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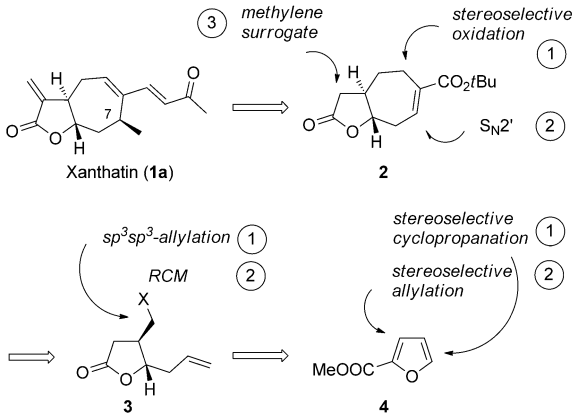
Total Synthesis

# Enantioselective Synthesis of Xanthatin

Andreas Bergmann[a] and Oliver Reiser*[a, b]

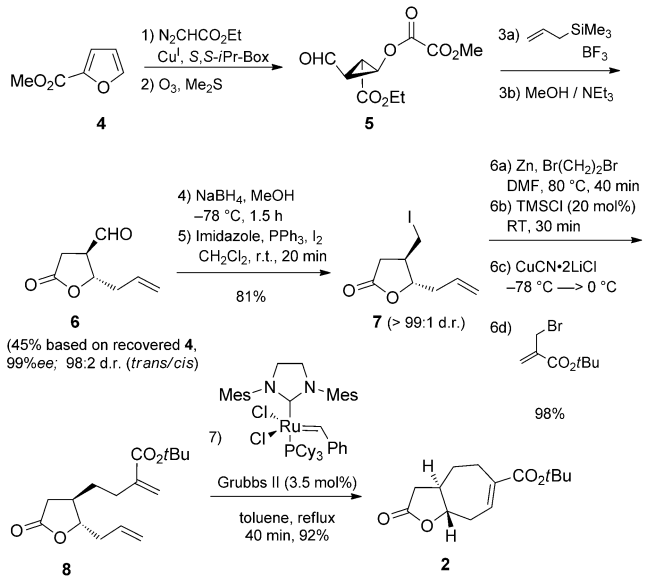
**Abstract:** The enantioselective synthesis of cytostatic and antibiotic xanthatin (**1a**) is reported. As a key intermediate, a bicyclic compound **2** was identified, which can be readily synthesized from methyl-2-furoic acid in diastereo- and enantiomerically pure form. Compound **2** can be functionalized regio- and stereoselectively at C-6 and C-7, allowing the facile introduction of the functionalities found in xanthatin, as well as the synthesis of derivatives thereof. Moreover, a robust strategy for the introduction of the *exo*-methylene group at C-3, commonly found in many sesquiterpenes, was developed that makes use of masking the alkene in the α,β-unsaturated carbonyl system by O-pivaoyl, which is stable under acidic and mild basic conditions but eliminated upon treatment with strong bases.

The sesquiterpene lactone xanthatin (**1a**) is found along with other xanthanolides in several members of the *Xanthium* family.[1] These substances have impressive biological activities, such as anticarcinogenic, antimycotic, antibacterial (among others, against methicillin-resistant staphylococcus areus (minimal inhibitory concentration (MIC) 7.8 $\mu g\,mL^{-1}$)[2f] and various other properties[2] along with low toxicity.[2b] For this reason, xanthanolides have become an important target for natural-product synthesis, starting with the first synthesis of 11,13-dihydroxanthatin reported by Evans and Morken in 2005.[3] Xanthatin itself was first synthesized by Shishido and co-workers in 2008[4] followed by a first and second generation synthesis by Shindo and co-workers in 2010[5a] and 2013,[5b] as well as by a formal synthesis converging with a key intermediate of Shindo[5a] and co-workers in 2012.[6] All these routes have in common that the chiral center at C-7 was set early on in the synthesis utilizing the stereoselective functionalization of chiral oxazolidinones (Evans auxiliary approach). In contrast, our synthetic approach utilizes an asymmetric catalytic cyclopropanation of methyl-2-furoate (**4**) leading to the bicyclic key intermediate **2**, which allows a flexible late-stage introduction of the functional groups at C-6 and C-7, for example, those required for xanthatin. Moreover, we disclose a robust strategy for the introduction of the chemically sensitive *exo*-methylene group at C-3 position, being a key element in many sesquiterpene lactones (Scheme 1).




