Detection of 2-substituted cyclobutanones as irradiation products of lipid-containing foods: synthesis and applications of *cis*- and *trans*-2-(tetradec-5′-enyl)cyclobutanones and 11-(2′-oxocyclobutyl)-undecanoic acid

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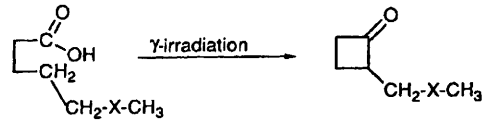
***cis*- (3_{cis}) and *trans*-2-(tetradec-5′-enyl)cyclobutanone (3_{trans}) have been chemically synthesised and used in the unambiguous identification of the *cis* isomer 3_{cis} in irradiated meat (example chicken) and fruit (example papaya). 11-(2′-Oxocyclobutyl)undecanoic acid 5 has been chemically synthesised, conjugated to bovine thyroglobulin and used to generate polyclonal antibodies in rabbits, which have been used in the development of an enzyme-linked immunosorbent assay for the detection of 2-substituted cyclobutanones in irradiated chicken meat.**

Introduction

Gamma irradiation has been used to enhance food safety and extend the shelf-life of foodstuffs including meat and fruit.[1–5] Thus, the development of reliable detection methods to study irradiated foods is a topic of current interest. A selection of methods is now available which include the use of ESR spectroscopy to detect long-lived free radicals,[1,2] the observation of thermoluminescence of irradiated products[3,4] and the detection of volatile compounds from irradiated fats.[5] The most abundant volatile compounds produced by irradiation of triglycerides are hydrocarbons, aldehydes, methyl and ethyl esters and free fatty acids. In addition to these major volatile products, the formation of a series of unusual 2-alkylcyclobutanones (structures were assumed in the absence of authentic reference samples) containing the same number of carbon atoms as the parent fatty acids was also postulated[6] when simple triglycerides were irradiated using gamma rays at 60 kGy *in vacuo*. Thus, it was suggested that the four major fatty acids found in most foods, namely palmitic, stearic, oleic and linoleic acid would give 2-dodecyl- **1**, 2-tetradecyl- **2**, 2-(tetradec-5′-enyl)- **3** and 2-(tetradeca-5′,8′-dienyl)-cyclobutanone **4** respectively, following irradiation (Scheme 1). Using chicken meat as a model for a lipid-containing food, a method



Scheme 1

X	Fatty acid	2-Substituted cyclobutanone
$(CH_2)_{10}$	Palmitic acid	**1**
$(CH_2)_{12}$	Stearic acid	**2**
$(CH_2)_3CH{=}CH(CH_2)_7$	Oleic acid	**3**
$(CH_2)_3(CH{=}CHCH_2)_2(CH_2)_3$	Linoleic acid	**4**

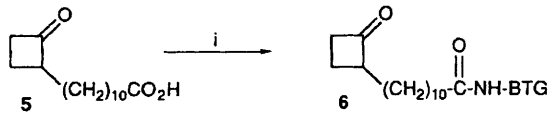
was developed in these laboratories for the chemical synthesis and identification by gas chromatography-mass spectroscopy (GC–MS) of the low levels of 2-dodecylcyclobutanone **1** present in irradiated chicken meat (< 600 ng g^{-1} lipid/kGy), which confirmed the earlier prosposal.[6] Cyclobutanone **1** has been shown to be a specific marker of gamma irradiation treatment in chicken meat.[7–11] 2-Tetradecylcyclobutanone **2** was later synthesised and shown to be a specific marker for irradiated liquid whole egg.[12] In both instances the presence of cyclobutanones **1** and **2** in the irradiated samples was confirmed by direct comparison with authentic standards, which were synthesised for this purpose. In addition to the cyclobutanones **1** and **2** a larger proportion of a third cyclobutanone was observed which was tentatively proposed to be 2-(tetradec-5′-enyl)cyclobutanone **3**, but in the absence of an authentic sample neither the structure nor relative stereochemistry could be unambiguously established.

This paper describes the synthesis and characterisation of *cis*-(3_{cis}) and *trans*-2-(tetradec-5′-enyl)cyclobutanone (3_{trans}) and the unambiguous identification of the *cis* isomer 3_{cis} in examples of irradiated meat (chicken) and fruit (papaya). Owing to the low concentration of cyclobutanone 3_{cis} identification was by direct GC–MS comparison with the authentic standard. Detection of 2-substituted cyclobutanone irradiation products in papaya was previously impossible when only cyclobutanones **1** and **2** were available as standards, owing to the low percentage composition of the precursors palmitic and stearic acid and, consequently, of the low concentration of the derived 2-substituted cyclobutanone products (Table 1), which was below the limits of the GC–MS detection method.

The paper also describes the synthesis and characterisation of 11-(2′-oxocyclobutyl)undecanoic acid **5**, a 2-substituted cyclobutanone containing a terminal carboxy group. This carboxylic acid has, in turn, been covalently bonded to bovine thyroglobulin in order to provide a suitable hapten for antibody production (Scheme 2) and is currently being used in the development of an enzyme-linked immunosorbent assay (ELISA) as an alternative to the GC–MS detection method for 2-substituted cyclobutanones in irradiated lipid-containing

Table 1 Fatty acid profiles of chicken and papaya prior to irradiation, and 2-substituted cyclobutanone products formed after irradiation of the triglycerides

Fatty acid		% Composition Chicken	Papaya	$O=\overset{\alpha}{C}CH_2CH_2\overset{\beta}{C}HR$
Oleic	$C_{18:1}$	45.5	69.2	R = $(CH_2)_4CH{=}CH(CH_2)_7CH_3$ (*cis*)
Palmitic	$C_{16:0}$	24.0	17.6	R = $(CH_2)_{11}CH_3$
Linoleic	$C_{18:2}$	11.9	6.6	R = $(CH_2)_4CH{=}CHCH_2CH{=}CH_2(CH_2)_4CH_3$ (*cis*, *cis*)
Stearic	$C_{18:0}$	5.0	6.3	R = $(CH_2)_{13}CH_3$



Scheme 2 i, 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide hydrochloride, bovine thyroglobulin (BTG), H_2O, pyridine

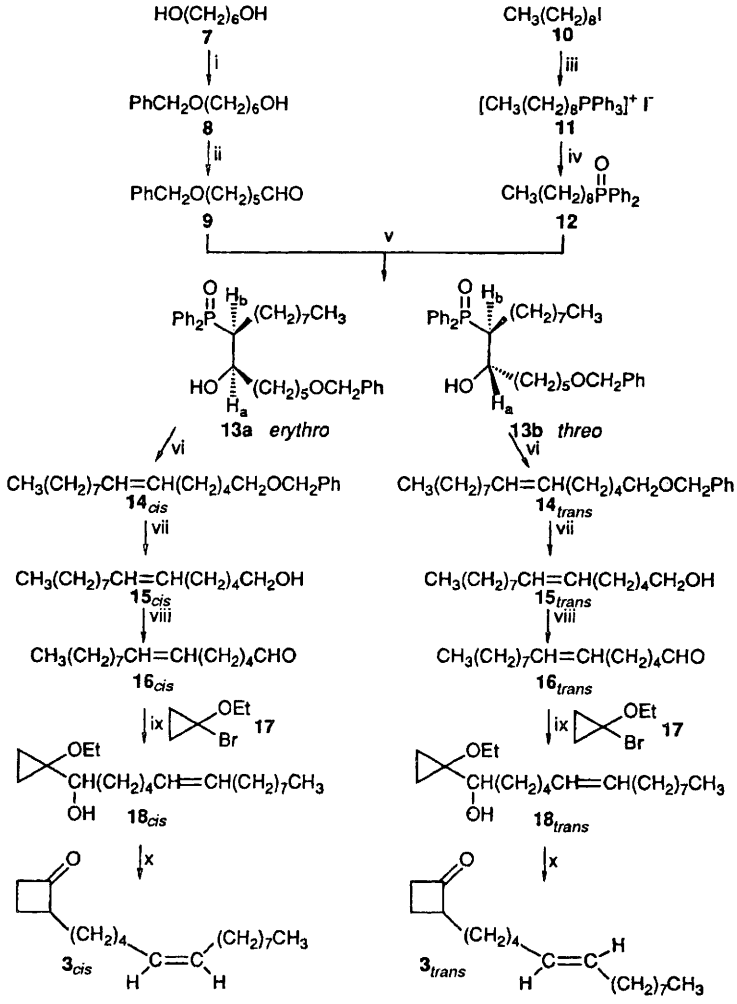
foods.[13,14] This is the first example of the application of an ELISA for the detection of food irradiation products. Previously the detection of 2-substituted cyclobutanones in irradiated foods has relied exclusively upon GC–MS analysis and although the technique is reliable, sensitive and reproducible, the instrumentation is expensive and the protocol is complex. However, the successful development of an ELISA offers a cheap and rapid screening method which may be used on site. Thus, only with the availability of 11-(2′-oxocyclobutyl)undecanoic acid **5** using the described synthetic method, has it been possible to develop an immunoassay for the detection of irradiated chicken meat.[14]

