Natural Products Synthesis

Mining the Tetraene Manifold: Total Synthesis of Complex Pyrones from *Placobranchus ocellatus*[**]

*Aubry K. Miller and Dirk Trauner**

Conjugated tetraenes featuring *Z*-configured double bonds can undergo various cyclizations to rapidly generate molecular complexity. Different modes of thermal or photochemical electrocyclizations and cycloadditions afford structurally diverse scaffolds from a relatively simple (*E*,*Z*,*Z*,*E*)-tetraene precursor (Scheme 1).[1] If the tetraene is unsymmetrical ($R^1 \neq R^2$), additional pathways exist that lead to regioisomers and diastereomers. Isomerizations of the polyene geometry further increase the number of potential cyclization products, thus rendering this reaction manifold dauntingly complex.

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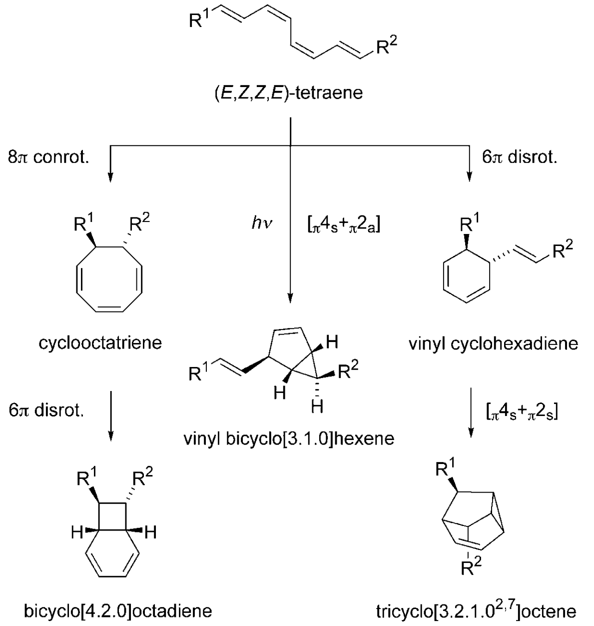
[*] A. K. Miller, Prof. D. Trauner
Department of Chemistry
University of California
Berkeley, CA 94720-1460 (USA)
Fax: (+1) 510-643-9480
E-mail: trauner@cchem.berkeley.edu

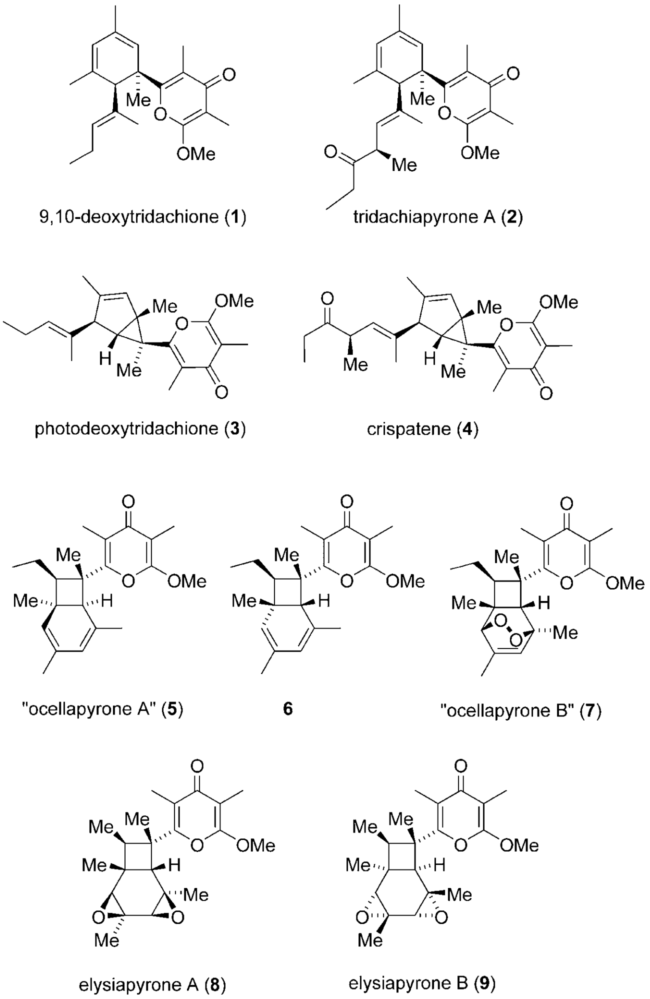
[**] This work was supported by the National Institutes of Health (Grant R01 GM067636). We thank Dr. Frederick J. Hollander and Dr. Alan G. Oliver (UC Berkeley) for X-ray crystal-structure determinations. A.K.M. thanks the NSF for a predoctoral fellowship.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

