ORGANIC LETTERS

2005
Vol. 7, No. 22
4959−4962

Photosensitized Conversion of 9,10-Deoxytridachione to Photodeoxytridachione

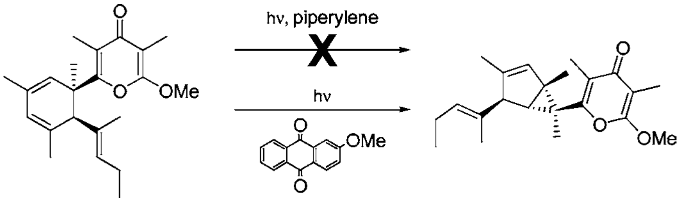
Daniel R. Zuidema,[†] Aubry K. Miller,[‡] Dirk Trauner,[‡] and Paul B. Jones*,[†]

Department of Chemistry, Wake Forest University, Winston-Salem, North Carolina 27109, and Department of Chemistry, University of California, Berkeley, California 94720

jonespb@wfu.edu

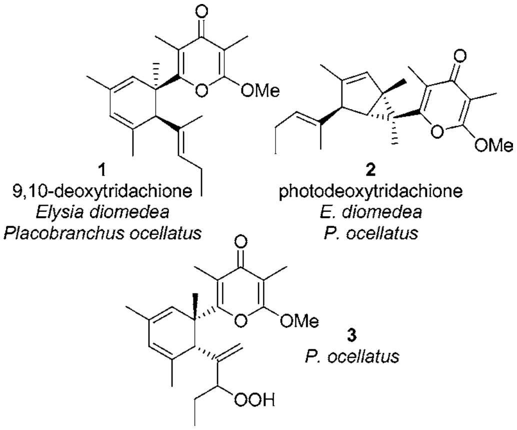
Received August 5, 2005

ABSTRACT



The photochemical conversion of 9,10-deoxytridachione to photodeoxytridachione has been photosensitized. The conversion was also quenched by piperylene. Photodeoxytridachione was produced in good yields under conditions in which only the cyclohexadiene group is sensitized. The results show that some, and perhaps all, of the photoreactions of 9,10-deoxytridachione occur through a triplet excited state. The mechanistic and biosynthetic implications of these results are discussed.

Polypropionate metabolites of sacoglossan mollusks have been an area of active research for natural products chemists and chemical ecologists since the 1970s.[1] These unusual metabolites have been found to undergo interesting chemistry and are implicated in molluscan chemical defenses.[2] Among the first reports in this area was the discovery that two such metabolites, 9,10-deoxytridachione (**1**) and photodeoxytridachione (**2**) (Figure 1), are photochemically related, with the latter being produced from the former upon exposure to sunlight.[3] Clever feeding experiments established that this photochemical conversion occurred in the animal (*Plancho-*



1
9,10-deoxytridachione
Elysia diomedea
Placobranchus ocellatus

2
photodeoxytridachione
E. diomedea
P. ocellatus

3
P. ocellatus

Figure 1.

[†] Wake Forest University.

