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A multicomponent coupling strategy suitable for the synthesis of the triene component of the oxazolomycin antibiotics †

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Concise and versatile routes suitable for the synthesis of three geometric isomers of an analogue of the left hand triene sub-unit of oxazolomycin are reported. A strategy based upon a key Heck reaction was unsuccessful, and this was traced to a combination of steric encumbrance and electronic deactivation of the alkene substrate. An alternative Stille coupling strategy, however, proved to be both versatile and high yielding, and is potentially applicable to the synthesis of analogues with variation both in the side-chain geometry and in the identity of the terminal aromatic or heteroaromatic residue.

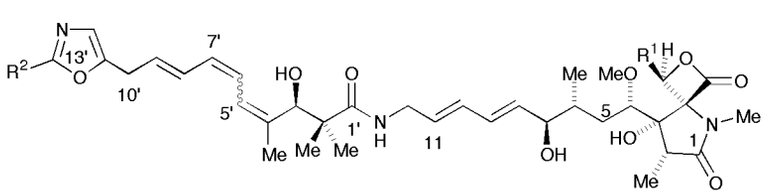
The rapid emergence of multi-drug resistance in a diverse range of organisms, exemplified by MRSA[1–3] and more recently VRSA,[4] and the prevalence of viral infections amongst immunocompromised sections of the community, have led to a widespread recognition that the "Golden Age of Antibiotics" is over, and that substantial efforts in the identification, design, synthesis and evaluation of new drug leads are urgently required.[5–8] Although recent developments in areas such as combinatorial chemistry and genomics are expected to provide important and valuable leads in this endeavour, natural product sources will nonetheless continue to generate new target structures.

Oxazolomycin A **1a** is the parent member of a class of antibiotics,[9] other members being oxazolomycin B and C **1b**,**c**,[10] 16-methyloxazolomycin **1d**, neooxazolomycin,[11] and the curromycins **1e**,**f**,[12–14] which are also variously known as inthomycins[15] and triedimycins.[16] They possess an unusual spiro fused β-lactone/γ-lactam linked *via* a triene and (*E*,*E*)-diene spacer to an oxazole terminal residue; these compounds generally differ either in triene double bond geometry (oxazolomycins A–C) or substitution pattern on the β-lactone ring (curromycins and 16-methyloxazolomycin). Truncated versions, the phthoxazolins, which are essentially the left hand domain terminating at the carboxylic acid, are also known,[17,18] although these have markedly different biological activity.[19–21]

The oxazolomycins and curromycins **1a**–**f** are isolated from *Streptomyces* spp. (typically 15–20 mg from a 10 L culture broth) and exhibit wide ranging and potent antibiotic activity, including inhibitory activity against Gram positive bacteria, antiviral activity against vaccinia, herpes simplex type I, and influenza A, as well as *in vivo* antitumour activity; notably, this biological activity is coupled with low toxicity (LD_{50} of 10.6 mg kg^{-1} for intraperitoneal injection in mice). At levels of only 30 μg ml^{-1}, the parent compound **1a** reduced the infectious virus yield of influenza A, vaccinia and herpes simplex type 1 viruses in both human and chicken cells by more than 99%.[22] Oxazolomycin also exhibits specific activity against *Agrobacterium tumefaciens* (MIC 3–6 μg ml^{-1}).[10] Oxazolomycin **1a** has been found to be an effective protonophore at pH < 7.0, but conveys both protons and monovalent cations (*e.g.* K^+) at 7.0 < pH < 7.5,[23] and it is thought that this activity is responsible for its antibacterial, antiviral and cytotoxic properties. The origin of this protonophoric activity, however, is not clear, since the oxazole unit is only a very weak base (pK_a 0.8). Oxazolomycins B **1b** and C **1c** display inhibitory activity against crown gall formation at the μg level (comparable to that of oxazolomycin **1a**), but exhibit weaker antibacterial activity than does oxazolomycin **1a**, presumably due to the different double bond geometries in the triene unit.[24] A recent report has described the potent antibacterial activity and cytotoxicity of 16-methyloxazolomycin (MIC against *Bacillus subtilis* 5 μg ml^{-1} and IC_{50} against P388 leukemia cells, 0.23 μg ml^{-1}).[25,26] The application of the oxazolomycins and derivatives as novel plant transformation inhibitors has also been reported,[24,27,28] and some of the details of the biosynthesis of this structurally novel class of compounds have been established.[29]

Notwithstanding the potent and wide-ranging but ill-understood biological activity of this class of compounds, the oxazolomycins present a considerable synthetic challenge, and in order both to develop the understanding of their biological mode of action and the therapeutic potential of this class of compounds, general and flexible synthetic routes are required, which will allow the synthesis not only of the natural products, but their analogues. Surprisingly, there is only one total synthesis of any of these compounds, namely for neooxazolomycin by Kende in 1990,[30] although we[31] and others[32] have examined routes for the synthesis of the lactam unit, and a recent synthesis of phthoxazolin[33,34] has been reported. The synthesis of the required oxazole unit has also received attention,[35] as has the central diene moiety.[36] We report here in detail a concise and versatile route for the synthesis of the three known geometric isomers of the C1′–C13′ subunit of oxazolomycin, generated from a standard amide-type disconnection (Fig. 1),[37] with the

† This is one of a number of contributions from the current members of the Dyson Perrins Laboratory to mark the end of almost 90 years of organic chemistry research in that building, as all its current academic staff move across South Parks Road to a new purpose-built laboratory.



1a Oxazolomycin A: R^1 = H, R^2 = H; 4'Z,6'Z,8'E
1b Oxazolomycin B: R^1 = H, R^2 = H; 4'E,6'E,8'E
1c Oxazolomycin C: R^1 = H, R^2 = H; 4'Z,6'E,8'E
1d 16-Methyloxazolomycin: R^1 = Me, R^2 = H; 4'Z,6'Z,8'E
1e Curromycin A: R^1 = CH_3OCH_2, R^2 = Me; 4'Z,6'Z,8'E
1f Curromycin B: R^1 = Me, R^2 = Me; 4'Z,6'Z,8'E

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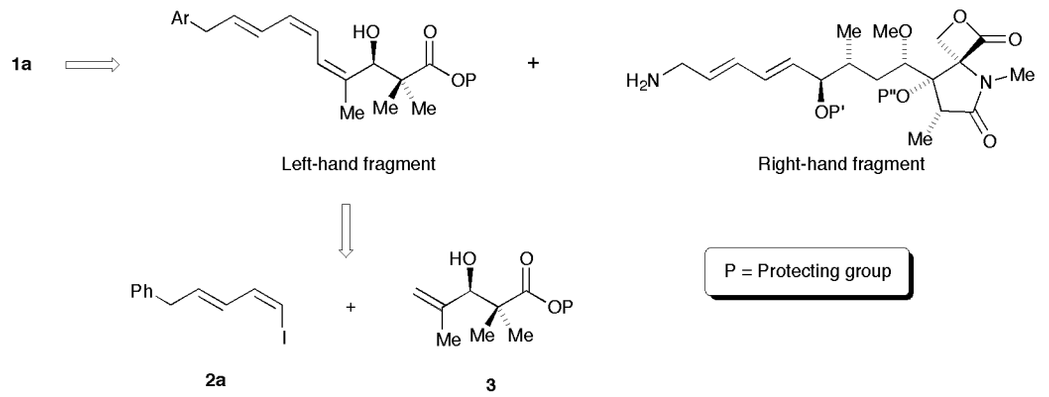


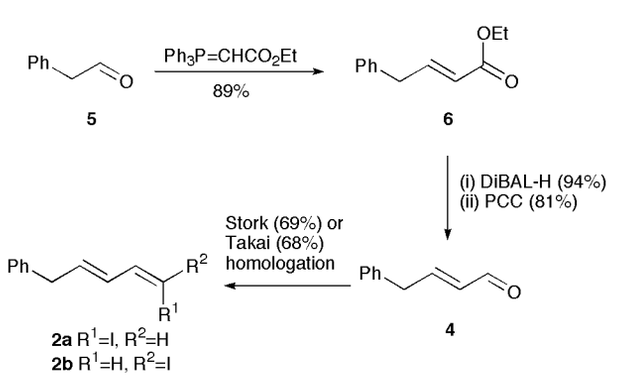
Fig. 1 Retrosynthetic scheme for oxazolomycin.

oxazole ring replaced by a phenyl group (Fig. 1, Ar = Ph). We anticipate that this route will permit convenient variation of the terminal aryl or heteroaryl unit, which will enable SAR details for the oxazolomycins to be elucidated.

Results and discussion

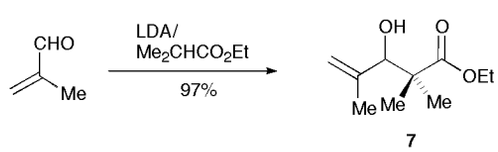
Heck coupling strategy

Our original plan was to synthesise the C1′–C13′ subunit of oxazolomycin using a Heck coupling reaction[38] between iodide **2a** and allylic alcohol **3**, both expected to be accessible by standard methodology, as the key step (Fig. 1). This would provide a rapid, flexible route to these compounds, since by using either 1(*Z*)- **2a** or 1(*E*)-iodide **2b**, selective synthesis of the isomeric triene systems would be expected. The (*Z*)-iodide **2a** proved to be available *via* aldehyde **4** (Scheme 1), which was prepared by a three step sequence involving Wittig homologation of phenylacetaldehyde **5** with (carboethoxymethylene)-triphenylphosphorane to give ester **6** as a separable 12 : 1 mixture of the (*E*) : (*Z*)-isomers, followed by reduction to the alcohol (DIBAL-H) and careful re-oxidation (PCC). Alternative and more direct routes, involving direct homologation with the phosphorane Ph_3P=CHCHO, or of selective reduction of ester **6**, proved to be unsuccessful. Aldehyde **4** was then converted into 1(*Z*),3(*E*)-iodide **2a** *via* a (*Z*)-selective Wittig olefination, following a procedure developed by Stork and Zhao.[39] Thus (iodomethyl)triphenylphosphonium iodide was prepared, in modest but serviceable yield (41%), by reaction of PPh_3 with CH_2I_2;[40] deprotonation using NaHMDS, followed by careful addition of aldehyde **4** at low temperature gave the product **2a** in a gratifying 69% yield and as an 8 : 1 ratio of 1(*Z*),3(*E*) : 1(*E*),3(*E*)-isomers, which proved to be inseparable by column chromatography (Scheme 1). The *cis*-stereochemistry was easily assigned from H-1 coupling data (*J* 7.1 Hz). Alternatively, the 1(*E*),3(*E*)-isomer **2b** was available by Takai olefination ($CrCl_2$–CHI_3)[41] of aldehyde **4** in 68% yield as an inseparable 3.3 : 1 mixture of (*E*) : (*Z*)-isomers; the *trans*-stereochemistry was easily assigned by H-1 coupling data (*J* 14.4 Hz). Similarly disappointing (*E*) : (*Z*)-ratios in the homologation of α,β-unsaturated aldehydes have been reported by Takai. It was necessary to use commercially available $CrCl_2$ for the reaction, as the reagent generated *in situ* from $CrCl_3$ and $LiAlH_4$[42] proved to be ineffective. Thus the synthesis of iodides **2a**,**b** was accomplished in four steps from phenylacetaldehyde, with overall yields of 47 and 46% respectively.



Scheme 1

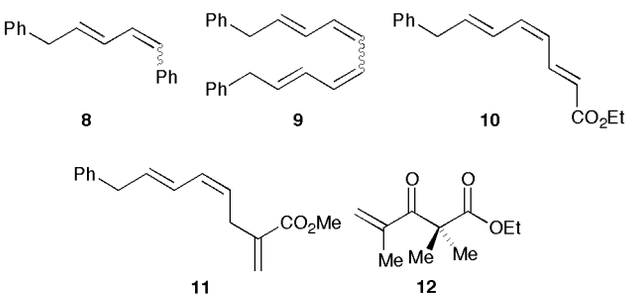
In order to prepare the required Heck coupling partner alcohol **7**, an aldol reaction[43] between ethyl isobutyrate and methacrolein was used. After considerable experimentation, the optimum reaction conditions were found to be addition of the freshly distilled aldehyde to the LDA-derived ester enolate at low temperature, followed by quenching after 10 minutes (Scheme 2). This procedure gave the aldol adduct **7** in excellent yield (97%). Different bases (LiHMDS, NaHMDS), temperatures (−40 °C, warming to RT) and reaction times (30 minutes, 1 hour, 3 hours) all led to lower yields.



Scheme 2

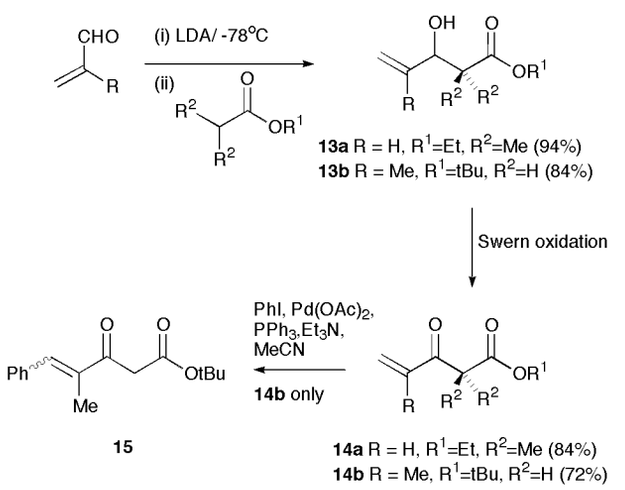
With gram quantities of iodides **2a**,**b** and allylic alcohol **7** in hand, the crucial Heck coupling reaction was then attempted. However, application of the Jeffery procedure[44] for the Heck reaction of allylic alcohols with vinyl iodides (cat. $Pd(OAc)_2$, Ag_2CO_3, DMF, 45 °C) proved to be unsuccessful; numerous other conditions involving variation of the catalyst, phosphine ligand, solvent, temperature and base, or using various additives known to increase the rate of certain Heck reactions (*e.g.* n-Bu_4NCl,[45] TlOAc,[46] or t-BuOH [47]) all proved to be fruitless. Although in each case iodide **2a** was consumed, no trace of the desired coupling product could be detected, and most of the allylic alcohol starting material could invariably be recovered unchanged. In some cases, small amounts of byproducts **8** (presumably formed by Ph transfer from triphenylphosphine) and **9** (formed by dimerisation) could be detected by ^{1}H NMR and mass spectrometry. The fact that the iodide **2a** was being consumed, but no product formed, suggested that oxidative addition of the iodide to the Pd(0) species was occurring, but that insertion of the vinyl-Pd complex into the double bond of the allylic alcohol (known to be the rate-limiting step in the catalytic cycle[48]) was not.

