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Biomimetic Synthesis of the Crispatene Core

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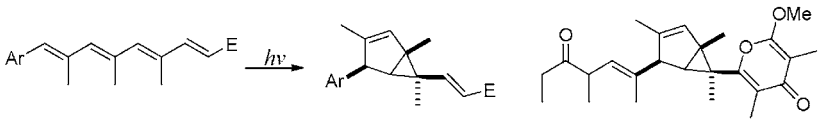
ABSTRACT



The biomimetic synthesis of the crispatene core is reported. The core framework was efficiently generated from an easily synthesized all (*E*)-tetraene precursor in one step, in good yield.

As part of our continuing efforts in the biomimetic synthesis of propionate-derived natural products, we became interested in the crispatene family of compounds.[1] Crispatene **1** and crispatone **2** are cytotoxic bicyclic structures isolated from the Californian mollusc *Tridachia crispata*.[2] They are believed to be mild cytotoxic agents; however, their full biological profile is still unknown.[3]

Structurally, the crispatenes exhibit a densely functionalized [3.1.0] bicyclic core with three or four stereogenic centers. Furthermore, there is a pyrone unit attached to the core structure, reminiscent of several bioactive natural products (Figure 1).[4,5,6]

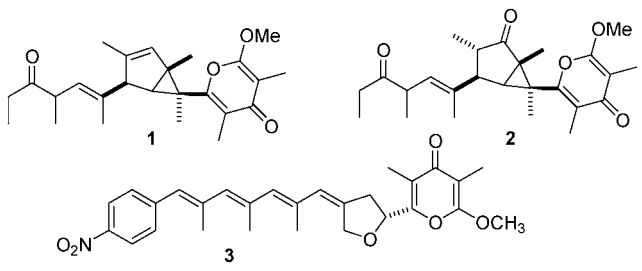
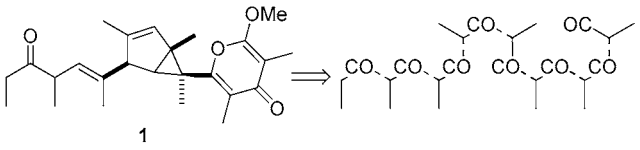


Figure 1. Crispatene **1**, Crispatone **2**, and Spectinabilin **3**.

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

Scheme 1. Proposed Biosynthesis of **1** and **2**



Furthermore, Faulkner et al. have demonstrated that the metabolite 9,10-deoxytridachione **5** can be photochemically transformed to the crispatene core **4**, both in vitro and in vivo. Faulkner suggests that 9,10-deoxytridachione **5** undergoes a $_{\sigma}2_{a} + _{\pi}2_{a}$ electrocyclization to generate **4** (Scheme

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(6) Kakinuma, K.; Hanson, C. A.; Rinehart, K. L. *Tetrahedron* **1976**, *32*, 217.

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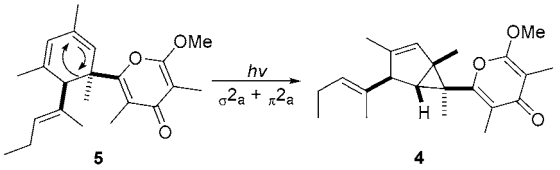
Scheme 2

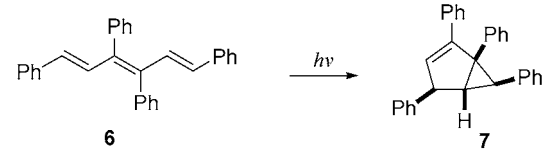


2).[7] A similar reaction has been reported by Barton in which case dehydroergosterol acetate was photolyzed to give photodehydroergosterol.[8]

Our proposed synthesis of the crispatenes was inspired by the results in the biomimetic synthesis of SNF4435C and SNF4435D.[1,9] We have shown that linear all (*E*)-polyenes such as **3** readily undergo *E*−*Z* double-bond isomerizations as a result of steric compressions. These changes in molecular geometry provide the necessary momentum for further chemical transformations.[1]

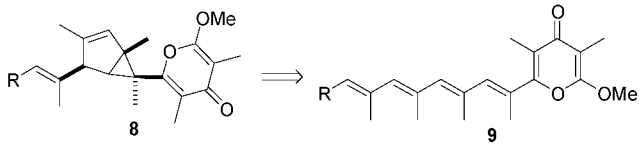
In addition, Dauben and co-workers have shown that irradiation of all (*E*)-1,3,4,6-tetraphenyl-1,3,5-triene **6** gives rise to 1,2,4,6-tetraphenylbicyclo[3.1.0]hex-2-ene **7**, a molecular core that displays a substitution pattern similar to that of crispatenes (Scheme 3).[10]

Scheme 3



This combination of facts prompted us to propose that the crispatene core **8** is biosynthetically derived from the (*E*,*E*,*E*,*E*)-tetraene pyrone **9**, through a photochemical transformation involving initial *E*−*Z* double-bond isomerizations of the tetraene chain (Scheme 4).

