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Enantioselective total synthesis of (+)-asteriscanolide *via* Rh(I)-catalyzed [(5 + 2) + 1] reaction†

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The total synthesis of (+)-asteriscanolide starting from two commercially available materials has been accomplished in 19 steps with a 3.8% overall yield. The key reaction is a chiral ene-vinylcyclopropane substrate induced Rh(I)-catalyzed [(5 + 2) + 1] cycloaddition that efficiently constructs the [6.3.0] carbocyclic core with complete asymmetric induction.

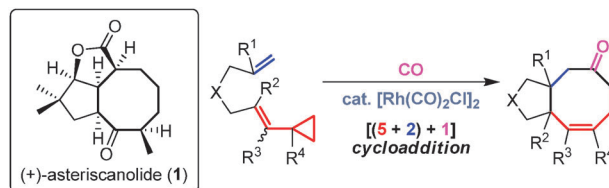
Isolated in 1985, (+)-asteriscanolide (**1**) has captured the attention of the synthetic community due to its unique structure.¹ Its challenging sesquiterpenoid framework contains an uncommon [6.3.0] carbocyclic system bridged by a butyrolactone fragment and five *cis* stereocenters (Scheme 1). There have been only a few successful total syntheses reported to date,^{2,3} although considerable amounts of efforts were devoted to its total synthesis.⁴ In all these syntheses, one of the most formidable tasks was to efficiently construct the eight-membered carbocycle of **1**.⁵ The Wender group employed a Ni(0)-catalyzed intramolecular [4 + 4] cycloaddition as the pivotal step to construct the tricyclic core and achieved the first enantioselective total synthesis of (+)-asteriscanolide in 13 steps.^{2a} In 2000, the Snapper group incorporated a ring-opening metathesis/Cope rearrangement strategy to reach the tricyclic skeleton and finished the asymmetric synthesis of **1** in 9 steps.^{2c} In the same year, using ring-closing metathesis strategies to build the tricyclic cyclooctenes, Paquette and co-workers completed the asymmetric synthesis of **1** in 13 steps,^{2b} and the Krafft group synthesized (±)-**1** in 19 steps,³ respectively.

Recently, a Rh(I)-catalyzed two-component [(5 + 2) + 1] cycloaddition of ene-vinylcyclopropanes (ene-VCPs) and CO was developed by our group (Scheme 1).⁶ This reaction provides an efficient way to obtain fused [5–8] and [6–8] ring systems.⁷ We have applied a tandem [(5 + 2) + 1] cycloaddition/aldol reaction strategy to the syntheses of three linear triquinane natural products, (±)-hirsutene, (±)-1-desoxyhypnophillin, and (±)-hirsutic acid C.⁸ The [(5 + 2) + 1] reaction has

also been proved efficient in the syntheses of (±)-pentalenene and (±)-asterisca-3(15),6-diene.⁹

Since (+)-asteriscanolide (**1**) has a [5–5–8] ring system, we were eager to use the [(5 + 2) + 1] reaction to achieve this goal. We also tried to employ a chiral precursor to build a chiral [(5 + 2) + 1] cycloadduct and to finish its asymmetric synthesis. Retrosynthetically, the bridging butyrolactone ring of **1** could be built up through a free-radical annulation of selenocarbonate **2**.¹⁰ Substrate **2** could be derived from the fused [5–8] bicyclic cyclooctenone **3**, product of a Rh(I)-catalyzed [(5 + 2) + 1] cycloaddition of ene-VCP **4** and CO (Scheme 2). However, in this synthetic route, there are several challenging problems to be solved. First and foremost, there had been no example of a chiral substrate induced [(5 + 2) + 1] reaction before we started the total synthesis.⁶ That is to say, the reactivity and diastereoselectivity of the key [(5 + 2) + 1] cycloaddition using substrates with a pre-existing chirality center were not well established at that moment. Second, in principle, four stereoisomers could be generated from this reaction. According to the structure of **1**, three stereocenters (C1, C2, and C9) are in *cis* configurations. If the configuration of one carbon is not correct, the inversion of the stereocenter should be considered. Last but not the least, the alkoxy carbonyl radical cyclization was rarely used to construct a bridged ring system,¹¹ and the stereoselectivity of this radical process is not clear. Herein, we report the asymmetric total synthesis of (+)-asteriscanolide (**1**) highlighting the use of a chiral substrate induced Rh(I)-catalyzed [(5 + 2) + 1] cycloaddition to efficiently construct the [6.3.0] carbocyclic skeleton and the alkoxy carbonyl radical annulation to build the bridging butyrolactone ring.

