Full Papers

Photochemical Relationships in Sacoglossan Polypropionates

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Cyercene A (**7**) has been synthesized and converted to placidene A (**3**) and isoplacidene A (**8**) through photoisomerization with sunlight. Hydroperoxide **4**, isolated form *Placida dendritica*, was synthesized both by singlet oxygenation of cyercene A using Rose Bengal and through the irradiation of cyercene A alone in aerobic solution. The observation that hydroperoxide **4** could be made by singlet oxygenation of cyercene A and that this occurs when cyercene A alone is irradiated supported the hypothesis that γ-pyrones may act as triplet sensitizers. This was confirmed using cyercene A and a model γ-pyrone to sensitize the photooxidation of *n*-butyl sulfide. The biosynthetic implications of these observations for Sacoglossan polypropionates are discussed.

Though unusual in nature, polypropionates are characteristic of marine mollusks of the Sacoglossa order.[1] These compounds have been implicated as mediators in chemical defense and tissue regeneration. It is generally believed that they are biosynthesized de novo by the mollusks, though proof for this exists in only a few examples.[2–4] A selection of polypropionates isolated from this family of mollusks is shown in Chart 1. All possess an oxygenated γ-pyrone (or dihydropyrone) ring. Two are known to be biosynthetically related; photodeoxytridachione (**2**) is derived from 9,10-deoxytridachione (**1**) in several mollusks.[2] Unusually, **1** is converted to **2** though a photochemical reaction. This photochemical link between natural products is especially interesting.
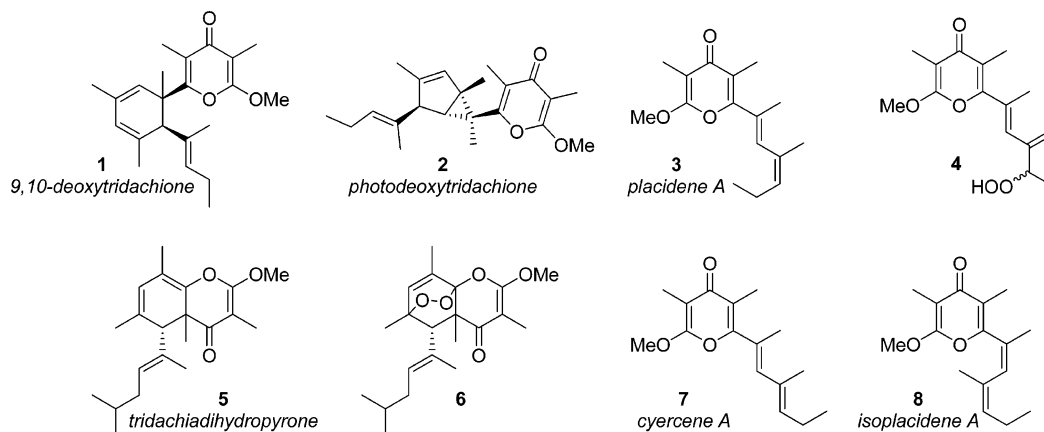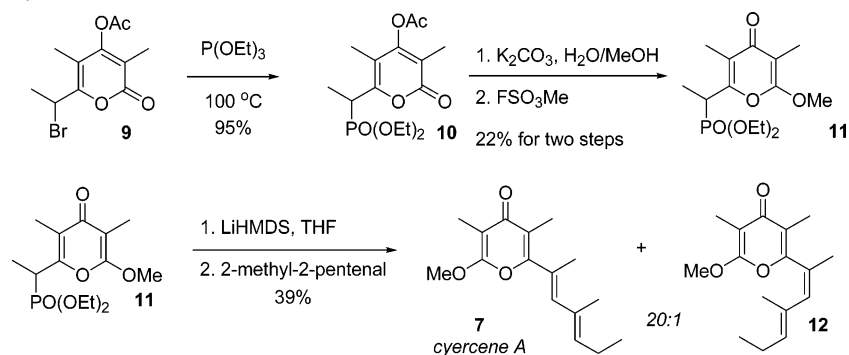
The photochemical relationship between 9,10-deoxytridachione (**1**) and photodeoxytridachione (**2**) in *Elysia diomedea* (formerly known as *Tridachia diomedea*) was discovered by Ireland in the 1970s.[2] Through feeding experiments, the photoconversion of 9,10-deoxytridachione (**1**) to photodeoxytridachione (**2**) was found to occur in the mollusks themselves. This established that the polypropionates in the animals are exposed to sunlight and are susceptible to photochemical reactions in vivo. The mechanism for this phototransformation is not precisely known, though a model has been proposed.[5]

