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Biomimetic studies on polyenes†

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The crispatenes and SNF4435 C&D are complex polypropionate derived natural products. The core structures of these compounds along with a complex unnatural structure can be easily prepared from a common polyene precursor simply by variation of the reaction conditions. The reaction pathways provide insight into the biosynthesis of these complex natural products.

Introduction

In recent years, many structurally novel polypropionate metabolites have been isolated from terrestrial and marine systems as phylogenetically diverse as bacteria and sponges. Many of the compounds isolated are biologically important, and display a diverse range of activity including immunosuppression, cytotoxicity and antibiotic properties. Examples of such compounds include erythromycin, monensin, methymycin, tylosin, and nonactic acid.[1]

As part of our continuing efforts directed towards the biomimetic synthesis of complex natural products, we became interested in a range of polypropionate derived compounds. Of initial interest were the immunosuppressants SNF4435C **1** and SNF4435D **2**, isolated in 2001 by Takahashi and co-workers.[2]

Results and discussion

The nitrophenyl pyrones SNF4435C and SNF4435D

SNF4435C **1** and SNF4435D **2** are members of a family of related biologically active propionate derived compounds, known broadly as the nitrophenyl pyrones. These include aureothin **3**, luteoreticulin **4**, and luteothin **5**, isolated from *Streptomyces thioluteu*, and *S. luteoreticuli*,[3,4] neoaureothin **6** isolated from *Streptomyces orinoci*, and spectinabilin **7** isolated as a metabolite from the same actinomycete as **1** and **2**, *Streptomyces spectabilis* (Fig. 1).[5,6]

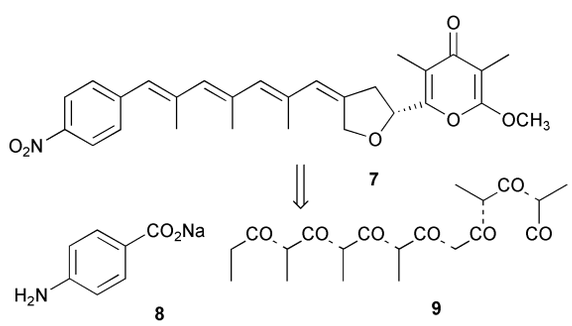
Many biosynthetic and synthetic studies of the nitrophenyl pyrones have been undertaken with a particular emphasis on aureothin **3**,[7,8] however the more complex structures of the family, namely **1**, **2** and **7** have yet to be synthesised.

Biologically, both SNF4435 C **1** and D **2** selectively suppress induced B-cell proliferation *versus* induced T-cell proliferation and show potent immunosuppressive activity *in vitro*.[9] This would indicate a different mode of action from that of the known immunosuppressants cyclosporin A (CsA) and FK-506. This mechanistic difference, however, opens up the possibility of developing new immunosuppressants based on these novel compounds.[10] In addition to their immunosuppressive activity, these novel compounds have been shown to reverse multidrug resistance in tumour cells, rendering them potentially useful in anticancer therapy.[11]

Structurally, SNF4435C **1** and D **2** are pentacyclic structures exhibiting a hexasubstituted bicyclo[4.2.0] core comprising a cyclohexadiene unit in the major ring. This bicyclo[4.2.0]octadiene is connected to a spirofuran unit, which in turn is connected to a γ-pyrone fragment, a common feature in polypropionates. However, the bicyclic core is also attached to a *p*-nitrophenyl ring, which is far less common.

It is believed that this class of compounds are biosynthesised from a *p*-aminobenzoate and a combination of propionate and acetate units, as demonstrated in the biosynthesis of aureothin **3**.[7]

It is apparent that spectinabilin **7** is a constitutional isomer of the SNF compounds **1** and **2**. In addition, it has also been reported that **7** is not a very stable substrate, with about 50% being converted to other substances during the course of one month at room temperature.[6] In the case of spectinabilin **7**, it is expected that a *p*-aminobenzoate unit **8** combines with an equimolar amount of acetate and six propionate units as **9**, the same ratio as found in the SNF compounds **1** and **2**. Hence, a clear link between these metabolites and spectinabilin **7** can be proposed (Scheme 1).



Scheme 1 Proposed biosynthesis of spectinabilin **7**.

The core bicyclo[4.2.0] carbon skeleton possessed by **1** and **2** had been previously identified in analogous natural products, including the endrianic acids isolated by the groups of Black,[12] and synthesised by Nicolaou.[13] The synthesis was inspired by an intriguing hypothesis proposed by Black for their biosynthesis, which centred around a cascade of electrocyclic reactions. Specifically, the appropriate (*E*,*Z*,*Z*,*E*)-tetraene undergoes a thermal conrotatory 8π electrocyclisation, immediately followed by a thermal disrotatory 6π electrocyclisation, to afford the relevant bicyclo[4.2.0] carbon skeleton. This methodology is now well established as demonstrated by the work of Widmer and co-workers in their studies of vitamin A.[14]

The combination of this biosynthetic information together with the inherent instability of spectinabilin **7** over a period of time, prompted us to consider the possibility that spectinabilin **7** is a direct precursor of SNF4435C **1** and SNF4435D **2** *via* either an *in vitro* or *in vivo* double bond isomerisation.

† 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.

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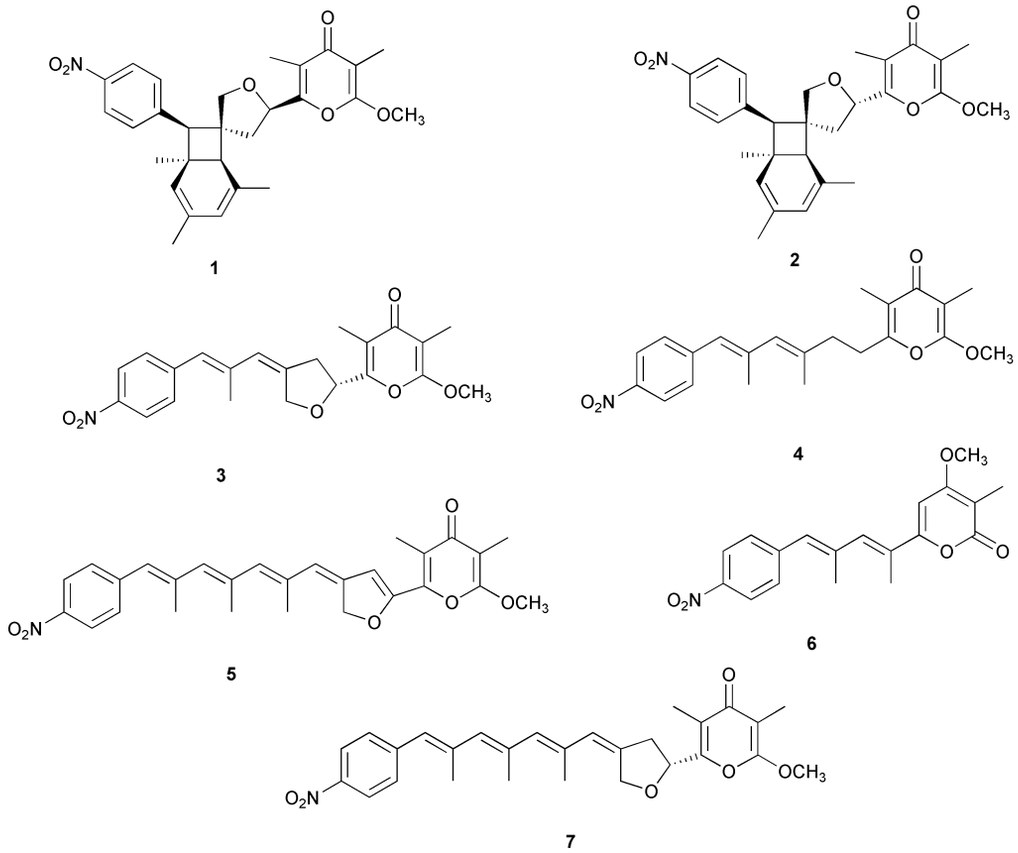


Fig. 1 Examples of the nitrophenyl pyrone family of compounds

In our proposed biosynthesis, we envisaged SNF4435C **1** and SNF4435D **2** as having originated from the (*E*,*Z*,*Z*,*Z*)-tetraene **10**, an isomeric form of spectinabilin **7**, which is necessary to initiate a thermal conrotatory 8π electrocyclisation to generate the cyclooctatetraene **11**. A subsequent stereoselective disrotatory thermal 6π electrocyclisation would afford compound **1** which could undergo epimerisation to give **2** (Scheme 2).

We have recently communicated evidence for our proposed biosynthesis, in which the model (*E*,*E*,*E*,*E*)-tetraene **12** was efficiently prepared using a stabilised ylide approach in good overall yield (Scheme 3).[15]

The (*E*,*E*,*E*,*E*)-double-bond stereochemistry was corroborated by X-ray analysis, which interestingly revealed a significant lack of planarity in the polyene backbone, due to the strong 1,3-steric interactions between the alkene methyl substituents (Fig. 2).[16] We envisaged that such a highly strained tetraene (as demonstrated by the >130° angle between C_4–C_5–C_6, and the 45° dihedral angle of the C_9–C_{10} bond) would be prone to isomerisation under the right conditions.

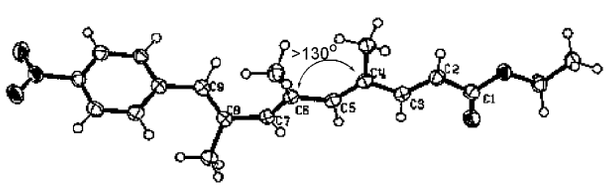


Fig. 2 X-Ray structure of tetraene **12**.

Our choice of conditions to effect isomerisation stemmed from the well known ability of palladium(II) salts to interact with, and isomerise conjugated double bond systems through either a carbocation or π-allyl complex.[17] Thus treatment of tetraene **12** with dichlorobis(acetonitrile)palladium(II) at room temperature effected the desired cyclisation, generating the bicyclo[4.2.0]octadiene core in good yield, and as a single diastereoisomer **26**, as established by nOe analysis. The observed product stereochemistry is consistent with a double bond isomerisation taking place to generate the (*E*,*Z*,*Z*,*E*)-tetraene **24**, which undergoes the expected tandem double electrocyclisation to give the product (Scheme 4). When methyl ester **23** was treated under the same conditions, the corresponding bicyclic **27** was isolated in 48% yield, whose spectral data matched that of the identical compound prepared by Beaudry and Trauner using a related approach.[18]

The same reaction sequence was observed when applied to tetraene **28**, itself prepared using the same stabilised ylide approach starting from aldehyde **29** (Scheme 5). Thus, upon exposure of **28** to the same metal catalysed conditions, bicyclo-**35** was formed as a single diastereoisomer in fair yield (Scheme 6). The structure of **28** was further corroborated by X-ray analysis of the dinitrobenzoyl derivative **34**, which also displayed a significant lack of planarity about the polyene backbone due to 1,3-strain (Fig. 3).[19]

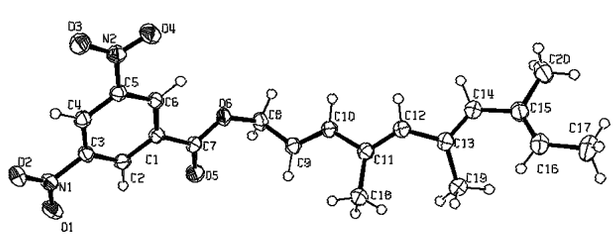
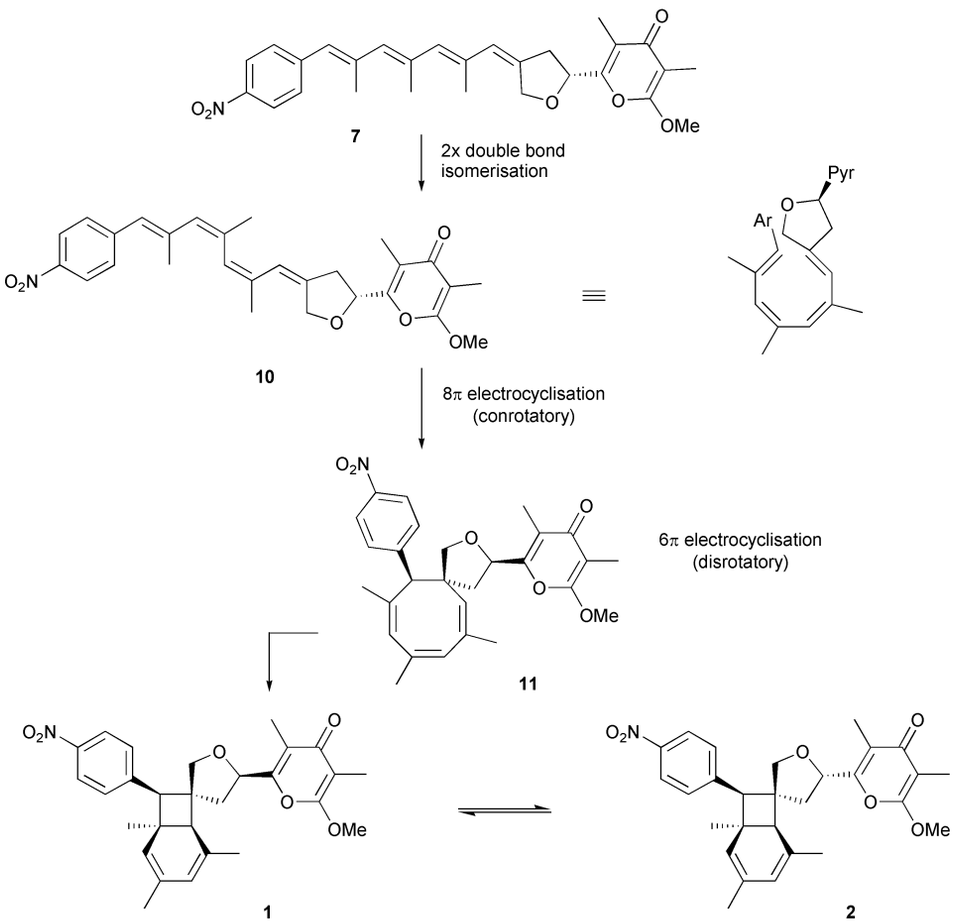
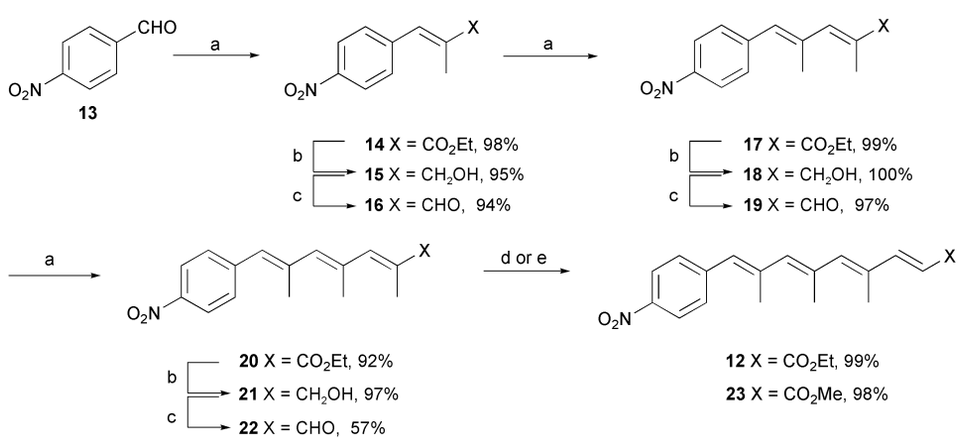


Fig. 3 X-Ray structure of **34**.

