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Asymmetric Synthesis of (–)-Dihydroxanthatin by the Stereoselective Oshima–Utimoto Reaction

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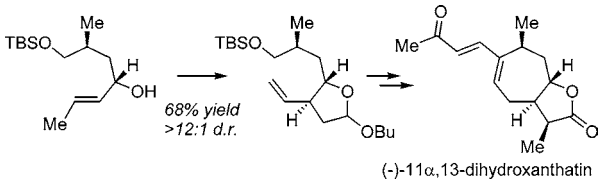
ABSTRACT

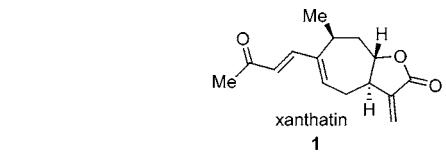


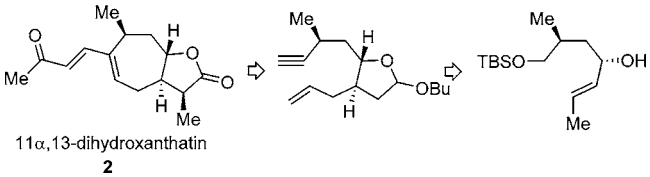
The catalytic stereoselective Oshima–Utimoto reaction is useful for the construction of five-membered oxacycles from simple starting materials and was employed for the preparation of the lactone group in the asymmetric synthesis of (–)-11α,13-dihydroxanthatin. Completion of the synthesis is facilitated by ring-closing enyne metathesis and alkene cross metathesis reactions.

α-Methylene butyrolactones are found in an unusually large number of natural products with one estimate being as high as 10% of naturally occurring compounds.[1] One member of this family is the sesquiterpene lactone xanthatin (**1**, Scheme 1), which was isolated from *Xanthium strumarium*, an annual herb which occurs widely in North America and in Mediterranean countries.[2] Extracts from this plant possess anti-inflammatory and anti-nociceptive activities, which appear to result from inhibition of NF-κB activation.[3] Xanthatin-rich fractions of the plant extract also exhibit in vitro and in vivo cytotoxicity against P-388 cell lines while maintaining a low toxicity (LD_{50} = 800 mg/kg).[4] In its purified form, xanthatin possesses notable activity against methicillin-sensitive and methicillin-resistant *Staphylococcus aureus*.[5]

The chemical structure of xanthatin includes an α-methylene butyrolactone, a potent biological electrophile[6] which often conveys beneficial activity but is often nonselective[7] and is implicated in allergic contact dermatitis.[8] Along these lines, we were intrigued to find that (−)-11α,13-dihydroxanthatin (**2**, Scheme 1), a compound lacking the reactive exocyclic methylene, is also produced by *Xanthium strumarium*, and herein, we report the development of its laboratory synthesis.[9]

Scheme 1





(1) Hoffmann, H. M. R.; Rabe, J. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 94.

(2) (a) Deuel, P. G.; Geissman, T. A. *J. Am. Chem. Soc.* **1957**, *79*, 3778. (b) For a recent approach to the xanthanolide ring system, see: Nosse, B.; Chhor, R. B.; Jeong, W. B.; Böhm, C.; Reiser, O. *Org. Lett.* **2003**, *5*, 941. (c) For a review of approaches to the synthesis of α-methylene butyrolactones, see ref 1.

(3) Kim, I. T.; Park, Y. M.; Won, J. H.; Jung, H. J.; Park, H. J.; Choi, J. W.; Lee, K. T. *Biol. Pharm. Bull.* **2005**, *28*, 94.

(4) Roussakis, C.; Chinou, I.; Vayas, C.; Harvala, C.; Verbist, J. F. *Planta Med.* **1994**, *60*, 473.

