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

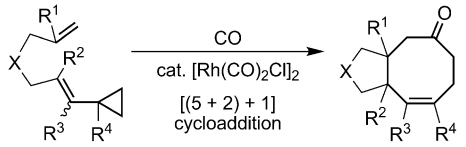
Yong Liang, Xing Jiang, Xu-Fei Fu, Siyu Ye, Tao Wang, Jie Yuan, Yuanyuan Wang, and Zhi-Xiang Yu*[a]

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

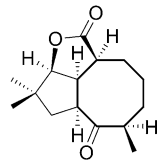
Introduction

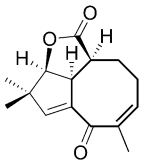
The value of new reactions becomes apparent when they are utilized in the synthesis of complex molecules. In exploring synthetic routes to the target molecule, we can further understand the scope and features of these new transformations. In 2007, we developed the rhodium-catalyzed two-component [(5+2)+1] 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: (±)-hirsutene, (±)-1-desoxyhypnophilin, and (±)-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]

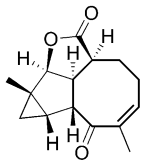


Scheme 1. Rhodium(I)-catalyzed [(5+2)+1] reaction of ene-vinylcyclopropanes and CO.

Since the discovery of (+)-asteriscanolide (**1**) in 1985,[5a] 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,[6,7] although a considerable amount of effort has been devoted to it.[8] In all of these syntheses, one of the most formidable tasks was to efficiently construct the eight-membered carbocycle.[9] In 1988, Wender et al. employed a nickel(0)-catalyzed intramo-


(+)-asteriscanolide (**1**)


tetradehydroasteriscanolide


naupliolide

[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

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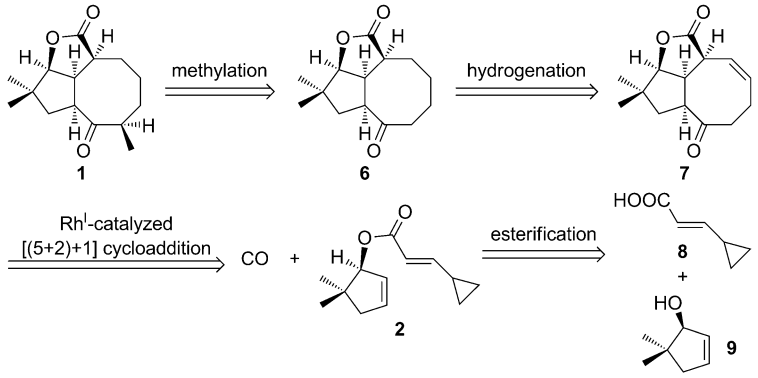
lecular [(4+4)] cycloaddition as the pivotal step in the construction of the tricyclic core and achieved the first total synthesis of (+)-asteriscanolide in 13 steps.[6a] In 2000, Limanto and Snapper incorporated a ring-opening-metathesis/Cope-rearrangement strategy to reach the tricyclic skeleton and finished the asymmetric synthesis of compound **1** in 9 steps.[6c] 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,[6b] and the Krafft group synthesized compound (±)-**1** in 19 steps.[7] 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.[10] 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.



Scheme 3. Retrosynthetic analysis of strategy **I**.