To determine whether the reason for the failure of the insertion was due to steric or electronic factors, either in the iodide or the alcohol, a series of further experiments were performed. Reaction of iodide **2a** with ethyl acrylate using the Jeffery conditions gave 2(*E*),4(*Z*),6(*E*)-triene **10** in moderate yield (52%); reaction with methyl methacrylate also led to coupling, but



surprisingly gave the exomethylene product **11** rather than the expected fully conjugated triene system. A possible explanation for the latter result is that it is due to steric effects in the β-elimination step of the catalytic cycle. Noting that successful reactions were obtained with electron-deficient double-bonds, coupling was attempted between ketone **12** (obtained by Swern oxidation of alcohol **7**) and iodide **2a**, but this also proved to be fruitless.

To investigate the effect of modifying the steric and electronic properties of the acceptor alkene, the substrates **13a**,**b** were prepared by aldol addition of the required ester with acrolein or methacrolein respectively, and **14a**,**b** by Swern oxidation of these aldol products (Scheme 3). Heck coupling was attempted with all compounds **13a**,**b** and **14a**,**b**, but reaction was only observed between ketone **14b** and the model substrate iodobenzene, giving the product **15** in poor yield (28%) and as an inseparable mixture of stereoisomers. This suggests that the unreactivity of allylic alcohol **7** towards coupling is due not only to steric hindrance imposed by the vinylic-methyl and gem-dimethyl groups, but also the electronic effects of the double-bond substituents (*i.e.* allylic alcohol *versus* α,β-unsaturated carbonyl).

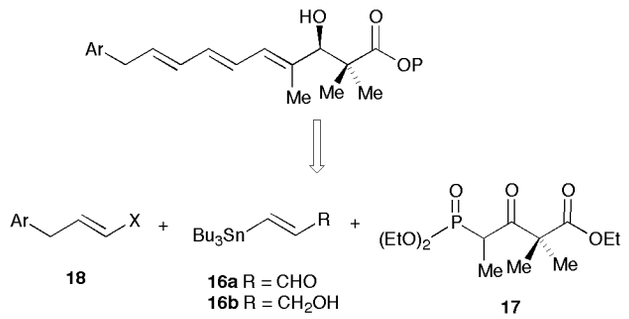


Scheme 3

Due to the failure of this key step, and because the problems associated with the intrinsic unreactivity of allylic alcohol **7** could not obviously be rectified, this approach was abandoned in favour of the alternatives discussed below.

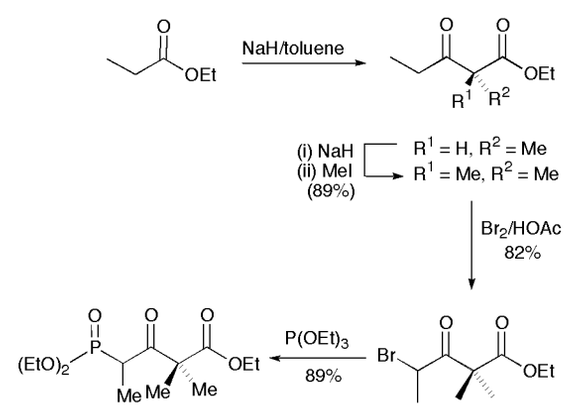
Stille coupling strategy

A successful route to the (*E*,*E*,*E*)-triene isomers made use of regioselective Stille couplings[49,50] in a three-component coupling strategy (Scheme 4). Thus, Wadsworth–Emmons reaction of aldehyde **16a** using phosphonate **17**, followed by Stille reaction with vinyl halide **18** was expected to construct the triene unit in a regio- and stereoselective manner under mild, neutral conditions. Asymmetric ketone reduction followed by ester to amide conversion would then give the final product.

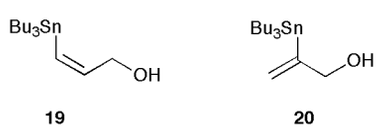


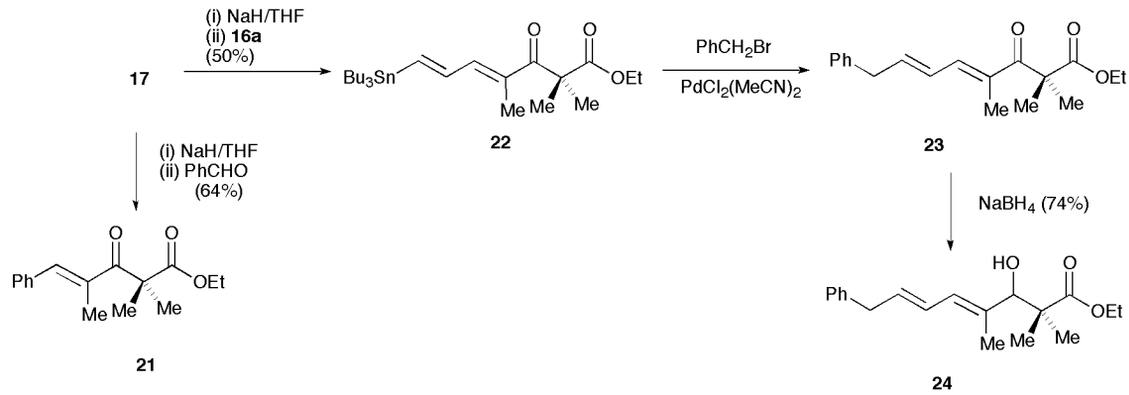
Scheme 4

Allylic alcohol **16b** was synthesised by AIBN-catalysed hydrostannylation of propargyl alcohol in a modification of the literature procedure[51] (involving purification by column chromatography rather than distillation followed by preparative HPLC), which gave the product in 67% isolated yield after separation from isomeric by-products **19** and **20** (Scheme 4). Swern oxidation then afforded aldehyde **16a** in excellent yield (90%), whereas oxidation with PCC gave only a 40% yield.[52] Phosphonate **17**, prepared as shown in Scheme 5, was treated with sodium hydride followed by benzaldehyde to give an efficient reaction (64% yield) leading to alkene **21** (Scheme 6), and similarly reacted with aldehyde **16a** to give (*E*,*E*)-diene **22** although in lower yield (50%); the (*E*,*E*)-geometry was consistent with a coupling constant of $J_{6,7}$ 18.5 Hz and the absence of allylic coupling for $J_{5,Me}$. As a test reaction, Stille coupling was first performed with benzyl bromide, which gave diene **23** with complete retention of alkene stereochemistry as expected; chemoselective ketone reduction with $NaBH_4$ then gave racemic alcohol **24**. Crucially, at no stage was isomerisation of the diene system into conjugation with the phenyl group observed, suggesting that this could be a viable strategy for construction of the more extended triene system in oxazolomycin. To incorporate the third double-bond required for the left-hand fragment of oxazolomycin, vinyl iodide **25** (prepared by Takai reaction of phenylacetaldehyde, and clearly the (*E*) isomer with a coupling constant of 14.4 Hz) was reacted with stannane **22** to give (*E*,*E*,*E*)-triene **26a** in 84% isolated yield (93% yield based on the recovered unreacted (*Z*)-iodide starting material **25**) (Scheme 7). Reduction with $NaBH_4$ then gave alcohol **26b**, in which the polyene system had again not been shifted into conjugation with the phenyl group. The (*E*,*E*,*E*)-geometry, corresponding to that of oxazolomycin B, was consistent with a coupling constant of $J_{6,7}$ 14.1 and $J_{8,9}$ 14.4 Hz as well as the absence of allylic coupling for $J_{5,Me}$.

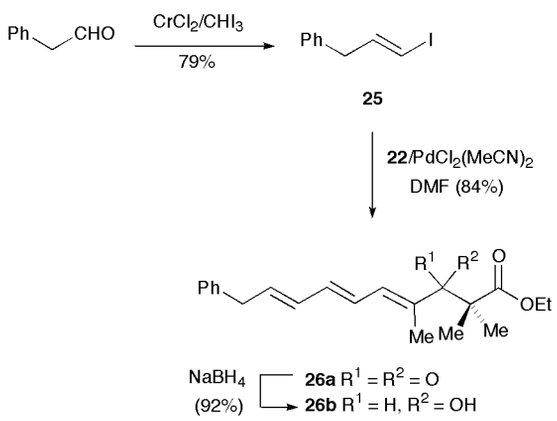


Scheme 5



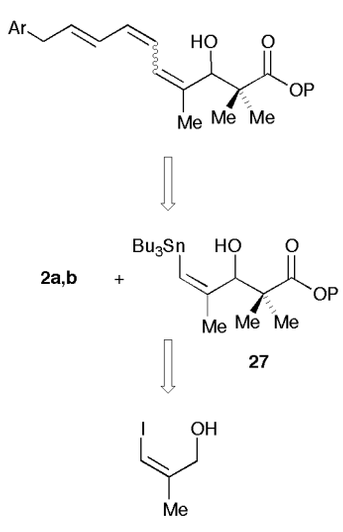


Scheme 6



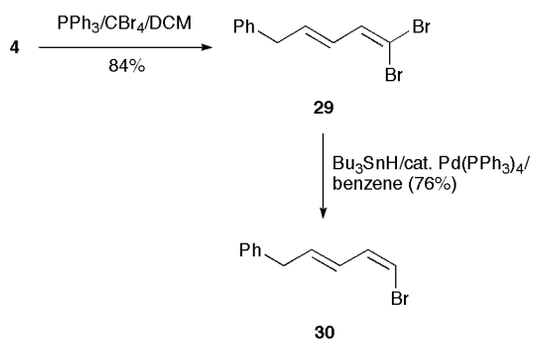
Scheme 7

Attention then turned to the (*Z*,*Z*,*E*)- and (*Z*,*E*,*E*)-triene systems present in oxazolomycin and oxazolomycin C respectively. It was decided to adopt a strategy involving coupling between the previously prepared isomeric vinyl halides **2a**,**b** and stannane **27** as the key step (Scheme 8); the latter would be derived from the known iodide **28**.[53]



Scheme 8

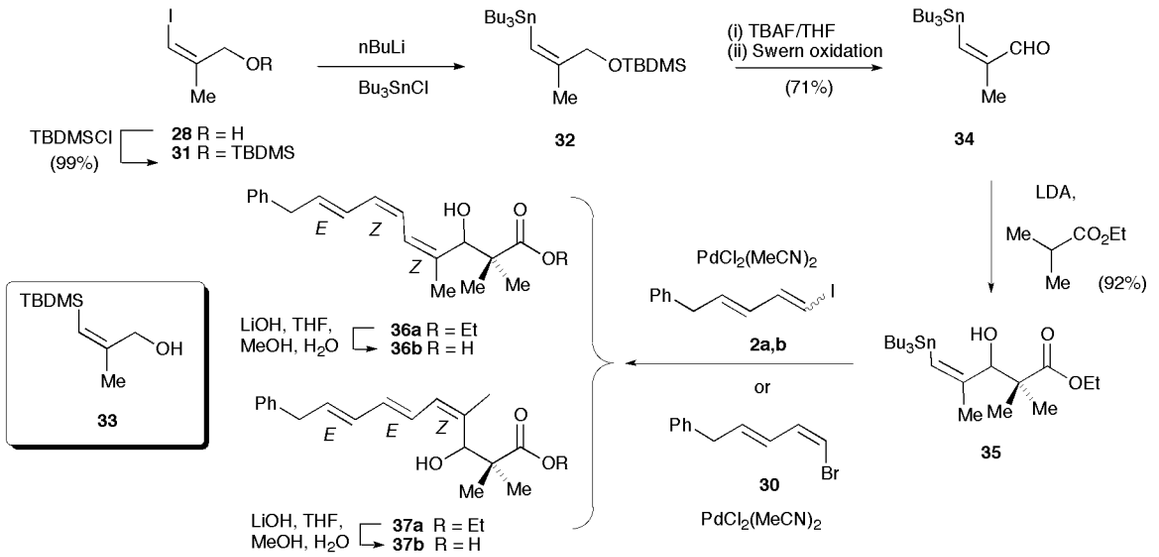
Although (*Z*)-iodide **2a** had been prepared previously as a 94 : 6 mixture of 1(*Z*) : 1(*E*)-isomers *via* a (*Z*)-selective Wittig olefination (*vide supra*), it was envisaged that separation of this isomeric mixture after the Stille reaction would be particularly troublesome, if not impossible, and so an alternative synthesis of the (*Z*)-halide which would deliver the product with greater stereoisomeric purity was desirable. To this end, conversion of aldehyde **4** to dibromide **29** followed by stereoselective palladium-catalysed monoreduction according to the recent literature protocol[54] gave vinyl bromide **30** in good yield (76%) and, crucially, as an excellent 99 : 1 mixture of 1(*Z*) : 1(*E*)-isomers (Scheme 9).



