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Synthesis of an Analogue of the Marine Polypropionate Tridachiahydropyrone

David W. Jeffery,[†] Michael V. Perkins,*[,†] and Jonathan M. White[‡]

School of Chemistry, Physics and Earth Sciences, Flinders University, G. P. O. Box 2100, S.A. 5001, Australia, and School of Chemistry, The University of Melbourne, Victoria 3010, Australia

mike.perkins@flinders.edu.au

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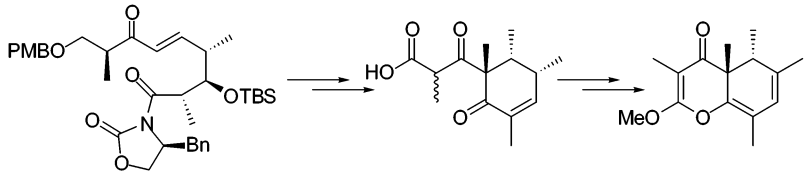
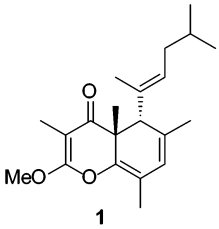
ABSTRACT



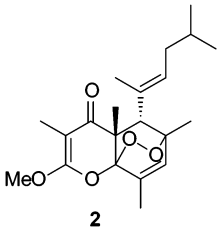
A novel approach to the formation of the unusual pyrone-containing ring systems as found in polypropionate metabolites from the *Tridachia* family of marine molluscs has been developed. This approach includes an intramolecular cyclization of a *β*-keto acid onto a cyclohexenone ring to afford a fused, bicyclic pyrone.

Tridachiahydropyrone (**1**) was isolated in 1996 by Cimino et al. from the sacoglossan mollusc, *Tridachia crispata*.[1] This compound is structurally interesting, possessing an unusual fused, bicyclic, pyrone-containing ring system. The function of such a polypropionate metabolite in the organism is unknown, but it has been postulated that it may act as a chemical defense agent against exposure to UV light.[1]

Subsequently, the metabolites tridachiahydropyrone-B (**2**) and -C (**3**) were isolated from *Placobranchus ocellatus*.[2] These peroxides appear to be photooxygenation products from tridachiahydropyrone (**1**). The biological activity of compounds **1**−**3** has not been evaluated and no syntheses or attempted syntheses of these compounds have been reported.

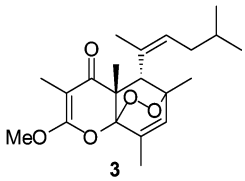


1



2

We have recently developed a method[3] for the formation of cyclohexenone derivatives that we require as synthons for the total synthesis of tridachione marine natural products.[1,2,4] We now report the extension of this methodology to the synthesis of the analogue **4** of tridachiahydropyrone (**1**), which lacks the vinyl side chain.



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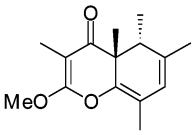

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In the absence of any relevant literature precedent we proposed the cyclization, dehydration, and methylation of

(1) Gavagnin, M.; Mollo, E.; Cimino, G.; Ortea, J. *Tetrahedron Lett.* **1996**, *37*, 4259−4262.
(2) Fu, X.; Hong, E. P.; Schmitz, F. J. *Tetrahedron* **2000**, *56*, 8989−8993.
(3) Jeffery, D. W.; Perkins, M. V. *Tetrahedron Lett.* **2004**, *45*, 8667−8671.
(4) (a) Ireland, C. M.; Scheuer, P. J. *Science* **1979**, *205*, 922−923. (b) Ireland, C. M.; Faulkner, D. J. *Tetrahedron* **1981**, *37* (Suppl. No. 1), 233−240. (c) Ksebati, M. B.; Schmitz, F. J. *J. Org. Chem.* **1985**, *50*, 5637−5642. (d) Dawe, R. D.; Wright, J. L. C. *Tetrahedron Lett.* **1986**, *27*, 2559−2562. (e) Gavagnin, M.; Marin, A.; Mollo, E.; Crispino, A.; Villani, G.; Cimino, G. *Comp. Biochem. Physiol.* **1994**, *108B*, 107−115. (f) Gavagnin, M.; Mollo, E.; Castelluccio, F.; Montanaro, D.; Ortea, J.; Cimino, G. *Nat. Prod. Lett.* **1997**, *10*, 151−156.

[†] Flinders University.
[‡] The University of Melbourne.

