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Enantioselective Total Synthesis of the Guaianolide (−)-Dehydrocostus Lactone by Enediyne Metathesis

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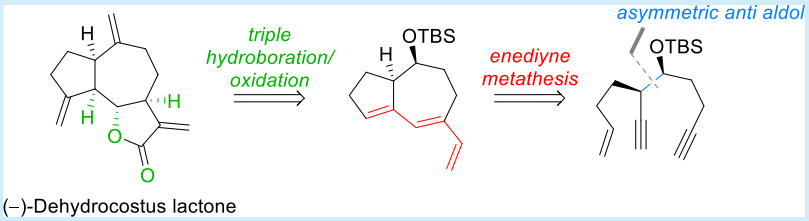
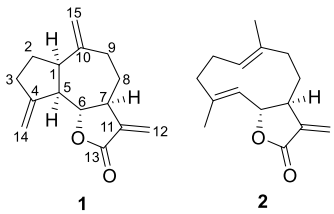


ABSTRACT: The hydroazulene core of the bioactive sesquiterpenoid (−)-dehydrocostus lactone was generated by domino enediyne metathesis. A triple hydroboration/oxidation of the resultant conjugated triene installed three out of four stereogenic centers of the target in a single step. The enantiopure acyclic metathesis substrate was readily available by an asymmetric *anti* aldol reaction. Masking of the γ-lactone as an acetal allowed for an efficient completion of the synthesis through late-stage double carbonyl olefination.

Over the recent years, the sesquiterpenoid (−)-dehydrocostus lactone (**1**) has drawn much attention, especially as a potential agent for the treatment of various cancer types such as breast cancer,[1] liver cancer,[2] lung cancer,[3] or leukemia[4] (Figure 1). A large number of studies have identified diverse



1 **2**

Figure 1. Sesquiterpenoids (−)-dehydrocostus lactone (**1**) and (+)-costunolide (**2**).

modes of action ranging from antiproliferation[1b,c,4b] and inhibition of metastasis and invasion,[5] over induction of apoptosis,[1c,3a] to even reversing multidrug resistance.[6] It is assumed that the α-methylene-γ-butyrolactone moiety plays a crucial role in the observed biological activities. Although these studies are very promising for potential therapeutic applications, there is still a lack of systematic evaluation, making **1** an interesting target for total synthesis.[7]

Sometimes a synergetic effect between **1** and (+)-costunolide (**2**), another sesquiterpenoid bearing an α-methylene-γ-butyrolactone, was reported.[7] These two compounds usually co-occur in plants, for example in *Saussurea costus*, a plant endemic to the sub-alpine region of India and China, which is well-known for its use in traditional medicine.[8] (−)-Dehydrocostus lactone (**1**) was isolated from this plant as one of the main sources of **1** for the first time in 1939 by Ukita.[9] Since the use of *S. costus* for commercial and medical purposes has increased rapidly, this species is listed in *Appendix I of Convention on International Trade in Endangered Species of Wild Fauna and Flora* (CITES), and it is furthermore banned from export by the government of India.[10]

Although this circumstance mandates the development of synthetic approaches to **1** even more, only two syntheses are known to date (Scheme 1). Ando and co-workers published the first enantioselective access to (−)-dehydrocostus lactone (**1**) in 1984.[11] Starting from the naturally occurring eudesmanolide (−)-α-santonin (**3**), mesylate **4** was prepared by a multistep sequence. In the key step, a solvolytic rearrangement of **4** to (+)-mokkolactone (**5**) along with other olefin isomers was realized to establish the guaianolide framework. Finally, **1** was prepared from **5** by α-selenenylation and oxidative *syn* elimination.