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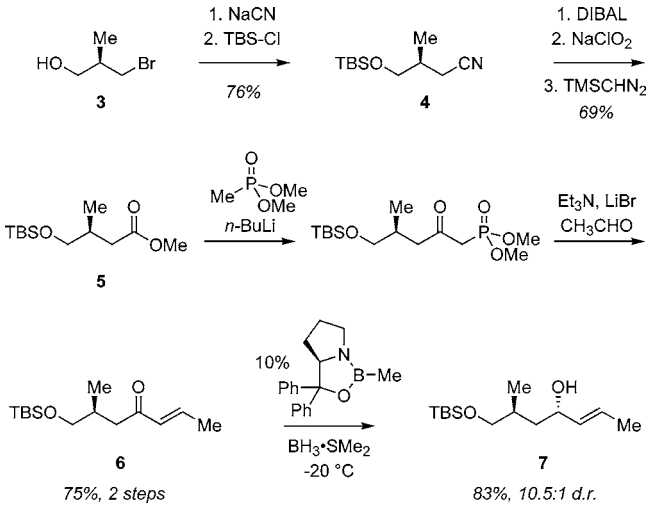
Scheme 2

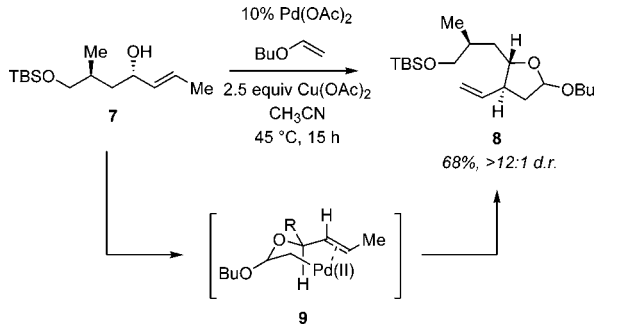


We anticipated construction of the seven-membered ring in dihydroxanthatin through an enyne metathesis reaction (Scheme 1), while the lactone portion of the molecule might be derived from the stereoselective Oshima−Utimoto reaction, which is currently under study in our laboratory.[10] This transformation would facilitate the asymmetric construction of dihydroxanthatin if nonracemic allylic alcohol is employed as the reaction substrate.

Synthesis of the chiral allylic alcohol, which is requisite for the synthesis of dihydroxanthatin, was initiated with commercially available bromo alcohol **3** (Scheme 2). A reaction sequence involving cyanide displacement of the bromide and protection of the primary alcohol provided **4** in 76% yield. Subsequent conversion of the nitrile to the ester by a sequence involving DIBAL reduction, oxidation, and esterification proceeded smoothly to give **5**. Claisen condensation of **5** with the lithium salt of dimethyl methyl phosphonate was followed by olefination with acetaldehyde under the Roush/Masamune conditions[11] and provided enone **6**, which was reduced to **7** using the *R* enantiomer of the Itsuno−Corey oxaborolidine.[12]

The allylic alcohol **7** was converted to tetrahydrofuran **8** by the catalytic Oshima−Utimoto reaction (Scheme 3). In

