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Biomimetic Synthesis and Structural Reassignment of the Tridachiahydropyrones

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Abstract: The biomimetic synthesis and structural reassignment of tridachiahydropyrone, tridachiahydropyrone B and tridachiahydropyrone C, isolated from mollusks of the order *Sacoglossa*, using a sequence of photochemical transformations from a common polyene precursor are described. These complex natural products may act as sunscreens for the producing organism, thus offering protection from harmful UV radiation and oxidative damage.

Introduction

In recent years, several chemical and ecological investigations of opisthobranch mollusks have been pursued, stimulated in part by the fact that these invertebrates are devoid of an external protective shell and thus appear particularly vulnerable to predation.[1,2] One of the most common forms of defense for these organisms is the use of toxic or noxious chemicals,[3,4] which have been traced in many cases to diet and in some instances de novo biosynthesis.[5]

These sacoglossan mollusks are known to assimilate chloroplasts from siphonaceous marine algae and maintain these organelles in their own tissues where they carry out photosynthesis.[6] Early investigations by Faulkner et al.,[7−9] of two such sacoglossans, *Tridachiella diomedea* and *Tridachia crispate*, resulted in the isolation of a novel group of propionate derived γ-pyrones, namely tridachione (**1**) and 9,10-deoxytridachione (**2**) from the former and crispatone (**3**) and crispatene (**4**) from the latter (Figure 1). Since these initial reports, a wealth of related compounds with an impressive breadth of biological activities and diverse molecular architectures have been isolated from sacoglossan mollusks. Figure 1 highlights the four most common structural motifs of this family including 1,3-cyclohexadiene derivatives **1** and **2**; bicylo[3.1.0]hexanes **3** and **4**; and photodeoxytridachione (**5**);[9,10] bicyclo[4.2.0]hexane structures belonging to ocellapyrone A (**6**), and B (**7**),[11] elysiapyrone A (**8**);[12] and the unusual tridachiahydropyrone (**9**),[13] tridachiahydropyrone B (**10**) and tridachiahydropyrone C (**11**).[14]

These interesting metabolites comprise a γ-pyrone 'headgroup' appended to a polyene, or polyene-derived carbon-frame/side chain, with the exception of the tridachiahydropyrones **9**−**11**, where the pyrone group forms part of the core framework. Unlike their congeners, the polypropionate carbon skeleton of the tridachiahydropyrones have undergone rearrangement with the C-12 methyl group shifted to the C-13 position.

In vitro experiments by Ireland and Faulkner[9] demonstrated the photochemical conversion of **2** into **5** with retention of optical activity, leading to the suggestion that the rearrangement occurred through a $[_{\sigma}2_a+_{\pi}2_a]$ mechanism. A common biosynthetic pathway for the *Tridachia* and *Tridachiella* metabolites was suggested, and confirmed by Ireland and Scheuer, who demonstrated photochemical conversion of **2** into **5** in vivo.[15] The results suggested that the in vivo process may not be enzymatic and was instigated when the level of UV radiation penetrating the dorsal surface of the mollusk exceeds the absorption limits of the γ-pyrone moiety.[15] The experiments led to speculation that the metabolites are biosynthesized and translocated to the tissue of the digestive diverticula,[16] where they serve as sunscreens to protect the mollusks from damaging UV radiation.[15] This hypothesis is reasonable, since these sacoglossans live in shallow lagoons where they are exposed to sunlight, thus representing a chemical adaptation of the creatures to their environment. The recent isolation of the oxidized propionate derivatives (e.g., **7**, **8**, **10**, and **11**) has also

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(16) The digestive diverticula flank the dorsal surface of the animal.