Scheme 9

Iodide **28** was prepared as a single diastereomer from propargyl alcohol following the literature procedure,[53] and the free hydroxyl group then protected as its TBDMS-ether in excellent yield (99%) (Scheme 10). Conversion of iodide **31** to stannane **32** was then effected *via* metal–halogen exchange followed by Bu_3SnCl quench, but the course of this reaction was found to be very solvent dependent: in THF, the major product was in fact vinyl silane **33** whereas in Et_2O the desired stannane **32** was obtained in excellent yield (90%). Purification of this stannane by column chromatography had to be performed with 1% Et_3N in the eluant in order to prevent protodestannylation. Removal of the silyl protecting group in stannane **32** using TBAF followed by Swern oxidation of the crude alcohol gave aldehyde **34**; aldol reaction with ethyl isobutyrate then gave racemic alcohol **35** in good overall yield (65%) over the three steps. The (*Z*)-stereochemistry of stannanes **32**, **34** and **35** was evident from allylic coupling constant (C*H*=C(Me)) values of 1.3–1.4 Hz, and the presence of significant NOE effects between the vinylic substituents; NOE effects also suggested that compound **35** appeared to exist in the preferred conformation indicated (Fig. 2). No isomerisation of the double-bond into the (*E*)-configuration was observed.

Stannane **35** was reacted under Stille coupling conditions ($PdCl_2(MeCN)_2$, DMF) with vinyl halides **2a**,**b**. Reaction for 10 h with a threefold excess of (*E*,*E*)-**2b** (3 : 1 mixture of stereoisomers) gave a 72% yield of a 3 : 1 mixture of (*Z*,*Z*,*E*) : (*Z*,*E*,*E*) triene products **36a** and **37a**, that is in which the expected (*Z*,*E*,*E*) triene is the minor product; this changed to a 1 : 1 ratio if the reaction time was lengthened to 24 h and the number of equivalents of (*E*,*E*)-**2b** was reduced to 1.3. Compound **36a** possesses the stereochemistry corresponding to



Scheme 10

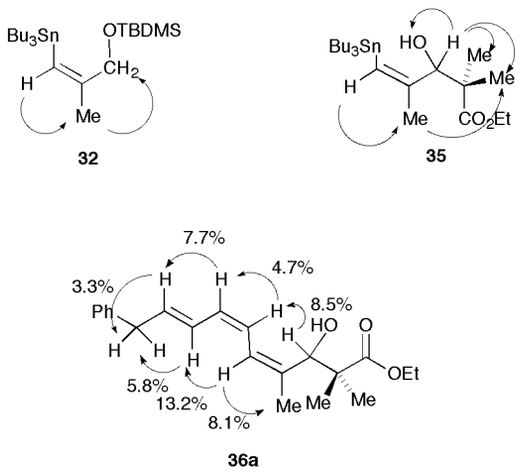


Fig. 2 NOE data for selected compounds.

oxazolomycin A, and **37a** that of oxazolomycin C. Use of (*Z*,*E*)-iodide **2a** in this reaction (8 : 1 ratio of isomers, 1.3 equiv.) with a reaction time of 24 h gave a 74% yield of a 1.2 : 1 mixture of (*Z*,*Z*,*E*) : (*Z*,*E*,*E*) triene products **36a** and **37a**. It was shown by ^{1}H NMR spectroscopic analysis that a mixture of **36a** and **37a** (1 : 1), when treated with $PdCl_2(MeCN)_2$ in deuterated DMF for 24 h, did not lead to a change in stereoisomer ratio, indicating that these compounds were stable under the Stille coupling conditions. However, experiments using iodides **2a**,**b** in deuterated DMF indicated rapid conversion of (*E*,*E*)-**2b** to (*Z*,*E*)-**2a** (but not the reverse) over a 16 h time period at room temperature in the absence of Pd(0) catalyst, but that both **2a** and **2b** do not isomerise when stored at −20 °C; thus, it would appear that equilibration of starting material rather than of product is responsible for the variable product ratios from the Stille reaction leading to **36a** and **37a**. When the coupling reaction of (*E*,*E*)-iodide **2b** (as a 3 : 1 (*E*,*E*) : (*Z*,*E*) mixture, 1.3 equiv.) with stannane **35** at low temperature (−20 °C) was investigated, the products **36a** and **37a** were obtained in 42% yield and a 1 : 3 ratio as expected. Unfortunately, the stereoisomers **36a** and **37a** are not readily separable by chromatography. The stereochemistry of the major (*Z*,*Z*,*E*) product **36a** was established by careful ^{1}H NMR analysis which gave coupling constant values of $J_{6,7}$ 11.7, $J_{8,9}$ 14.8 Hz and confirmed by NOE analysis (Fig. 2), and the stereochemistry of **37a** from coupling constant values of $J_{6,7}$ 14.2, $J_{8,9}$ 14.0 Hz. The isomerically pure bromide (*Z*)-**30** was also investigated in the coupling reaction, but reaction was found to be unreliable, probably due to the lower intrinsic reactivity of vinyl bromides, and this was further confirmed by the lack of reactivity of stannane **35** with benzyl bromide under Stille conditions. Hydrolysis of a 3 : 1 mixture of (*Z*,*Z*,*E*) : (*Z*,*E*,*E*) triene products **36a** and **37a** gave acids **36b : 37b** in 70% yield. These trienes are analogues of oxazolomycins A and C and inthomycins C and B respectively.

Conclusion

Flexible and efficient synthetic routes using Stille coupling reactions as the key step permitting access to the triene system present in the oxazolomycin class of antibiotics have been developed; however, facile (*E*)-->(*Z*) isomerism complicates the stereochemical outcome of the sequence, although this can be alleviated to some extent by judicious choice of reaction conditions. Future work will involve utilisation of this strategy for the synthesis of analogues for studies of biological mechanism.

Experimental

For general experimental procedures, see our earlier reports.[55,56] 'Usual work up' refers to separation of the organic and aqueous layers, extraction of the aqueous layer three times with the indicated solvent, washing the combined organic extracts once with brine, drying with the indicated drying agent, filtration and concentration under reduced pressure. n-Butyllithium was titrated with diphenylacetic acid[57] before use.

General method for aldol reactions using LDA

A solution of n-BuLi in hexane (1.6 M, 1.2 equiv.) was added dropwise over 5 minutes to a stirred solution of dry diisopropylamine (1.2 equiv.) in dry THF (2 ml/mmol n-BuLi) at −78 °C. After 50 minutes a solution of the ester or ketone (1.0 equiv.) in THF was added dropwise over 5 minutes. The mixture was then stirred for a further 50 minutes, before a solution of the aldehyde (1.2 equiv.) in THF was added dropwise over 10 minutes. After a further 10 minutes, the cold-bath was removed and sat. aq. NH_4Cl (0.5 ml/ml THF) immediately added with vigorous stirring. The cold slurry was then partitioned between Et_2O and water. Usual work-up (EtOAc, $MgSO_4$) gave the crude product.

General method for Swern oxidation

A solution of dry DMSO (2.5 equiv.) in dry DCM (0.5 ml/mmol DMSO) was added dropwise over 5 minutes to a stirred solution of oxalyl chloride (1.3 equiv.) in DCM

(7 ml/mmol oxalyl chloride) at −78 °C. After 10 minutes, a solution of the alcohol (1 equiv.) in DCM was added dropwise over 10 minutes. After a further 20 minutes, dry triethylamine (10 equiv.) was added dropwise over 5 minutes. The cold-bath was then removed, the mixture allowed to warm to RT, and then stirred for another 10 minutes. $NaHCO_3$ (0.75 ml/ml DCM) was then added. Usual work-up (DCM, $MgSO_4$) gave the crude product.

General method for Heck reaction

To a stirred solution of the palladium catalyst, phosphine (if used), base and additive (if used) in dry, degassed reaction solvent (2 ml/mmol iodide) was added a solution of the alkene and the iodide in the same solvent at RT. The mixture was then stirred at the indicated temperature for the indicated time. After cooling to RT, Et_2O (5 ml/ml reaction solvent) was added, and the mixture filtered through a pad of Celite, washing the cake thoroughly with Et_2O. The filtrate was washed twice with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*.

Ethyl 4-phenylbut-2-enoate 6

To a stirred solution of freshly distilled phenylacetaldehyde **5** (18.0 g, 150 mmol), in dry DCM (250 ml) was added (carboethoxymethylene)triphenylphosphorane (62.6 g, 180 mmol) in one portion at RT. The mixture was stirred for 16 hours, concentrated *in vacuo*, redissolved in 10 : 1 (v:v) petrol : Et_2O, filtered and concentrated. This was repeated twice more. Purification of the residue by column chromatography (24 : 1 petrol : EtOAc) gave the (*Z*)-isomer (1.8 g, 7%) as a colourless oil, followed by the (*E*)-isomer (24.4 g, 89%) as a colourless oil: (*Z*)-isomer: R_f 0.36 (24 : 1 petrol : EtOAc); ν_{max}(film)/cm^{-1} 3030(m), 2984(m), 1720(s), 1651(s), 1273(s), 985(m); δ_H(200 MHz; $CDCl_3$) 1.37 (3H, t, *J* 7.1, OCH_2CH_3), 4.07 (2H, dd, *J* 7.5 and 1.6, $PhCH_2$), 4.25 (2H, q, *J* 7.1, OCH_2CH_3), 5.90 (1H, dt, *J* 11.4 and 1.6, H-2), 6.40 (1H, dt, *J* 11.4 and 7.5, H-3), 7.20–7.45 (5H, m, ArH); δ_C(50.3 MHz; $CDCl_3$) 14.3 (OCH_2CH_3), 39.3 ($PhCH_2$), 61.1 (OCH_2CH_3), 122.4 (*ortho*-CH), 127.1 (*para*-CH), 128.7 (C-2), 130.3 (*meta*-CH), 138.0 (*ipso*-C), 146.4 (C-3), 170.1 (CO); *m*/*z* (APCI) 191 (100, MH$^+$), 145 (54), 122 (23); (*E*)-isomer: R_f 0.30 (24 : 1 petrol : EtOAc); ν_{max}(film)/cm^{-1} 3029(m), 2982(m), 1720(s), 1654(s), 1271(s); δ_H(200 MHz; $CDCl_3$) 1.35 (3H, t, *J* 7.2, OCH_2CH_3), 3.55 (2H, dd, *J* 6.8 and 1.5, $PhCH_2$), 4.22 (2H, q, *J* 7.2, OCH_2CH_3), 5.85 (1H, dt, *J* 15.5 and 1.5, H-2), 7.15 (1H, dt, *J* 15.5 and 6.8, H-3), 7.22–7.43 (5H, m, ArH); δ_C(50.3 MHz; $CDCl_3$) 14.7 (OCH_2CH_3), 38.9 ($PhCH_2$), 60.7 (OCH_2CH_3), 122.8 (*meta*-CH), 127.1 (*ortho*-CH), 129.1 (*para*-CH), 129.3 (C-2), 138.1 (*ipso*-C), 147.7 (C-3), 166.9 (CO); *m*/*z* (APCI) 191 (4, MH$^+$), 145 (14), 117 (25).

4-Phenylbut-2-en-1-ol

DIBAL-H (18.2 ml of a 1.5 M solution in toluene, 27.3 mmol) was added dropwise over 20 minutes to a stirred solution of ester **6** (2.00 g, 10.5 mmol) in dry THF (40 ml) at −78 °C. The mixture was stirred for 1 hour at −78 °C, then for 1 hour at −10 °C, before being quenched by the cautious addition of 1 M HCl (40 ml). It was then stirred at RT for 5 minutes until 2 clear phases were formed. Usual work-up (EtOAc, $MgSO_4$) followed by column chromatography (7 : 3 petrol : EtOAc) gave the title compound (1.47 g, 94%) as a colourless oil: R_f 0.32 (7 : 3 petrol : EtOAc); ν_{max}(film)/cm^{-1} 3340(br s), 2901(m), 1603(w), 1094(m), 972(s); δ_H(200 MHz; $CDCl_3$) 1.95 (1H, br s, OH), 3.50 (2H, d, *J* 6.6, $PhCH_2$), 4.18 (2H, dd, *J* 5.6 and 1.1, H-1), 5.70–6.03 (2H, m, H-2 and H-3), 7.20–7.35 (5H, m, ArH); δ_C(50.3 MHz; $CDCl_3$) 39.1 ($PhCH_2$), 63.9 (C-1), 126.9 (*meta*-CH), 129.0 (*para*-CH), 129.1 (*ortho*-CH), 130.8 (C-2), 132.0 (*ipso*-C), 140.5 (C-3); *m*/*z* (APCI) 167 (4%, MNH_4^+), 149 (100, MH$^+$), 121 (22), 113 (50).

4-Phenylbut-2(*E*)-enal 4

To a stirred suspension of PCC (655 mg, 3.0 mmol) in dry DCM (8 ml) was added a solution of the above alcohol (300 mg, 2.0 mmol) in dry DCM (5 ml) in one portion at RT. After 2.5 hours, Et_2O (30 ml) was added. The mixture was then filtered through Celite, washing thoroughly with fresh Et_2O. Concentration of the filtrate followed by column chromatography (17 : 3 petrol : EtOAc) gave the title compound (239 mg, 81%) as an orange oil: R_f 0.36 (17 : 3 petrol : EtOAc); ν_{max}(film)/cm^{-1} 3029(s), 2819(s), 1690(s), 1639(s), 1124(s), 978(s), 751(s); δ_H(200 MHz; $CDCl_3$) 3.72 (2H, dd, *J* 6.7 and 1.6, $PhCH_2$), 6.18 (1H, ddt, *J* 15.5, 7.9 and 1.6, H-2), 7.05 (1H, dt, *J* 15.5 and 6.7, H-3), 7.22–7.53 (5H, m, ArH), 9.61 (1H, d, *J* 7.9, CHO); δ_C(50.3 MHz; $CDCl_3$) 39.5 ($PhCH_2$), 126.8 (C-2), 128.9 (*ortho*-CH), 129.3 (*para*-CH), 134.0 (*meta*-CH), 137.5 (*ipso*-C), 156.9 (C-3), 194.3 (CO); *m*/*z* (GCMS) 164 (86%, MNH_4^+), 147 (100, MH$^+$), 145(30), 117 (74), 115 (50), 91 (42), 65 (17).