Results and discussion

cis- and *trans*-2-Tetradec-5′-enylcyclobutanone $\mathbf{3}_{cis}$, $\mathbf{3}_{trans}$ were synthesised by the route shown in Scheme 3 and the intermediates were fully characterised. Initially *cis*- $\mathbf{16}_{cis}$ and *trans*-pentadec-6-enal $\mathbf{16}_{trans}$, which were not commercially available, were synthesised by a multi-step route. Thus, hexane-1,6-diol **7** was monobenzylated to give 6-benzyloxyhexan-1-ol **8** (64%) and the free hydroxy group was subsequently oxidised using PCC in CH_2Cl_2 to give 6-benzyloxyhexanal **9** (60%). Nonyl(diphenyl)phosphine oxide **12** was prepared by reaction of triphenylphosphine and 1-iodononane **10** in MeCN to yield the phosphonium salt **11**, which was subsequently treated with aqueous sodium hydroxide to afford the phosphine oxide **12** (67%). The Wittig–Horner reaction between the phosphine oxide **12** and the aldehyde **9** in the presence of BuLi in THF at −78 °C gave a mixture of *erythro*- **13a** (40%) and *threo*-1-benzyloxy-7-diphenylphosphinoylpentadecan-6-ol **13b** (10%) in the ratio 4:1. The diastereoisomers were separated by flash chromatography and were identified by characteristic features in the ^{1}H NMR spectra. The *erythro* diastereoisomer **13a** shows a higher positive δ_H value for proton H_a (δ 4.08) than that of the *threo* isomer **13b** (δ 3.92), and a lower positive δ_H value for proton H_b (δ 2.20) than that of the *threo* isomer **13b** (δ 2.40). Treatment of the individual pure *erythro* **13a** and *threo* **13b** diastereoisomers with NaH in DMF yielded pure *cis*- ($\mathbf{14}_{cis}$, 55%) and *trans*-1-benzyloxypentadec-6-ene ($\mathbf{14}_{trans}$, 53%) respectively. The *erythro* isomer **13a** yielded the *cis* alkene $\mathbf{14}_{cis}$ exclusively, which was identified by the smaller *cis* coupling pattern ($J_{6,7}$ 10.0 Hz), while the *threo* isomer **13b** yielded exclusively the *trans* alkene $\mathbf{14}_{trans}$ with a larger coupling constant ($J_{6,7}$ 14.8 Hz). Each of the alkenes was found to be distinguishable by capillary GC analysis and found to have a purity >99%. The *cis* $\mathbf{14}_{cis}$ and *trans* alkenes $\mathbf{14}_{trans}$ were used separately in the synthesis of *cis*- $\mathbf{3}_{cis}$ and *trans*-2-(tetradec-5′-enyl)cyclobutanone $\mathbf{3}_{trans}$, respectively, using identical reaction conditions. The benzyl protecting groups could not be removed *via* the standard catalytic hydrogenolysis procedure (H_2, Pd–C) owing to the presence of the alkene groups. The protecting groups were thus removed using Na–NH_3 to yield *cis*- $\mathbf{15}_{cis}$ (29%) and *trans*-pentadec-6-en-1-ol $\mathbf{15}_{trans}$ (32%) and the alcohols were subsequently oxidised using PCC to give the corresponding aldehydes $\mathbf{16}_{cis}$ (81%) and $\mathbf{16}_{trans}$ (78%). Reaction of the individual aldehydes $\mathbf{16}_{cis}$ and $\mathbf{16}_{trans}$ with 1-bromo-1-ethoxycyclopropane[15] **17** in the presence of Bu^{t}Li under the conditions previously reported using different aldehydes,[15] gave the cyclopropane derivatives $\mathbf{18}_{cis}$ (62%) and $\mathbf{18}_{trans}$ (65%). These underwent rearrangements when treated with 48% aqueous fluoboric acid (HBF_4) to give *cis*- ($\mathbf{3}_{cis}$, 65%) and *trans*-2-(tetradec-5′-enyl)cyclobutanone ($\mathbf{3}_{trans}$, 60%) as low-melting point solids. Baseline separation and analysis of the individual isomers $\mathbf{3}_{cis}$ and $\mathbf{3}_{trans}$ was achieved by capillary GC analysis.

The ^{1}H NMR assignments of the *cis* $\mathbf{3}_{cis}$ and *trans* $\mathbf{3}_{trans}$ isomers of 2-(tetradec-5′-enyl)cyclobutanone were made on the basis of high resolution (500 MHz) and COSY (2-D correlation spectroscopy) spectra and were in many respects similar to those previously reported for cyclobutanones **1**[8] and **2**.[12] However, in this case the presence of characteristic alkene peaks at δ 5.35 confirmed that the unsaturated cyclobutanones $\mathbf{3}_{cis}$ and $\mathbf{3}_{trans}$ had been synthesised. ^{13}C NMR spectroscopy of the *cis* $\mathbf{3}_{cis}$ and *trans* $\mathbf{3}_{trans}$ isomers gave separate signals for each of the 18 carbon atoms present in both cases. Electron impact mass spectra of the isomers confirmed this identification. A peak at *m*/*z* 98 was observed for both *cis*- $\mathbf{3}_{cis}$ and *trans*-2-(tetradec-5′-enyl)cyclobutanone $\mathbf{3}_{trans}$, although this ion was not the base peak as previously noted for cyclobutanones **1** and **2**, and a molecular ion at *m*/*z* 264 was also present for both the *cis* $\mathbf{3}_{cis}$ and *trans* $\mathbf{3}_{trans}$ isomers. Additional confirmation on the structures were obtained from the IR spectra, which showed strong absorptions at *ca.* 2900 cm^{-1} owing to CH stretching by the alkyl side chain and absorptions at 1798 cm^{-1}, which is characteristic of a ketone group in a four-membered carbocyclic ring and has previously been reported for cyclobutanones **1**[10] and **2**.[12]

cis-2-(Tetradec-5′-enyl)cyclobutanone $\mathbf{3}_{cis}$ was used as a reference in the unambiguous identification of this compound as the major cyclobutanone product in both irradiated chicken meat (Fig. 1), and papaya (Fig. 2) which is a good example of a low fat food. This was achieved using the GC–MS method and in the case of irradiated chicken meat, the mass spectrometer was operated in the selected ion monitoring mode measuring ion currents at 236, and 264 amu and the peaks in the gas chromatogram were recorded as the sum of the two ions monitored. The chromatogram of chicken meat which had been irradiated at 2.5 kGy [Fig. 1(b)] showed a peak with similar ion ratios, at a retention time (16.3 min) identical with that of the authentic *cis* $\mathbf{3}_{cis}$ standard [Fig. 1(c)]. No peak was present in the unirradiated sample [Fig. 1(a)], thus demonstrating that the *cis* $\mathbf{3}_{cis}$ isomer, is formed during the irradiation process as



Scheme 3 *Reagents and conditions:* i, NaH, benzyl bromide, THF; ii, PCC–CH_2Cl_2; iii, PPh_3–MeCN; iv, NaOH aq; v, BuLi/THF, −78 °C; vi, NaH–DMF; vii, Na–NH_3; viii, PCC–CH_2Cl_2; ix, Bu^tLi–Et_2O, −78 °C; x, HBF_4 (48% aq.)

