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LETTERS

Mechanistic evidence supporting the biosynthesis of photodeoxytridachione

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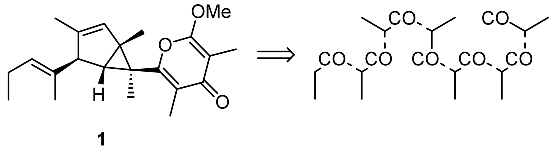
Abstract—This letter describes a two-step photochemical rearrangement of a conjugated pentaene. The results provide evidence that the marine product photodeoxytridachione is formed in two sequential photochemical reactions.

Biosynthetically, it is believed that photodeoxytridachione **1** arises from the assembly of seven propionate units (Scheme 1), the same building blocks used in the biosynthesis of spectinabilin and the SNF family of compounds.[1–3]

Furthermore, it has been demonstrated that photodeoxytridachione **1** can be generated from the metabolite 9,10-deoxytridachione **2** both in vitro and in vivo photochemically (Scheme 2).[1] However, there has been some uncertainty regarding the mechanism of formation of **2**. Faulkner[1b] suggested the non-isolated molecule **3** might be a possible precursor of both 9,10-deoxytridachione **2** and photodeoxytridachione **1**, via a photochemical 6π conrotatory and consecutive σ2a+π2a electrocyclisation,[4] respectively (Scheme 2).

This prompted us to investigate further the biomimetic synthesis of photodeoxytridachione **1**.

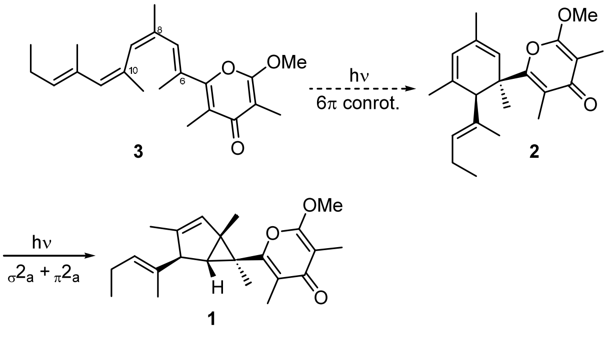
Recently, a synthetic model study of this compound has been reported by our laboratory;[2] tetraene **4** has been synthesised and photolysed. The photochemical rearrangement, which took place, allowed the formation of photodeoxytridachione's core **6** in 60% yield. Since no intermediate was isolated, we previously could only suggest a mechanism for this transformation (Scheme 3).



Scheme 1.

Our proposed mechanism involved initial selective *E–Z* isomerisation to give **5**, the presence of which has been confirmed by NMR during irradiation. This would be followed by a π4s+π2a electrocyclisation to give bicyclo[3.1.0]hexene **6**. However, our findings did not seem to be in agreement with Faulkner's proposals and observations.[1b]

Therefore, we investigated a more appropriate pentaene model system analogous to **3**. With this in mind, the



Scheme 2.

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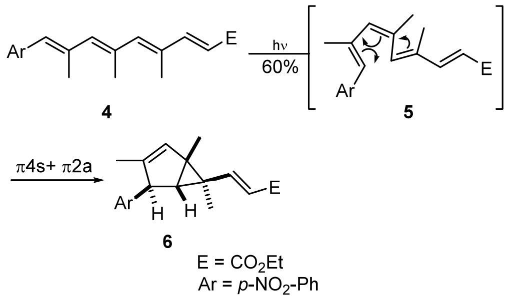
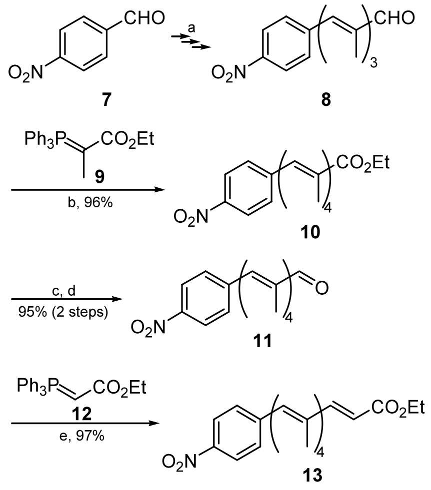
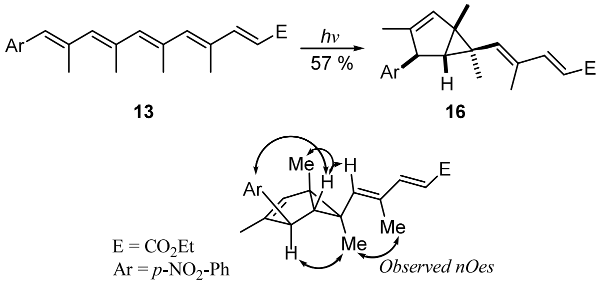


Scheme 3.



Scheme 4. *Reagents and conditions*: (a) Ref. 3; (b) toluene, reflux; (c) Dibal-H, Et_2O, 0°C; (d) MnO_2, $CHCl_3$, rt; (e) benzene, reflux.

