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To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201904404
Angew. Chem. 10.1002/ange.201904404

Link to VoR: http://dx.doi.org/10.1002/anie.201904404
http://dx.doi.org/10.1002/ange.201904404

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10.1002/anie.201904404

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Total Syntheses of (+)-Aquatolide and Related Humulanolides

Ken-ichi Takao,*[a] Hirotaka Kai,[a] Ai Yamada,[a] Yuuki Fukushima,[a] Daisuke Komatsu,[a] Akihiro Ogura,[a] and Keisuke Yoshida[b]

Abstract: The short, efficient total synthesis of (+)-aquatolide was achieved by a biomimetic transannular [2+2] photocycloaddition, which provides the first example of constructing a 5/5/4/8-ring system from asteriscunolides. Furthermore, the reaction leading to a 5/4/4/7-ring system, the originally proposed structure of aquatolide, was also developed. This strategy achieved syntheses of five more humulanolides, (–)-asteriscunolides A, C, D, and I, and (+)-tetradehydroasteriscanolide.

Sesquiterpenes contained in *Asteriscus* (Compositae) have attracted considerable attention from the community. (–)-Asteriscunolide A (**1**), isolated from *Asteriscus aquaticus* along with *cis-trans* isomers (–)-asteriscunolides B–D (**2**–**4**), is the first elucidated sesquiterpene lactone containing a humulane skeleton, known as a humulanolide[1] (Figure 1A). The same plant also afforded tricyclic (+)-asteriscanolide (**5**),[2] and its tetradehydro- analog (+)-tetradehydroasteriscanolide (**6**) was isolated from *A. graveolens*.[3] In 1989, San Feliciano found a new humulanolide called aquatolide in *A. aquaticus*.[4] The structure of (+)-aquatolide was originally assigned mainly by NMR analysis as **7a**, which consists of a tetracyclic 5/4/4/7-ring system with an unusual embedded [2]-ladderane motif. Later, its structure was revised based on quantum chemical NMR calculations and X-ray crystallography of the re-isolated sample by Shaw and Tantillo.[5] Revised structure **7b** possesses an unprecedented, intricate 5/5/4/8-ring system containing five contiguous stereogenic centers. In particular, a bicyclo[2.1.1]hexane core is uncommon in natural products. The proposed biosynthesis of **7b** involves a transannular crossed [2+2] cycloaddition of **3**, in which the C2–C9 and C3–C10 bonds are formed (Figure 1B). Although the alternative parallel cycloaddition leading to originally proposal **7a** seems likely, such a closure has not been discovered so far in *A. aquaticus*. Recently, another congener, (–)-asteriscunolide I (**8**), was isolated from *A. graveolens*.[6] With prominent cycotoxicity of humulanolides including **1** and **4**,[7,8] the development of a practical synthesis of **7b** and related compounds might allow the discovery of new antitumor agents.