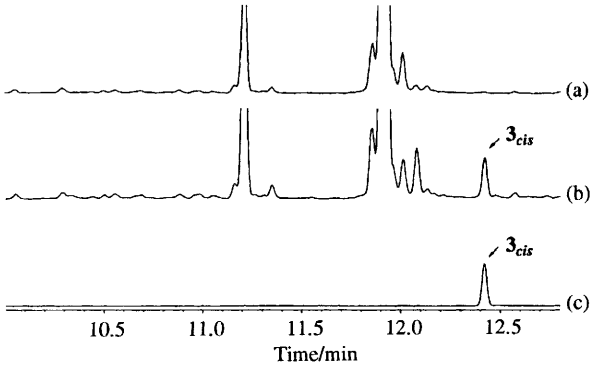


Fig. 1 Selective ion monitored (ion currents 236 and 264 amu) MS chromatograms of (a) unirradiated chicken meat, (b) irradiated (2.5 kGy) chicken meat and (c) standard *cis*-2-tetradec-5′-enylcyclobutanone $\mathbf{3}_{cis}$

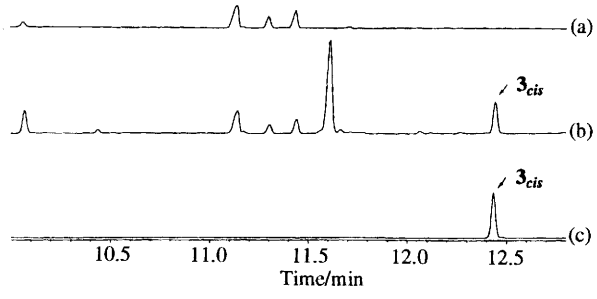


Fig. 2 Selective ion monitored (ion currents 165, 179, 236 and 264 amu) MS chromatograms of (a) unirradiated papaya, (b) irradiated (0.11 kGy) papaya and (c) standard *cis*-2-tetradec-5-enylcyclobutanone $\mathbf{3}_{cis}$

expected. In the case of irradiated papaya fruit, the mass spectrometer was operated in the selected ion monitoring mode measuring ion currents at 165, 179, 236 and 264 amu and the peaks in the gas chromatogram were recorded as the sum of the four ions monitored. A similar pattern was obtained for papaya (Fig. 2). Papaya which were irradiated at 0.11 kGy showed a chromatogram peak again with similar ion ratios and at a retention time (12.45 min) identical with that of *cis*-2-(tetradec-5′-enyl)cyclobutanone $\mathbf{3}_{cis}$, while no peak was present in unirradiated papaya. The absence of the *trans* isomer $\mathbf{3}_{trans}$ suggests that *cis–trans* alkene isomerisation (a common photochemical process occurring under UV irradiation) does not occur to a significant degree during the gamma irradiation process. Previous work by this group provided tentative evidence for the formation of 2-(tetradec-5′-enyl)cyclobutanone in irradiated liquid whole egg.[12] However, as neither *cis*- $\mathbf{3}_{cis}$ nor *trans*-2-(tetradec-5′-enyl)cyclobutanone $\mathbf{3}_{trans}$ was available as a standard at that time, hydrogenation of the unsaturated cyclobutanone irradiation product was required before identification by comparison with the analogous saturated cyclobutanone **2**. This identification method did not allow either the position or stereochemistry of the alkene group in the cyclobutanone product to be assigned. The MS and IR spectra (Fig. 3) of the chemically synthesised *cis*-2-(tetradec-5′-enyl)cyclobutanone $\mathbf{3}_{cis}$ were found to be identical with those of compound $\mathbf{3}_{cis}$ resulting from irradiation of the chicken meat and papaya in the present study. The availability of chemically

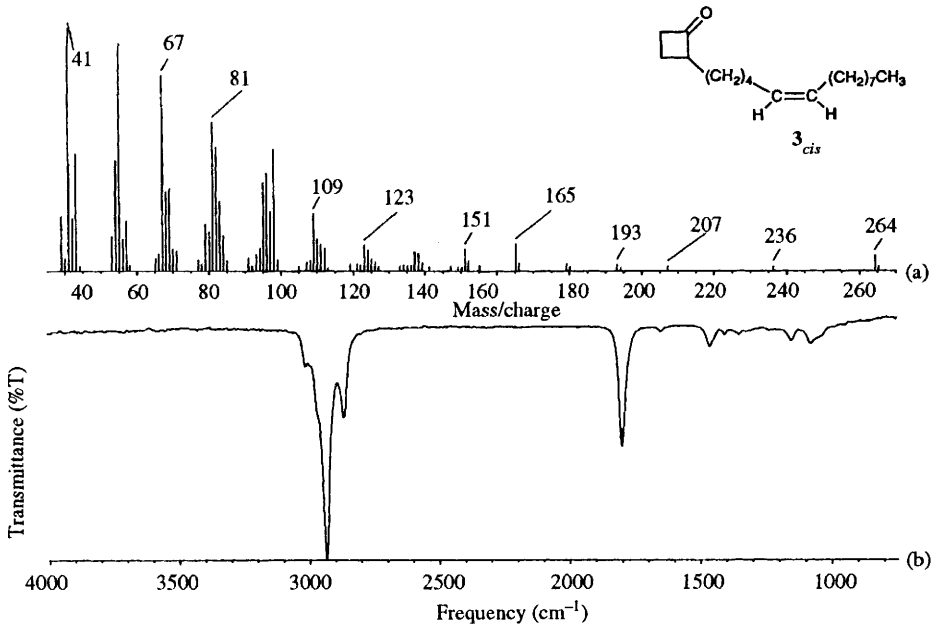
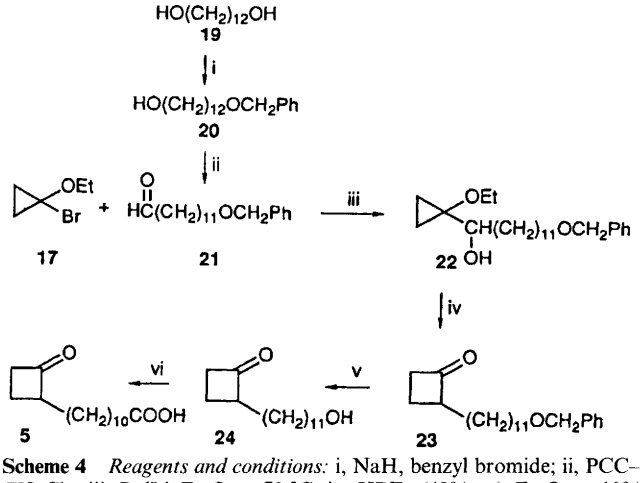


Fig. 3 (a) Electron impact mass spectrum and (b) IR spectrum of *cis*-2-tetradec-5′-enylcyclobutanone $\mathbf{3}_{cis}$ obtained using GC-MS and GC-IR methods

synthesised samples of 2-dodecyl- **1**, 2-tetradecyl- **2**, and now *cis*- $\mathbf{3}_{cis}$ and *trans*-2(tetradec-5′-enyl)cyclobutanone $\mathbf{3}_{trans}$ as reference compounds now allows the GC–MS method of analysis for 2-substituted cyclobutanones to be applied to a much wider range of foodstuffs than was previously possible.

As an alternative method for the detection of 2-substituted cyclobutanones in irradiated lipid-containing foods, a cyclobutanone derivative containing a terminal carboxy group, 11-(2′-oxocyclobutyl)cyclobutanone **5**, was synthesised and used in the development of an ELISA [13,14] for 2-substituted cyclobutanones. Cyclobutanone **5** was synthesised by the multi-step route shown in Scheme 4 and each of the intermediates was



Scheme 4 *Reagents and conditions:* i, NaH, benzyl bromide; ii, PCC–CH_2Cl_2; iii, Bu^{t}Li–Et_2O, −78 °C; iv, HBF_4 (48% aq)–Et_2O; v, 10% Pd–C/H_2, 55 psi; vi, DMD–acetone

fully characterised. In the first stage dodecane-1,12-diol **19** was heated in benzyl bromide with sodium hydride in a 1:1 molar ratio, to yield 12-benzyloxydodecanol **20** (49%). It was necessary to use benzyl bromide as both reagent and solvent to overcome initial solubility problems which were encountered when tetrahydrofuran (THF) and dimethylformamide (DMF) were used as solvents. The monobenzylated alcohol **20** was oxidised to the corresponding aldehyde **21** (80%) using pyridinium chlorochromate (PCC). Reaction of aldehyde **21** with 1-bromo-1-ethoxycyclopropane **17** in the presence of *tert*-butyllithium gave a cyclopropane derivative **22** (47%), which underwent rearrangement when it was treated with 48% aqueous fluoboric acid to give 2-(11′-benzyloxyundecyl)cyclobutanone **23** (67%). The benzyl-protecting group was removed by catalytic hydrogenation using 10% palladium-on-charcoal under a hydrogen atmosphere of 55 psi, to give 11-(2′-oxocyclobutyl)undecanol **24** (100%). The hydroxy group was oxidised using 3 equiv. of freshly prepared dimethyldioxirane,[16] to give 11-(2′-oxocyclobutyl)undecanoic acid **5** (91%).