Two other examples suggest additional photochemical conversions in Sacoglossan mollusks. Fontana proposed the photooxygenation of placidene A (**3**) to explain the existence of hydroperoxide **4** in *Placida dendritica*.[6] A similar photooxygenation is plausible in the conversion of tridachiadihydropyrone (**5**) to tridachiahydropyrone B (**6**) in *Placobranchus ocellatus*.[7,8] Furthermore, placidene A (**3**) and isoplacidene A (**8**) are stereoisomers of cyercene A (**7**), differing only in the stereochemistry of one or both of the acyclic alkenes, suggesting that they may derive from cyercene A via photoisomerization.[3,6]

The mechanism of these photoreactions is not known. All could plausibly involve triplet excited states, although Baldwin has published data introducing the possibility that photodeoxytridachione (**2**) is produced from 9,10-deoxytridachione (**1**) in a sequence of reactions most likely involving singlet excited states.[5] Trauner has also shown that analogues of photodeoxytridachione (**2**) may be obtained from analogues of 9,10-deoxytridachione (**1**) via dark reactions.[9] Products containing peroxides (e.g., **4** and **6**) most likely arise from singlet oxygenations, and if this is the case, these reactions must necessarily involve triplet sensitization.

Our laboratory is generally interested in photodynamic therapy and was intrigued by the possibility that triplet excited states were being generated in these mollusks. We

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Chart 1. Some Sacoglossan Polypropionates

1
9,10-deoxytridachione

2
photodeoxytridachione

3
placidene A

4

5
tridachiadihydropyrone

6

7
cyercene A

8
isoplacidene A

Scheme 1. Synthesis of Cyercene A (**7**)

speculated that the γ-pyrones common to the natural products in Sacoglossa could act as photosensitizers. Furthermore, if this were true, it opens the possibility that their biological role may be directly tied to their photochemistry. To begin our investigation of the photochemistry of these polypropionates, we set out to synthesize cyercene A (**7**). We successfully prepared this compound and began an investigation of its photochemistry and related γ-pyrones. A recent report of the synthesis of cyercene A,[10] using a route similar to our own, has prompted us to publish the results of our photochemical investigation of cyercene A (**7**).

Our goals in this study were to (a) prepare cyercene A; (b) determine if irradiation of cyercene A produced placidenes; (c) test the hypothesis that **4** could be prepared by singlet oxygenation of cyercene A and/or placidene A; (d) determine whether any of these reactions are due to triplet sensitization initiated by the γ-pyrone. Our results are described below.

Results and Discussion

Synthesis of Cyercene A. Scheme 1 shows our synthesis of cyercene A, **7**. Cyercene A was prepared in our laboratory earlier in 2004, after which we began our photochemical studies. In August 2004, Baldwin reported a superior synthesis of cyercene A (**7**) that used an approach similar to our unreported synthesis.[10] The synthesis of cyercene A, in both our laboratory and that reported by Baldwin, involves a Horner–Emmons olefination of 2-methyl-2-pentenal using phosphonate **11**. In our hands, the reaction proceeded with a high degree of stereoselectivity. However, **12** was obtained as 5% of the crude reaction mixture. Interestingly, **12**, with *Z:E* arrangement of the two exocyclic alkenes, is the only one of the four stereoisomers of cyercene A (**3, 7, 8**, and **12**) not

(yet) isolated from the Sacoglossan mollusks. We refer to compound **12** as isocyercene A. The ^{1}H NMR spectral data for **12** do not match those of any of the three known stereoisomers.[3,6]
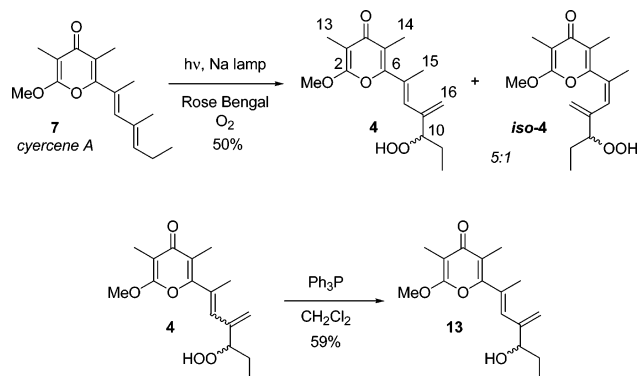
Photochemistry of Cyercene A (7). Irradiation of cyercene A (**7**), under any of the conditions we employed, led mostly to isomerization of the alkene directly bonded to the pyrone ring, giving isocyercene A (**12**). When cyercene A (**7**) is dissolved in anaerobic hexane and exposed to sunlight while in a quartz vessel, a photostationary state is reached in which the ratio of isocyercene A (**12**) to cyercene A (**7**) is 4:1. In addition, signals that corresponded to placidene A (**3**) and isoplacidene A (**8**) were detected in the crude mixture. GC-MS analysis revealed isocyercene A (**12**), cyercene A (**7**), and several other products with a mass of 262. To positively identify placidene A (**3**) and isoplacidene A (**8**), the crude mixture was eluted on a preparatory TLC plate, and a wide band surrounding cyercene A and **12**, which coeluted, was cut from the plate. The material isolated from this band was then examined by ^{1}H NMR and GC-MS. Figure 1 shows the relevant NMR spectrum.

