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The Singlet Oxygen Conversion of Oxazoles to Triamides. Application in the Synthesis of (±)-Pyrenolide C. Assignment of Stereochemistry.

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Abstract: Pyrenolide C has been synthesized for the first time using an oxazole template to construct the framework of the ten-membered unsaturated lactone system. The stereochemical assignment of the allylic alcohol substituent, based on the mode of synthesis, has been confirmed by NMR studies.

The conversion of oxazoles to triamides by singlet oxygen is a general reaction which takes place in high yields under the mild conditions of dye-sensitized photooxidation. In the rearrangement, each carbon atom of the oxazole ring is converted to a carbonyl group which, as part of the triamide functionality, shows enhanced reactivity toward nucleophilic attack.[1]

We have previously employed this reaction in the synthesis of macrocyclic lactones such as antimycin A_3,[1a] building up the framework of the target molecule by electrophilic substitution at the 2-methyl group of the starting 2-methyl-4,5-diphenyloxazole. Lactone formation was achieved in the final steps of the procedure by photooxidation of the oxazole to the triamide followed by selective intramolecular attack at the acyl carbonyl by a ω-hydroxyl group. In the above process, the substituted oxazole ring served as the equivalent of an activated acetic acid carbanion (Figure 1). In the present studies on the synthesis of pyrenolide C described below, we have extended the use of diphenylmethyloxazoles as templates for macrolide formation to cases where the heterocyclic system plays the role of an activated acetic acid carbonium ion equivalent (Figure 2).[2]

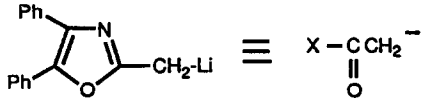


Figure 1

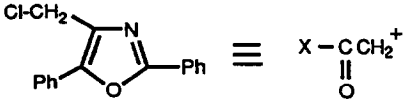
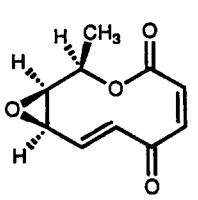
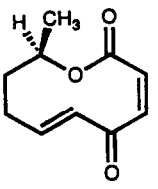


Figure 2

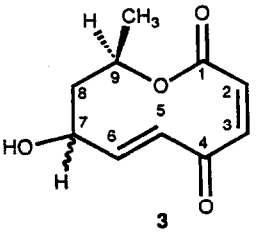
The bioactive substances recently isolated by Nukina from *Pyrenophora teres*, pyrenolides A (**1**), B (**2**) and C (**3**),[2] are highly functionalized unsaturated lactones which inhibit hyphae growth of phytopathogenic fungi and are therefore of interest as antifungal agents. Each of these systems has a secondary methyl group in the (R) configuration at C-9 and the 2,3-Z, 5,6-E-diene dione unsaturated grouping in common, and differ only in the pattern of substitution at the C_7-C_8 positions. Thus far, only the synthesis of pyrenolide B has been reported.[4]



1



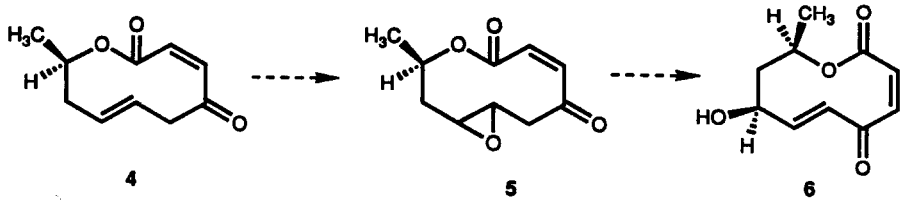
2



3

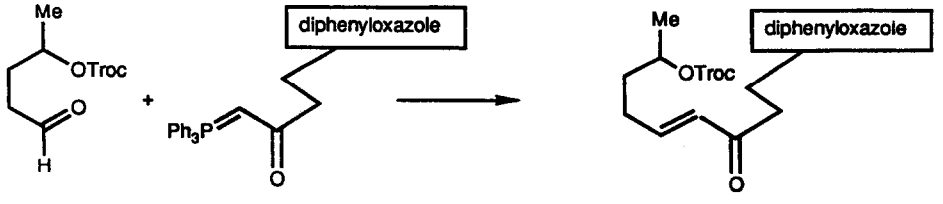
We chose pyrenolide C as our objective for synthesis, using a route which would provide an application of the oxazole template methodology in the formation of a polyfunctional, ten-membered macrolide, and also serve as a vehicle for clarifying the remaining stereochemical ambiguity at C-7.

Our strategy for generating the target lactone involved the formation of the 2,3-Z, 6,7-E-unsaturated keto lactone **4** which we would then transform to the corresponding epoxide **5** for base-promoted eliminative ring-opening to the allyl alcohol **6**. Conversion of epoxides to allyl alcohols by β-elimination processes is a well-documented reaction,[5] and, in this case, the regiochemistry of epoxide opening would be controlled by participation of the more acidic protons alpha to the carbonyl group. Considering the most probable conformation of the intermediate alkene product **4**, one could quite reasonably predict the course of the epoxidation, and the stereochemistry of the ring-opening accompanying β-elimination. This result would then give insight as to the stereochemical relationship between the (R) secondary methyl group and the allyl alcohol, a question left unresolved by Nukina in his studies on the pyrenolides.



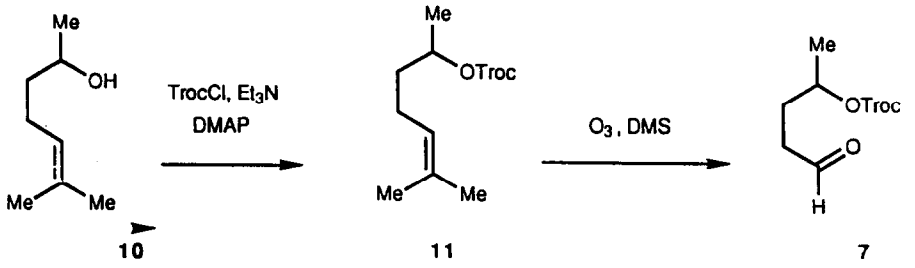
4 5 6

In the first stage of the synthesis, we planned to couple aldehyde **7** with a diphenyloxazole-ylide **8** to form the α,β-unsaturated ketone **9**, containing a protected ω-hydroxyl group suitably disposed for the formation of the ten-membered macrolide. To prepare aldehyde **7**, commercially available 6-methyl-5-heptene-2-ol **10** was treated with 2,2,2-trichloroethyl chloroformate and triethylamine in the presence of DMAP catalyst to form the Troc-protected derivative **11** which was subjected to ozonolysis in a methylene chloride/methanol mixture generating **7** in 81% overall yield (Scheme 1).



