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Collective Synthesis of Humulanolides Using a Metathesis Cascade Reaction

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Supporting Information

ABSTRACT: A new method has been developed for the concise and asymmetric synthesis of seven humulanolides in 5−7 steps without the need for protecting groups. Notably, the challenging 11-membered ring and bridged butenolide moieties in asteriscunolide D and 6,7,9,10-tetrahydroasteriscunolide were introduced in one step using a ring-opening/ring-closing metathesis cascade reaction. Asteriscunolide D was used as a versatile synthetic precursor to prepare asteriscunolides A−C via a photoinduced isomerization reaction, asteriscanolide via a unique transannular Michael reaction, and 6,7,9,10-tetradehydroasteriscanolide via a transannular Morita−Baylis−Hillman-type reaction. The unique bicyclo[6.3.0]-undecane core was introduced diastereoselectively.

The humulanolides are a series of sesquiterpene lactones, and most of the compounds belonging to this class have a unique and challenging structure. Asteriscunolides A−D (**1**−**4**)[1] and 6,7,9,10-tetrahydroasteriscunolide (**5**)[2] have a synthetically challenging 11-membered ring[3] combined with a bridged cyclic butenolide (Figure 1). Asteriscanolide (**6**),[4] 6,7,9,10-tetradehydroasteriscanolide (**7**),[5] naupliolide (**8**),[6] and aquatolide (**9**)[7] have a rather unusual bicyclo[6.3.0]undecane core and an adjoining butyrolactone moiety. Several humulanolide compounds have been reported to exhibit anticancer activity. For example, asteriscunolide A (**1**) induces apoptosis in human cancer cell lines[8] and asteriscunolide D (**4**) has more cytotoxicity than cisplatin, with good potency against the HT-29 (human colon carcinoma), A-549 (human lung carcinoma), and MEL-28 (human melanoma) cell lines.[2b]

Taken together, the fascinating structural motifs and promising pharmacological properties of humulanolides have prompted significant interest in the synthetic community.[9−11] Asteriscunolide D (**4**) was first synthesized by Trost et al.[9a] in nine steps. The first total synthesis of asteriscanolide (**6**) was completed in 13 steps by Wender et al.[10a] in 1988, and the current shortest route (nine steps) was developed by Limanto and Snapper[10c] in 2000. Although several elegant synthetic strategies for the construction of humulanolide compounds have been reported, these routes can only be applied to a single natural product in the series. Furthermore, no studies have been reported to date pertaining to the chemical or biological synthesis of compounds **5**, **7**, **8**, and **9**. Herein we describe the collective synthesis of these humulanolides using a ring-opening/ring-closing metathesis (ROM/RCM) cascade reaction.

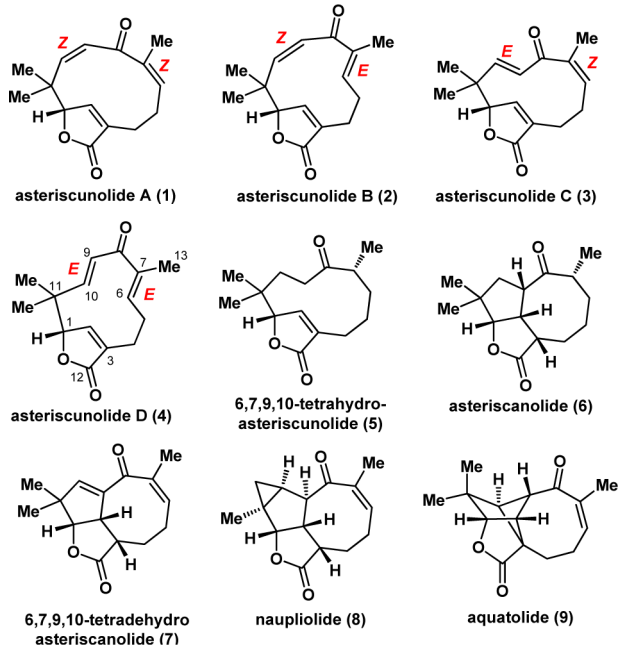

Figure 1. Humulanolides.