10.1021/ja900369z CCC: $40.75

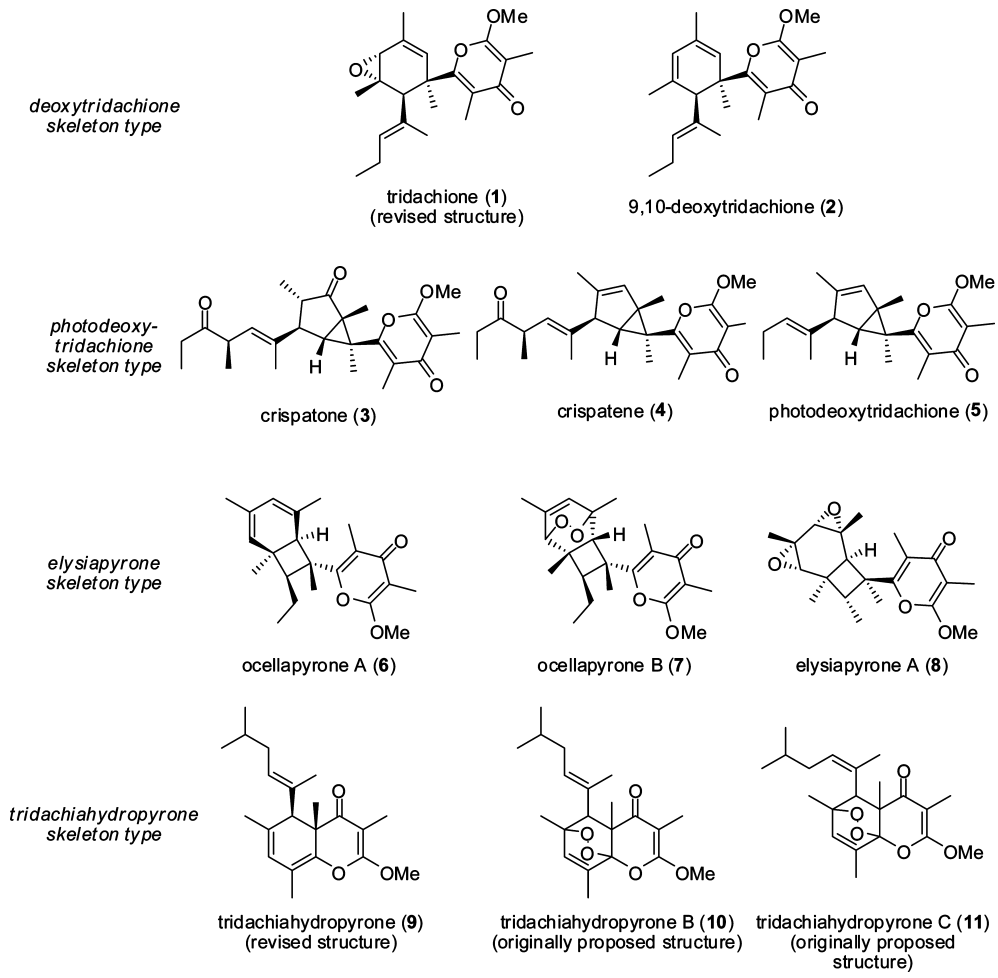

Figure 1. Structural diversity of polypropionate γ-pyrone metabolites.

raised speculation that this family of metabolites may serve to scavenge harmful reactive oxygen species (ROS).[12]

The structural diversity, varied biological activities, and interesting chemical relationships make this family of natural products attractive targets for synthesis. In addition to our own studies,[17] the groups of Trauner,[18] Jones,[19] Parker,[20] and Nicolaou[21] have produced numerous elegant syntheses of unsaturated polyketides.[22] We previously put forward the hypothesis[17b] that many complex polypropionate metabolites may be derived biosynthetically, from linear polyenes with all-*E*-configuration.[23] We proposed that $E-Z$ double bond isomerization followed by thermal and/or photochemical electrocyclization, [4 + 2] cycloaddition reactions or [2 + 2] concerted rearrangements would account for the formation of all the core structures apparent in this family. The driving force for the $E-Z$ isomerization provided by the strained polyene backbone, resulting from unfavorable 1,3-eclisping methyl interactions.[17d] Supporting this hypothesis, we recently demonstrated that a number of diverse natural products, including **2**, **5**, and **6**, are directly accessible from a common tetraene-pyrone precursor.[24]

Intrigued by the unusual structure of the tridachiahydropyrone family and our interest in their biosynthetic relationships, we initiated a program to explore the biomimetic synthesis of these novel metabolites. Very recently, we completed the first total synthesis of **9** and in the course of this work revised its