1-Iodo-5-phenylpenta-(1*Z*,3*E*)-diene 2a

NaHMDS (2.5 ml of a 1 M solution in THF, 2.5 mmol, 1.5 equiv.) was added dropwise to a stirred suspension of (iodomethyl)triphenylphosphonium iodide (1.36 g, 2.5 mmol, 1.5 equiv.) at RT. After 5 minutes the red solution was cooled to −78 °C, before a solution of aldehyde **4** (250 mg, 1.71 mmol, 1.0 equiv.) in dry THF (5 ml) was added at such a rate as to keep the internal temperature below −70 °C. The mixture was stirred at −78 °C for 15 min, allowed to warm to RT and stirred for 2 h. Sat. aq. NH_4Cl (10 ml) was added, the layers separated and the aqueous layer extracted with Et_2O (3 × 25 ml), the combined organic layers were dried ($MgSO_4$) and concentrated to yield the crude product. Purification by column chromatography (petrol) yielded the title compound (320 mg, 69%), a yellow/orange oil, as an 8 : 1 mixture of 1(*Z*) : 1(*E*) isomers: R_f 0.53 (24 : 1 petrol : EtOAc); ν_{max} ($CHCl_3$)/cm^{-1} 3062(m), 3025(m), 1640(m), 1602(m), 1494(m), 1452(m), 972(s), 748(s), 698(s), 576(s). Data for major 1(*Z*)-isomer only: δ_H(400 MHz; $CDCl_3$) 3.51 (4H, d, *J* 7.1, H-5), 6.14 (1H, dt, *J* 15.1 and 7.2, H-4), 6.18 (1H, d, *J* 7.1, H-1), 6.32 (1H, dd, *J* 15.1 and 9.8, H-3), 6.73 (1H, dd, *J* 9.8 and 7.7, H-2), 7.30–7.49 (10H, m, ArH); δ_C(400 MHz; $CDCl_3$) 39.4 (C-5), 80.6 (C-4), 126.3 (*para*-C), 128.5 (*ortho*-C), 128.6 (*meta*-C), 131.5 (C-2), 138.1 (C-3), 138.2 (C-1), 139.3 (*ipso*-C); *m*/*z* (GCMS, EI) 270 (18, MH$^+$), 254(51), 143(98), 128(100), 115(72), 91(52), 65(42); HRMS (TOF MS FI$^+$) Found 269.9904, $C_{11}H_{11}I$ requires 269.9906.

1-Iodo-5-phenylpenta-(1*E*,3*E*)-diene 2b

To a stirred suspension of $CrCl_2$ (1.64 g, 13.3 mmol, 6.0 equiv.) in dry THF (20 ml) was added dropwise a solution of aldehyde **4** (324 mg, 2.22 mmol, 1.0 equiv.) and CHI_3 (1.75 g, 4.5 mmol, 2.0 equiv.) in dry THF (8 ml) at 0 °C. The mixture was stirred at 0 °C for 1 h then for 30 minutes at RT. Water (50 ml) was added, the layers separated and the aqueous layer extracted with Et_2O (4 × 25 ml). The combined organic layers were washed with sat. aq. $Na_2S_2O_3$ (1 × 50 ml), brine (1 × 50 ml), dried (Na_2SO_4), filtered and concentrated. Purification by column chromatography (99 : 1 petrol : Et_2O) yielded the title compound (340 mg, 77%) in a ratio of 1(*E*) : 1(*Z*) = 3 : 1 by NMR spectroscopic analysis as an orange oil: R_f 0.37 (petrol); ν_{max} (film)/cm^{-1} 3024(s), 2359(m), 1494(s), 1451(m), 979(s), 749(m), 697(s). Data for major 1(*E*)-isomer only: δ_H(400 MHz; $CDCl_3$) 3.39 (2H, d, *J* 6.8, H-5), 5.89 (1H, dt, *J* 6.8 and 15.1, H-4), 6.07 (1H, dd, *J* 10.4 and 15.1, H-3), 6.28 (1H, d, *J* 14.4, H-1), 7.07 (1H, dd, *J* 10.4 and 14.4, H-2), 7.15–7.35 (5H, m, Ar*H*); δ_C(100 MHz; $CDCl_3$) 38.6 (C-5), 77.3 (C-1), 126.2 (*ortho*-*C*H), 128.3 (*para*-*C*H), 131.2 (C-3), 134.1 (C-4), 139.2 (*ipso*-*C*), 145.0 (C-2); HRMS: Found 269.9911, $C_{11}H_{11}I$ requires 269.9906.

Ethyl 3-hydroxy-2,2,4-trimethylpent-4-enoate 7

According to the general method for aldol reactions using LDA, ethyl isobutyrate (4.35 g, 37.4 mmol) was reacted with freshly distilled methacrolein (3.20 g, 45.7 mmol). Purification by column chromatography (22 : 3 petrol : EtOAc) gave the title compound (6.8 g, 97%) as a colourless oil: R_f 0.26 (22 : 3 petrol : EtOAc); ν_{max}(film)/cm^{-1} 3400(br s), 3981(s), 1720(s), 1469(m), 1258(s), 1135(s); δ_H(400 MHz; $CDCl_3$) 1.11 (3H, s, CH_3), 1.18 (3H, s, CH_3), 1.25 (3H, t, *J* 7.1, OCH$_2$CH_3), 1.65 (3H, s, CH$_2$=C(CH_3)), 3.42 (1H, br s, OH), 4.10 (1H, dd, *J* 6.5 and 0.8, H-3), 4.12 (2H, q, *J* 7.1, OCH_2CH$_3$), 4.87–4.92 (2H, m, H-5); *m*/*z* (GCMS) 187 (87, MH$^+$), 169 (100), 116 (40), 71 (66); HRMS: Found 187.1335 (MH$^+$). $C_{10}H_{19}O_3$ requires 187.1334.

Ethyl 8-phenylocta-(2*E*,4*Z*,6*E*)-trienoate 10

According to the general method for Heck reaction, iodide **2a** (150 mg, 0.55 mmol) and ethyl acrylate (67 mg, 0.66 mmol) were reacted with palladium acetate (7 mg, 0.03 mmol), triphenylphosphine (15 mg, 0.05 mmol) and silver carbonate (153 mg, 0.55 mmol) in dry DMF at 50 °C for 18 hours. Purification by column chromatography (24 : 1 petrol : EtOAc) gave the title compound (70 mg, 52%) as a yellow oil: R_f 0.49 (21 : 4 petrol : EtOAc); ν_{max}(film)/cm^{-1} 2926(s), 1711(s), 1620(s), 1270(s), 1168(m); δ_H(400 MHz; $CDCl_3$) 1.37 (3H, t, *J* 7.1, OCH$_2$CH_3), 3.53 (2H, d, *J* 7.2, PhCH_2), 4.30 (2H, q, *J* 7.1, OCH_2CH$_3$), 5.89 (1H, d, *J* 15.1, H-2), 6.00–6.10 (2H, m, H-4 and H-7), 6.32 (1H, dd, *J* 11.0 and 11.0, H-5), 6.73 (1H, m, H-6), 7.15–7.35 (5H, m, ArH), 7.76 (1H, dd, *J* 15.1 and 12.2, H-3); δ_C(100.6 MHz; $CDCl_3$) 14.3 (OCH$_2$CH_3), 39.4 (PhCH_2), 60.3 (OCH_2CH$_3$), 121.3 (C-2), 126.2 (C-4), 126.3 (C-6), 128.4 (*ipso*-C), 128.8 (*meta*-CH), 128.7 (*para*-CH), 128.8 (*ortho*-CH), 137.1 (C-5), 138.3 (C-7), 139.1 (C-3), 167.2 (*C*O); *m*/*z* (GCMS) 260 (52%, MNH$_4^+$), 243 (100, MH$^+$), 168 (17); HRMS: Found 243.1385 (MH$^+$). $C_{16}H_{19}O_2$ requires 243.1385.

Methyl 2-methylene-8-phenylocta-(4*Z*,6*E*)-dienoate 11

According to the general method for Heck reaction, iodide **2a** (400 mg, 1.48 mmol) and methyl methacrylate (296 mg, 2.96 mmol) were reacted with palladium acetate (17 mg, 0.07 mmol), triphenylphosphine (39 mg, 0.15 mmol), and silver carbonate (408 mg, 1.48 mmol) in dry DMF at 55 °C for 16 hours. Purification by column chromatography (24 : 1 petrol : EtOAc) gave the title compound (149 mg, 42%) as a yellow oil: R_f 0.42 (24 : 1 petrol : EtOAc); ν_{max}(film)/cm^{-1} 2950(m), 1721(s), 1631(s), 1603(m), 1436(s), 1208(s), 951(m); δ_H(400 MHz; $CDCl_3$) 3.26 (2H, dd, *J* 7.6 and 0.9, H-3), 3.52 (2H, d, *J* 7.1, PhCH_2), 3.83 (3H, s, OCH_3), 5.47 (1H, m, H-4), 5.75 (1H, dt, *J* 1.5 and 0.9, = CH), 5.93 (1H, dt, *J* 15.0 and 7.1, H-7), 6.20 (1H, dd, *J* 10.9 and 10.9, H-5), 6.27 (1H, d, *J* 1.5, =CH′), 6.48 (1H, dd, *J* 15.0 and 10.9, H-6), 7.22–7.30 (5H, m, ArH); δ_C(100.6 MHz; $CDCl_3$) 29.8 (C-3), 39.2 (Ph*C*H$_2$), 51.8 (O*C*H$_3$), 126.2 (C-2), 126.4 (*ipso*-C), 126.5 (C(*C*H$_2$)CO), 127.0 (*para*-CH), 128.4 (*ortho*-CH), 128.5 (C-6), 128.6 (C-4), 130.4 (*meta*-CH), 134.0 (C-5), 138.8 (C-7), 167.4 (CO); *m*/*z* (GCMS) 260 (86%, MNH$_4^+$), 243 (100, MH$^+$), 207 (12), 183 (27), 158 (10), 128 (21), 108 (69), 91 (63); HRMS: Found 243.1388 (MH$^+$). $C_{16}H_{19}O_2$ requires 243.1385.

Ethyl 3-oxo-2,2,4-trimethylpent-4-enoate 12

Alcohol **7** (1.00 g, 5.37 mmol) was oxidised according to the general method for Swern oxidation. Purification by column chromatography (23 : 2 petrol : EtOAc) gave the title compound (854 mg, 86%) as a colourless oil: R_f 0.42 (22 : 3 petrol : EtOAc); ν_{max}(film)/cm^{-1} 2937(m), 1737(s), 1680(s), 1632(w), 1261(s), 1052(s); δ_H(400 MHz; $CDCl_3$) 1.18 (3H, t, *J* 7.2, OCH$_2$CH_3), 1.40 (6H, s, 2 × CH_3), 1.88 (3H, d, *J* 1.5, CH$_2$=C(CH_3)), 4.13 (3H, q, *J* 7.2, OCH_2CH$_3$), 5.66 (1H, s, H-5), 5.70 (1H, q, *J* 1.5, H-5′); δ_C(100.6 MHz; $CDCl_3$) 13.8 (OCH$_2$*C*H$_3$), 19.2 (CH$_2$=C(*C*H$_3$)), 24.1 (2 × *C*H$_3$), 52.9 (C-2), 61.2 (O*C*H$_2$CH$_3$), 123.9 (C-5), 142.1 (C-4), 174.9 (ester-CO), 199.5 (ketone-CO); *m*/*z* (GCMS) 202 (19%, MNH$_4^+$), 185 (92, MH$^+$), 69 (100), 58 (5); HRMS: Found 185.1184 (MH$^+$). $C_{10}H_{17}O_3$ requires 185.1178.

Ethyl 2,2-dimethyl-3-hydroxypent-4-enoate 13a

According to the general method for aldol reactions using LDA, ethyl isobutyrate (3.48 g, 29.9 mmol) was reacted with freshly distilled acrolein (1.93 g, 34.4 mmol). Purification by column chromatography (4 : 1 petrol : EtOAc) gave the title compound (4.85 g, 94%) as a colourless oil: R_f 0.30 (4 : 1 petrol : EtOAc); ν_{max}(film)/cm^{-1} 3495(br s), 2981(s), 1719(s), 1470(s), 1261(s), 1144 (s); δ_H(400 MHz; $CDCl_3$) 1.11 (3H, s, CH_3), 1.13 (3H, s, CH_3), 1.22 (3H, t, *J* 7.1, OCH$_2$CH_3), 2.90 (1H, br s, OH), 4.07 (1H, dd, *J* 6.6 and 0.8, H-3), 4.10 (3H, q, *J* 7.1, OCH_2CH$_3$), 5.17 (1H, dd, *J* 10.5 and 1.5, H-5), 5.25 (1H, ddd, *J* 17.1, 1.5 and 0.8, H-5′), 5.80 (1H, ddd, *J* 17.1, 10.5 and 6.6, H-4); δ_C(100.6 MHz; $CDCl_3$) 14.5 (OCH$_2$*C*H$_3$), 20.4 and 22.8 (C(*C*H$_3$)$_2$), 47.0 (C-2), 61.1 (O*C*H$_2$CH$_3$), 78.3 (C-3), 117.8 (C-5), 136.7 (C-4), 177.7 (CO); *m*/*z* (GCMS) 190 (25%, MNH$_4^+$), 173 (100, MH$^+$), 157 (40), 155(48), 116 (21), 83 (14); HRMS: Found 173.1182 (MH$^+$). $C_9H_{17}O_3$ requires 173.1178.

