ORGANIC LETTERS

2012
Vol. 14, No. 7
1661–1663

Total Synthesis of the Terpenoid Buddledone A: 11-Membered Ring-Closing Metathesis

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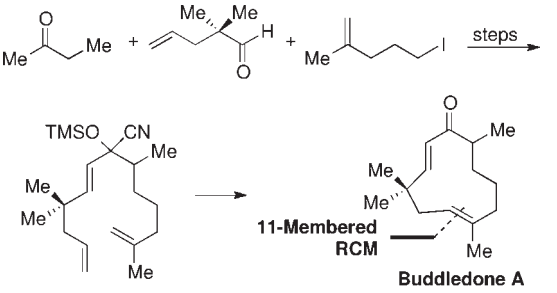
Received February 17, 2012

ABSTRACT



The first total synthesis of buddledone A was accomplished in seven steps from methyl ethyl ketone (MEK). The key step in the sequence featured an 11-membered ring formation by ring-closing metathesis.

Buddledone A (**1**, Figure 1) was isolated from the plant *Buddleja globosa*, which has been used in traditional Chinese herbal medicine.[1] Other species in this genus have been used similarly.[2] Also isolated were buddledone B (**1b**), buddledins A, B, C, and zerumbone (Figure 1).[3] While its dehydro congener zerumbone (**1a**) exhibits various promising biological properties including plant growth-regulatory,[2] cytotoxic,[4] anti-inflammatory,[5] anticancer (lung, liver and leukemia),[6] and anti-HIV[7] activitiy, the bioactivity of buddledone A has not been reported on extensively, though it is known to not be an inhibitor of the hedgehog/GLI signaling pathway.[8]

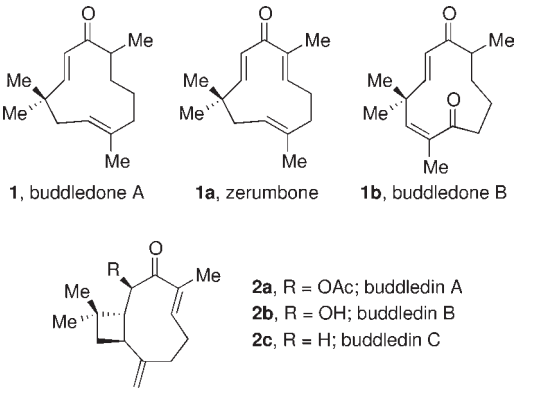


Figure 1. Structures of buddledone A and its congeners.

We developed an interest in buddledone A as part of a broader interest in developing routes to zerumbone analogues and accessing the buddledin family of natural products.

(1) Liao, Y. H.; Houghton, P. J.; Hoult, J. R. S. *J. Nat. Prod.* **1999**, *62*, 1241–1245.

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(3) Zerumbone is a major component of the essential oil of wild ginger, *Zingiber zerumbet*: Dev, S. *Tetrahedron*. **1960**, *8*, 171–180.

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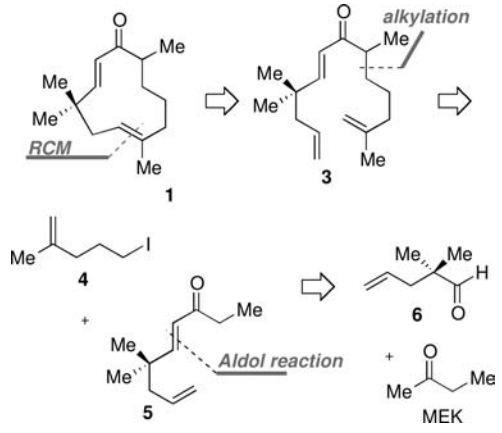
10.1021/ol300400x
Published on Web 03/20/2012

Our goal was to produce buddledone A by a ring-closing metathesis (RCM) as the ultimate or penultimate step in the synthesis. We were concerned that although there are examples of RCM to form 11-membered rings, particularly in systems with a conformational bias,[9] they are not nearly as common as those that lead to less strained ring systems.[10] Small changes in diastereomer composition can have dramatic effects on the yields and/or the stereochemistry of such reactions.[11] Simple substrates can work in the process, but yields are variable.[12] Our plan called for the use of a relatively simple substrate, one that would not likely have any particular conformational bias toward ring closure and would certainly be prone to side reactions like dimerization.