The cyclobutanone **5** was fully characterised as a crystalline solid. The ^{1}H NMR assignments of 11-(2′-oxocyclobutyl)undecanoic acid **5** were made on the basis of high resolution (500 MHz) and COSY (2-D correlation spectroscopy) spectra and were similar in many respects to those previously reported for cyclobutanone **1**.[7] However, in this case a triplet which integrated for two protons, was present at δ 2.35, indicating that a terminal carboxy group had been introduced. 11-(2′-Oxocyclobutyl)undecanoic acid **5** was methylated and analysed by GC–MS and GC–IR. The electron impact mass spectrum showed a base peak at *m*/*z* 98, as had prevously been reported for cyclobutanones **1**[8] and **2**,[12] and a peak at *m*/*z* 237 corresponding to the molecular ion minus OCH_3. The IR spectrum showed a strong absorption at 1798 cm^{-1}, which is characteristic of a ketone group in a four-membered ring, and absorptions at 1760 and 1173 cm^{-1} due to the ester C=O and the C–O bonds respectively.

11-(2′-Oxocyclobutyl)undecanoic acid **5** was used in the development of an ELISA for the detection of 2-substituted cyclobutanones in irradiated chicken meat by analysis of lipid extracts.[13,14] This involved conjugation of compound **5** to the carrier protein bovine thyroglobulin, by a carbodiimide condensation reaction [17] using 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide hydrochloride (Scheme 2). Polyclonal antibodies were raised in rabbits by immunizing with the conjugate. The antibodies were characterised [14] and used in an ELISA for the detection of 2-alkylcyclobutanone standards. The conditions of the assay were optimised and it was validated using chicken meat irradiated over the dose range 0.5–10.0 kGy. The assay was successful in detecting 2-substituted cyclobutanones in chicken meat which had been irradiated at and above that normally applied (2.5 kGy) to this tissue type. This novel method of detecting irradiated chicken meat combines an immunoassay, which is a screening technique, with 2-substituted cyclobutanones which are known markers for lipid-containing irradiated foods. It is expected that this and similar

immunoassays will be capable of detecting 2-substituted cyclobutanone irradiation products at the pg level and will be applied to the analysis of a variety of irradiated foods in the future.

Experimental

^{1}H NMR spectra were recorded at 300 and 500 MHz on GE-QE 300 and GN-Omega 500 instruments, respectively, using $CDCl_3$ solvent with tetramethylsilane as reference; *J* values are given in Hz. Decoupling was carried out to determine coupling constants in some cases. ^{13}C NMR spectra were recorded at 75 and 125 MHz on GE-QE 300 and GN-Omega 500 instruments respectively, using $CDCl_3$ solvent and tetramethylsilane as reference. ^{31}P NMR spectra were recorded at 202.5 MHz on a GN-Omega 500 instrument, using $CDCl_3$ solvent and phosphoric acid as reference. IR spectra were recorded on a Perkin–Elmer 983G spectrometer equipped with a Perkin–Elmer 3700 data station. Mass spectra were recorded at 70 eV on an AE1-MS 902 instrument updated by V. G. Instruments. Accurate molecular weights were determined by the peak-matching method using perfluorokerosene as reference. GC–MS analyses were carried out using a Hewlett Packard 5890A gas chromatograph directly linked to a Hewlett Packard 5970 Mass Selective Detector. GC–IR analyses were carried out using a Hewlett Packard 5890A gas chromatograph directly linked to a 5965B Infra-red Detector. Chromatographic separations were performed using a CP-SIL 88 WCOT fused silica capillary column (50 m × 0.25 mm i.d.) supplied by Chrompack U.K. Ltd. The oven was initially held at 55 °C for 1 min and progammed at 10 °C min^{-1} to 225 °C and held at this temperature for 15 min. The sample (1 mm^3) was injected in the splitless mode. Methods used for irradiation and extraction of both chicken and papaya were identical with those previously reported.[14]

6-Benzyloxyhexan-1-ol 8

Hexane-1,6-diol **7** (15 g. 0.127 mol) and tetrabutylammonium iodide (2.0 g) were dissolved in anhydrous THF (120 cm^3) and the solution stirred under nitrogen for 20 min. Sodium hydride (60% dispersion in oil; 5.1 g, 0.127 mol) was added over a 10 min period to the mixture which was then stirred for 1.5 h at room temperature. Benzyl bromide (21.74 g, 0.127 mol) was added dropwise over a 20 min period to the mixture which was then stirred for a further 18 h at room temperature, after which it was refluxed for 1 h. On cooling, the mixture was diluted with water (25 cm^3) and evaporated under reduced pressure to remove the solvent. The residue was treated with further water (100 cm^3) after which it was extracted with diethyl ether (3 × 100 cm^3). The combined extracts were dried (Na_2CO_3) and concentrated under reduced pressure to afford the crude product as a viscous orange oil. Purification of this by flash chromatography [3:1 diethyl ether–light petroleum (bp 40–60 °C) as eluent] yielded the title compound **8** as a colourless viscous oil (17.0 g, 64%), bp 163–165 °C at 12 mmHg (Found: C, 74.7; H, 9.5. $C_{13}H_{20}O_2$ requires C, 74.9; H, 9.7%); ν_{max}/cm^{-1}(neat) 3395 (OH) and 3063 (CH, aromatic); δ_H(300 MHz, $CDCl_3$) 1.53 [8 H, m, $(CH_2)_4$], 3.47 (2 H, t, *J* 6.6, CH_2OCH_2Ph), 3.60 (2 H, t, *J* 6.6, CH_2OH), 4.50 (2 H, s, OCH_2Ph), 7.28 (1 H, m, Ph) and 7.34 (4 H, m, Ph); *m*/*z* 208 (M^+, 17%) and 91 (100).

6-Benzyloxyhexanal 9

Pyridinium chlorochromate (10.4 g, 0.048 mol) was added to anhydrous dichloromethane (150 cm^3) and the suspension was stirred at room temperature for 20 min. 6-Benzyloxyhexan-1-ol **8** (5 g, 0.024 mol) in anhydrous dichloromethane (10 cm^3) was added dropwise to the reaction flask. The resulting mixture was stirred for 4 h, after which it was diluted with anhydrous diethyl ether (300 cm^3) and stirring continued for a further 20 min. The mixture was filtered through a pad of Florisil, and then evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel [1:1 diethyl ether–light petroleum ether (bp 40–60 °C) as eluent] to yield the *title compound* **9** as a colourless oil (3.0 g, 60%), bp 124–126 °C at 10 mmHg (Found: C, 75.9; H, 8.5. $C_{13}H_{18}O_2$ requires C, 75.7; H, 8.8%); ν_{max}/cm^{-1}(neat) 1724 (C=O); δ_H(300 MHz, $CDCl_3$) 1.46 (2 H, m, CH_2), 1.60 [4 H, m, $(CH_2)_2$], 2.44 (2 H, t, *J* 7.3, CH_2CHO), 3.47 (2 H, t, *J* 6.4, CH_2OCH_2Ph), 4.50 (2 H, s, OCH_2Ph), 7.28 (1 H, m, Ph), 7.34 (4 H, m, Ph) and 9.76 (1 H, s, CHO); *m*/*z* 206 (M^+, 13%) and 91 (100).

Nonyl(triphenyl)phosphonium iodide 11

Triphenylphosphine (24 g, 92 mmol) and 1-iodononane **10** (23.2 g, 92 mmol) were dissolved in anhydrous acetonitrile (250 cm^3) and the solution was heated at reflux for 24 h. After cooling, the mixture was evaporated under reduced pressure to remove the solvent and to give the crude product **11** as a colourless viscous oil. This intermediate was used in the preparation of the phosphine oxide **12** without purification; crude yield 51.4 g, δ_H(300 MHz, $CDCl_3$) 0.86 (3 H, t, *J* 6.8, CH_3), 1.25 [10 H, m, $(CH_2)_5$], 1.65 [4 H, m, $PCH_2(CH_2)_2$], 3.65 (2 H, m, PCH_2), 7.72 (5 H, m, Ph) and 7.84 (10 H, m, 2 × Ph).

Nonyl(diphenyl)phosphine oxide 12

The crude phosphonium iodide salt **11** (25 g) was refluxed in aqueous sodium hydroxide (30%; 150 cm^3) for 1.5 h and then distilled under water pressure, to remove the benzene by-product. The remaining mixture was extracted with dichloromethane (3 × 80 cm^3). The combined extracts were washed with water (2 × 50 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure, to yield the phosphine oxide **12** as a white solid (10.1 g, 67%), mp 49–51 °C (from ethyl acetate) (Found: C, 76.6; H, 9.0; P, 9.1. $C_{21}H_{29}OP$ requires C, 76.8; H, 8.9; P, 9.4%); ν_{max}/cm^{-1}(KBr) 1170 (P=O); δ_H(300 MHz, $CDCl_3$) 0.86 (3 H, t, *J* 6.7, CH_3), 1.22 [10 H, m, $(CH_2)_5$], 1.38 [2 H, m, $CH_2(CH_2)_2P$], 1.61 (2 H, m, CH_2CH_2P), 2.26 (2 H, dt, *J* 10.8 and 8.4, CH_2P), 7.50 (5 H, m, Ph) and 7.74 (5 H, m, Ph); *m*/*z* 328 (M^+, 15%) and 215 (100).