Ethyl 2,2-dimethyl-3-oxopent-4-enoate 14a

Alcohol **13a** (1.50 g, 8.71 mmol) was oxidised according to the general method for Swern oxidation. Purification by column chromatography (22 : 3 petrol : EtOAc) gave the title compound (1.24 g, 84%) as a colourless oil: R_f 0.50 (4 : 1 petrol : EtOAc); ν_{max}(film)/cm^{-1} 2983(s), 1740(s), 1702(s), 1614(s), 1468(s); δ_H(400 MHz; $CDCl_3$) 1.21 (3H, t, *J* 7.1, OCH$_2$CH_3), 1.34 (6H, s, C(CH_3)$_2$), 4.14 (2H, q, *J* 7.1, OCH_2CH$_3$), 5.69 (1H, dd, *J* 10.2 and 1.8, H-5), 6.35 (1H, dd, *J* 16.9 and 1.8, H-5′), 6.50 (1H, dd, *J* 16.9 and 10.2, H-4); δ_C(50.3 MHz; $CDCl_3$) 13.7 (OCH$_2$CH_3), 21.4 (C(*C*H$_3$)$_2$), 52.3 (C-2), 61.3 (O*C*H$_2$CH$_3$), 129.3 (C-5), 131.4 (C-4), 173.8 (ester-CO), 196.5 (ketone-CO); *m*/*z* (GCMS) 188 (25%, MNH$_4^+$), 171 (100, MH$^+$), 142 (23), 125 (4), 70 (19), 55 (50); HRMS: Found 171.1015 (MH$^+$). $C_9H_{15}O_3$ requires 171.1021.

***tert*-Butyl 3-hydroxy-4-methylpent-4-enoate 13b**

tert-Butyl acetate (3.45 g, 29.7 mmol) was reacted with LDA and freshly distilled methacrolein (2.39 g, 34.1 mmol) added to the reaction mixture. Purification by column chromatography (4 : 1 petrol : EtOAc) gave the title compound (4.63 g, 84%) as a colourless oil: R_f 0.27 (21 : 4 petrol : EtOAc); ν_{max}(film)/cm^{-1} 3450(br s), 2979(s), 1731(s), 1652(w), 1369(s), 1152(s); δ_H(400 MHz; $CDCl_3$) 1.44 (9H, s, C(CH_3)$_3$), 1.72 (3H, s, CH$_2$=C(CH_3)), 2.45 (2H, m, H-2), 3.08 (1H, br s, OH), 4.40 (1H, dd, *J* 6.9 and 4.4, H-3), 4.81 (1H, s, H-5), 5.00 (1H, s, H-5′); δ_C(50.3 MHz; $CDCl_3$) 18.7 (CH$_2$=C(*C*H$_3$)), 28.5 (C(CH$_3$)$_3$), 41.4 (C-2), 72.1 (C-3), 81.8 (O*C*(CH$_3$)$_3$), 111.7 (C-5), 146.0 (C-4), 172.4 (CO); *m*/*z* (GCMS) 204 (75%, MNH$_4^+$), 187 (94, MH$^+$), 148 (100, [M − OH]$^+$), 131 (30); HRMS: Found 209.1154 (MNa$^+$). $C_{10}H_{18}O_3Na$ requires 209.1154.

***tert*-Butyl 4-methyl-3-oxopent-4-enoate 14b**

Alcohol **13b** (1.50 g, 8.05 mmol) was oxidised according to the general method for Swern oxidation. Purification by column chromatography (23 : 2 petrol : EtOAc) gave the title compound (1.1 g, 72%) as a colourless oil: R_f 0.41 (22 : 3 petrol : EtOAc); ν_{max}(film)/cm^{-1} 2980(m), 1737(s), 1686(s), 1633(m), 1298(m), 1151(s); δ_H(400 MHz; $CDCl_3$) 1.45 (9H, s, C(CH_3)$_3$), 1.89 (3H, s, CH$_2$=C(CH_3)CO), 3.62 (2H, s, H-2), 5.86 (1H, s, H-5), 5.94 (1H, s, H-5′); δ_C(100.6 MHz; $CDCl_3$) 17.2 (CH$_2$=C(*C*H$_3$)CO), 27.9 (C(*C*H$_3$)$_3$), 46.3 (C-2), 81.7 (O*C*(CH$_3$)$_3$), 126.2 (C-5), 127.9 (C-4), 170.3 (ester-CO), 194.6 (ketone-CO).

Ethyl 2,2-dimethyl-3-oxopentanoate

To a stirred solution of ethyl 2-methyl-3-oxopentanoate[58] (15.0 g, 94.8 mmol) in dry THF (100 ml) at 0 °C was added NaH (4.55 g of a 60% dispersion in mineral oil, 113 mmol) over 5 minutes. The mixture was stirred at 0 °C for 10 minutes, then for 1 hour at RT, then cooled back to 0 °C before neat iodomethane (16.8 g, 119 mmol) was added dropwise over 10 minutes. The mixture was stirred at 0 °C for 3 hours then at RT for 19 hours. Sat. aq. NH_4Cl (80 ml) was added, the THF removed *in vacuo* and the residue redissolved in Et_2O (80 ml). Usual work-up (Et_2O, $MgSO_4$) followed by distillation under reduced pressure gave the title compound (14.5 g, 89%, bp 84–86 °C/16 mmHg) as a colourless oil: R_f 0.33 (4 : 1 petrol : EtOAc); ν_{max}(film)/cm^{-1} 2983(m), 1743(s), 1715(s), 1270(s), 1151(s); δ_H(200 MHz; $CDCl_3$) 1.08 (3H, t, *J* 7.2, H-5), 1.27 (3H, t, *J* 7.1, OCH_2CH_3), 1.37 (6H, s, $C(CH_3)_2$), 2.49 (2H, q, *J* 7.2, H-4), 4.18 (2H, q, *J* 7.1, OCH_2CH_3); δ_C(50.3 MHz; $CDCl_3$) 8.6 (C-5), 14.4 (OCH_2CH_3), 22.4 ($C(CH_3)_2$), 31.6 (C-4), 55.8 (C-2), 61.6 (OCH_2CH_3), 174.2 (ester-CO), 209.2 (ketone-CO); *m*/*z* (GCMS) 190 (8%, MNH_4^+), 173 (100, MH^+), 116 (37); HRMS: Found 173.1178 (MH^+). $C_9H_{17}O_3$ requires 173.1177.

Ethyl 4-bromo-2,2-dimethyl-3-oxopentanoate

Bromine (1.2 ml, 23.2 mmol) was added dropwise over 5 minutes to a stirred solution of the above β-keto ester (4.00 g, 23.2 mmol) in acetic acid (9 ml) at RT. After 3 hours the dark mixture turned light orange, and ^{1}H NMR of an aliquot showed the complete consumption of starting material. Sat. aq. $Na_2S_2O_3$ (40 ml), water (10 ml) and Et_2O (50 ml) were added. The aqueous and organic layers were separated, the aqueous phase extracted with Et_2O (4 × 30 ml), the combined organic layers washed with sat. aq. $NaHCO_3$ (1 × 100 ml), brine (1 × 100 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Distillation under reduced pressure gave the title compound (4.79 g, 82%, bp 94–95 °C/22 mmHg) as a yellow oil: R_f 0.68 (2 : 3 petrol : EtOAc); ν_{max}(film)/cm^{-1} 2985(m), 1749(s), 1720(s), 1258(m), 1151(s), 1031(m); δ_H(200 MHz; $CDCl_3$) 1.32 (3H, t, *J* 7.2, OCH_2CH_3), 1.47 (s, 3H, CH_3), 1.64 (3H, s, CH_3), 1.83 (3H, d, *J* 6.6, H-5), 4.23 (2H, q, *J* 7.2, OCH_2CH_3), 4.72 (1H, q, *J* 6.6, H-4); δ_C(50.3 MHz; $CDCl_3$) 14.6 (OCH_2CH_3), 21.3 (C-5), 22.6 and 22.7 ($C(CH_3)_2$), 41.6 (C-4), 56.1 (C-2), 61.4 (OCH_2CH_3), 175.0 (ester-CO), 210.2 (ketone-CO); *m*/*z* (GCMS) 268 and 270 (6%, MNH_4^+), 251 and 253 (5, MH^+), 190 (25), 173 (100), 116 (19); HRMS: Found 268.0550 (MNH_4^+). $C_9H_{19}{}^{79}BrNO_3$ requires 268.0548.

Triethyl 2,2-dimethyl-3-oxo-4-phosphonopentanoate 17

The above bromide (34.9 g, 19.4 mmol) and triethyl phosphite (12.9 g, 77.5 mmol) in dry toluene (25 ml) were stirred at reflux for 30 hours. The mixture was cooled to RT, another portion of triethyl phosphite (6.44 g, 38.7 mmol) was added, then the mixture refluxed for another 20 hours. After cooling to RT the mixture was concentrated *in vacuo*. Purification by column chromatography (2 : 3 petrol : EtOAc) gave the title compound (5.32 g, 89%) as a colourless oil: R_f 0.25 (2 : 3 petrol : EtOAc); ν_{max}(film)/cm^{-1} 2985(m), 1741(s), 1712(s), 1259(s), 1028(s), 964(s); δ_H(400 MHz; $CDCl_3$) 1.3–1.7 (18H, m, 6 × CH_3), 3.53 (1H, dq, *J* 19.6 and 7.1, H-4), 4.09 (4H, m, $(CH_3CH_2O)_2PO$), 4.15 (2H, q, *J* 7.1, $CO_2CH_2CH_3$); δ_C(100.6 MHz; $CDCl_3$) 14.0 ($CO_2CH_2CH_3$), 14.4 (C-5), 16.4 (($CH_3CH_2O)_2P$), 22.0 (CH_3), 41.9 (d, $^1J_{^{13}C,^{31}P}$ 133.0, C-4), 56.9 (C-2), 61.5 ($CO_2CH_2CH_3$), 62.6 (d, $^2J_{^{13}C,^{31}P}$ 31, ($CH_3CH_2O)_2PO$), 173.0 (ester-CO), 205.1 (ketone-CO); *m*/*z* (GCMS) 309 (100%, MH^+), 193 (32); HRMS: Found 308.1386 (M^+, EI). $C_{13}H_{25}O_6P$ requires 308.1389.

Ethyl 3-oxo-5-phenyl-2,2,4-trimethylpent-4-enoate 21

A solution of phosphonate **17** (600 mg, 1.91 mmol, 1.2 equiv.) in dry THF (4 ml) was added dropwise over 10 minutes to a stirred suspension of NaH (73 mg of a 60% dispersion in mineral oil, 1.83 mmol, 1.15 equiv.) in dry THF (10 ml) at 0 °C. The mixture was stirred, cooled to 0 °C and a solution of benzaldehyde (168 mg, 1.59 mmol, 1.0 equiv.) in dry THF (3 ml) was added dropwise. The mixture was allowed to warm to RT over 3 hours and stirred for a further 4 hours. The reaction was quenched with sat. aq. NH_4Cl (20 ml), and the usual work-up (EtOAc, $MgSO_4$) followed by column chromatography (23 : 2 petrol : EtOAc) gave the title compound (266 mg, 64%, 5 : 1 (*E*) : (*Z*)-isomer ratio by ^{1}H NMR) as a colourless oil: R_f 0.31 (23 : 2 petrol : EtOAc), ν_{max}(film)/cm^{-1} 2983 (m), 1733 (s), 1704 (s), 1669 (s), 1627 (m), 1386 (m), 1264 (s), 1140 (s), 1045 (s); δ_H(400 MHz; $CDCl_3$) (*E*)-isomer: 1.20 (3H, t, *J* 7.1, OCH_2CH_3), 1.52 (6H, s, $C(CH_3)_2$), 2.05 (3H, d, *J* 1.0, $C(CH_3)CO$), 4.19 (2H, q, *J* 7.1, OCH_2CH_3), 7.25 (1H, q, *J* 1.0, PhC*H*), 7.30–7.50 (5H, m, Ar*H*); (*Z*)-isomer: 1.25 (3H, t, *J* 7.2, OCH_2CH_3), 1.52 (6H, s, $C(CH_3)_2$), 2.03 (3H, d, *J* 1.4, $C(CH_3)CO$), 4.10 (2H, q, *J* 7.2, OCH_2CH_3), 6.43 (1H, q, *J* 1.4, PhC*H*), 7.30–7.50 (5H, m, Ar*H*); δ_C(100 MHz; $CDCl_3$) (*E*)-isomer: 14.0 (OCH_2CH_3), 14.3 ($C(CH_3)CO$), 24.5 ($C(CH_3)_2$), 53.0 ($C(CH_3)_2$), 61.2 (OCH_2CH_3), 128.4 (Ph*C*H), 128.5 (*meta*-*C*H), 129.6 (*ortho*-*C*H), 129.7 (*para*-*C*H), 135.2 (*ipso*-*C*), 135.6 ($C(CH_3)CO$), 175.3 (ester-*C*O), 200.2 (ketone-*C*O); (*Z*)-isomer: 14.1 (OCH_2CH_3), 15.0 ($C(CH_3)CO$), 24.5 ($C(CH_3)_2$), 53.0 ($C(CH_3)_2$), 60.9 (OCH_2CH_3), 128.0 (*ortho*-*C*H), 128.1 (*para*-*C*H), 128.8 (Ph*C*H), 128.9 (*meta*-*C*H), 134.5 (*ipso*-*C*), 134.8 ($C(CH_3)CO$), 175.2 (ester-*C*O), 199.6 (ketone-*C*O); *m*/*z* (GCMS) 261 (71%, MH^+), 145 (100), 115 (23), 91 (18), 71 (4); HRMS: Found 260.1406 (M^+, EI). $C_{16}H_{20}O_3$ requires 260.1412.