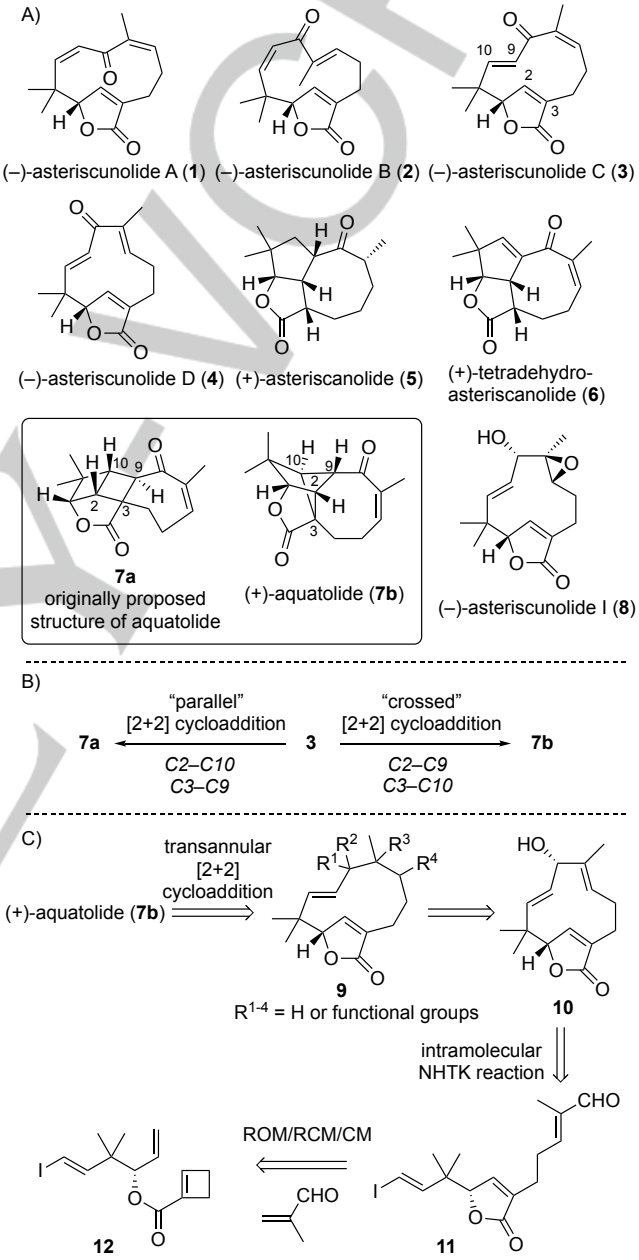

Figure 1. (A) (+)-Aquatolide and related humulanolides. (B) Proposed biosynthesis of (+)-aquatolide. (C) Retrosynthetic analysis of (+)-aquatolide.

Owing to their fascinating structure, these humulanolides have been exciting synthetic targets.[9] Five groups have published total syntheses of **5**.[10-14] The structurally related naupliolide[15] was also synthesized by Ito and co-workers.[16] With regard to asteriscunolides, total syntheses of **3** and **4** were achieved by Fernandes[17] and Trost,[18] respectively. Eventually,

