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Biomimetic Synthesis and Structural Revision of (±)-Tridachiahydropyrone

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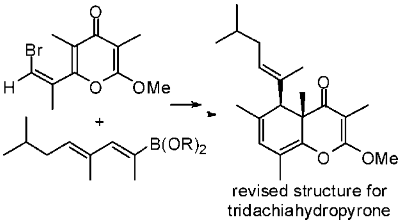
ABSTRACT

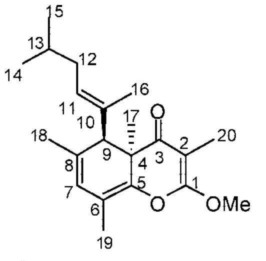


A short synthesis of the revised structure of the marine natural product tridachiahydropyrone is described. A novel biomimetic photochemical electrocyclization was employed to construct the bicyclic carbon framework from an open-chain polyene precursor. The spectroscopic data matched that of the isolated natural product, supporting a revised structure of this complex metabolite.

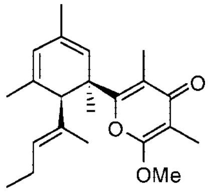
(−)-Tridachiahydropyrone (**1**) is a marine-derived natural product isolated in 1996 by Cimino et al. from the sacoglossan mollusk *Tridachia crispata*.[1] Metabolite **1** is a unique member of the tridachiapyrone family of natural products, which includes, among others, 9,10-deoxytridachione (**2**),[2] tridachiapyrone I (**3**),[3a] and tridachiapyrone A (**4**)[3b] (Figure 1). Tridachiahydropyrone is structurally interesting, comprising an unusual fused bicyclic pyrone-containing ring system, and unlike its congener tridachiapyrone A (**4**), the polypropionate skeleton of **1** has rearanged so that the C-12 methyl group is shifted to the C-13 position.

The initially assigned structure **1** was supported by extensive NMR and NOE spectroscopic analysis, although the absolute configuration was not determined.[1]

Recently, Perkins et al.,[4,5] reported an unambiguous total synthesis of **1**. However, their spectroscopic data did not match that of the isolated natural product. This has led to the suggestion that diastereoisomer **5** could be the true structure of tridachiahydropyrone.[6]



Original structure assigned to tridachiahydropyrone (**1**)



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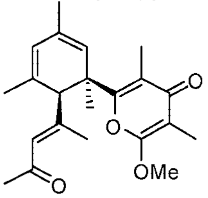

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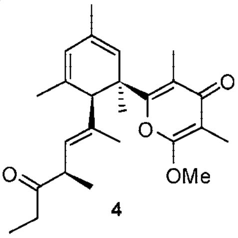

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Figure 1. Members of the tridachiapyrone family of natural products. The originally proposed structure **1** is shown.

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(1) Gavagnin, M.; Mollo, E.; Cimino, G.; Ortea, J. *Tetrahedron Lett.* **1996**, *37*, 4259–4262.

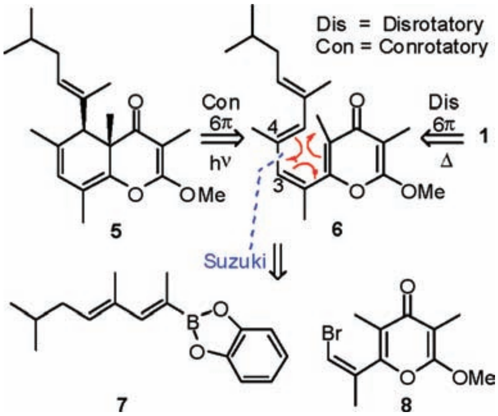
(2) Ireland, C.; Faulkner, D. J *Tetrahedron* **1981**, *37*, 233–240, Suppl. 1.

(3) (a) Fu, X.; Hong, E. P.; Schmitz, F. J. *Tetrahedron* **2000**, *56*, 989–8993. (b) Ksebati, M. B.; Schmitz, F. J. *J. Org. Chem.* **1985**, *50*, 5637–5642.

10.1021/ol8015836 CCC: $40.75

It has been proposed that compound **5** may arise, in nature, from (2*Z*,4*E*,6*E*)-polyene **6** via photochemical, conrotatory 6π electrocyclization (Scheme 1).[6,7] However, it is clearly more complicated in vivo since (−)-tridachiahydropyrone was isolated as a single enantiomer. This issue does not discount our hypothesis since biomimetic chemistry seeks to mimic predisposed chemical reactivity that may occur in nature whether in vivo or otherwise.[8] The proposal is somewhat supported by photochemical studies by Trauner[9] and by our own work[10] on related pyrone-propionate-derived natural products. Furthermore, it has also been suggested that tridachiahydropyrone (and cometabolites) may act as a chemical defense agent against exposure to UV light since the producing mollusks are devoid of protective shells and live in relatively shallow waters.[1,2] Interestingly, a thermally induced disrotatory 6π electrocyclization of **6** would, in principle, yield the initially proposed trans diastereoisomer **1**.