These analyses confirm that placidene A (**3**) and isoplacidene A (**8**) are produced upon exposure of cyercene A (**7**) to sunlight. Specifically, the singlet at δ 6.41 and the triplet at δ 5.31 correspond with those published for isoplacidene A (**8**), and the triplet at δ 5.39 and singlet at δ 3.97 (not shown) correspond exactly with the data published for placidene A (**3**) (the vinyl proton for **3** overlaps with the vinyl proton for **12**).[3,6] Remarkably, isocyercene A (**12**) (singlet at δ 6.18 and triplet at δ 5.46) is, by far, the major component at the photostationary state. The UV spectra of cyercene A (**7**) and isocyercene A (**12**) (Figure 2) show that the former absorbs slightly

Scheme 2. Photoisomerization of Cyercene A (**7**) by Sunlight
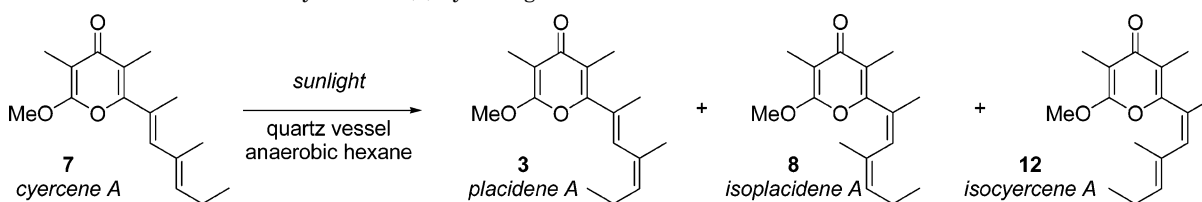
farther to the red and with a slightly higher ϵ, which presumably accounts for the preference for isocyercene A (**12**).

Singlet Oxygenation of Cyercene A. When cyercene A (**7**) was irradiated with a sodium lamp in the presence of Rose Bengal and oxygen, hydroperoxide **4** was produced in 50% yield (Scheme 3). The spectral data for synthetic **4** matched exactly that published for **4** isolated from *Placida dendritica*.[6b] As reported, **4** was surprisingly stable;[6b] it could be chromatographed and survived short periods of photolysis with a Hg vapor lamp (Pyrex filter). However, for long-term storage and analysis by GC, it was necessary to reduce the hydroperoxide to alcohol **13** by treatment with triphenylphosphine (Scheme 3). The alcohol was indefinitely stable and survived analysis by GC. A second product is also produced, along with **4**, in the singlet oxygenation reaction shown in Scheme 3. The ratio of hydroperoxide **4** to the minor product was 5:1. The signals for the minor product shadowed those of **4**, leading us to believe that the minor product was ***iso*-4**. We confirmed the identity of ***iso*-4** by irradiating pure **4** with a Hg lamp through a Pyrex filter. Conversion of **4** to ***iso*-4** proceeded smoothly for 3 h, at which point significant decomposition of both hydro-

Figure 1. ^{1}H NMR of a fraction from cyercene A photolysis. Note that the methine vinyl signal for isocyercene A (**12**) (δ 6.18) overlaps the same signal for placidene A (**3**).[3,6]

Figure 2. UV−vis absorbance spectra for cyercene A (**7**) (0.0125 mM) and isocyercene A (**12**) (0.0125 mM) in methanol.

Scheme 3. Synthesis of Hydroperoxide **4**

peroxides prevented determination of a photostationary state.

Having confirmed that hydroperoxide **4** is produced via singlet oxygenation of cyercene A (**7**), we tested our hypothesis that cyercene A (**7**) itself might be the photosensitizer that generates singlet oxygen. A number of marine products are capable of acting as a photosensitizer: could cyercene A (**7**) be one of them?

Oxygen was bubbled through a solution of cyercene A (**7**) in methanol for 1 h. The solution was placed in a Pyrex flask and irradiated for 6 h using a medium-pressure Hg lamp while under an oxygen atmosphere. The usual isomerization products were produced: isocyercene A (**12**), placidene A (**3**), and isoplacidene A (**8**). GC analysis of the crude reaction mixture showed no peaks where purified alcohol **13** eluted (Figure 3a). Hydroperoxide **4** does not survive GC analysis and, therefore, could not be detected at this stage (Figure 3b). The crude photolysis mixture was then treated with triphenylphosphine. GC analysis of the crude product from this reduction now showed a peak where **13** was expected to elute (Figure 3c); the identity of this peak was confirmed by co-injection with pure **13** (Figure 3d). Thus, hydroperoxide **4** is produced, albeit in low yield, when an aerobic solution of cyercene A (**7**) is irradiated in the absence of any other photosensitizer (Scheme 4).