The retrosynthetic strategy used in the current study is shown in Figure 2A. Briefly, asteriscunolides A−D (**1**−**4**) could be generated from tetraene **10** via a ruthenium-catalyzed ROM/RCM cascade. Tetraene **10** could be synthesized from cyclobut-1-enecarboxylic acid (**12**) and chiral diol **11**.[12] 6,7,9,10-Tetrahydroasteriscunolide (**5**) could be prepared from asteriscunolide through a regio- and stereoselective hydrogenation reaction, and asteriscanolide (**6**) could be derived from **5** via a transannular Michael addition reaction.[11f,13] Aquatolide (**9**) and naupliolide (**8**) could be prepared from asteriscunolide C via a [2 + 2] photocycloaddition reaction[7] and by the proposed acid-induced cyclization,[6] respectively. Finally, 6,7,9,10-tetradehydroasteriscanolide could be synthesized from asteriscunolide via a transannular Morita−Baylis−Hillman-type reaction.[14]

The key step in our current strategy was the intramolecular ROM/RCM cascade. This reaction was developed by Grubbs

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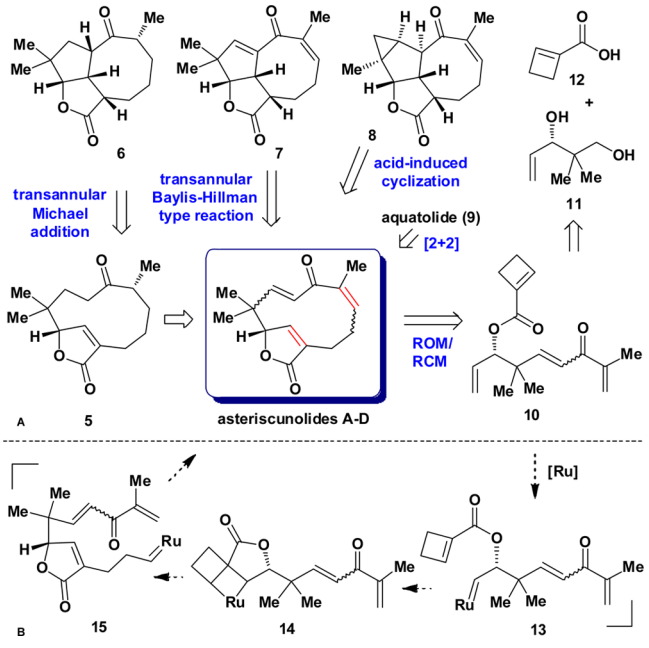
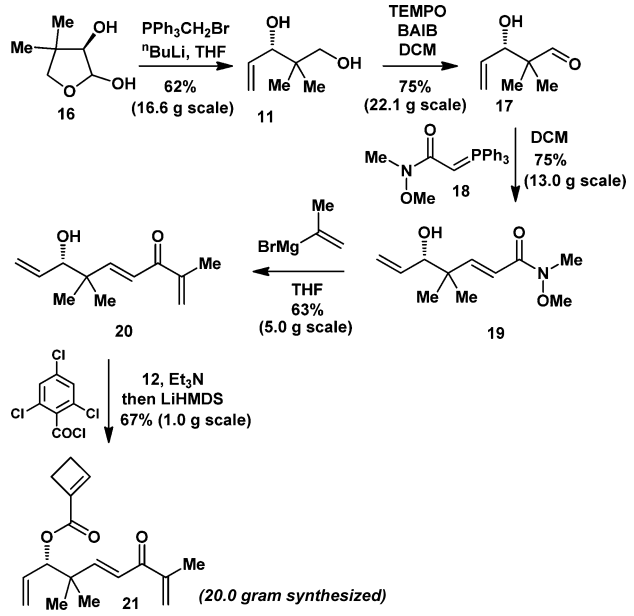