The second approach was published later in 1984 by Rigby and co-workers.[12] Their strategy for racemic **1** was based on the annulation of a five-membered onto a seven-membered ring by acid catalyzed cyclization of diene **6**. This compound was obtained as a diastereomeric mixture via 1,8-addition of a

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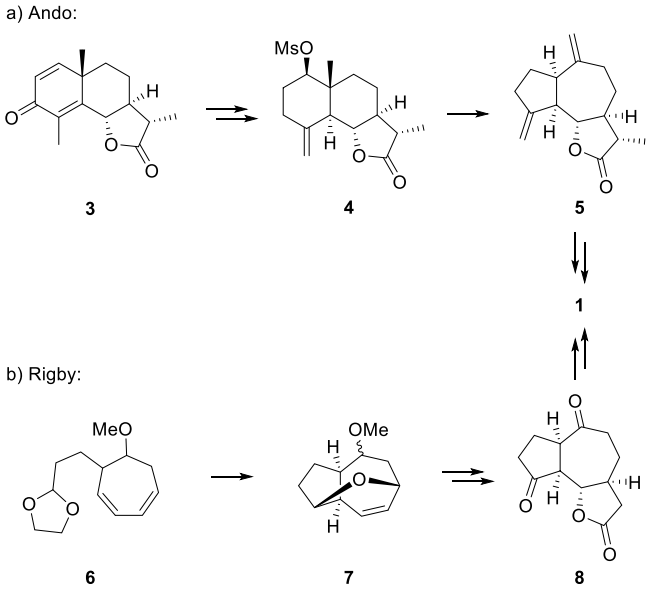
Scheme 1. Previous Approaches to (−)-1 (a) and Racemic 1 (b) by the Groups of Ando and Rigby

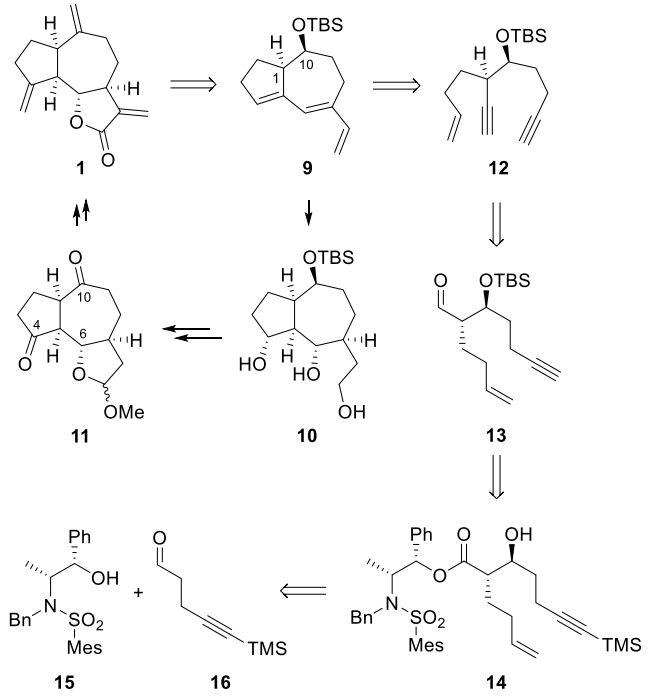


Grignard reagent to tropone. The cyclic ether **7** was further transformed to diketone **8** by a multistep route. However, ketone olefination of **8** was found to be inefficient owing to the competing opening of the γ-butyrolactone by β-elimination and proceeded at best[13] in only 15% yield. Finally, racemic dehydrocostus lactone (**1**) was isolated after α-methylenation of the lactone using Eschenmoser's salt.