7 8 9

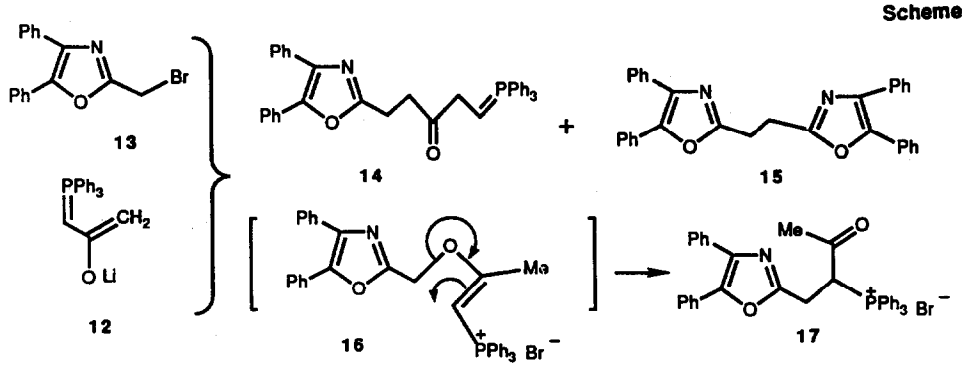
Scheme 1



10 11 7

The oxazole ylide fragment was originally envisioned as a simple alkylation product of the appropriate enolate and 2-bromomethyl-4,5-diphenyloxazole (**13**). The enolate of choice (**12**) was derived from commercially available 1-triphenylphosphoranylidene-2-propanone. Cooke and Wolfe[6] have reported that this enolate anion reacts smoothly with alkyl halides, aldehydes, ketones and esters. More electrophilic species such as TMSCl and methyl iodide yield a mixture of C- and O- alkylation products. The precedent for anionic displacement of a bromide in the 2-methyl position of an oxazole was derived from our earlier work in the synthesis of polyether lactones where the displacement of bromide in **13** by an alkoxide salt readily yielded the corresponding ether.[1b]

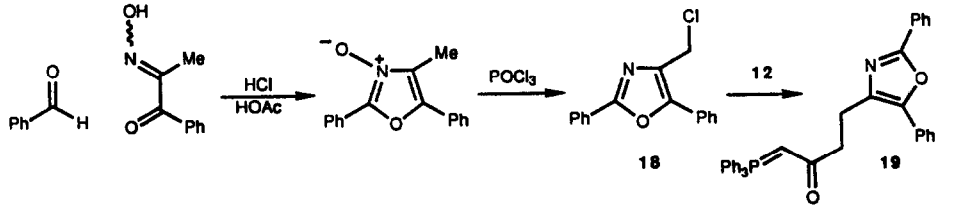
Scheme 2



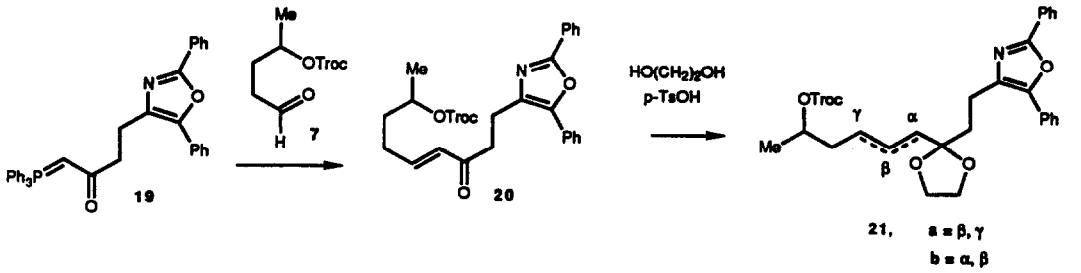
The reaction of enolate **12** with **13**, however, was accompanied by many side reactions and resulted in unsatisfactory yields of the desired product **14**. One complication was due to the generation of the bis-methyloxazole **15**, most probably by lithium-halogen exchange, followed by rapid coupling with a second molecule of bromooxazole. Another side-reaction involved formation of **17**, most probably through the O-acylated intermediate **16** (Scheme 2).

It appeared that the stability of the α-anion at the 2-oxazole position militated against carbon-carbon bond formation in the reaction of the ylide **12** with the 2-bromomethyl derivative **13**. We therefore turned to the 4-halomethyl oxazole derivative **18** since it was expected that a carbanion formed by metal-halogen exchange at that position would enjoy less stabilization. Accordingly, 4-chloromethyl-2,5-diphenyloxazole (**18**) was prepared from 1-phenyl-1,2-propanedione-2-oxime by the method of Goto[7] (Scheme 3). For our needs, this derivative served the same purpose as the 2-bromomethyl isomer, since photooxidation of the oxazole converts each of the carbon atoms at C-2, C-4, and C-5 to the carbonyl groups of the triamide. When enolate **12** was treated with **18** in THF at -78 °C to -20 °C, the oxazole ylide **19** was formed cleanly (91%) without the unwanted side reactions.

Scheme 3



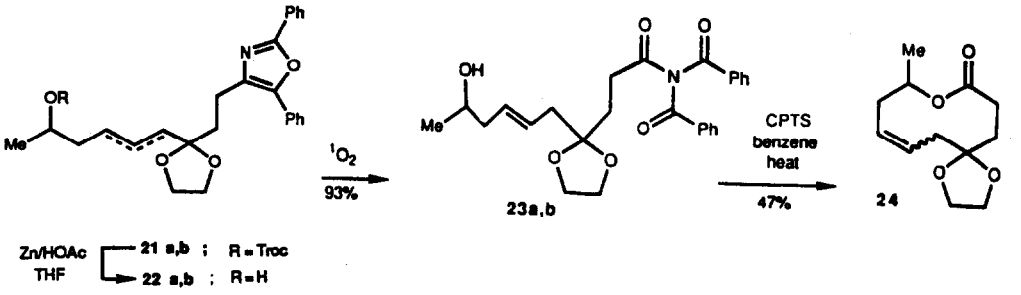
Scheme 4



Stabilized Wittig coupling of ylide **19** with aldehyde **7** in toluene at 60 °C formed the E-enone **20** (80%). At this stage, it was desirable to shift the alkene into the β,γ position as required for the synthesis of **3**. At the same time, it was necessary to protect the ketone because of the possibility that the alkene might shift back into conjugation in the subsequent cyclization step. Both of these requirements were satisfied by the ketalization of the enone carbonyl with ethylene glycol (Scheme 4). In this way, a mixture (98%) of ketals **21a** and **21b** was formed containing a favorable (4:1) ratio of β,γ- to α,β-isomers.

