Total Synthesis of (+)-Asteriscanolide: Further Exploration of the Rhodium(I)-Catalyzed [(5 + 2) + 1] Reaction of Ene-Vinylcyclopropanes and CO

Yong Liang, Xing Jiang, Xu-Fei Fu, Siyu Ye, Tao Wang, Jie Yuan, Yuanyuan Wang, and Zhi-Xiang Yu*\([a]\)

Abstract: The total synthesis of (+)-asteriscanolide is reported. The synthetic route features two key reactions: 1) the rhodium(I)-catalyzed [(5+2)+1] cycloaddition of a chiral ene-vinylcyclopropane (ene-VCP) substrate to construct the [6.3.0] carbocyclic core with excellent asymmetric induction, and 2) an alkoxycarbonyl-radical cyclization that builds the bridging butyrolactone ring with high efficiency. Other features of this synthetic route include the catalytic asymmetric alkynylation of an aldehyde to synthesize the chiral ene-VCP substrate, a highly regioselective conversion of the [(5+2)+1] cycloadduct into its enol triflate, and the inversion of the inside–outside tricycle to the outside–outside structure by an ester-reduction/elimination to enol-ether/hydrogenation procedure. In addition, density functional theory (DFT) rationalization of the chiral induction of the [(5+2)+1] reaction and the diastereoselectivity of the radical annulation has been presented. Equally important is that we have also developed other routes to synthesize asteriscanolide using the rhodium(I)-catalyzed [(5+2)+1] cycloaddition as the key step. Even though these routes failed to achieve the total synthesis, these experiments gave further useful information about the scope of the [(5+2)+1] reaction and paved the way for its future application in synthesis.

Keywords: annulation · cycloaddition · radical reactions · rhodium · total synthesis

Introduction

The value of new reactions becomes apparent when they are utilized in the synthesis of complex molecules. In exploring synthetic routes to the target molecule, we can further understand the scope and features of these new transformations. In 2007, we developed the rhodium-catalyzed two-component [(5+2)+1] cycloaddition reaction of ene-vinylcyclopropanes (ene-VCPs) and CO (Scheme 1).\(^1\) This reaction provides an efficient way to obtain fused [5–8] and [6–8] ring-systems.\(^2\) To demonstrate the utility of this new [(5+2)+1] reaction, we have applied a tandem [(5+2)+1] cycloaddition/aldol reaction strategy to the syntheses of three linear triquinane natural products: (+)/C6-hirsutene, (+)/C6-1-desoxyhypnophilin, and (+)/C6-hirsutic acid C.\(^3\) The [(5+2)+1] reaction has also been shown to be effective in the syntheses of (+)-pentalenene and (+)-asterisca-3(15),6-diene.\(^4\)

Since the discovery of (+)-asteriscanolide (1) in 1985,\(^5\) it has captured the attention of the organic chemical community because of its unique structure; its challenging sesquiterpenoid framework contains an uncommon [6.3.0] carbocyclic system bridged by a butyrolactone fragment and five cis stereocenters. There have only been a few successful total syntheses of (+)-asteriscanolide reported to date,\(^6\) although a considerable amount of effort has been devoted to it.\(^7\) In all of these syntheses, one of the most formidable tasks was to efficiently construct the eight-membered carbocycle.\(^8\)

Scheme 1. Rhodium(I)-catalyzed [(5+2)+1] reaction of ene-vinylcyclopropanes and CO.

[a] Dr. Y. Liang, X. Jiang, X.-F. Fu, Dr. S. Ye, T. Wang, J. Yuan, Dr. Y. Wang, Prof. Dr. Z.-X. Yu
Beijing National Laboratory for Molecular Sciences (BNLMS)
Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education
College of Chemistry, Peking University
Beijing 100871 (China)
Fax: (+86)-10-6275-1708
E-mail: yuzx@pku.edu.cn

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/asia.201100805.