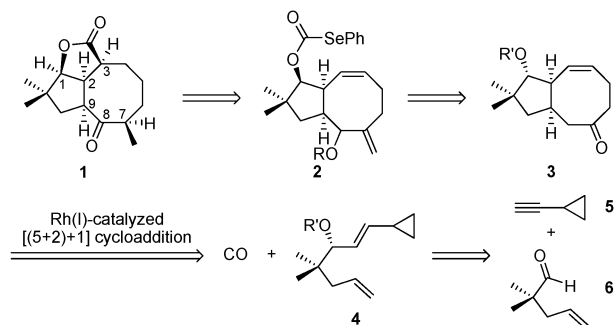
Our total synthesis began with the catalytic asymmetric alkynylation of aldehyde **6** (Scheme 3).¹² We found that the nucleophilic addition of cyclopropylacetylene (**5**) to aldehyde **6** gave propargylic alcohol **7** in 94% ee and 90% yield in the



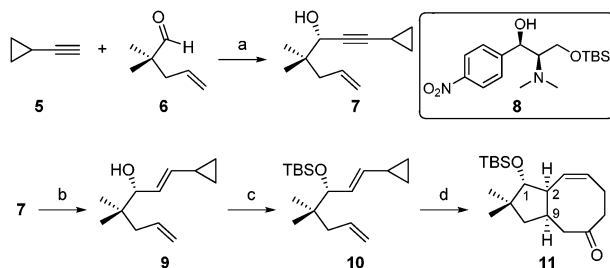
Scheme 1 Asteriscanolide and Rh(I)-catalyzed [(5 + 2) + 1] cycloaddition.

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Scheme 2 Retrosynthetic analysis.



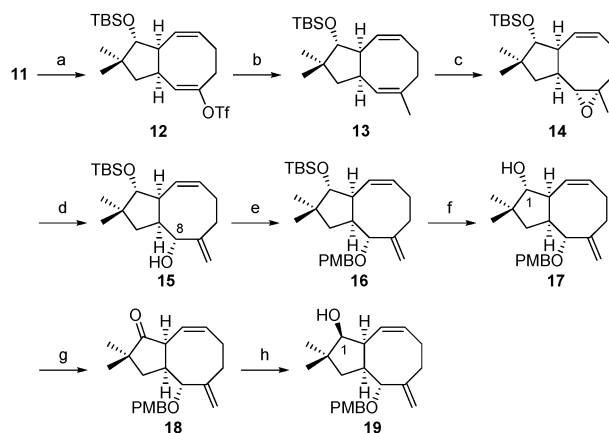
Scheme 3 Reagents and conditions: (a) 18 mol% $\text{Zn}(\text{OTf})_2$, 22 mol% chiral ligand **8**, 65 mol% Et_3N , toluene, 55 °C, 90%, 94% ee; (b) Red-Al, THF, 40 °C, 92%; (c) TBSCl, imidazole, DMAP, DMF, 40 °C, 96%; (d) 0.2 atm CO + 0.8 atm N_2 , 5 mol% $[\text{Rh}(\text{CO})_2\text{Cl}]_2$, toluene, 90 °C, 70%.