DOI: 10.1002/ange.200500488



Scheme 1. The tetraene manifold. conrot. = conrotatory, disrot. = disrotatory.



Scheme 2. Polypropionate pyrones isolated from saccoglossan mollusks.

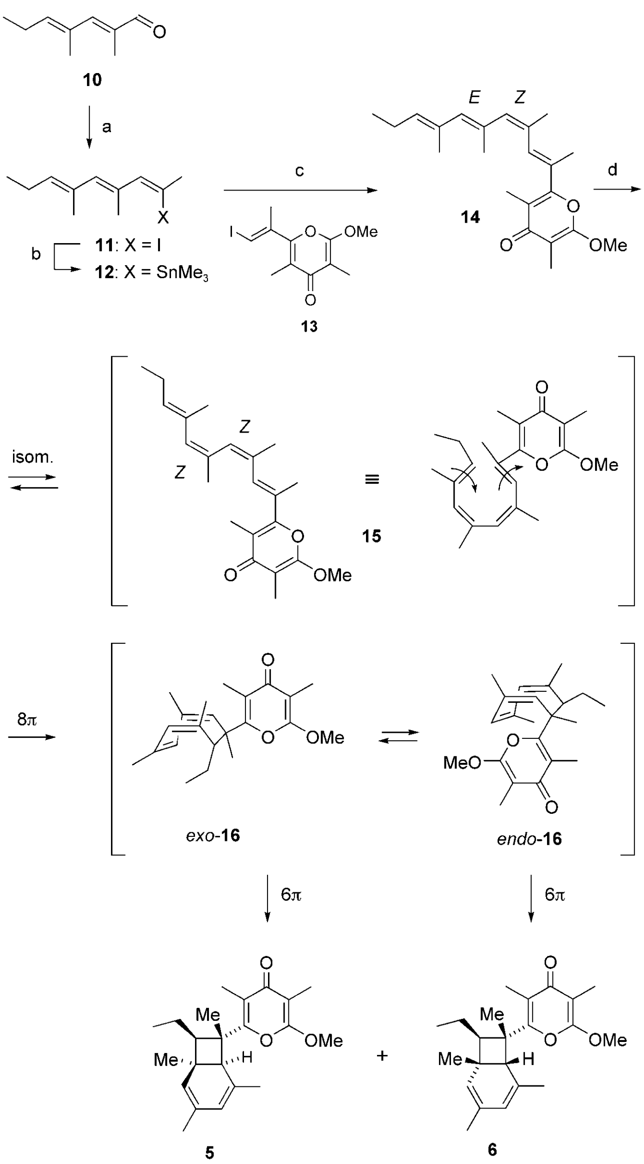
Many of the molecular scaffolds shown in Scheme 1 have been found among natural products isolated from saccoglossan mollusks (Scheme 2). The cyclohexadienes 9,10-deoxytridachione (**1**) and tridachiapyrone A (**2**) were isolated from sea slugs of the genus *Elysia*, which also yielded the bicyclo[3.1.0]hexenes photodeoxytridachione (**3**) and crispatene (**4**).[2]