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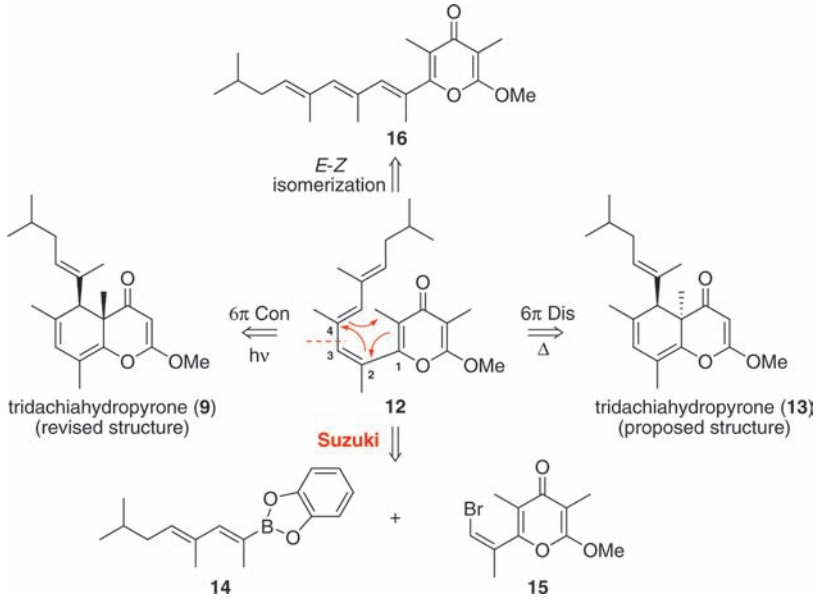
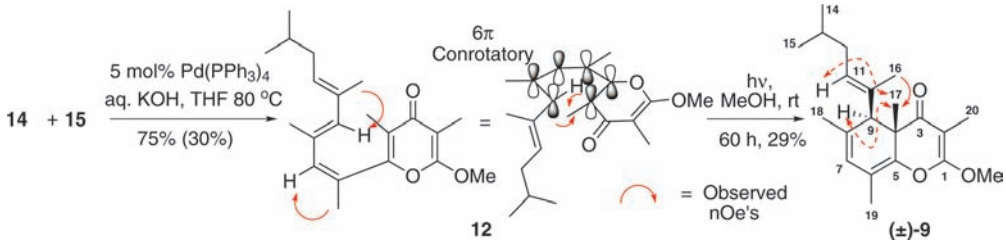
Scheme 1. Biomimetic Retrosynthetic Analysis of **9**



Scheme 2. Biomimetic Photochemical Synthesis of **9**



structure.[25] In this paper we report details of our synthetic investigations in the tridachiahydropyrone field, including the biomimetic syntheses and structural reassignment of **9**, **10**, and **11**, using a sequence of photochemical transformations from a common polyene precursor. Our observations support the notion that these natural products may act as sunscreens for the producing orgnanism, thus offering protection from harmful UV radiation and oxidative damage.

Results and Discussion

Retrosynthetic Biomimetic Analysis. 9 is comprised of an unusual fused bicyclic pyrone-containing ring. Both Trauner et al.[22] and ourselves[23] have proposed that **9** may arise in nature from the (2*Z*,4*E*,6*E*)-polyene pyrone **12** via a photochemical conrotatory 6π electrocylization (Scheme 1). Initially, tridachiahydropyrone was assigned as the trans-diastereoisomer **13** by Cimino et al.,[13] based upon extensive spectroscopic studies. However, an unambiguous synthesis of *trans*-**13** by Perkins et al. led to the speculation that the cis-diastereoisomer **9** was the true structure, since their spectroscopic data were not consistent with those of the natural product.[26] Interestingly, **13** could also, in principle, arise from **12** through a thermal disrotatory 6π electrocylization (Scheme 1).

Indeed, this hypothesis formed the basis of our biomimetic synthesis.[25] Retrosynthetically, the polyene **12** was disconnected at the C3−C4 bond, which presented a convenient cleavage point for a convergent synthesis. Unification of the corresponding boronate ester **14** and the vinyl bromide **15** through a Suzuki cross-coupling reaction[23−25] would present an opportunity to install the required *Z*-double bond in an unambiguous manner. Alternatively, mirroring our previous studies, a selective photochemical *E*−*Z* isomerization of C2−C3 double bond in the all-*E* isomer **16** would also render the required precursor **12**, which in turn could also be obtained using a Suzuki type coupling of **14** with the *E*-isomer of **15**.

Biomimetic Synthesis of 9. The synthetic precursor for (*Z*,*E*,*E*)-**12** and (*E*,*E*,*E*)-**16** polyene pyrones were readily obtained using our previously established chemistry.[24] Thus, a Suzuki cross-coupling reaction between the known fragments **14** and **15** provided the polyene pyrone (*Z*,*E*,*E*)-**12** in 75% crude yield [>95% purity by ^{1}H NMR], based on conversion of **15** (Scheme 2). The polyene **12** was found to be sensitive to silica gel chromatography and underwent significant decomposition upon purification (30% isolated yield). The (*Z*,*E*,*E*)-configuration was confirmed by NOE analysis in the ^{1}H NMR spectrum.

Smooth conversion of the (*Z*,*E*,*E*)-**12** to **9** was achieved when a solution of **12** in methanol was left in natural daylight for 3 days.[27] The target natural product (±)-**9** was isolated in 29% yield along with 57% recovered starting material.[25] With **9** in hand, the controversial stereochemical disposition of the 2-hex-

(25) Sharma, P.; Griffiths, N.; Moses, J. E. *Org. Lett.* **2008**, *10*, 4025–4026.