Due to our interest in the synthesis of hydroazulene natural products by domino metathesis,[14] we developed a new approach to (−)-dehydrocostus lactone (**1**) by an enediyne strategy. Noteworthy, there are only a few examples for domino metathesis reactions with substrates bearing more than one triple bond.[14e,15] As depicted in Scheme 2, our synthesis was based on the disassembly of guaianolide **1** to a hydroazulene core structure, which should allow facile functionalization in the desired stereochemical fashion. We assumed triene **9** to be a suitable intermediate that might undergo exhaustive hydroboration/oxidation to give triol **10** in a substrate-induced diastereoselective manner. Blocking of the concave face by a bulky substituent at C-10 should increase the preference for attack on the convex face. Compound **10** would be transformed to diketone **11** by acetal formation, cleavage of the silyl ether, and twofold oxidation. Since Rigby and co-workers encountered severe difficulties during methylenation of the diketo-γ-lactone **8**,[12] we decided to mask the lactone unit as the corresponding methyl acetal.[16] This should disfavor cleavage of the C-6 oxygen bond by β-elimination upon introduction of the methylene unit at C-4. Finally, unmasking the lactone and subsequent α-methylenation would complete the synthesis of **1**.

We envisioned enediyne **12** as a suitable substrate for the key metathesis event to give triene **9**. Compound **12** in turn was traced back to aldehyde **13** revealing an *anti* aldol pattern that might be generated according to the procedure by Masamune and Abiko.[17] Thus, aldehyde **13** should emerge from the *anti* aldol adduct **14** after C-desilylation/O-silylation and reductive removal of the auxiliary. Ester **14** can be disconnected to the known aldehyde **16**,[18] hex-5-enoic acid, and the commercially available chiral auxiliary **15**.

Scheme 2. Synthetic Strategy for (−)-Dehydrocostus Lactone (1)



With our synthetic strategy set, we initially focused on the asymmetric aldol reaction. The donor component **17** was readily prepared by DCC/DMAP-mediated esterification[19] of auxiliary **15** and hex-5-enoic acid (Scheme 3). Aldol addition of the dicyclohexylboron enolate derived from **17** to aldehyde **16**[18] led to a mixture of the two *anti* diastereomers with good diastereoselectivity (*dr* = 9:1). The isomers were separated by flash chromatography to give the pure diastereomer (*S*,*S*)-**14** in 90% yield. The aldol product (*S*,*S*)-**14** was then transformed into aldehyde **13** in four steps. After C-desilylation of the alkyne with TBAF and TBS protection of the hydroxyl group, the resulting ester **18** was cleaved using an excess of DIBAL to give alcohol **19** and the reisolated auxiliary **15** in high yields. Subsequently, alcohol **19** was smoothly oxidized to aldehyde **13** using TEMPO/PIDA.[20] For conversion of **13** to the metathesis substrate **12**, alkynylation with Wu's reagent (**20**)[21a] performed best from a variety of conditions[21] screened and gave enediyne **12** quantitatively.

With enediyne **12** in hand, the stage was set to investigate the domino metathesis to give **9** as the key step of our synthesis (Scheme 4). Earlier we applied both the Grubbs II (for dieneyne[14b,d] and trieneyne[14c,e] metathesis) and the Grubbs I catalysts (for dienediyne metathesis)[14e] for related domino transformations. Whereas reaction of **12** with the Grubbs II catalyst always delivered mixtures of the desired triene **9** and its isomer **9′**, enediyne **12** was converted to the pure triene **9** by treatment with the more chemoselective Grubbs I catalyst in 86% yield (calculated from ^{1}H NMR data of **9** still containing some pentane). We assume that the formation of **9′** is triggered by initiation of the domino process at the alkyne carbon C-7 rather than at C-5. Initiation at C-5 would first lead to the monocyclic compounds **A** or **B**, and we found that **A** could not be transformed to **9** by treatment with the Grubbs II catalyst.[22]

As hydroazulene **9** tended to oligomerize under neat conditions, it had to be subjected to the following hydro-

