Thionium Ion Initiated Medium-Sized Ring Formation: The Total Synthesis of Asteriscunolide D

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S *Supporting Information*

ABSTRACT: The first synthesis of the biologically active humulene natural product asteriscunolide D has been accomplished in nine steps without the use of protecting groups. The challenging 11-membered ring was forged via a diastereoselective thionium ion initiated cyclization, which constitutes a formal aldol disconnection to form a strained macrocycle. A stereospecific thioether activation—elimination protocol was developed for selective E-olefin formation, thus providing access to the most biologically active asteriscunolide. The absolute stereochemical configuration was established by the Zn-ProPhenol catalyzed enantioselective addition of methyl propiolate to an aliphatic aldehyde to afford a γ-hydroxy propiolate as a handle for butenolide formation via Ru-catalyzed alkene—alkyne coupling.

Humulene (**1**)[1] and humulene-derived natural products (e.g., **2**)[2] have been the focus of many synthetic studies (Figure 1). This is due in part to the challenge of generating the
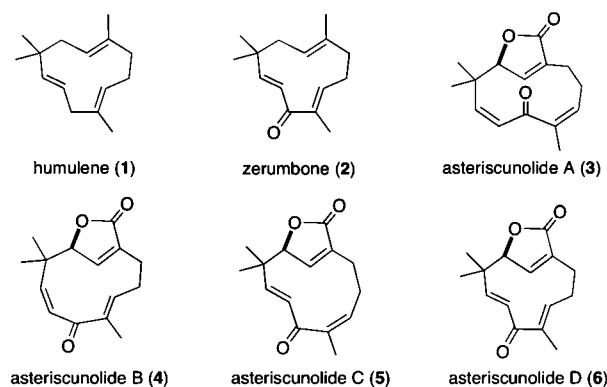
Figure 1. Structures of humulene, zerumbone, and asteriscunolides A—D.

11-membered ring, which has been described as a major impediment in synthesis.[3] Furthermore, many of these compounds possess biological activity, and this has provided motivation for their respective biological studies.[4] More specifically, asteriscunolides A—D[5] (**3**—**6**) possess anticancer activity, with **6** being the most potent toward the A-549 (human lung carcinoma), HT-29 (human colon carcinoma), and MEL-28 (human melanoma) cell lines.[6] Recently, **3** has been found to induce apoptosis in human tumor cell lines.[7] We became interested in these targets (i.e., **3**—**6**) because we

envisioned that a dimethyl(methylthio)sulfonium tetrafluoroborate (DMTSF)-mediated formal aldol disconnection could provide a mild and irreversible pathway to the relatively strained 11-membered ring (**8**→**7**, Figure 2). To the best of our
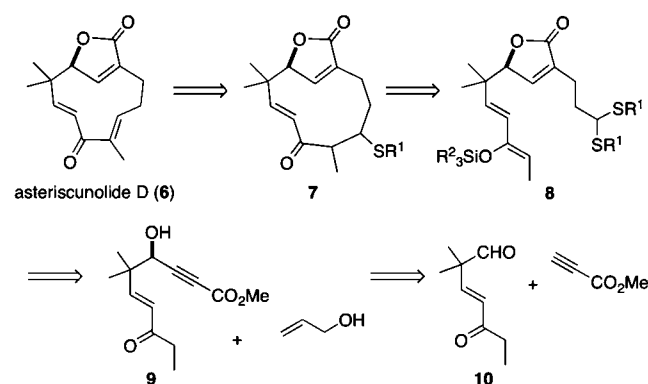
Figure 2. Retrosynthetic analysis of **6**.

knowledge, an aldol addition has not been reported to effect medium-sized carbocyclic ring formation.[8,9] Previously our group has noted that thionium ions behave as "super carbonyl" equivalents and effectively react with nucleophilic olefins;[10] however, medium-sized ring formation using this technology has not been reported. Herein we disclose the first total synthesis of asteriscunolide D (**6**) by implementation of this strategy of a sulfur analog of an aldol addition.