1-Benzyloxy-7-diphenylphosphinoylpentadecan-6-ol 13

Nonyl(diphenyl)phosphine oxide **12** (3.2 g, 9.7 mmol) in anhydrous THF (100 cm^3) was stirred at −78 °C under nitrogen with butyllithium (1.5 mol dm^{-3} in hexane; 6.1 cm^3) for 20 min to give a red solution. On addition of 6-benzyloxyhexanal **9** (2.0 g, 9.7 mmol) in anhydrous THF (10 cm^3) to this over a period of 5 min the red colour disappeared. The solution was allowed to reach room temperature and then treated with water (50 cm^3). The aqueous layer was separated and extracted with dichloromethane (3 × 100 cm^3) and the combined organic layer and extracts were washed with water (100 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure, to yield a pale yellow oil which contained the two diastereoisomers (*erythro* **13a** and *threo* **13b**) of the alcohol. These were separated by flash chromatography [3:1, diethyl ether–light petroleum (bp 40–60 °C), as eluent] to give the high R_F diastereoisomer (R_F 0.7, *erythro* **13a**) (2.1 g, 40%), mp 59–60 °C (from ethyl acetate) (Found: C, 76.7; H, 9.2; P, 5.6. $C_{34}H_{47}O_3P$ requires C, 76.4; H, 8.9; P, 5.8%); ν_{max}/cm^{-1}(KBr) 3408 (OH), 1440 (PPh) and 1170 (P=O); δ_H(500 MHz, $CDCl_3$) 0.91 (3 H, t, *J* 7.2, CH_3), 0.94–1.23 [12 H, m, 3-H, 4-H, $(CH_2)_4$], 1.28 (2 H, m, CH_2CH_3), 1.37 (2 H, m, $CH_2CH_2OCH_2Ph$), 1.42 (1 H, m, CH_2CHOH), 1.63 (3 H, m, CH_2CH_2CHPO, CH_2CHPO), 1.71 (1 H, m, CH_2CHOH), 1.92 (1 H, m, CH_2CHPO), 2.20 (1 H, m, $CHPO$), 3.47 (2 H, t, *J* 6.5, CH_2OCH_2Ph), 4.08 (1 H, m, $CHOH$), 4.53 (2 H, s, OCH_2Ph), 7.34 (5 H, m, CH_2Ph), 7.55 (6 H, m, PPh) and 7.85 (4 H, m, PPh); δ_P(202.5 MHz, $CDCl_3$) 41.75 (*P*Ph); *m*/*z* 535 (M^+, 7%), 516 (10%), 91 (100%) and the low R_F diastereoisomer (R_F 0.6, *threo* **13b**) (0.54 g, 10%), mp 66–67 °C (from ethyl acetate) (Found: C, 76.1; H, 8.8; P, 5.9.

$C_{34}H_{47}O_3P$ requires C, 76.4; H, 8.9; P, 5.8%); ν_{max}/cm^{-1}(KBr) 3426 (OH), 1436 (PPh) and 1170 (P=O); δ_H(500 MHz, $CDCl_3$) 0.86 (3 H, t, *J* 7.2, CH_3), 1.05–1.24 [12 H, m, 3-H, 4-H, $(CH_2)_4$], 1.26 (2 H, m, CH_2CH_3), 1.37–1.52 (7 H, m, 2-H, 5-H, CH_2CHPO, CH_2CH_2CHPO), 1.65 (1 H, m, CH_2CHPO), 2.40 (1 H, m, CHPO), 3.40 (2 H, t, *J* 6.7, CH_2OCH_2Ph), 3.92 (1 H, m, CHOH), 4.47 (2 H, s, OCH_2Ph), 7.32 (5 H, m, CH_2Ph), 7.48 (6 H, m, PPh) and 7.78 (4 H, m, PPh); δ_P(202.5 MHz, $CDCl_3$) 40.38 (PPh); *m*/*z* 535 (M^+, 10%), 516 (40%) and 202 (100). The ^1H NMR assignments were made on the basis of 2D-COSY (correlation spectroscopy) spectra. Analysis of the *erythro* **13a** and *threo* **13b** diastereoisomers by ^{31}P NMR spectroscopy indicated that each isomer was >99% pure.

cis- and *trans*-1-Benzyloxypentadec-6-ene 14_{cis},14_{trans}

Sodium hydride (60% dispersion in oil; 150 mg) was added to a solution of the *erythro* isomer of 1-benzyloxy-7-diphenylphosphinoylpentadecan-6-ol **13a** (2 g, 3.7 mmol) in anhydrous DMF (80 cm^3) and the mixture was stirred at 50 °C for 1.5 h. On cooling, the mixture was diluted with water and the DMF was removed under reduced pressure. The residue was extracted with diethyl ether (3 × 100 cm^3) and the combined organic extracts were washed with water (2 × 100 cm^3), dried ($MgSO_4$) and concentrated to yield the crude product as a pale yellow oil. Purification of this by flash chromatography (ethyl acetate–hexane) gave *cis*-1-benzyloxypentadec-6-ene $\mathbf{14}_{cis}$ as a colourless oil (0.65 g, 55%), bp 136–138 °C at 8 mmHg (Found: C, 83.6; H, 11.2. $C_{22}H_{36}O$ requires C, 83.5; H, 11.5%); ν_{max}/cm^{-1}(neat) 3083 (=C–H) and 1670 (C=C); δ_H(300 MHz, $CDCl_3$) 0.88 (3 H, t, *J* 6.6, CH_3), 1.27 [13 H, m, 2-H, $CH_2(CH_2)_2OCH_2Ph$, $(CH_2)_5CH_3$], 1.37 (1 H, m, 2-H), 1.62 (4 H, m, $CH_2CH_2CH{=}CHCH_2CH_2$), 2.01 (4 H, m, $CH_2CH{=}CHCH_2$), 3.46 (2 H, t, *J* 6.6, CH_2OCH_2Ph), 4.50 (2 H, s, OCH_2Ph), 5.32 (1 H, dt, *J* 10.5 and 5.8, CH=CH), 5.39 (1 H, dt, *J* 10.5, 5.8, CH=CH), 7.29 (1 H, m, Ph) and 7.33 (4 H, m, Ph); δ_C(75 MHz, $CDCl_3$) 14.01 (CH_3), 22.57 (14-C), 25.74 (3-C), 27.03 (5-C), 27.10 (8-C), 29.21–29.65 (4-C, 9-C, 10-C, 11-C, 12-C, 2-C), 31.79 (13-C), 70.33 (1-C), 72.75 (1′-C), 127.35–128.21 (Ar–C), 129.49 (6-C) and 129.97 (7-C); *m*/*z* 316 (M^+, 25%) and 91 (100). Analysis of the product $\mathbf{14}_{cis}$ by capillary GC–MS indicated a purity of >99%.

trans-1-Benzyloxypentadec-6-ene 14_{trans}

The title compound was obtained by treating the *threo* isomer of 1-benzyloxy-7-diphenylphospinoylpentadecan-6-ol **13b** in a similar manner (0.47 g, 53%), bp 158–159 °C at 12 mmHg (Found: C, 83.7; H, 11.2. $C_{22}H_{36}O$ requires C, 83.5; H, 11.5%); ν_{max}/cm^{-1}(neat) 3088 (=CH) and 1620 (C=C); δ_H(300 MHz, $CDCl_3$) 0.88 (3 H, t, *J* 6.6, CH_3), 1.27 [13 H, m, 2-H, $CH_2(CH_2)_2OCH_2Ph$, $(CH_2)_5CH_3$], 1.38 (1 H, m, 2-H), 1.62 (4 H, m, 4-H, 9-H), 1.97 (4 H, m, 5-H, 8-H), 3.47 (2 H, t, *J* 6.7, CH_2OCH_2Ph), 4.50 (2 H, s, OCH_2Ph), 5.34 (1 H, dt, *J* 14.8, 6.0, CH=CH), 5.41 (1 H, dt, *J* 14.8, 5.9, CH=CH), 7.30 (1 H, m, Ph) and 7.34 (4 H, m, Ph); *m*/*z* (M^+, 36%) and 91 (100). Analysis of $\mathbf{14}_{trans}$ by capillary GC–MS indicated a purity of >99%.