In order to expand the scope of this methodology, we decided to prepare pentaene **36** according to the route shown in Scheme 7. Unfortunately exposure of pentaene **36** to the same palladium catalysed conditions gave no evidence of the desired bicyclo-[3.2.0] core. Instead, cyclohexadiene **39** was formed in fair yield presumably through a disrotatory 6π-electrocyclisation of the (*E*,*Z*,*E*,*E*,*E*)-pentaene **40**, thus providing a novel route to this



Scheme 2 Proposed biogenesis of SNF4435C **1** and SNF4435D **2**.



a) $Ph_3PC(CH_3)CO_2Et$, Toluene, Reflux; b) Dibal-H, Et_2O, 0 °C; c) Swern, -78 °C; d) $Ph_3PC(H)CO_2Et$, Benzene, Reflux; e) $Ph_3PC(H)CO_2Me$, Benzene, Reflux.

Scheme 3 Stabilised ylide approach to the construction of the tetraene model system.

class of structure also common in polypropionates (Scheme 8).[20] The structure of **39** was implied by nOe analysis, and further corroborated by X-ray analysis of the dinitrobenzoyl derivative **41** (Fig. 4).[21]

The positive results prompted us to consider if the relationship between the linear polyene spectinabilin, and the complex core of the SNF compounds was a general feature of polypropionate biosynthesis. That is, we considered the possibility that other complex polypropionate compounds isolated could be tandem pericyclic reaction products of initial relatively simple all (*E*)-polyenes. Thus in biosynthetic terms, units of propionate would condense to yield a thermodynamically favoured all (*E*)-polyene backbone. When provided with an appropriate energy source reversible selective (*E*–*Z*) double

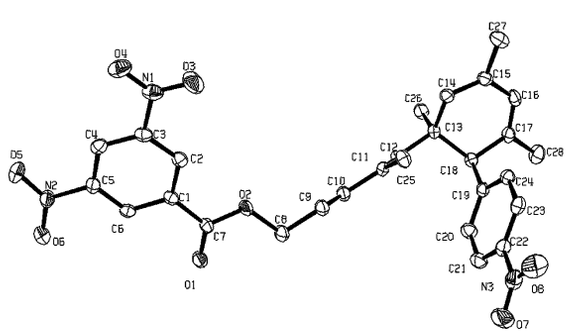
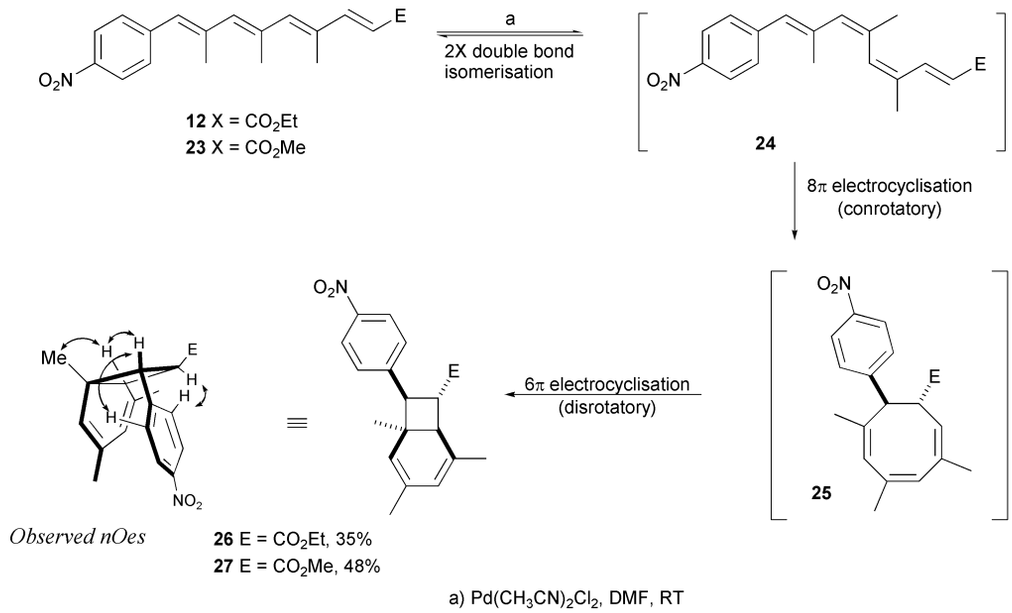
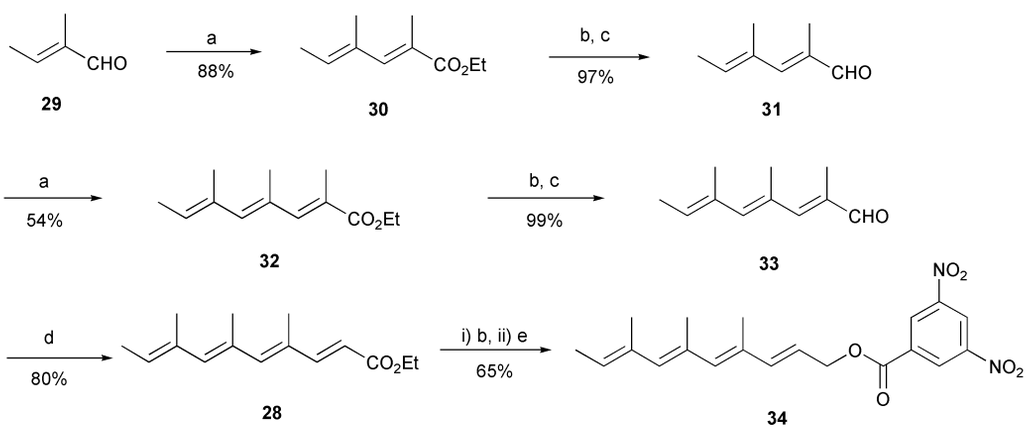


Fig. 4 X-Ray structure of **41**.



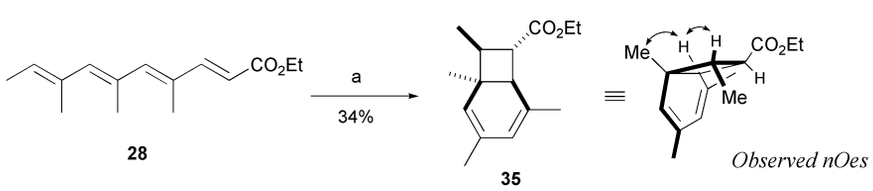
a) $Pd(CH_3CN)_2Cl_2$, DMF, RT

Scheme 4 Palladium catalysed tandem rearrangement.



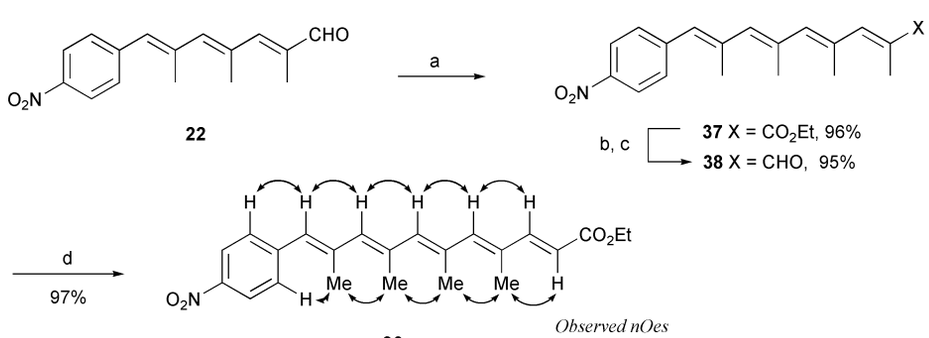
a) $Ph_3PC(CH_3)CO_2Et$, Toluene, Reflux; b) Dibal-H, Et_2O, 0 °C; c) MnO_2, $CHCl_3$, RT; d) $Ph_3PC(H)CO_2Et$, Benzene, Reflux; e) 3,5-dinitrobenzoyl chloride, pyridine, CH_2Cl_2, 0°C.

Scheme 5 Synthesis of tetraene **28** and the crystalline derivative **34**.



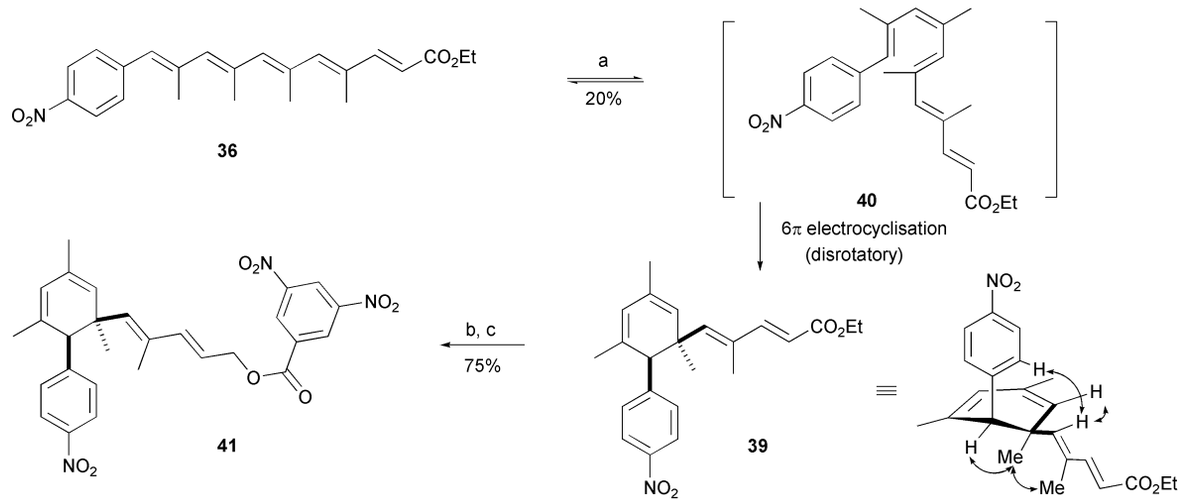
a) $Pd(CH_3CN)_2Cl_2$, DMF, RT.

Scheme 6 Tandem electrocyclic reaction of tetraene **28**.



a) $Ph_3PC(CH_3)CO_2Et$, Toluene, Reflux; b) Dibal-H, Et_2O, 0 °C; c) MnO_2, $CHCl_3$, RT; d)$Ph_3PC(H)CO_2Et$, Benzene, Reflux.

Scheme 7 Synthesis of pentaene **36**.



a) $Pd(MeCN)_2Cl_2$, DMF, RT. b) DIBAL-H, Et_2O, 0°C. c) 3,5-dinitrobenzoyl chloride, pyridine, CH_2Cl_2, RT.

Scheme 8 Palladium catalysed rearrangement of **36**.

bond isomerisations could ensue, encouraged by 1,3 strain. When the appropriate geometry requirements are met, a pericyclic reaction could proceed, thus driving the equilibrium in favour of the product.

In order to further substantiate our proposal we decided to investigate marine sources, known to be rich in polypropionates. In particular, we chose to concentrate on mollusc metabolites which often appear to be derived from the condensation of propionate units. Examples of such acyclic polypropionates include cyercenes A **42** and B **43** (Fig. 5).[22]

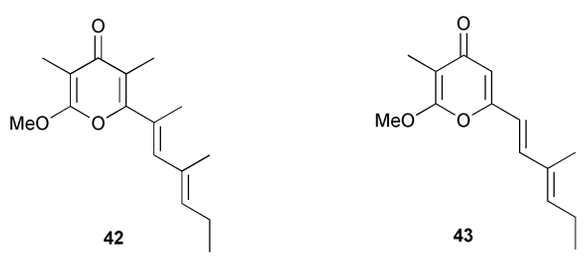


Fig. 5 Cyercene A **42** and cyercene B **43**.

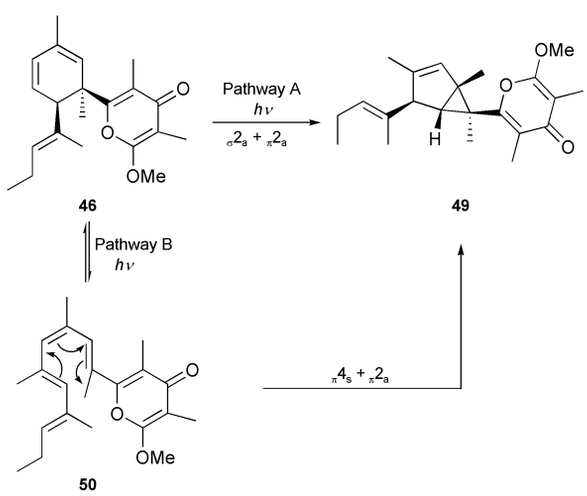
As part of our investigations, we became interested in the crispatenes and related family of compounds, which we believed were ideally suited to our biosynthetic studies.[23]

Crispatene and related polypropionates

Many sacoglossan molluscs sequester active chloroplasts from algae and use these organelles to carry out photosynthesis in their own tissues. These creatures are devoid of a protective shell and have therefore evolved with reliance on secondary metabolites for defence against predators. Many of these metabolites are highly unsaturated polypropionates that feature an α-methoxy-γ-pyrone moiety; examples include crispatene **44**, crispatone **45** isolated from the Californian mollusc *Tridachia Crispata*,[24] 9,10-deoxytridachione **46**, tridachiapyrone **47**, tridachiapyrone A **48** and photodeoxytridachione **49** (Fig. 6).