In this communication, we report a straightforward synthetic strategy toward the total synthesis of buddledone A that successfully implements an RCM to create an eleven-membered ring. The retrosynthetic analysis is shown in Scheme 1. Buddledone A (**1**) would be prepared by RCM from triene **3**. This compound (**3**) would be available through the alkylation of the enolate derived from enone **5**. Finally, **5** would arise from an aldol reaction between **6** and methyl ethyl ketone (MEK).

Scheme 1. Retrosynthetic Analysis

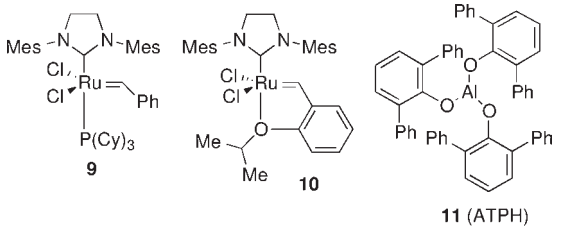


Treatment of MEK with LDA followed by the aldehyde **6** afforded the aldol adduct **7** in high yield (Scheme 2). Dehydration using a standard two-step protocol involving mesylation and elimination gave a nearly quantitative yield of **5**. While the enolate derived from **5** could be alkylated with **6** in THF, the yield of the product was low (29%). Inclusion of HMPA in the reaction mixture afforded a good yield (72%) of the alkylation product **3**.

The attempts to prepare **1** via ring-closing metathesis of an α,β-unsaturated ketone precursor **3** under various conditions were not successful. The reactions afforded a dimer **8** as a major product in high yield in one case, along with trace amounts of the cross metathesis product between styrene and starting material **3**, and complex mixtures in other cases.

The structure of **8** was established by proton NMR spectroscopy. The assignment of the *E* stereochemistry of the central double bond is based on the predilection of metathesis catalysts to afford 1,2-disubstituted alkenes with said stereochemistry when terminal alkenes are combined via metathesis. However, the ^{13}C NMR of **8** was complex. We presume this is due to the formation of diastereomers based on the presence of two stereogenic centers in **8**, which result from the metathesis of a racemic precursor.

Our initial attempts to avoid the formation of **8** met with little success. Various catalytic conditions for ring-closing metathesis of triene **3** afforded dimer **8** as a major product. The reactions using the Grubbs second-generation catalyst (**9**) and the Hoveyda–Grubbs catalyst (**10**)[13] under an ethylene atmosphere gave a complex mixture. Moreover, the capsule-like Lewis acid **11**,[14] which is an effective Lewis acid for the formation of medium-sized lactones using ring-closing metathesis,[15] was not useful for our work, affording the dimer **8** in combination with **9** after 6 h at reflux in toluene. We also subjected the dimer **8** to the metathesis conditions using 20% mol of **10** in DCM. The reaction was refluxed for 6 h, but the dimer remained in the reaction and there was no desired product observed by ^1H NMR.



We believed that the problem with RCM for **3** might have stemmed, at least in part, from a combination of conformational freedom and angle strain that prevented product formation, either kinetically or thermodynamically. We