**Scheme 1.** Retrosynthetic analysis of xanthatin.

γ-Butyrolacton **6** is readily available in a four-step sequence in high enantio- (>99% *ee*) and diastereoselectivity (*trans/cis* 98:2) on multigram scale from methyl-2-furoate, featuring an asymmetric cyclopropanation, ozonolysis, and an allylation/retroaldol/lactonization cascade process.[7] The latter was previously reported by us after allylation of **5** by a work-up with




**Scheme 2.** Synthesis of the bicyclic core structure **2** of xanthatin.

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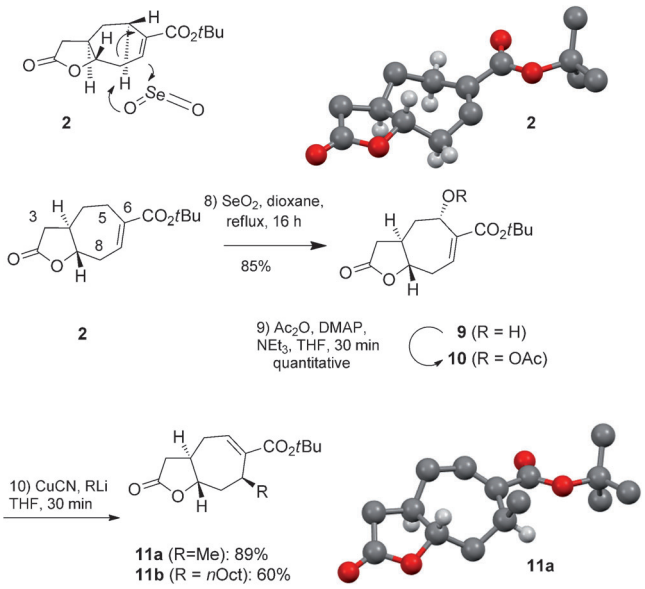


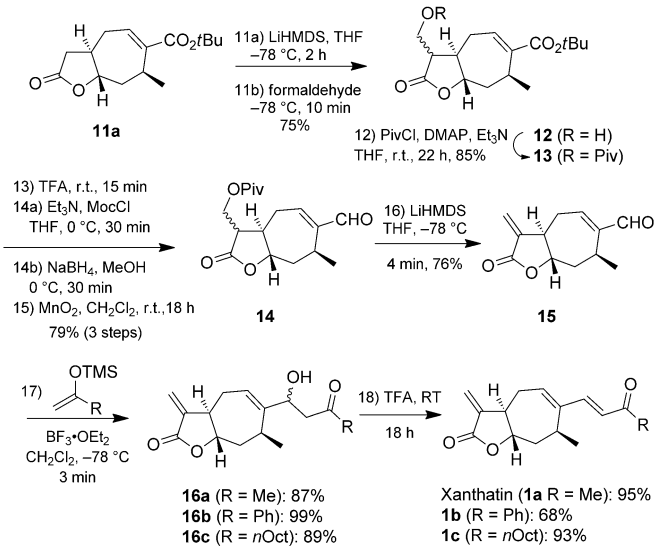

**Scheme 3.** Stereoselective functionalization of **2** at C-5 and C-7 positions.

$Ba(OH)_2 \cdot 8H_2O$,[7d] the protocol developed here ($MeOH/NEt_3$) allows this transformation in considerable improved yields, especially on larger scale. From compound **6**, iodide **7** was obtained as a single stereoisomer by an Appel-type reaction from its corresponding alcohol, which in turn was generated by chemoselective reduction of the aldehyde in **6**. Following Knochel's protocol[8] in the modification[9] introduced by Kiyota, the $sp^3$–$sp^3$ coupling of **7** with *tert*-butyl-2-(bromomethyl)acrylate[10] proceeded with remarkable efficiency, giving rise to **8** in quantitative yield. Ring-closing metathesis completed the synthesis of **2**, representing the bicyclic core structure of xanthatin (Scheme 2).

The X-ray structure of **2** revealed the chair-like conformation of its seven-membered ring, with allylic hydrogens on C-5 and C-8 positions being differentiated by their axial and equatorial positions (Scheme 3). The axial hydrogens are ideally aligned with the adjacent π system of the C=C double bond to undergo an ene reaction. In combination with the steric preference of an eneophile to attack the sterically less hindered side of the double bond, we were pleased to see that indeed the allylic oxidation[11] of **2** with selenium dioxide took place with perfect regio- and 1,3-diastereoinduction, giving rise to **9** as single stereoisomer. Given that 5,7-bicyclic *trans*-anellated lactones are a widely occurring structural motif in sesquiterpene natural products, showing a broad substitution pattern in the seven-membered ring, we believe that the transformations shown herein will be of value for stereoselective modification of such systems in general. Thus, transforming **9** to the allyl acetate **10** set the stage for the introduction of nucleophiles at C-7: Alkyl cuprates,[12] generated in situ from their corresponding alkyl lithium compound and CuCN, cleanly reacted in an $S_N2'$ process *anti*-selective to **11**, as was exemplified for the methyl derivative **11 a** being required for the synthesis of xanthatin, as well as for the octyl derivative **11 b**, having a potential anchor point for binding to a cell membrane. The structure of **11 a** was unambiguously confirmed by X-ray structure analysis.