presence of $\text{Zn}(\text{OTf})_2$, triethylamine, and chiral ligand **8** developed by Jiang and co-workers.¹³ Reduction with Red-Al converted **7** into allylic alcohol **9**. Substrate **9** was then subjected to the key $[(5+2)+1]$ cycloaddition reaction under the standard conditions (0.2 atm CO + 0.8 atm N_2 , 5 mol% $[\text{Rh}(\text{CO})_2\text{Cl}]_2$ as catalyst, dioxane as solvent, 90 °C).^{6a} The desired fused $[5-8]$ bicyclic cyclooctenone was isolated in 30% yield with a diastereomeric ratio of 75:25. We envisioned that a bulkier substituent at the allylic position of the VCP moiety could greatly improve the diastereoselectivity.¹⁴ Therefore, we transformed allylic alcohol **9** to a TBS-protected substrate **10** and then examined the key $[(5+2)+1]$ cycloaddition reaction (Scheme 3). Under the standard conditions, bicyclic cyclooctenone **11** was obtained with excellent diastereoselectivity ($\text{dr} > 95:5$), but the reaction yield was only 30%. To our delight, when toluene (rather than dioxane) was used as solvent, the yield can be improved to 70% together with the same diastereoselectivity ($\text{dr} > 95:5$). In this reaction, two new stereocenters (C2 and C9) are generated with a *cis* configuration, which is in accordance with the configuration in **1**. However, the hydrogen atom at C1 is in a *trans* configuration with respect to the bridgehead hydrogen atoms at C2 and C9. This is opposite to that in **1**. Considering the possibility that the C1 stereocenter with a hydroxyl substituent can be inverted through the traditional oxidation/reduction strategy, we believed that the success of this highly diastereoselective asymmetric $[(5+2)+1]$ reaction laid the foundation for the enantioselective total synthesis of **1**.

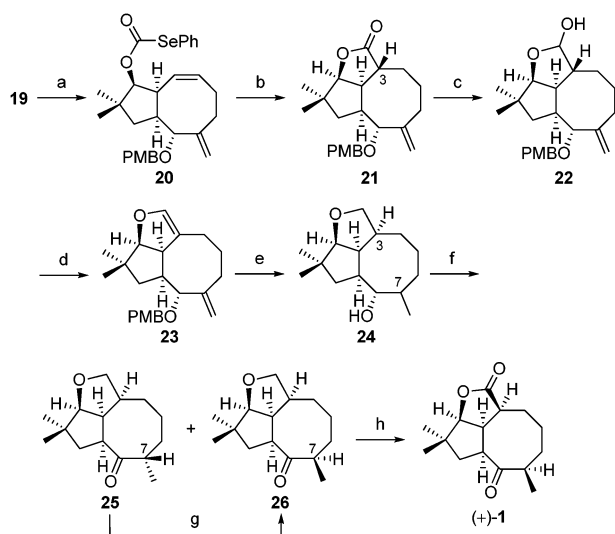
After constructing the $[6.3.0]$ carbocyclic core with high efficiency, we turned our attention toward the introduction of the oxygen at C8 and inversion of the C1 stereocenter

(Scheme 4). It was found that ketone **11** could be converted into enol triflate **12** using trifluoromethanesulfonic anhydride and 2,6-di-*tert*-butyl-4-methylpyridine with good regioselectivity (regioisomeric ratio = 88:12).¹⁵ Enol triflate **12** was then subjected to an iron-catalyzed cross-coupling reaction to give cyclooctadiene **13**.¹⁶ Subsequent epoxidation with *m*CPBA regioselectively occurred on the more electron-rich trisubstituted olefin and afforded epoxide **14** with excellent diastereoselectivity ($\text{dr} > 95:5$). Treatment of **14** with diethylaluminum 2,2,6,6-tetramethylpiperidine led to regioselective formation of **15**.¹⁷ Protection of **15** with PMBCl, followed by deprotection of the TBS group, gave alcohol **17** with opposite configuration at C1 with respect to that in **1**. To invert this configuration, **17** was oxidized to ketone **18** by Dess–Martin periodinane. Then using a bulky reducing reagent DIBAL-H at -78 °C, the desired alcohol **19** with correct configuration at C1 was generated exclusively.

