($OCH_2CH_3$), 16.0 ($CH_3C{=}CH$), 17.7 ($CH_3C{=}CH$), 22.2 ($CH_2CH_2C{=}O$), 25.7 ($CH_3C{=}CH$), 26.6 and 39.4 ($(CH_3)_2C{=}CHCH_2CH_2$), 43.1 ($CH_2CH_2CO$), 49.4 ($COCH_2CO$), 61.4 ($OCH_2CH_3$), 122.1 and 122.4 (2 × $C{=}CH$), 131.5 and 136.8 (quaternary C), 167.3 (ester C=O) and 202.7 (ketone C=O); *m/z* ($CI^+$) 284.2 (100%, $[M + NH_4]^+$), 267.2 (86, $[M + H]^+$).

### (1*Z*,5*E*)-1-(Ethoxycarbonyl)-6,10-dimethylundeca-1,5,9-trien-2-yl trifluoromethanesulfonate (33)[16]

A stirred solution of **32** (546 mg, 2.05 mmol) in anhydrous THF (15 $cm^3$) under $N_2$ was cooled to −78 °C then potassium bis(trimethylsilyl)amide (0.5 M in THF, 4.93 $cm^3$, 2.46 mmol) was added. The resulting mixture was stirred at −78 °C for 30 min. Trifluoromethanesulfonic anhydride (414 $mm^3$, 2.46 mmol) was added at −78 °C and the solution stirred for 16 h whilst slowly warming to room temperature. Diethyl ether (20 $cm^3$) was added and the solution was washed with 10% citric acid solution (2 × 15 $cm^3$) and water (15 $cm^3$). The separated organic layer was dried over $MgSO_4$ and filtered. Evaporation of the solvent gave a yellow oil which was purified by flash chromatography on silica gel with hexane and ethyl acetate (4 : 1) as eluent to give **33** as light yellow oil (0.42 g, 51%); $R_f$ 0.41 (hexane–EtOAc = 4 : 1); $\nu_{max}$ (thin film)/$cm^{-1}$ 2975.6, 2905.3, 2855.1, 2353.0, 1731.9, 1676.1, 1427.9, 1209.1, 1141.0, 1037.6, 923.1 and 840.1; $\delta_H$ (500 MHz, $C^2HCl_3$) 1.24 (3 H, t, *J* 7.0, $OCH_2CH_3$), 1.53 (3 H, s, $CH_3C{=}CH$), 1.54 (3 H, s, $CH_3C{=}CH$), 1.61 (3 H, s, $CH_3C{=}CH$), 1.91 (4 H, m, $(CH_3)_2C{=}CHCH_2CH_2$), 2.20 (2 H, t, *J* 7.5, $CH_2CH_2C{=}O$), 2.34 (2 H, t, *J* 7.5, $CH_2CH_2C{=}O$), 4.17 (2 H, q, *J* 7.0, $OCH_2CH_3$), 4.99 (2 H, t, *J* 7.0, 2 × $C{=}CHCH_2CH_2$) and 5.67 (1 H, s, $O–C{=}CH$);

$\delta_C$ (125 MHz, $C^2HCl_3$) 14.1 ($OCH_2CH_3$), 16.1 ($CH_3C{=}CH$), 17.7 ($CH_3C{=}CH$), 24.4 ($CH_2CH_2CO$), 25.7 ($CH_3C{=}CH$), 26.5 and 39.6 ($(CH_3)_2C{=}CHCH_2CH_2$), 34.6 ($CH_2CH_2C{=}O$), 61.3 ($OCH_2CH_3$), 112.0 (O–C=*C*H), 120.6 and 123.9 (2 × C=*C*H), 131.7 and 138.2 (2 × *C*=CH), 158.5 (CH=*C*$OSO_2CF_3$) and 162.5 (C=O); $\delta_F$ (283 MHz, $C^2HCl_3$) −74.6 (s). *m*/*z* ($CI^+$) 398.1 (2%, $M^+$), 358.0 (80), 314.1 (18), 267.0 (21), 190 (23) and 114 (100).