DOI: 10.1002/asia.201100805
Molecular [4+4] cycloaddition as the pivotal step in the construction of the tricyclic core and achieved the first total synthesis of (+)-asteriscanolide in 13 steps. In 2000, Limanto and Snapper incorporated a ring-opening-metathesis/Cope-rearrangement strategy to reach the tricyclic skeleton and finished the asymmetric synthesis of compound 1 in 9 steps. In the same year, using ring-closing-metathesis strategies to build the tricyclic cyclooctene, Paquette and co-workers completed the enantioselective total synthesis of compound 1 in 13 steps, and the Krafft group synthesized compound (+)-1 in 19 steps. Recently, we reported our approach to the enantioselective total synthesis of (+)-asteriscanolide based on a chiral substrate-induced rhodium(I)-catalyzed [(5+2)+1] reaction. Herein, we report a full account of our cumulative efforts that eventually led to the successful synthesis of the target molecule, and which also serves as further exploration of the scope and features of the rhodium(I)-catalyzed [(5+2)+1] reaction in synthesis.

Results and Discussion

Attempts towards the Single-Step Construction of the Tricyclic Core of Asteriscanolide

Because (+)-asteriscanolide (1) is a [5,5,8] tricyclic natural product, in our initial synthesis, we were eager to use the [(5+2)+1] reaction to construct its tricyclic core in one step. Analysis of the structure of compound 1 allowed us to propose that the most-efficient and appealing strategy for the synthesis of compound 1 using the [(5+2)+1] cycloaddition reaction would be to employ ester-tethered cyclopentene-VCP 2 as the substrate (strategy I; Scheme 2). We envisioned that strategy I would provide a new route to this complex natural product in only 4 steps from two known compounds (Scheme 3). In addition to strategy I, we came up with three other strategies (Scheme 2) for constructing the tricyclic skeleton of compound 1 in a single step. These attempts, whether successful or not, would tell us more information about the scope of the [(5+2)+1] reaction.

Test of Strategy I

As shown in Scheme 3, ester 2 can be easily synthesized from allylic alcohol 9 and (E)-3-cyclopropylacrylic acid (8). This substrate incorporates two features not previously studied in the rhodium(I)-catalyzed [(5+2)+1] reaction, namely, an ester group as the tethering chain and the inclusion of an olefin moiety in a pre-existing five-membered ring. When substrate 2 was tested under the standard reaction conditions (CO/N_2 0.2:0.8, 1 atm, 5 mol% [{Rh(CO)_2Cl}_2] catalyst, 1,4-dioxane as solvent, 90°C; Scheme 4), no desired [(5+2)+1] product 7 was observed and most of the unreacted starting material was recovered (Scheme 4). To investigate why substrate 2 did not undergo the [(5+2)+1] reaction, another ester-tethered ene-VCP (10), which did not contain a five-membered ring, was synthesized and subjected to the reaction (Scheme 4). Again, no [(5+2)+1] product 11 was obtained under the catalysis of [{Rh(CO)_2Cl}_2], and only compound 10 was recovered. The failure of the ester-tethered substrate in the [(5+2)+1] reaction could be due to the fact that the ester adopts a transoid form, thereby keeping the ene and VCP moieties far away from one another (Scheme 4).

Scheme 2. Strategies I-IV for the one-step construction of the tricyclic core of asteriscanolide.

Scheme 3. Retrosynthetic analysis of strategy I.
tried the [(5+2)+1] reaction of compound 10 and CO using (CF$_3$)$_2$CHOH as solvent. However, the desired reaction did not work under these conditions either. These results indicate that the [(5+2)+1] reaction cannot tolerate ene-VCPs with an ester group in the tethering chain.

Test of Strategy II

Our previous studies indicated that the [(5+2)+1] reaction was tolerant of ether-tethered ene-VCP substrates. Therefore, we turned our attention to strategy II (Scheme 2). After a four-step synthesis,[13] substrate 3 was prepared. However, after many attempts under various conditions, the desired tricyclic product 12 could not be obtained (Scheme 5). Substrate 3 was either recovered or decomposed in all cases. This result suggests that cyclopentene-VCP substrates are not suitable for the [(5+2)+1] cycloaddition reaction. The failure of cyclopentene as the alkene substrate prompted us to investigate whether the ene moiety in the [(5+2)+1] reaction could only be a terminal alkene. To address this issue, an ene-VCP substrate with a methyl substituent at the terminal position of the ene moiety (13) was prepared and tested (Scheme 5). We found that the [(5+2)+1] reaction of 13 could occur, but the presence of a methyl group in the ene moiety greatly decreased the reaction rate and yield (the transformation of 13 into 14 needed 90 h at 90°C to afford the product in 40% yield) as compared with the reaction of its parent ene-VCP 15[1a] (36 h, 80°C, 81% yield; Scheme 5). This result indicates that the [(5+2)+1] reaction is sensitive to the substitution of the ene moiety. Based on previous mechanistic studies,[14] we believe that the introduction of a methyl group into the ene moiety of the ene-VCP increases the energy of the alkene-insertion transition state, thus making the [(5+2)+1] reaction more difficult than that of the unsubstituted ene-VCP.