Structurally, these compounds fall into two classes. The first class which includes **46**, **47** and **48** are cyclohexadiene derivatives, whereas the second class, which include **44**, **45** and **49** feature a bicyclo[3.1.0]hexene core. Clearly, both ring systems are isomeric and this relationship has encouraged speculation as to their biogenetic relationship.

It has been shown that 9,10-deoxytridachione **46** can be photochemically converted *in vivo* and *in vitro* into photodeoxytridachione **49**.[25] Ireland and Faulkner have proposed that 9,10-deoxytridachione **46** undergoes a $_{\sigma}2_a + _{\pi}2_a$ electrocyclisation to generate photodeoxytridachione **49** directly, which is reasonable since no racemisation was observed.[26] However it could also be proposed that 9,10-deoxytridachione **46**, during conversion undergoes a retro-electrocyclisation giving tetraene **50**, which undergoes a photochemical enzyme mediated Diels–Alder reaction giving photodeoxytridachione **49** (Scheme 9).



Scheme 9 Two proposed mechanistic pathways for the conversion of **46** into **49**.

It was this combination of structural complexity and biosynthetic information that prompted us to propose a biomimetic synthesis to the crispatene family of compounds, based upon our general biosynthetic hypothesis. In our approach, we envisioned the bicyclo[3.1.0]hexene core of **49** as having arisen from the photochemical transformation of 9,10-deoxytridachione **46**, itself arising from the corresponding (*E*,*E*,*Z*,*E*)-tetraene pyrone **51** through a thermal 6π electrocyclisation [the (*E*,*E*,*Z*,*E*)-tetraene pyrone itself obtained from the (*E*,*E*,*E*,*E*)-tetraene **52** through either a thermally or photochemically induced isomerisation]. Although tetraene **52** is not reported to have been isolated, it is likely that it could indeed exist as a metabolite, considering its similarity to cyercene A **42** (Scheme 10).

In order to test this hypothesis, we decided to start from the (*E*,*E*,*E*,*E*)-tetraene **12** originally developed for our studies in the biomimetic synthesis of SNF4435C **1** and SNF4435D **2**. As was previously found, tetraene **12** has a large degree of strain which could provide the driving force for the initial isomerisation.

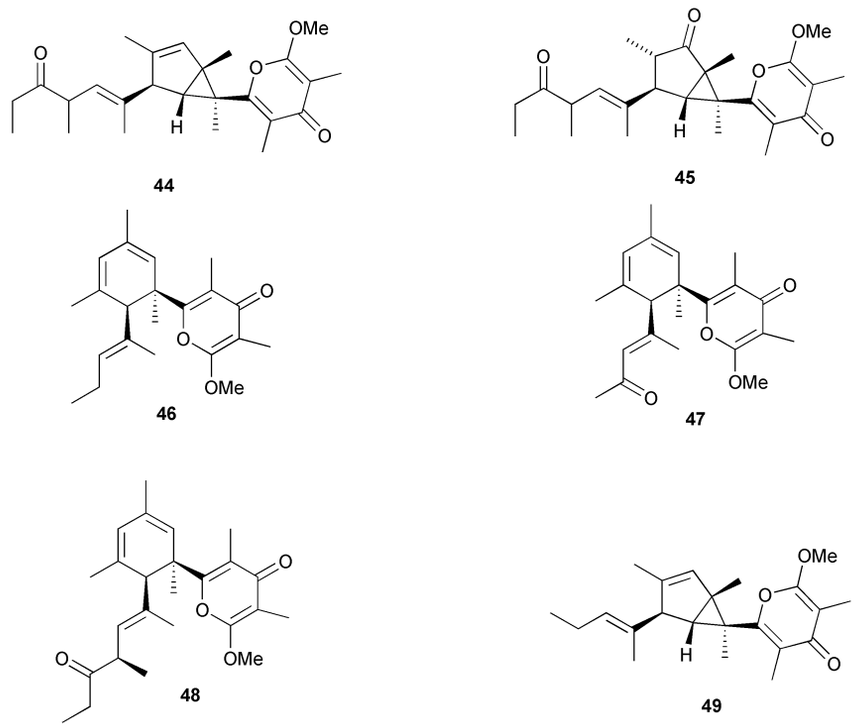
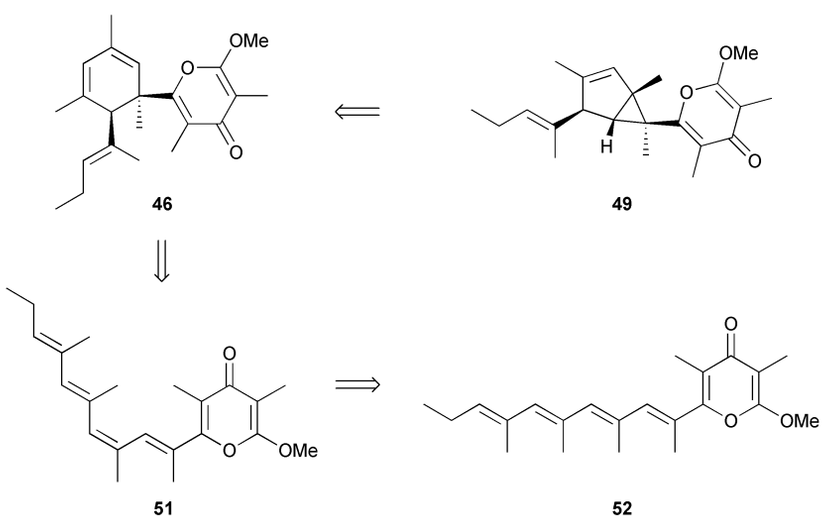


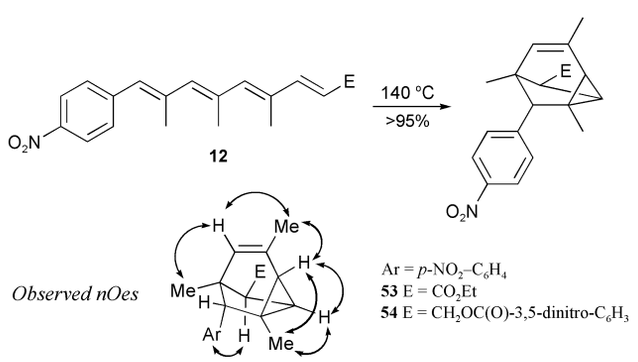
Fig. 6 Structurally related marine polypropionates.



Scheme 10 A biomimetic inspired retrosynthetic analysis of compound **49**.

Once the initial isomerisation had taken place, we expected the (*E*,*E*,*Z*,*E*)-tetraene to undergo electrocyclisation. However, treatment of tetraene ester **12** at 140 °C failed to afford the desired cyclohexadiene core, affording instead the tricyclic structure **53** in excellent yield (95%) as a single product (Scheme 11). The structure was determined by a combination of NMR methods, including nOe and 2-D NMR analyses, and further corroborated by X-ray analysis of the crystalline derivative **54** (Fig. 7).[27]

Formation of this product can be proposed by an isomerisation of the appropriate double bond to generate the required (*E*,*E*,*Z*,*E*)-tetraene ester **55**. This ester can then undergo the desired thermal 6π disrotatory electrocyclisation to generate cyclohexadiene **56**, which undergoes a final intramolecular



Scheme 11 Thermally induced conversion of **12** into **53**.

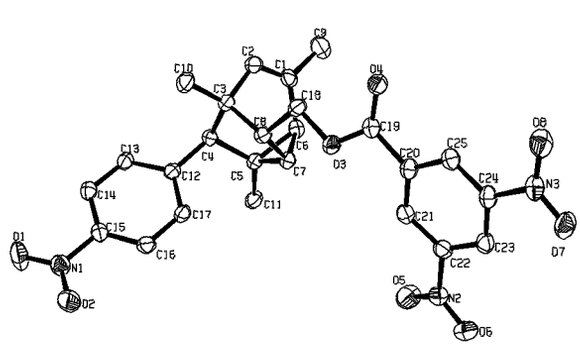
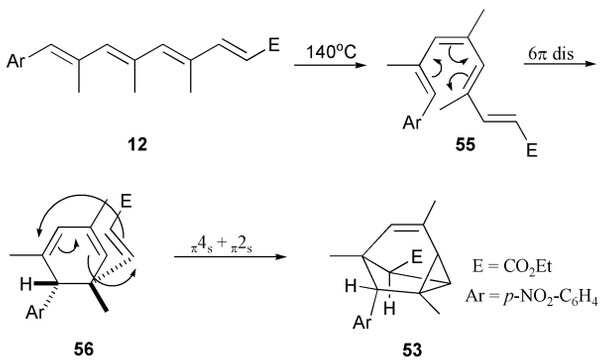


Fig. 7 X-Ray structure of tricyclic derivative **54**.

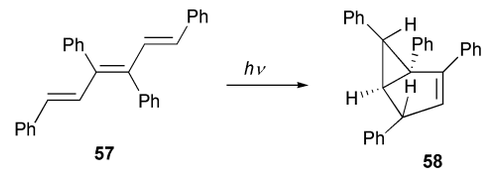
Diels–Alder reaction to generate the tricyclic structure **53** (Scheme 12).[28] Efforts to isolate the cyclohexadiene core **56** at lower temperatures were unsuccessful.



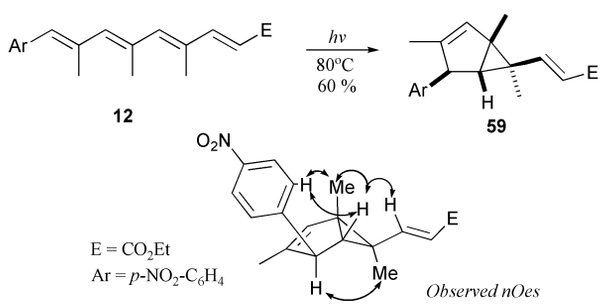
Scheme 12 Proposed mechanism for the thermal conversion of tetraene **12** into tricyclic **53**.

Although disappointing from our biosynthesis point of view, formation of the tricyclic ester **53** demonstrated the feasibility of the selective double bond isomerisation and of the efficiency of the 6π electrocyclisation. Furthermore, it provides us with a rapid and efficient entry into this novel class of compounds with yet to be determined potential.

Since we could not isolate the cyclohexadiene under thermal conditions, we considered the possibility of a photochemically induced double bond isomerisation. Dauben and Smith have shown that irradiation of all (*E*)-1,3,4,6-tetraphenylhexa-1,3,5-triene **57** gives rise to 1,2,4,6-tetraphenylbicyclo[3.1.0]hexene **58**, whose molecular core displays a similar substitution pattern to the crispatene type core (Scheme 13).[29] With this in mind, ester **12** was irradiated with light from a 600 W tungsten lamp source, which successfully generated the crispatene core **59** (as determined by 2-D NMR) in good yield (60%). The relative stereochemistry was corroborated by a combination of NMR methods including 1-D pulsed field gradient NOESY analysis (Scheme 14). Interestingly, it was found that daylight also facilitated this transformation.



Scheme 13 Photochemical transformation of triene **57**.



Scheme 14 The photochemical conversion of **12** into **59**.

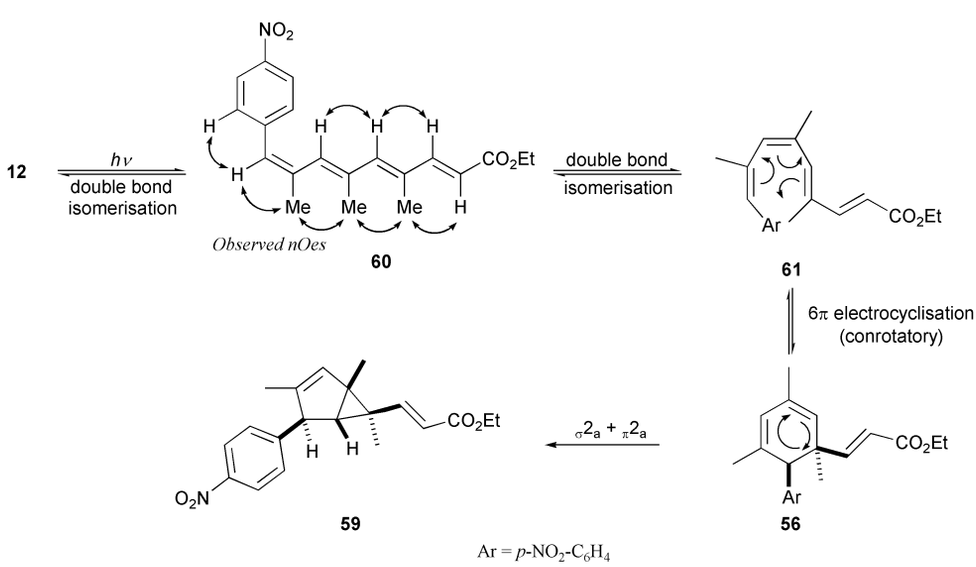
Mechanistic discussion

It is possible that **59** is formed in a manner consistent with our biomimetic hypothesis. That is, tetraene **12** undergoes a photochemically induced selective double bond isomerisation to yield the (*E*,*E*,*E*,*Z*)-tetraene **60**, which was observed by NMR to appear during irradiation and disappear as the product **59** was formed. Tetraene **60** then undergoes another double bond isomerisation to give the (*E*,*E*,*Z*,*Z*)-tetraene **61**, which then undergoes a photochemical 6π conrotatory electrocyclisation to give the cyclohexadiene **56**, which can then undergo a direct $_\sigma 2_a + {}_\pi 2_a$ electrocyclisation to generate bicyclic **59** (Scheme 15).