As depicted by our retrosynthetic strategy (Figure 2), 11-membered ring formation could be effected by implementation of a chemoselective DMTSF-mediated cyclization (**8**→**7**). Such a method would also be compatible with potentially labile functional groups (e.g., the butenolide) and would complement forty years of prior art in humulene-based 11-membered ring formation.[1] Subsequent activation of the thioether in **7** and elimination would provide the requisite olefin. If the cyclization process could be rendered diastereoselective, this would offer the most likely opportunity for the development of a stereospecific elimination event. The silyl enol ether **8** could be accessed by thioacetal generation and subsequent enol ether formation of a respective keto aldehyde. The butenolide moiety could be obtained by utilization of a Ru-catalyzed alkene—alkyne coupling of **9** with allyl alcohol to provide a transient enol that would tautomerize to an aldehyde and concomitantly
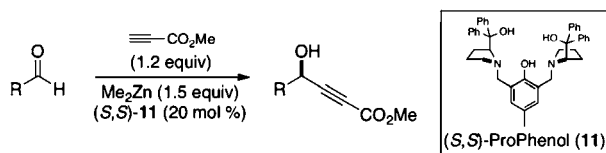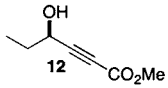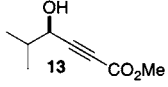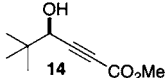
form the butenolide following engagement of the allylic alcohol with the newly formed enoate carbonyl.[11] The chiral propargylic alcohol could be obtained using a chemoselective Zn-ProPhenol catalyzed asymmetric methyl propiolate addition to the keto aldehyde **10**.[12,13]

Since the Zn-ProPhenol catalyzed enantioselective addition of ketone enolates to aldehydes had been established, it was unclear whether an enolizable ketone functional group, as in **10**, would be compatible with the reaction conditions.[14] However, unpublished concurrent efforts within our group indicated that with respect to enantioselective additions of alkynes, enolizable substrates function well as electrophiles (Table 1). Notably, it is

**Table 1. Zn-ProPhenol Catalyzed Enantioselective Addition of Methyl Propiolate to Aliphatic Aldehydes**[a]

entry	substrate	product	% yield	% ee
1	CHO	**12**	64	88
2	CHO	**13**	67	92
3[b]	CHO	**14**	97	90

[a]Reactions were carried out with methyl propiolate (0.390 mmol, 1.2 equiv), aldehyde (0.325 mmol, 1.0 equiv), dimethyl zinc (0.488 mmol, 1.5 equiv), and (S,S)-**11** (65.0 μmol, 20 mol %) in toluene (847 μL) for 48 h at 4 °C. [b](S,S)-**11** (32.5 μmol, 10 mol %) used.

possible to reduce the excess of dimethyl zinc and methyl propiolate relative to our initial disclosures[12] to access **12**−**14** with good yields and enantioselectivities. Encouraged by the success of the addition of methyl propiolate to aliphatic aldehydes, we set out to test whether this method would be compatible with a ketone moiety of **10**, which would provide the most direct route to **9** (vide infra).

The keto aldehyde **10** was prepared in three steps from isobutyraldehyde. Aldol addition of isobutyraldehyde to formaldehyde conveniently provided the β-hydroxy aldehyde by precipitation of the dimer **15**, which could be triturated and used without further purification.[15] As depicted in Scheme 1, cracking of the dimer (60 °C, CH₃CN) and subsequent HWE-olefination using the Masamune−Roush conditions (dimethyl 2-oxobutanephosphonate)[16] provided enone **16**, which was oxidized (Moffatt−Swern) to afford the aldehyde **10**. Gratifyingly, **10** served as an excellent substrate in the chemoselective Zn-ProPhenol catalyzed enantioselective addition with methyl propiolate to provide the γ-hydroxy propiolate **9** in good yield and enantiopurity. Treatment of **9** with catalytic CpRu-(CH₃CN)₃PF₆ and allyl alcohol effected the alkene−alkyne coupling, directly providing the butenolide with the appended aldehyde.[11c] Thioacetal formation and a Z-selective TMS-enol ether formation[17−19] (supported by NOE experiments) afforded test substrate **19** for the DMTSF-mediated cyclization. To our delight, the cyclization smoothly provided the medium-

Scheme 1. Synthesis of Asteriscunolide D (6)[a]