### (2*Z*,6*E*)-Ethyl-7,11-dimethyl-3-phenyldodeca-2,6,10-trienoate (34)

To a stirred solution of **33** (0.36 g, 0.91 mmol) in anhydrous THF (10 $cm^3$) under $N_2$, was added palladium(II) acetate (0.02 g, 0.09 mmol), triphenylarsine (0.11 g, 0.36 mmol), silver oxide (0.42 g, 1.81 mmol) and phenylboronic acid (0.17 g, 1.36 mmol) in quick succession. The complete mixture was then heated under reflux for 15 h. Water (20 $cm^3$) and diethyl ether (20 $cm^3$) were added, and the organic layer was separated. The aqueous layer was extracted with diethyl ether (2 × 15 $cm^3$). The combined ethereal extracts were washed with water (2 × 10 $cm^3$) and brine (10 $cm^3$), dried over $MgSO_4$ filtered and concentrated under reduced pressure. Purification by flash chromatography on silica gel with hexane and ethyl acetate (9 : 1) as eluent gave **34** as a light yellow oil (0.19 g, 66%); $R_f$ 0.35 (hexane–EtOAc = 9 : 1); HRMS ($ES^+$, $[M + H]^+$) found 327.2324, $C_{22}H_{31}O_2$ requires 327.2319; $\nu_{max}$ (thin film)/$cm^{-1}$ 2975.7, 2926.3, 2361.9, 1727.2, 1638.2, 1442.5, 1377.2, 1276.4, 1223.8, 1159.0, 1042.6, 865.8 and 698.6; $\delta_H$ (500 MHz, $C^2HCl_3$) 0.99 (3 H, t, *J* 7.0, $OCH_2CH_3$), 1.45 (3 H, s, $CH_3C{=}CH$), 1.53 (3 H, s, $CH_3C{=}CH$), 1.60 (3 H, s, $CH_3C{=}CH$), 1.88 (6 H, m, $(CH_3)_2C{=}CHCH_2CH_2$ and $CH_2CH_2CPh$), 2.40 (2 H, dt, *J* 1.0, *J* 8.0, $CH_2CH_2CPh$), 4.90 (2 H, q, *J* 7.0, $OCH_2CH_3$), 5.01 (2 H, dt, *J* 1.0, *J* 7.0, 2 × C=C*H*), 5.81 (1 H, s, C=C*H*$CO_2Et$) and 7.07 (5 H, m, Ar–CH); $\delta_C$ (125 MHz, $C^2HCl_3$) 14.0 ($OCH_2CH_3$), 16.1 ($CH_3C{=}CH$), 17.7 ($CH_3C{=}CH$), 25.7 ($CH_3C{=}CH$), 25.9, 26.7, 39.7 and 40.5 (2 × $CH_2CH_2$), 59.7 ($OCH_2CH_3$), 117.4 (C=*C*$HCO_2Et$), 122.7 and 124.2 (2 × C=*C*$HCH_2CH_2$), 127.2, 127.5 and 127.8 (Ar–CH) and 131.4, 136.3, 140.2, 159.3 and 166.1 (quaternary C); *m*/*z* ($CI^+$) 344.4 (53%, $[M + NH_4]^+$) and 327.4 (100, $[M + H]^+$).

### (2*Z*,6*E*)-7,11-Dimethyl-3-phenyldodeca-2,6,10-trien-1-ol (35)

This compound was prepared from **34** in a manner identical to that for the alcohol **15**; purification by flash chromatography on silica gel using hexane and ethyl acetate (2 : 1) as eluent gave **35** as a light yellow oil (0.11 g, 85%); $R_f$ 0.38 (hexane–EtOAc = 2 : 1); HRMS ($EI^+$, $M^+$) found 284.2147, $C_{20}H_{28}O$ requires 284.2140; $\nu_{max}$ (thin film)/$cm^{-1}$ 3355.5, 2965.4, 2922.2, 2855.4, 1650.6, 1491.7, 1442.2, 1379.7, 1080.3, 1005.6, 830.9 and 769.8; $\delta_H$ (500 MHz, $C^2HCl_3$) 1.42 (1 H, b, $CH_2OH$), 1.54 (3 H, s, $CH_3C{=}CH$), 1.59 (3 H, s, $CH_3C{=}CH$), 1.71 (3 H, s, $CH_3C{=}CH$), 1.97 (6 H, m, $(CH_3)_2C{=}CHCH_2CH_2$ and $CH_2CH_2CPh$), 2.44 (2 H, t, *J* 7.5, $CH_2CH_2CPh$), 4.07 (2 H, d, *J* 7.0, $CH_2OH$), 5.11 (2 H, m, 2 × C=C*H*), 5.72 (1 H, t, *J* 7.0, C=C*H*$CH_2OH$) and 7.15 (5 H, m, Ar–CH); $\delta_C$ (125 MHz, $C^2HCl_3$) 16.0 ($CH_3$), 17.7 ($CH_3$), 25.7 ($CH_3$), 26.5, 26.7, 39.0 and 39.7 (2 × $CH_2CH_2$), 60.3 ($CH_2OH$), 123.5 and 124.4 (2 × C=*C*H), 125.7 (C=*C*$HCH_2OH$), 127.1, 128.1 and 128.2 (Ar–CH) and 131.3, 135.5, 140.0 and 144.6 (quaternary C); *m*/*z* ($EI^+$) 284.2 (10%, $M^+$) and 266.2 (100, $[M - H_2O]^+$).

### Molecular mechanics simulations

The X-ray crystal structure of AS from *P. roqueforti* containing a docked FPP molecule (PDB 1FIP) was used as the starting structure.[34] For each docking experiment, the FPP substrate was converted to the relevant substrate analogue **19**, **29** and **36**, respectively, using the molecule builder module of the software package MOE.§ Hydrogen atoms were added to both the protein and FPP automatically using the software. The inhibitor and all amino acid residues containing heavy atoms within 6.5 Å of the inhibitor were selected as the key active site atoms and the MMFF94 molecular mechanics forcefield was applied to these atoms only.[35] The energy of the system was minimised and the resulting coordinates used to generate Fig. 3.

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