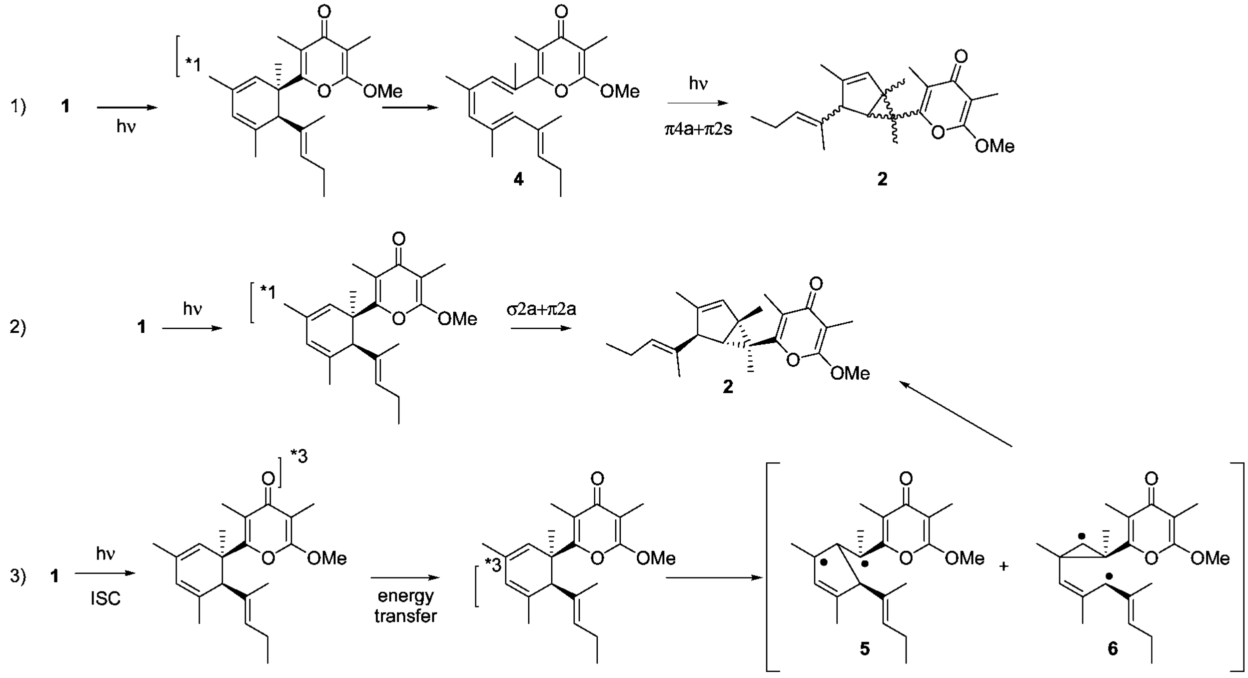
[‡] The University of California at Berkeley.

[1] (a) Cimino, G.; Ciavatta, M. L.; Fontana, A.; Gavagnin, M. In *Bioactive Compounds from Natural Sources*; Corrado Tringali, Ed.; Taylor and Francis: London, 2001; Chapter 15, pp 577−637. (b) Di Marzo, V.; Vardaro, R. R.; De Petrocellis, L.; Villani, G.; Minei, R.; Cimino, G. *Experientia* **1991**, *47*, 1221−1227. (c) Gavagnin, M.; Mollo, E.; Cimino, G.; Ortea, J. *Tetrahedron Lett.* **1996**, *37*, 4259−4262. (d) Ksebati, M. B.; Schmitz, F. J. *J. Org. Chem.* **1985**, *50*, 5637−5642. (e) Gavagnin, M.; Spinella, A.; Castelluccio, F.; Cimino, G. *J. Nat. Prod.* **1994**, *57*, 298−304.

[2] (a) Marin, A.; Ros, J. *Sci. Mar.* **2004**, *68 Supp. 1*, 227−241. (b) Gavagnin, M.; Mollo, E.; Montanaro, D.; Ortea, J.; Cimino, G. *J. Chem. Ecol.* **2000**, *26*, 1563−1578. (c) Cimino, G.; Fontana, A.; Gavagnin, M. *Curr. Org. Chem.* **1999**, *3*, 327−372. (d) Gavagnin, M.; Marin, A.; Mollo, E.; Crispino, A.; Villani, G.; Cimino, G. *Comp. Biochem. Physiol., B* **1994**, *108*, 107−115.

10.1021/ol051887c CCC: $30.25

Scheme 1. Possible Mechanisms for the Conversion of **1** to **2**



brachus ocellatus).[3b] The animals in which these two metabolites were found all lived on sandy reef flats in shallow water and, thus, were exposed to significant quantities of sunlight.

