ORGANIC LETTERS

2008
Vol. 10, No. 18
4025−4027

Biomimetic Synthesis and Structural Revision of (±)-Tridachiahydropyrone

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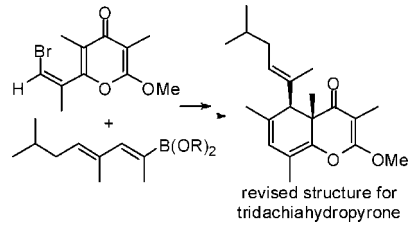
Received July 7, 2008

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]

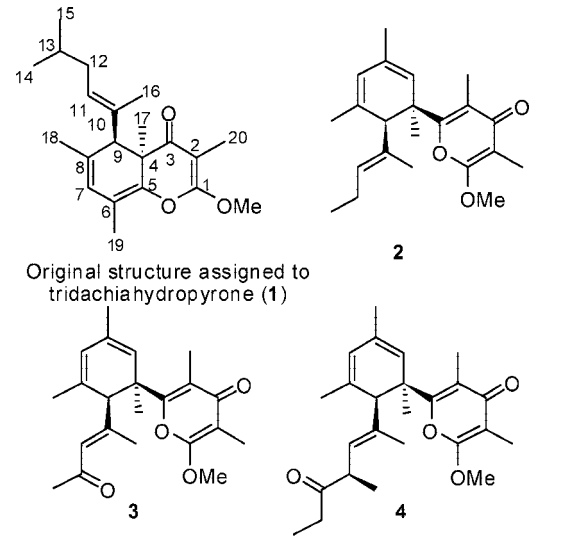


Figure 1. Members of the tridachiapyrone family of natural products. The originally proposed structure **1** is shown.

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

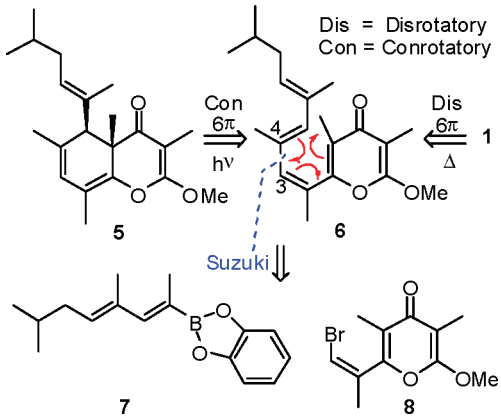
(2) Ireland, C.; Faulkner, D. J *Tetrahedron* **1981**, *37*, 233–240, Suppl. 1.

(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
Published on Web 08/22/2008

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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(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.
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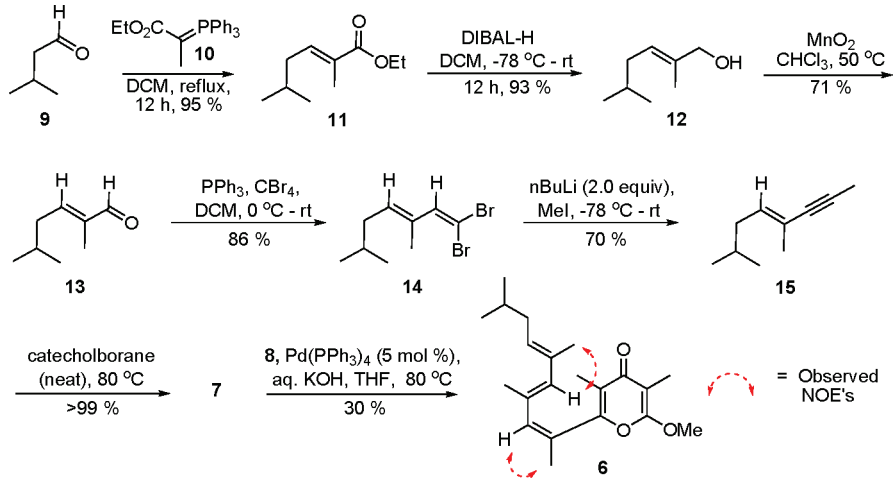
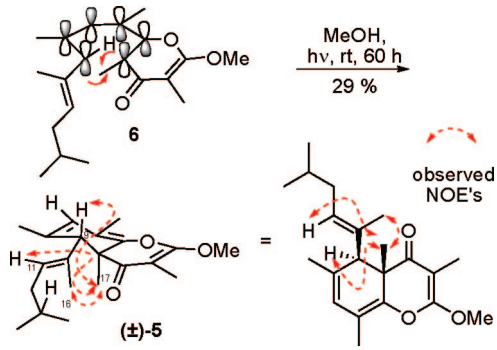
(8) Heathcock, C. H. *Proc. Natl. Acad. Sci. U.S.A.* **1996**, *93*, 14323–14327.
(9) (a) Zuidema, D. R.; Miller, A. K.; Trauner, D.; Jones, P. B. *Org. Lett.* **2005**, *7*, 4959–4962. (b) Miller, A. K.; Byun, D. H.; Beaudry, C. M.; Trauner, D. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 12019–12023.
(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]

Acknowledgment. We wish to thank the EPSRC for funding P.S. and J.E.M. and the University of Nottingham for its support and facilities. Thanks to Dr. R. Rodriguez for fruitful discussions. We are grateful to the School of Chemistry NMR service for support.

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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