Scheme 1. Proposed Biosynthetic Origin of the Revised Structure of Tridachiahydropyrone (**5**)



Continuing our efforts directed toward the biomimetic synthesis of polyene-derived natural products,[7,10,11] we endeavored to investigate the biosynthetic hypothesis and corroborate the proposed true structure of tridachiahydropyrone **5**, and we now wish to report on our findings. Scheme 1 illustrates our retrosynthetic strategy toward **6**. We considered that the C3−C4 σ bond would provide a suitable cleavage point for a convergent approach, thus revealing borate ester **7** and known vinyl bromide **8**[11] as key intermediates, which could be united through a Suzuki cross-coupling reaction.[7,11] This strategy would enable us to install the (*Z*,*E*,*E*)-polyene stereochemistry in a controlled and unambiguous manner.

The synthesis of **7** began with isovaleraldehyde (**9**), which underwent a Wittig reaction with the stabilized ylide **10**, to yield known ester **11** as the only observed stereoisomer.[12] Reduction of ester **11** with DIBAL-H afforded allylic alcohol **12**, which underwent smooth oxidation to aldehyde **13** using an excess of activated MnO_2. Compound **13** was readily converted to alkyne **15** using Corey−Fuchs methodology[13] via the dibromo species **14**. Finally, hydroboration of **15** with freshly distilled catecholborane furnished the desired borate ester **7** in excellent yield as a single stereoisomer (Scheme 2).[11]

With both borate **7** and the readily available vinyl bromide **8** in hand,[11] the stage was set to attempt the key Suzuki cross-coupling reaction. Using previously established conditions,[11] the desired (*Z*,*E*,*E*)-polyene-pyrone **6** was obtained in a moderate 30% isolated yield.[14] The (*Z*,*E*,*E*)-double bond geometry of **6** was confirmed by NOE analyis (Scheme 2).

In order to test our biomimetic hypothesis, compound **6** was dissolved in methanol and placed under direct sunlight for 3 days.[15] TLC analyis of the reaction mixture revealed the appearance of a new spot, indicating conversion of the starting material. Isolation of the products by preparative TLC gave a new white solid (29%), along with recovered starting material (57%). The ^{1}H and ^{13}C NMR spectra of the new compopund, matched that of the isolated natural product initially reported by Cimino and co-workers.[1] Furthermore, measurement of the UV/vis absorbance (in MeOH) revealed identical λ_{max} 271 nM for the synthetic and natural tridachiahydropyrone.

Extensive NMR and NOE analysis of the synthetic product strongly supported the proposed structure **5** for tridachiahydropyrone (Scheme 3). In their original report, the authors assigned the trans diastereoisomer **1**, based upon a diagnostic NOE effect between H-9 and H_3-17.[1] We also observed the same NOE effect. However, stronger and more significant interactions between H_3-17 and H_3-16 and between H_3-17 and H-11 were consistent with a cis configuration about the C4−C9 bond, leading us to support **5** as the correct structure for tridachiahydropyrone. Furthermore, structure **5** is consistent with a photochemically allowed conrotatory 6π electrocyclisation.[16] Interestingly, attempts to synthesize **1**

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(4) Jeffery, D. W.; Perkins, M. V.; White, J. M. *Org. Lett.* **2005**, *7*, 407–409.

(5) Jeffery, D. W.; Perkins, M. V.; White, J. M. *Org. Lett.* **2005**, *7*, 1581–1584.

(6) For an excellent review, see: Beaudry, C. M.; Malerich, J. P.; Trauner, D. *Chem. Rev.* **2005**, *105*, 4757–4778.

(7) Rodriguez, R.; Moses, J. E.; Adlington, R. M.; Baldwin, J. E. *Tetrahedron* **2007**, *63*, 4500–4509.

(8) Heathcock, C. H. *Proc. Natl. Acad. Sci. U.S.A.* **1996**, *93*, 14323–14327.

(9) (a) Zuidema, D. R.; Miller, A. K.; Trauner, D.; Jones, P. B. *Org. Lett.* **2005**, *7*, 4959–4962. (b) Miller, A. K.; Byun, D. H.; Beaudry, C. M.; Trauner, D. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 12019–12023.