The synthesis was continued (Scheme 5) without separation of ketals **21a** and **21b**. The Troc protecting group was removed with zinc in 10% acetic acid/THF to give alcohols **22a** and **22b** (89%) (4:1; β,γ: α,β) which was then treated with oxygen, light and sensitox for 1 h to form the triamides, **23a** and **23b** in 93% isolated yield. The triamides were then warmed in benzene (80 °C) in the presence of collidine *p*-toluenesulfonate to provide lactone **24** (47%) as a mixture of *cis* - and *trans* -β,γ-isomers.[8] None of the α,β-unsaturated isomers were observed after the cyclization step.[13]

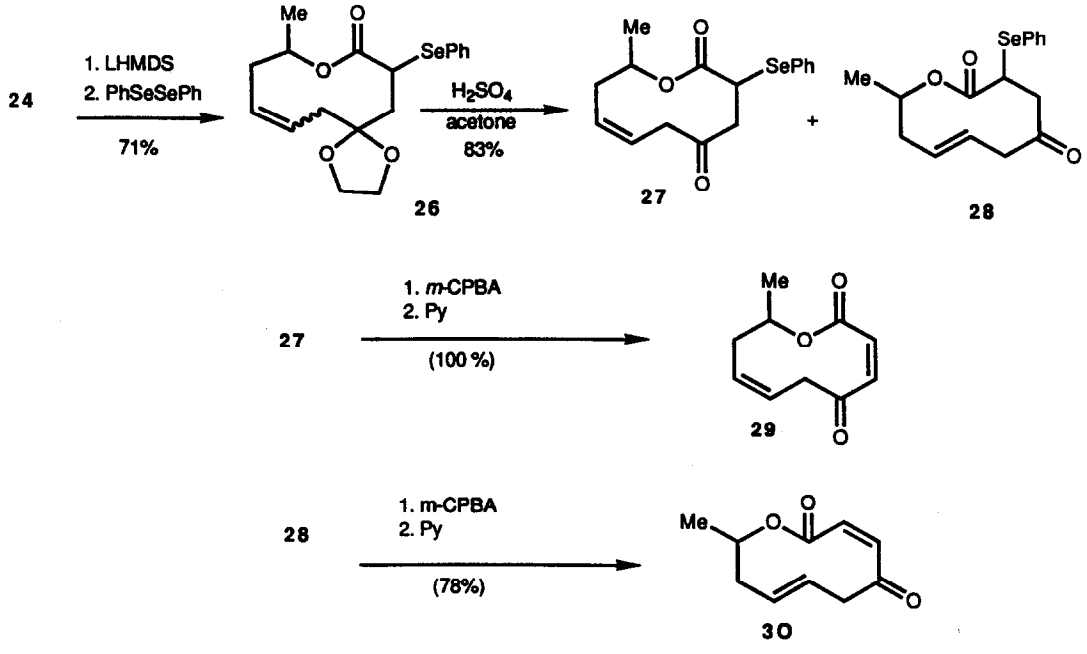
Scheme 5



Formation of the Z-olefin at the 2,3-position was the next problem to address. Examination of Dreiding models showed that with one unit of unsaturation already in the ring system, formation of a *trans*-ene dione unit at the C_1-C_4 segment of the molecule would introduce greater steric congestion than that due to the corresponding *cis*-ene dione alternative. We therefore expected that a selenation-oxidation/elimination sequence would lead predominantly to the Z-alkene.

In order to introduce the Z-double bond at the 2,3-position, **24** was treated with lithium bis-trimethylsilylamide and diphenyl diselenide, forming the α-selenolactone **26** (71%) as a mixture of *cis* and *trans* - isomers (Scheme 6). Reaction of **26** with acetone/H_2SO_4 at 60 °C for two days then gave deketalized products *cis*-**27** and *trans*-**28** in 83% combined yield. These isomers could now be separated by flash chromatography to yield **27** (43%) and **28** (57%). Each of the selenium derivatives was then subjected to oxidation with *m*-CPBA at -40 °C followed by treatment with pyridine.[9] The elimination step occurred readily on warming to room temperature, providing, exclusively, the Z-alkene for each isomer: **29** (100%), **30** (78%) (Scheme 6).[10]

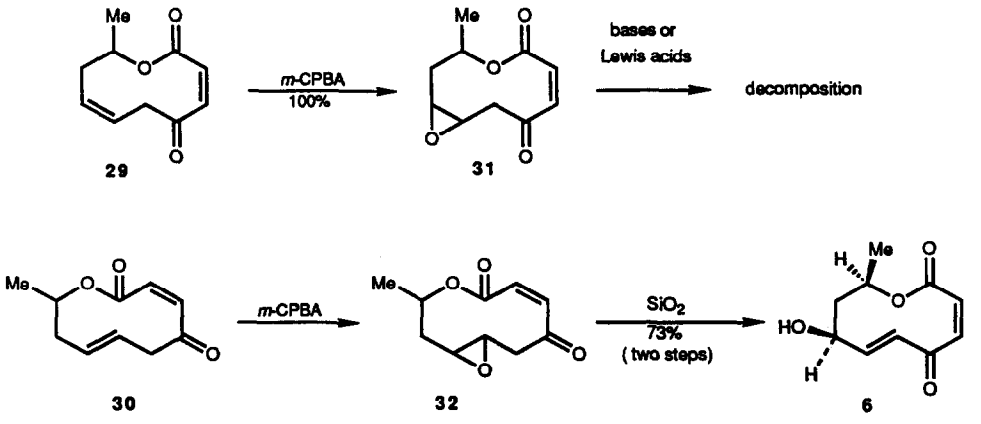
Scheme 6



In the final steps of the synthesis , the epoxidation and eliminative openings for both the *cis*-and *trans*-products were carried out separately as shown in Scheme 7. In the case of the *cis*-alkene **29**, epoxidation with *m*-CPBA gave the *cis*-epoxide **31** in 100% yield. Various conditions were tried to open the epoxide. Use of bases such as sodium *t*-butoxide and DBU resulted in the formation of many products and low mass recovery. In a synthesis of pyrenophorin, Fujitsawa opened a similar system with ethyl-α-trimethylsilyl acetate/*n*-Bu_4NF. When these conditions were applied to *cis*-epoxide **31**, the results were identical to those obtained with stronger bases. Using a Lewis acid such as $FeCl_3$-SiO_2 resulted only in destruction of the starting material.

On the other hand, the *trans*-alkene **30** provided favorable results. The epoxidation with *m*-CPBA gave a quantitative conversion to the *trans*-epoxide **32**, which, in the presence of silica gel, underwent ready rearrangement to a UV-active product which co-spotted with natural pyrenolide C. When the crude epoxide was passed through a packed silica gel column and eluted with mixtures of ether/hexanes, pure product **6** (73%) was obtained which was identical in all respects to natural pyrenolide C.[11]

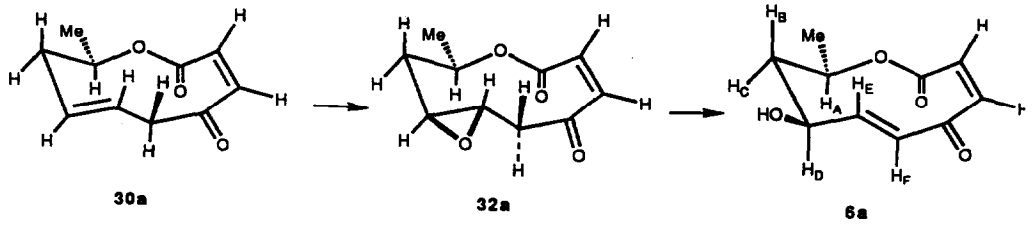
Scheme 7



Stereochemical Determination of Pyrenolide C

The relative stereochemistry between the allyl alcohol and the secondary methyl group was the last problem to be solved. Since the secondary methyl groups in all of these types of compounds are known to be in the (R) configuration it was only necessary to determine if the hydroxy group was *syn*-or *anti*-to the methyl group.