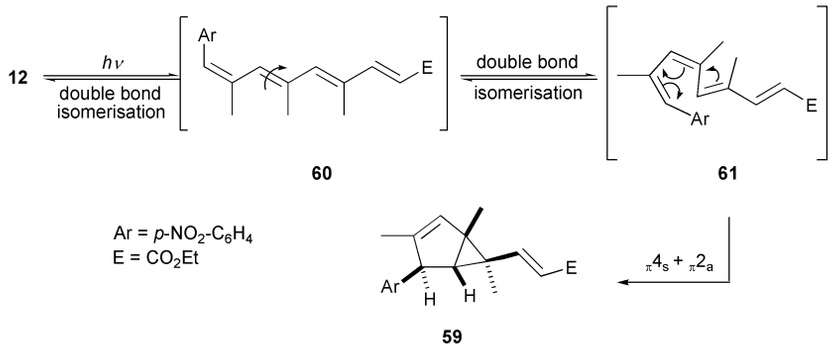
Alternatively, the formation of **59** may be considered as arising from an intramolecular photochemical Diels–Alder reaction, which is consistent with the results reported by Padwa *et al.* on their studies of 1,3,5-hexatrienes.[30] The observed stereochemistry can be explained by the following mechanistic rationale. In the first instance ester **12** undergoes a photochemically induced selective double bond isomerisation to yield the (*E*,*E*,*E*,*Z*)-tetraene **60**. The direct conversion of ester **60** into **59** by a photochemical Diels–Alder reaction is forbidden by the Woodward–Hoffman rules.[31] Therefore, in agreement with Padwa's findings, it is proposed that a two photon reaction involving initial (*E*–*Z*) photoisomerisation about the C_6–C_7 double bond occurs affording the (*E*,*E*,*Z*,*Z*)-tetraene **61**. This is immediately followed by a symmetry allowed $_\pi 4_s + {}_\pi 2_a$ photocycloaddition giving **59** as the thermodynamically favoured product (Scheme 16).

Although both mechanisms are potentially feasible, we cannot discount a highly selective diradical process for the formation of **59**.

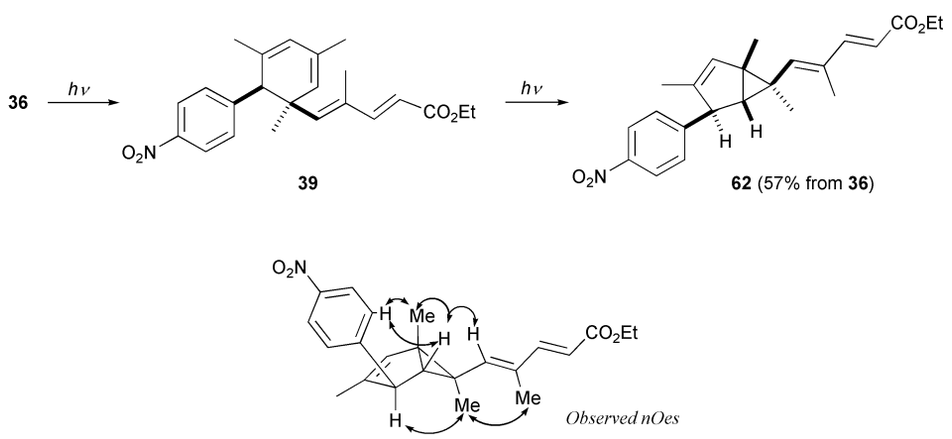
When pentaene **36** was exposed to the same photochemical conditions, bicyclic **62** was successfully formed in 40% yield.



Scheme 15 Possible mechanism for the conversion of tetraene **12** into **59**.



Scheme 16 An alternative mechanism for the conversion of **12** into **59**.



Scheme 17 The photochemical transformation of pentaene **36** into **62**.

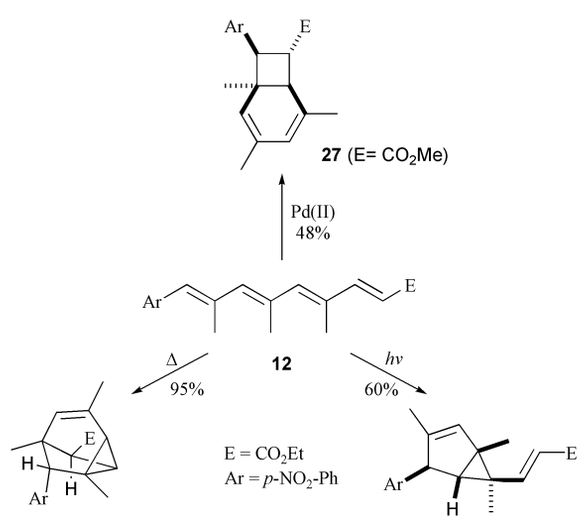
However, cyclohexadiene **39** was also isolated from the reaction mixture in 17% yield. Interestingly it was also found that cyclohexadiene **39** could be directly converted to bicyclic **62** upon standing in daylight, without any evidence for reversion to **36** by ^{1}H NMR. This indicates that **39** could be a true reaction intermediate (Scheme 17).

This observation supports Faulkner's and our own biosynthetic hypothesis for the formation of the crispatene family of compounds. Studies directed towards the total biomimetic synthesis of photodeoxytridachione **49** are underway and shall be reported in due course.

Conclusion

We have demonstrated that several classes of complex polypropionate derived core structures can be prepared from simple polyene precursors. These tandem transformations share the common feature that they are instigated by strain, resulting from steric compressions of the 1,3 methyl substituents on the polyene backbone. We believe that the same strain is the driving force in the biosynthesis of the SNF and crispatene family of compounds, which are likely to be derived from linear all-(*E*)-polyenes.

In conclusion, we have shown a diversity of high yielding synthetic possibilities originating from this class of highly strained polyene esters by simple modification of the reaction conditions (Scheme 18). We are now working on ways to expand the synthetic and mechanistic scope of these transformations, and at the same time explore new synthetic transformations.



Scheme 18 Cascade electrocyclisation pathways of tetraene ester **12**.

Experimental

^{1}H NMR spectra were recorded at 200, 400 and 500 MHz using Varian Gemini 200, Bruker DPX400, Bruker AM500 and Bruker AMX500 instruments. For ^{1}H NMR spectra recorded in $CDCl_3$, CD_3OD and d_6-DMSO, chemical shifts are quoted in parts per million (ppm) and are referenced to the residual solvent peak. The following abbreviations are used: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad. Proton assignments are supported by ^{1}H–^{1}H COSY where necessary. Data are reported in the following manner: chemical shift (integration, multiplicity, coupling constant if appropriate, assignment). Coupling constants (*J*) are reported in Hertz to the nearest 0.5 Hz.^{13}C NMR spectra were recorded at 50.3, 100.6 and 125.8 MHz using Varian Gemini 200, Bruker DPX400, Bruker AM500 and Bruker AMX500 instruments. Carbon spectra assignments are supported by DEPT-135 spectra, and ^{13}C–^{1}H (HMQC and HMBC) correlations where necessary. Chemical shifts are quoted in ppm and are referenced to the appropriate residual solvent peak.

Flash column chromatography was carried out using Sorbsil™ C60 (40–63 mm, 230–40 mesh) silica gel. Thin layer

chromatography was carried out on glass plates pre-coated with Merck silica gel 60 F_{254} which were visualised by quenching of UV fluorescence or by staining with 10% w/v ammonium molybdate in 2 M sulfuric acid or 1% w/v potassium permanganate in aqueous alkaline solution followed by heat, as appropriate.

Melting points were recorded using a Cambridge Instruments Gallen™ III Kofler Block melting apparatus or a Buchi 510 capillary apparatus and are uncorrected.

Infrared spectra were recorded either as a thin film between NaCl plates or as a KBr disc (as indicated) on a Perkin-Elmer Paragon 1000 Fourier Transform spectrometer with internal referencing. Absorption maxima are reported in wavenumbers (cm^{-1}) and the following abbreviations are used: w, weak; m, medium; s, strong; br, broad.

Low resolution mass spectra were recorded on V. G. Micromass ZAB 1F and V. G. Masslab instruments as appropriate with modes of ionisation being indicated as CI, EI, ES or APCI with only molecular ions, molecular ion fragments and major peaks being reported. High resolution mass spectrometry was measured on a Waters 2790-Micromass LCT electrospray ionisation mass spectrometer and on a VG autospec chemical ionisation mass spectrometer.

All solvents and reagents were purified by standard techniques reported in ref. 32 or used as supplied from commercial sources as appropriate.

All experiments were carried out under an inert atmosphere unless otherwise stated.

The star notation found in the naming of compounds * = racemic mixture of products.

Ethyl (2*E*)-2-methyl-3-(4-nitrophenyl)prop-2-enoate (14)[33]

To a stirred solution of 4-nitrobenzaldehyde **13** (17.3 g, 115 mmol) in toluene (150 mL) was added (1-ethoxycarbonylethylidene)triphenylphosphorane (41.6 g, 115 mmol). The mixture was refluxed overnight, then allowed to cool to RT. Pentane (100 mL) was added, and the resulting triphenylphosphine oxide precipitate removed by filtration. The yellow filtrate was then concentrated under reduced pressure and purified by flash silica gel chromatography (9 : 1 30–40 P.E. : EtOAc) to give the title compound as a yellow solid (26.48 g, 98%). R_F 0.7 (4 : 1 30–40 P.E. : EtOAc); mp 69–71 °C (from pet. ether, lit. value 67–68 °C);[33] ν_{max}/cm^{-1} (KBr) 1701, 1515, 1347, 1110; δ_H (400 MHz, $CDCl_3$) 1.37 (3H, t, *J* 7.0 Hz), 2.12 (3H, s), 4.28 (2H, q, *J* 7.0 Hz), 7.54 (2H, d, *J* 8.5 Hz), 7.68 (1H, s), 8.23 (2H, d, *J* 8.5 Hz); δ_C (100.6 MHz, $CDCl_3$) 14.2, 14.3, 61.3, 123.6, 130.2, 132.3, 136.0, 142.5, 147.2, 167.8. *m*/*z* (CI) 253 (MNH_4^+, 100%), 235 (M^+, 22), 206 (16).

(2*E*)-2-Methyl-3-(4-nitrophenyl)prop-2-en-1-ol (15)[34]

To a stirred solution of ester **14** (24.0 g, 0.102 mol) in dry Et_2O (150 mL) was added DIBAL-H (230 mL of a 1 M solution in hexanes, 0.23 mol) under argon at 0 °C. After 1 hour the reaction was quenched by the cautious addition of MeOH (1 mL). A saturated solution of potassium sodium tartrate (200 mL) was added, and the mixture was left to stir for several hours until the organic and aqueous layers had completely separated. The organic layer was separated, washed with brine (100 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude yellow oil obtained was purified by flash silica gel chromatography (1:1 30–40 P.E. : EtOAc), to give the title compound as a yellow solid (18.72 g, 95%). R_F 0.2 (1 : 1 30–40 P.E. : EtOAc); mp 42–44 °C (lit. value 41–43 °C);[34] $\nu_{max}./cm^{-1}$ (KBr) 3403 (br, OH), 1515, 1343, 1110; δ_H (200 MHz, $CDCl_3$) 1.93 (3H, s), 4.25 (2H, s), 6.60 (1H, s), 7.40 (2H, d, *J* 8.5 Hz), 8.19 (2H, d, *J* 8.5 Hz); δ_C (50.33 MHz, $CDCl_3$) 15.5, 68.0, 122.4, 123.5, 129.5, 142.0, 144.6, 146.0; *m*/*z* (CI) 211 (MNH_4^+, 100%), 193 (M^+, 5), 175 (4).

(2*E*)-2-Methyl-3-(4-nitrophenyl)prop-2-enal (16)[35]

To a stirred solution of oxalyl chloride (4.5 mL, 51.2 mmol) in dry DCM (200 mL) was added DMSO (7.3 mL, 102.4 mmol) dropwise at −78 °C under argon. After 10 minutes alcohol **15** (6.17 g, 32 mmol) in dry DCM (50 mL) was added dropwise, and the mixture stirred for a further 20 minutes at −78 °C. Et_3N (28 mL, 205 mmol) was then added, and the reaction allowed to warm up to RT over 1 hour, and then quenched with water (100 mL). The organic layer was separated, washed with brine (100 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by flash silica gel chromatography (9 : 1 30–40 P.E. : EtOAc) to give the title compound as a yellow solid (5.74 g, 94%). R_F 0.35 (4 : 1 30–40 P.E. : EtOAc); mp 112–114 °C (from EtOH, lit. value 111–112 °C);[35] ν_{max}/cm^{-1} (KBr) 1677, 1593, 1514, 1344; δ_H (250 MHz, $CDCl_3$) 2.10 (3H, s), 7.32 (1H, s), 7.68 (2H, d, *J* 8.5 Hz), 8.31 (2H, d, *J* 8.5 Hz), 9.67 (1H, s); δ_C (62.9 MHz, $CDCl_3$) 11.5, 124.3, 130.9, 141.7, 141.8, 146.5, 148.1, 195.1; *m*/*z* (CI) 209 (MNH_4^+, 100%), 191 (M^+, 38), 174 (100), 162 (27).

Ethyl (2*E*,4*E*)-2,4-dimethyl-5-(4-nitrophenyl)penta-2,4-dienoate (17)[36]

To a stirred solution of aldehyde **16** (6.0 g, 31.4 mmol) in toluene (100 mL) was added (1-ethoxycarbonylethylidene)triphenylphosphorane (11.40 g, 31.50 mol). The mixture was refluxed overnight, then allowed to cool to RT. Pentane (100 mL) was added, and the resultant triphenylphosphine oxide precipitate removed by filtration. The yellow filtrate was concentrated under reduced pressure, and purified by flash silica gel chromatography (4 : 1 30–40 P.E. : EtOAc), giving the title compound as a yellow solid (8.60 g, 99%). R_F 0.45 (4 : 1 30–40 P.E. : EtOAc); mp 80–83 °C (lit. value 81–83 °C);[36] ν_{max}/cm^{-1} (KBr) 1701, 1592, 1515, 1341, 111; δ_H (200 MHz, $CDCl_3$) 1.33 (3H, t, *J* 7.0 Hz), 2.1 (6H, s), 4.25 (2H, q, *J* 7.0 Hz), 6.62 (1H, s), 7.29 (1H, s), 7.49 (2H, d, *J* 8.5 Hz), 8.23 (2H, d, *J* 8.5 Hz); δ_C (50.3 MHz, $CDCl_3$) 14.3, 14.4, 18.6, 61.0, 123.6, 128.8, 129.8, 131.4, 138.1, 142.0, 143.8, 146.8, 168.6; *m*/*z* (CI^+) 557 (9%), 363 (44), 293 (MNH_4^+, 35), 279 (100).