New sacoglossan metabolites have been continually discovered over the past several decades.[1] Synthetic chemists and photochemists were slow to enter the field. The synthesis of **2** was first reported[4] in 2003 and that of **1** in 2005.[5]

Aside from the initial photochemical experiments that established the relationship between **1** and **2**, no additional photochemical studies appeared until 2003.[6] The continuing work of natural products chemists provided several additional examples of possible photochemical relationships in the mollusks.[7] Cyercene A was shown to be photochemically converted to both placidene A and isoplacidene A via photochemical isomerization of acyclic alkenes.[8] The same study showed that cyercene A is converted to a known hydroperoxide metabolite when irradiated in the presence of oxygen.[8]

Each of these reactions was found to proceed through a triplet excited state. It is important to note that **1** contains two chromophores linked via a saturated carbon. These are a γ-pyrone and a 1,3-cyclohexadiene. We have shown that γ-pyrones are effective triplet sensitizers.[8] This raised a question in regard to the spin-multiplicity of the photochemical conversion of **1** to **2** given that cyclohexadienes have been used as triplet quenchers.[9] The simplest member of the class, 1,3-cyclohexadiene itself, has a T_1 energy of 53 kcal/mol.[9] One additional piece of evidence that also suggests that irradiation of **1** results in triplet excited states was the isolation of hydroperoxide **3**, reported in 2000, from *P. ocellatus*.[10] Hydroperoxides such as **3** have been shown to derive from polypropionate precursors via reactions with singlet oxygen, which can be sensitized by the pyrone itself.[8,11]

There are a number of examples of 1,3-cyclohexadienes being converted photochemically to bicyclo[3.1.0]hex-2-enes (e.g., **2**) in the literature.[12] There are three mechanistic possibilities in the conversion of **1** to **2** (Scheme 1). The first is that excited **1** undergoes a six-electron conrotatory ring-opening electrocyclization to give acyclic polyene **4**. Excitation of **4** then gives **2** via a ${}_{\pi}4_a + {}_{\pi}2_s$ electrocyclization.

---

[3] (a) Ireland, C.; Faulkner, J. *Tetrahedron* **1981**, *37 Suppl. 1*, 233−240. (b) Ireland, C.; Scheuer, P. J. *Science* **1979**, *205*, 922−923.

[4] Miller, A. K.; Trauner, D. *Angew. Chem., Int. Ed.* **2003**, *42*, 549−552.

[5] (a) Moses, J. E.; Adlington, R. M.; Rodriguez, R.; Eade, S. J.; Baldwin, J. E. *Chem. Commun.* **2005**, 1687−1689. (b) Miller, A. K.; Trauner, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4602−4606.

[6] (a) Moses, J.; Baldwin, J. E.; Bruckner, S.; Eade, S. J.; Adlington, R. M. *Org. Biomol. Chem.* **2003**, *1*, 3670−3684. (b) Bruckner, S.; Baldwin, J. E.; Moses, J.; Adlington, R. M.; Cowley, A. *Tetrahedron Lett.* **2003**, *44*, 7471−7473.

[7] (a) Ciavatta, M. L.; Trivellone, E.; Villani, G.; Cimino, G. *Tetrahedron Lett.* **1993**, *34*, 6791−6794. (b) Vardaro, R. R.; Di Marzo, V.; Crispino, A.; Cimino, G. *Tetrahedron* **1991**, *47*, 5569−5576. (c) Vardaro, R. R.; Di Marzo, V. D.; Cimino, G. *Tetrahedron Lett.* **1992**, *33*, 2875−2878. (d) Cutignano, A.; Fontana, A.; Renzulli, L.; Cimino, G. *J. Nat. Prod.* **2003**, *66*, 1399−1401.

[8] Zuidema, D. R.; Jones, P. B. *J. Nat. Prod.* **2005**, *68*, 481−486.

[9] Murov, S. L.; Carmichael, I.; Hug, G. L. Triplet State Energies: Ordered. In *Handbook of Photochemistry*, 2nd ed.; Dekker: New York, 1993; pp 54−98.

[10] Fu, X.; Hong, E. P.; Schmitz, F. J. *Tetrahedron* **2000**, *56*, 8989−8993.

[11] (a) Cueto, M.; D'Croz, L.; Mate, J. L.; San-Martin, A.; Darias, J. *Org. Lett.* **2005**, *7*, 415. (b) Barbarow, J. E.; Miller, A. K.; Trauner, D. *Org. Lett.* **2005**, *7*, 2901−2903.