cis- and *trans*-Pentadec-6-en-1-ol 15_{cis},15_{trans}

cis-1-Benzyloxypentadec-6-ene $\mathbf{14}_{cis}$ (3 g, 9.5 mmol) was cooled to −20 °C and liquid ammonia (100 cm^3) was added to it with stirring. Sodium (500 mg, 21.7 mmol) was then added portionwise to the mixture causing a blue coloration, after which stirring was continued for 1.5 h; during this time ammonia was allowed to evaporate. Ethanol (3 cm^3) was added to the mixture after which the solvent was removed under reduced pressure and saturated aqueous ammonium chloride (50 cm^3) was added to the residue. The mixture was extracted with diethyl ether (3 × 80 cm^3) and the extracts were dried (Na_2SO_4) and concentrated to yield the crude product as a red-orange oil. Purification of this by flash chromatography [10% diethyl ether–light petroleum (bp 40–60 °C) to 100% diethyl ether, gradient elution] afforded the product $\mathbf{15}_{cis}$ as a colourless oil, which crystallised with time to give a white solid (0.62 g, 29%), mp 45–47 °C (from pentane) (Found: C, 80.0; H, 13.6. $C_{15}H_{30}O$ requires C, 79.6; H, 13.4%); ν_{max}/cm^{-1}(KBr) 3350 (OH), 3030 (=C–H) and 1640 (C=C); δ_H(300 MHz, $CDCl_3$) 0.88 (3 H, t, *J* 6.9, CH_3), 1.27 [13 H, m, 2-H, 3-H, $CH_3(CH_2)_5$], 1.37 (1 H, m, 2-H), 1.57 (4 H, m, 4-H, 9-H), 2.01 (4 H, m, 5-H, 8-H), 3.64 (2 H, t, *J* 6.6, CH_2OH) and 5.35 (2 H, m, 6-H, 7-H); δ_C(75 MHz, $CDCl_3$) 14.00 (15-C), 22.56 (14-C), 25.26 (3-C), 27.02 (5-C), 27.11 (8-C), 29.07–29.63 (4-C, 9-C, 10-C, 11-C, 12-C), 31.78 (13-C), 32.57 (2-C), 62.89 (1-C), 129.37 (6-C) and 130.07 (7-C); *m*/*z* 226 (M^+, 25%) and 82 (100).

trans-Pentadec-6-en-1-ol 15_{trans}

The title compound was obtained by treatment of the *trans* alkene $\mathbf{14}_{trans}$ in a similar manner (0.23 g, 32%), mp 59–61 °C (from pentane) (Found: C, 79.3; H, 13.8. $C_{15}H_{30}O$ requires C, 79.6; H, 13.4%); ν_{max}/cm^{-1} (KBr) 3402 (OH); δ_H(300 MHz, $CDCl_3$) 0.88 (3 H, t, *J* 7.0, CH_3), 1.27 [13 H, m, 2-H, 3-H, $(CH_2)_5CH_3$], 1.39 (1 H, m, 2-H), 1.60 (4 H, m, 4-H, 9-H), 1.98 (4 H, m, 5-H, 8-H), 3.66 (2 H, t, *J* 6.7, CH_2OH) and 5.36 (2 H, m, 6-H, 7-H); δ_C(75 MHz, $CDCl_3$) 13.99 (15-C), 22.54 (14-C), 25.10 (3-C), 27.00 (5-C), 27.10 (8-C), 29.02–29.61 (4-C, 9-C, 10-C, 11-C, 12-C), 31.77 (13-C), 32.53 (2-C), 62.88 (1-C), 129.83 (6-C) and 130.56 (7-C); *m*/*z* 226 (M^+, 28%) and 82 (100).

cis- and *trans*-Pentadec-6-enal 16_{cis},16_{trans}

cis-Pentadec-6-en-1-ol $\mathbf{15}_{cis}$ (900 mg, 4 mmol) in anhydrous dichloromethane (10 cm^3) was added dropwise to a suspension of pyridinium chlorochromate (1.7 g, 8 mmol) in anhydrous dichloromethane (70 cm^3) and the resulting mixture was stirred at room temperature for 4 h. Diethyl ether (400 cm^3) was added to the mixture which was then filtered through a pad of Florisil and the filtrate evaporated. Purification of the mixture by flash chromatography [75% diethyl ether–light petroleum (bp 40–60 °C), as eluent] yielded the *cis* isomer $\mathbf{16}_{cis}$ as a yellow oil (0.72g, 81%), bp 93–95 °C at 12 mmHg (Found C, 80.5; H, 13.0. $C_{15}H_{28}O$ requires C, 80.3; H, 12.6%); ν_{max}/cm^{-1}(neat) 2855 (CH, aldehyde) and 1711 (C=O); δ_H(300 MHz, $CDCl_3$) 0.88 (3 H, t, *J* 6.9, CH_3), 1.28 [11 H, m, 3-H, $CH_3(CH_2)_5$], 1.38 (1 H, m, 3-H), 1.64 (4 H, m, 4-H, 9-H), 2.02 (4 H, m, 5-H, 8-H), 2.44 (2-H, t, *J* 1.9, CH_2CHO), 5.34 (2 H, m, 6-H, 7-H) and 9.78 (1 H, s, CHO); δ_C(75 MHz, $CDCl_3$), 13.91 (15-C), 21.50 (14-C), 22.49 (3-C), 26.69 (5-C), 27.06 (8-C), 28.86–29.54 (4 C, 9-C, 10-C, 11-C, 12-C), 31.72 (13-C), 43.60 (2-C), 128.68 (6-C), 130.39 (7-C) and 203.48 (1-C); *m*/*z* 224 (M^+, 45%) and 55 (100).

trans-Pentadec-6-enal $\mathbf{16}_{trans}$ was obtained by the oxidation of the *trans* alcohol $\mathbf{15}_{trans}$, in a similar manner (0.23g, 78%), bp 112–115 °C at 10 mmHg (Found: M^+, 224.2141. $C_{15}H_{28}O$ requires *M*, 224.2140); ν_{max}/cm^{-1}(neat) 1730 (C=O); δ_H(300 MHz, $CDCl_3$) 0.88 (3 H, t, *J* 6.9, CH_3), 1.27 [11 H, m, 3-H, $(CH_2)_5CH_3$], 1.38 (1 H, m, 3-H), 1.63 (4 H, m, 4-H, 9-H), 1.99 (4-H, m, 5-H, 8-H), 2.43 (2 H, t, *J* 2.0, CH_2CHO), 5.34 (2 H, m, 6-H, 7-H) and 9.78 (1 H, s, CHO); δ_C(75 MHz, $CDCl_3$) 13.91 (15-C), 21.35 (14-C), 22.49 (3-C), 26.68 (5-C), 27.02 (8-C), 28.82–29.54 (4-C, 9-C, 10-C, 11-C, 12-C), 32.05 (13-C), 43.61 (2-C), 129.16 (6-C), 130.93 (7-C) and 203.46 (1-C); *m*/*z* 224 (M^+, 36%) and 55 (100).

cis- and *trans*-1-Ethoxy-1-(1′-hydroxypentadec-6′-enyl)cyclopropane 18_{cis},18_{trans}

tert-Butyllithium (1.7 mol dm^{-3} solution in pentane; 4.0 cm^3, 6.9 mmol) was added by syringe to anhydrous diethyl ether (20 cm^3), which was stirred at −78 °C under an atmosphere of nitrogen. Freshly prepared 1-bromo-1-ethoxycyclopropane[15] **17** (470 mg, 2.9 mmol) was added to the chilled solution over 5 min and the resulting pale yellow mixture was stirred for 20 min. *cis*-Pentadec-6-enal $\mathbf{16}_{cis}$ (400 mg, 1.8 mmol) in anhydrous diethyl ether (3 cm^3) was added to the reaction mixture which was then stirred at −78 °C for an additional