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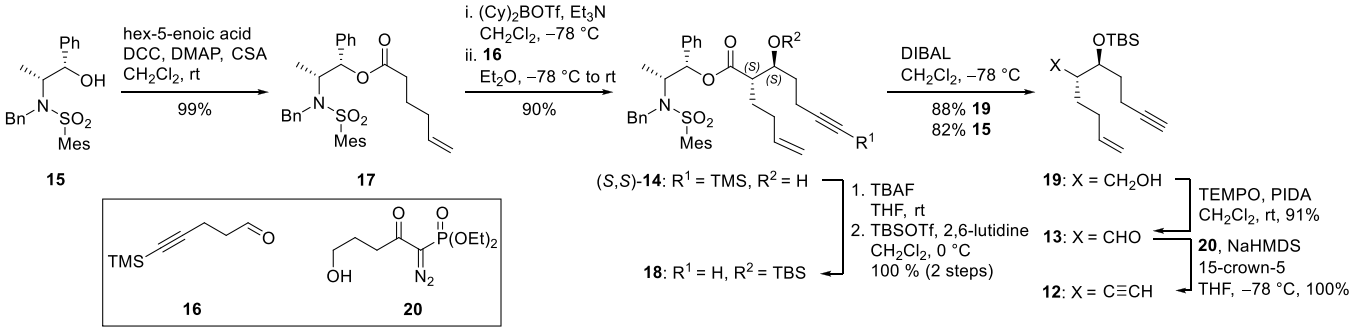
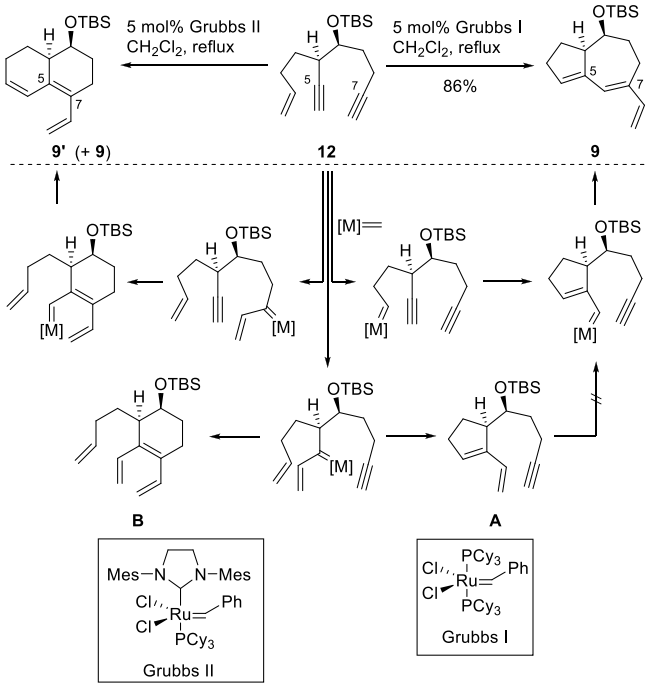
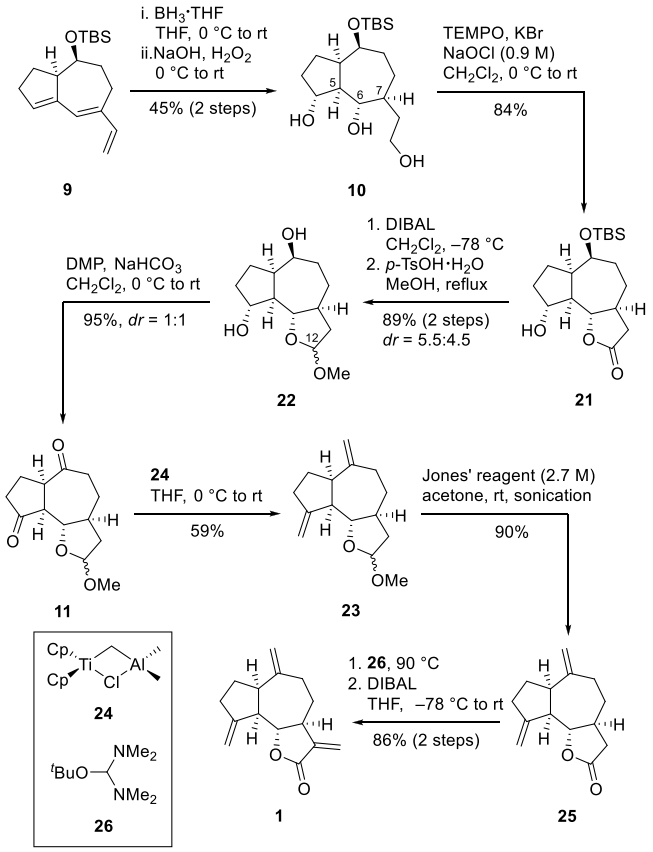
Scheme 3. Synthesis of Enediyne 12 via Asymmetric Aldol Reaction