(2*E*,4*E*)-2,4-Dimethyl-5-(4-nitrophenyl)penta-2,4-dienal (19)[37]

To a stirred solution of ester **17** (12.2 g, 44.4 mol) in dry Et_2O (150 mL) was added DIBAL-H (97.0 mL of a 1 M solution in hexanes, 97.0 mmol) under argon at 0 °C. After 1 hour the reaction was quenched by the cautious addition of MeOH (1 mL). A saturated solution of potassium sodium tartrate (200 mL) was added, and the mixture allowed to stir for several hours until the organic and aqueous layers had completely separated. The organic layer was separated, washed with brine (100 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to afford the crude alcohol **18** as an orange oil (10.3 g, 100%), which was used without further purification in the next step. δ_H (200 MHz, $CDCl_3$) 1.90 (3H, s), 2.08 (3H, s), 4.15 (2H, s), 6.10 (1H, s), 6.44 (1H, s), 7.44, (2H, d, *J* 8.5 Hz), 8.21 (2H, d, *J* 8.5 Hz).

To a stirred solution of oxalyl chloride (6.20 mL, 71.2 mmol) in dry DCM (200 mL) was added DMSO (10.0 mL, 140 mmol) dropwise at −78 °C under argon. After 10 min, the crude alcohol **18** (10.3 g, 44.2 mmol) in dry DCM (50 mL) was added dropwise, and the mixture stirred for a further 20 minutes. Et_3N (40 mL, 285 mmol) was then added, and the reaction allowed to warm to RT over 1 hour, then quenched with saturated ammonium chloride solution (100 mL). The organic layer was separated, washed with brine (100 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by flash silica gel chromatography (9 : 1 30–40 P.E. : EtOAc) to give the title compound as a yellow solid (9.9 g, 97%). R_F 0.6 (4 : 1 30–40 P.E. : EtOAc); mp 94–95 °C (lit. value 94–96 °C);[37] ν_{max}/cm^{-1} (KBr) 1670, 1558, 1339; δ_H

(400 MHz, $CDCl_3$,) 2.05 (3H, s), 2.25 (3H, s), 6.89 (1H, s), 6.98 (1H, s), 7.55 (2H, d, *J* 8.5 Hz), 8.21 (2H, d, *J* 8.5 Hz), 9.5 (1H, s); δ_C (100.6 MHz, $CDCl_3$) 11.1, 18.3, 123.7, 128.4, 128.5, 130.0, 131.9, 132.0, 134.4, 153.1, 195.6; *m*/*z* (CI) 279 (100%), 249 (MNH_4^+, 10), 232 (MH^+, 26).

Ethyl (2*E*,4*E*,6*E*)-2,4,6-trimethyl-7-(4-nitrophenyl)hepta-2,4,6-trienoate (20)

To a stirred solution of aldehyde **19** (9.8 g, 42.4 mmol) in toluene (100 mL) was added (1-ethoxycarbonylethylidene)triphenylphosphorane (17 g, 47 mmol). The mixture was refluxed overnight, then allowed to cool to RT. Pentane (100 mL) was added, and the resulting triphenylphosphine oxide precipitate removed by filtration. The yellow filtrate was then concentrated under reduced pressure and purified by flash silica gel chromatography (9 : 1 30–40 P.E. : EtOAc), to give the title compound as a yellow solid (12.3 g, 92%). R_F 0.4 (4 : 1 30–40 P.E. : EtOAc); mp 38–40 °C; ν_{max}./cm^{-1} (KBr) 1704, 1593, 1516, 1341, 1111; δ_H (400 MHz, $CDCl_3$) 1.32 (3H, t, *J* 7.0 Hz), 2.05 (3H, s), 2.08 (3H, s), 2.10 (3H, s), 4.22 (2H, q, *J* 7.0 Hz), 6.19 (1H, s), 6.5 (1H, s), 7.21 (1H, s), 7.46 (2H, d, *J* 8.5 Hz), 8.21 (2H, d, *J* 8.5 Hz); δ_C (100.6 MHz, $CDCl_3$) 14.2, 14.3, 18.72, 19.19, 60.76, 123.5, 127.3, 129.0, 129.6, 134.7, 137.8, 138.8, 142.9, 144.3, 146.1, 168.8; *m*/*z* (CI) 333 (MNH_4^+, 100%), 316 (MH^+, 20), 293 (12), 162. HRMS (CI) Calculated for $C_{18}H_{22}NO_4$ (MH^+): 316.1548. Found: 316.1550.

(2*E*,4*E*,6*E*)-2,4,6-Trimethyl-7-(4-nitrophenyl)hepta-2,4,6-trien-1-ol (21)

To a stirred solution of ester **20** (3.15 g, 9.96 mmol) in dry Et_2O (100 mL) was added DIBAL-H (21.0 mL of a 1 M solution in hexanes, 21.0 mmol) under argon at 0 °C. The reaction was stirred at RT until completion as indicated by TLC analysis (1 h), then quenched by the cautious addition of MeOH (1 mL). A saturated solution of potassium sodium tartrate (100 mL) was added, and the mixture was left to stir for several hours until the organic and aqueous layers had completely separated. The organic layer was separated, washed with brine (100 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude yellow oil obtained was purified by flash silica gel chromatography (1 : 1 30–40 P.E. : EtOAc), to give the title compound as a yellow oil (2.46 g, 97%). R_F 0.25 (1 : 1 30–40 P.E. : EtOAc); ν_{max}/cm^{-1} (film) 3422, 1636, 1592, 1516, 1340, 1109, 1020; δ_H (200 MHz, $CDCl_3$) 1.80 (3H, s), 2.03 (3H, s), 2.09 (3H, s), 4.10 (2H, s), 5.95 (1H, s), 6.00 (1H, s), 6.45 (1H, s), 7.45 (2H, d, *J* 8.5 Hz), 8.20 (2H, d, *J* 8.5 Hz); δ_C (50.3 MHz,$CDCl_3$) 15.7, 19.3, 19.5, 69.1, 123.5, 127.7, 129.5, 129.9, 133.7, 135.6, 136.5, 139.6, 144.9, 145.8; *m*/*z* (CI) 291 (MNH_4^+, 4%), 274 (MH^+, 4), 256 (100), 226 (10). HRMS (CI) Calculated for $C_{16}H_{18}NO_2$ (MH^+): 256.1337. Found: 256.1335.

(2*E*,4*E*,6*E*)-2,4,6-Trimethyl-7-(4-nitrophenyl)hepta-2,4,6-trienal (22)

To a stirred solution of oxalyl chloride (0.95 mL, 10.7 mmol) in dry DCM (100 mL) was added DMSO (1.52 mL, 21.4 mmol) dropwise at −78 °C under argon. After 10 minutes a solution of the alcohol **21** (1.71 g, 6.7 mmol) in dry DCM (50 mL) was added dropwise, and the mixture stirred for a further 20 minutes at −78 °C. Et_3N (6.0 mL, 42.8 mmol) was then added, and the reaction allowed to warm up to RT over 1 hour, then quenched with saturated ammonium chloride solution (100 mL). The organic layer was separated, washed with brine (100 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by flash silica gel chromatography (9 : 1 30–40 P.E. : EtOAc) to give the title compound as a yellow solid (1.03 g, 57%). R_F 0.65 (4 : 1 30–40 P.E. : EtOAc); mp 94–96 °C; ν_{max}/cm^{-1} (KBr) 1727, 1661, 1592, 1512, 1340; δ_H (400 MHz, $CDCl_3$) 2.06 (3H, s), 2.13 (3H, s), 2.27 (3H, s), 6.40 (1H, s), 6.69 (1H, s), 6.82 (1H s), 7.49 (2H, d, *J* 8.5 Hz), 8.25 (2H, d, *J* 8.5 Hz), 9.52 (1H, s); δ_C (100.6 MHz, $CDCl_3$) 10.9, 18.4, 19.11, 123.6, 129.7, 130.3, 134.9, 137.3, 138.4, 141.2, 143.9, 146.3, 154.5, 195.7; *m*/*z* (CI) 272 (MH^+, 100), 254 (24), 244 (95). HRMS (CI) Calculated for $C_{16}H_{18}NO_3$ (MH^+): 272.1286. Found: 272.1282.

Ethyl (2*E*,4*E*,6*E*,8*E*)-4,6,8-trimethyl-9-(4-nitrophenyl)nona-2,4,6,8-tetraenoate (12)

To a stirring solution of aldehyde **22** (520 mg, 1.92 mmol) in benzene (50 mL) was added (ethoxycarbonylmethylene)-triphenylphosphorane (3.30 g, 9.1 mmol). The flask was fitted with a reflux condenser and the solution heated at 80 °C for 2 hours, then left to cool to RT. Pentane (50 mL) was added, and the resulting triphenylphosphine oxide precipitate was removed by filtration. The yellow filtrate was concentrated under reduced pressure, and the crude residue purified by flash silica gel chromatography (9 : 1 30–40 P.E. : EtOAc), to afford the desired tetraene ester **12** as a yellow solid (648.2 mg, 99%). R_F 0.7 (4 : 1 30–40 P.E. : EtOAc); mp = 104–107 °C; ν_{max}./cm^{-1} (KBr) 1707, 1612, 1516, 1338, 1172; λ_{max}(DCM)/nm 373.2 (ε/dm^3 mol^{-1} cm^{-1}; δ_H (250 MHz, $CDCl_3$) 1.32 (3H, t, *J* 7.0 Hz), 2.04 (3H, s), 2.12 (6H, s), 4.24 (2H, q, *J* 7.0 Hz), 5.92 (1H, d, *J* 16.0 Hz), 6.16 (1H, s), 6.39 (1H, s), 6.52 (1H, s), 7.42 (1H, d, *J* 16.0 Hz), 7.47 (2H, d, *J* 8.5), 8.26 (2H, d, *J* 8.5 Hz); δ_C (62.9 MHz, $CDCl_3$) 14.5, 14.8, 19.6, 19.8, 60.7, 117.6, 124.0, 129.4, 130.0, 133.6, 135.2, 137.6, 138.9, 144.0, 144.8, 146.4, 150.5, 167.8; *m*/*z* (CI) 342 (MH^+, 5%), 341 (M^+, 12), 340 (100), 323 (48). HRMS (CI) Calculated for $C_{20}H_{24}NO_4$ (MH^+): 342.1705. Found: 342.1705.

Single crystals from diethyl ether of compound **12** suitable for X-ray diffraction were selected.

Crystal data. $C_{20}H_{23}NO_4$, *M* = 341.41, monoclinic, *a* = 15.0086(5), *b* = 8.0675(3), *c* = 15.1036(5) Å, *α* = 90, *β* = 98.916(2), *γ* = 90°, *U* = 1806.7 Å^3, *T* = 150(1) K, space group *P*21/*a*, *Z* = 4, μ(Mo-Kα) = 0.087mm^{-1}, 12982 reflections measured, 4392 unique (R_{int} = 0.042) which were used in calculations. The final *wR* was 0.0527.

CCDC reference number 190072. See http://www.rsc.org/suppdata/ob/b3/b306933h/ for crystallographic files in CIF or other electronic format.

Methyl (2*E*,4*E*,6*E*,8*E*)-4,6,8-trimethyl-9-(4-nitrophenyl)nona-2,4,6,8-tetraenoate (23)

To a stirring solution of aldehyde **22** (32 mg, 0.118 mmol) in benzene (10 mL) was added (methoxycarbonylmethylene)-triphenylphosphorane (200 mg, 0.60 mmol). The flask was fitted with a reflux condenser and the solution heated at 80 °C for 2 hours, then left to cool to RT. Pentane (50 mL) was added, and the resulting triphenylphosphine oxide precipitate removed by filtration. The yellow filtrate was concentrated under reduced pressure, and the crude residue purified by flash silica gel chromatography (9 : 1 30–40 P.E. : EtOAc), to afford the tetraene ester **23** as a yellow solid (38 mg, 98%). R_F 0.2 (5 : 1 30–40 P.E. : EtOAc); mp = 110 °C; ν_{max}/cm^{-1} (KBr disc) 1712, 1590, 1514, 1339, 1167; δ_H (400 MHz, $CDCl_3$) 2.02 (3H, s), 2.10 (6H, s), 3.77 (3H, s), 5.91 (1H, d, *J* 15.5 Hz), 6.12 (1H, s), 6.36 (1H, s), 6.50 (1H, s), 7.40 (1H, d, *J* 15.5 Hz), 7.47 (2H, d, *J* 8.5 Hz), 8.20 (2H, d, *J* 8.5 Hz); δ_C (100.6 MHz, $CDCl_3$) 14.1, 19.2, 19.3, 51.5, 116.7, 123.5, 129.0, 129.7, 133.1, 135.3, 137.3, 139.0, 143.8, 144.4, 146.0, 150.4, 167.8; *m*/*z* (CI) 345 (MNH_4^+, 49%), 328 (MH^+, 100), 298 (64), 178 (34). HRMS (CI) Calculated for $C_{19}H_{22}NO_4$ (MH^+): 328.1548. Found: 328.1553.

Ethyl (1*R,6*S**,7*R**,8*R**)-1,3,5-trimethyl-8-(4-nitrophenyl)-bicyclo[4.2.0]octa-2,4-diene-7-carboxylate (26)**

Ester **12** (30.0 mg, 0.088 mmol) and $(MeCN)_2PdCl_2$ (7.6 mg, 0.029 mmol) were placed in a dry flask, which was purged with

argon. DMF (1 mL) was added, and the solution was stirred for 2 hours at RT, and then water (10 mL) was added. The mixture was extracted with DCM (2 × 5 mL), and the combined organic fractions were washed with brine (5 mL) and dried over anhydrous $MgSO_4$. The drying agent was removed by filtration, and the mixture concentrated under reduced pressure. The crude yellow residue was purified by flash silica gel chromatography (9 : 1 30–40 P.E. : EtOAc) to give the title compound as a yellow oil (10.6 mg, 35%). R_F 0.75 (9 : 1 30–40 P.E. : EtOAc); mp 110–111 °C; ν_{max}/cm^{-1} (KBr) 1709, 1518, 1346; δ_H (500 MHz, $CDCl_3$) 1.24 (3H, t, *J* 7.0 Hz), 1.29 (3H, s), 1.64 (3H, s), 1.83 (3H, s), 2.74 (1H, d, *J* 9.0 Hz), 3.47 (1H, dd, *J* 10.0, 9.0 Hz), 3.78 (1H, d, *J* 10.0 Hz), 4.18 (2H, q, *J* 7.0 Hz), 4.45 (1H, s), 5.48 (1H, s), 7.35 (2H, m), 8.19 (2H, m); δ_C (125.7 MHz, $CDCl_3$,) 14.1, 21.5, 21.9, 28.3, 44.0, 45.7, 45.8, 55.8, 60.6, 121.1, 122.2, 123.4, 128.1, 130.9, 134.1, 145.7, 146.6, 173.3; *m*/*z* (CI) 359 (MNH_4^+, 25%), 342 (MH^+, 100), 312 (21), 279 (45), 268 (10), 192 (22), 120 (27). HRMS (CI) Calculated for $C_{20}H_{24}NO_4$ (MH^+): 342.1705. Found: 342.1709.