Ethyl 3-oxo-7-(tributylstannyl)-2,2,4-trimethylhepta-(4*E*,6*E*)-dienoate 22

A solution of phosphonate **17** (2.23 g, 7.32 mmol) in dry THF (5 ml) was added dropwise over 5 minutes to a stirred suspension of NaH (0.29 g of a 60% dispersion in mineral oil, 7.23 mmol) in dry THF (30 ml) at 0 °C. The mixture was stirred at 0 °C for 10 minutes then at RT for 1 hour, then cooled back to 0 °C before a solution of aldehyde **16a**[52] (1.56 g, 4.52 mmol) in dry THF (6 ml) was added dropwise over 5 minutes. The mixture was stirred for 21 hours, being allowed to warm to RT. Sat. aq. $NaHCO_3$ (10 ml) and brine (20 ml) were added, the THF removed *in vacuo*, and the residue dissolved in Et_2O (40 ml). Usual work-up (EtOAc, $MgSO_4$) followed by purification by column chromatography (24 : 1 petrol : EtOAc + 1% Et_3N) gave the title compound (1.12 g, 50%) as a colourless oil: R_f 0.26 (24 : 1 petrol : EtOAc); ν_{max}(film)/cm^{-1}2952 (s), 2928 (s), 1735 (s), 1665 (s), 1614 (w), 1545 (w), 1465 (s), 1270 (s), 1138 (s), 988 (m); δ_H(500 MHz; $CDCl_3$) 0.89–0.99 (15H, m, ($CH_3CH_2CH_2CH_2)_3Sn$ and ($CH_3CH_2CH_2CH_2)_3Sn$), 1.20 (3H, t, *J* 7.1, OCH_2CH_3), 1.32–1.55 (12H, m, ($CH_3CH_2CH_2CH_2)_3Sn$ and ($CH_3CH_2CH_2CH_2)_3Sn$), 1.44 (6H, s, $C(CH_3)_2$), 1.96 (3H, s, $CH=C(CH_3)$), 4.17 (2H, q, *J* 7.1, OCH_2CH_3), 6.72 (1H, d, *J* 11.0, $CH=C(CH_3)$), 6.76 (1H, d, *J* 18.5, SnC*H*=CH), 6.90 (1H, dd, *J* 18.5 and 11.0, SnCH=C*H*); δ_C(100.6 MHz; $CDCl_3$) 9.6 (($CH_3CH_2CH_2CH_2)_3Sn$), 12.6 ($CH=C(CH_3)$), 13.6 (($CH_3CH_2CH_2CH_2)_3Sn$), 13.9 (OCH_2CH_3), 24.5 ($C(CH_3)_2$), 27.2 (($CH_3CH_2CH_2CH_2)_3Sn$), 29.1 (($CH_3CH_2CH_2CH_2)_3Sn$), 52.7 ($C(CH_3)_2$), 61.1 (OCH_2CH_3), 131.8 ($CH=C(CH_3)$), 140.2 ($CH=C(CH_3)$), 141.9 (SnCH=*C*H), 147.4 (Sn*C*H=CH), 175.42 (ester-*C*O), 200.0 (ketone-*C*O); *m*/*z* (GCMS) 501 (100%, MH^+), 347 (53), 308 (74), 289 (40); HRMS: Found 501.2395 (MH^+). $C_{24}H_{45}O_{31}{}^{20}Sn$ requires 501.2390.

Ethyl 3-oxo-8-phenyl-2,2,4-trimethylocta-(4*E*,6*E*)-dienoate 23

To a stirred solution of bis(acetonitrile)dichloropalladium(II) (6 mg, 0.02 mmol) in dry, degassed DMF (3 ml) was added a solution of benzyl bromide (98 mg, 0.57 mmol) in dry DMF (1 ml) followed by a solution of stannane **22** (300 mg, 0.6 mmol) in dry DMF (1 ml) at RT. After 2 hours 2 M NH_4OH(aq.)

(5 ml) was added, and the mixture partitioned between Et_2O (40 ml) and brine (10 ml). Usual work-up (Et_2O, Na_2SO_4) followed by column chromatography (23 : 2 petrol : EtOAc + 1% Et_3N) gave the title compound (100 mg, 58%) as a colourless oil: R_f 0.31 (23 : 2 petrol : EtOAc); ν_{max}(film)/cm^{-1} 2982(m), 2935(m), 1732(s), 1663(s), 1634(s), 1604(w), 1454(m), 1268(s), 1146(s), 700(m); δ_H(400 MHz; $CDCl_3$) 1.17 (3H, t, *J* 7.1, OCH_2CH_3), 1.43 (6H, s, $C(CH_3)_2$), 1.88 (3H, s, $C(CH_3)CO$), 3.54 (2H, d, *J* 7.0, $PhCH_2$), 4.15 (2H, q, *J* 7.1, OCH_2CH_3), 6.19 (1H, dt, *J* 15.0 and 7.0, H-7), 6.44 (1H, dd, *J* 15.0 and 10.7, H-6), 6.82 (1H, d, *J* 10.7, H-5), 7.16–7.35 (5H, m, ArH); δ_C(100.6 MHz; $CDCl_3$) 12.7 (OCH_2CH_3), 14.0 ($C(CH_3)CO$), 24.4 ($C(CH_3)_2$), 39.6 ($PhCH_2$), 52.6 ($C(CH_3)_2$), 61.1 (OCH_2CH_3), 126.4 (C-7), 127.1 (*ortho*-CH), 128.6 (*para*-CH), 128.6 (*meta*-CH), 132.5 (*ipso*-C), 138.2 (C-6), 138.9 (C-4), 141.8 (C-5), 175.4 (ester-CO), 199.3 (ketone-CO); *m*/*z* (APCI) 301 (60%, MH^+), 91 (100), 71 (70); HRMS: Found 301.1801 (MH^+). $C_{19}H_{25}O_3$ requires 301.1803.

Ethyl 3-hydroxy-8-phenyl-2,2,4-trimethylocta-(4*E*,6*E*)-dienoate 24

$NaBH_4$ (12 mg, 0.32 mmol) was added to a stirred solution of ketone **23** (32 mg, 0.11 mmol) in MeOH (3 ml) at 0 °C. After 1 hour at the same temperature another portion of $NaBH_4$ (8 mg, 0.21 mmol, 2.0 equiv.) was added, and stirring continued for a further hour. Sat. aq. NH_4Cl (3 ml) was added, and the mixture partitioned between Et_2O (40 ml) and brine (5 ml). Usual work-up (Et_2O, Na_2SO_4), followed by column chromatography (21 : 4 petrol : EtOAc + 1% Et_3N) gave the title compound (24 mg, 74%) as a colourless oil: R_f 0.24 (21 : 4 petrol : EtOAc); ν_{max}($CHCl_3$)/cm^{-1} 3560(br s), 2983(s), 2928(s), 1722(s), 1698(m), 1602(w), 1453(m), 1252(s), 1142(s), 743(s); δ_H(400 MHz; $CDCl_3$) 1.15 (3H, s, CH_3), 1.22 (3H, s, CH_3), 1.29 (3H, t, *J* 7.1, OCH_2CH_3), 1.73 (3H, s, $CH{=}C(CH_3)$), 3.17 (1H, br s, OH), 3.45 (2H, d, *J* 7.0, $PhCH_2$), 4.13 (1H, d, *J* 6.6, H-3), 4.15 (2H, q, *J* 7.1, OCH_2CH_3), 5.82 (1H, dt, *J* 15.0 and 7.0, H-7), 5.99 (1H, d, *J* 10.8, H-5), 6.33 (1H, dd, *J* 15.0 and 10.8, H-6), 7.18–7.34 (5H, m, ArH); δ_C(100.6 MHz; $CDCl_3$) 13.7 (CH_3), 14.1 (CH_3), 20.8 (OCH_2CH_3), 23.9 ($CH{=}C(CH_3)$), 39.3 ($PhCH_2$), 46.5 (C-2), 60.9 (OCH_2CH_3), 82.4 (C-3), 126.1 (C-7), 126.9 (*para*-CH), 128.4 (C-6), 128.5 (*meta*-CH), 128.5 (*ortho*-CH), 133.4 (C-5), 134.9 (*ipso*-C), 140.2 (C-4), 177.9 (CO); *m*/*z* (GCMS) 302 (2%, MH^+), 285 (35, $[M - OH]^+$), 204 (32), 187 (100); HRMS: Found 320.2219 (NH_4^+). $C_{19}H_{27}O_3$ requires 320.2226.

(*E*)-1-Iodo-3-phenylpropene 25

To a stirred suspension of $CrCl_2$ (568 mg, 462 mmol) in dry THF (20 ml) was added a solution of iodoform (606 mg, 1.54 mmol) and freshly distilled phenylacetaldehyde (93 mg, 0.77 mmol) in dry THF (7 ml) over 5 minutes at 0 °C. The mixture was stirred at 0 °C for 1 hour then at RT for 2 hours, before being poured into water (50 ml). The layers were separated, and the aqueous layer extracted with EtOAc (4 × 20 ml). The combined organic layers were washed with sat. aq. $Na_2S_2O_3$ (25 ml), brine (25 ml), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by column chromatography (hexane) gave the title compound (188 mg, 79%, 10 : 1 (*E*) : (*Z*)-ratio by ^{1}H NMR) as a colourless oil: R_f 0.34 (hexane); ν_{max}(film)/cm^{-1} 3025(m), 1605(m), 1495(s), 1452(s), 1219(m), 951(s), 747(s), 697(s); δ_H(400 MHz; $CDCl_3$) (*E*)-isomer: 3.38 (2H, dd, *J* 7.0 and 0.9, $PhCH_2$), 6.08 (1H, dt, *J* 14.4 and 1.0, H-1), 6.67 (1H, dt, *J* 14.4 and 7.0, H-2), 7.14–7.33 (5H, m, ArH); (*Z*)-isomer: 3.52 (1H, d, *J* 5.3, $PhCH_2$), 6.37–6.50 (2H, m, H-1 and H-2); δ_C(50.3 MHz; $CDCl_3$) (*E*)-isomer 42.2 ($PhCH_2$), 76.6 (C-1), 126.9 (*para*-CH), 128.9 (*ortho*-CH), 129.0 (*meta*-CH), 138.3 (*ipso*-C), 145.1 (C-2); (*Z*)-isomer: 41.0 ($PhCH_2$), 83.8 (C-1), 126.8 (*para*-CH), 128.9 (*meta*-CH), 129.0 (*ortho*-CH), 138.8 (*ipso*-C), 140.3 (C-2); *m*/*z* (APCI) 245 (4%, MH^+), 117 (100); HRMS: Found 243.1388 (MH^+). $C_9H_{10}I$ requires 243.1385.

Ethyl 3-oxo-10-phenyl-2,2,4-trimethyldeca-(4*E*,6*E*,8*E*)-trienoate 26a

To a stirred solution of bis(acetonitrile)dichloropalladium(II) (8 mg, 0.03 mmol) in dry, degassed DMF (3 ml) was added a solution of iodide **25** (188 mg, 0.77 mmol) in dry DMF (1 ml), followed by a solution of stannane **22** (442 mg, 0.89 mmol) in dry DMF (1 ml) at RT. After 5.5 hours the mixture was diluted with Et_2O (50 ml), washed with aq. KF (2 × 20 ml) then brine (20 ml). The combined aqueous layers were back-extracted with EtOAc (3 × 20 ml), then the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography (47 : 3 petrol : EtOAc) gave the title compound (211 mg, 84%) as a pale yellow oil: R_f 0.31 (23 : 2 petrol : EtOAc); ν_{max}(film)/cm^{-1} 2934(m), 1731(s), 1660(s), 1607(s), 1264(s), 1149(s), 993(m); δ_H(400 MHz; $CDCl_3$) 1.17 (3H, t, *J* 7.1, OCH_2CH_3), 1.45 (6H, s, $C(CH_3)_2$), 1.92 (3H, s, $C(CH_3)CO$), 3.48 (2H, d, *J* 6.8, $PhCH_2$), 4.14 (2H, q, *J* 7.1, OCH_2CH_3), 6.07 (1H, dt, *J* 15.0 and 7.1, H-9), 6.20 (1H, dd, *J* 15.0 and 9.8, H-8), 6.47 (2H, m, H-6 and H-7), 6.83 (1H, d, *J* 10.1, H-5), 7.17–7.34 (5H, m, ArH); δ_C(100.6 MHz; $CDCl_3$) 13.4 (OCH_2CH_3), 13.6 ($C(CH_3)CO$), 24.3 ($C(CH_3)_2$), 39.1 ($PhCH_2$), 52.6 (C-2), 61.1 (OCH_2CH_3), 126.5 (*para*-CH), 126.8 (*meta*-CH), 127.1 (*ipso*-C), 128.5 (C-6), 128.7 (C-7), 129.0 (*ortho*-CH), 131.4 (C-5), 133.2 (C-8), 138.1 (C-4), 138.7 (C-9), 175.8 (ester-CO), 199.2 (ketone-CO); *m*/*z* (APCI) 327 (17%, MH^+), 211 (23), 155 (29), 143 (100), 115 (33).

Ethyl 3-hydroxy-10-phenyl-2,2,4-trimethyldeca-(4*E*,6*E*,8*E*)-trienoate 26b

To a stirred solution of ketone **26a** (62 mg, 0.19 mmol) in EtOH (4 ml) was added $NaBH_4$ (29 mg, 0.77 mmol) at 0 °C. The mixture was then stirred at RT for 2 hours, before another portion of $NaBH_4$ (22 mg, 58 mmol) was added. After a further 8 hours sat. aq. NH_4Cl (4 ml) was added, and the mixture partitioned between Et_2O (40 ml) and 1 M HCl (10 ml). Usual work-up followed by column chromatography (45 : 5 petrol : EtOAc) gave the title compound (58 mg, 92%) as a colourless oil: R_f 0.19 (23 : 2 petrol : EtOAc); λ_{max}(MeOH)/nm 269 (ε/dm^3 mol^{-1} cm^{-1} 24030), 278 (31190), 287 (24440); ν_{max}(film)/cm^{-1} 3490(br s), 2981(m), 1719(s), 1453(m), 1253(s), 1131(s), 989(s), 699(s); δ_H(400 MHz; $CDCl_3$) 1.18 (3H, s, CH_3), 1.22 (3H, s, CH_3), 1.20 (3H, t, *J* 7.1, OCH_2CH_3), 1.75 (3H, s, $C(CH_3)COH$), 3.21 (1H, d, *J* 6.0, OH), 3.46 (2H, d, *J* 7.2, $PhCH_2$), 4.11 (2H, q, *J* 7.1, OCH_2CH_3), 4.12 (1H, d, *J* 6.0, CH(OH)), 5.87 (1H, dt, *J* 7.2, 14.4, H-9), 6.03 (1H, d, *J* 11.1, H-5), 6.21 (2H, m, H-7 and H-8), 6.37 (1H, dd, *J* 14.1 and 11.1, H-6), 7.18–7.32 (5H, m, ArH); δ_C(100.6 MHz; $CDCl_3$) 13.9 ($C(CH_3)CHOH$), 14.1 (OCH_2CH_3), 23.8 (CH_3), 20.8 (CH_3), 39.1 ($PhCH_2$), 46.8 (C-2), 60.9 (OCH_2CH_3), 82.3 (C-3), 126.0 (*ortho*-CH), 126.1 (*para*-CH), 126.8 (C-6), 127.0 (*meta*-CH), 128.0 (C-5), 128.4 (C-9), 128.5 (*ipso*-C), 133.0 (C-8), 133.3 (C-7), 140.1 (C-4), 177.8 (CO); *m*/*z* (APCI) 329 (4%, MH^+), 283 (15), 213 (100), 143 (43), 116 (32). HRMS: Found 329.4569 (MH^+). $C_{21}H_{29}O_3$ requires 329.4571.

