

## Convergent Total Synthesis of Murisolin

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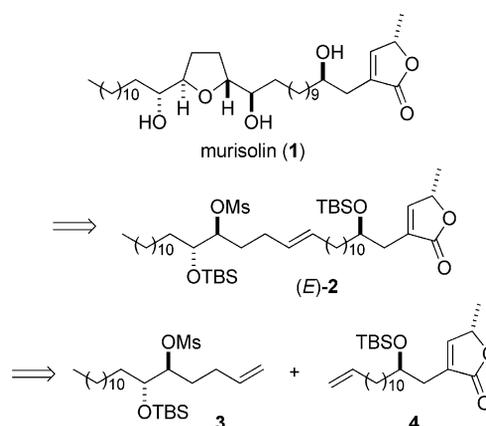
A convergent total synthesis of the mono(tetrahydrofuran) annonaceous acetogenin murisolin, with a longest linear sequence of nine steps, is reported. Assembly of the complete

carbon framework by cross metathesis and late-stage tetrahydrofuran formation on the intact backbone are key elements of the synthesis.

## Introduction

To date, more than 400 members of the annonaceous acetogenin family of polyketide natural products have been isolated from *Annonaceae* plant species. Most possess a common, unbranched 32- or 34-carbon skeleton, with a core of one or two tetrahydrofuran (THF) rings, terminated by a  $\gamma$ -methylbutenolide. Annonaceous acetogenins display a wide range of biological activities and are highly cytotoxic as a result of their ability to inhibit complex I (NADH-ubiquinone oxidoreductase) in mitochondrial electron transport systems.<sup>[1]</sup>

Murisolin (**1**, Scheme 1) is a mono(THF) acetogenin that was first isolated from the seeds of *Annona muricata* in 1990.<sup>[2]</sup> Subsequent isolations of **1** from *Asimina triloba* (along with two diastereomers, 16,19-*cis* murisolin and murisolin A), *Goniothalamus donnaiensis*, *Annona montana*, and *Annona muricata* have been reported.<sup>[3]</sup> Biological evaluation of murisolin has revealed selective cytotoxic activity against human lung carcinoma (A-549), human colon adenocarcinoma (HT-29), and human kidney carcinoma (A-498) with potencies of  $10^5$  to  $10^6$  those of adriamycin.<sup>[3a]</sup> Despite its chemotherapeutic potential, the first total synthesis of **1** was not reported until 2004 with two additional syntheses following shortly thereafter.<sup>[4]</sup> Curran's approach to murisolin as a part of a 28-member stereoisomer library is particularly noteworthy.<sup>[4d,4e]</sup> All three total syntheses follow a convergent strategy, employed almost universally in acetogenin synthesis,<sup>[5]</sup> involving late-stage coupling of a fully realized THF-containing fragment and a  $\gamma$ -methylbutenolide-containing fragment.

Scheme 1. Retrosynthetic analysis of murisolin (**1**).

Herein, we describe an alternative approach to murisolin in which THF formation is preceded by assembly of the complete carbon framework of the natural product as outlined retrosynthetically in Scheme 1. Thus, we envisioned **2**, possessing an appropriately positioned (*E*)-configured C=C bond, as a potential precursor to **1** with construction of the central THF ring by Sharpless asymmetric dihydroxylation (SAD)<sup>[6]</sup> and  $S_N2$  mesylate displacement. (*E*)-Alkene **2**, in turn, would be prepared by cross metathesis (CM)<sup>[7]</sup> of relatively simple terminal alkenes **3** and **4**, both of which should be readily available from known or commercially available starting materials. While we recognized the potential difficulties of the key CM coupling of **3** and **4** (both type I alkenes),<sup>[8]</sup> the high level of convergency built into this approach encouraged us to pursue it.