Test of Strategies III and IV

At this point, we considered the tricyclic cyclooctadiene 17, which was synthesized from the nickel(0)-catalyzed [(4+4)] cycloaddition in the synthesis of asteriscanolide reported by Wender et al.[6a] as a potential target (Scheme 6). Retrosyn-
Synthesis of (±)-Asteriscanolide Using a Stepwise [(5+2)+1] Cycloaddition/Radical-Annulation Strategy

To reach the target molecule, we designed a stepwise strategy (strategy V) to build the tricyclic skeleton of asteriscanolide. As shown in Scheme 8, the bridging butyrolactone ring could be constructed through the free-radical-annulation of selenocarbonate, and the [6.3.0] carbocyclic system could be achieved by the rhodium(I)-catalyzed [(5+2)+1] reaction of ene-VCP with a hydroxy group at the allylic position of the VCP moiety. However, in this synthetic route, there were several challenging problems to be solved. First and foremost, there were no established strategies for performing the key [(5+2)+1] cycloaddition step using substrates with a pre-existing chiral center with good reactivities and diastereoselectivities. Second, four stereoisomers could be generated from this substrate-induced [(5+2)+1] reaction. According to the structure of 1, three stereocenters (C1, C2, and C9) have a cis configuration. If the configuration of one carbon atom is not correct, inversion of the stereocenter should be considered. Last but not the least, only a few examples have been reported for the use of an alkoxy carbonyl-radical-cyclization reaction to construct a bridged ring system, and the stereoselectivity of this radical process was not clear.

Study of the Chiral Induction of the [(5+2)+1] Reaction

Our execution of this plan began with the alkynylation of aldehyde 28 (Scheme 9). The resulting propargylic alcohol 29 was converted into allylic alcohol 26 by treatment with Red-Al. Substrate 26 was then subjected to the key [(5+2)+1] cycloaddition reaction under the standard conditions. The desired fused [5–8] bicyclic cyclooctenone 25 was isolated in 30% yield with a diastereomeric ratio of 75:25 (Scheme 9). When this reaction was conducted in toluene, the reaction yield increased to 47%, but the diastereoselectivity decreased to 55:45. We envisioned that a bulkier substituent at the allylic position of the VCP moiety could greatly improve the diastereoselectivity. Therefore, we transformed allylic alcohol 26 into TBS-protected and then examined the key [(5+2)+1] reaction (Scheme 9). Under the standard conditions, bicyclic cyclooctenone 31 was obtained with excellent diastereoselectivity (d.r. > 95:5), but the reaction yield was only 30%. To our delight, when toluene (rather than 1,4-dioxane) was used as the solvent, the yield was improved to 70%, together with the same diastereoselectivity (d.r. > 95:5). In this substrate-induced [(5+2)+1] cycloaddition reaction, two new stereocenters (C2 and C9) were generated with a cis configuration, which corresponded to their analogous configurations in compound 1. However, the hydrogen atom at the C1 position is in a trans configuration with respect to the bridgehead hydrogen atoms at the C2 and C9 positions. This configuration is opposite to that in compound 1. Considering the possibility that the stereocenter at the C1 position, which contains a hydroxy substituent,
can be inverted by a traditional oxidation/reduction strategy, we believed that, if the chiral propargylic alcohol \( \text{29} \) could be synthesized, the success of this highly diastereoselective \([(5+2)+1]\) reaction would lay the foundation for the final enantioselective total synthesis of compound \( \text{1} \).