To confirm that cyercene A (**7**), and other γ-pyrones, can act as photosensitizers, we studied the photosensitized oxidation of *n*-butyl sulfide (**14**) by cyercene A (**7**) and model pyrone **15**.[11] Photolysis of either pyrone in the presence of excess **14** produced *n*-butyl sulfoxide (**16**), indicating the presence of singlet oxygen (Scheme 5).[12] Under the conditions employed (irradiation of an aerobic methanolic solution with a medium-pressure Hg lamp and Pyrex filter) sulfoxide **16** was slowly produced even in the absence of pyrone (or other sensitizer). However, sulfoxide **16** was produced nearly twice as fast in the reaction containing 2 mM cyercene A (**7**) and almost four times as fast in the reaction containing 2mM **15** (Figure 4). Importantly, greater than a stoichiometric amount of sulfoxide **16** is produced when either pyrone is used as the sensitizer, indicating a true sensitization reaction: excited pyrone
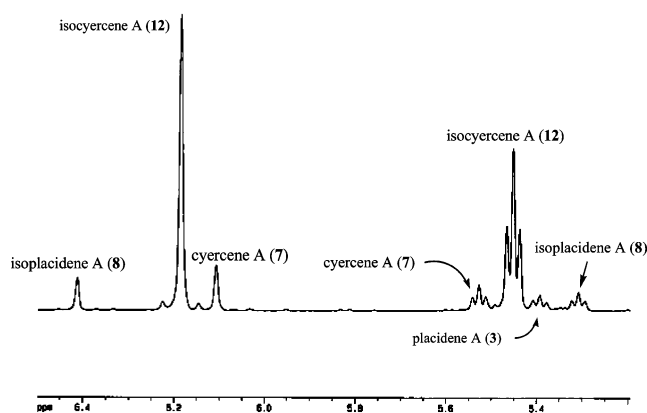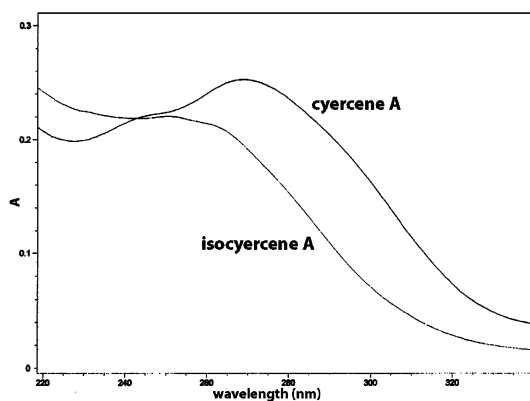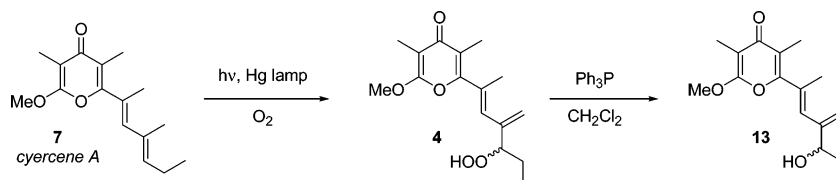
Scheme 4. Photooxygenation of Cyercene A (**7**) Irradiated in the Absence of Any Other Photosensitizer

Scheme 5. Singlet Oxygenation of *n*-Butyl Sulfide (**14**)

undergoes intersystem crossing to a triplet state and then produces singlet oxygen in a triplet−triplet annhilation that regenerates the pyrone. That cyercene A (**7**) is a less efficient sensitizer than **15** is most likely due to the available deactivation pathway of isomerization in cyercene A (**7**). This is the first explicit demonstration that γ-pyrones can act as triplet sensitizers.

The data demonstrate that cyercene A (**7**), placidene A (**3**), isoplacidene A (**8**), and hydroperoxide **4** are photochemically linked. The known natural products placidene A (**3**) and isoplacidene A (**8**) are produced from cyercene A (**7**) when the latter is exposed to sunlight. Irradiation of cyercene A (**7**) in the presence of oxygen and Rose Bengal produces hydroperoxide **4** in good yield. This is the first

synthesis of **4** and confirms that it is produced by a photochemical singlet oxygenation, as suggested by its discoverers.[6b] Our results also show that cyercene A (**7**) and, more generally γ-pyrones, can act as triplet sensitizers. Thus, hydroperoxide **4** is produced directly from cyercene A (**7**) when the latter is irradiated in the presence of oxygen.

We propose that **4** is produced in *Placida dendritica* by a self-sensitization of placidene A (**3**). The photochemical conversion of 9,10-deoxytridachione (**1**) to photodeoxytridachione (**2**) in various mollusks in their natural habitat illustrates that the polypropionates in such mollusks are exposed to significant quantities of sunlight and are capable of undergoing photochemical reactions in vivo.[2] Several additional examples of peroxide-containing polypropionates have been isolated from Sacoglossan mollusks.[7,13] A logical conclusion is that these are also examples of pyrone-sensitized singlet oxygenations.