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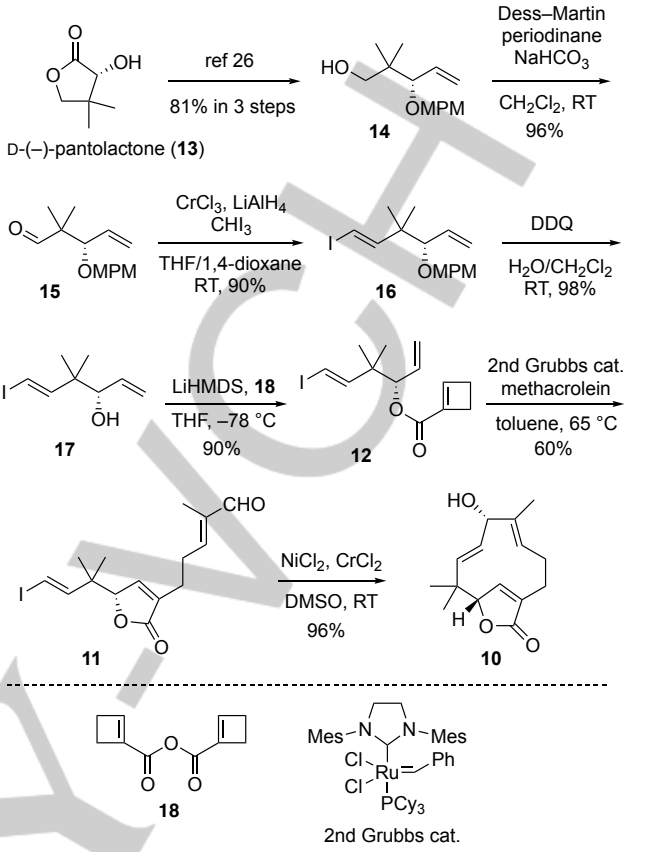
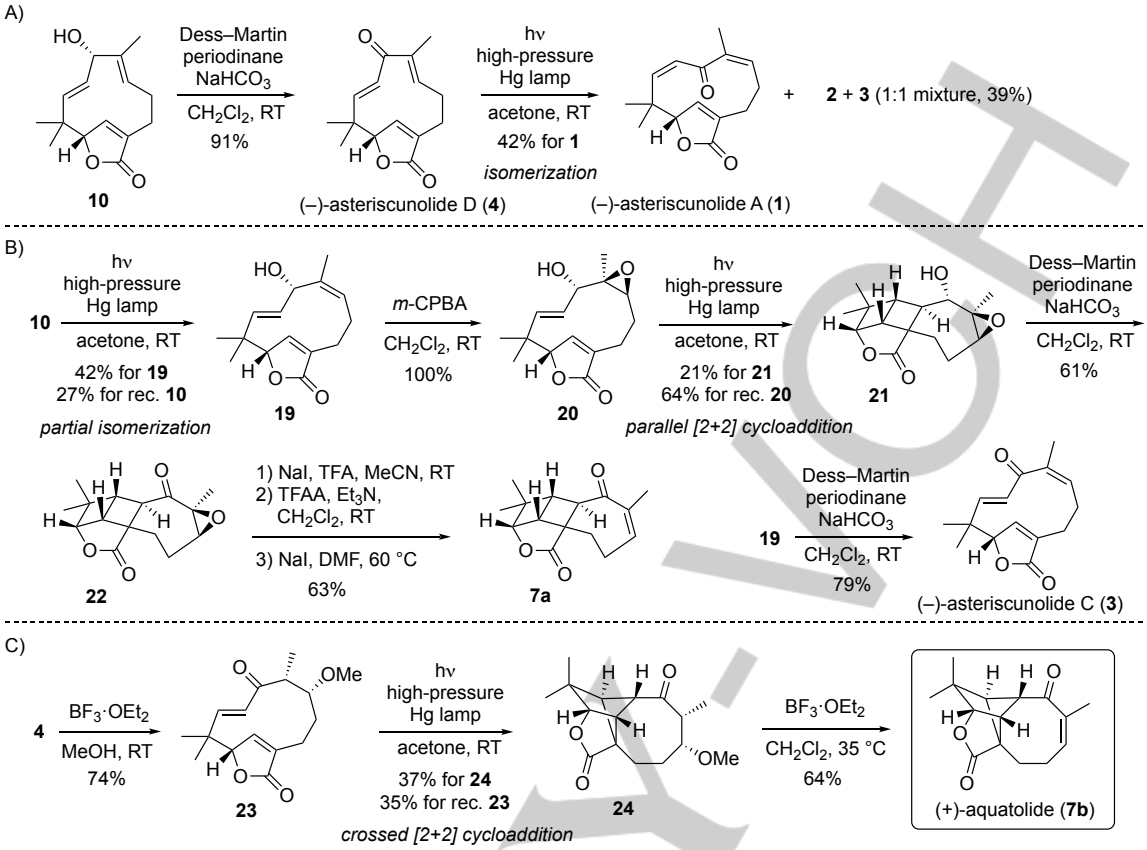
Li's group reported an elegant collective synthesis of compounds **1**–**6**.[19] The total synthesis of the challenging revised structure of aquatolide **7b** has been completed by two groups. Hiemstra and co-workers accomplished the first total synthesis of racemic (±)-**7b** through intramolecular [2+2] photocycloaddition of an allenic pentenolide in 16 steps (longest linear chain) with 2.2% overall yield.[20] Zhang and Gu's group synthesized (±)-**7b** using the Wolff rearrangement of bicyclo[2.2.1]heptane in 22 steps with 0.8% overall yield.[21] In both syntheses, the strained bicyclo[2.1.1]hexane skeleton was constructed at an earlier stage, and biomimetic transannular [2+2] cycloaddition of an asteriscunolide-type compound has not been reported. Here, we report a concise, high-yielding synthetic route towards the natural enantiomer of (+)-aquatolide (**7b**) by the biomimetic transannulation strategy. This approach allowed the total syntheses of six natural products, (–)-asteriscunolides A, C, D, and I (**1**, **3**, **4**, and **8**), (+)-tetradehydroasteriscanolide (**6**), and **7b**. Furthermore, the originally proposed structure of aquatolide (**7a**) was also synthesized for the first time.