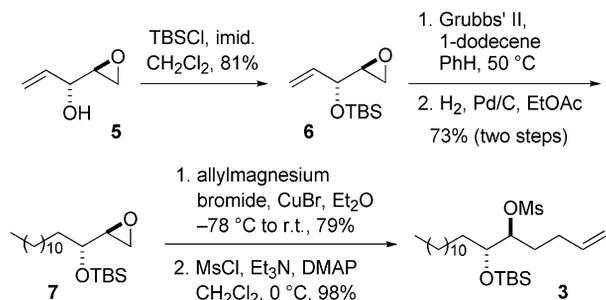
## Results and Discussion

The synthesis of CM coupling fragment **3** began with known (2*S*,3*R*)-1,2-epoxy-4-penten-3-ol (**5**)<sup>[9]</sup> and is shown in Scheme 2. Following TBS protection, incorporation of

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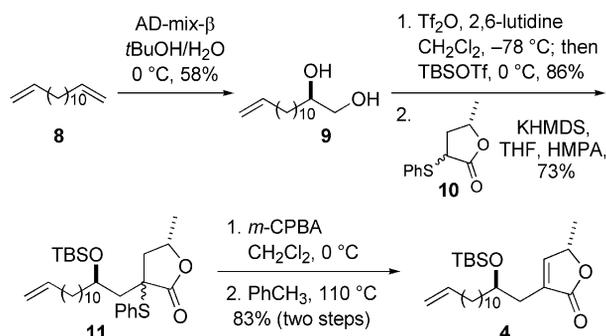
Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/ejoc.201000875>.

the alkyl side chain was accomplished by CM with 1-dodecene in the presence of Grubbs' second-generation catalyst<sup>[10]</sup> and subsequent hydrogenation. Epoxide opening with allylmagnesium bromide and mesylation of the resulting secondary alcohol provided **3** in five steps and 46% overall yield from **5**.



Scheme 2. Synthesis of **3**.

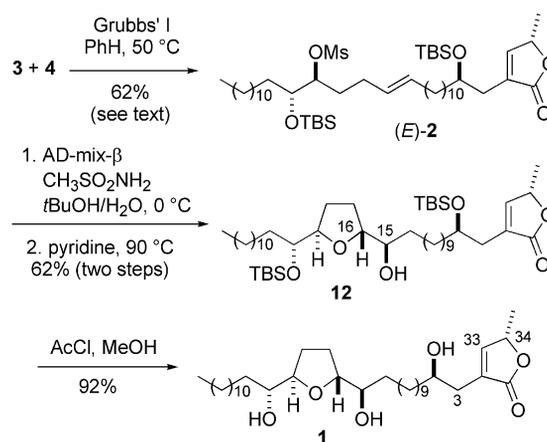
Preparation of butenolide-containing CM coupling fragment **4** is outlined in Scheme 3. Establishment of the acyclic stereocenter present in **4** was achieved by SAD of commercially available 1,13-tetradecadiene with AD-mix- $\beta$  to afford 58% of diol **9** in a 92:8 enantiomeric ratio. Selective activation of the primary alcohol as a triflate and subsequent silylation of the remaining secondary alcohol were achieved in an efficient one-pot process. Substitution of the triflate with the enolate of (5*S*)-methyl-3-phenylsulfanyldihydrofuran-2-one (**10**)<sup>[11]</sup> then provided **11** as an inconsequential mixture of diastereomers in 73% yield. Sulfide oxidation and thermal elimination completed the synthesis of **4**, which required five steps and proceeded in 30% overall yield from **8**.<sup>[12]</sup>



Scheme 3. Synthesis of **4**.

With practical routes to coupling partners **3** and **4** established, we turned our attention to the key CM coupling (Scheme 4). Initial attempts employing either the Grubbs' second-generation catalyst or Hoveyda–Grubbs' second-generation catalyst<sup>[13]</sup> at temperatures of 25 to 80 °C led to the formation of complex mixtures from which the desired CM product **2** could not be isolated cleanly. We were pleased to find that the use of the Grubbs' first-generation catalyst<sup>[14]</sup> (PhH, 50 °C) gave much cleaner reactions of **3** and **4** and resulted in the formation of four separable products (in order of elution): the CM dimer of **3**, (*Z*)-**2**, (*E*)-**2**,