We applied DFT calculations to investigate the origin of the high diastereoselectivity observed for the \([(5+2)+1]\) reaction of compound \( \text{30} \). DFT calculations had previously shown that the stereoselective step of the \([(5+2)+1]\) reaction is the alkene insertion into the Rh–C bond of the rhodacycle, which is generated from the alkene coordination of VCP to rhodium and a subsequent cyclopropane-cleavage step. In principle, four stereoisomers could be generated from the irreversibly alkene-insertion step in the reaction of compound \( \text{30} \) (the corresponding transition states located by DFT calculations are shown in Figure 1). It was found that the most-favored alkene-insertion transition state is TS-trans\(_{\text{cis}_{2,9}}\), which leads to the observed product, compound \( \text{31} \). The other three transition states are all 3–5 kcal mol\(^{-1}\) higher in terms of Gibbs free energy. Therefore, the three corresponding stereoisomers would not be generated in this \([(5+2)+1]\) reaction. Through analyzing the structures of these four transition states, we found that, in the disfavored transition states, TS-trans\(_{\text{cis}_{2,9}}\) and TS-cis\(_{\text{trans}_{2,9}}\), the O-C1-C2-C3 dihedral angles were both about 25°, thereby indicating that there was obvious steric repulsion between the OTBS and C12 groups. In another disfavored transition state, TS-cis\(_{\text{trans}_{2,9}}\), the bulky OTBS group occupied a position on the more-encumbered endo face, which also led to severe steric repulsion between the OTBS group and the C3 and C12 groups. In contrast, in TS-trans\(_{\text{cis}_{2,9}}\), there was no serious steric repulsion, as shown by the O-C1-C2-C3 dihedral angle of 72° and the O-C1-C11-C12 dihedral angle of 46° (Figure 1).

**Radical Annulations to Build the Bridging Butyrolactone Ring**

After efficiently constructing the [6.3.0] carbocyclic core with excellent asymmetric induction, we turned our attention to the introduction of the bridging butyrolactone ring. Wittig olefination of ketone \( \text{31} \), followed by deprotection of the TBS group, gave alcohol \( \text{33} \) with the opposite configuration at the C1 position with respect to that in compound \( \text{1} \) (Scheme 10). To invert this configuration, compound \( \text{33} \) was converted into ketone \( \text{34} \) by Dess–Martin oxidation. Then using the bulky reducing reagent DIBAI-H at \(-78^\circ\text{C}\), the desired alcohol \( \text{35} \) with correct configuration at the C1 position was generated (Scheme 10). After alcohol \( \text{35} \) was converted into selenocarbonate \( \text{36} \), we conducted the radical cyclization of compound \( \text{36} \) in the presence of AIBN and \( n\text{Bu}_3\text{SnH} \). Gratifyingly, the tricyclic compound \( \text{37} \) was obtained as a single stereoisomer in good yield (Scheme 10). However, the configuration of the stereocenter at the C3 position was opposite to that of \( \text{1} \).

Next, we performed DFT calculations to better understand the diastereoselectivity of this radical process. When compound \( \text{36} \) underwent the radical annulation reaction, the trans-radical-addition transition state TS-trans\(_{\text{37}}\) was 1.6 kcal mol\(^{-1}\) lower in terms of Gibbs free energy than the cis-radical-addition transition state TS-cis\(_{\text{38}}\) (in benzene; Figure 2a), thereby suggesting that the radical addition greatly favors the trans product \( \text{37} \). This observation agrees with the experimental data (Scheme 10). Through examining these two transition states, we found that, in the disfavored cis-addition state TS-cis\(_{\text{38}}\), the alkoxycarbonyl radical and

