

Application of a Domino Intramolecular Enyne Metathesis/Cross Metathesis Reaction to the Total Synthesis of (+)-8-*epi*-Xanthatin

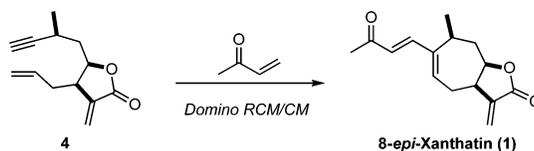
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ABSTRACT



The first total synthesis of the novel sesquiterpene lactone (+)-8-*epi*-xanthatin (**1**) has been achieved starting from the commercially available ester **8**. The synthesis features an asymmetric aldol reaction and palladium-catalyzed carbonylation/lactonization sequence leading to **4** and a domino ring-closing enyne metathesis/cross metathesis reaction to afford **1**.

The sesquiterpene lactone (+)-8-*epi*-xanthatin (**1**), which was isolated from the extracts of the aerial parts of various species in the genus *Xanthium*,¹ has also been obtained from the elimination of acetic acid from the related natural product, xanthumin **2** (Figure 1).² 8-*epi*-Xanthatin inhibits the larval growth of *Drosophila melanogaster* (fruit fly)^{1b} and also displays antimalarial activity against the chloroquine-resistant *Plasmodium falciparum* strain K1 with an IC₅₀ of 125 μg/mL.³ More recently, **1** has been shown to inhibit the in vitro proliferation of several cultured human tumor cell lines, including A-549 (non-small cell lung), SK-OV-3 (ovary), SK-MEL-2 (melanoma), XF-498 (central nervous system), and HCT-15 (colon) with IC₅₀ values ranging between 0.8 and 6.1 μM.⁴ In conjunction with the tumor inhibition studies, **1** was found to inhibit the farnesylation of human lamin-B by farnesyltransferase.^{4b}

Despite their biological activities and interesting structures, synthetic efforts directed toward any of the xanthanolides has been lacking until recently.⁵ In the first reported total synthesis of a xanthanolide, Morcken utilized sequential ruthenium-catalyzed metathesis reactions to prepare (–)-dihydroxanthatin (**3**), a related xanthanolide lacking the reactive exocyclic methylene.⁶

Our interest in 8-*epi*-xanthatin arose as a result of our ongoing efforts to expand the scope of ruthenium-catalyzed

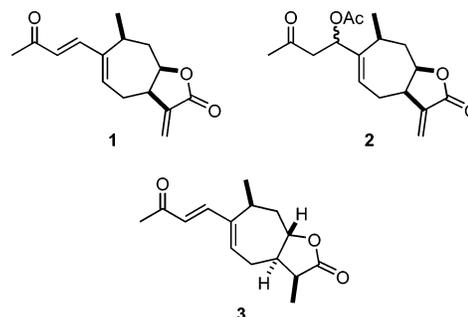


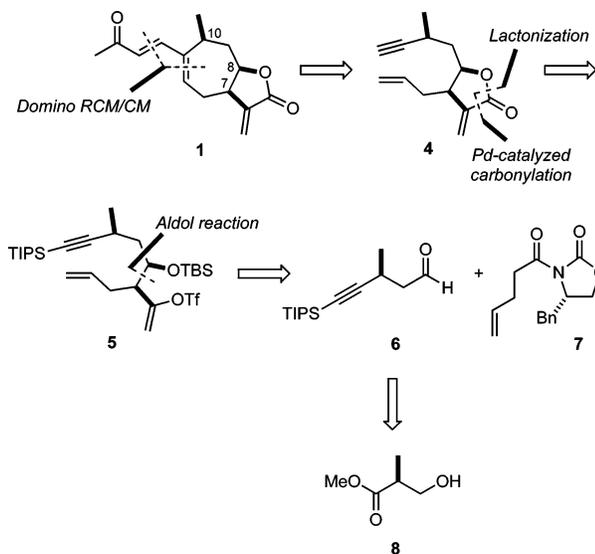
Figure 1. Representative xanthanolides: (+)-8-*epi*-xanthatin (**1**), xanthumin (**2**), and (–)-dihydroxanthatin (**3**).