1,1-Dibromo-5-phenylpenta-(1*Z*,3*E*)-diene 29

PPh_3 (1.22 g, 4.66 mmol) was added portionwise over 1 minute to a stirred solution of CBr_4 (0.77 g, 2.33 mmol) in dry DCM (10 ml) at 0 °C. After 3 minutes a solution of aldehyde **4** (0.31 g, 2.12 mmol) in dry DCM (2 ml) was added dropwise over 3 minutes to the reaction mixture. The solution was stirred at 0 °C for 3 hours, then washed with water (10 ml), sat. aq. $Na_2S_2O_3$ (10 ml), dried ($MgSO_4$), filtered and concentrated. Purification by column chromatography (hexane) gave the title compound (0.56 g, 84%) as an orange oil: R_f 0.39 (hexane); ν_{max}(film)/cm^{-1} 3027(m), 1765(m), 1602(w), 1495(m), 1453(m), 1235(w), 967(s), 803(s), 748(s), 698(s); δ_H(400 MHz; $CDCl_3$) 3.45 (2H, d, *J* 6.5, $PhCH_2$), 6.04 (1H, dt, *J* 15.1 and 6.5, H-4),

6.18 (1H, dd, *J* 15.1 and 9.5, H-3), 6.94 (1H, d, *J* 9.5, H-2), 7.16–7.37 (5H, m, ArH); δ_C(100.6 MHz; $CDCl_3$) 39.3 (C-5), 89.6 (C-1), 125.2 (C-3), 127.6 (*meta*-CH), 128.6 (*para*-CH), 129.2 (*ortho*-CH), 136.7 (C-4), 137.3 (C-2), 139.0 (*ipso*-C); *m*/*z* (EI) 304, 302 and 300 (3, 6 and 3%, M^+), 223 and 221 (23, $[M - Br]^+$), 142 (100, $[M - Br_2]^+$), 128 (19), 115 (29), 90 (43), 65(14).

1-Bromo-5-phenylpenta-(1*Z*,3*E*)-diene 30

To a stirred solution of dibromide **29** (326 mg, 1.08 mmol) [NB crude material prepared as indicated above reacts smoothly, but carefully purified material does not] and $Pd(PPh_3)_4$ (75 mg, 0.07 mmol) in dry benzene (7 ml) was added dropwise Bu_3SnH (345 mg, 1.19 mmol) over 3 minutes at RT. After 3 hours water (5 ml) was added. Usual work-up (hexane, Na_2SO_4) followed by column chromatography (hexane) gave the title compound (183 mg, 76%, 1(*Z*) : 1(*E*)-ratio 99 : 1 by ^{1}H NMR) as a colourless oil: R_f 0.39 (hexane); ν_{max}(film)/cm^{-1} 3027(s), 1644(w), 1603(w), 1582(w), 1494(s), 1452(s), 1334(m), 973(s), 697(s); δ_H(400 MHz; $CDCl_3$) 3.48 (2H, d, *J* 7.2, PhCH_2), 6.05 (1H, dt, *J* 15.1 and 7.2, H-4), 6.09 (1H, d, *J* 7.0, H-1), 6.48 (1H, dd, *J* 15.1 and 10.2, H-3), 6.63 (1H, dd, *J* 10.2 and 7.0, H-2), 7.20–7.34 (5H, m, ArH); δ_C(100.6 MHz; $CDCl_3$) 39.4 (C-5), 106.7 (C-1), 126.3 (*para*-CH), 127.1 (C-3), 128.5 (*meta*-CH), 128.7 (*ortho*-CH), 132.4 (C-2), 137.4 (C-4), 139.4 (*ipso*-C); *m*/*z* (EI) 224 and 222 (8%, M^+), 143 (100, $[M - Br]^+$), 128 (89), 115 (43), 90 (25), 65 (19); HRMS: Found: 222.0015 (M^+). $C_{11}H_{11}{}^{79}Br$ requires 222.0044.

1-(*tert*-Butyldimethylsilyloxy)-3-iodo-2-methylprop-2(*Z*)-ene 31

To a stirred solution of alcohol **28**[53] (2.90 g, 14.7 mmol) in dry DMF (15 ml) at 0 °C was added imidazole (1.50 g, 22.0 mmol) in portions over 1 minute, followed by a solution of TBDMSCl (3.09 g, 20.5 mmol) in dry DMF (6 ml) dropwise over 10 minutes. The mixture was stirred for 1 hour at 0 °C, then for 22 hours at RT. The mixture was partitioned between Et_2O (150 ml) and 2 M HCl (50 ml). The aqueous layer was separated, and extracted with Et_2O (2 × 20 ml). The combined organic layers were washed with sat. aq. $NaHCO_3$ (80 ml), brine (80 ml), dried (Na_2SO_4), filtered and concentrated. Purification by column chromatography (23 : 2 hexane : Et_2O) gave the title compound (4.6 g, 99%) as a colourless oil: R_f 0.34 (hexane); ν_{max}(film)/cm^{-1} 2955(s), 2929(s), 1471(m), 1463(m), 1252(s), 1100(s), 839(s), 777(s), 666(m); δ_H(400 MHz; $CDCl_3$) 0.12 (6H, s, Si(CH_3)$_2$), 0.92 (9H, s, SiC(CH_3)$_3$), 1.91 (3H, d, *J* 1.4, CH=C(CH_3)), 4.27 (2H, s, H-1), 5.87 (1H, q, *J* 1.4, H-3); δ_C(100.6 MHz; $CDCl_3$) −3.6 (Si(*C*H$_3$)$_2$), 18.2 (Si*C*(CH$_3$)$_3$), 21.4 (C(*C*H$_3$)O), 25.8 (SiC(*C*H$_3$)$_3$), 68.6 (C-1), 72.4 (C-3), 146.7 (C-2); *m*/*z* (GCMS CI) 330 (15%, MNH_4^+), 313 (75, MH^+), 255 (32, $[M - tBu]^+$), 185 ($[M - I]^+$), 75 (52), 73 (46), 53 (34), 43 (95); HRMS: Found 330.0752 (MNH_4^+). $C_6H_{16}INOSi$ requires 330.0750.

1-(*tert*-Butyldimethylsilyloxy)-2-methyl-3-(tributylstannyl)prop-2(*Z*)-ene 32

To a stirred solution of iodide **31** (1.00 g, 3.20 mmol) in dry Et_2O (15 ml) was added n-BuLi (2.45 ml of a 2.1 M solution in hexanes, 5.12 mmol) dropwise over 20 minutes at −78 °C. After 90 minutes at the same temperature a solution of Bu_3SnCl (1.66 g, 5.12 mmol) in dry Et_2O (5 ml) was added dropwise over 10 minutes. The mixture was stirred at −78 °C for 3 hours, then at 0 °C for 2 hours, before being quenched with sat. aq. NH_4Cl (10 ml). Usual work-up (Et_2O, Na_2SO_4) followed by column chromatography (hexane + 1% Et_3N) gave the title compound (1.37 g, 90%) as a colourless oil: R_f 0.33 (hexane); ν_{max}(film)/cm^{-1} 2957(s), 2928(s), 2856(s), 1610(w), 1463(s), 1254(s), 1251(s), 1084(s), 856(s), 836(s), 776(s), 666(m); δ_H(400 MHz; $CDCl_3$) 0.08 (6H, s, Si(CH_3)$_2$), 0.85–0.94 (15H, m, alkyl), 0.89 (9H, s, SiC(CH_3)$_3$), 1.25–1.58 (12H, m, alkyl), 1.92 (3H, d, *J* 1.3, C(CH_3)CH$_2$O), 4.03 (2H, s, H-1), 5.60 (1H, q, *J* 1.3, SnC*H*=C, ^{117,119}Sn satellites gave $^2J_{H,Sn}$ 66 Hz); δ_C(100.6 MHz; $CDCl_3$) −5.4 (Si(*C*H$_3$)$_2$), 10.3 (*C*H$_2$Sn), 13.6 (*C*H$_3$), 18.4 (Si*C*(CH$_3$)$_3$), 23.6 (C(*C*H$_3$)O), 25.9 (SiC(*C*H$_3$)$_3$), 27.3 (*C*H$_2$), 29.1 (*C*H$_2$), 69.4 (*C*H$_2$O), 124.3 (Sn*C*H=C), 154.1 (*C*(CH$_3$)CH$_2$O); *m*/*z* (EI) 419 (100%, $[M - Bu]^+$), 291 (23), 267 (14), 235 (34), 177 (48), 121 (21), 73 (35), 58 (32).

2-Methyl-3-(tributylstannyl)prop-2(*Z*)-enal 34[59]

To a stirred solution of silyl ether **32** (200 mg, 0.46 mmol) in dry THF (7 ml) at RT was added TBAF (1.4 ml of a 1 M solution in THF, 1.40 mmol) dropwise over 5 minutes. The mixture was stirred for 2 hours, then quenched with sat. aq. NH_4Cl (3 ml). The THF was removed *in vacuo*, and the residue partitioned between Et_2O (20 ml) and brine (15 ml). The layers were separated, and the aqueous layer extracted with Et_2O (3 × 10 ml). The combined organic layers were dried ($MgSO_4$), filtered and concentrated to afford the crude alcohol.

To a stirred solution of $(COCl)_2$ (122 mg, 1.00 mmol) in dry DCM (8 ml) at −78 °C was added dry DMSO (140 ml, 2.00 mmol) dropwise. After 10 minutes a solution of the above crude alcohol in dry DCM (2.5 ml) was added dropwise, followed by dry Et_3N (0.70 ml, 5.00 mmol) added dropwise. The mixture was stirred at −78 °C for 5 minutes, warmed to RT, and then stirred for another 10 minutes. Sat. aq. $NaHCO_3$ (10 ml) was added. The layers were separated, and the aqueous layer extracted with DCM (3 × 8 ml). The combined organic layers were dried ($MgSO_4$), filtered and concentrated. Purification by column chromatography (24 : 1 hexane : EtOAc +1% Et_3N) gave the title compound (118 mg, 71%) as a colourless oil: R_f 0.46 (24 : 1 hexane : EtOAc); ν_{max}(film)/cm^{-1} 2957(s), 2925(s), 1692(s), 1464(m), 1072(w); δ_H(200 MHz; $CDCl_3$) 0.86–1.54 (27H, m, ($CH_2CH_2CH_2$-CH_3)$_3$), 1.97 (3H, d, *J* 1.4, C(CH_3)CHO), 7.42 (1H, d, *J* 1.4, H-3, ^{117,119}Sn satellites gave $^2J_{H,Sn}$ 48 Hz), 9.49 (1H, s, H-1, ^{117,119}Sn satellites gave $^4J_{H,Sn}$ 2 Hz); *m*/*z* (EI) 303 (100%, $[M - Bu]^+$), 291 (6%), 269 (9), 247 (52), 189 (48), 177 (27), 161 (19), 121 (25).

Ethyl 3-hydroxy-5-(tributylstannyl)-2,2,4-trimethylpent-4(*Z*)-enoate 35

To a stirred solution of dry iPr_2NH (113 mg, 1.11 mmol) in dry THF (3 ml) at −78 °C was added n-BuLi (0.53 ml, 1.11 mmol) dropwise over 3 minutes. After 1 hour a solution of ethyl isobutyrate (123 mg, 1.0 mmol) in dry THF (0.5 ml) was added dropwise over 5 minutes. After a further hour a solution of aldehyde **34** (120 mg, 0.33 mmol) in dry THF (1 ml + 0.3 ml rinse) was added dropwise over 5 minutes. The mixture was stirred at −78 °C for 30 minutes, then the cold-bath was removed and sat. aq. NH_4Cl (4 ml) immediately added. The cold slurry was partitioned between Et_2O (20 ml) and water (10 ml). The layers were separated, and the aqueous layer extracted with EtOAc (4 × 10 ml). The combined organic layers were washed with brine (25 ml), dried (Na_2SO_4), filtered and concentrated. Purification by column chromatography (23 : 2 hexane : EtOAc + 1% Et_3N) gave the title compound (146 mg, 92%) as a colourless oil: R_f 0.42 (23 : 2 hexane : EtOAc); ν_{max}(film)/cm^{-1} 3487(br s), 2957(s), 1704(s), 1604(w), 1466(s), 1253(s), 1140(s), 667(s); δ_H(200 MHz; $CDCl_3$) 0.84–0.93 (15H, m, alkyl C-*H*), 1.18 (3H, s, CH_3), 1.29 (3H, s, CH_3), 1.31 (3H, t, *J* 7.1, OCH$_2$CH_3), 1.36 (6H, m, alkyl C-*H*), 1.50 (6H, m, alkyl C-*H*), 1.79 (3H, d, *J* 1.3, SnCH=C(CH_3)), 3.72 (1H, d, *J* 7.2, exch. D_2O, OH), 3.93 (1H, d, *J* 7.2, H-3), 4.18 (2H, q, *J* 7.1, OCH_2CH$_3$), 5.72 (1H, d, *J* 1.3, H-5, ^{117,119}Sn satellites gave $^2J_{H,Sn}$ 62 Hz); δ_C(50.3 MHz; $CDCl_3$) 10.5 (alkyl *C*), 13.5 (alkyl *C*), 13.9 (O*C*H$_2$CH$_3$), 14.0 (SnCH=C(*C*H$_3$)), 21.3 (*C*H$_3$), 21.5 (*C*H$_3$), 25.4 (alkyl *C*), 27.3 (alkyl *C*), 44.8 (*C*(CH$_3$)$_2$), 61.0 (OCH$_2$*C*H$_3$), 83.9 (*C*H(OH)), 131.0 (C-5), 152.8 (C-4), 178.6 (C-1); *m*/*z* (EI) 419 (11%, $[M - Bu]^+$), 349 (22), 303 (100), 279

(21), 269 (23), 247 (49), 191 (39), 177 (39), 121 (25), 81 (28), 69 (47).