The first indication of a *syn*-relationship between the hydroxyl and methyl groups came from the epoxide-opening reaction. The predicted conformation of *trans*-alkene **30** based on the Dreiding models is shown as **30a**. The corresponding *trans*-epoxide is represented as **32a**. In order for the eliminative opening to give a *trans*-α,β-enone system, the proton abstraction and ring opening would have to follow the indicated course where the hydroxy and methyl groups are *syn*- to one another.



Confirmation of this conclusion was obtained from extensive decoupling experiments at 250 and 500 MHz on the synthetic compound. After the connectivity and proton assignments (A-H) were established, the coupling constants for each set of protons were allotted. Examination of the coupling constants and the corresponding angles estimated from a Karplus diagram for vicinal protons[12] suggested that protons A and B are *ca.* 160-180 ° apart, as are protons B and D. It follows that protons A and D are *syn*- to one another, and therefore the corresponding methyl and hydroxy groups are *syn*.

Final, conclusive evidence was obtained from an NOE experiment performed on product **6**. When proton D was irradiated, enhancement was observed at protons C (5.3%), F (8.5%) and A (5.3%). The converse experiment, irradiation of proton A, gave enhancement at protons C (5.5%), -CH_3 (5.5%) and D (5.3%). The enhancement of protons A and D in the NOE indicated that these protons are indeed *syn* -to one another, hence, the methyl and hydroxy also have a *syn*-relationship.

Based on the information presented, the relative stereochemistry for pyrenolide C can unambiguously be assigned as shown in **6a**. The methyl group is known to be in the (R) configuration so the hydroxyl group must be in the (S) configuration.

EXPERIMENTAL

Melting points were determined using a Thomas-Hoover capillary melting point apparatus and are uncorrected. The ^1H NMR spectra were recorded on a Varian EM-390, Bruker WM-250, or Bruker WM-500 spectrometer operating at 90, 250, or 500 MHz respectively. The infrared (IR) spectra were recorded on a Perkin-Elmer 700A spectrophotometer. Mass spectra (MS) were obtained on a Hewlett-Packard GC 5840A/MS 5985A system. Non-volatile compounds were analyzed by direct input (DIP) whereas volatile compounds were analyzed by GC/MS. High resolution mass spectra were obtained at Yale University on a Kratos Ms-80 RFA system using direct input and electron ionization techniques unless noted by (CI) in which case chemical ionization was utilized.

Reaction solvents and reagents were prepared for use as follows. Dichloromethane, triethylamine and diisopropylamine were distilled from calcium hydride. Toluene, benzene and tetrahydrofuran were distilled from potassium/benzophenone. Ethyl acetate was distilled prior to use. Unless otherwise noted, all other reagents were utilized as obtained by the suppliers. Throughout this work 1/3 saturated $NaHCO_3$ refers to a 1:2 mixture of saturated aqueous $NaHCO_3$:H_2O. Solutions dried as (pentane, Na_2SO_4) refer to adding pentane to a diethyl ether solution until it turned cloudy, followed by addition of Na_2SO_4.

4-Chloromethyl-2,5-diphenyloxazole (18). To a magnetically stirred solution of 4-methyl-2,5-diphenyloxazole N-oxide (10.0 mmole, 2.51 g) in $CHCl_3$ (10 mL) under nitrogen at room temperature was added dropwise *via* addition funnel a solution of $POCl_3$ (11.0 mmole, 1.02 mL) in $CHCl_3$ (10 mL). When addition was complete, the reaction was heated to reflux and then stirred for 30 min. The solution was cooled to 0 °C, then made slightly basic by addition of NH_4OH (conc.). Water (50 mL) was added and the solution extracted with $CHCl_3$ (2 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered through cotton, and concentrated *in vacuo* to a yellow solid. Pure 4-chloromethyl-2,5-diphenyloxazole was obtained by recrystallization from ethanol to give white crystals (1.66 g, 62%).

m.p. 138-139 °C, m.p. lit. 139 °C.[7] ^1H NMR (90 MHz, $CDCl_3$): δ 8.11 (m, 2H); 7.78 (m, 2H); 7.50 (m, 6H); 4.79 (s, 2H).

2-(2',2',2'-Trichloroethylcarbonoyl)-6-methyl-5-heptene (11). To a magnetically stirred solution of 6-methyl-5-hepten-2-ol (5.0 mmole, 641 mg), triethylamine (6.0 mmole, 0.84 mL) and 4-dimethylaminopyridine (cat.) in CH_2Cl_2 (50 mL) at room temperature under nitrogen was added 2,2,2-trichloroethyl chloroformate (5.5 mmole, 0.760 mL). The reaction was stirred for 24 h then diluted with CH_2Cl_2 (50 mL). The solution was extracted with 1N HCl (1 x 50 mL) and 1/3 saturated $NaHCO_3$ (1 x 60 mL). The organic layer was dried over Na_2SO_4, filtered through cotton, and concentrated *in vacuo* to a clear yellow oil. The pure product was obtained by gradient flash chromatography (SiO_2, petroleum ether → 2% Et_2O: petroleum ether) to yield a clear colorless oil (1.50 g, 99%).

b.p. *ca.* 145 °C at 0.3 mm Hg. ^1H NMR (250 MHz, $CDCl_3$): δ 5.08 (m, 1H); 4.85 (m, 1H); 4.76 (s, 2H); 2.10 (m, 2H); 1.76 (m, 2H); 1.69 (s, 3H); 1.59 (s, 3H); 1.33 (d, 3H, J = 6.3 Hz). IR ($CDCl_3$): 2980, 2950, 1760, 1450, 1380, 1270, 1120, 1060, 820 cm^{-1}. MS (20 eV, DIP) m/z (relative per cent): 111 (13.6); 110 (40.8); 96 (14.2); 95 (100.0); 81 (11.5); 69 (69.2); 68 (23.2); 67 (15.6).

HRMS (CI) Calcd. for $C_{11}H_{17}Cl_3O_3$ (+H): 303.0323; Found: 303.0318.

4-(2',2',2'-Trichloroethylcarbonoyl)pentanal (7). A solution of the Troc-hydroxyalkene (12.19 mmole, 3.70 g) and solid $NaHCO_3$ (*ca.* 100 mg) in a solution of 1:1/CH_2Cl_2:MeOH (abs.) (50 mL) was treated with ozone at -78 °C until the reaction turned a pale blue color. The system was then purged with nitrogen at -78 °C until the color vanished. Dimethylsulfide was added with stirring and the mixture slowly warmed to room temperature overnight. The $NaHCO_3$ was filtered off and the solvent removed *in vacuo*. The residue was taken up in CH_2Cl_2 (150 mL) then washed with 1/3 saturated $NaHCO_3$ solution (1 x 90 mL), dried over Na_2SO_4, filtered through cotton and concentrated *in vacuo*. The product was purified by flash chromatography (SiO_2, 3:1/petroleum ether:Et_2O) to give a clear colorless oil (2.77 g, 82%).