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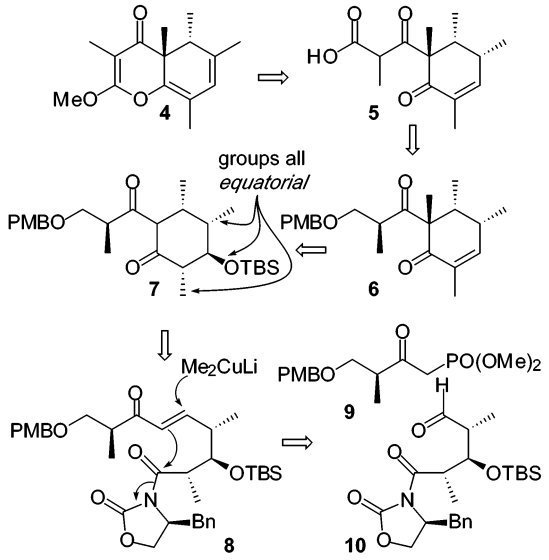
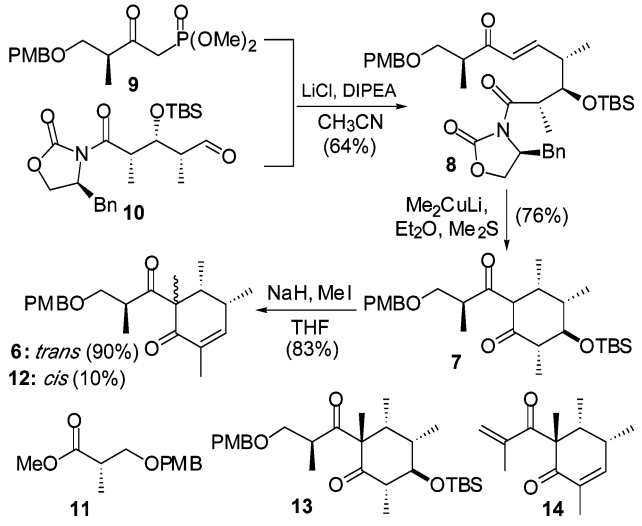
Scheme 1



acid **5** as the final pyrone ring-forming step (Scheme 1). We envisaged the formation of acid **5** by deprotection and oxidation of a suitable precursor **6**. This precursor was proposed to be formed by the tandem conjugate addition/cyclization (to give **7**) and methylation procedure we have developed[3] for the preparation of highly substituted cyclohexenones of this type. The enone **8** required in this case was to be formed by the H/W/E coupling of the phosphonate **9** with aldehyde **10** (Scheme 1).

Phosphonate **9** (enantiomer known[5]) was prepared (90%) by reaction of known chiral ester[6] **11** with the lithium anion of dimethyl methylphosphonate[7] in THF at −78 °C. A H/W/E coupling of known[3] aldehyde **10** with phosphonate **9** under Roush conditions (LiCl, DIPEA, MeCN, room temperature)[8] afforded enone **8** (64%) as a single detectable *E* isomer on a multigram scale (Scheme 2).[9]

Scheme 2



Tandem addition/cyclization of enone **8** with methyl cuprate, as previously described,[3] gave cyclohexanone **7** in 70−80% yield (Scheme 2). The cyclic product existed as a mixture of keto:enol tautomers, but as a single, detectable diastereomer, indicating that the addition was highly facially selective. Treatment of cyclic product **7** with a 2-fold excess of NaH, followed by MeI as previously described[3] afforded a 3:2 mixture of trans:cis products **6** and **12** which were inseparable by column chromatography. However, treatment of cyclohexanone **7** with 1 equiv of NaH followed by MeI and subsequent treatment of the reaction mixture with a second portion of NaH to promote elimination of the OTBS gave an improved 9:1 trans:cis (**6**:**12**) selectivity (determined by GC/MS) in 83% yield.[10] This method also gave a small amount of the OPMB eliminated alkene **14**. Intermediate **13** could also be isolated, and its stereochemistry and that of **6** were assigned by NOE experiments (Figure 1).

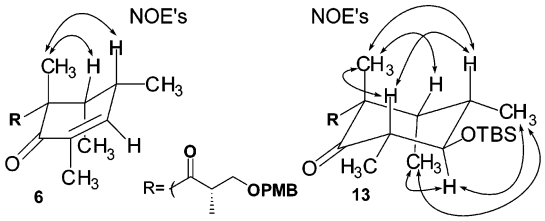


Figure 1. NOE correlations for **6** and **13**.

Primary alcohol **15** was obtained (96%) by deprotection of PMB ether **6** with DDQ in CH_2Cl_2/pH 7 buffer at 0 °C.[11] Alcohol **15** was very acid sensitive and cyclized/dehydrated to afford pyrone **16** in $CDCl_3$ (depending on its acidity) or by treatment of an NMR sample with *p*-TsOH (Scheme 3). Although we are interested in forming bicyclic, pyrone-containing rings, **16** is at the wrong oxidation state for our purposes.