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(27) The solution of compound **12** was exposed to UK sunlight in the month of May for 3 consecutive, partially sunny, days.

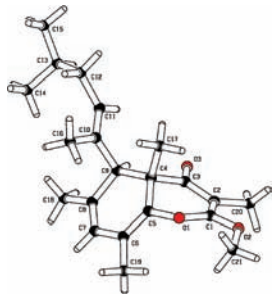
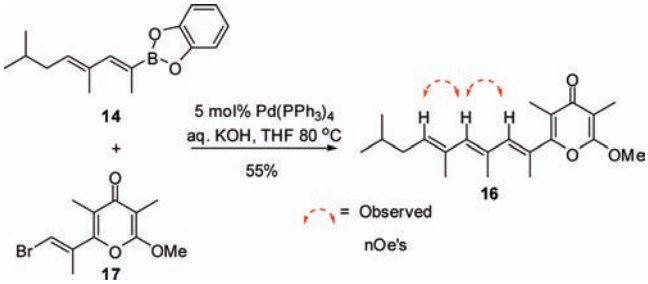


Figure 2. X-ray crystal structure of **9**.

Scheme 3. Synthesis of Polyene **16**



enyl side chain and the methyl group at C-4 in **9** was elucidated by extensive NOE studies. Strong and significant NOE correlations between H_3-17 and H_3-16, and between H_3-17 and H-11 were observed, supporting the cis-diastereoisomer as the true structure. Measurement of the UV absorbance (in MeOH) revealed identical λ_{max} 271 nm for the synthetic and natural tridachiahydropyrone. The stereochemistry was confirmed by single crystal X-ray crystallography of a crystal of synthetic **9**, obtained by slow crystallization from petroleum ether/ethyl acetate (Figure 2).[28] The cis-orientation between the 2-hexenyl side chain and methyl group at C-4 in **9** is consistent with a photochemically allowed conrotatory 6π electrocyclization.[29] Attempts to synthesize the corresponding trans-isomer **13** by thermally induced cyclization were not successful. Prolonged heating of the polyene **12** in xylene at 150 °C in a sealed tube gave only starting material.

The photochemical transformation of **12** into **9** is the first example of such a cyclization onto a γ-pyrone ring and, more importantly, it provides evidence to support our biomimetic hypothesis.[24] The observation also lends weight to the belief that such polyene metabolites may have evolved to protect the producing species from photochemically induced damage.[13,15]

We were intrigued to determine whether the all-*E*-polyene pyrone **16** could also be transformed photochemically into the target **9** via the (*Z,E,E*)-isomer **12**. In this case, there would also be the need to isomerize the *E*-double bond at C-2 to the corresponding *Z*-isomer.

The synthesis of the (*E*,*E*,*E*)-polyene **16** was achieved in 55% isolated yield using a palladium-catalyzed cross coupling reaction between the known vinyl bromide **17**,[24] and the boronate ester **14** (Scheme 3). The (2*E*,4*E*,6*E*)-geometry of **17** was confirmed by NOE analysis.

In our initial studies, natural daylight was used to mediate the photochemical electrocyclic transformation of **12** to **9**. However, these conditions gave inconsistent results, and a uniform and continuous light source was considered more appropriate for our broader studies. Thus, a solution of the polyene **16** in methanol was irradiated using a UV lamp (125 W mercury lamp). After ~1 h, ^{1}H NMR spectroscopic analysis of an aliquot of the reaction mixture revealed formation of the (2*Z*,4*E*,6*E*)-polyene **12**, corresponding to selective photochemically induced 2*E*,2*Z* -isomerization.[30] The mixture was irradiated further and the reaction progress monitored by ^{1}H NMR spectroscopy (Figure 3). The gradual disappearance of **16** and **12** was accompanied by the formation of **9**. Prolonged irradiation showed the appearance of a new set of peaks in the ^{1}H NMR spectra (after 7 h). Isolation by preparative TLC gave recovered starting material 20%, the (*Z*,*E*,*E*)-isomer **12** 30%, tridachiahydropyrone **9** in 25% yield, and a new compound **18** in 18% yield (Scheme 4). The structure of the new photoproduct **18**, which we name "phototridachiahydropyrone", was determined by extensive analysis of its spectroscopic data, further corroborated by X-ray crystallographic analysis (Figure 4).[31] Furthermore, prolonged exposure of a solution **16** in methanol to natural daylight, resulted in 75% conversion of **16** into **12**, **9**, and **18** in a 20:7:1 ratio, respectively (by ^{1}H NMR).[32]

The formation of **18** may be explained as arising from **9** through a photochemical 1,3-sigmatropic migration of the 2-hexenyl side chain, which is consistent with the observed stereochemical outcome. This impressive and selective tandem sequence of photochemical transformations is quite remarkable. In terms of the producing organism, the photoactive metabolites could, in principle, offer significant protection from harmful radiation per mole.