^1H NMR (250 MHz, $CDCl_3$): δ 9.79 (t, 1H, J = 1.1 Hz); 4.87 (m, 1H); 4.76 (s, 2H); 2.58 (t, 2H, J = 7.5 Hz); 2.00 (m, 2H); 1.36 (d, 3H, J = 6.2 Hz). IR ($CDCl_3$): 3090, 1760, 1730, 1385, 1260, 930, 820 cm^{-1}. MS (20 eV, DIP) m/z (relative per cent): 133 (30.5); 131 (31.4); 95 (12.8); 85 (100.0); 84 (43.7); 69 (10.6); 67 (21.1); 63 (12.2); 59 (15.6); 58 (12.7); 57 (22.2); 56 (98.7); 55 (14.3).

HRMS (CI) Calcd. for $C_8H_{11}Cl_3O_3$ (+H): 276.9799; Found: 276.9782.

4-(4-Triphenylphosphoranylidene-3-butanon)-2,5-diphenyloxazole (19). To a stirred solution of 1-triphenylphosphoranylidene-2-propanone (25.25 mmole, 8.04 g) in THF (250 mL) at -78 °C was added dropwise *n*-butyllithium (Aldrich, 1.5 M, 25.50 mmole, 17.0 mL in hexanes) until the faint red color of the anion persisted. A solution of 4-chloromethyl-2,5-diphenyloxazole (25.17 mmole, 6.79 g) in THF (100 mL) was added, *via* cannula, 15 min after complete addition of the *n*-butyllithium. The reaction was stirred for 1 h at -78 °C, then overnight at -20 °C. The color slowly changed from red to yellow. The reaction was quenched by addition of saturated aqueous NH_4Cl (25 mL). H_2O (250 mL) was added and the mixture extracted with Et_2O (2 x 250 mL). The organic layers were combined, dried (pentane, Na_2SO_4) and concentrated *in vacuo* to a yellow solid. Pure product was obtained by gradient flash chromatography (SiO_2, EtOAc→ 5% MeOH:EtOAc) to yield a white solid (10.2 g, 74%; 91% based on 1.35 g of recovered chloromethyloxazole).

m.p. 191-193 °C. ^1H NMR (250 MHz, $CDCl_3$): δ 8.10 (m, 2H); 7.79 (m, 2H); 7.62 (m, 6H); 7.40 (m, 15H); 3.80 (br d, 1H, J = 26.1 Hz); 3.23 (t, 2H); 2.88 (t, 2H). IR (CH_2Cl_2): 3055, 1540, 1490, 1440, 1400,

1110 cm^{-1}. MS (20 eV, DIP) m/z (relative per cent): M^+ 551 (1.5), 432 (27.1), 431 (100), 305 (13.0), 304 (59.9), 275 (10.4), 248 (26.0) 236 (18.0), 235 (98.1), 165 (17.5), 105 (10.5), 104 (12.5), 103 (28.8).

HRMS Calcd. for $C_{37}H_{30}NO_2P$: 551.2016; Found: 551.2014.

4-[3-Oxo-8-(2', 2', 2'-trichloroethylcarbonoyl)-4-E-nonenl-2,5-diphenyloxazole (20). A solution of the aldehyde **7** (8.6 mmole, 2.40 g) and the ylide **19** (8.6 mmole, 4.74 g) in dry toluene (40 mL) was heated to 60 °C and stirred under nitrogen (2 days). The reaction was cooled to room temperature and the toluene removed *in vacuo* to give a brown solid. The product was obtained by gradient flash chromatography (SiO_2, CH_2Cl_2→1% EtOAc:CH_2Cl_2→ 2% EtOAc:CH_2Cl_2→5% EtOAc:CH_2Cl_2) to yield a clear, viscous, slightly yellow oil (4.04 g, 80%).

^1H NMR (250 MHz, $CDCl_3$): δ 8.10-8.06 (m, 2H); 7.74-7.70 (m, 2H); 7.51-7.44 (m, 5H); 7.38-7.32 (m, 1H); 6.88 (dt, 1H, J = 16, 1 Hz); 6.18 (dt, 1H, J = 16, 1 Hz); 4.93-4.80 (m, 1H); 4.77 (s, 2H); 3.25-3.05 (m, 4H); 2.45-2.20 (m, 2H); 1.90-1.74 (m, 2H); 1.35 (d, 3H, J = 6 Hz). IR (CH_2Cl_2): 3090, 3010, 1765, 1680, 1640, 1560, 1490, 1455, 1385, 1285, 1250, 1130, 1080 cm^{-1}. MS (20 eV, DIP) m/z (relative per cent): M^+ 551 (2.9), 248 (100.0).

HRMS Calcd. for $C_{27}H_{26}NO_5Cl_3$: 549.0879; Found: 549.0858.

4-[3-Dioxolan-8-(2', 2', 2'-trichloroethylcarbonoyl)-5-E-nonenl-2,5-diphenyloxazole (21a and 21b). A solution of the enone (6.35 mmole, 3.50 g), ethylene glycol (7.62 mmole, 473 mg) and *p*-TsOH·H_2O (0.63 mmole, 120 mg) in dry benzene (70 mL) was heated to reflux under nitrogen with azeotropic removal of water (24 h). The reaction was cooled to room temperature then washed with 1/3 saturated $NaHCO_3$ (1 x 50 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (1x 100 mL). The organic layers were combined, dried over Na_2SO_4, filtered through cotton and concentrated *in vacuo*. Gradient flash chromatography (SiO_2, CH_2Cl_2 -> 5% EtOAc/CH_2Cl_2) of the crude material gave an inseparable mixture of deconjugated to conjugated ketal (*ca.* 4:1) as a clear colorless oil (3.72 g, 98%).

^1H NMR for deconjugated product **21a** (250 MHz, $CDCl_3$): δ 8.10-8.06 (m, 2H); 7.72-7.68 (m, 2H); 7.49-7.41 (m, 5H); 7.36-7.30 (m, 1H); 5.70-5.40 (m, 2H); 4.90-4.79 (m, 1H); 4.73 (s, 2H); 4.00 (s, 4H); 2.95-2.88 (m, 2H); 2.49-2.31(m, 4H); 2.17-2.08 (m, 2H); 1.30 (d, 3H, J = 6.3 Hz). Irradiation of absorbances at 2.49-2.31 simplified the alkene region to show mainly E geometry (J = 16 Hz). NMR evidence indicated that a small amount of the α,β-isomer **21b** was also present in the product. IR ($CDCl_3$): 2960, 1760, 1600, 1550, 1490, 1450, 1385, 1290-1250 cm^{-1}. MS (20 eV, DIP) m/z (relative per cent): M^+ 595 (1.1), 593 (1.0), 321 (21.7), 320 (100.0), 248 (10.5), 234 (16.2).

HRMS Calcd. for $C_{29}H_{30}NO_6Cl_3$: 593.1141; Found: 593.1129.