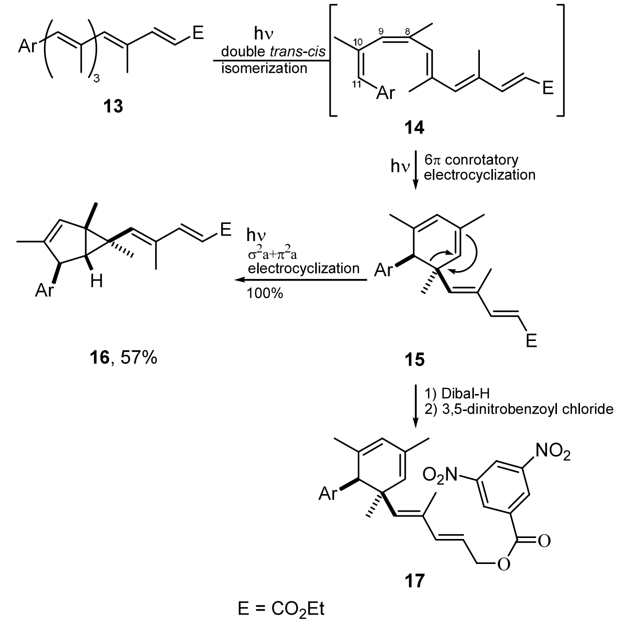


Scheme 5.

(*E*,*E*,*E*,*E*,*E*)-pentaene ester **13** has been synthesised using the strategy previously reported.[3] Thus aldehyde **8** was coupled to the stabilised ylide **9** to give the fourth propionate unit (Scheme 4). After reduction of the ester **10** to the alcohol stage, an oxidation gave the aldehyde **11**. Finally a Wittig reaction with the functionalised ylide **12** afforded the expected all (*E*)-pentaene **13** in good overall yield.

As was found with tetraene **4**,[2] ester **13** is transformed, under photochemical conditions (UV_{DCM}: **13**: λ_{max} = 373 nm, ε = 35200, 2 days irradiation with a 600 W tungsten bulb), to give the photodeoxytridachione core **16** (Scheme 5).

Moreover, while the bicyclo[3.1.0] hexene **16** (determined by two-dimensional NMR and NOE) has been obtained in 40% yield, compound **15** was also isolated in 17% yield after 2 days irradiation of **13** (Scheme 6). This structure was corroborated by X-ray analysis of the derivatised ester **17**[5] (Scheme 6, Fig. 1). Furthermore, ester **15** was shown to be an intermediate in the formation of **16**. An NMR study clearly showed a direct and complete conversion of **15** (UV_{DCM}: **15**: λ_{max} = 264 nm, ε = 18400) into **16** upon irradiation of **15** under direct sunlight. No evidence for **14** by retro-electrocyclisation was observed. The stereochemistry of **15** results from a double isomerisation followed by an electrocyclisation. Indeed, together with the C_8–C_9 alkene the C_{10}–C_{11} double bond must undergo a photochemically induced *E*–*Z* isomerisation to generate **14**. This intermediate can undergo a symmetry-allowed photochemically induced 6π conrotatory electrocyclisation[4] to give cyclohexadiene **15**. This is followed by a photochemical allowed σ2a+π2a electrocyclisation[4,6] which completely converts the cyclodiene **15** into **16**, raising the yield of **16** to 57%.



Scheme 6.

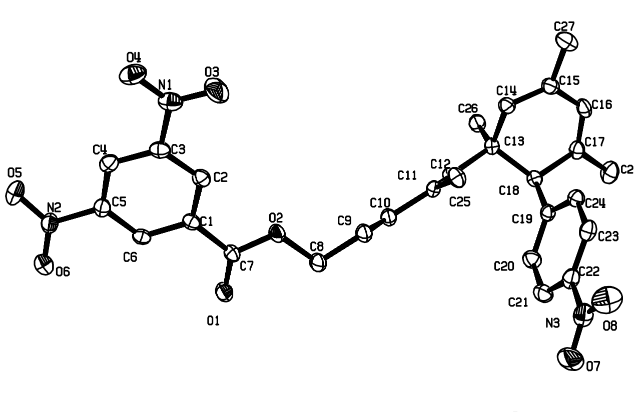


Figure 1. X-Ray structure of cyclohexadiene **17**.[5]

In conclusion, we have demonstrated the connection between the linear all *E*-pentaene **13**, intermediate **15** and the bicyclic[3.1.0] compound **16**. The established mechanism supports a conversion of metabolite **3** into 9,10-deoxytridachione **2**, which then undergoes a direct photochemically induced $\sigma 2a+\pi 2a$ electrocyclisation to afford photodeoxytridachione **1**. This is fully in accordance with the proposed biological pathway.[1] Full detail of these and other results of polyenic compounds will be reported in due course.

Acknowledgements

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4. Woodward, R. B.; Hoffmann, R. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 781.
5. The atomic coordinates for **17** are available upon request from the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW (Deposition number CCDC 209300). The crystallographic numbering system differs from that used in the text; therefore any request should be accompanied by the full literature citation of this paper.
6. Although such photocyclisations have been well studied, we cannot discard the possibility that the reaction mechanism involves a highly stereoselective diradical process.