Methyl (1*R**,6*S**,7*R**,8*R**)-1,3,5-trimethyl-8-(4-nitrophenyl)-bicyclo[4.2.0]octa-2,4-diene-7-carboxylate (27)[18]

Ester **23** (38 mg, 0.116 mmol) and $(MeCN)_2PdCl_2$ (10.0 mg, 0.029 mmol) were placed in a dry flask, which was purged with argon. DMF (1 mL) was added, and the solution was stirred for 2 hours at RT, and then water (10 mL) was added. The mixture was extracted with DCM (2 × 5 mL), and the combined organic fractions were washed with brine (5 mL) and dried over anhydrous $MgSO_4$. The drying agent was removed by filtration, and the mixture concentrated under reduced pressure. The crude yellow residue was purified by flash silica gel chromatography (9 : 1 30–40 P.E. : EtOAc) to give the title compound as a yellow solid (18.3 mg, 48%). R_F 0.75 (9 : 1 30–40 P.E. : EtOAc); ν_{max}/cm^{-1} (KBr) 1734, 1517, 1345; δ_H (400 MHz, $CDCl_3$) 1.25 (3H, s), 1.6 (3H, s), 1.78 (3H, s), 2.73 (1H, d, *J* 9.0 Hz), 3.45 (1H, dd, *J* 10.0, 9.0 Hz), 3.70 (3H, s), 3.74 (1H, d, *J* 10.0 Hz), 4.41 (1H, s), 5.46 (1H, s), 7.33 (2H, m), 8.17 (2H, m); δ_C (100.6 MHz, $CDCl_3$) 21.5, 22.0, 28.4, 44.2, 45.6, 45.8, 51.9, 55.9, 121.2, 122.3, 123.5, 128.2, 130.9, 134.2, 145.6, 146.8, 173.8; *m*/*z* (CI) 345 (MNH_4^+, 100), 328 (MH^+, 55), 315 (15), 298 (52), 178 (88), 162 (75), 120 (40), 105 (12). HRMS (CI) Calculated for $C_{19}H_{22}NO_4$ (MH^+): 328.1548. Found: 328.1562.

Ethyl (2*E*,4*E*)-2,4-dimethylhexa-2,4-dienoate (30)[38]

To a stirred solution of tiglic aldehyde **29**, (9.95 g, 118 mmol) was added (1-ethoxycarbonylethylidene)triphenylphosphorane (47.40 g, 131 mmol) in benzene (250 mL) at RT. The mixture was refluxed for 48 hours then allowed to cool to RT and concentrated under reduced pressure. Et_2O was added, and the resulting triphenylphosphine oxide removed by filtration. The yellow filtrate was concentrated under reduced pressure and purified by flash silica gel chromatography (19 : 1 30–40 P.E. : Et_2O) to give the title compound as a colourless oil (17.44 g, 88%). R_F 0.5 (4 : 1 30–40 P.E. : Et_2O); ν_{max}/cm^{-1} (film)[38] 2981, 2933, 2862, 1707, 1627, 1446, 1366, 1255, 1119, 1038, 748; δ_H (400 MHz, $CDCl_3$) 1.31 (3H, t, *J* 7.0 Hz), 1.76 (3H, d, *J* 7.5 Hz), 1.85 (3H, s), 2.00 (3H, s), 4.21 (2H, q, *J* 7.0 Hz), 5.73 (1H, q, *J* 7.5 Hz), 7.13 (1H, s); δ_C (100.6 MHz, $CDCl_3$) 14.0, 14.1, 14.3, 15.97, 60.6, 124.9, 130.9, 133.1, 143.0, 169.3.

(2*E*,4*E*)-2,4-Dimethylhexa-2,4-dienal (31)[39]

To a stirred solution of ester **30** (18.0 g, 107 mmol) in dry Et_2O (250 mL) was added DIBAL-H (225 mL of a 1 M solution in hexanes, 225 mmol) under argon at 0 °C. After 1 h, the reaction was quenched by the cautious addition of MeOH (1 mL). A saturated solution of potassium sodium tartrate tetrahydrate (300 mL) was added and the mixture was left to stir for several hours until the organic and aqueous layers had completely separated. The organic layer was separated, washed with brine (200 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give the corresponding alcohol (13.10 g, 97%) as a colourless oil, which was used without further purification in the next step. R_F 0.15 (4 : 1 30–40 P.E. : Et_2O); ν_{max}/cm^{-1} (film)[39] 3350, 1460, 1030; δ_H (400 MHz, $CDCl_3$) 1.69 (3H, d, *J* 7.0 Hz), 1.76 (3H, s), 1.82 (3H, s), 4.05 (2H, s), 5.43 (1H, q, *J* 7.0 Hz), 5.88 (1H, br s); δ_C (100.6 MHz, $CDCl_3$) 13.7, 15.3, 16.5, 69.6, 124.7, 129.6, 133.0, 133.8.

To a stirred solution of crude alcohol (2.29 g, 18.1 mmol) in $CHCl_3$ (200 mL) was added MnO_2 (23.65 g, 272 mmol) at RT. After 72 h, the mixture was filtered through Celite and the filtrate was concentrated under reduced pressure to give the crude product as a yellow oil (2.22 g, 99%), which needed no further purification. R_F 0.5 (4 : 1 30–40 P.E. : Et_2O); ν_{max}/cm^{-1} (film)[39] 2900, 1700, 1630; δ_H (400 MHz, $CDCl_3$) 1.83 (3H, d, *J* 7.5 Hz), 1.96 (3H, s), 1.98 (3H, s), 6.00 (1H, q, *J* 7.5 Hz), 6.74 (1H, s), 9.38 (1H, s); δ_C (100.6 MHz, $CDCl_3$) 10.6, 14.4, 15.6, 134.1, 135.0, 135.7, 155.1, 196.3.

Ethyl (2*E*,4*E*,6*E*)-2,4,6-trimethylocta-2,4,6-trienoate (32)[40]

To a stirred solution of aldehyde **31**, (7.10 g, 57.2 mmol) was added (1-ethoxycarbonylethylidene)triphenylphosphorane (43.50 g, 120 mmol) in benzene (250 mL) at RT. The mixture was refluxed for 48 hours then allowed to cool to RT and concentrated under reduced pressure. Et_2O was added, and the resulting triphenylphosphine oxide removed by filtration. The yellow filtrate was then concentrated under reduced pressure and purified by flash silica gel chromatography (19 : 1 30–40 P.E. : Et_2O) to give the title compound as a colourless oil (6.48 g, 54%). R_F 0.5 (4 : 1 30–40 P.E. : Et_2O); ν_{max}/cm^{-1} (film)[40] 1708; δ_H (400 MHz, $CDCl_3$) 1.31 (3H, t, *J* 7.0 Hz), 1.73 (3H, d, *J* 7.0 Hz), 1.79 (3H, s), 2.00 (3H, s), 2.03 (3H, s), 4.21 (2H, q, *J* 7.0 Hz), 5.54 (1H, q, *J* 7.0 Hz), 6.04 (1H, br s), 7.17 (1H, br s); δ_C (100.6 MHz, $CDCl_3$) 13.9, 14.1, 14.3, 16.5, 18.3, 60.6, 125.5, 127.0, 131.0, 133.2, 139.2, 144.0, 169.2.

(2*E*,4*E*,6*E*)-2,4,6-Trimethylocta-2,4,6-trienal (33)[39]

To a stirred solution of ester **32** (6.38 g, 30.7 mmol) in dry Et_2O (100 mL) was added DIBAL-H (64 mL of a 1 M solution in hexanes, 64 mmol) under argon at 0 °C. After 1 h, the reaction was quenched by the cautious addition of MeOH (1 mL). A saturated solution of potassium sodium tartrate tetrahydrate (100 mL) was added and the mixture was left to stir for several hours until the organic and aqueous layers had completely separated. The organic layer was separated, washed with brine (75 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give the crude alcohol (5.06 g, 99%) as a colourless oil, which was used without further purification in the next step. R_F 0.2 (4 : 1 30–40 P.E. : Et_2O); ν_{max}/cm^{-1} (film)[39] 3300, 1450; δ_H (400 MHz, $CDCl_3$) 1.71 (3H, d, *J* 7.0 Hz), 1.76 (3H, br s), 1.85 (3H, br s), 1.91 (3H, br s), 4.07 (2H, br s), 5.45 (1H, q, *J* 7.0 Hz), 5.80 (1H, s), 5.94 (1H, s); δ_C (100.6 MHz, $CDCl_3$) 13.8, 15.5, 16.7, 18.7, 69.6, 124.7, 130.5, 131.4, 133.4, 134.1, 134.7.

To a stirred solution of the crude alcohol (4.64 g, 27.95 mmol) in $CHCl_3$ (100 mL) was added MnO_2 (37 g, 418 mmol) at RT. After 72 h, the mixture was filtered through Celite and the filtrate concentrated under reduced pressure to give the crude product as a yellow oil (4.54 g, 99%), which needed no further purification. R_F 0.45 (3 : 1 30–40 P.E. : Et_2O); ν_{max}/cm^{-1} (film)[39] 2970, 2930, 1690, 1630; δ_H (400 MHz, $CDCl_3$) 1.76 (3H, d, *J* 7.0 Hz), 1.83 (3H, br s), 1.99 (3H, s), 2.14 (3H, s), 5.64 (1H, q, *J* 7.0 Hz), 6.27 (1H, s), 6.77 (1H, br s), 9.40 (1H, s); δ_C (100.6 MHz, $CDCl_3$) 10.8, 14.0, 16.4, 17.9, 129.1, 131.5, 133.2, 133.7, 143.1, 156.4, 196.1.

Ethyl (2*E*,4*E*,6*E*,8*E*)-4,6,8-trimethyldeca-2,4,6,8-tetraenoate (28)[40]

To a stirred solution of aldehyde **33**, (56 mg, 0.34 mmol) was added (ethoxycarbonylmethylene)triphenylphosphorane (1.0 g, 2.87 mmol) in benzene (5 mL) at RT. The mixture was refluxed for 48 hours then allowed to cool to RT and concentrated under reduced pressure. Et_2O was added, and the resulting triphenylphosphine oxide removed by filtration. The yellow filtrate was then concentrated under reduced pressure and purified by flash silica gel chromatography (19 : 1 30–40 P.E. : Et_2O) to give the title compound as a yellow oil (64 mg, 80%). R_F 0.65 (4 : 1 30–40 P.E. : Et_2O); ν_{max}/cm^{-1} (film)[40] 1713; λ_{max}(DCM)/nm 322.2 (ε/dm^3 mol^{-1} cm^{-1} 11119); δ_H (400 MHz, $CDCl_3$) 1.31 (3H, t, *J* 7.0 Hz), 1.74 (3H, d, *J* 7.0 Hz), 1.80 (3H, br s), 1.97 (3H, br s), 1.99 (3H, br s), 4.22 (2H, q, *J* 7.0 Hz), 5.52 (1H, q, *J* 7.0 Hz), 5.85 (1H, d, *J* 15.5 Hz), 5.97 (1H, s), 6.32 (1H, s), 7.37 (1H, d, *J* 15.5 Hz); δ_C (100.6 MHz, $CDCl_3$) 13.8, 14.1, 14.2, 16.5, 18.5, 60.0, 115.9, 126.2, 128.2, 131.5, 133.3, 138.1, 144.8, 150.6, 167.5.

(2*E*,4*E*,6*E*,8*E*)-4,6,8-Trimethyldeca-2,4,6,8-tetraenyl 3,5-dinitrobenzoate (34)

To a stirred solution of ester **28** (0.50 g, 2.13 mmol) in dry Et_2O (10 mL) was added DIBAL-H (4.5 mL of a 1 M solution in hexanes, 4.5 mmol) under argon at 0 °C. After 1 h, the reaction was quenched by the cautious addition of MeOH (1 mL). A saturated solution of potassium sodium tartrate tetrahydrate (20 mL) was added and the mixture was left to stir for several hours until the organic and aqueous layers had completely separated. The organic layers were collected, washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give the crude alcohol (0.4 g, 98%) as a colourless oil, which was used without further purification in the next step. R_F 0.15 (4 : 1 34–40 P.E. : Et_2O); ν_{max}/cm^{-1} (film) 3391, 2928, 2870; δ_H (500 MHz, $CDCl_3$) 1.71 (3H, d, *J* 7.0 Hz), 1.78 (3H, br s), 1.93–1.95 (6H, m), 4.24 (2H, d, *J* 6.0 Hz), 5.48 (1H, q, *J* 7.0 Hz), 5.82 (1H, dt, *J* 15.5, 6.0 Hz), 5.83 (1H, s), 5.98 (1H, s), 6.32 (1H, d, *J* 15.5 Hz); δ_C (125.6 MHz, $CDCl_3$) 13.7, 14.0, 16.6, 18.9, 63.9, 125.2, 126.3, 131.5, 133.4, 135.2, 135.2, 137.3, 137.6. HRMS (CI) Calculated for $C_{13}H_{19}$ (M–OH)$^+$: 175.1487. Found: 175.1488.

To a stirred solution of the crude alcohol (0.28 g, 1.44 mmol) in dry DCM (2 mL) was added 3,5-dinitrobenzoyl chloride (0.40 g, 1.73 mmol) followed by pyridine (0.14 mL) at RT. After 2.5 h, water (5 mL) was added. The layers were separated and the aqueous layer extracted with DCM (3 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was recrystallised from ether to give orange crystals (0.362 g, 65%). R_F 0.46 (8 : 2 30–40 P.E. : Et_2O); δ_H (500 MHz, $CDCl_3$) 1.70 (3H, d, *J* 7.0 Hz), 1.75 (3H, br s), 1.92–1.95 (6H, m), 4.99 (2H, m), 5.45 (1H, q, *J* 7.0 Hz), 5.72 (1H, d, *J* 15.5 Hz), 5.80 (1H, s), 6.05 (1H, s), 6.45 (1H, d, *J* 15.5 Hz), 9.10–9.24 (3H, m); δ_C (125.6 MHz, $CDCl_3$) 13.9, 14.3, 16.6, 19.0, 72.8, 119.2, 122.2, 125.7, 129.3, 131.3, 133.3, 134.1, 135.5, 139.4, 142.6, 148.6, 162.3. HRMS (CI) Calculated for $C_7H_4N_2O_6$ (M$^+$): 175.1487. Found: 175.1486.