To our knowledge, **18** has not been isolated from a natural source. However, given the photochemical relationship between **9** and **18**, it is reasonable to propose that **18** may be a natural product yet to be discovered. Prolonged irradiation (24 h) of **9** lead to its complete conversion into **18**, with no evidence of reversibility under the reaction conditions. It appears therefore that **18** is the preferred photochemical product.

Synthesis and Structural Revision of 10 and 11. In 2000, Schmitz et al., isolated six new propionate-derived metabolites form extracts of *P. ocellatus* (order *Sacoglossa*, family Elysioidea) including **10** and **11**. Compounds **10** and **11** were reported as a mixture of nonseparable isomers differing in the geometry of the C-10/C-11 double bond, in a ratio of 4:5, determined by ^{1}H NMR analysis. The relative or absolute configuration of the chiral centers was not elucidated.[14,33]

We previously suggested that **10** and **11** are derived biosynthetically from **9**, via a photochemical [4 + 2] cycloaddition with singlet oxygen.[23] Accordingly, a mixture of diastereomeric compounds would be expected to arise from a facially selective addition of singlet oxygen to either the concave or convex face

(28) Atomic coordinates for **9** are available upon request from the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW (Deposition number CCDC 705489).
(29) Woodward, R. B.; Hoffmann, R. *J. Am. Chem. Soc.* **1965**, *87*, 395–397.
(30) We have previously observed similar selective photochemically induced double bond isomerisation with model tetraene systems: (a) Moses, J. E.; Baldwin, J. E.; Marquez, R.; Adlington, R. M.; Claridge, T. D. W.; Odell, B. *Org. Lett.* **2003**, *5*, 661–663.
(31) Atomic coordinates for **18** are available upon request from the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW (Deposition number CCDC 705490).
(32) The solution of compound **16** was exposed to UK sunlight in the month of March for 3 consecutive, partially sunny, days.
(33) In their manuscript, Schimitz et al., reported that their sample had totally decomposed before a NOESY experiment could be conducted. We found the synthetic sample to be stable.

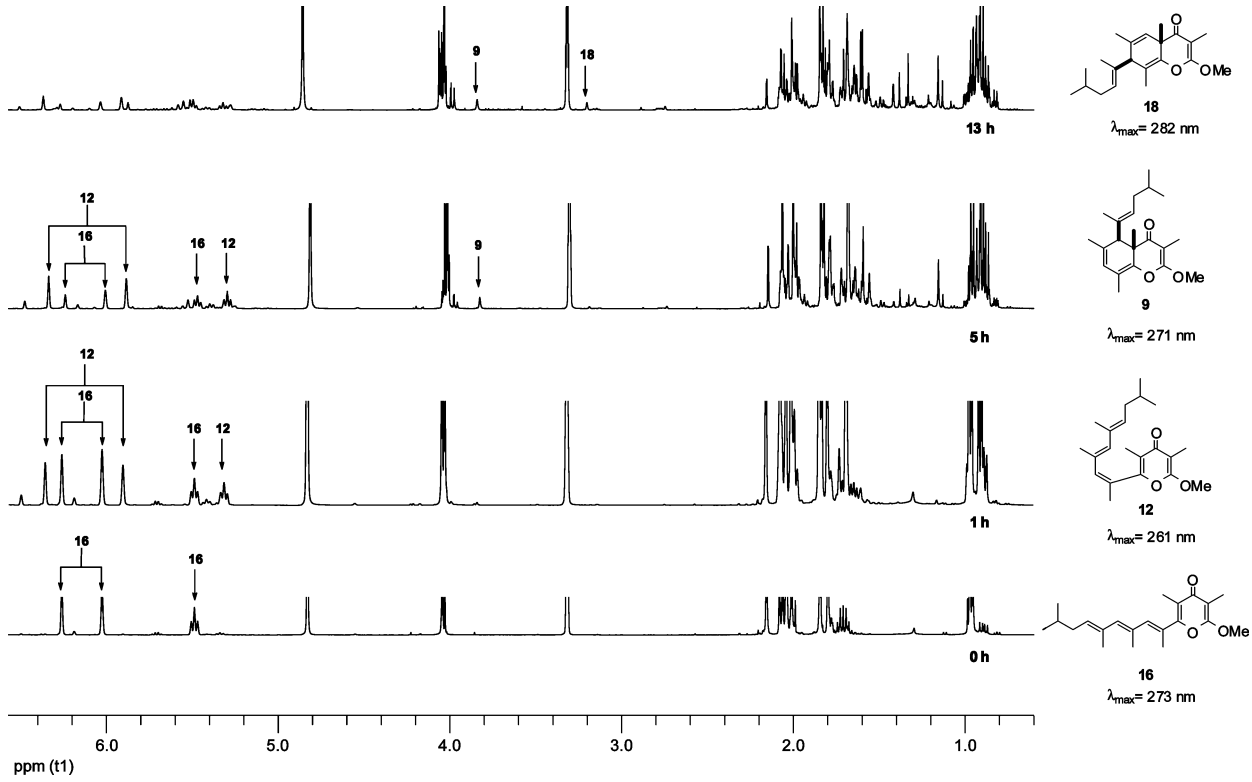
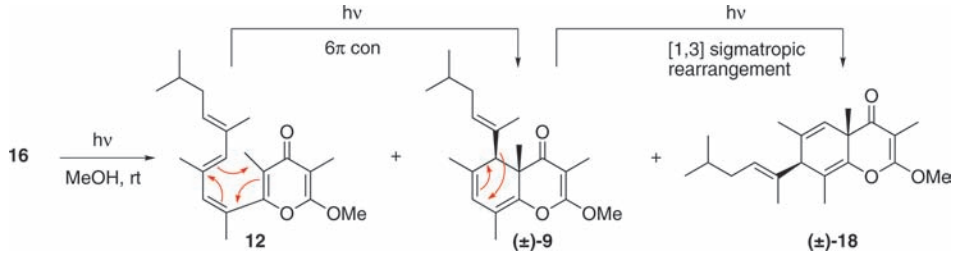