At this point, we intended to utilize the key alkoxycarbonyl radical annulation to construct the bridging butyrolactone ring of **1** (Scheme 5). After selenocarbonate **20** was synthesized, we conducted the radical cyclization of **20** in the presence of AIBN and *n*- Bu_3SnH .¹⁰ Gratifyingly, the tricyclic compound **21** was obtained as a single stereoisomer in 95% yield.¹⁸ However, the configuration of C3 was opposite to that in **1**. To complete the synthesis, epimerizing the C3 stereocenter of **21** was necessary. Attempts to convert the inside–outside tricycle through the deprotonation/protonation strategy were unsuccessful.¹⁹ A similar problem was also encountered by Krafft and co-workers in their total synthesis of asteriscanolide.³ As an alternative strategy, lactone **21** was reduced by DIBAL-H to give a mixture of hemiacetals, which were smoothly converted into enol ether **23** with methanesulfonyl chloride and triethylamine (Scheme 5).²⁰ Subsequent hydrogenation of **23** successfully installed the hydrogen at C3 with correct configuration. Meanwhile, the PMB group was removed and the *exo* C=C double bond was



Scheme 4 Reagents and conditions: (a) Trf_2O , 2,6-di-*tert*-butyl-4-methylpyridine, CH_2Cl_2 , 25 °C, regioisomeric ratio = 88:12; (b) $\text{Fe}(\text{acac})_3$, 1-methyl-2-pyrrolidinone, MeMgBr , THF, -10 °C, 58% over two steps; (c) *m*CPBA, ethyl acetate, 0 °C; (d) 2,2,6,6-tetramethylpiperidine, *n*-BuLi, Me_2AlCl , benzene, 0 °C, 86% over two steps; (e) NaH, PMBCl, DMF, 50 °C, 82%; (f) TBAF, THF, 40 °C, 90%; (g) DMP, NaHCO_3 , CH_2Cl_2 , 25 °C; (h) DIBAL-H, CH_2Cl_2 , -78 °C, 84% over two steps.



Scheme 5 Reagents and conditions: (a) (1) Py, DMAP, THF, triphosgene, benzene, 30 °C; (2) PhSeH, 30 °C; (b) *n*-Bu₃SnH, AIBN, benzene, reflux, 95% over two steps; (c) DIBAL-H, CH₂Cl₂, -78 °C; (d) CH₃SO₂Cl, Et₃N, CH₂Cl₂, 25 °C, 85% over two steps; (e) H₂, Pd/C, EtOH, 60 °C, dr = 66:34; (f) DMP, NaHCO₃, CH₂Cl₂, 25 °C, 46% (**25**) and 24% (**26**) over two steps; (g) (1) TMSOTf, 2,6-lutidine, CH₂Cl₂, 25 °C; (2) 1 M HCl, Et₂O, 25 °C, 48% brsm; (h) RuCl₃, NaIO₄, CH₃CN/CCl₄/H₂O (1:1:1), 25 °C, 59%.

hydrogenated with 66:34 diastereoselectivity. Subsequent Dess–Martin oxidation of **24** gave two separable tricyclic ketones **25** and **26**. Treatment of **25** with trimethylsilyl triflate and 2,6-lutidine, followed by acidic hydrolysis, resulted in partial formation of the desired tricyclic ketone **26**. Finally, compound **26** was regioselectively oxidized to natural product (+)-**1** by ruthenium tetroxide using Paquette's approach.^{2b,21} Therefore, (+)-asteriscanolide was synthesized from two commercially available materials in 19 steps and 3.8% overall yield.

In summary, we have successfully achieved the asymmetric total synthesis of (+)-asteriscanolide based on a chiral substrate induced Rh(I)-catalyzed [(5+2)+1] cycloaddition to build the [6.3.0] carbocyclic core with high efficiency. This further demonstrates that the [(5+2)+1] reaction is a powerful method for the construction of complex molecules with eight-membered carbocycles. Other merits from this synthesis include the utilization of catalytic asymmetric alkynylation of aldehyde to synthesize the chiral ene-VCP substrate, highly regioselective conversion of the [(5+2)+1] cycloadduct to its enol triflate, the introduction of the bridging butyrolactone ring by a radical process, and the inversion of the inside–outside tricycle to the outside–outside structure by an ester-reduction/elimination to enol ether/hydrogenation procedure.

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