15 min. Upon warming to 0 °C, the mixture was treated with ice and saturated aqueous ammonium chloride (5 cm^3). The layers were shaken and separated, and the aqueous phase was extracted with diethyl ether (3 × 20 cm^3). The combined organic layer and extracts were dried ($MgSO_4$) and concentrated under reduced pressure to yield a brown oil, purification of which by flash chromatography on silica gel [light petroleum (bp 40–60 °C)–5% diethyl ether→light petroleum, gradient elution] yielded the *cis* compound **18**$_{cis}$ (340 mg, 62%), mp 57–58 °C (from pentane) (Found: M^+, 310.2881. $C_{20}H_{38}O$ requires *M*, 310.2872); ν_{max}/cm^{-1}(KBr) 3442 (OH), 3089 and 3008 (cyclopropyl); δ_H(300 MHz, $CDCl_3$) 0.60 (2 H, m, cyclopropyl), 0.82 (2 H, m, cyclopropyl), 0.88 (3 H, t, *J* 7.1, 15-H), 1.14 (3 H, t, *J* 7.0, OCH_2CH_3), 1.37 [15 H, m, 3′-H, 4′-H, $(CH_2)_6CH_3$], 1.53 (3 H, m, 2′-H, 3′-H), 1.79 (1 H, br s, OH, disappears on D_2O shake), 2.03 (4 H, m, 5′-H, 8′-H), 3.50 (2 H, m, OCH_2CH_3, CHOH), 3.73 (1 H, dq, *J* 7.0 and 9.1, OCH_2CH_3) and 5.36 (2 H, m, 6′-H, 7′-H); δ_C(75 MHz, $CDCl_3$) 9.80 (2-C), 10.69 (3-C), 14.01 (15′-C), 15.90 (OCH_2CH_3), 22.58 (14′-C), 25.30 (3′-C), 27.01 (5′-C), 27.14 (8′-C), 29.10–29.70 (4′-C, 9′-C, 10′-C, 11′-C, 12′-C), 31.82 (13′-C), 32.65 (2′-C), 63.86 (OCH_2CH_3), 64.50 (1-C), 74.72 (1′-C), 129.45 (6′-C) and 130.10 (7′-C); *m*/*z* 310 (M^+, 22%) and 116 (100).

The analogous *trans* compound **18**$_{trans}$ was prepared from the *trans* aldehyde **16**$_{trans}$ in a similar manner (0.224 g, 65%), mp 68–70 °C (from pentane) (Found: C, 77.8; H, 12.1. $C_{20}H_{38}O_2$ requires C 77.3; H 12.3%); ν_{max}/cm^{-1} (KBr) 3465 (OH), 3089 and 3010 (cyclopropyl); δ_H(300 MHz, $CDCl_3$), 0.58 (2 H, m, cyclopropyl), 0.82 (2 H, m, cyclopropyl), 0.88 (3 H, t, *J* 7.0, CH_3), 1.13 (3 H, t, *J* 6.9, CH_2CH_3), 1.37 [15 H, m, 3′-H, 4′-H, $(CH_2)_6CH_3$], 1.53 (3 H, m, 2′-H, 3′-H), 2.02 (4 H, m, 5′-H, 8′-H), 3.51 (2 H, m, OCH_2CH_3, CHOH), 3.72 (1 H, dq, *J* 6.9 and 9.0, OCH_2CH_3) and 5.37 (2 H, m, 6′-H, 7′-H); δ_C(75 MHz, $CDCl_3$) 9.80 (2-C), 10.66 (3-C), 13.99 (15′-C), 15.90 (OCH_2CH_3), 22.57 (14′-C), 25.28 (3′-C), 27.00 (5′-C), 27.11 (8′-C), 29.07–29.72 (4′-C, 9′-C, 10′-C, 11′-C, 12′-C), 31.81 (13′-C), 32.61 (2′-C), 63.85 (OCH_2CH_3), 64.49 (1-C), 74.68 (1′-C), 130.01 (6′-C) and 130.62 (7′-C); *m*/*z* 310 (M^+, 35%) and 116 (100).

cis- and *trans*-2-Tetradec-5′-enylcyclobutanone 3$_{cis}$,3$_{trans}$

To a stirred solution of compound **18**$_{cis}$ (585 mg, 1.9 mmol) in diethyl ether (30 cm^3) was added 48% aqueous fluoboric acid (1.5 cm^3, 11.3 mmol). The reaction mixture was stirred at room temperature for 4 days and then treated with aqueous sodium carbonate (1 mol dm^{-3}; 5 cm^3) to quench the reaction. The layers were shaken and separated and the organic phase was washed with water (3 × 15 cm^3) and the washings were combined and extracted with diethyl ether. The combined ethereal extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (hexane–3.5% ethyl acetate→hexane, gradient elution) to yield *cis*-2-tetradec-5′-enylcyclobutanone **3**$_{cis}$ (320 mg, 65%), mp 25–26 °C (Found: C, 82.1; H, 12.6. $C_{18}H_{32}O$ requires C, 81.7; H, 12.2%); ν_{max}/cm^{-1}(neat) 2926 and 2854 (CH), 1782 (C=O) and 1651 (C=C); ν_{max}/cm^{-1}-(GC–IR) 2900 (CH) and 1798 (C=O); δ_H(500 MHz, $CDCl_3$) 0.88 (3 H, t, *J* 6.9, CH_3), 1.27 [15 H, m, 2′-H, 3′-H, $(CH_2)_6CH_3$], 1.35 (1 H, m, 2′-H), 1.47 (1 H, m, 1′-H), 1.58–1.73 (2 H, m, 1′-H, 3-H), 2.01 (4 H, m, 4′-H, 7′-H), 2.17 (1 H, m, 3-H), 2.91 (1 H, m, 4-H), 3.02 (1 H, m, 4-H), 3.29 (1 H, m, 2-H) and 5.35 (2 H, m, 5′-H, 6′-H); δ_C(75 MHz, $CDCl_3$) 14.01 (CH_3), 16.80 (3-C), 22.57 (13′-C), 26.03 (2′-C), 26.89 (4′-C), 27.12 (7′-C), 29.07–29.64 (1′-C, 3′-C, 8′-C, 9′-C, 10′-C, 11′-C), 31.79 (12′-C), 44.30 (4-C), 60.47 (2-C), 129.28 (5′-C), 130.14 (6′-C) and 212.63 (1-C); *m*/*z* (GC–MS) 264 (M^+, 10%), 98 (56) and 41 (100). Analysis of the product **3**$_{cis}$ by capillary GC indicated a purity of > 99%.

trans-2-Tetradec-5′-enylcyclobutanone **3**$_{trans}$ was prepared from **18**$_{trans}$ in an identical manner (0.115g, 60%), mp 37–39 °C (from pentane) (Found: C, 82.0; H, 12.1. $C_{18}H_{32}O$ requires C, 81.7; H, 12.2%); ν_{max}/cm^{-1}(KBr) 2938 and 2846 (CH), 1760 (C=O) and 1642 (C=C); ν_{max}/cm^{-1}(GC–IR) 2900 (CH) and 1798 (C=O); δ_H(500 MHz, $CDCl_3$) 0.88 (3 H, t, *J* 6.9, CH_3), 1.27 [15 H, m, 2′-H, 3′-H, $(CH_2)_6CH_3$], 1.34 (1 H, m, 2′-H), 1.49 (1 H, m, 1′-H), 1.60–1.73 (2 H, m, 1′-H, 3-H), 2.01 (4 H, m, 4′-H, 7′-H), 2.17 (1 H, m, 3-H), 2.91 (1 H, m, 4-H), 3.01 (1 H, m, 4-H), 3.28 (1 H, m, 2-H) and 5.35 (2 H, m, 5′-H, 6′-H); δ_C(75 MHz, $CDCl_3$) 13.99 (CH_3), 16.79 (3-C), 22.57 (13′-C), 26.01 (2′-C), 26.90 (4′-C), 27.11 (7′-C), 29.05–29.66 (1′-C, 3′-C, 8′-C, 9′-C, 10′-C, 11′-C), 31.79 (12′-C), 44.29 (4-C), 60.49 (2-C), 129.73 (5′-C), 130.61 (6′-C) and 212.48 (1-C); *m*/*z* (GC–MS) 264 (M^+, 10%), 98 (58) and 41 (100). Analysis of the product **3**$_{trans}$ by capillary GC indicated a purity of > 99%.

12-Benzyloxydodecanol 20

Dodecane-1,12-diol **19** (5.0 g, 24.8 mmol) was added to benzyl bromide (50 cm^3) and the resulting suspension was heated to 100 °C under nitrogen. The heat was removed and sodium hydride (60% dispersion in oil; 1.0 g, 25 mmol) was added portionwise to the reaction mixture whilst it was stirred. Hydrogen was evolved and sodium bromide formed. The reaction mixture was heated at 100 °C for a further 4 h and then cooled, filtered and concentrated by removal of the excess of benzyl bromide by distillation under an aspirator vacuum to yield the crude product **20** as an orange solid. Purification of this by flash chromatography on silica gel [2:1, light petroleum (bp 40–60 °C)–diethyl ether as eluent] followed by recrystallization from light petroleum (bp 40–60 °C) gave the *title compound* **20** (3.53 g, 49%), mp 34–35 °C (Found: C, 77.9; H, 11.0. $C_{19}H_{32}O_2$ requires C, 78.1; H, 11.0%); ν_{max}/cm^{-1}(KBr) 3427br (OH); δ_H(300 MHz, $CDCl_3$) 1.27 [14 H, m, $(CH_2)_7$], 1.58 [6 H, m, $(CH_2)_3$], 3.46 (2 H, t, *J* 6.5, CH_2OCH_2Ph), 3.64 (2 H, t, *J* 6.5, CH_2CH_2OH), 4.50 (2 H, s, OCH_2Ph), 7.28 (1 H, m, Ph) and 7.34 (4 H, m, Ph); *m*/*z* 292 (M^+, 10%) and 91 (100).