and the CM dimer of **4**.<sup>[15]</sup> Because **3** and **4** are both type I alkenes, a statistical distribution of CM products was expected.<sup>[8]</sup> This proved to be the case, with combined yields of (*Z*)- and (*E*)-**2** never exceeding the statistical maximum and proportional to the ratio of coupling partners **3** and **4**. For example, metathesis of a 1.5:1 molar ratio of **4** to **3** provided 49% of (*E*)-**2** and 7% of (*Z*)-**2**, corresponding to 93% of the statistical 60% maximum. When the ratio of **4** to **3** was increased to 4:1, the yield of (*E*)- and (*Z*)-**2** improved to 62 and 9%, respectively (89% of the statistical 80% maximum). This yield enhancement is somewhat artificial, as it comes at a significant material expense; however, this cost is largely negated, as the CM dimer of **4** can be recycled quantitatively by metathesis cleavage with the Hoveyda–Grubbs' second-generation catalyst in the presence of ethylene.<sup>[16]</sup>



Scheme 4. Completion of the synthesis.

Completion of the synthesis required incorporation of the central THF ring into (*E*)-**2**, the intact carbon framework of the natural product. This was accomplished by SAD with AD-mix- $\beta$  and methanesulfonamide, setting the C15 and C16 stereocenters, and subsequent  $S_N2$  cyclization of the resulting crude diol, upon heating to 90 °C in pyridine,<sup>[17]</sup> to give diprotected murisolin (**12**) in 62% yield. Finally, deprotection by treatment with in situ generated HCl in MeOH provided murisolin (**1**) in 92% yield. Synthetic **1** displayed spectral and physical data (<sup>1</sup>H NMR, <sup>13</sup>C NMR, IR, HRMS, MP, specific rotation) in good agreement with those reported previously.<sup>[2,4]</sup> Interestingly, we observed extra splitting of the resonances for the C3 protons ( $\delta$  = 2.52 ppm, ddt,  $J$  = 15.1, 3.4, 1.5 Hz and  $\delta$  = 2.39 ppm, ddt,  $J$  = 15.1, 8.2, 1.5 Hz), C33 proton ( $\delta$  = 7.19 ppm, q,  $J$  = 1.5 Hz), and C34 proton ( $\delta$  = 5.06 ppm, qq,  $J$  = 6.8, 1.5 Hz) in the <sup>1</sup>H NMR spectrum (CDCl<sub>3</sub>, 400 MHz) of **1** not reported in the published spectroscopic data. While this additional splitting, which can be attributed to allylic and homoallylic coupling, is not commonly reported in <sup>1</sup>H NMR spectra of  $\gamma$ -methylbutenolide-containing acetogenins, it has been noted previously,<sup>[3a,4e]</sup> and we observed it for all compounds possessing this substructure [**4**, (*E*)-**2**, **12**, and **1**].

## Conclusions

In conclusion, a novel approach to the synthesis of annonaceous acetogenin natural products by CM carbon backbone assembly/late-stage THF formation has been demonstrated by application in the total synthesis of murisolin with a longest linear sequence of just nine steps. The route described herein is the shortest and most efficient reported to date and serves to further validate the powerful utility of olefin metathesis in acetogenin synthesis.<sup>[18]</sup> The convergency and flexibility inherent in this approach will make it broadly applicable in the efficient synthesis of other acetogenins and more complex oxacyclic natural products. These studies are ongoing and will be reported in due course.

**Supporting Information** (see footnote on the first page of this article): Experimental procedures, characterization data, and <sup>1</sup>H and <sup>13</sup>C NMR spectra for **1**, (*E*)-**2**, **3**, **4**, **6**, **7**, **9**, **11**, and **12**.

## Acknowledgments

Financial support of this research by the National Science Foundation (CHE-0848128) and the Sherman Fairchild Foundation is gratefully acknowledged. Mass spectroscopic data were obtained at the University of Massachusetts Mass Spectrometry Facility, which is supported, in part, by the National Science Foundation.

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Received: June 17, 2010

Published Online: September 22, 2010