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Scheme 1



domino olefin metathesis reactions in the context of natural product total synthesis.⁷ Thus, we envisioned that the ring-closing enyne metathesis (RCM) of **4** would generate an intermediate ruthenium carbene that would participate in a subsequent cross metathesis (CM) reaction with methyl vinyl ketone to generate the seven-membered carbocycle and (*E*)-conjugated dienone subunits present in **1** in a single synthetic transformation (Scheme 1). The exocyclic α -methylene lactone functionality present in **4** would be introduced via the palladium-catalyzed carbonylation of enol triflate **5**. Because Paquette has shown that α -methylene- γ -butyrolactones are unaffected by ruthenium-catalyzed RCM conditions, we reasoned that this reactive moiety in **4** would not interfere with the desired metathesis cascade.⁸ An asymmetric aldol reaction⁹ between the functionalized aldehyde **6** and the known oxazolidinone **7**¹⁰ would establish the two stereocenters at C(7) and C(8) in **1**, whereas the remaining

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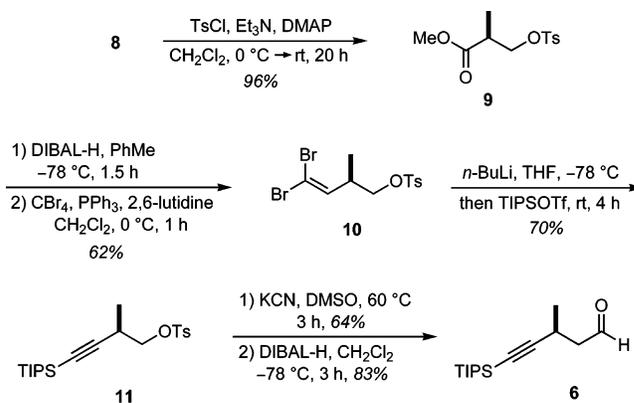
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Scheme 2

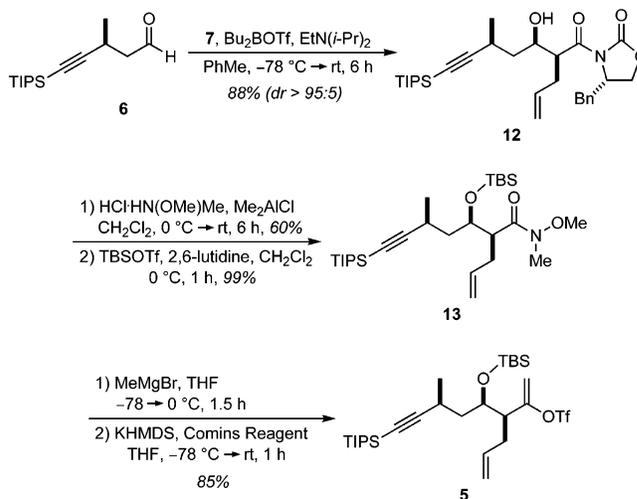


stereocenter at C(10) would be obtained from enantiomerically pure **8**, which is commercially available. We now report the reduction of this strategy to practice.