It appears that **4** is produced photochemically in *P. dendritica*, demonstrating that the pyrone-containing molecules in this animal are exposed to light. However, to date, no organism is known to contain stereochemically related cyercenes and placidenes.[14] How can **4** be produced photochemically in *P. dendritica* without simultaneous photoisomerization of the placidenes to cyercenes? There are several possibilities, but we suggest that cyercenes and the stereochemically related placidenes eventually will be found in the same organism.

Since the discovery that photodeoxytridachione **2** is produced photochemically from 9,10-deoxytridachione **1** in *E. diomedea*, it has been suggested that pyrone-containing polypropionates serve as "sunscreens" in protecting the mollusks from sunlight-induced damage.[2] Compounds that can photoisomerize, such as cyercene A (**7**), placidene A (**3**), and isoplacidene A (**8**), would be excellent in this capacity. Furthermore, the discovery that the ubiquitous γ-pyrones in Sacoglossan polypropionates can catalyze the production of highly reactive singlet oxygen provides the possibility that photosensitization may play a part in the function of these marine products.
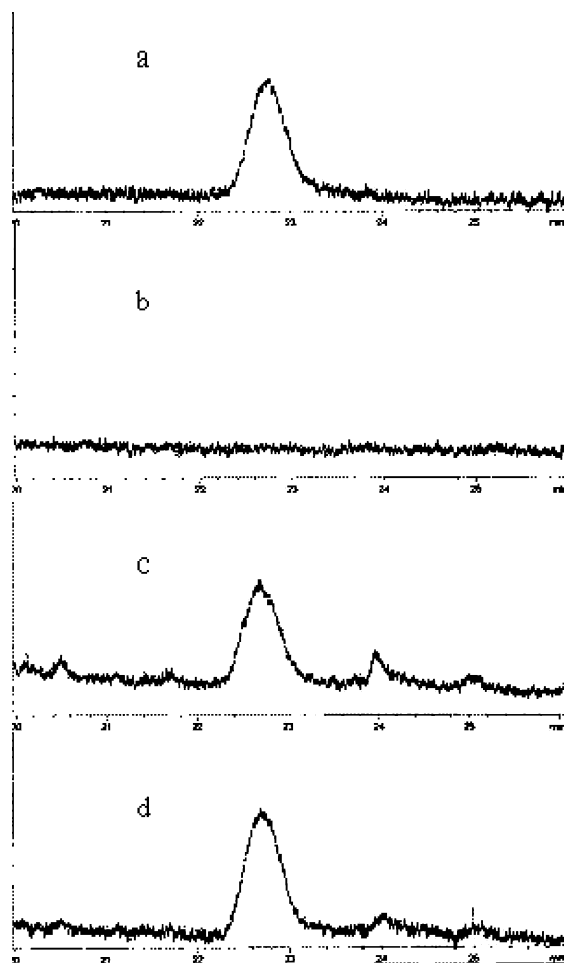

Figure 3. GC traces for the experiment described in Scheme 4: (a) purified alcohol **13**; (b) crude photolysis mixture, not reduced; (c) photolysis mixture reduced with PPh₃; (d) co-injection of pure **13** and the reduced photolysis mixture.
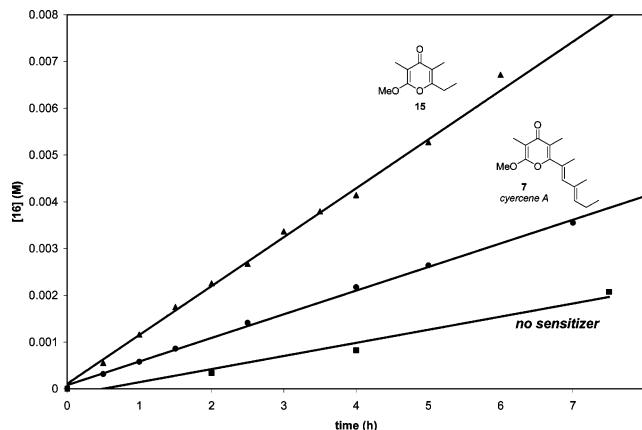

Figure 4. Photosensitized oxidation of *n*-butyl sulfide (**14**) by cyercene A (**7**) and pyrone (**15**).

Experimental Section

General Experimental Procedures. Melting points are uncorrected. UV–vis spectra were obtained on a Hewlett-Packard 8453 spectrometer. ^{1}H NMR (300, 500 MHz) and ^{13}C NMR (75, 125 MHz) spectra were recorded on Bruker Avance 300 and 500 MHz spectrometers. Unless otherwise indicated, all reagents and solvents were obtained commercially and used without further purification: all compounds were purchased from Sigma-Aldrich or Fisher Scientific. Tetrahydrofuran was distilled over Na/benzophenone. CH_2Cl_2 was distilled over calcium hydride. Thin-layer chromatography was performed on silica gel (250 μm thickness doped with fluorescein) unless otherwise indicated. The chromatograms were visualized with UV light (254 nm) unless otherwise indicated. Column chromatography was performed using silica gel (60 Å) or alumina (neutral, 58 Å). GC analyses were conducted on an Agilent 6890 GC and analytes detected by FID following elution from a 30 m β-cyclodextrin column (Supelco 24304). GC-MS analyses were carried out on an Agilent 6850 GC system coupled to an Agilent 5973 mass spectrometer. Anaerobic photolyses were degassed by three cycles of freeze–pump–thaw. The light sources for reactions were either a 450 W medium-pressure Hg vapor lamp (Hanovia), a Na lamp (Rudolph Research, Model 90), or sunlight.