Scheme 4. Formation of Hydroazulene 9 and Decalin 9′ via Enediyne Metathesis



Scheme 5. Final Steps to (−)-Dehydrocostus Lactone (1)



boration reaction immediately (Scheme 5). Gratifyingly, we found that treating **9** with an excess of borane in THF at 0 °C and subsequent oxidative workup with H_2O_2/NaOH effected a selective formation of triol **10** along with three additional diastereomers in 65% yield (*dr* = 69:9:8:14) over two steps. While the relative configuration of the minor three diastereomers could not be determined unequivocally, the relative configuration of the major diastereomer **10** isolated as a pure compound in 45% yield over two steps was characterized unambiguously. This confirmed our prediction of a favored attack on the convex face of the molecule leading to the desired configurations at C-5/C-6/C-7.

In order to install the acetal unit, we first planned a chemoselective oxidation with TEMPO/NaOCl of the primary alcohol allowing a spontaneous formation of a five-membered lactol.[23] However, regardless of the amount of oxidizing agent used, the lactol was always further oxidized to the corresponding lactone **21**. Therefore, we optimized the conditions for this oxidative lactonization[24] to yield **21** and subsequently treated this lactone with DIBAL. The resultant crude lactol was then refluxed in MeOH with *p*-toluenesulfonic acid.[16] Under these conditions, desilylation took place as well to afford a mixture of C-12 epimers (*dr* = 5.5:4.5) of diol acetal **22** in 89% yield over two steps. Oxidation of this mixture with the Dess-Martin periodinane (DMP) then provided the diketone **11** (*dr* = 1:1) efficiently.

Much to our delight, double carbonyl olefination of **11** was cleanly achieved with Tebbe's reagent (**24**)[25] to give diene **23** in good yield without competing *β*-elimination or epimerization *α* to the ketone functions.[26] For *α*-methylenation, the *γ*-butyrolactone needed to be reinstalled. Following a procedure by Srikrishna,[27] acetal **23** was treated with Jones' reagent and briefly sonicated. After workup and purification by column chromatography, lactone **25** was directly obtained as a colorless solid in 90% yield. While **25** can be converted to **1** using Eschenmoser's salt,[12] application of Ziegler's methodology was superior in our hands.[28] Thus, *α*-methylenation by condensation of **25** with Bredereck's reagent (**26**)[29] and subsequent reduction with DIBAL gave (−)-dehydrocostus

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lactone (**1**) in 86% yield over two steps.[14c,28] The analytical data of **1** were in full agreement with those reported in the literature.[11]

In summary, we have completed a highly efficient asymmetric total synthesis of the bioactive sesquiterpenoid (−)-dehydrocostus lactone (**1**) in 17 steps with an overall yield of 12%. A domino metathesis of an enediyne prepared in enantiopure form by an *anti* aldol reaction served as the key step. Triple hydroboration/oxidation of the resultant triene set up three out of four stereogenic centers of the target molecule in a single operation. Masking of the γ-lactone as an acetal was crucial for installing the exocyclic alkenes of the hydroazulene fragment by a double carbonyl olefination.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00008.

Experimental procedures, spectroscopic data, ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

This paper is dedicated to Professor Günter Domschke (TU Dresden) on the occasion of his 90th birthday.

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