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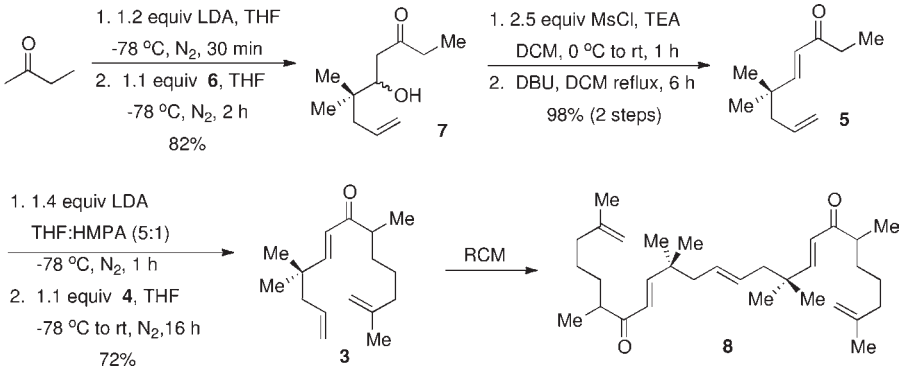
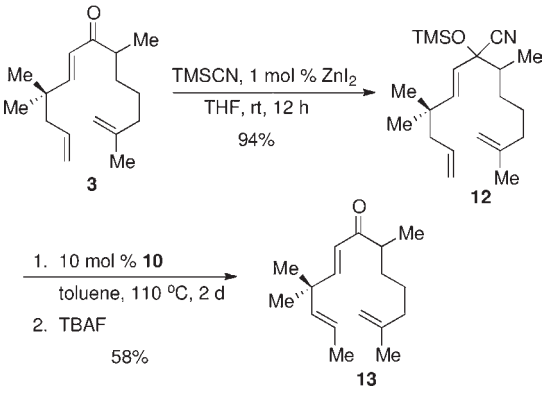
Scheme 2. Initial Synthetic Approach and Failed RCM



decided to use the ketone functionality as a handle and take advantage of geminal disubstitution[16] at that carbon atom to address both conformational and strain issues.[17] Whether this rationalization has merit, in fact, has yet to be determined. Nevertheless, the strategy worked.

The triene **3** was thus transformed to a TMS-protected cyanohydrin **12** by standard methods in excellent yield. Initial attempts using **12** and catalyst **10** generated buddledone A after hydrolysis of the corresponding cyanohydrin with TBAF in only 10% yield, contaminated with varying amounts (up to 58%) of the isomerization product **13** (Scheme 3).[18] This is an established problem in certain

Scheme 3. An Isomerization Reaction



metathesis reactions, and one solution is the oxidative removal of the ruthenium hydride species that are likely responsible for the process.[19] Thus, treating **12** with 20 mol % of Hoveyda–Grubbs second generation catalyst and 20 mol % of benzoquinone in refluxing toluene yielded buddledone A (**10**) with the desired geometry of the double bond after converting the cyclized cyanohydrin to an enone by treatment with TBAF in THF (59% yield) (Scheme 4).

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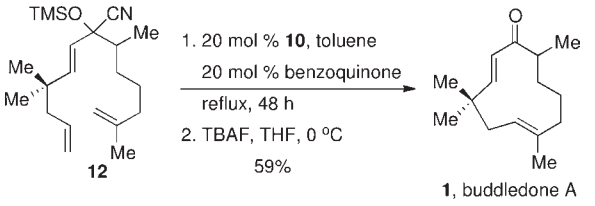
The spectral data on the synthetic material matched that in the literature.[1] Further, although buddledone A was reported as an oil, the racemic, synthetic material turned out to be a low-melting solid and we were able to confirm its structure by X-ray analysis. Unfortunately, there does not appear to be any information in the literature regarding a chiral or chiroptical property associated with natural buddledone A. It will likely require another isolation and characterization to obtain that information.

Scheme 4. Successful Total Synthesis of Buddledone A



In summary, the terpenoid buddledone A was synthesized successfully from commercially available starting materials in seven steps with an overall yield of 31%. The work demonstrated that both modification of the substrate and the reaction conditions could afford an eleven-membered RCM product in reasonable yield. It should be possible to use this methodology to make congeners of zerumbone and the buddledone and buddledin families of compounds. Further results will be reported in due course.

Acknowledgment. This work was supported by the National Science Foundation to whom we are grateful. Thanks to Dr. Charles L. Barnes (Missouri-Columbia) for acquisition of X-ray data.

Supporting Information Available. Experimental procedures and spectral data for all new compounds. X-ray data for **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.