12-Benzyloxydodecanal 21

Pyridinium chlorochromate (2.5 g, 11.6 mmol) was added to a solution of compound **20** (3.4 g, 11.6 mmol) in dry dichloromethane (80 cm^3) and the resulting suspension was stirred at room temperature for 2 h. A second portion of pyridinium chlorochromate (1.25 g, 5.8 mmol) was added to the mixture which was then stirred for a further 2 h before being filtered through a pad of Florisil and evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel [2:1, light petroleum (bp 40–60 °C)–diethyl ether as eluent]. Recrystallization of the product from light petroleum (bp 40–60 °C) with refrigeration gave the title compound **21** as a low-melting solid (2.7 g, 80%), mp 18–20 °C (Found: C, 78.3; H, 10.5. $C_{19}H_{30}O_2$ requires C, 78.6; H, 10.3%); ν_{max}/cm^{-1}(neat) 1725s (C=O); δ_H(300 MHz, $CDCl_3$) 1.27 [14 H, m, $(CH_2)_7$], 1.61 [4 H, m, $(CH_2)_2$], 2.41 (2 H, t, *J* 6.6, CH_2CHO), 3.46 (2 H, t, *J* 6.6, CH_2OCH_2Ph), 4.50 (2 H, s, OCH_2Ph), 7.28 (1 H, m, Ph), 7.34 (4 H, m, Ph) and 9.76 (1 H, s, CHO); *m*/*z* 290 (M^+, 9%) and 91 (100).

1-(12′-Benzyloxydodecyl)-1-ethoxycyclopropane 22

The title compound **22** was prepared from 1-bromo-1-ethoxycyclopropane[15] **17** (2.3 g, 13.9 mmol) and 12-benzyloxydodecanal **21** (2.5 g, 8.6 mmol) in the presence of *tert*-butyllithium (1.7 mol dm^{-3} solution in pentane; 15.3 cm^3, 26 mmol), under conditions identical with those used in the preparation of compound **18**$_{cis}$. The crude product was purified by flash chromatography (5–7.5% ethyl acetate–hexane, gradient elution) and crystallized from pentane at 0 °C (1.55 g, 47%), mp 36–37 °C (Found: C, 76.6; H, 10.9. $C_{24}H_{40}O_3$ requires C, 76.6; H, 10.6%); ν_{max}/cm^{-1}(KBr) 3459br (OH); δ_H(500 MHz, $CDCl_3$) 0.59 (2 H, m, cyclopropyl), 0.81 (2 H, m, cyclopropyl), 1.14 (3 H, t, *J* 7.1, OCH_2CH_3), 1.26 [12 H, m, $(CH_2)_6$], 1.50 [4 H, m, $(CH_2)_2$], 1.60 [4 H, m, $(CH_2)_2$],

1.78 (1 H, br s, OH, disappears on D_2O shake), 3.48 (4 H, m, C*H*OH, OC*H*HCH$_3$, CH_2OCH$_2$Ph), 3.73 (1 H, m, OCH*H*CH$_3$), 4.50 (2 H, s, OCH_2Ph), 7.28 (1 H, m, Ph) and 7.34 (4 H, m, Ph); *m/z* 376 (M^+, 0.3%) and 91 (100).

2-(11′-Benzyloxyundecyl)cyclobutanone 23

Compound **22** (1.5 g, 4 mmol) was treated in a similar manner to cyclopropane **18**$_{cis}$ with 48% aqueous fluoroboric acid (2.4 cm^3, 17.8 mmol). The crude product was purified by flash chromatography on silica gel [0–10% diethyl ether–petroleum (bp 40–60 °C) gradient elution] to give the *title compound* **23** (0.88 g, 67%), mp 43–44 °C (from pentane) (Found: C, 79.8; H, 10.5. $C_{22}H_{34}O_2$ requires C, 80.0; H, 10.3%); ν_{max}/cm^{-1}(GC–IR) 1797s (C=O); δ_H(500 MHz, $CDCl_3$) 1.26 [16 H, m, $(CH_2)_8$], 1.47 (1 H, m, 3-H), 1.63 [4 H, m, $(CH_2)_2$], 2.17 (1 H, m, 3-H), 2.92 (1 H, m, 4-H), 3.00 (1 H, m, 4-H), 3.27 (1 H, m, 2-H), 3.46 (2 H, t, *J* 6.7, CH_2OCH$_2$Ph), 4.50 (2 H, s, OCH_2Ph), 7.27 (1 H, m, Ph) and 7.34 (4 H, m, Ph); *m/z* 330 (M^+, 4%), 98 (22) and 91 (100).

11-(2′-Oxocyclobutyl)undecanol 24

10% Palladium-on-charcoal (100 mg) was added to a solution of compound **23** (400 mg, 1.2 mmol) in ethyl acetate (20 cm^3) and the mixture was shaken at room temperature under an hydrogen atmosphere of 55 psi. The hydrogen was removed and the mixture was filtered through Celite and the filtrate evaporated under reduced pressure to give the *title compound* **24** (0.29 g, 100%), mp 52–53 °C (from pentane–diethyl ether) (Found: C, 75.0; H, 11.9. $C_{15}H_{28}O_2$ requires C, 75.0; H, 11.7); ν_{max}/cm^{-1}(GC–IR) 1797s (C=O); δ_H(500 MHz, $CDCl_3$) 1.27 [16 H, m, $(CH_2)_8$], 1.49 (1 H, m, 3′-H), 1.56 (2 H, m, CH_2), 1.67 (2 H, m, CH_2), 2.17 (1 H, m, 3′-H), 2.92 (1 H, m, 4′-H), 3.01 (1 H, m, 4′-H), 3.28 (1 H, m, 2′-H) and 3.65 (2 H, t, *J* 6.6, CH_2OH); *m/z* 240 (M^+, 1.2%) and 98 (100).

11-(2′-Oxocyclobutyl)undecanoic acid 5

Freshly prepared dimethyldioxirane[16] (0.08 mol dm^{-3} in acetone; 26 cm^3, 2.08 mmol) was added to a stirred solution of compound **24** (0.25 g, 1.04 mmol) in acetone (6 cm^3) at 0 °C. After the mixture had been stirred at 0 °C for 2 h a further portion of dimethyldioxirane (13 cm^3, 1.04 mmol) was added to it and stirring continued at 0 °C for 2 h and then at room temperature overnight. The mixture was then evaporated under reduced pressure and the crude product taken up in dichloromethane and the solution dried ($MgSO_4$) and evaporated to give the title compound **5** (0.24 g, 91%), mp 75–77 °C (from diethyl ether) (Found: C, 70.6; H, 9.9. $C_{15}H_{26}O_3$ requires C, 70.9; H, 10.2); ν_{max}/cm^{-1}(KBr) 1769s (C=O) and 1690s (C=O); δ_H(500 MHz, $CDCl_3$) 1.26 [14 H, m, $(CH_2)_7$], 1.48 (1 H, m, 3′-H), 1.64 [4 H, m, $(CH_2)_2$], 2.17 (1 H, m, 3′-H), 2.35 (2 H, t, *J* 7.4, CH_2CO$_2$H), 2.91 (1 H, m, 4′-H), 3.00 (1 H, m, 4′-H) and 3.28 (1 H, m, 2′-H); δ_C(125 MHz, $CDCl_3$) 16.87 (3-C), 24.64 (9′-C), 26.98 (2′-C), 28.99–29.51 (1′-C, 3′-C, 4′-C, 5′-C, 6′-C, 7′-C, 8′-C), 33.97 (10′-C), 44.36 (4-C), 60.47 (2-C), 179.73 (CO_2H) and 212.73 (1-C); *m/z* (GC–MS) 254 (M^+, 1.1%) and 98 (100).

Compound **5** was treated with diazomethane to give the methyl ester; ν_{max}/cm^{-1}(GC–IR) 1797s (C=O), 1760s (C=O) and 1173s (C–O); *m/z* 237 ($M^+ - OCH_3$, 5%) and 98 (100).

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