asteriscunolide D (**6**)
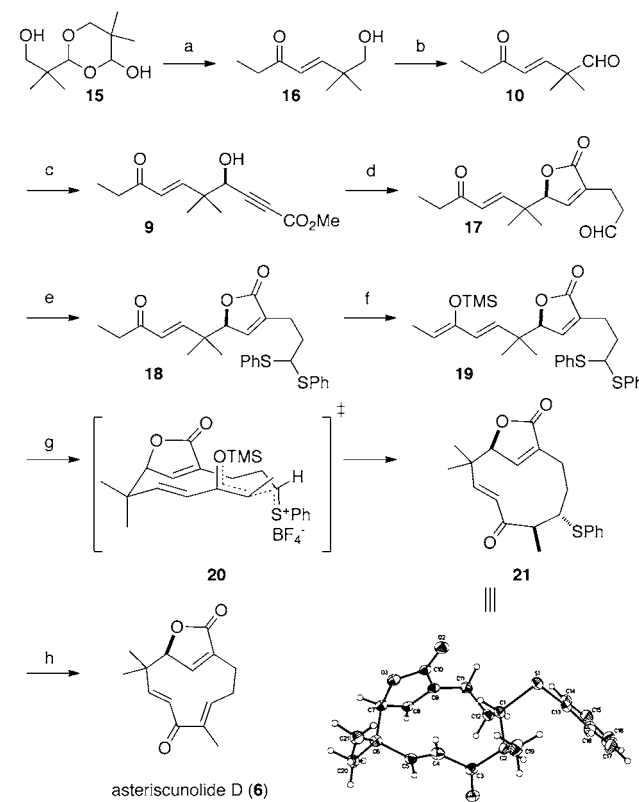
[a](a) (MeO)₂P(O)CH₂C(O)CH₂CH₃ (1.0 equiv), LiCl (1.8 equiv), i-Pr₂NEt (1.8 equiv), CH₃CN, 4 h, 91%. (b) (COCl)₂ (1.5 equiv), DMSO (3.0 equiv), Et₃N (6.0 equiv), CH₂Cl₂, −78 °C, 99%. (c) (S,S)-**11** (20 mol %), Me₂Zn (2.95 equiv), methyl propiolate (2.8 equiv), toluene, 4 °C, 36 h, 83% yield, 84% ee. (d) allyl alcohol (1.5 equiv), CpRu(CH₃CN)₃PF₆ (5 mol %), CSA (0.25 equiv), THF, acetone, 50 °C, 4.5 h, 55%. (e) thiophenol (2.0 equiv), BF₃·Et₂O (15 mol %), CH₂Cl₂, 15 h, 79%. (f) TMSOTf (1.4 equiv), i-Pr₂NEt (1.5 equiv), CH₂Cl₂, 0 °C, 1.5 h, 90%, (g) DMTSF (1.2 equiv), 4 Å MS, CH₂Cl₂, −30 °C, 1.5 h, 32−41%. (h) Me₃OBF₄ (1.8 equiv), CH₂Cl₂, 16 h; then i-Pr₂NEt (1.8 equiv), 40 °C, 6 h, 82%.

sized ring with nearly complete diastereoselectivity. Furthermore, recrystallization of **21** allowed for the structural determination by X-ray crystallographic analysis and provided a means to upgrade the ee from 84% to greater than 98%. In contrast, recrystallization of asteriscunolide D did not provide material with enhanced ee. Interestingly, thermal elimination of the corresponding sulfoxide led to regioselective formation of the β,γ-unsaturated ketone. In contrast to this result, alkylative thioether elimination[20] provided the geometrically pure E-olefin present in **6**. This result is consistent with the cyclooctene studies of Cope et al.: Hoffman elimination provides predominately E-cyclooctene (anti-elimination) while Cope elimination gives only Z-cyclooctene (syn-elimination).[21] It is also clear that racemization does not occur during the elimination procedure, or at any stage of the synthesis, as the ee of each intermediate was confirmed by chiral HPLC relative to the racemic compounds (cf. Supporting Information (SI)). In addition to disclosing the first synthesis of the most biologically potent asteriscunolide member in nine steps from commercial material, preliminary experiments (cf. SI) have demonstrated that **6** can be isomerized to an approximately 3:3:1:1 mixture of asteriscunolides A−D (PhSeSePh, hν) (cf. Figure 1, **3**−**6**). This

speaks to the relatively similar thermodynamic stabilities of the four olefin isomers and provides potential access to the remaining asteriscunolides.[22]

In summary, the first synthesis of asteriscunolide D (**6**) has been accomplished in nine steps without the use of protecting groups. The challenging 11-membered ring was forged via a diastereoselective DMTSF-mediated cyclization. The addition of a silyl enol ether to a transient thionium intermediate represents a mild and irreversible alternative to an intramolecular aldol addition, which would be complicated by facile retro-aldol cleavage due to the inherent ring strain and the kinetic lability of the β-hydroxy ketone product. The success of this new macrocyclization protocol for such a difficult ring size bodes well for its broad applicability as a versatile macrocyclization. In addition, a stereospecific elimination protocol was identified allowing for the exclusive formation of the most biologically active asteriscunolide. The absolute stereochemical configuration of **6** was introduced by a chemoselective Zn-ProPhenol catalyzed enantioselective addition of methyl propiolate to an aliphatic aldehyde bearing an acidic ketone functional group, thus providing a facile asymmetric synthesis of butenolides in a direct two-step sequence when combined with the Ru-catalyzed alkene−alkyne coupling. Extension of the DMTSF-mediated cyclization strategy toward other bioactive natural products containing medium-sized rings is currently underway.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENTS

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(19) An enolization model consistent with the observed *Z*-selectivity avoids steric interaction of the methyl group with the nearly coplanar vinyl hydrogen atom compared to a lone pair of electrons on oxygen as depicted in **i**.
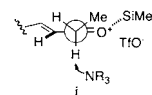
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