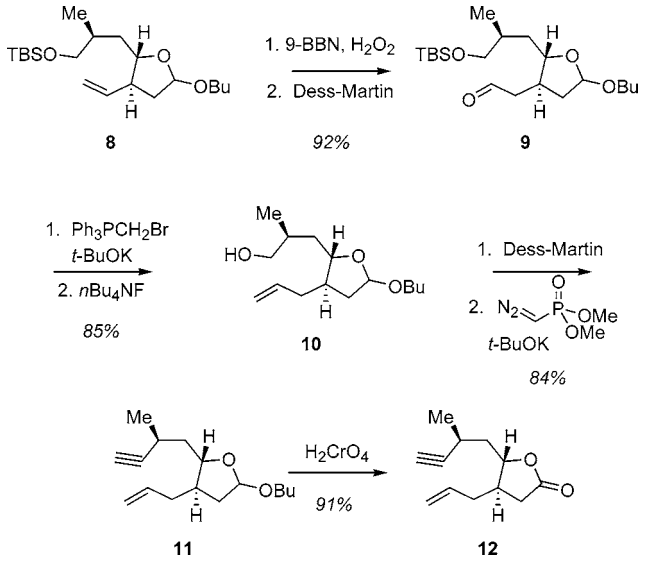
Scheme 3



the event, **7** was subjected to butyl vinyl ether, catalytic $Pd(OAc)_2$, and 2.5 equiv of $Cu(OAc)_2$ as a stoichiometric oxidant. This transformation provided the desired tetrahydrofuran in 68% yield and with >12:1 1,2-stereoinduction. Presumably, the Pd-catalyzed process proceeds through the intermediacy of chairlike transition structure **9** and is observed to result in a separable 1:1 mixture of α and *β* anomers. The production of a mixture of anomers is inconsequential to the synthetic goal since both are ultimately converted to the same lactone, and they were, therefore, carried through the synthesis together.

After the Oshima−Utimoto reaction, substrate **8** was modified in preparation for an ensuing ring-closing enyne metathesis (Scheme 4). Accordingly, the terminal olefin was

Scheme 4



homologated by a hydroboration/oxidation/olefination sequence. The hydroboration was best accomplished with

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(6) (a) Kupchan, S. M.; Fessler, D. C.; Eakin, M. A.; Giacobbe, T. J. *Science* **1970**, *168*, 376. (b) Cassady, J. M.; Byrn, S. R.; Stamos, S. M.; McKenzie, A. *J. Med. Chem.* **1978**, *21*, 815. (c) Schlewer, G.; Stampf, J.-L.; Benezra, C. *J. Med. Chem.* **1980**, *23*, 1031.

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(10) (a) Evans, M. A.; Morken, J. P. *Org. Lett.* **2005**, *7*, 3367. (b) Fugami, K.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1987**, *28*, 809. (c) Fugami, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2050. For a related palladium-catalyzed dimerization of allyl alcohol, see: (d) Hafner, W.; Prigge, H.; Smidt, J. *Liebigs Ann. Chem.* **1966**, 109. For application of a related process to the synthesis of mycalamide A, see: (e) Sohn, J. E.; Waizumi, N.; Zhong, H. M.; Rawal, V. H. *J. Am. Chem. Soc.* **2005**, ASAP. For application of this process to cyclic substrates, see: (f) Larock, R. C.; Lee, N. H. *J. Am. Chem. Soc.* **1991**, *113*, 7815. (g) Larock, R. C.; Stinn, D. E. *Tetrahedron Lett.* **1989**, *30*, 2767. See also: (h) Kraus, G. A.; Thurston, J. *J. Am. Chem. Soc.* **1989**, *111*, 9203.

(11) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfield, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.

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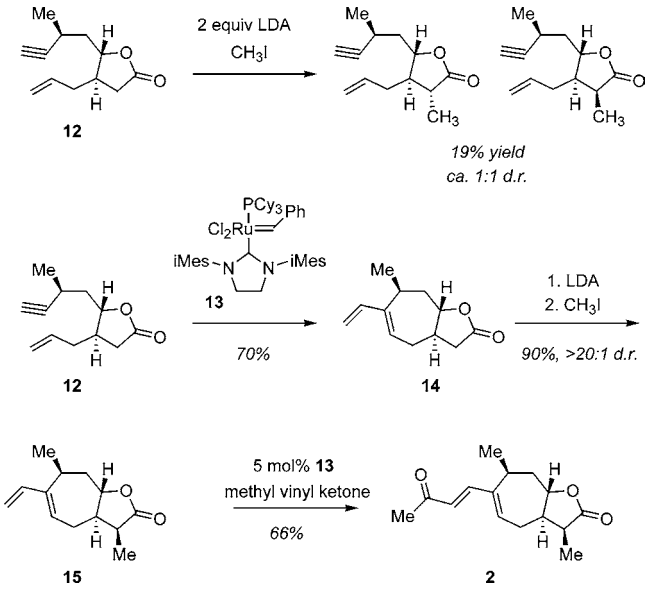
Scheme 5



9-BBN and the oxidation with Dess−Martin periodinane.[13] After olefin homologation, the silyl ether was removed to give **10**, the substrate oxidized, treated with the Gilbert−Seyferth reagent,[14] and last oxidized with chromic acid to give lactone **12**.