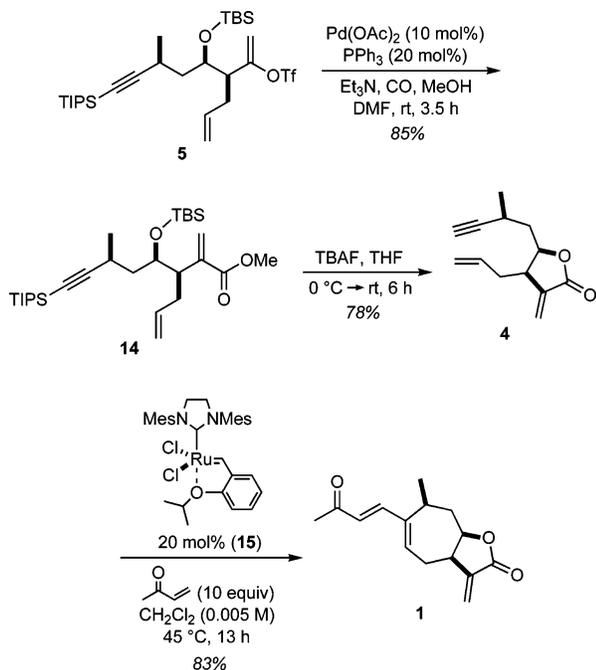
The synthesis commenced with the conversion of commercially available ester **8** into the corresponding tosylate **9** (Scheme 2). Reduction of **9** provided an unstable aldehyde that was immediately subjected to the Corey–Fuchs olefination protocol in the presence of 2,6-lutidine to provide the vinyl dibromide **10** in 62% yield over the two steps.¹¹ When **10** was treated with excess *n*-BuLi and the resultant acetylide anion trapped with TIPSOTf, the protected alkyne **11** was obtained in 70% yield. One-carbon homologation of **11** via reaction with KCN afforded the corresponding nitrile in 64% yield, reduction of which with DIBAL-H furnished aldehyde **6** in 83% yield.

With aldehyde **6** in hand, our attention was focused upon establishing the two remaining stereocenters in **1** via an asymmetric aldol reaction.⁹ Toward this end, the boron enolate derived from oxazolidinone **7** was allowed to react with aldehyde **6** to provide alcohol **12** in 88% yield (dr >95:5 based upon the ¹H NMR spectrum) (Scheme 3). Exchange

Scheme 3



Scheme 4



of the chiral auxiliary with the corresponding *N,O*-dimethyl amide was accomplished in 60% yield by treating alcohol **12** with the preformed aluminum amide derived from $\text{HCl}\cdot\text{HN}(\text{OMe})\text{Me}$.¹² Subsequent protection of the secondary alcohol as a silyl ether afforded **13** in nearly quantitative yield. Treatment of amide **13** with MeMgBr provided the corresponding ketone, which was readily transformed into the enol triflate **5** in 85% overall yield by kinetic deprotonation with KHMDS followed by trapping of the resultant enolate with *N*-(5-chloro-2-pyridyl)triflimide (Comins reagent).¹³

The enol triflate **5** was then converted into the acrylate **14** in 85% yield under standard conditions for palladium-catalyzed carbonylation (Scheme 4).¹⁴ Removal of the silyl protecting groups from **14** using TBAF was accompanied by spontaneous lactonization of the intermediate hydroxy ester to provide **4** in 78% yield.¹⁵

With enyne **4** in hand, the stage was set for the pivotal domino enyne RCM/CM sequence. The enyne RCM reaction has emerged as a powerful synthetic transformation,¹⁶ but only recently has this process been coupled in a domino process with a subsequent CM.¹⁷ In the event, reaction of

enyne **4** and methyl vinyl ketone in the presence of catalyst **15** (20 mol %) provided **1** in 83% yield (Scheme 4). The phosphine-free ruthenium catalyst **15**¹⁸ was employed in this step because it had been reported to be superior as a catalyst in previously reported tandem RCM/CM reactions^{17b} and in CM reactions involving electron-deficient olefins.¹⁹ The ^1H and ^{13}C NMR spectral data of the synthetic **1** thus obtained were consistent with those previously reported.^{1b,4a,b,20} Moreover, it exhibited an optical rotation $\{[\alpha]_{\text{D}}^{24} = +23.4$ (c 0.333, CHCl_3) $\}$ in close accord with the previously reported value $\{[\alpha]_{\text{D}}^{20} = +25$ (c 0.5, CHCl_3) $\}$.^{4b}

In summary, the first total synthesis of (+)-8-*epi*-xanthatin (**1**) has been achieved in 14 steps from the ester **8** in 5.5% overall yield. The approach featured a palladium-catalyzed carbonylation/lactonization sequence for the construction of the α -methylene- γ -butyrolactone functionality and a domino enyne RCM/CM reaction to elaborate the seven-membered carbocycle and complete the synthesis. Other applications of olefin metathesis to solving challenging problems in total synthesis are under active investigation, and the results of these studies will be disclosed in due course.

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Supporting Information Available: ^1H NMR spectra for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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