Figure 3. Time-dependent study of the photochemical transformation of the all-*E* isomer **16** by ^{1}H NMR (MeOH-d_4, 400 MHz) analysis.

Scheme 4. Biomimetic Conversion of Polyene **16** into **9** and **18**



of **9**. The origin of **11** would arise either through isomerization of the C10−C11 double bond of **10** or its precursor. To explore this hypothesis, we set out to synthesize **10** according to the proposed photochemical transformation. On the basis of the fact that α-methoxy-γ-pyrones are known to be photosensitizers,[19a] we felt that the fused pyrone ring of tridachiahydropyrone may also function analogously. Hence, irradiation of a solution of **9** in anhydrous chloroform under continuous flow of molecular oxygen for 4 h, resulted in the formation of a new product. ^{1}H NMR spectroscopic analysis of the isolated compound was in complete agreement with the reported data for the nonseparable mixture of **10** and **11** and in identical ratio [4:5] (Scheme 5). Alternatively, when the reaction was carried out under analogous condition in the presence of 0.2 equiv of methylene blue, complete conversion into the desired products was realized in 0.5 h in quantitative yield.[34]

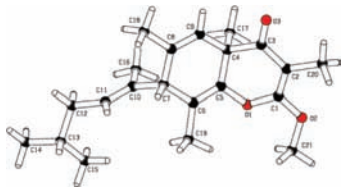
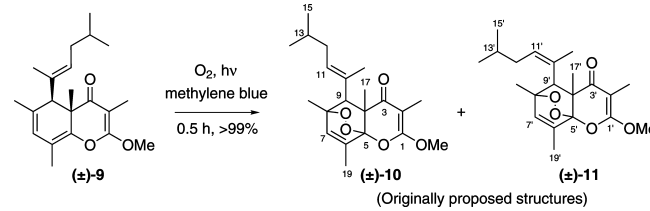


Figure 4. X-ray crystal structure of **18**.

Scheme 5. Biomimetic Synthesis of **10** and **11**



To gain further structural insight into the structures of **10** and **11**, extensive spectroscopic analysis of the mixture of compounds was performed. The bond connectivity agreed with reported layout, as supported by HMBC, HMQC, and COSY experiments. Attempts to elucidate the relative stereochemistries of **10** and **11** by NOE led us to conclude that the two proposed nonseparable diastereoisomers were in fact rotamers.

Figure 5 depicts the key NOE experiment. Irradiation of the alkene proton at 5.86 ppm (H_1-11), resulted in negative

(34) When a solution of either **12** or **16** in methanol was exposed to air and natural daylight (3 days in an open vessel), no formation of compound **19** was observed.