Our retrosynthetic analysis of **7b** is shown in Figure 1C. Li and co-workers reported that irradiation of (–)-asteriscunolide D (**4**) afforded the *cis-trans* isomers including (–)-asteriscunolide C (**3**), a putative biosynthetic precursor of (+)-aquatolide, but that **7a** or **7b** were not formed in the reaction.[19] Given our experience with biomimetic total synthesis,[22] we expected that the [2+2] cycloaddition could be achieved by tuning the structure of the substrate. An asteriscunolide-type precursor **9** would be derived from humulene lactone **10**, the common intermediate for the divergent synthesis of related natural products. To form the 11-membered ring, an intramolecular Nozaki–Hiyama–Takai–Kishi (NHTK) reaction of iodoalkene–aldehyde **11** would be used because this reaction gave good results in some difficult cyclizations.[23,24] The disubstituted γ-butenolide skeleton would be constructed by a ring-opening/ring-closing/cross-metathesis (ROM/RCM/CM) reaction from cyclobutenecarboxylate **12** and methacrolein, which is an extension of our ring-opening/ring-closing metathesis (ROM/RCM) of cyclobutenecarboxylate derivatives for concise access to γ-butenolides.[25]



Scheme 1. Construction of the asteriscunolide skeleton. MPM = 4-methoxyphenylmethyl, THF = tetrahydrofuran, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, LiHMDS = lithium bis(trimethylsilyl)amide, DMSO = dimethylsulfoxide.

With this retrosynthetic analysis in mind, we first investigated the construction of the asteriscunolide skeleton (Scheme 1). According to a known three-step procedure, D-(–)-pantolactone (**13**) was converted into alcohol **14**.[26] Oxidation of **14** with the Dess–Martin reagent provided aldehyde **15**, which was subjected to Takai–Utimoto olefination[27,28] to afford alkenyl iodide **16** with high *E*-selectivity. Removal of the MPM group from **16** provided allylic alcohol **17**, which was acylated with acid anhydride **18**[25] to provide cyclobutenecarboxylate **12**. After optimization of the reaction conditions, we found that the ROM/RCM/CM reaction of **12** proceeded in a cascade manner to produce desired (*E*)-α,β-unsaturated aldehyde **11** directly in a good yield (60%). In this reaction, the iodoalkene moiety remained intact. The cascade ROM/RCM/CM reaction substantially improved the yield of **11** and provided an operationally simple method. The next stage of the synthesis involved construction of the 11-membered carbocycle. The intramolecular NHTK reaction of **11** achieved efficient cyclization and key intermediate **10** was obtained as a single diastereomer in excellent yield.[29] We attribute this high diastereoselectivity to the general tendency of NHTK reaction to afford a pseudoequatorial hydroxyl group.[23,24] Considering the highly strained structure of the 11-membered ring, the high yield of **10** was remarkable.



Scheme 2. (A) Syntheses of (–)-asteriscunolides D (**4**) and A (**1**).(B) Syntheseis of the originally proposed structure of aquatolide (**7a**) and (–)-asteriscunolides C (**3**). (C) Total synthesis of (+)-aquatolide (**7b**). *m*-CPBA = *m*-chloroperbenzoic acid, TFA = trifluoroacetic acid, TFAA = trifluoroacetic anhydride, DMF = *N*,*N*-dimethylformamide.