Single crystals of compound **53** suitable for X-ray diffraction were selected.

Crystal data. $C_{20}H_{22}N_2O_6$, *M* = 386.40, monoclinic, *a* = 13.1953(2), *b* = 8.0054(2), *c* = 19.1169(4) Å, *α* = 90, *β* = 107.7083(8), *γ* = 90°, *U* = 1923.7 Å^3, *T* = 150(1) K, space group $P2_1/n$, *Z* = 4, μ(Mo–Kα) = 0.099 mm^{-1}, 16330 reflections measured, 4625 unique (R_{int} = 0.026) which were used in calculations. The final *wR* was 0.0513.

CCDC reference number 190073. See http://www.rsc.org/suppdata/ob/b3/b306933h/ for crystallographic files in CIF or other electronic format.

Ethyl (1*R,6*S**,7*S**,8*S**)-1,3,5,8-tetramethylbicyclo[4.2.0]octa-2,4-diene-7-carboxylate (35)**

Ester **28** (239 mg, 1.02 mmol) and $(MeCN)_2PdCl_2$ (66 mg, 0.26 mmol) were dissolved in DMF (1 mL), and the mixture stirred at RT. After 2 h another portion of catalyst (26 mg, 0.41 g) was added and stirring was continued for a further 1 h. H_2O (2.5 mL) was then added and the mixture extracted with DCM (3 × 10 mL). The combined organic layers were washed with brine (2 × 10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Purification by preparative TLC (1% Et_2O in 30–40 P.E.) gave the title compound (81 mg, 34%) as a colourless oil. R_F 0.7 (9 : 1 30–40 P.E. : EtOAc); δ_H (500 MHz, $CDCl_3$) 1.03 (3H, s), 1.06 (3H, d, *J* 7.0 Hz), 1.25 (3H, t, *J* 7.0 Hz), 1.73 (3H, s), 1.75 (3H, s), 2.46 (1H, dq, *J* 9.5, 7.0 Hz), 2.53 (1H, d, *J* 9.0 Hz), 2.57 (1H, dd, *J* 9.5, 9.0 Hz), 4.12 (1H, q, *J* 7.0 Hz), 4.97 (1H, s), 5.42 (1H, br s); δ_C (126 MHz, $CDCl_3$) 14.3, 14.7, 21.9, 22.7, 28.2, 40.6, 46.5, 47.9, 50.6, 60.6, 122.1, 122.8, 130.6, 134.9, 175.0. HRMS (CI) Calculated for $C_{15}H_{23}O_2$ (MH$^+$): 235.1699. Found: 235.1706.

Ethyl (2*E*,4*E*,6*E*,8*E*)-2,4,6,8-tetramethyl-9-(4-nitrophenyl)nona-2,4,6,8-tetraenoate (37)

To a stirred solution of aldehyde **22** (0.658 g, 2.424 mmol) in toluene (10 mL) was added (1-ethoxycarbonylethylidene)-triphenylphosphorane (0.967 g, 2.668 mmol). The mixture was refluxed overnight, then allowed to cool to RT. Pentane (10 mL) was added, and the resulting triphenylphosphine oxide precipitate removed by filtration. The yellow filtrate was then concentrated under reduced pressure and purified by flash silica gel chromatography (9 : 1: 30–40 P.E. : EtOAc), to give the title compound as a yellow oil (0.827 g, 96%). R_F 0.6 (4 : 1 30–40 P.E. : EtOAc); ν_{max}/cm^{-1} ($CHCl_3$) 2983, 1698, 1594, 1517, 1343, 1111, 908, 733, 651; δ_H (400 MHz, $CDCl_3$) 1.33 (3H, t, *J* 7.5 Hz), 2.07 (3H, s), 2.07 (3H, s), 2.08 (3H, s), 2.10 (3H, s), 4.23 (2H, q, *J* 7.5 Hz), 6.05 (1H, s), 6.12 (1H, s), 6.49 (1H, s), 7.20 (1H, s), 7.45 (2H, d, *J* 8.0 Hz), 8.21 (2H, d, *J* 8.0 Hz); δ_C (100.6 MHz, $CDCl_3$) 14.2, 14.3, 18.6, 19.4, 19.4, 60.7, 123.5, 126.6, 129.5, 130.5, 133.3, 135.3, 135.4, 139.0, 139.3, 143.4, 144.6, 145.9, 169.0; *m*/*z* (CI) 373 (MNH_4^+, 100%), 356 (MH$^+$, 6), 343 (7), 333 (13), 326 (7). HRMS (CI) Calculated for $C_{21}H_{29}N_2O_4$ (MNH_4^+): 373.2127. Found: 373.2137.

(2*E*,4*E*,6*E*,8*E*)-2,4,6,8-Tetramethyl-9-(4-nitrophenyl)nona-2,4,6,8-tetraenal (38)

To a stirred solution of ester **37** (0.827 g, 2.33 mmol) in dry Et_2O (200 mL) was added DIBAL-H (4.89 mL of a 1 M solution in hexanes, 4.89 mmol) under argon at 0 °C. The reaction was stirred at RT until completion as indicated by TLC analysis (2 h), then quenched by the cautious addition of MeOH (2 × 233 μL). A saturated solution of potassium sodium tartrate (200 mL) was added, and the mixture was left to stir for several hours until the organic and aqueous layers had completely separated. The organic layer was separated, washed with brine (20 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to afford crude alcohol as a yellow oil. R_F 0.1 (4 : 1 30–40 P.E. : EtOAc). Without further purification, this oil was used in the next step.

To a stirred solution of crude alcohol (0.729 mg, 2.33 mmol) in chloroform (20 mL) was added MnO_2 (3.03 g, 34.9 mmol). After stirring overnight at RT, the solution was filtered, concentrated under reduced pressure and purified by flash silica gel chromatography (8 : 1 30–40 P.E. : EtOAc), to give the title compound as an orange oil (0.688 g, 95%, 2 steps). R_F 0.35 (4 : 1 30–40 P.E. : EtOAc); ν_{max}/cm^{-1} ($CHCl_3$) 2921, 1673, 1592, 1516, 1342, 911, 733; δ_H (400 MHz, $CDCl_3$) 2.02 (3H, s), 2.12 (3H, s), 2.12 (3H, s), 2.22 (3H, s), 6.13 (1H, s), 6.35 (1H, s), 6.52 (1H s), 6.81 (1H s), 7.46 (2H, d, *J* 8.0 Hz), 8.22 (2H, d, *J* 8.0 Hz), 9.44 (1H, s); δ_C (100.6 MHz, $CDCl_3$) 11.0, 18.3, 19.3, 19.3, 123.6,

129.0, 129.6, 133.6, 135.0, 136.7, 139.0, 142.7, 144.4, 146.0, 148.1, 155.3, 195.9; *m/z* (CI) 329 (MNH_4^+, 26%), 312 (MH^+, 100), 294 (32), 282 (18). HRMS (CI) Calculated for $C_{19}H_{22}NO_3$ (MH^+): 312.1600. Found: 312.1612.

Ethyl (2*E*,4*E*,6*E*,8*E*,10*E*)-4,6,8,10-tetramethyl-11-(4-nitrophenyl)undeca-2,4,6,8,10-pentaenoate (36)

To a stirring solution of aldehyde **38** (518 mg, 1.663 mmol) in benzene (50 mL) was added (ethoxycarbonylmethylene)-triphenylphosphorane (2.90 g, 8.317 mmol). The flask was fitted with a reflux condenser and the solution heated at 80 °C for 3 hours, then left to cool to RT. Pentane (50 mL) was added, and the resulting triphenylphosphine oxide precipitate was removed by filtration. The filtrate was concentrated under reduced pressure, and the crude residue purified by flash silica gel chromatography (9 : 1 30–40 P.E. : EtOAc), to afford the desired pentaene ester **36** as an orange oil (616 mg, 97%). R_F 0.3 (7 : 1 30–40 P.E. : EtOAc); ν_{max}/cm^{-1} (CCl_4) 2979, 1708, 1615, 1590, 1515, 1444, 1340, 1298, 1166, 793; λ_{max}(DCM)/nm 373 (ε/dm^3 mol^{-1} cm^{-1} 35200); δ_H (400 MHz, C_6D_6) 1.08 (3H, t, *J* 8.0 Hz), 1.73 (3H, s), 1.78 (3H, s), 1.85 (3H, s), 1.86 (3H, s), 4.16 (2H, q, *J* 8.0 Hz), 5.93 (1H, s), 5.94 (1H, s), 6.07 (1H, d, *J* 16.0 Hz), 6.11 (1H, s), 6.22 (1H, s), 6.84 (2H, d, *J* 8.0 Hz), 7.71 (1H, d, *J* 16.0 Hz), 7.89 (2H, d, *J* 8.0 Hz); δ_C (100.6 MHz, C_6D_6) 14.3, 14.8, 19.4, 19.6, 19.8, 60.6, 118.1, 124.0, 129.2, 129.9, 133.3, 133.8, 134.6, 135.8, 136.0, 138.7, 139.4, 144.3, 144.5, 150.7, 167.3; *m/z* (CI) 399 (MNH_4^+, 44%), 382 (MH^+, 100), 364 (15), 336 (43), 308 (40). HRMS (CI) Calculated for $C_{23}H_{28}NO_4$ (MH^+): 382.2018. Found: 382.2018.

Ethyl (2*E*,4*E*)-4-methyl-5-[(1*R,6*R**)-1,3,5-trimethyl-6-(4-nitrophenyl)cyclohexa-2,4-dien-1-yl]penta-2,4-dienoate (39)**

Ester **36** (800 mg, 2.1 mmol) and $(MeCN)_2PdCl_2$ (109 mg, 0.419 mmol) were placed in a dry flask, which was purged with argon. DMF (20 mL) was added, and the solution was stirred for 2 days at RT, and then water (10 mL) was added. The mixture was extracted with DCM (3 × 3 mL), and the combined organic fractions were washed with water (3 × 3 mL), brine (5 mL) and dried over anhydrous $MgSO_4$. The drying agent was removed by filtration, and the mixture concentrated under reduced pressure. The crude yellow residue was purified by flash silica gel chromatography (99.5 : 0.5 30–40 P.E. : EtOAc) to give the title compound as a yellow oil (160 mg, 20%). R_F 0.5 (3 : 1 30–40 P.E. : EtOAc); ν_{max}/cm^{-1} ($CHCl_3$) 2964, 2927, 2858, 1713, 1618, 1521, 1453, 1330, 1165; λ_{max}(DCM)/nm 264 (ε/dm^3 mol^{-1} cm^{-1} 18400); δ_H (400 MHz, C_6D_6) 0.85 (3H, s), 0.99 (3H, t, *J* 8.0 Hz), 1.18 (3H, s), 1.42 (3H, s), 1.64 (3H, s), 2.63 (1H, s), 4.06 (2H, q, *J* 8.0 Hz), 5.12 (1H, s), 5.37 (1H, s), 5.58 (1H, s), 5.68 (1H, d, *J* 16.0 Hz), 6.71 (2H, d, *J* 8.0 Hz), 7.42 (1H, d, *J* 16.0 Hz), 7.72 (2H, d, *J* 8.0 Hz); δ_C (100.6 MHz, C_6D_6) 13.6, 14.8, 21.6, 22.9, 29.7, 44.4, 56.5, 60.5, 117.4, 123.0, 124.3, 127.8, 129.6, 131.1, 135.5, 136.3, 146.5, 146.8, 147.6, 150.3, 167.3; *m/z* (CI) 399 (MNH_4^+, 8%), 382 (MH^+, 100), 352 (11), 336 (43), 308 (40). HRMS (CI) Calculated for $C_{23}H_{28}NO_4$ (MH^+): 382.2018. Found: 382.2026.

(2*E*,4*E*)-4-Methyl-5-[(1*R,6*R**)-1,3,5-trimethyl-6-(4-nitrophenyl)cyclohexa-2,4-dienyl 3,5-dinitrobenzoate (41)**

To a stirred solution of ester **39** (56.6 mg, 148.3 μmol) in dry Et_2O (5 mL) was added DIBAL-H (311.4 μL of a 1 M solution in hexanes, 311.4 μmol) under argon at 0 °C. The reaction was stirred at 0 °C until completion as indicated by TLC analysis (2 h), then quenched by the cautious addition of MeOH (2 × 300 μL). A saturated solution of potassium sodium tartrate (6 mL) was added, and the mixture was left to stir for 3 hours until the organic and aqueous layers had completely separated. The organic layer was separated, washed with brine (2 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to afford crude alcohol as a yellow oil. R_F 0.15 (7 : 2 30–40 P.E. : EtOAc). Without further purification, this oil was used in the next step.

To a solution of crude alcohol (49.4 mg, 145.5 μmol) in dry DCM (3 mL), was added 3,5-dinitrobenzoyl chloride (67 mg, 291.0 μmol) and pyridine (14.1 μL, 174.6 μmol). The reaction was allowed to stir for 1 h at RT, then quenched with water (1 mL). The layers were separated, and the aqueous layer extracted with DCM (3 × 2 mL). The combined organic fractions were then dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by flash silica gel chromatography (1 : 9 30–40 P.E. : EtOAc), to afford the title compound as a yellow solid (59.8 mg, 75%, 2 steps) which was recrystallized from DCM. R_F 0.4 (7 : 2 30–40 P.E. : EtOAc); mp = 190–192 °C; ν_{max}/cm^{-1} (KBr disc) 1737, 1630, 1552, 1346, 1170; δ_H (500 MHz, C_6D_6) 1.03 (3H, s), 1.36 (3H, s), 1.47 (3H, s), 1.67 (3H, s), 2.73 (1H, s), 4.54 (1H, dd, *J* 15.0, 5.0 Hz), 4.59 (1H, dd, *J* 15.0, 5.0 Hz), 5.24 (1H, s), 5.25 (1H, s), 5.31 (1H, dt, *J* 15.0, 5.0 Hz), 5.60 (1H, s), 6.12 (1H, d, *J* 15.0 Hz), 6.83 (1H, d, *J* 10 Hz), 7.76 (1H, d, *J* 10.0 Hz), 8.44 (1H, d, *J* 5.0 Hz), 8.65 (1H, d, *J* 5.0 Hz); δ_C (125.7 MHz, C_6D_6) 14.1, 21.6, 22.9, 30.0, 44.1, 57.0, 67.3, 120.0, 122.3, 123.0, 124.3, 128.3, 129.0, 129.6, 131.4, 133.6, 135.4, 136.4, 141.2, 142.2, 147.4, 147.6, 148.7, 162.5; *m/z* (CI) 551 (MNH_4^+, 100%), 521 (14), 474 (16), 447 (16). HRMS (CI) Calculated for $C_{28}H_{30}N_4O_8$ (MNH_4^+): 551.2142. Found: 551.2134.