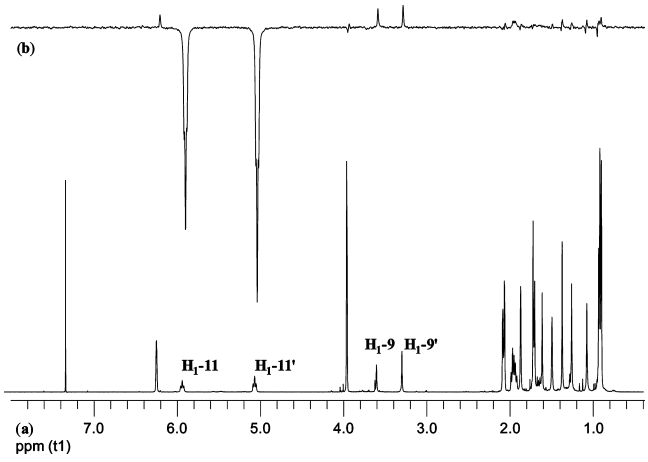


Figure 5. (a) ^{1}H NMR ($CDCl_3$, 400 MHz); (b) NOE spectra of compound **10** and **11** showing the effect of irradiation of H_1-11 being sensed equally by H_1-11′.

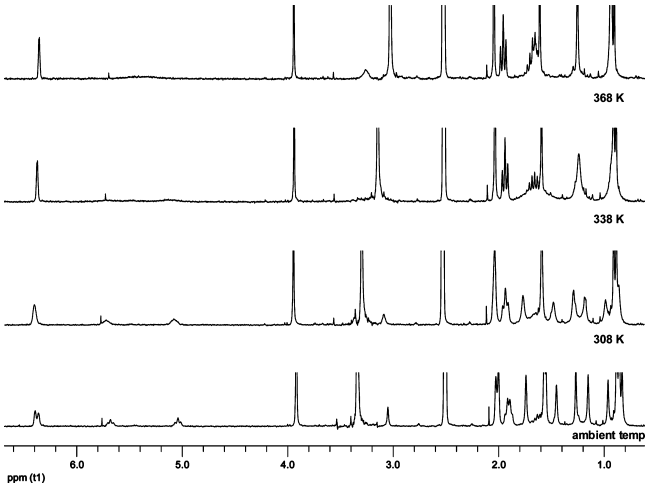


Figure 6. Ramp VT ^{1}H NMR (DMSO-d_6, 270 MHz) of a mixture of compounds **10** and **11**.

enhancement of the alkene proton at 5.00 ppm (H_1-11′), along with significant positive enhancement of both C-9 and C-9′ methine protons at 3.55 and 3.25 ppm, respectively. This phenomenon was observed with all other sets of isomeric peaks, leading to the conclusion that the irradiated protons were one and the same, rapidly exchanging at ambient temperature, maintaining a ratio of 4:5. The chance of irradiation spillover was ruled out on the basis that the protons were separated by almost 1.0 ppm, with this pattern being observed for all other irradiations. A ramp variable temperature experiment further corroborated our NOE interpretation, with the proton NMR spectrum at elevated temperature showing coalescence of the rotameric peaks, as illustrated in Figure 6. Cooling of the sample to ambient temperature gave identical ratio of the rotamers [4:5].

At ambient temperature, we propose that the steric congestion due to the formation of the oxo-bicyclic ring system and the flanking methyl groups at C-8 and C-4 restricts the free rotation of the 2-hexenyl side chain leading to time dependent appearance of two rotameric compounds in ^{1}H NMR. A plausible view of hindrance to rotation is depicted in Figure 7.

The NOE experiments revealed a strong and significant correlation between H_1-11 and H_1-7, indicating that singlet oxygen approaches through the concave face of **9** leading exclusively to the endo product **19**. As depicted in Figure 7,

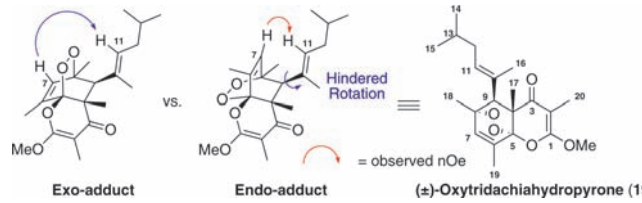


Figure 7. Exo vs endo adduct and view of plausible hindered rotation in **19**.