4-Acetoxy-3,5-dimethyl-6-(1-diethylphosphonoethyl)-2-pyrone (10). 4-Acetoxy-3,5-dimethyl-6-(1-bromoethyl)-2-pyrone (9)[15] (4.00 g, 13.8 mmol) was dissolved in 20 mL of triethyl phosphite. The flask was purged with Ar, warmed to 110 °C, sealed, and heated for 17 h. The reaction mixture was allowed to cool to room temperature, and excess solvent was removed under high vacuum (55 mTorr) to yield 4.53 g (13.1 mmol) of a colorless oil. The product was isolated in 95% yield: ^{1}H NMR (300 MHz, CDCl$_3$) δ 4.02–4.20 (m, 4H, OC*H*$_2$CH$_3$), 3.35 (dq, J = 23.7, 7.3 Hz, 1H, PC*H*CH$_3$), 2.33 (s, 3H, C*H*$_3$C(O)), 1.90 (d, J = 2.6 Hz, 3H, C*H*$_3$C=CO), 1.88 (d, J = 3.6 Hz, 3H, C*H*$_3$CC-(O)O), 1.54 (dd, J = 10.6, 17.9 Hz, 3H, C*H*$_3$CH), 1.25–1.35 (m, 6H, OCH$_2$C*H*$_3$); ^{13}C NMR (75 MHz, CDCl$_3$) δ 166.7 (C, *C*(O)CH$_3$), 163.6 (d, J = 1.7 Hz, C, *C*(O)O), 158.9 (d, J = 4.0 Hz, C, *C*OC(O)CH$_3$), 154.0 (d, J = 12.1 Hz, C, *C*CHP), 114.0 (d, J = 3.4 Hz, C, *C*C(O)O), 110.1 (d, J = 10.3 Hz, C, CH$_3$*C*=CO), 62.8 (d, J = 6.9 Hz, CH$_2$, O*C*H$_2$CH$_3$), 62.3 (d, J = 6.3 Hz, CH$_2$, O*C*H$_2$CH$_3$), 34.9 (d, J = 139.7 Hz, CH, *C*HP), 20.3 (CH$_3$, C(O)*C*H$_3$), 16.44 (d, J = 3.4 Hz, CH$_3$, OCH$_2$*C*H$_3$), 16.37 (d, J = 3.4 Hz, CH$_3$, OCH$_2$*C*H$_3$), 12.3 (d, J = 5.7 Hz, CH$_3$, *C*H$_3$CH), 10.6 (d, J = 1.7 Hz, CH$_3$, *C*H$_3$C=CCH), 10.2 (CH$_3$, *C*H$_3$CC-(O)O); HREIMS *m/z* 369.1066 (calcd for C$_{15}$H$_{23}$O$_7$PNa$^+$, 369.1074).

4-Hydroxy-3,5-dimethyl-6-(1-diethylphosphonoethyl)-2-pyrone. 4-Acetoxy-3,5-dimethyl-6-(1-diethylphosphonoethyl)-2-pyrone (10) (3.46 g, 10 mmol) was dissolved in 35 mL of MeOH. Water (35 mL) and 6.70 g of K$_2$CO$_3$ were added. The mixture was stirred for 40 min. The solution was then washed 2× with 100 mL of Et$_2$O. The aqueous layer was acidified with concentrated HCl to pH 1 and then extracted 4× with 100 mL portions of 1:1 Et$_2$O/CH$_2$Cl$_2$. All organic layers were then combined and washed 2 × with 150 mL of brine. The combined organic layers were dried with anhydrous MgSO$_4$ and concentrated to afford 2.76 g (9.08 mmol) of white crystals. The product was isolated in 91% yield: mp 159.0–161.0 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 4.05–4.33 (m, 4H, OC*H*$_2$CH$_3$), 3.34 (dq, J = 7.2, 22.8 Hz, 1H, PC*H*CH$_3$), 1.91 (d, J = 1.9 Hz, 3H, C*H*$_3$C=CO), 1.86 (d, J = 3.4 Hz, 3H, C*H*$_3$CC(O)O), 1.46 (dd, J = 7.2, 17.7 Hz, 3H, C*H*$_3$CH), 1.34 (t, J = 7.2 Hz, 6H, OCH$_2$C*H*$_3$); ^{13}C NMR (75 MHz, CDCl$_3$) δ 165.3 (d, J = 1.7 Hz, C, *C*(O)O), 164.8 (d, J = 2.9 Hz, C, *C*CHP) 152.4 (d, J = 11.5 Hz, C, *C*OH), 109.7 (d, J = 9.8 Hz, C, *C*=CCHP), 99.2 (d, J = 2.9 Hz, C, *C*=COH), 63.9 (d, J = 6.9 Hz, CH$_2$, O*C*H$_2$CH$_3$), 62.3 (d, J = 6.9 Hz, CH$_2$, O*C*H$_2$CH$_3$), 34.5 (d, J = 140.8 Hz, CH, *C*HP), 16.4 (d, J = 5.7 Hz, CH$_3$, OCH$_2$*C*H$_3$), 16.3 (d, J = 6.3 Hz, CH$_3$, OCH$_2$*C*H$_3$) 12.9 (d, J = 5.7 Hz, CH$_3$, *C*H$_3$CH), 10.1 (d, J = 1.1 Hz, CH$_3$, *C*H$_3$C=CCH), 9.1 (d, J = 1.1 Hz, CH$_3$,