Ethyl 3-hydroxy-10-phenyl-2,2,4-trimethyldeca-(4*Z*,6*Z*,8*E*)-trienoate 36a and ethyl 3-hydroxy-10-phenyl-2,2,4-trimethyldeca-(4*Z*,6*E*,8*E*)-trienoate 37a

To a stirred solution of $PdCl_2(MeCN)_2$ (3.4 mg, 0.012 mmol) in dry DMF (5 ml) at RT was added a solution of iodide **2b** (200 mg, 0.74 mmol) in dry DMF (2 ml) followed by a solution of stannane **35** (118 mg, 0.25 mmol) in dry DMF (1 ml). The mixture was stirred for 7–13 h, diluted with Et_2O (50 ml) and washed with 50% sat. aq. KF (2 × 20 ml). The combined aqueous washings were extracted with EtOAc (3 × 15 ml), the combined organic layers were washed with brine (2 × 25 ml), dried (Na_2SO_4), filtered and concentrated. Purification by column chromatography (22 : 3 petrol : EtOAc + 1% Et_3N) yielded a 3 : 1 mixture of (4*Z*,6*Z*,8*E*) **36a** and (4*Z*,6*E*,8*E*) **37a** (60 mg, 72%) as a viscous yellow oil: R_f 0.16 (22 : 3 petrol : EtOAc); λ_{max}(MeOH)/nm 269sh (ε/dm^3 mol^{-1} cm^{-1} 26970), 279 (33600), 290 (26970, sh); ν_{max}(film)/cm^{-1} 3470(br s), 2980(s), 1720(s), 1450(m), 1255(s), 1140(s); *m*/*z* (APCI$^+$) 311 (18%, [M − OH]$^+$), 237 (28), 195 (48), 167(25), 149 (50), 118 (100), 113 (30); HRMS (TOF MS FI$^+$): Found 328.2128 (M$^+$), $C_{21}H_{28}O_3$ requires 328.2038. HRMS (CI$^+$): Found 311.2009 ([M − OH]$^+$). $C_{21}H_{27}O_2$ requires 311.2011. **(4***Z*,6*Z*,8*E*)-isomer: δ_H(500 MHz; $CDCl_3$) 1.30 (9H, m, 3 × C*H*$_3$), 1.85 (3H, s, C-4(C*H*$_3$)), 3.50 (1H, d, *J* 7.6, OH), 3.52 (2H, d, *J* 7.0, H-10), 4.20 (2H, q, OC*H*$_2$CH$_3$), 4.81 (1H, s, H-3), 5.93 (1H, dt, *J* 14.8 and 7.1, H-9), 6.03 (1H, m, H-7), 6.20 (1H, dd, *J* 11.1 and 11.9, H-6), 6.52 (1H, d, *J* 12.1, H-5), 6.66 (1H, dd, *J* 14.8 and 11.2, H-8), 7.15–7.35 (5H, m, ArH); δ_C(400 MHz; $CDCl_3$); 14.1 (OCH$_2$-*C*H$_3$), 19.6 (C(CH$_3$)(*C*H$_3$)), 20.9 (C(*C*H$_3$)(CH$_3$)), 24.5 (*C*H$_3$), 39.3 (C$_6$H$_5$*C*H$_2$), 61.0 (O*C*H$_2$CH$_3$), 75.0 (*C*-OH), 125.1 (C(5)), 126.1 (C(9)), 126.6 (Ar*C*), 128.5 (Ar*C*), 128.7 (ArC), 131.6 (C(6)), 132.5 (C(7)), 133.1 (C(8)), 134.4 (ArC); **(4***Z*,6*E*,8*E*)-isomer: δ_H(500 MHz; $CDCl_3$) all signals overlapping with major isomer, except 3.41 (1H, d, *J* 7.6, O*H*); δ_C(400 MHz; $CDCl_3$) 13.9 (OCH$_2$*C*H$_3$), 19.4 (C(CH$_3$)(*C*H$_3$)), 20.9 (C(*C*H$_3$)(CH$_3$)), 23.7 (*C*H$_3$), 39.1 (C$_6$H$_5$*C*H$_2$), 60.8 (O*C*H$_2$CH$_3$), 74.6 (*C*-OH), 122.9 (C(5)), 126.0 (C(9)), 126.4 (Ar*C*), 128.4 (Ar*C*), 128.5 (ArC), 131.3 (C(6)).

Ethyl 3-hydroxy-10-phenyl-2,2,4-trimethyldeca-(4*Z*,6*Z*,8*E*)-trienoate 36a and ethyl 3-hydroxy-10-phenyl-2,2,4-trimethyldeca-(4*Z*,6*E*,8*E*)-trienoate 37a

To a stirred solution of $PdCl_2(MeCN)_2$ (4 mg, 0.015 mmol) in dry DMF (5 ml) at RT was added a solution of iodide **2b** (105 mg, 0.31 mmol) in dry DMF (2 ml) followed by a solution of stannane **35** (143 mg, 0.30 mmol) in dry DMF (1 ml). The mixture was stirred for 24 h, diluted with Et_2O (50 ml) and washed with 50% sat. aq. KF (2 × 20 ml). The combined aqueous washings were extracted with EtOAc (3 × 15 ml), the combined organic layers were washed with brine (2 × 25 ml), dried (Na_2SO_4), filtered and concentrated. Purification by column chromatography (22 : 3 petrol : EtOAc + 1%Et_3N) yielded the title compound as a 1 : 1 mixture of (4*Z*,6*Z*,8*E*) **36a** and (4*Z*,6*E*,8*E*) **37a** (76 mg, 77%) as a viscous yellow oil. Spectroscopic data were as reported above.

Ethyl 3-hydroxy-10-phenyl-2,2,4-trimethyldeca-(4*Z*,6*Z*,8*E*)-trienoate 36a and ethyl 3-hydroxy-10-phenyl-2,2,4-trimethyldeca-(4*Z*,6*E*,8*E*)-trienoate 37a

To a stirred solution of $PdCl_2(MeCN)_2$ (20 mg, 0.6 mmol) in dry DMF (5 ml) at RT was added a solution of iodide **2b** (391 mg, 1.45 mmol) in dry DMF (2 ml) followed by a solution of stannane **35** (300 mg, 1.15 mmol) in dry DMF (1 ml). The reaction solution was kept at −20 °C for 14 days. The mixture was diluted with Et_2O (50 ml) and washed with 50% sat. aq. KF (2 × 20 ml). The combined aqueous washings were extracted with EtOAc (3 × 15 ml), the combined organic layers were washed with brine (2 × 25 ml), dried (Na_2SO_4), filtered and concentrated. Purification by column chromatography (43 : 7 petrol : EtOAc + 1% Et_3N) yielded the title compound as a 1 : 3 mixture of (4*Z*,6*Z*,8*E*) **36a** and (4*Z*,6*E*,8*E*) **37a** (160 mg, 0.48 mmol, 42%) as a viscous yellow/orange oil: R_f 0.58 (43 : 7 petrol : EtOAc); λ_{max} (MeOH)/nm 269sh (ε/dm^3 mol^{-1} cm^{-1} 26970), 279 (33560), 290sh (26970); ν_{max} ($CHCl_3$)/cm^{-1} 2980(s), 1723(s), 1453(m), 1254(s), 1136(s); *m*/*z* (APCI) 311 (5, M − OH$^+$), 295 (100), 195 (30), 167 (50), 148 (45), 118 (20); HRMS (CI) Found 311.2003, $C_{21}H_{27}O_2$ requires 311.2011 (M − OH$^+$); **(4***Z*,6*Z*,8*E*)-isomer: δ_H(500 MHz; C_6D_6) 0.91 (3H, t, *J* 7.4, OCH$_2$C*H*$_3$), 1.25 (6H, s, C(2)-(C*H*$_3$)$_2$), 1.84 (1H, d, O*H*), 1.85 (3H, m, C(4)-C*H*$_3$), 3.25 (2H, d, *J* 7.3, H-10), 3.82 (2H, q, *J* 7.4, OC*H*$_2$), 4.83 (1H, s, H-3), 5.72 (1H, dd, *J* 14.7 and 7.3, H-9), 5.93 (1H, m, H-7), 6.23 (1H, t, *J* 11.7 and 11.7, H-6), 6.50 (1H, d, *J* 12.5, H-5), 6.57 (1H, dd, *J* 14.8 and 11.2, H-8), 7.15–7.3 (5H, m, Ar*H*); δ_C(400 MHz; $CDCl_3$) 14.2 (OCH$_2$-*C*H$_3$), 21.1 (C(5)-*C*H$_3$), 23.3 (C(*C*H$_3$)(CH$_3$)), 24.3 (C(CH$_3$)-(*C*H$_3$)), 39.6 (C-10), 61.0 (O*C*H$_2$CH$_3$), 80.7 (C-3), 123.8 (C-6), 125.3 (C-5), 127.0 (C-8), 127.94 (*m*-Ar*C*), 128.42 (*m*-Ar*C*), 128.53 (*o*-Ar*C*), 128.91 (*o*-Ar*C*), 129.0 (C-7), 134.8 (C-9), 137.23 (*ipso*-Ar*C*). **(4***Z*,6*E*,8*E*)-isomer: δ_H(500 MHz; C_6D_6) 0.91 (3H, t, OCH$_2$C*H*$_3$), 1.27 (6H, s, C(2)-(C*H*$_3$)$_2$), 1.71 (1H, d, O*H*), 1.81 (3H, m, C(4)-C*H*$_3$), 3.22 (2H, d, *J* 7.3, H-10), 3.91 (2H, q, OC*H*$_2$), 4.90 (1H, s, H-3), 5.70 (1H, dd, *J* 14.7 and 7.0, H-9), 6.02 (1H, d, *J* 12.1, H-5), 6.03 (1H, dd, *J* 14.0 and 11.7, H-8), 6.09 (1H, dd, *J* 11.4 and 14.2, H-7), 6.45 (1H, dd, *J* 11.7 and 14.2, H-6), 7.15–7.3 (5H, m, Ar*H*); δ_C(400 MHz; $CDCl_3$) 14.2 (OCH$_2$*C*H$_3$), 21.5 (C(5)-*C*H$_3$), 24.8 (C(*C*H$_3$)(CH$_3$)), 24.9 (C(CH$_3$)(*C*H$_3$)), 39.6 (C-10), 61.1 (O*C*H$_2$CH$_3$), 80.8 (C-3), 126.6 (*p*-Ar*C*), 127.6 (C-6), 128.2 (*m*-Ar*C*), 128.5 (*m*-Ar*C*), 129.1 (*o*-Ar*C*), 130.6 (C-5), 132.3 (C-8), 133.0 (C-7), 133.4 (C-9), 137.2 (*ipso*-Ar*C*).

3-Hydroxy-10-phenyl-2,2,4-trimethyldeca-(4*Z*,6*Z*,8*E*)-trienecarboxylic acid 36b and 3-hydroxy-10-phenyl-2,2,4-trimethyldeca-(4*Z*,6*E*,8*E*)-trienecarboxylic acid 37b

A solution of lithium hydroxide (0.09 g, 2.1 mmol) in THF–MeOH–H_2O (1 : 1 : 1) (30 ml) was added dropwise to a solution of esters **36a** and **37a** (3 : 1) (220 mg, 0.67 mmol) and stirred for 24 h. The solution was washed with 10% HCl (5 ml) and water (3 ml), immediately extracted with ethyl acetate (3 × 50 ml), dried (sodium sulfate) and the solvent removed. The crude product was purified by column chromatography (43 : 7 petrol : ethyl acetate + 1% Et_3N) to yield the product **36b** and **37b** (3 : 1) as a yellow oil (105 mg, 52%). R_f 0.30 (24 : 1 petrol : EtOAc); ν_{max} (film)/cm^{-1} 2850(br, s), 1727(s), 1453(m), 1254(w), 1137(w); *m*/*z* (APCI) 283 [MH − OH$^+$] (30%), 237 (60), 195 (100), 180 (40), 155 (50), 149 (40), 127 (35), 117 (50), 102 (70); HRMS (CI) Found 283.1696, $C_{19}H_{23}O_2$ requires 283.1698 (M − OH$^+$); **(4***Z*,6*Z*,8*E*)-isomer: δ_H (400 MHz; $CDCl_3$) 1.30 (9H, m, 3 × C*H*$_3$), 1.45 (3H, m, C(4)-C*H*$_3$), 3.45 (1H, d, *J* 7.6, O*H*), 3.46 (2H, d, *J* 7.0, H-10), 5.71 (1H, s, H-3), 5.83 (1H, dt, *J* 14.8 and 7.1, H-9), 5.91 (1H, m, H-7), 6.20 (1H, dd, *J* 11.1 and 11.9, H-6), 6.52 (1H, d, *J* 12.1, H-5), 6.59 (1H, dd, *J* 14.8 and 11.2, H-8), 7.15–7.35 (5H, m, Ar*H*).

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