Attempted alkylation of lactone **12** proceeded in low yield and with low diastereoselection (Scheme 5). This outcome was not particularly surprising based on the observations of Herradón involving the alkylation of a similar trans 4,5-disubstituted lactone.[15,16] Molecular modeling (MM2) suggested that the desired alkylation product might be better accessed from a substrate with a minimal dihedral angle between the C4 and C5 substituents on the furan, and therefore, the alkylation was postponed until after ring-closing metathesis.[17] As depicted in Scheme 5, enyne metathesis using the Grubbs' carbene-derived catalyst proceeded uneventfully to afford the conjugated diene **14**.[18] Subsequently, lactone **14** was deprotonated with LDA and

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(14) (a) Gilbert, J. C.; Weerasooriya, U. *J. Org. Chem.* **1982**, *47*, 1837. (b) Seyferth, D.; Marmor, R. S.; Hilbert, P. *J. Org. Chem.* **1971**, *36*, 1379.
(15) Sánchez-Sancho, F.; Valverde, S.; Herradón, B. *Tetrahedron: Asymmetry* **1996**, *7*, 3209.
(16) For a review that includes the stereoselection in the alkylation of butyrolactones, see: Evans, D. A. *Asymmetric Synthesis* **1984**, *3*, 1.
(17) ,2-Stereoinduction in the alkylation at C3 appears to result from interaction with substituents at C4, with the C4 hydrogen better aligned to interact with the incoming nucleophile as compared to the C4 alkyl group.

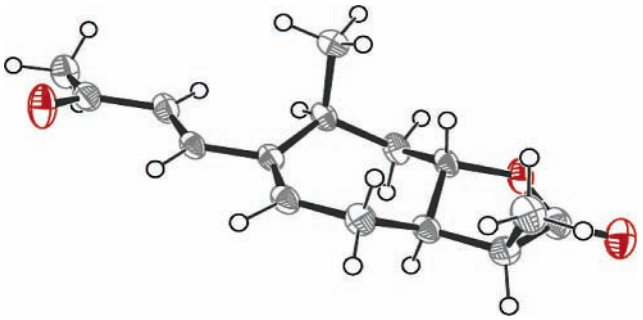

Figure 1. X-ray Structure of **2**

treated with iodomethane to give a 90% yield of compound **15** in >20:1 diastereoselectivity.[19] Finally, cross metathesis with MVK completed the synthesis by affording the target structure **2** in 66% yield.

Target structure **2** could be crystallized from a pentane−chloroform mixture, and this facilitated structural characterization. X-ray crystallographic analysis established that the relative configuration of synthetic dihydroxanthatin is the same as that reported for the natural compound (Figure 1). While the NMR spectra obtained for synthetic **2** compare well with that reported for the natural product, the measured optical rotation for the synthetic material $[\alpha]_D^{25} = -49°$ ($c = 0.83$, $CHCl_3$) does not compare well to the reported value for the natural material $[\alpha]_D^{25} = -9.3°$ ($c = 0.83$, $CHCl_3$). We are currently working to understand this discrepancy.

In summary, we have described the asymmetric synthesis of the nominal structure of (−)-11α,13-dihydroxanthatin using a combination of the stereoselective Oshima−Utimoto reaction and ring-closing enyne metathesis to install the fused ring system. Future efforts will examine the utility of the Oshima−Utimoto reaction in the construction of other natural product targets.

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Supporting Information Available: Characterization data, spectra, and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) The sense of stereoinduction finds precedent in the alkylation of trans-fused bicyclic lactones. See: Devreese, A. A.; DeClercq, P. J.; Vandewalle, M. *Tetrahedron Lett.* **1980**, *21*, 4767.