Figure 2. (A) Retrosynthetic analysis of the humulanolides. (B) Metathesis (ROM/RCM) cascade reaction for the construction of the asteriscunolides.

and co-workers[15] and has subsequently been used for the preparation of fused bicyclic rings.[16] The RCM cascade reaction was recently used in our group for the synthesis of flueggine A and virosaine B.[17] In the current study, this reaction has been applied to the synthesis of the asteriscunolides. It was envisaged that the ruthenium catalyst would react preferentially with the monosubstituted terminal olefin of **10** to generate ruthenium carbene complex **13** (Figure 2B). Subsequent intramolecular ROM with the strained cyclobutene would then afford butenolide-based **15** via intermediate **14**. The driving force for this reaction would be the opening of the highly strained four-membered ring. Finally, RCM would give the 11-membered ring of the asteriscunolide.[18] Furthermore, it was envisaged that changing the *E*/*Z* geometry of the internal olefin in **10** or using an *E*- or *Z*-selective Ru catalyst[19] would allow the preparation of asteriscunolides A–D. Although the ROM/RCM reaction has been used previously to generate the butenolide moiety,[20] there have been no reports pertaining to the use of an intramolecular ROM/RCM cascade reaction for the construction of the bicyclic skeleton of medium-sized rings because of ring strain. In this transformation, the 11-membered ring and fused butenolide moieties could be generated in a single-step using a ROM/RCM cascade reaction. This reaction would allow the formation of two sterically hindered, trisubstituted, electron-deficient double bonds, although it would be challenging to control the chemoselectivity of the transformation because of the four olefins in **10**.

The synthesis began with the asymmetric preparation of tetraene **21** (Scheme 1). The Wittig olefination of the readily available starting material **16**[21] gave known diol **11** {$[\alpha]_D^{26}$ −23.5 (*c* 2.0, $CHCl_3$); lit.[12a] $[\alpha]_D^{25}$ −20.5 (*c* 0.74, $CHCl_3$)}, which was oxidized with TEMPO/BAIB to give aldehyde **17** in 75% yield (22.1 g scale). Aldehyde **17** was found to be unstable under basic conditions. Pleasingly, however, aldehyde **17** reacted cleanly with Wittig reagent **18** to give the desired diene **19** in 75% yield (13.0 g scale). Treatment of Weinreb amide **19** with isopropenylmagnesium bromide afforded triene **20** in good yield (5.0 g scale),

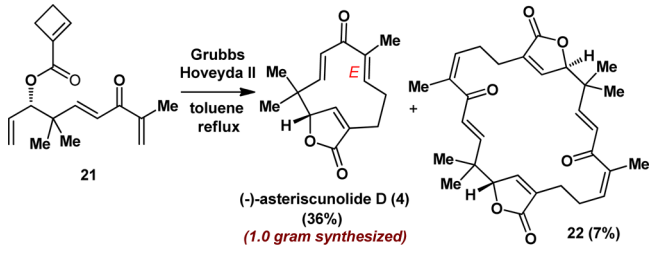
Scheme 1. Asymmetric Synthesis of Compound 21



which underwent an esterification reaction with cyclobut-1-enecarboxylic acid (**12**) in the presence of DCC or EDCI to provide tetraene **21**. Unfortunately, however, the yield of this reaction was very low, and a byproduct that could not be identified was also formed. Finally, the mixed acid anhydride of acid **12** was generated as an intermediate using Yamaguchi conditions (i.e., 2,4,6-trichorobenzoyl chloride/Et_3N) and reacted with alcohol **20** in the presence of LiHMDS to give **21** in 67% yield (1.0 g scale) [see the Supporting Information (SI) for details].