4-(3-Dioxolan-8-hydroxy-5-E-nonen)-2,5-diphenyloxazole (22a and 22b). To the Troc-protected mixture of alcohols **21a** and **21b** (3.10 mmole, 1.845 g) in a magnetically stirred solution of 10% HOAc/THF (30 mL) at room temperature under nitrogen was added zinc dust (31.0 mmole, 2.026 g). The reaction was stirred for 8 h then filtered directly into an Erlenmyer flask containing vigorously stirred, saturated $NaHCO_3$ (50 mL). Et_2O (100 mL) was poured through the filter to rinse the solids. When effervescence in the flask had stopped, the biphasic mixture was transferred to a separatory funnel and shaken until CO_2 evolution had ceased.

The layers were separated and the aqueous layer extracted with Et_2O (1 x 100 mL). The combined organic layers were dried with $MgSO_4$ and concentrated *in vacuo*. The alcohols (*ca.* 4:1/deconjugated:conjugated) were obtained as an inseparable mixture by gradient flash chromatography (SiO_2, $CH_2Cl_2 \rightarrow$1:1/Et_2O:CH_2Cl_2) to yield a clear colorless oil (1.156 g, 89%).

^1H NMR for deconjugated alcohol **22a** (250 MHz, $CDCl_3$): δ 8.16-8.06 (m, 2H); 7.71-7.67 (m, 2H); 7.49-7.41 (m, 5H); 7.36-7.29 (m, 1H); 5.70-5.56 (m, 2H); 4.00 (s, 4H); 3.97-3.80 (m, 1H); 3.00-2.88 (m, 2H); 2.60-2.07 (m, 6H); 1.98 (br s, 1H); 1.19 (d, 3H, J = 6.2 Hz). IR ($CDCl_3$): 3590, 3460, 2970, 2900, 1600, 1555, 1490, 1450 cm^{-1}. MS (20 eV, DIP) m/z (relative per cent): M^+ 419 (3.1), 321 (21.3), 320 (100.0), 248 (13.4), 234 (23.9), 103 (10.6).

HRMS Calcd. for $C_{26}H_{29}NO_4$: 419.2097; Found: 419.2084.

N,N-Dibenzoyl-4-dioxolan-9-hydroxy-6-E-decenamide (**23a and 23b**). A solution of hydroxy oxazole (2.45 mmole, 1.03 g) and sensitox (10 wt%, 103 mg) in dry CH_2Cl_2 (25 mL) was treated with oxygen in the presence of strong light for 1 h to effect quantitative conversion to the triamide. The reaction was filtered through a long-stemmed funnel to remove the sensitox, then concentrated *in vacuo* to give a viscous yellow oil (1.021 g, 93%).

^1H NMR (250 MHz, $CDCl_3$): δ 7.80 (m, 4H); 7.55 (m, 2H); 7.40 (m, 4H); 5.65-5.45 (m, 2H); 3.97 (m, 4H); 3.80 (m, 1H); 2.92 (m, 2H); 2.55-2.00 (m, 6H); 1.72 (br s, 1H); 1.16 (d, 3H, J = 6 Hz). IR (CH_2Cl_2): 3610, 2980, 1715, 1690, 1485, 1455, 1270 cm^{-1}. MS (20 eV, DIP) m/z (relative per cent): 352 (14.8); 231 (25.3); 171 (30.2), 149 (30.9), 105 (100.0).

HRMS (CI) Calcd. for $C_{26}H_{29}NO_6$ (+H): 452.2074; Found: 452.2092.

4-Dioxolan-6-decen-9-olide (**24**). A solution of the triamide (5.07 mmole, 2.13 g) in dry benzene (20.0 mL) was added slowly (65 h), *via* syringe pump, to a refluxing solution of CPTS (1.0 mmole, 293 mg) in dry benzene (750 mL) under argon atmosphere. The reaction was stirred for 3 h upon complete addition of the triamide. The reaction was cooled to room temperature, extracted with 1/3 saturated $NaHCO_3$ (1 x 250 mL), the layers were separated and the aqueous layer extracted with CH_2Cl_2 (1 x 300 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to a yellow oil with white solid. The residue was dissolved in a minimal amount of CH_2Cl_2, and the product was then obtained by flash chromatography (SiO_2, 1:3/Et_2O: hexanes) to give a clear colorless oil as an inseparable mixture of E and Z isomers (542 mg, 47%).

^1H NMR (250 MHz, $CDCl_3$): δ 5.70-5.47 (br m, 1H); 5.38 (dd, 1H, J = 7-8 Hz, 2Hz); 5.2-5.0 (m, 1H); 3.94 (m, 4H); 2.5-1.7 (m, 8H); 1.28 (d, 3H, J = 6 Hz). IR (CH_2Cl_2): 1725, 1440, 1365, 1175 cm^{-1}. GCMS (20 eV) m/z (relative per cent): M^+ 226 (16.5), 145 (100.0), 101 (12.2), 100 (13.7), 99 (42.0), 82 (29.8), 67 (44.8).

HRMS Calcd. for $C_{12}H_{18}O_4$: 226.1205; Found: 226.1220.

E- and Z-4-Oxo-6-decen-9-olide (**25a and 25b**). A solution of the ketal in a 2 mg/mL mixture of H_2SO_4 (conc.)/acetone (5.0 mL) was heated to 60 °C under nitrogen and stirred for 2 days. The reaction was cooled to room temperature, diluted with CH_2Cl_2 (50 mL) and washed with 1/3 saturated $NaHCO_3$ (50 mL). The layers were separated, then the aqueous layer was extracted again with CH_2Cl_2 (50 mL). The combined organic layers

were dried over Na_2SO_4, filtered through cotton, and concentrated *in vacuo*. The E and Z isomers were separated by flash chromatography (SiO_2, 1:4/ Et_2O:petroleum ether) to give clear colorless oils (starting material, 14 mg; E-isomer, 43 mg, 62%, Z-isomer, 20 mg, 30%; total yield, 92% based on recovered starting material).

E-4-oxo-6-decen-9-olide (**25a**): ^1H NMR (250 MHz, $CDCl_3$): δ 5.60-5.30 (m, 2H); 5.30-5.10 (m, 1H); 3.20-2.95 (m, 2H); 2.95-2.35 (m, 5H); 2.20-1.95 (m, 1H); 1.31 (d, 3H, J = 6.4 Hz). IR ($CDCl_3$): 3000, 2950, 1730, 1715, 1660, 1440, 1360, 1340, 1275, 1265, 1235, 1220, 1160, 1140, 1050, 990, 975 cm^{-1}. GCMS (20 eV) m/z (relative per cent): M^+ 182 (<1.0), 95 (6.3), 82 (52.8), 67 (100.0), 54 (10.6).

HRMS Calcd. for $C_{10}H_{14}O_3$(+H) : 183.1021; Found: 183.1028.