*C*H$_3$CC(O)O); *anal*. C 51.38%, H 6.97%, calcd for C$_{13}$H$_{21}$O$_6$P, C 51.32%, H 6.96%.

3,5-Dimethyl-6-(1-diethylphosphonoethyl)-2-methoxy-4-pyrone (11). To a stirred solution of 4-hydroxy-3,5-dimethyl-6-(1-diethylphosphonoethyl)-2-pyrone (2.48 g, 8.14 mmol) in 10 mL of CH$_2$Cl$_2$ was added methyl fluorosulfonate (3.03 mL, 38.6 mmol) **(caution: this compound is highly toxic and must be handled only in a fume hood and with suitable skin protection)**. The reaction vessel was flushed with Ar, sealed, and stirred at room temperature for 2 h. The reaction mixture was poured into 50 mL of CHCl$_3$ and washed 1× with 50 mL of 1 N NaOH. The aqueous layer was then washed 2× with 50 mL portions of CHCl$_3$. The combined organic layers were dried with anhydrous MgSO$_4$, concentrated, and purified by flash column chromatography (silica gel) with an ethyl acetate/methanol mobile phase (10:1 EtOAc/MeOH). The product was isolated as a white amorphous solid in 24% yield (0.622 g, 1.95 mmol): mp 54.0–55.5 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 4.02–4.16 (m, 4H, OC*H*$_2$CH$_3$), 4.01 (s, 3H, OC*H*$_3$), 3.43 (dq, J = 7.3, 23.2 Hz, 1H, C*H*P), 1.98 (d, J = 3.2 Hz, 3H, C*H*$_3$C=CCH), 1.85 (s, 3H, C*H*$_3$C=COCH$_3$), 1.55 (dd, J = 7.2, 17.9 Hz, 3H, C*H*$_3$CH), 1.29 (dt, J = 7.2, 19.4 Hz, 6H, OCH$_2$C*H*$_3$); ^{13}C NMR (75 MHz, CDCl$_3$) δ 180.5 (C, *C*=O), 162.2 (C, *C*OCH$_3$), 153.4 (d, J = 11.5 Hz, C, *C*CH), 120.0 (C, *C*=CCH), 99.4 (C, *C*=COCH$_3$), 62.7 (d, J = 7.5 Hz, CH$_2$, O*C*H$_2$-CH$_3$), 62.4 (d, J = 6.9 Hz, CH$_2$, O*C*H$_2$CH$_3$), 55.6 (CH$_3$, O*C*H$_3$), 34.4 (d, J = 141 Hz, CH, *C*HP) 16.5 (d, J = 5.7 Hz, CH$_3$, O*C*H$_2$CH$_3$), 12.0 (d, J = 5.2 Hz, CH$_3$, *C*H$_3$CH), 10.1 (d, J = 1.7 Hz, CH$_3$, *C*H$_3$C=CCH), 6.8 (CH$_3$, *C*H$_3$CC(O)O); *anal*. C 53.00%, H 7.33%, calcd for C$_{14}$H$_{23}$O$_6$P, C 52.83%, H 7.28%.

Cyercene A (7). To an oven-dried 10 mL round-bottom flask were charged 2.6 mL of distilled THF and 132 mg (0.415 mmol) of **11**. A solution of LiHMDS (0.42 mL, 1.0 M) was added dropwise, upon which the solution turned yellow. Care was taken to keep the reaction under a blanket of dry Ar. This solution was stirred for 15 min, and then 0.019 mL (0.166 mmol) of 2-methyl-2-pentenal was added. The reaction mixture was stirred for 18 h. The reaction mixture was poured into 30 mL of Et$_2$O and then washed with 30 mL of dilute HCl, 10 mL of water, 30 mL of dilute NaHCO$_3$, and 30 mL of brine, successively. The organic layers were combined, dried over MgSO$_4$, and concentrated to give a pale yellow amorphous solid (42.4 mg, 0.162 mmol, 39%). Spectral data for cyercene A correlated with the published spectra. Cyercene A could be further purified by column chromatography through silica gel using 2:1 hexane/EtOAc as eluent.