[12] (a) Dauben, W. G.; Kellogg, M. S. *J. Am. Chem. Soc.* **1972**, *94*, 8951−8953. (b) Dauben, W. G.; Smith, J. H. *J. Org. Chem.* **1967**, *32*, 3244−3246. (c) Evanega, G. R.; Bergmann, W.; English, J., Jr. *J. Org. Chem.* **1962**, *27*, 13−20. (d) Dauben, W. G. *Pure Appl. Chem.* **1973**, *33*, 197−215.

Both of these photochemical steps would most likely come from an excited singlet state. The second possibility, suggested by Ireland and Scheuer[3b] and later by Baldwin,[6a] is that excited **1** undergoes a ${}_{\sigma}2_{a} + {}_{\pi}2_{a}$ electrocyclizaton to directly give **2**. Again, this photoreaction would most likely involve an excited singlet state. The third involves direct conversion of **1** to **2** via a diradical pathway, which would most likely be a triplet state process. The first mechanism can likely be excluded as the observed retention of stereochemistry in the conversion of **1** to **2** argues against the intermediacy of achiral polyene **4**.[1e,3,6a] However, the concerted reaction in the second mechanism would proceed through a singlet excited state allowing the observed retention of stereochemistry to be easily explained, as short-lived singlet states generally display a high degree of stereoselectivity in their reactions.[13] In the third mechanism, two steps are required to go from **1** to **2**. Triplet cyclohexadiene first undergoes a rearrangement that produces a diradical. Both diradicals **5** and **6** would lead to **2**. In either case, the recombination of the diradical to give **2** must be relatively fast (for a triplet diradical) in order to account for the retention of stereochemistry observed in the reaction.[13]

Most observers have favored the second mechanism as a result of the need to explain retention of stereochemistry in **2**.[1e,3a,6a] However, 1,3-cyclohexadienes in the S_1 state generally undergo a ring-opening electrocyclization.[14] Also, the γ-pyrone moiety in **1** dominates the absorption spectrum of the molecule. Given the observation that γ-pyrones act as triplet sensitizers,[8] the possibility that the excited state responsible for the conversion of **1** to **2** is a triplet cannot be discounted. If so, the third mechanism shown above is most likely as excited triplets rarely, if ever, undergo concerted electrocyclization reactions and excited singlets generally do not undergo diradical reactions.[14]

Therefore, we sought to establish the spin-multiplicity of the excited state of **1** responsible for production of **2**. Having samples of synthetic **1** and **2** in hand,[5b] we set out to test the effect of triplet quenchers and sensitizers on the photoconversion of **1** to **2**. If the photoreaction proceeds through a triplet state, the conversion should be slowed or stopped by quenchers and accelerated by sensitizers.[15] Our results are presented below.

The effect of piperylene on the reaction was first examined. Piperylene generally quenches excited triplets at nearly diffusion-controlled rates.[9] However, in this instance an available energy sink, the 1,3-cyclohexadiene, is covalently attached to the γ-pyrone chromophore. Thus, in our first attempt, we chose to use neat piperylene as the quencher. Two equimolar solutions of **1** were prepared. In the first, **1** was dissolved in hexane, while in the second, **1** was dissolved in piperylene.

The two samples were degassed and then irradiated using a 450 W medium-pressure Hg lamp and a uranium oxide doped glass filter ($\lambda > 350$ nm). The reactions were followed by GC using an internal standard (octyl ether). In the reaction in hexane, **1** was quickly converted to **2**, in 49% yield (as measured by GC), along with several other minor products (Figure 2c). When the reaction was run identically using piperylene as the solvent, the ratio of **1** to internal standard did not change and no photodeoxytridachione was observed after 10 h (Figure 2b). None of the additional peaks observed in the chromatogram of the reaction in hexane were produced in the reaction in piperylene (Figure 2c).