The ROM/RCM cascade sequence was then evaluated using tetraene **21** with a variety of different catalysts (i.e., Grubbs I, Grubbs II, Grubbs–Hoveyda I, Grela II, Zhan-1B, and Grubbs–Hoveyda II) and solvents (i.e., DCM, DCE, and toluene). These screening experiments revealed that the best results were obtained using the Grubbs–Hoveyda II catalyst and toluene. The use of a commercially available *Z*-selective Ru catalyst[22] did not afford any of the expected asteriscunolide C product. Compound **21** readily underwent the ROM/RCM cascade reaction in the presence of the Hoveyda–Grubbs II catalyst in refluxing toluene to afford asteriscunolide D (**4**) in 36% yield as well as dimer **22** and several unidentified byproducts (Scheme 2). The ^1H and ^{13}C NMR spectra of synthetic compound **4** as well as its optical rotation {synthetic $[\alpha]_D^{26}$ −142.4 (*c* 0.50, $CHCl_3$); natural $[\alpha]_D^{23}$ −158.0 (*c* 0.37, $CHCl_3$)} were identical to those of the natural product.[1] This route provided facile access to a total of 1.0 g of **4** (see the SI for details), thereby highlighting the robust nature of the chemistry. It is noteworthy that in the Trost

Scheme 2. Asymmetric Synthesis of 4



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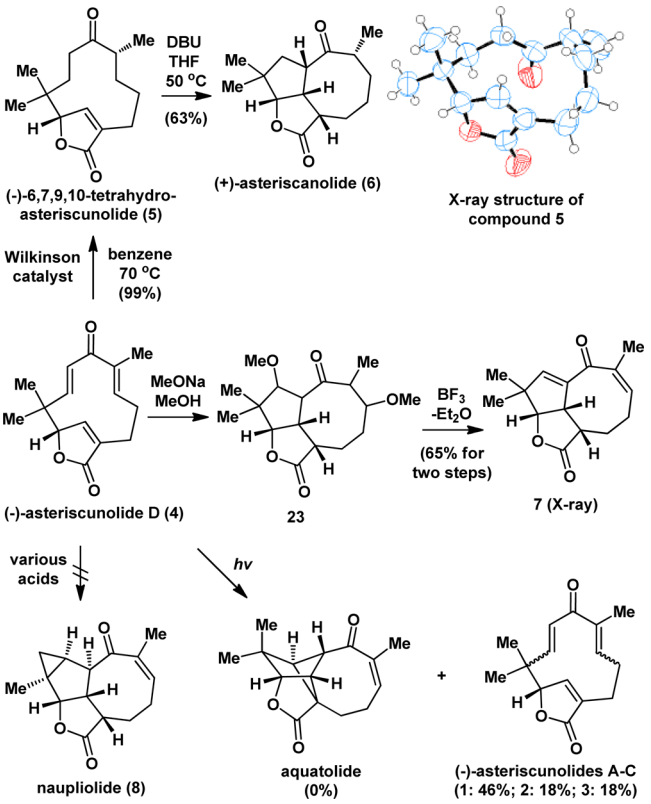
synthesis the 11-membered ring of **4** was generated via a DMTSF-mediated cyclization followed by an elimination reaction, with the desired product being formed in an overall yield of 26−33%.[9a] Furthermore, Fernandes and Chavan[9b] reported that it was very difficult to directly generate the 11-membered ring of these compounds using an RCM reaction. In contrast to both of these reports, the current ROM/RCM cascade reaction allowed the efficient construction of the two rings of **4** in a single step with exclusive *E* selectivity.