![Figure 1. DFT-computed structures and Gibbs free energies of alkene-insertion transition states in the rhodium(I)-catalyzed \([(5+2)+1]\) cycloaddition reaction (distances are given in Å, \( G_{\text{toluene}} \) = Gibbs free energy in toluene, \( G_{\text{gas}} \) = Gibbs free energy in the gas phase).](image-url)
the endo alkene of the eight-membered carbocycle are in an almost-eclipsed conformation, as shown by the O-C1-C2-C3 dihedral angle of only 19° (Figure 2a). However, the corresponding dihedral angle became much bigger in TS-trans-37 (38°, Figure 2a), thus making the trans addition (TS-trans-37) more favorable. Based on this mechanistic information, we envisioned that if the exo methylidene group of the eight-membered carbocycle was changed into a much-bulkier ethylenedioxy group, the cis-radical addition might become favored owing to the change of conformation of the eight-membered carbocycle. Therefore, we calculated the free energies of the trans- and cis-radical-addition transition states, TS-trans-43 and TS-cis-44, respectively (for precursor 42, see Scheme 11; Figure 2b). The computational results suggested that the energy difference between these two competing transition states was negligible, and predicted that both the trans and cis products (43 and 44, respectively) would be generated without selectivity. Through analyzing the transition-state structures, we found that the strain of forming the five-membered ring in TS-cis-44 was still much larger than that in TS-trans-43, thus favoring the trans addition (Figure 2b). However, there was an additional steric repulsion between the alkene and ketal moieties in TS-trans-43 compared with TS-cis-44, which favors the cis-addition instead (Figure 2b). Consequently, these two conflicting factors render the two transition states very close in energy.

To confirm the above DFT prediction, radical-annulation precursor 42 was prepared and tested (Scheme 11). As expected, a mixture of two inseparable diastereomers (43 and 44) was obtained from the radical-cyclization reaction. Unfortunately, the compound with the desired configuration at the C3 position, tricyclic compound 44, was only a minor product (Scheme 11).

![Scheme 10. Reagents and conditions: a) methyltriphenylphosphonium bromide, tBuOK, C6H6, 40°C; b) TBAF, THF, 40°C, 77% over two steps; c) DMP, NaHCO3, CH2Cl2, RT; d) DIBAl-H, CH2Cl2, –78°C, 88% over two steps; e) (1) Py, DMAP, THF, triphosgene, C6H6, RT; (2) PhSeH, 40°C; f) nBu3SnH, AIBN, C6H6, reflux, 78% over two steps. TBAF = tetrabutylammonium fluoride, DMP = Dess–Martin periodinane, DIBAl-H = diisobutylaluminum hydride, Py = pyridine, AIBN = azobisisobutyronitrile.](image)

![Figure 2. DFT-computed structures and Gibbs free energies of radical addition transition states in the radical annulations (distances are given in Å, ΔGbenzene = Gibbs free energy in benzene, ΔGgas = Gibbs free energy in the gas phase).](image)
At this stage, we intended to epimerize the stereocenter at the C3 position. Deprotonation of the "inside" hydrogen at the C3 position (shown in a circle, Scheme 12) of the tricyclic compound 37 was difficult to achieve under kinetically controlled conditions owing to the steric congestion on the concave face. Such a problem was also encountered by Krafft et al. in their total synthesis of asteriscanolide. After many attempts, they discovered that the "inside" hydrogen at the C3 position of compound 45 (Scheme 12) could be partially transformed into the "outside" hydrogen using TBAT [21] as a base in refluxing acetonitrile for 29 hours. However, in our case, this method was unsuccessful for converting compound 37 into compound 38.

We reasoned that if the hydroxy group at the C8 position could be introduced into compound 37 to give a compound similar to compound 45, maybe in this case, the stereocenter at the C3 position could be inverted by using the method reported by Krafft et al.[7] Therefore, we decided to obtain the tricyclic compound 48 with the endo C7=C8 double bond through an acid-catalyzed alkene isomerization and then convert the endo C7=C8 double bond into the hydroxy group at the C8 position by hydroboration/oxidation. However, in the presence of para-methylbenzenesulfonic acid, the exo C=C double bond of compound 37 shifted to the endo C6=C7 double bond, and no desired compound 48 was observed (Scheme 13). Then we tried the allylic oxidation of compounds 37 or 47 in order to introduce the hydroxy group at the C8 position. Unfortunately, treatment of compounds 37 or 47 with SeO₂/TBHP only produced the allylic-oxidation product with undesired regioselectivity (Scheme 13). Therefore, we had to explore other approaches to build the bridging butyrolactone ring with the correct configuration.