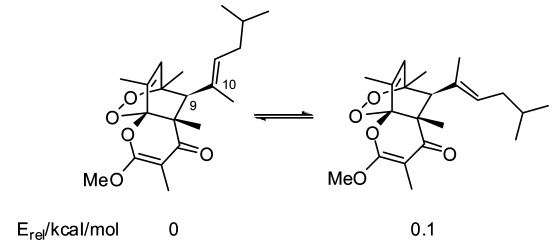


Figure 8. Relative energies of two low-energy conformations about C9−C10 predicted by PM3 calculations.

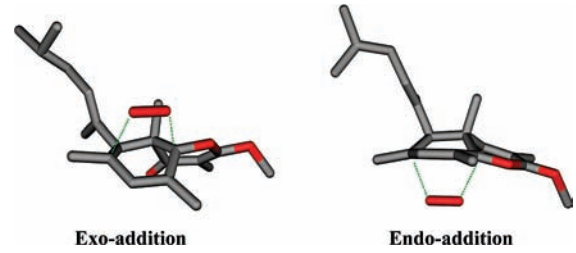


Figure 9. Predicted transition state structures[35] for exo- and endo-addition of singlet oxygen to diene **9**.

the close proximity of the H-11 and H-7 of the endo isomer supports our spectroscopic interpretation.

In an effort to provide further support for these conclusions we have examined the conformation of the C9−C10 bond using semiempirical calculations.[35] The two low-energy conformations about the C9−C10 bond in endo-cycloadduct **19** are predicted to be roughly equal in energy (Figure 8) and the minimum barrier to interconversion was estimated to be ca. 13 kcal/mol.

These results are in broad agreement with the data presented in Figure 5 and so provide further support for the arguments presented. We have also generated transition state structures for endo- and exo-cycloaddition of singlet oxygen to diene **9** using semiempirical methods (Figure 9).

The transition state diagrams suggest that endo addition involves reaction via the less hindered face of the diene. This mode of addition is predicted to be favored by ca. 9 kcal/mol, and although semiempirical calculations do not give accurate estimations of transition state energies, the magnitude of this difference suggests that endo-addition should be greatly favored.

Taking into consideration the natural habitat of these mollusks and the fact that they are devoid of a protective shell, it has been widely discussed that the metabolites are produced as a self-defensive mechanism to protect from predators and too long exposure to UV radiation. Our own results, which connect all the members of the tridachiahydropyrone family through a series of photochemical transformations, supports this hypothesis. It

(35) All calculations reported here were performed using Spartan'04, Wavefunction, Inc., Irvine, CA Kong, J.; et al. *J. Comput. Chem.* **2000**, *21*, 1532.

is important to note that though the isolated natural products are chiral in nature, the putative polyene precursors are achiral. The successful in vitro and in vivo experiments by Faulkner and Ireland[8,15] for the related propionate metabolites rule out the possibilities that these transformation are enzyme driven and support them to be purely photochemical. As realized by Trauner et al.,[22] isolation of optically pure compounds perhaps can be linked to the electrocyclization occurring in the polyketide synthases (PKS) directly after synthesis of the polyene precursors.

We speculate that the chiral environment of the cell membrane could also be responsible for the observed chirality. For example, the structure of key polyene precursor **16** has properties similar to that of a lipid, i.e., a polar headgroup (pyrone ring) and long hydrophobic chain. It is reasonable that **16** would align itself comfortably in the lipid bilayer of cell membrane. During the photoinduced transformation of **16** into its various products the surrounding chiral environment, provided by the complex composition of the cell membrane namely proteins, carbohydrates, and cholesterol, would influence the transition state of the reaction favoring the torquoselective formation of one enantiomer over the other. However, we cannot discount selective metabolism as the origin of enantiomeric enrichment.

Conclusion

To summarize, our present studies demonstrate that all the members of the tridachiahydropyrone family are accessible from a single all-*E*-polyene precursor (**16**) via photochemical transformations. The results strengthen our belief that the all-*E*-polyene **16** could serve as the common achiral precursor to these polypropionate natural products, and perhaps 1,3-methyl strain provides the driving force. Furthermore, we have revised the structure of **9**,[36] and proven that **10** and **11**, are not distinct natural products but instead rotamers. We propose to rename **10** and **11** as **19**. The synthesis of the photochemically rearranged product **18**, not yet isolated from any natural source, demands further study of correlation between the production of these metabolites as self-defense mechanism against UV light and their natural habitat. An extensive study into the mechanism adopted by these marine organisms to fend off predators and to cope with their physical short comings may lend useful insights into lead discovery of potential antibiotics, anti-inflammatory agents, molecular probes, sunscreens, and anticancer agents.

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Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds. CIF files for **9** and **18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(36) Nicolaou, K. C.; Snyder, S. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1012–1044.