With (−)-asteriscunolide D (**4**) in hand, we proceeded to investigate our proposed syntheses of the remaining humulanolides (Scheme 3). Compound **4** underwent a regio- and

Scheme 3. Asymmetric Synthesis of 5−7 and 1−3 from 4



stereoselective hydrogenation reaction in the presence of Wilkinson's catalyst to give 6,7,9,10-tetrahydroasteriscunolide (**5**) as the sole product in 99% yield. The ^{1}H and ^{13}C NMR spectra of **5** were almost identical to those of the natural product except for the chemical shifts of two carbon atoms.[2] Despite this small difference, the optical rotation of the synthetic material $\{[\alpha]_D^{26}$ −6.3 (*c* 0.40, $CHCl_3$)} was in agreement with that of the natural product $\{[\alpha]_D^{20}$ −17.5 (*c* 1.0, $CHCl_3$)}. The structure of the newly synthesized **5** was subsequently confirmed by X-ray crystallography, therefore suggesting that the original ^{13}C NMR spectra of the material should be revised. Treatment of **5** with DBU in THF at 50 °C gave (+)-asteriscanolide (**6**) in 63% yield. It is noteworthy that there have been no reports in the literature, to the best of our knowledge, concerning the use of a transannular Michael reaction for the construction of an eight-membered ring.[13] One of the major limitations of this approach has traditionally been the high kinetic barrier imposed by the initial bond-forming reaction.[23]

Our initial efforts to synthesize compounds **7**−**9** involved the use of acid-induced cyclization[6] and [2 + 2] photocycloaddition reactions.[7] Although a wide variety of conditions were screened (i.e., $BF_3{\cdot}Et_2O$, Et_2AlCl, $TiCl_4$, and TsOH), none of these reactions afforded any of the desired products. It was envisaged that a transannular Morita−Baylis−Hillman-type reaction would give 6,7,9,10-tetradehydroasteriscanolide (**7**) from asteriscunolide D, but the reaction of asteriscunolide D under standard conditions (i.e., Et_3N, DBU, DABCO, Ph_3P) did not afford any **7**. Interestingly, when the reaction was carried out in the presence of MeONa and MeOH, the presumed tricycle **23** was obtained as a complex mixture of inseparable isomers. In this particular transformation, MeONa was used as a nucleophile to attack the dienone, which was followed by 1,4-addition of the resulting enolate to the butenolide to close the eight-membered ring. Subsequent treatment of **23** with $BF_3{\cdot}Et_2O$ led to the elimination of the methoxy groups to give **7** in an overall yield of 65%. The structure of **7** was confirmed by X-ray crystallography, and the physical properties of synthetic **7** were found to be in agreement with those in the literature for the natural product.[5] Initial experiments involving exposure of compound **4** to UV light did not lead to the formation of the expected aquatolide (**9**) (see the SI for details). Pleasingly, however, the irradiation of a 5:1 (v/v) CH_3CN/acetone solution of **4** with a UV lamp (10 W, 254 nm) at room temperature in a photochemical reactor for 3 h resulted in a mixture of asteriscunolides A−C, which were separated by preparative thin-layer chromatography in yields of 46%, 18%, and 18%, respectively.[9a]

In summary, a highly concise and asymmetric synthesis has been developed for the construction of a series of humulanolides in 5−7 steps from the known diol **11** without the requirement for any protecting groups.[24] Notably, this includes the first reported synthesis of 6,7,9,10-tetrahydroasteriscunolide and 6,7,9,10-tetradehydroasteriscanolide. The challenging 11-membered ring and fused butenolide moieties of biologically active asteriscunolide D were successfully installed in only one step using a novel ROM/RCM cascade reaction. To the best of our knowledge, this work represents the first reported example of an intramolecular ROM/RCM cascade reaction for the construction of a bicyclic skeleton with an 11-membered ring. Furthermore, we have demonstrated that asteriscunolide D can be used as a versatile biomimetic synthetic precursor for the construction of several other humulanolides. Asteriscanolide and its derivative 6,7,9,10-tetradehydroasteriscanolide with a bicyclo[6.3.0]undecane core were synthesized diastereoselectively from asteriscunolide D using an unusual transannular Michael reaction and a transannular Morita−Baylis−Hillman-type reaction, respectively.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental and computational procedures, compound characterization data, and CIFs for **5** and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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