Next, we wanted to prepare selenocarbonate 52 from readily available [(5+2)+1] adduct 31; we expected that this adduct would then undergo radical cyclization, to obtain another tricyclic intermediate (51) that contained a C7=C8 double bond (Scheme 14). However, the conversion of the C7-ketone group of compound 31 into the C7=C8 double bond with high regioselectivity was challenging. Deprotonation of the hydrogen atom at the C8 position was difficult to achieve using a strong base under kinetically controlled conditions because the C8 position is sterically more-hindered than the C6 position. For example, the treatment of ketone 31 with LDA at -78°C, followed by triflation with 2-[(N,N-bis(trifluoromethanesulfonyl)amino)pyridine, only gave the desired enol triflate 53 with the C7=C8 double bond as a minor product (53/54 = 33:67, as determined by integration of the 1H NMR spectrum of the crude reaction mixture;
However, to our delight, ketone 31 was converted into enol triflate 53 using trifluoromethanesulfonic anhydride and 2,6-di-tert-butyl-4-methylpyridine with good regioselectivity (53/54 = 88:12; Scheme 15).[22]

Enol triflate 53 was then subjected to an iron-catalyzed cross-coupling reaction to give cyclooctadiene 55 (Scheme 16).[23] Subsequent deprotection with TBAF gave alcohol 56 with the opposite configuration at the C1 position. After Dess–Martin oxidation and reduction with DIBAl-H, the desired alcohol 58, which contained the correct configuration at the C1 position, was generated; this alcohol was then smoothly transformed into selenocarbonate 52. However, when selenocarbonate 52 was treated under the radical cyclization conditions, no desired tricyclic compound 51 was obtained, but rather a mixture of unexpected tetracyclic compounds (59) was isolated (Scheme 16). In this radical process, the tricyclic radical intermediate B further underwent an intramolecular 5-exo-trig secondary-alkyl-radical/alkene cyclization to form a more-stable tetracyclic tertiary radical (C), which was then quenched with nBu3SnH to give compound 59 (Scheme 16).[24]

After these attempts, we wanted to synthesize another precursor (61) that contained an oxygen atom at the C8 position to test the radical-annulation reaction (Scheme 17). Epoxidation of readily available cyclooctadiene 55 with mCPBA occurred regioselectively on the more-electron-rich trisubstituted olefin and afforded epoxide 62 with excellent diastereoselectivity (d.r. > 95:5). Treatment of 62 with diethylaluminum 2,2,6,6-tetramethylpiperidide led to the regioselective formation of compound 63 (Scheme 18).[25] Protection of 63 with PMBCl, followed by deprotection of the TBS group and the inversion of the stereocenter at the C1 position, gave alcohol 67, which was transformed into the radical annulation precursor 68. We then conducted the radical cyclization of 68 in the presence of AIBN and nBu3SnH.[15] Gratifyingly, the expected tricyclic compound 69 was obtained in excellent yield, although the configuration of the stereocenter at the C3 position was opposite to that of compound 1 (Scheme 18). The reason for this stereochemistry should be similar to that in the radical-annulation reaction of compound 36. All efforts to directly invert the configuration at the C3 position in compound 69 using the deprotonation/protonation strategy were unsuccessful. Next, we removed the PMB group of compound 69 by DDQ oxidation, and tried to epimerize the stereocenter at the C3 position of the resulting alcohol (70; confirmed by X-ray diffraction)[26] using the method reported by Krafft et al.[7] However, none of the expected product 71 was observed under the reported conditions.
tions (Scheme 18). Therefore, the next challenging problem was to efficiently convert the inside–outside tricyclic of compound 69 into the outside–outside tricycle.[27]

**Completion of the Total Synthesis of (±)-Asteriscanolide**

We then tried to use ester-reduction/elimination to enol-ether/hydrogenation as an alternative strategy to the direct inversion of the C3 configuration in compound 69. We began by reducing lactone 69 with DIBAL-H to afford a mixture of hemiacetals (72), which was then smoothly converted into enol ether 73 with methanesulfonyl chloride and triethylamine (Scheme 19).[28,29] Subsequent hydrogenation of the enol ether successfully installed the hydrogen atom at the C3 position with correct configuration. Meanwhile, the PMB group was removed, and the exo C=C double bond was also hydrogenated with 66:34 diastereoselectivity. The resulting alcohols 74 were formed as a mixture of two inseparable diastereomers. Fortunately, Dess–Martin oxidation of compound 74 gave two separable tricyclic ketones (75 and 76).