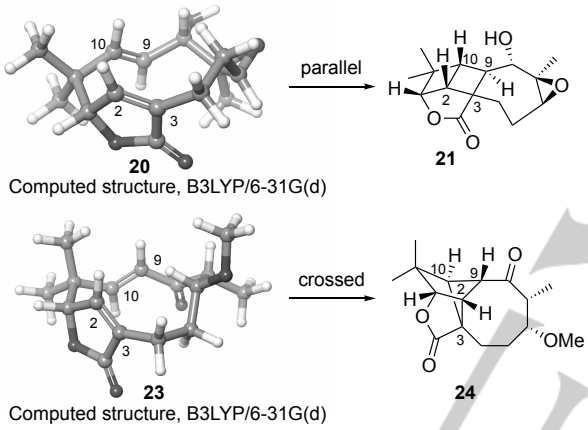
Having rapidly assembled the asteriscunolide skeleton, we turned to the transannular [2+2] photocycloaddition to construct the bicyclo[2.1.1]hexane core.[30] First, alcohol **10** was oxidized to **4** (Scheme 2A). Thus we achieved the total synthesis of **4** in 10 steps from **13** with a 32% overall yield. Compared with previous routes,[18,19] our approach gave a yield of **4** that was several times higher. With substrate **4** in hand, we used a high-pressure Hg lamp (100 W) emitting over a wide range of wavelengths to irradiate **4** through Pyrex glass. The results were similar to those obtained previously with a UV lamp (10 W, 254 nm)[19] and only isomerization of the olefins occurred. As a major product, (–)-asteriscunolide A (**1**) was isolated in 42% yield (an overall yield of 14% in 11 steps).

The irradiation of dienol **10**, instead of dienone **4**, chemoselectively isomerized the trisubstituted olefin to the *Z*-configuration to produce compound **19** in 42% yield (67% based on recovered starting material [brsm]),[31] but the ensuing [2+2] cycloaddition failed (Scheme 2B). We suspected that the olefin would require masking. Therefore, **19** was treated with *m*-CPBA. The epoxidation chemo- and stereoselectively gave single isomer **20**.[29] As expected, the [2+2] photocycloaddition of **20** proceeded. However, the cycloaddition mode was parallel and **20** was converted into [2]-ladderane adduct **21** in 21% yield (58% brsm). Oxidation of **21**, followed by deoxygenation of resulting epoxide **22** via iodohydrin,[32] provided the originally proposed structure of aquatolide (**7a**).[29] Remarkably, the ^{1}H and ^{13}C NMR chemical shifts and the ^{1}H–^{1}H coupling constants for synthetic **7a** matched those calculated by Shaw and Tantillo's group quite well.[5,33] Thus we succeeded in synthesizing a non-natural product **7a**. On the other hand, oxidation of **19** gave (–)-asteriscunolide C (**3**) (11 total steps, 13% overall yield).

As an alternative strategy, we examined a 1,4-addition of alcohol to **4** to mask the olefin (Scheme 2C). The reaction using acids in methanol regio- and stereoselectively provided 1,4-adduct **23** as a single isomer.[29] Fortunately, the transannular crossed [2+2] photocycloaddition of **23** proceeded to construct the bicyclo[2.1.1]hexane core, giving desired cycloadduct **24** in 37% yield (57% brsm). This is the first example of a biomimetic transannular [2+2] cycloaddition of an asteriscunolide-type compound being used to form the aquatolide skeleton. The elimination of methanol from **24** proceeded under acidic conditions and the first total synthesis of the natural enantiomer of (+)-aquatolide (**7b**) was completed. Our synthetic route was a total of 13 steps from **13** with an overall yield of 5.7%, and was more concise and efficient than the previous racemic syntheses.[20,21] The results of this experiment suggested that 1,4-adducts of **3** or **4** with alcohols or thiols in the plant may

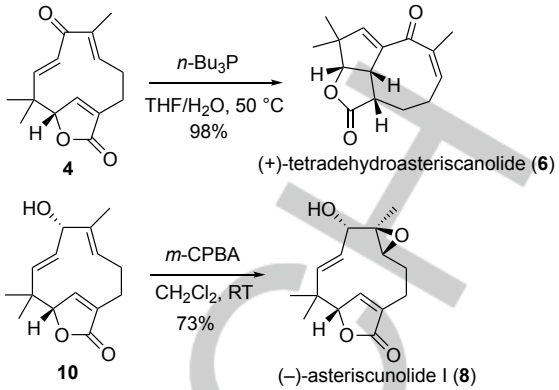
contribute to the assembly of the aquatolide skeleton in nature.[34]