Hydroperoxide 4. To a 100 mL round-bottom flask were charged 68 mL of a 2.0 mM solution of cyercene A (**7**) (0.136 mmol) in MeOH and 14 mg of Rose Bengal. The reaction vessel was flushed with oxygen, outfitted with an oxygen balloon, and irradiated at 25 °C with a sodium vapor street lamp for 24.5 h, at which point TLC confirmed that starting material was consumed. The reaction mixture was concentrated and then partitioned between 100 mL of EtOAc and 100 mL of water. The organic layer was washed with 100 mL of water, 100 mL of dilute HCl, 100 mL of dilute NaHCO$_3$, and 100 mL of water, successively. The organic layer was dried with anhydrous MgSO$_4$, concentrated, and purified via preparative thin-layer chromatography (mobile phase of 2:1 hexanes/EtOAc). The hydroperoxide was isolated as a colorless, amorphous solid in 50% yield (19.8 mg, 0.067 mmol). The NMR data that follows matched that reported in the literature;[5] ^{1}H NMR (300 MHz, CDCl$_3$) δ 6.21 (s, 1H, H-8), 5.50 (s, 1H, H-16a), 5.35 (s, 1H, H-16b), 4.37 (t, J = 6.8 Hz, 1H, H-10), 3.97 (s, 3H, OC*H*$_3$), 2.12 (d, J = 1.5 Hz, 3H, H-15), 2.02 (s, 3H, H-14), 1.87 (s, 3H, H-13), 1.60–1.71 (m, 1H, H-11a), 1.45–1.55 (m, 1H, H-11b), 0.95 (t, J = 7.3 Hz, 3H, H-12); ^{13}C NMR (75 MHz, CDCl$_3$) δ 181.4 (C, C-4), 161.6 (C, C-2), 157.8 (C, C-6), 131.6 (CH, C-8), 131.4 (C, C-9), 131.1 (C, C-7), 118.5 (CH$_2$, C-16), 118.2 (C, C-5), 99.7 (C, C-3), 90.5 (CH, C-10), 55.3 (OCH$_3$), 24.8 (CH$_2$, C-11), 16.5 (CH$_3$, C-15), 11.9 (CH$_3$, C-14), 10.0 (CH$_3$, C-12), 6.9 (CH$_3$, C-13).

Alcohol 13. To a 25 mL round-bottom flask were charged 19.8 mg of hydroperoxide **4** (0.0673 mmol), 3 mL of CH$_2$Cl$_2$, and 35 mg of triphenylphosphine (0.133 mmol). The reaction

vessel was sealed and stirred for 8.5 h. After TLC confirmed that starting material was consumed, the sample was concentrated and loaded on a small silica plug (4 cm). The excess triphenylphosphine was eluted from the plug with 40 mL of 1:1 hexanes/EtOAc. The alcohol was then eluted with a 40 mL rinse of 10:1 EtOAc/MeOH. The crude alcohol was purified via preparative thin-layer chromatography (mobile phase of 5:1 EtOAc/hexanes). The alcohol was isolated as a colorless, amorphous solid in 59% yield (11.1 mg, 0.040 mmol): ^{1}H NMR (300 MHz, CDCl$_3$) δ 6.21 (s, 1H, H-8), 5.46 (s, 1H, H-16a), 5.19 (s, 1H, H-16b), 4.13 (br t, $J = 6.4$ Hz, 1H, H-10), 3.97 (s, 3H, OCH_3), 2.10 (d, $J = 1.5$ Hz, 3H, H-15), 2.03 (s, 3H, H-14), 1.87 (s, 3H, H-13), 1.55–1.63 (m, 2H, H-11), 0.94 (t, $J = 7.5$ Hz, 3H, H-12); ^{13}C NMR (75 MHz, CDCl$_3$) δ 181.2 (C, C-4), 161.8 (C, C-2), 157.9 (C, C-6), 132.1 (CH, C-8), 131.0 (C, C-7), 118.0 (CH$_2$, C-5), 115.5 (C, C-16), 99.3 (C, C-3), 76.7 (CH, C-10), 55.1 (OCH_3), 28.7 (CH$_2$, C-11), 16.4 (CH$_3$, C-15), 11.7 (CH$_3$, C-14), 9.6 (CH$_3$, C-12), 6.8 (CH$_3$, C-13); HREIMS m/z 301.1402 (calcd for C$_{16}$H$_{22}$O$_4$Na$^+$, 301.1410).

Supporting Information Available: ^{1}H NMR spectra and characterization data for **4**, **7**, **11**, **12**, and **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

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NP049607+