Treatment of compound 75 with trimethylsilyl triflate and 2.6-lutidine, followed by acidic hydrolysis, resulted in the partial formation of the desired tricyclic ketone 76. Finally, compound 76 was regioselectively oxidized into compound (±)-1 by ruthenium tetroxide using the approach reported by Paquette et al. (Scheme 19).[30]

### Asymmetric Synthesis of (±)-Asteriscanolide

Having finished the total synthesis of racemic asteriscanolide, the asymmetric synthesis of (±)-asteriscanolide (1) can be accomplished by using chiral [(5+2)+1] cycloadduct 31, which can be prepared from (S)-propargylic alcohol 29 in 3 steps with excellent asymmetric induction. Gratifyingly, the catalytic asymmetric alkynylation of the aldehyde has been well-developed.[30] We found that nucleophilic addition of cyclopropylacetylene (27) to aldehyde 28 gave propargylic alcohol (S)-29 in 94% ee and 90% yield in the presence of Zn(OTf)₂, triethylamine, and chiral ligand 77 (developed by Jiang and co-workers,[31] Scheme 20). With this chiral building block in hand, we repeated the above successful synthetic route (Scheme 21). Finally, natural (±)-asteriscanolide (1) was synthesized from two commercially available materials in 19 steps and 3.8% overall yield.[10]

### Conclusions

In summary, we have successfully achieved the asymmetric total synthesis of (±)-asteriscanolide based on a chiral-substrate-induced rhodium(I)-catalyzed [(5+2)+1] cycloaddition reaction to build the [6,3,0] carbocyclic core with high efficiency. This accomplishment further demonstrates that the [(5+2)+1] reaction is a powerful method for the construction of complex molecules with eight-membered carbocycles. During this total synthesis, the asymmetric induction of the [(5+2)+1] reaction with a pre-existing chiral center was investigated both experimentally and theoretically.
Indeed, despite several unsuccessful attempts, we have further clarified the scope and limitations of the \((5+2)+1\) reaction. Other merits of this synthesis include the introduction of the bridging butyrolactone ring using a radical process, the utilization of a catalytic asymmetric alknylation of an aldehyde to synthesize the chiral ene-VCP substrate, a highly regioselective conversion of the \((5+2)+1\) cycloaduct into its enol triflate, and the inversion of the inside–outside tricycle to the outside–outside structure by an ester-reduction/elimination to enol-ether/hydrogenation procedure. In addition, the unusual stereochemical alignment involving inside–outside bridgehead centers from the radical cyclization was explained by DFT calculations. This result will be helpful for understanding the stereochemistry of similar type of radical-mediated ring-closing processes.

**Experimental Section**

**General**

Full experimental procedures and characterization data can be found in the Supporting Information.

\((1R,3aR,9aR,Z)\)-1-(tert-Butyldimethylsilyloxy)-2,2-dimethyl-2,3,3a,4,6,7-hexahydro-1H-cyclopenta[8]annulen-5(9aH)-one (31)

A solution of 30 (1.50 g, 5.1 mmol) and [[Rh(CO)\(_2\)Cl]\(_2\)] (100 mg, 0.26 mmol) in anhydrous C\(_6\)H\(_5\)Me (310 mL) was degassed by bubbling CO/N\(_2\) (balloon, pressurized mix of CO and N\(_2\) gas, 1:4 VV\(^{-1}\)) for 5 min. Then, the reaction mixture was immersed in an oil bath heated at 90°C and stirred under the above atmosphere for 50 h. Next, the reaction mixture was cooled to room temperature and concentrated under reduced pressure.