Recently, several new α-methoxy-γ-pyrones that feature a bicyclo[4.2.0]octane, -octene, or -octadiene skeleton were also found in saccoglossan mollusks. Two unnamed natural products, bicyclo[4.2.0]octadiene **5** and endoperoxide **7**, were found in *Placobranchus ocellatus* which we propose to call ocellapyrones A and B, respectively.[3] Although structure **6** was originally proposed for the bicylco[4.2.0]octadiene natural product (ocellapyrone A), our results (see below) and a recent report by Baldwin and co-workers[4] lead to the reassignment of its structure as **5**. Furthermore, two pyrones with a bicyclo[4.2.0]octane skeleton, elysiapyrones A (**8**) and B (**9**), were isolated from *Elysia diomedea*.[5] Their unusual bisepoxide moiety was proposed to arise biosynthetically from rearrangement of an *endo* peroxide analogous to **7**, which in turn would stem from the corresponding bicyclo[4.2.0]hexadiene through a Diels–Alder reaction that involved singlet oxygen. Note that the elysiapyrones contain one carbon atom less than the ocellapyrones, presumably because of the incorporation of an acetate moiety rather than a propionate unit into their biosynthetic precursor.

Biosynthetically, bicyclo[4.2.0]octadienes **5** and **6** and their oxidized analogues **7**–**9** probably stem from 8π–6π electrocyclization cascades.[6] Similar cascades have been proposed in the biosynthesis of the endiandric acids,[7] as well as the immunosuppressants SNF4435 C/D,[8] and verified by total synthesis.[9]

Herein, we report a synthesis of the racemic ocellapyrones A (**5**) and B (**7**), which originated from a serendipitous discovery. In our previous reports on the total synthesis of photodeoxytridachione (**3**) and crispatene (**4**), we speculated on the possibility of a unified synthetic approach toward both the bicyclo[3.1.0]hexene and cyclohexadiene natural products that would start from an α-methoxy-γ-pyronyl tetraene of type **14** (Scheme 3).[10] To test this hypothesis, vinyl stannane **12** was prepared from the known aldehyde **10** in two steps[11] and then subjected to the Stille coupling procedure[12] with the previously described pyrone building block **13**.[10c,13] The resultant pyronyl tetraene **14**, however, turned out to be quite unstable, as judged by TLC and NMR spectroscopic analysis.

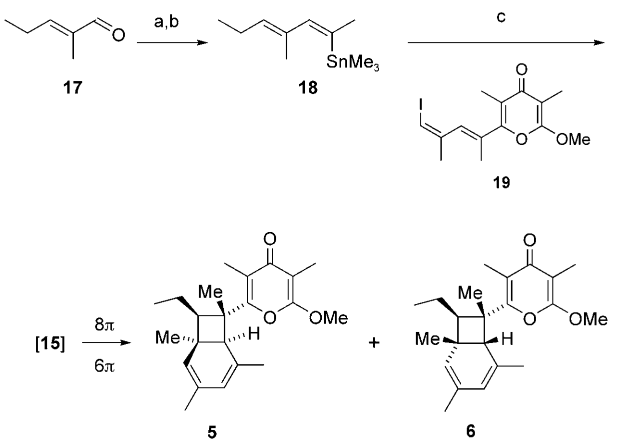
When **14** was heated to 45 °C in $CHCl_3$, a very complex mixture of isomers was formed initially, which over five days gradually converged into bicylo[4.2.0]octadiene **6** accompanied by smaller amounts of ocellapyrone A (**5**). Presumably, *E/Z* isomerization of **14** took place under these conditions to yield (*E*,*Z*,*Z*,*E*)-tetraene **15**. This intermediate then underwent conrotatory 8π electrocyclization to afford cyclooctatriene **16**, which exists as a mixture of *exo* and *endo* conformers. Subsequent 6π electrocyclization of *exo*-**16** gave (±)-ocellapyrone A (**5**), whereas cyclization of *endo*-**16** afforded **6**. Since purified ocellapyrone A (**5**) could not be converted into **6** under the same reaction conditions, this product ratio presumably reflects kinetic control.[14]



Scheme 3. Synthesis of γ-pyronyl tetraene **14** and cyclization to **5** and **6**. Reagents and conditions: a) $Ph_3P{=}CHCH_3$, I_2, NaHMDS, −78 °C, THF (59 %); b) *n*BuLi, $SnMe_3Cl$, −78 °C, THF (69 %); c) **13**, 5 mol % $[Pd(PPh_3)_4]$, 350 mol % CsF, 10 mol % CuI, DMF, 1.5 h, 45 °C (89 %); d) $CDCl_3$, 45 °C, 5 days (13 % **5**; 66 % **6**). HMDS = hexamethyldisilazide, DMF = *N*,*N*-dimethylformamide, isom. = isomerization.