We verified the clear-cut regioselectivity in the transannular [2+2] photocycloadditions of **20** and **23** by conformational analysis of substrates using calculations (Scheme 3).[35] In the most stable conformer of **20**, H-2 and H-10 adopt a β-orientation and H-9 adopts an α-orientation. The [2+2] cycloaddition of **20** to form a [2]-ladderane structural unit is the likely preferred path to **21**. The alternative path to form a bicyclo[2.1.1]hexane structure apparently does not occur. In contrast to **20**, the most stable conformer of **23** contains *trans* H-2 and H-10. Therefore, C2–C10/C3–C9 closure would produce an unrealistic *trans*-fused [2]-ladderane structure, but C2–C9/C3–C10 closure would proceed in accordance with the rule of five[36] to assemble the aquatolide skeleton. Consequently, we reasoned that the conformation of substrates controlled the regioselectivity (parallel or crossed) of the [2+2] photocycloaddition.



Scheme 3. Regioselectivity of transannular [2+2] photocycloadditions of **20** and **23**.

Having proved that asteriscunolide-type compounds underwent irradiation to form a 5/4/4/7- or 5/5/4/8-ring system, we then turned our attention to the formation of asteriscanolide skeleton, namely a tricyclic 5/5/8-ring system. We considered that a one-step formation of (+)-tetradehydroasteriscanolide (**6**) from **4** could be performed by the intramolecular Rauhut–Currier (vinylogous Morita–Baylis–Hillman) reaction.[37,38] Compound **4** was treated with *n*-Bu_3P to construct the 5/5/8-ring system and synthesis of **6** was thus directly achieved efficiently (11 total steps, 32% overall yield) (Scheme 6). Finally, the synthesis of (–)-asteriscunolide I (**8**), a new congener, was carried out. Epoxidation of **10** with *m*-CPBA gave **8** as a single product. This is the first total synthesis of **8** (10 total steps, 26% overall yield).



Scheme 4. Syntheses of (+)-tetradehydroasteriscanolide (**6**) and (–)-asteriscunolide I (**8**).

In summary, we have achieved the total synthesis of (+)-aquatolide (**7b**) by using a biomimetic transannular [2+2] photocycloaddition. To synthesize a substrate for the cycloaddition, the asteriscunolide skeleton was efficiently constructed through a cascade ROM/RCM/CM reaction and an intramolecular NHTK reaction. Our strategy provided a divergent route to six humulanolides, including **7b**, **6**, and (–)-asteriscunolides A, C, D, and I (**1**, **3**, **4**, and **8**) in 10–13 steps with good efficiency. In addition, the originally proposed structure of aquatolide (**7a**) was also synthesized, which suggests that a 5/4/4/7-ring system humulanolide may also occur naturally in *Asteriscus*. Future studies will focus on applying this strategy to the synthesis of humulanolide derivatives as well as investigating their bioactivity.

Acknowledgements

This work was supported by JSPS KAKENHI Grant Number 15K05504 and the Naito Foundation.

Keywords: biomimetic synthesis • cycloaddition • metathesis • terpenoids • total synthesis

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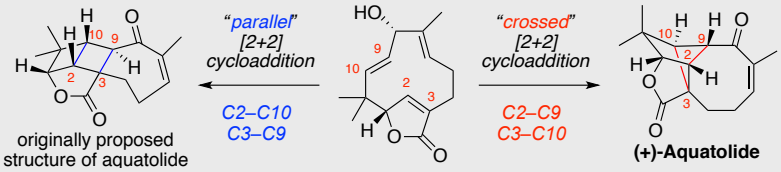

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