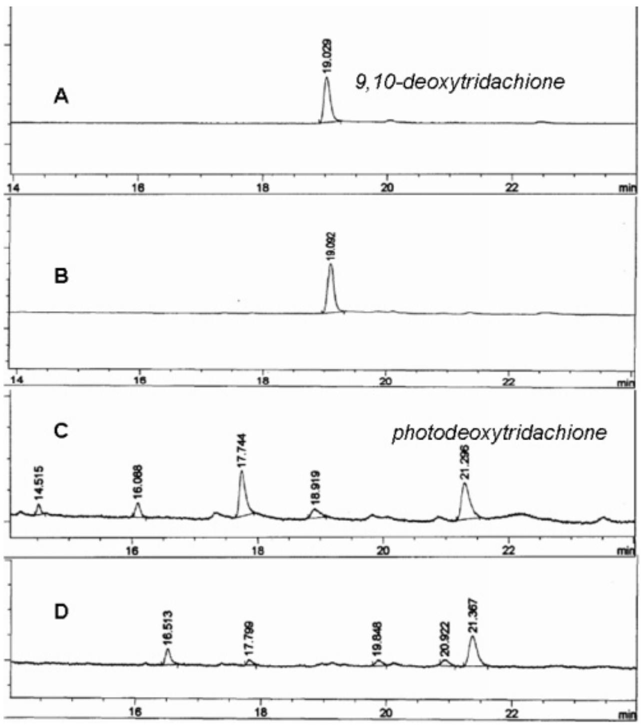


Figure 2. Photolysis of **1**: (A) $t = 0$ h, (B) $t = 10$ h in piperylene, 366 nm, (C) $t = 10$ h in hexane, 366 nm, (D) $t = 2$ h in benzene with 5 mol % **7**, 419 nm. Internal standard (octyl ether, $t_R = 8.45$ min) not shown.

When piperylene was added to reactions run in hexane (0.1 and 0.01 M), quenching was again observed, though some conversion of **1** to **2** did occur (Table 1). The absence of conversion of **1** to **2** in the triplet-quenching solvent

Table 1. Conversion of **1** after 3 h of Irradiation ($\lambda > 350$ nm) in Varying Quantities of Piperylene

[M] piperylene	% conversion **1**
10	0
0.1	32
0.01	74
0	100

---

(13) (a) Turro, N. J. Theoretical Organic Photochemistry. In *Modern Molecular Photochemistry*, 2nd ed.; University Science Books: Mill Valley, CA, 1991; pp 199–231. (b) Giese, B.; Wettstein, P.; Stahelin, C.; Barbosa, F.; Neuberger, M.; Zehnder, M.; Wessig, P. *Angew. Chem., Int. Ed.* **1999**, *38*, 2586. (c) Bartlett, P. D.; Porter, N. A. *J. Am. Chem. Soc.* **1968**, *90*, 5317.

(14) Zimmerman, H. E.; Epling, G. *J. Am. Chem. Soc.* **1972**, *94*, 8749–8761.

(15) Engel, P. S.; Monroe, B. C. *Adv. Photochem.* **1971**, *8*, 245–313.

piperylene suggested that the conversion proceeded through a triplet excited state. Presumably, this occurs when the pyrone absorbs light and undergoes intersystem crossing to give a T_1 pyrone. Intramolecular energy transfer from the T_1 pyrone to the attached cyclohexadiene gives T_1 cyclohexadiene. The T_1 cyclohexadiene then reacts to give **2**. To further test the hypothesis that T_1 cyclohexadiene is responsible for production of **2**, we attempted to sensitize the conversion. The sensitizer used was 2-methoxy-9,10-anthraquinone, **7**.[16] Thus, two equimolar solutions of **1** were prepared. The first contained **1** dissolved in benzene. The second was identical to the first except that 5 mol % of sensitizer **7** was included. The two samples were then irradiated in a Rayonet reactor with lamps having peak emission at 419 nm (no emission <400 nm). The use of these lamps ensured that only the sensitizer **7** (and not **1**) would be excited. In the sensitized reaction (Figure 2d), little **1** remained after 1 h while **2** had been produced in good yield. At this point no photo products were detected in the unsensitized reaction. Note that in the sensitized reaction, the 1,3-cyclohexadiene unit of **1** is taken directly to the T_1 state without passing through the intervening S_1 state or either S_1 or T_1 of the pyrone. From the T_1 state, the excited cyclohexadiene gave **2** directly.