The ^1H and ^{13}C NMR spectra of synthetic ocellapyrone A (**5**) match the reported spectra of the previously unnamed bicyclo[4.2.0]octadiene natural product isolated from *Placobranchus ocellatus*, whereas the spectra of **6**, which represents the originally proposed structure, show marked differences.[15] The detailed structures of **5** and **6** were elucidated by extensive NOE interaction studies and the conversion of **6** into ocellapyrone B (**7**), whose relative configuration has been unequivocally assigned.[3,16]

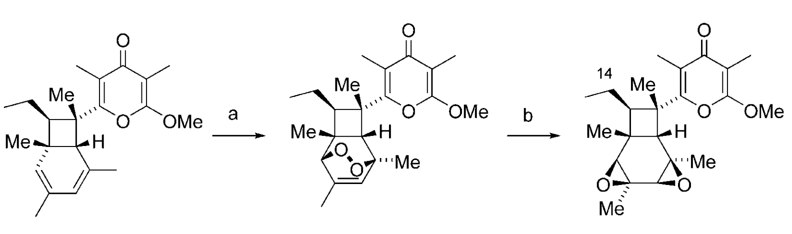
A more rational synthesis of **5** and **6** is shown in Scheme 4. Olefination of the known aldehyde **17**[17] followed by iodine–tin exchange, as before, gave vinyl stannane **18**. This material was then coupled to the known vinyl iodide **19**[4,18] under Stille conditions. The resultant tetraene **15** underwent 8π–6π electrocyclization in situ to give a 1:9 mixture of **5** and **6**. Note that the *endo* isomer **6** again prevailed. The much faster formation of the bicyclo[4.2.0]octadienes under these conditions presumably reflects the fact that **15** does not need to undergo *E*/*Z* isomerization to trigger the electrocyclization cascade, which is apparently the rate-determining step in the conversion of **14** into **5** and **6**.



Scheme 4. Rational synthesis of ocellapyrones A and B. Reagents and conditions: a) $Ph_3PCHICH_3$, NaHMDS, −78 °C, THF (12 %); b) *n*BuLi, $SnMe_3Cl$, −78 °C, THF (86 %); c) **13**, 6 mol % $[Pd(PPh_3)_4]$, 180 mol % CsF, 17 mol % CuI, DMF, 1 h, 45 °C (8 % **5**; 78 % **6**).

Racemic ocellapyrone B (**7**) was obtained in high yield from cyclohexadiene **6** by a [4+2] cycloaddition of singlet oxygen (Scheme 5). The synthetic material was identical in all respects (^1H and ^{13}C NMR, IR, MS) to the natural product.[3] Finally, ruthenium-catalyzed isomerization[19] of ocellapyrone B (**7**) gave bisepoxide **20**, which is a homologue of elysiapyrone A. Although this compound has not been isolated from natural sources so far, it seems entirely possible that it could be found, as endoperoxides can be readily converted into bisepoxides both under thermal and photochemical conditions.[20] The X-ray crystal structure of **20**, with its appealing "crouched" shape, is shown in Figure 1.[21]

In summary, we have demonstrated that complex pyrones isolated from saccoglossan molluscs can be synthesized by isomerization of stereochemically labile tetraenes followed by pericyclic reaction cascades. In combination with our previous



Scheme 5. Synthesis of ocellapyrone B and 14-methylelysiapyrone A. Reagents and conditions: a) O_2, methylene blue, $CHCl_3$, *hv*, reflux, 30 min (89 %); b) 10 mol % $[RuCl_2(PPh_3)_3]$, CH_2Cl_2, 2 h (86 %).