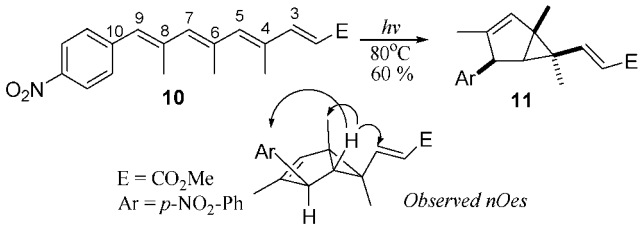
Scheme 4. Retrosynthesis of the Crispatene Core



To test this hypothesis, we started from the (*E*,*E*,*E*,*E*)-tetraene **10** originally developed for our studies on the biomimetic synthesis of SNF4435C and SNF4435D.[1] As was previously found, tetraene **10** has a large degree of strain (as demonstrated by the >130° angle between $C_4-C_5-C_6$ and the 45° dihedral angle of the C_9-C_{10} single bond), which could provide the driving force for such a transformation.[11]

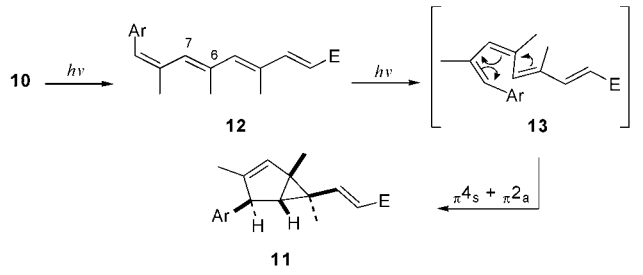
Irradiation of ester **10** with a 600 W tungsten light bulb successfully generated the crispatene core **11** (as determined by two-dimensional NMR) in good yield (60%). The relative stereochemistry was corroborated by a combination of NMR methods, including one-dimensional pulsed field gradient NOESY analysis (Scheme 5). Interestingly, direct sunlight was also effective in slowly promoting this transformation.

Scheme 5



The formation of bicycle **11** may be explained as arising from an intramolecular photochemical Diels Alder reaction, similar to that reported by Padwa et al. in their studies of 1,3,5-hexatrienes.[12] The observed stereochemistry can be rationalized by the following mechanism. In the first instance, ester **10** undergoes a photochemically induced selective double-bond isomerization to yield the (*E*,*E*,*E*,*Z*)-tetraene **12**, which was observed by NMR to appear during irradiation and disappear as the product **11** was formed. Tetraene **12** then undergoes a two-photon-induced C_6-C_7 double-bond isomerization followed by a symmetry-allowed $_{\pi}4_s + {}_{\pi}2_a$ photocycloaddition to afford the crispatene core **11** (Scheme 6).[13,14] Although such photocycloadditions have been well studied, we cannot discard the possibility the reaction mechanism involves a highly stereoselective diradical process.

Scheme 6



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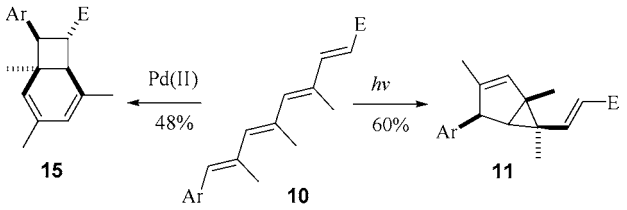
(10) Dauben, W. G.; Smith, J. H. *J. Org. Chem.* **1967**, *32*, 3244.
(11) In erratum: The dihedral angle quoted in our previous communication (*Org. Lett.* **2002**, *4*, 3731) should have been denoted as that of the C_9-C_{10} single bond, not that of the C_8-C_9 double bond.
(12) Padwa, A.; Brodsky, L.; Clough, C. *J. Am. Chem. Soc.* **1972**, *94*, 6769. (b) Jacobs, H. J. C.; Havinga, E. *Adv. Photochem.* **1979**, 11, 305.

Scheme 7



In conclusion, we have shown that the crispatene core can be constructed in reasonable yield from the easily prepared (*E*,*E*,*E*,*E*)-tetraene, which supports our biosynthetic proposal. In addition, we have further demonstrated the diversity of synthetic possibilities originating from this class of highly strained polyene esters by simple modification of the reaction conditions. We are now working on ways to expand the synthetic and mechanistic scope of these transformations and, at the same time, explore new synthetic transformations (Scheme 7).

Acknowledgment. We thank the EPSRC for funding to J.E.M. We thank Dr. M. Robinson for fruitful discussions on the mechanistic aspects.

Supporting Information Available: Experimental procedures and NMR data for compound **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL020242Z

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