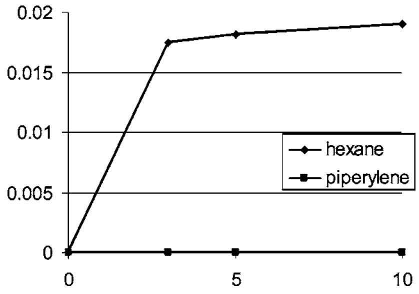


Figure 3. Progression of the photolysis of **1** to **2** in hexane and piperylene. Photolysis with a 450 W Hg lamp and UO_2 doped glass filter (λ > 350 nm). IS = internal standard (octyl ether).

The GC traces under all conditions studied (quencher present, sensitizer present, no additive with Hg lamp, and sunlight) all look qualitatively the same. However, the peak eluting at 17.8 min ($\mathbf{P_{17.8}}$) was much larger when **1** was excited directly than when the reaction was sensitized. It did not appear that $\mathbf{P_{17.8}}$ was an intermediate between **1** and **2**. It was not produced in significant quantity in the sensitized reaction that produced **2** in good yield nor did its slow degradation upon prolonged irradiation lead to an increase in **2**. Because of the amount of material in our possession, we were unable to run the reactions on a scale large enough to observe minor products by NMR. (Because we did not know the identity of $\mathbf{P_{17.8}}$, it was impossible to calculate a response factor for the substance.) However, it seemed possible that $\mathbf{P_{17.8}}$ was the result of a photochemical ring-opening of **1** (i.e., **4**). Polyene **4** is converted to **1** and ocellapyrone A when heated.[5b] Thus, two aliquots containing $\mathbf{P_{17.8}}$ were heated, separately, to 45 °C in $CHCl_3$ and to 150 °C in toluene via microwave.[5b] In neither case was **1** produced. Therefore, it did not appear that $\mathbf{P_{17.8}}$ was polyene **4**. Furthermore, **4** should result from a reaction of S_1 of **1**, yet the production, and photodegradation, of $\mathbf{P_{17.8}}$ was quenched by piperylene. In addition, ocellapyrone A was not observed in any of the photolyses conducted, suggesting that **4** is never produced in the photolysis of **1**.

The principal difference in expected triplet states between direct and sensitized photolysis of **1** is that in the former case T_1 pyrone would precede T_1 cyclohexadiene whereas in the latter T_1 cyclohexadiene should result without the formation of T_1 pyrone. From this we conclude that $\mathbf{P_{17.8}}$ resulted from a reaction of T_1 pyrone that competed with energy transfer to the cyclohexadiene yet did not lead to **2**.

Our results show that photoreactions of 9,10-deoxytridachione (**1**) can be quenched and sensitized and that the excited state of **1** responsible for the production of photodeoxytridachione (**2**) is a triplet excited state localized on the 1,3-cyclohexadiene chromophore of **1**. This is consistent with other studies that have shown γ-pyrones to be effective triplet sensitizers.[8] These results indicate that an unusually selective diradical mechanism, such as that proposed in Scheme 1, is most likely operative in going from **1** to **2**. Furthermore, the observation that the conversion of **1** to **2** is a triplet state process is another piece of evidence that the γ-pyrone metabolites in Sacoglossa act as triplet sensitizers in their native environment. The prevalence of apparent triplet state photoreactions in these metabolites suggest a possible role in the biological function of these molecules. We continue to investigate the chemistry of this interesting class of molecules.

Acknowledgment. This work was supported by National Institutes of Health Grant R01 GM067636 and ACS Petroleum Research Fund grant PRF 37882-G4. D.T. acknowledges Eli Lilly, Glaxo Smith Kline, Amgen, and AstraZeneca Young Investigator Awards. A.K.M. was supported by an NSF predoctoral fellowship. Financial support by Merck & Co. is gratefully acknowledged.

Supporting Information Available: Experimental details and ^{1}H NMR spectrum of **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL051887C

---

[16] Yoshida, Z.; Takabayashi, F. *Tetrahedron* **1968**, *24*, 933−943.