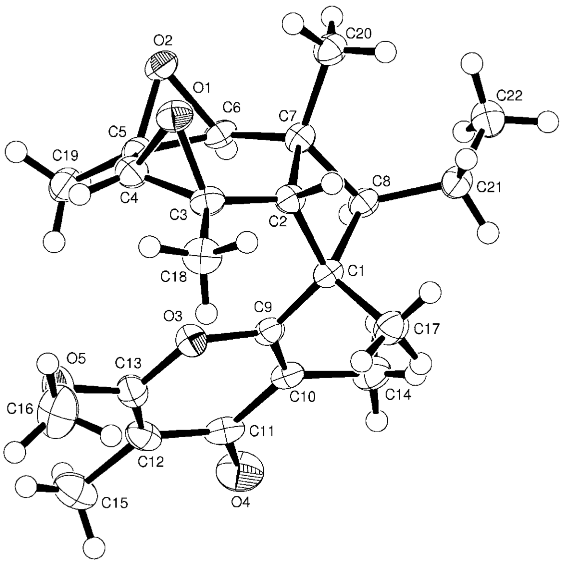


Figure 1. X-ray structure of 14-methylelysiapyrone A (20).

total syntheses of photodeoxytridachione[10a,b] and crispatene,[10c] these results demonstrate the remarkable versatility of conjugated polyenes as precursors for complex polycyclic molecular skeleta. On the basis of our experience with these compounds,[22] we predict that further bicyclo[4.2.0]octadiene natural products and oxidized versions thereof, in particular isomers of crispatene and tridachiapyrone A, will be found. Studies toward asymmetric electrocyclization cascades and the total synthesis of the elysiapyrones are well underway and will be reported in due course.

Received: February 9, 2005
Published online: June 27, 2005

Keywords: biomimetic synthesis · electrocyclic reactions · isomerization · natural products synthesis · reaction cascades

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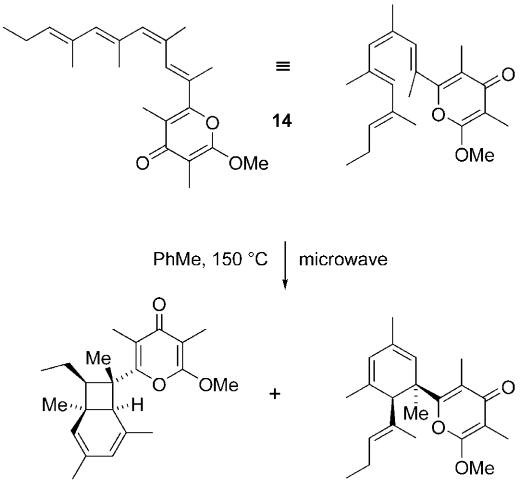
[14] The outcome of this isomerization was found to be strongly dependent on the conditions employed; for example, tetraene **14** underwent isomerization under microwave irradiation (PhMe, 150 °C, 20 min) to afford 9,10-deoxytridachione (**1**) and ocellapyrone A (**5**) in approximately equal amounts.



ocellapyrone A (**5**)
38%

deoxytridachione (**1**)
32%

[15] In the reported isolation of bicyclo[4.2.0]octadiene **5** and endoperoxide **7** (Ref. [3]), the relative structure of ocellapyrone A was "... mainly determined on the basis of NOE difference and NOESY experiments recorded on the peroxide derivative [= ocellapyrone B]".

[16] Independent confirmation of the structure of **5** was obtained by conversion into the corresponding *endo* peroxide, whose structure was determined by X-ray crystallographic analysis. CCDC-269389 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[22] In our previous reports on photodeoxytridachione (Ref. [10a,b]), we erroneously reported the 6π electrocyclization

of tetraenoic ester **21** to afford cyclohexadiene **22**. The "upfield shift" of a vinyl proton ($\delta = 2.93$ ppm) was rationalized with an anisotropic effect exerted by the nearby ester carbonyl group. In fact, double-bond isomerization followed by a stereoselective 8π–6π electrocyclization cascade had taken place. Therefore, the product of this very high-yielding and stereoselective reaction is reassigned as **23**. The structure of **23** was confirmed by reduction of the ester function to a primary alcohol followed by acid-catalyzed ring closure to the caged tricyclic compound **24**. (DIBAH = diisobutylaluminum hydride.)