Scheme 20. Preparation of the chiral propargylic alcohol using the chiral ligand reported by Jiang and co-workers.[31]

Scheme 21. Asymmetric synthesis of (±)-asteriscanolide.
pressure. The crude mixture was purified by flash column chromatography on silica gel (petroleum ether/EtOAc 100:1 to 50:1) to afford compound 31 (1.5 g, 70%) as a pale-yellow oil: \( R_f = 0.19 \) (petroleum ether/ EtOAc = 9:1); \( \delta^1 H = 3.8, 18.2, 21.2, 23.8, 26.0, 26.8, 27.8, 32.0, 38.3, 40.7, 46.0, 50.5, 88.7, 123.8, 133.6, 1468, 2935 \text{ cm}^{-1}; \) IR (neat): 1274, 1475, 1635, 1700, 2957 \text{ cm}^{-1}; HRMS (ESI) calec for C\textsubscript{23}H\textsubscript{30}NaO\textsubscript{4}: 393.2036; found: 393.2035.

**Tricyclic Enol Ether (73)**

To a solution of 69 (104 mg, 0.28 mmol) in anhydrous CH\textsubscript{2}Cl\textsubscript{2} (2.5 mL) at \(-78^\circ C \) was added DIBAL-H (1.0 \text{ m} \text{ in} \text{ hexane, 0.9 mL, 0.9 mmol). After stirred at \(-78^\circ C \) for 3 h, the reaction mixture was diluted with Et\textsubscript{2}O (30 mL) and quenched with saturated potassium sodium tartrate solution (30 mL). The aqueous layer was separated and extracted with Et\textsubscript{2}O. The combined organic extracts were washed with brine, dried over MgSO\textsubscript{4}, and concentrated under reduced pressure to give a residue, which was used in the next step without further purification. To a solution of the crude 72 and triethylamine (291 mg, 2.88 mmol) in anhydrous CH\textsubscript{2}Cl\textsubscript{2} (8 mL) was added methanesulfonyl chloride (85 mL, 0.74 mmol). The resulting mixture was stirred at 25\textdegree C for 2 h before it was diluted with Et\textsubscript{2}O and washed with saturated NaHCO\textsubscript{3} solution and brine. The organic phase was dried over MgSO\textsubscript{4}, filtered, and concentrated under reduced pressure to give a residue, which was purified by flash column chromatography on silica gel (petroleum ether/EtOAc 50:1 to 20:1) to give compound 73 (85 mg, 85% over two steps) as a colorless oil: \( R_f = 0.10 \) (petroleum ether/EtOAc = 50:1); \( \delta^1 H = 3.8, 7.6, 17.4 \text{ ppm; IR: } 1255, 1367, 1455, 1700 \text{ cm}^{-1}; \) HRMS (ESI) calec for C\textsubscript{28}H\textsubscript{34}O\textsubscript{4}N\textsubscript{2}: 423.2267; found: 423.2268.

### (+)-Asteriscanolid (4)

To a mixture of compound 76 (10.5 mg, 0.044 mmol) and sodium periodate (47.0 mg, 0.22 mmol) in CH\textsubscript{2}CN/CCl\textsubscript{3}H\textsubscript{2}O (3 mL, 1:1, V/V) was added ruthenium trichloride (4.7 mg, 0.023 mmol). After stirring at 25\textdegree C for 9 h, the reaction mixture was diluted with CH\textsubscript{2}Cl\textsubscript{2} washed with water, dried over MgSO\textsubscript{4}, and filtered. After the solvent was evaporated under reduced pressure, the residue was subjected to flash column chromatography on silica gel (petroleum ether/EtOAc = 3:1) to give compound 7 (6.6 mg, 59%) as a white solid: \( R_f = 0.16 \) (petroleum ether/ EtOAc = 3:1); m.p. = 155–156\textdegree C (lit. m.p. = 178\textdegree C); \( ^1\text{H} \) NMR: \( \delta^1 H = 3.8, 6.8, 11.0, 12.4, 15.8 \text{ ppm; IR: } \nu = 1241, 1305, 1610 \text{ cm}^{-1}; \) HRMS (ESI) calec for C\textsubscript{18}H\textsubscript{20}NaO\textsubscript{4}: 329.1597; found: 329.1598.

**Acknowledgements**

We thank the Natural Science Foundation of China (20825205–National Science Fund for Distinguished Young Scholars and 20672005) and the National Basic Research Program of China (2010CB833203 and 2011CB808603-973 Program) for financial support.


(4) For details, see the Supporting Information.