Dess−Martin oxidation[12] of alcohol **15** afforded aldehyde **17** (99%, crude, Scheme 3) with no apparent epimerization of the stereocenter α to the aldehyde and no formation of

(5) Mulzer, J.; Berger, M. *Tetrahedron Lett.* **1998**, *39*, 803−806.
(6) Walkup, R. D.; Kane, R. R.; Boatman, P. D., Jr.; Cunningham, R. T. *Tetrahedron Lett.* **1990**, *31*, 7587−7590.
(7) (a) Corey, E. J.; Kwiatkowski, G. T. *J. Am. Chem. Soc.* **1966**, *88*, 5654−5656. (b) Coe, J. W.; Roush, W. R. *J. Org. Chem.* **1989**, *54*, 915−930.
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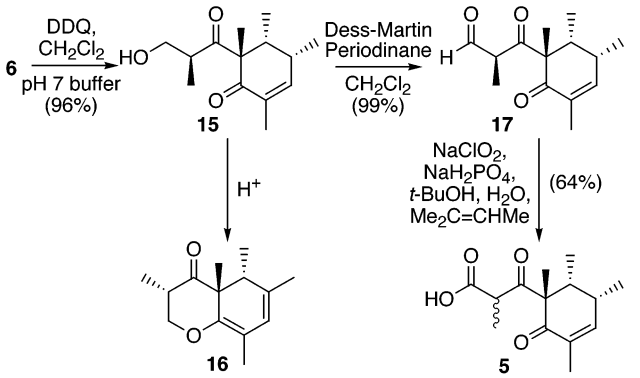
(9) All new compounds gave spectroscopic data in agreement with the assigned structures and copies of NMR spectra and spectral data for all new compounds are available in the Supporting Information.
(10) Subsequent reactions were performed on this 9:1 mixture but only the major (trans) isomer is shown for simplicity. The proportion of trans isomer **6** was enriched during chromatographic purifications of the products of subsequent reactions such that cis isomer **12** was undetectable after purification of acid **5**.
(11) Paterson, I.; Florence, G. J.; Gerlach, K.; Scott, J. P.; Sereinig, N. *J. Am. Chem. Soc.* **2001**, *123*, 9535−9544.
(12) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277−7287.

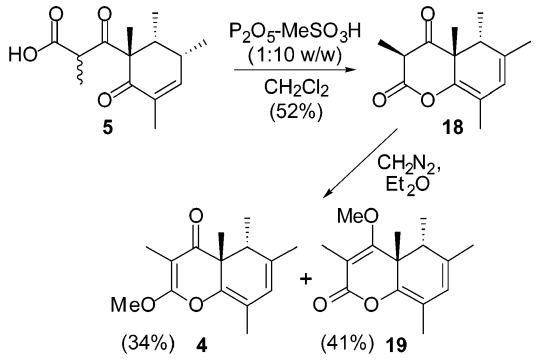
Scheme 3



pyrone **16**. Aldehyde **17** was oxidized with $NaClO_2$[13] to give acid **5** (64%) as a 1:1 mixture of epimers.

Without specific precedent for the formation of the unusual pyrone ring system required for pyrone **4**, we investigated a number of conditions used for the formation of normal pyrone rings[14] (which have readily enolizable, acyclic trione precursors) without success. It was apparent that we required mild, acidic, dehydrating conditions and to this end acid **5** was treated with freshly prepared Eaton's reagent (1:10 w/w $P_2O_5{-}MeSO_3H$)[15] in CH_2Cl_2 at room temperature. This gave pyrone **18** (52%), predominantly in the keto form with stereochemistry as shown (assigned by NOE experiments, Scheme 4).

Scheme 4



Pyrone **18** was *O*-methylated with CH_2N_2 to give close to a 1:1 mixture of the readily separable α-pyrone **19** (41%) and γ-pyrone **4** (34%) (Scheme 4). Resonances in the ^{13}C NMR spectrum of γ-pyrone **4** were consistent with typical α-methoxy-β-methyl-γ-pyrone ^{13}C resonances, and α-pyrone **19** lost CO_2 as a fragment in its mass spectrum, which γ-pyrone **4** did not. Both isomers displayed large, negative optical rotations (**4** had $[\alpha]_D$ −780 and **19** had $[\alpha]_D$ −806). Furthermore, both **4** and **19** were crystalline and single-crystal X-ray analysis confirmed their structures and relative stereochemistry (Figure 2).

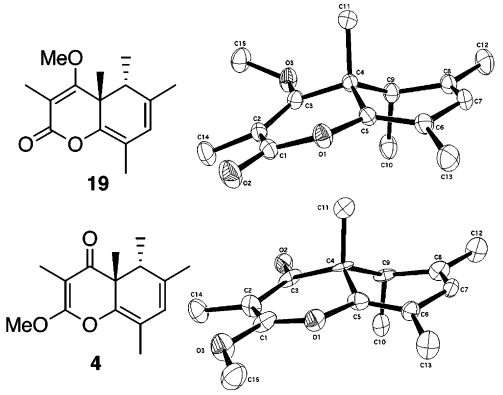


Figure 2.

In conclusion, we have applied our previously developed[3] cyclohexenone strategy to install the cyclohexadiene moiety into an enantiopure model pyrone that is analogous to tridachiahydropyrone (**1**). We have also developed a novel pyrone-forming reaction that affords fused, bicyclic, pyrone-containing ring systems. We are currently applying this strategy to the convergent synthesis of tridachiahydropyrone (**1**) as a single enantiomer.

Acknowledgment. We wish to thank the Australian Research Council for funding and Flinders University for its support and facilities.

Supporting Information Available: Copies of NMR spectra and spectral data for all new compounds and experimental procedures for compounds **4**, **6**, **13**, **18**, and **19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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