(10) (a) Moses, J. E; Baldwin, J. E.; Marquez, R.; Adlington, R. M.; Claridge, T. D.W.; Odell, B. *Org. Lett.* **2003**, *5*, 661–663. (b) Moses, J. E.; Baldwin, J. E.; Brückner, S.; Eade, S. J.; Adlington, R. M. *Org. Biomol. Chem.* **2003**, *1*, 3670–3684. (c) Brückner, S.; Baldwin, J. E.; Moses, J. E.; Adlington, R. M. *Tetrahedron Lett.* **2003**, *44*, 7471–7473.

(11) (a) Eade, S. J.; Walter, M. W.; Byrne, C.; Odell, B.; Rodriguez, R.; Baldwin, J. E.; Adlington, R. M.; Moses, J. E *J. Org. Chem.* **2008**, *73*, 4830–4839. (b) Jacobsen, M. F.; Moses, J. E.; Adlington, R. M.; Baldwin, J. E *Tetrahedron* **2006**, *62*, 1675–1689. (c) Moses, J. E.; Adlington, R. M.; Rodriguez, R.; Eade, S. J.; Baldwin, J. E. *Chem. Commun.* **2005**, *13*, 1687–1689. (d) Jacobsen, M. F.; Moses, J. E.; Adlington, R. M.; Baldwin, J. E *Org. Lett.* **2005**, *7*, 2473–2476.

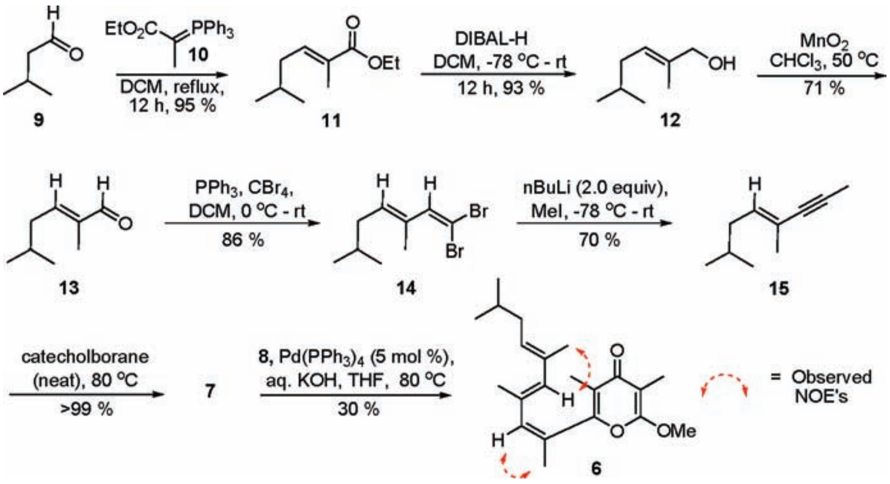
(12) Concellón, J. M.; Rodríguez-Solla, H.; Díaz, P.; Llavona, R. *J. Org. Chem.* **2007**, *72*, 4396–4400.

(13) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *36*, 3769–3772.

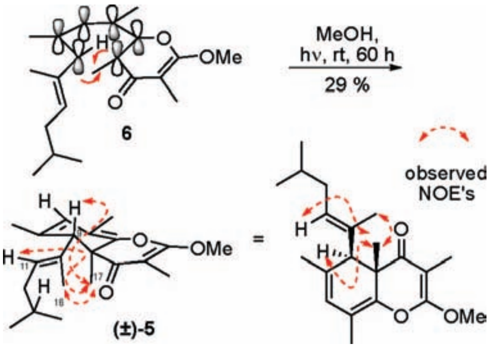
(14) Polyene **6** was found to be unstable and decomposed during purification over silica gel.

(15) The sample was exposed to British summer sunlight in June for 3 consecutive days.

Scheme 2



Scheme 3



by thermally induced cyclization were unsuccessful. Prolonged heating of **6** at 150 °C in a sealed tube with xylene gave no observed formation of disastereoisomer **1**.

In conclusion, a racemic synthesis of the complex propionate derived natural product (±)-tridachiahydropyrone has been achieved. The synthesis involved a key biomimetic photochemically induced electrocycliziation which supports the cis diastereoisomer **5** as the correct structure for tridachiahydropyrone. This is the first example of such a cyclization onto a *γ*-pyrone unit, further supporting our general biosynthetic hypothesis as to the origins of pyrone-propionate natural products from mollusks.[7,10]

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Supporting Information Available: Copies of NMR spectra for all new compounds, data for all new compounds, and experimental procedures for compounds **5**−**7** and **11**−**15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Woodward, R. B.; Hoffmann, R. *J. Am. Chem. Soc.* **1965**, *87*, 395–397.