To finish the synthesis of xanthatin, the introduction of the α-*exo*-methylene group at C-3 and the side chain had to be accomplished. In deciding the order of events, we were faced with the dilemma that once the desired functionality at C-6 is installed, various positions along the conjugated α,β,γ,δ-unsaturated carbonyl chain become highly acidic and thus enolizable. Although various methods for the introduction of *exo*-methylene groups at the α-position of a lactone are known,[13] they all require enolization of the lactone. On the other hand, the α-*exo*-methylene-γ-butyrolactone moiety is a strong Michael acceptor, making it unstable in the presence of even weak nucleophiles under acidic and basic conditions; moreover, isomerization of the *exo*-methylene double bond into the γ-butyrolactone ring occurs under basic conditions. Thus, once this group is installed, considerable constrains on the transformations possible are present to convert the ester group to the side chain at C-6. Orienting experiments indeed revealed that introduction of any type of electrophile at C-3 is not feasible once the unsaturated side chain at C-6 is present. Likewise, we were unable to cleanly reduce the ester group at C-6 to an aldehyde once the *exo*-methylene group at C-3 was installed.

However, the following strategy proved to be successful: Base-induced hydroxymethylation with gaseous formaldehyde followed by pivalylation gave rise to **13** as a mixture of C-3 epimers, which was without consequences, because this stereocenter is destroyed in the later course of the synthesis.[14] The pivaloyl group proved to be a very suitable choice to mask the α-*exo*-methylene-γ-butyrolactone unit, being stable under reductive, oxidative, acidic and weak basic conditions. Conversion of the *tert*-butyl ester to aldehyde **14** proceeded best in a stepwise fashion involving ester hydrolysis, activation of the carboxylic acid as a mixed anhydride,[15] reduction to its corresponding alcohol, and reoxidation with manganese diox-




**Scheme 4.** Final steps in the synthesis of xanthatin **1 a** and side-chain analogues **1 b–c**.

ide. Elimination of pivalic acid under strong basic conditions rapidly occurred to give rise to the desired α-*exo*-methylene-γ-butyrolactone **15**. Although any type of Wittig elongation of the aldehyde was not successful either on **14** or **15**, borontrifluoride-mediated Mukaiyama aldol reaction of **15** and with trimethyl(prop-1-en-2-yloxy)silane[16] to **16** followed by acid-induced dehydration turned out to be highly effective, which completed the synthesis of xanthatin **1a**. Likewise, the synthesis of side chain analogs **1b** and **c** was accomplished by using the appropriate silylenol ethers in the reaction with **15** (Scheme 4).

In conclusion, we have developed a new strategy to xanthatin (**1a**) that allows the stereoselective late-stage functionalization of its seven-membered ring, thus allowing the facile synthesis of xantathin analogues with variation of both side chains present as exemplified in **1b**, **1c**, and **11b**. The biological evaluation of these and other analogues is currently underway and will be reported in due course.

## *Acknowledgement*

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**Keywords:** allylic oxidation · *exo*-methylene group · synthetic methods · total synthesis · xanthanolides

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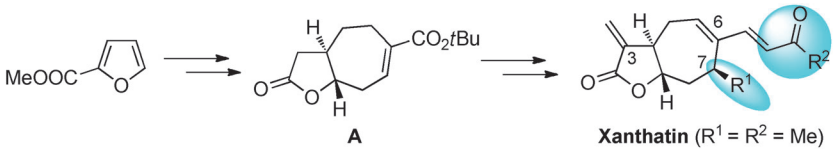


**Organic hardcore**: The enantioselective synthesis of cytostatic and antibiotic xanthatin is reported. As a key intermediate, the bicyclic compound **A** was identified (see scheme), which can be readily synthesized from 2-furoic acid in diastereo- and enantiomerically pure form. Moreover, a new strategy for the introduction of the *exo*-methylene group at C-3, commonly found in many sesquiterpenes, was developed.