Single crystals from dichloromethane of compound **41** suitable for X-ray diffraction were selected.

Crystal data. $C_{28}H_{27}N_3O_8$, M = 533.54, triclinic, a =9.5061(2), b = 11.9924(3), c = 12.1678(3) Å, α = 73.7785(11), β = 84.7859(9), γ = 80.7467(13)°, U = 1313.0 Å^3, T = 150(1) K, space group $P\bar{1}$, Z = 2, μ(Mo-Kα) = 0.100 mm^{-1}, 19776 reflections measured, 5959 unique (R_{int} = 0.051) which were used in calculations. The final wR was 0.0427.

CCDC reference number 209300. See http://www.rsc.org/suppdata/ob/b3/b306933h/ for crystallographic files in CIF or other electronic format.

Ethyl (1*S,2*S**,5*S**,6*S**,7*R**,8*S**)-1,3,5-trimethyl-8-(4-nitrophenyl)tricyclo[3.2.1.0^{2,7}]oct-3-en-6-carboxylate (53)**

A solution of ester **12** (0.40 g, 1.17 mmol) in xylene (80 mL) was refluxed overnight (140–145 °C). The solution was allowed to cool to RT and the solvent evaporated under reduced pressure. The crude residue was purified by flash silica gel chromatography (9 : 1 30–40 P.E. : EtOAc) to afford the title compound as a yellow solid (0.38 g, 95%). R_F 0.65 (4 : 1 30–40 P.E. : EtOAc); mp = 127–130 °C; ν_{max}/cm^{-1} (KBr) 1718, 1593, 1514, 1343; δ_H (500 MHz, $CDCl_3$) 0.91 (3H, s), 1.17 (3H, s), 1.23 (3H, t, *J* 7.5 Hz), 1.76–1.79 (1H, m), 1.94–1.96 (1H, m), 1.98 (3H, s), 2.21 (1H, s), 2.8–2.82 (1H, m), 4.08 (2H, q, *J* 7.5 Hz), 5.36 (1H, s), 7.27 (1H, dd, *J* 8.5, 2.0 Hz), 7.31 (1H, dd, *J* 8.5, 2.0 Hz), 8.22 (1H, dd, *J* 8.5, 2.5 Hz), 8.28 (1H, dd, *J* 8.5, 2.5 Hz); δ_C (125.7 MHz, $CDCl_3$) 14.2, 17.6, 20.7, 20.9, 26.4, 27.5, 29.9, 46.1, 47.2, 58.5, 59.9, 123.2, 123.4, 125.1, 127.2, 132.7, 134.7, 146.6, 148.1, 172.25; *m/z* (CI) 359 (MNH_4^+, 18%), 342 (MH^+, 100), 312 (9), 279 (13), 268 (7). HRMS (CI) Calculated for $C_{20}H_{24}NO_4$ (MH^+): 342.1705. Found: 342.1707.

[(1*S,2*S**,5*S**,6*S**,7*R**,8*S**)-1,3,5-Trimethyl-8-(4-nitrophenyl)-tricyclo[3.2.1.0^{2,7}]oct-3-en-6-yl]methyl 3,5-dinitrobenzoate (54)**

To a stirred solution of ester **53** (250 mg, 0.73 mmol) in dry Et_2O (50 mL) was added DIBAL-H (1.50 mL of a 1 M solution in hexanes, 1.50 mmol) under argon at 0 °C. After 1 hour at 0 °C the reaction was quenched by the cautious addition of MeOH (1 mL). A saturated solution of potassium sodium tartrate (50 mL) was added, and the mixture was left to stir at RT until the organic and aqueous layers had completely separated (3 h). The organic layer was separated, washed with brine (50 mL),

dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude yellow oil obtained was purified by flash silica gel chromatography (1 : 1 30–40 P.E. : EtOAc) to give the title compound as a yellow solid (213.8 mg, 98%). R_F 0.10 (4 : 1 30–40 P.E. : EtOAc); mp = 99–103 °C; ν_{max}/cm^{-1} (KBr) 3402, 2926, 1595, 1517, 1346; δ_H (400 MHz, $CDCl_3$) 0.64 (3H, s), 1.11 (3H, s), 1.28 (1H, s), 1.56–1.58 (1H, m), 1.78–1.80 (1H, m), 1.89 (3H, s), 2.0–2.05 (1H, m), 2.08 (1H, s), 3.18–3.20 (1H, m), 3.39–3.41 (1H, m), 5.27 (1H, s), 7.25 (1H, d, *J* 8.5 Hz), 7.29 (1H, d, *J* 8.5 Hz), 8.13 (1H, dd, *J* 8.5, 2.5 Hz), 8.19 (1H, dd, *J* 8.5, 2.5 Hz); δ_C (100.6 MHz, $CDCl_3$) 17.9, 20.2, 20.9, 26.9, 28.4, 29.3, 44.7, 44.8, 58.8, 61.7, 123.4, 123.6, 125.2, 127.9, 132.6, 134.0, 146.5, 148.2; *m*/*z*(CI) 317 (MNH_4^+, 10%), 300 (MH^+, 100), 282 (9), 270 (12), 230 (8). HRMS (CI) Calculated for $C_{18}H_{22}NO_3$ (MH^+): 300.1600. Found: 300.1600.

To a solution of the alcohol (113.5 mg, 0.382 mmol) in dry DCM (10 mL), was added 3,5-dinitrobenzoyl chloride (176.2 mg, 0.76 mmol) and a catalytic amount of DMAP. The reaction was allowed to stir overnight at RT, then quenched with water (10 mL). The layers were separated, and the aqueous layer extracted with DCM (3 × 10 mL). The combined organic fractions were then dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by flash silica gel chromatography (9 : 1 30–40 P.E. : EtOAc), to afford the title compound as a yellow solid (151.8 mg, 80%). R_F 0.2 (5 : 1 30–40 P.E. : EtOAc); mp = 218–220 °C; ν_{max}/cm^{-1} (KBr) 1732, 1628, 1551, 1347, 1172; δ_H (400 MHz, $CDCl_3$) 0.79 (3H, s), 1.19 (3H, s), 1.65 (1H, m), 1.83 (1H, m), 2.01 (3H, s), 2.19 (1H, s), 2.20–2.30 (1H, m), 4.07 (1H, br d, *J* 11.0 Hz), 4.18 (1H, br d, *J* 11.0 Hz), 5.38 (1H, s), 7.29 (1H, d, *J* 8.5 Hz), 7.31 (1H, d, *J* 8.5 Hz), 8.20 (1H, dd, *J* 8.5, 2.5 Hz), 8.28 (1H, dd, *J* 8.5, 2.5 Hz), 9.13 (2H, d, *J* 2.0 Hz), 9.22 (1H, t, *J* 2.0 Hz); δ_C (100.6 MHz, $CDCl_3$) 17.7, 20.3, 20.9, 27.1, 28.2, 29.9, 41.2, 45.0, 58.5, 66.7, 122.3, 123.2, 123.4, 124.9, 127.6, 129.3, 132.7, 133.9, 134.4, 146.7, 147.5, 148.7, 162.5.

Single crystals from diethyl ether of compound **53** suitable for X-ray diffraction were selected.

Crystal data. $C_{25}H_{23}N_3O_8$, M = 493.47, triclinic, a = 8.0506(4), b = 12.3846(5), c = 13.2746(7) Å, α = 64.465(2), β = 86.930(2), γ = 73.060(2)°, U = 1138.4 Å^3, T = 150(1) K, space group $P\bar{1}$, Z = 2, μ(Mo-Kα) = 0.109 mm^{-1}, 15400 reflections measured, 5161 unique (R_{int} = 0.042) which were used in calculations. The final wR was 0.0578.

CCDC reference number 209361. See http://www.rsc.org/suppdata/ob/b3/b306933h/ for crystallographic files in CIF or other electronic format.

Ethyl (2*E*)-3-[(1*S,4*R**,5*S**,6*S**)-1,3,6-trimethyl-4-(4-nitrophenyl)bicyclo[3.1.0]hex-2-en-6-yl]prop-2-enoate (59)**

A solution of ester **12** (120 mg, 0.35 mmol) in chloroform (25 mL) was refluxed overnight, whilst simultaneously being exposed to the light from a 600 W tungsten lamp source. The solution was allowed to cool to RT and the solvent evaporated under reduced pressure. The crude residue was purified by flash silica gel chromatography (9 : 1 30–40 P.E. : EtOAc) to afford the title compound as a yellow oil (72 mg, 60%). R_F 0.3 (4 : 1 30–40 P.E. : EtOAc); ν_{max}/cm^{-1} (film) 1707, 1634, 1520, 1347; δ_H (400 MHz, $CDCl_3$) 1.12 (3H, s), 1.24 (3H, t, *J* 7.0 Hz), 1.47 (3H, s), 1.54 (3H, s), 1.59 (1H, s), 3.32 (1H, s), 4.18 (2H, q, 7.0 Hz), 5.48 (1H, s), 5.37 (1H, d, *J* 15.5 Hz), 6.78 (1H, d, *J* 15.5 Hz), 7.34 (2H, d, *J* 8.5 Hz), 8.19 (2H, d, *J* 8.5 Hz); δ_C (100.6 MHz, $CDCl_3$) 10.8, 13.8, 14.3, 16.3, 33.2, 43.8, 44.2, 55.1, 60.1, 118.3, 123.9 (2C), 128.8 (2C), 131.7, 143.2, 146.8, 150.4, 153.7, 166.9. HRMS (CI) Calculated for $C_{20}H_{24}NO_4$ (MH^+): 342.1705. Found: 342.1702.

A crude ^{1}H NMR spectrum was taken after 4 hours of reaction time The vinylic region of the ^{1}H NMR clearly showed two isomeric linear tetraenes, one which had an identical ^{1}H NMR spectrum to that of **12**. The other isomer was identified as intermediate **60** by nOe, specifically, the major nOe between the C8 methyl protons and the C9 vinylic proton. The other double bonds were identified as having (*E*) configuration. δ_H (500 MHz, $CDCl_3$) 1.35 (3H, t, *J* 7.0 Hz), 1.77 (3H, s), 2.04 (3H, s), 2.18 (3H, s), 4.28 (2H, q, *J* 7.0 Hz), 5.93 (1H, d, *J* 16.0 Hz), 6.20 (1H, s), 6.36 (1H, s), 6.50 (1H, s), 7.40 (1H, d, *J* 16.0 Hz), 7.49 (2H, d, *J* 8.5 Hz), 8.15 (2H, d, *J* 8.5 Hz).

Ethyl (2*E*,4*E*)-4-methyl-5-[(1*S,4*R**,5*S**,6*S**)-1,3,6-trimethyl-4-(4-nitrophenyl)bicyclo[3.1.0]hex-2-en-6-yl]penta-2,4-dienoate (62)**

A solution of pentaene **36** (100 mg, 0.262 mmol) in $CHCl_3$ (15 mL) was refluxed for 2 days whilst simultaneously being exposed to a 600 W tungsten lamp. The solution was then allowed to cool to RT and the solvent evaporated under reduced pressure. The crude residue was purified by flash silica gel chromatography (99.5 : 0.5 30–40 P.E. : EtOAc) to afford **62** as a yellow oil (40 mg, 40%). R_F 0.35 (7 : 1 30–40 P.E. : EtOAc); ν_{max}/cm^{-1} (CCl_4) 2963, 2925, 2857, 1713, 1619, 1521, 1452, 1347, 1330, 1174, 1027, 812; δ_H (400 MHz, C_6D_6) 0.83 (1H, s), 0.93 (3H, s), 1.05 (3H, t, *J* 6.33 Hz), 1.10 (3H, s), 1.26 (3H, s), 1.61 (3H, s), 2.94 (1H, s), 4.13 (2H, q, *J* 6.33 Hz), 5.15 (1H, s), 5.67 (1H, s), 6.00 (1H, d, *J* 16.0 Hz), 6.78 (2H, d, *J* 10.0 Hz), 7.59 (1H, d, *J* 16.0 Hz), 7.89 (2H, d, *J* 10.0 Hz); δ_C (100.6 MHz, C_6D_6) 13.8, 14.0, 14.1, 14.8, 16.6, 31.5, 41.1, 42.5, 55.4, 60.5, 117.5, 124.3, 129.0, 131.5, 137.0, 143.2, 144.7, 147.6, 149.3, 151.0, 167.3; *m*/*z* (CI) 399 (MNH_4^+, 3%), 382 (MH^+, 100), 366 (8), 352 (29), 336 (30), 308 (27). HRMS (CI) Calculated for $C_{23}H_{28}NO_4$ (MH^+): 382.2018. Found: 382.2023.

Compound **39** was also isolated as a yellow oil (17 mg, 17%).

Direct conversion of ethyl (2*E*,4*E*)-4-methyl-5-[(1*R,6*R**)-1,3,5-trimethyl-6-(4-nitrophenyl)cyclohexa-2,4-dien-1-yl]penta-2,4-dienoate (39) into ethyl (2*E*,4*E*)-4-methyl-5-[(1*S**,4*R**,5*S**,6*S**)-1,3,6-trimethyl-4-(4-nitrophenyl)bicyclo[3.1.0]hex-2-en-6-yl]penta-2,4-dienoate (62)**

A solution of hexadiene **39** (15 mg, 39.3 μmol) in benzene (0.5 mL) was exposed to direct sunlight. Periodic observations using ^{1}H NMR indicated conversion to **62** without any evidence for **36**. After 2 weeks of irradiation, compound **39** has been completely converted into bicyclic compound **62** (15 mg, 100%). The ^{1}H NMR spectra data matched with that found for **62** given above.

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