Z-4-oxo-6-decen-9-olide (**25b**): ^1H NMR (250 MHz, $CDCl_3$): δ 5.90-5.70 (m, 2H); 5.00 (m, 1H); 3.31 (dd, 1H, J = 7.9, 15.3 Hz); 3.02 (dd, 1H, J = 7.0, 15.2 Hz); 2.80 -2.40 (m, 4H); 2.27 (m, 2H); 1.28 (d, 3H, J = 6.3 Hz). IR ($CDCl_3$): 3000, 2950, 1730, 1715, 1440, 1325, 1265, 1165, 1065, 1035, 990, 755 cm^{-1}. GCMS (20 eV) m/z (relative per cent): M^+ 182 (<1.0), 95 (4.7), 82 (47.4), 67 (100.0), 54 (10.4).

HRMS Calcd. for $C_{10}H_{14}O_3$(+H): 183.1021; Found: 183.1022.

2-Phenylselenyl-4-dioxolan-6-decen-9-olide (**26**). To a solution of LHMDS [Aldrich, 1.0 M in hexanes] (1.90 mmole, 1.90 mL) in THF (12.0 mL) at -78 °C under argon atmosphere was added slowly (*ca.* 30 min *via* syringe pump) a solution of the decenolide **24** (1.72 mmole, 390 mg) in THF (4.0 mL). The reaction was stirred for 30 min upon complete addition, and then a solution of diphenyldiselenide (2.06 mmole, 645 mg) in THF (2.0 mL) was added dropwise at -78 °C. The reaction was warmed to -20 °C and left to stand overnight. Saturated aqueous NH_4Cl (4.0 mL) and H_2O (50 mL) were added then the mixture was extracted with Et_2O (3 x 50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to a yellow oil. The product was purified by flash chromatography (SiO_2, 5% Et_2O:petroleum ether) to give an inseparable mixture of E and Z isomers as a clear colorless oil (1.3:1/E:Z, 45% yield, 71% based on recovered starting material).

^1H NMR (250 MHz, $CDCl_3$): δ 7.62 (m, 2H); 7.30 (m, 3H); 5.70-5.30 (m, 2H); 5.07 (m, 1H); 4.00-3.80 (m, 4H); 3.80 - 3.70 (m, 1H); 3.00-2.23 (m, 4H); 2.15-1.75 (m, 2H); 1.19 (m, 3H). IR ($CDCl_3$): 3000, 2910, 1725, 1670, 1480, 1440, 1370, 1335, 1190, 1145, 1125, 1105, 1090, 1055, 985, 770 cm^{-1}. MS (20 eV, DIP) m/z (relative per cent): M^+ 382 (21.0), 380 (11.8), 300 (10.0), 256 (40.5), 254 (16.2), 225 (53.3), 181 (10.1), 153 (50.7), 143 (30.8), 99 (100.0), 81 (17.0).

HRMS Calcd. for $C_{18}H_{22}O_4Se$: 382.0683 ; Found: 382.0655.

2-Phenylselenyl-4-oxo-6-decen-9-olide (**27** and **28**). A solution of the decenolide **26** (0.26 mmole, 100 mg) in a 4 mg/mL mixture of H_2SO_4 (conc.)/acetone (5.0 mL) was heated to a gentle reflux and stirred for 2 days. The reaction was cooled to room temperature, diluted with CH_2Cl_2 (50 mL) then washed with 1/3 saturated $NaHCO_3$ (60 mL). The layers were separated then the aqueous layer was extracted with more CH_2Cl_2 (50 mL). The combined organic layers were dried over Na_2SO_4, filtered through cotton and concentrated *in vacuo* to a brown oil. The pure E and Z isomers were obtained by flash chromatography (SiO_2, 10% Et_2O:hexanes) to give a clear colorless oil (72 mg total, 83%: E-isomer, 41 mg; Z-isomer, 31 mg).

E-2-Phenylselenyl-4-oxo-6-decen-9-olide (**28**); ^1H NMR (250 MHz, $CDCl_3$): δ 7.62 (m, 2H); 7.32 (m, 3H); 5.65-5.48 (m, 1H); 5.20-5.05 (m, 2H); 3.73 (dd, 1H, J = 1.6, 11.4 Hz); 3.22 (dt, 2H, J = 12.0, 16.6 Hz); 3.05 (m, 1H); 2.64 (dt, 1H, J = 1.6, 12.3 Hz); 2.40 (m, 1H); 2.00-1.85 (m, 1H); 1.21 (d, 3H, J = 6.4 Hz). IR

($CDCl_3$): 2990, 2940, 1720, 1710, 1475, 1435, 1360, 1330, 1205, 1135, 1085, 1045, 980 cm^{-1}. MS (20 eV, DIP) m/z (relative per cent): M^+ 338 (18.6), 256 (15.0), 184 (11.9), 99 (17.9), 82 (100.0), 81 (40.4), 67 (82.1), 55 (40.0).

HRMS Calcd. for $C_{16}H_{18}O_3Se$: 338.0421; Found: 338.0407.

Z-2-Phenylselenyl-4-oxo-6-decen-9-olide (27): ^1H NMR (250 MHz, $CDCl_3$): δ 7.63 (m, 2H); 7.35 (m, 3H); 5.63 (m, 2H); 4.97 (m, 1H); 3.82 (dd, 1H, J = 4.0, 11.7 Hz); 3.45 (m, 1H); 3.09 (dd, 1H, J = 11.9, 11.8 Hz); 2.89 (dd, 1H, J = 5.4, 13.1 Hz); 2.73 (dd, 1H, J = 4.0, 12.0 Hz); 2.38-2.15 (m, 2H); 1.23 (d, 3H, J = 6.4 Hz). IR (CH_2Cl_2): 1725, 1710, 1220, 910 cm^{-1}. MS (20 eV, DIP) m/z (relative per cent): M^+ 338 (40.8), 336 (20.7), 256 (33.0), 254 (14.0), 184 (36.6), 183 (11.6), 182 (17.1), 181 (13.7), 157 (13.8), 109 (10.0), 82 (71.5), 81 (44.6), 79 (10.6), 67 (100.0), 55 (64.5).

HRMS Calcd. for $C_{16}H_{18}O_3Se$: 338.0421; Found: 338.0444.

Z,Z-4-Oxo-2,6-decadien-9-olide (29). *m*-CPBA (80%, 0.037 mmole, 8 mg) was added to a stirred solution of the ketoselenide **27** (0.029 mmole 10 mg) in CH_2Cl_2 (1.5 mL) at -40 °C under argon. The reaction was stirred for 30 min, and then pyridine (0.081 mmole, 7 μL) was added and the reaction was warmed to room temperature as it stirred overnight (18 h). The reaction was stopped by addition of 1/3 saturated $NaHCO_3$ (20 mL), followed by extraction with CH_2Cl_2 (2 x 40 mL). The combined organic layers were dried over Na_2SO_4, filtered through cotton and concentrated *in vacuo*. Pure product was obtained by flash chromatography (SiO_2, 1:4/Et_2O:petroleum ether) to give a clear colorless oil (5 mg, 100%).

^1H NMR (250 MHz, $CDCl_3$): δ 6.44 (d, 1H, J = 12 Hz); 6.22 (d, 1H, J = 12 Hz); 5.97 (ddd, 1H, J = 10, 10, 6.7 Hz); 5.80 (m, 1H); 5.42 (m, 1H); 3.43 (dd, 1H, J = 10, 15 Hz); 3.03 (dd, 1H, J = 6.7, 15 Hz); 2.54 (m (ddd), 1H); 2.12 (m (ddd), 1H); 1.25 (d, 3H, J = 6.5 Hz). IR ($CDCl_3$): 1720, 1705, 1650 cm^{-1}. GCMS (20 eV) m/z (relative per cent): 82 (64.8), 67 (100.0), 54 (28.5).

HRMS Calcd. for $C_{10}H_{12}O_3$: 180.0786; Found: 180.0779.

Z,E-4-Oxo-2,6-decadien-9-olide (30). The same procedure was followed as for the Z,Z isomer utilizing E-2-phenylselenyl-4-oxo-6-decen-9-olide **28** (0.106 mmole, 36 mg), *m*-CPBA (80%, 0.133 mmole, 29 mg) and pyridine (0.293 mmole, 24 μL). The product obtained was a clear colorless oil (15 mg, 78%).

^1H NMR (250 MHz, $CDCl_3$): δ 6.42 (d, 1H, J = 13.5 Hz); 6.00 (d, 1H, J = 13.5 Hz); 5.55 (m, 2H); 5.19 (m, 1H); 3.35-3.05 (m, 2H); 2.43 (m, 1H); 2.05 (m, 1H); 1.38 (d, 3H, J = 6.3 Hz). IR ($CDCl_3$): 3000, 2950, 1725, 1695, 1635, 1610, 1380, 1280, 1210, 1125, 1050, 1000, 980, 890, 800 cm^{-1}. GCMS (20 eV) m/z (relative per cent): M^+ 180 (<1.0), 82 (79.7), 67 (100.0), 54 (21.5).

HRMS Calcd. for $C_{10}H_{12}O_3$: 180.0786; Found: 180.0784.

Z-6,7-cis-Epoxy-4-oxo-2-decen-9-olide (31). To a magnetically stirred solution of decadienolide **29** (0.016 mmole, 3 mg) in CH_2Cl_2 (1.0 mL) at room temperature under nitrogen was added *m*-CPBA (0.20 mmole, 5 mg) in one portion as a solid. The reaction was stirred for 2 days then concentrated *in vacuo* to a white solid.

The *cis*-epoxide was obtained directly by flash chromatography (SiO_2, 1:1/Et_2O:petroleum ether) to give a clear colorless oil (3 mg, *ca.* 100%).

^1H NMR (250 MHz, $CDCl_3$): δ 6.51 (d, 1H, J = 12.3 Hz); 6.16 (d, 1H, J = 12.3 Hz); 5.43 (m, 1H); 3.65 (ddd, 1H, J = 10.8, 4, 3.5 Hz); 3.25 (ddd, 1H, J = 11, 4, 4 Hz); 2.91 (dd, 1H, J = 15.6, 3.5 Hz); 2.64 (dd, 1H, J = 10.9, 15.6 Hz); 2.31 (dm, 1H); 1.65 (m, 1H); 1.39 (d, 3H, J = 6.9 Hz). IR (CH_2Cl_2): 3090, 3015, 2965, 1730, 1700, 1610, 1130, 1050, 990 cm^{-1}. GCMS (20 eV) m/z (relative per cent): 126 (14.0), 99 (9.5), 97 (100.0), 83 (19.2), 82 (69.4), 69 (20.9), 55 (20.8), 54 (18.7).

HRMS Calcd. for $C_{10}H_{12}O_4$ (+H): 197.0814; Found: 197.0813.

(±)-Pyrenolide C (3). To a stirred solution of the E,Z-decadienolide **30** (0.077 mmole, 14 mg) in CH_2Cl_2 (1.0 mL) at 0 °C under nitrogen was added *m*-CPBA (80%, 0.093 mmole, 20 mg) in one portion as a solid. The reaction was warmed to room temperature and stirred for 2 days to effect complete conversion to the *trans*-epoxide **32** as evidenced by TLC (SiO_2, 1:1/Et_2O:petroleum ether). The reaction was diluted with CH_2Cl_2 (25 mL) then washed with 1/3 saturated $NaHCO_3$ (25 mL). The layers were separated and the aqueous layer extracted once more with CH_2Cl_2 (25 mL). The combined organic layers were dried by filtration through cotton and concentrated *in vacuo* to a crude mixture of epoxide, *m*-CPBA, and *m*-chlorobenzoic acid. ^1H NMR (250 MHz, $CDCl_3$): (disregarding aromatic peaks) δ 6.52 (d, 1H, J = 12.8 Hz); 6.26 (d, 1H, J = 12.8 Hz); 5.43 (m, 1H); 3.13 (dm, 1H); 2.98 (dm, 1H); 2.81 (dm, 1H); 2.50-2.30 (m, 2H); 1.39 (d, 3H, J = 6.5 Hz); 1.25-1.10 (m, 1H). The crude product was dissolved in a small amount of CH_2Cl_2 and loaded onto a flash silica gel column (ca. 100:1 SiO_2:substrate). The column was slowly eluted by gravity with 1:2/Et_2O:hexanes (ca. 100 mL/h) for 3 h. The solvent system was then changed to 2:1/Et_2O:hexanes and the column run as normal for flash chromatography. Pure synthetic pyrenolide C was obtained as the sole product as a clear colorless oil (11 mg, 73%). The synthetic product was identical to the natural sample provided by Professor Nukina.

^1H NMR (250 MHz, $CDCl_3$): δ 6.70 (d, 1H, J = 12.4 Hz); 6.28 (dd, 1H, J = 9.4, 16.5 Hz); 6.14 (d, 1H, J = 12.4 Hz); 6.11 (d, 1H, J = 16.5 Hz); 5.23 (m, 1H); 4.34 (m, 1H); 2.20-1.95 (m, 2H); 1.83 (br s, 1H); 1.36 (d, 3H, J = 6.4 Hz). GCMS (20 eV) m/z (relative per cent): M^+ 196 (1.5), 152 (6.8), 126 (34.8), 125 (50.8), 109 (13.2), 100 (18.3), 97 (20.0), 82 (100.0).

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References and Footnotes

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8. At this stage, it was not possible to tell the *cis/trans* ratio by spectroscopic methods and the isomers were inseparable by chromatography. However, deketalization by exchange with acetone using H_2SO_4 as catalyst gave the *cis*- and *trans*-deketalized products, E or Z-4-oxo-6-decen-9-olide (**25a** and **25b**) as separable isomers in yields of 30% and 62%, respectively.

9. The oxidation/elimination sequence was attempted on **25** but the yields were low and forcing conditions were required (refluxing CCl_4, diisopropyl amine). A much better pathway involved removal of the ketal followed by oxidative elimination. Additionally, the deketalized *cis* -and *trans* -selenides **27** and **28** were separable by chromatography at this stage.

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11. We thank Professor M. Nukina for generously providing us with samples of natural pyrenolides A, B, and C.

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13. It appears as though any α,β-isomer formed may have decomposed *via* the pathway shown below, which would not be available to the β,γ-isomers