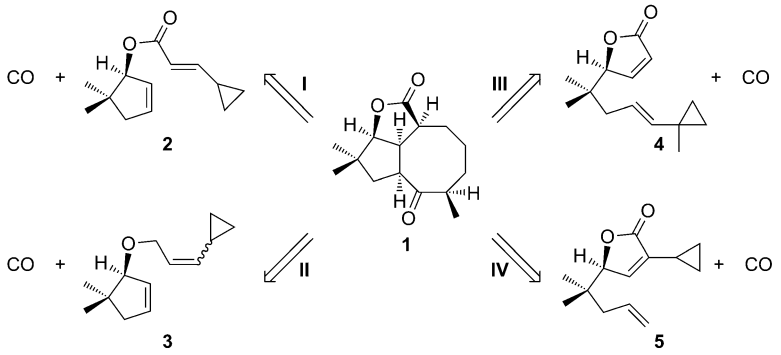
Results and Discussion

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

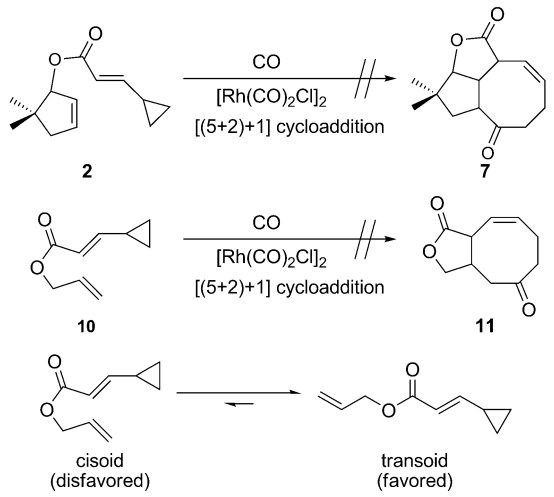
Because (+)-asteriscanolide (**1**) is a [5-5-8] tricyclic natural product, in our initial synthesis, we were eager to use the [(5+2)+1] reaction to construct its tricyclic core in one step. Analysis of the structure of compound **1** allowed us to propose that the most-efficient and appealing strategy 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**[6c] and (*E*)-3-cyclopropylacrylic acid (**8**).[11] 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[1a] (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], 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). It has been reported that such a conformational disadvantage could be overcome by the use of a polar solvent.[12] For instance, a cationic rhodium(I) species, derived from $[\{Rh(cod)Cl\}_2]$ (cod = 1,5-cyclooctadiene) and $AgSbF_6$ efficiently catalyzed the intramolecular [(5+2)] reaction of ester-tethered yne-VCP derivatives in $(CF_3)_2CHOH$.[12] Therefore, we



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

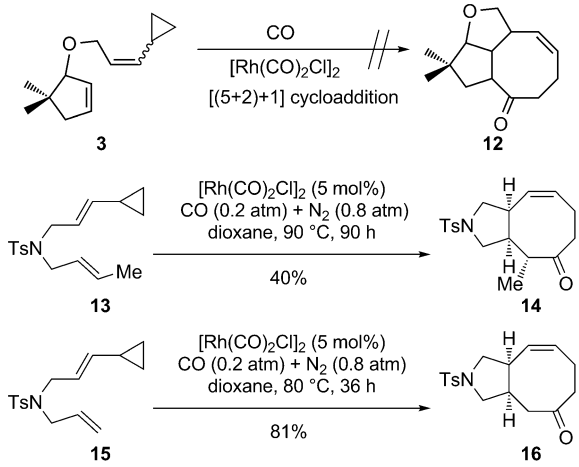


Scheme 4. Test of strategy **I**.

tried the [(5+2)+1] reaction of compound **10** and CO using $(CF_3)_2CHOH$ 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***

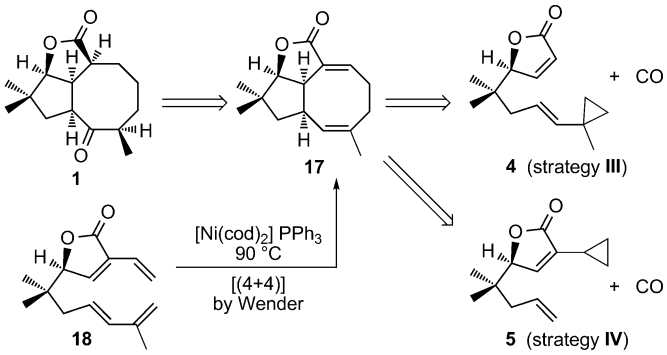
Our previous studies indicated that the [(5+2)+1] reaction was tolerant of ether-tethered ene-VCP substrates.[1a,b] Therefore, we turned our attention to strategy **II** (Scheme 2). After a four-step synthesis,[13] substrate **3** was prepared. However, after many attempts under various conditions, the 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.



Scheme 5. Test of strategy **II**.

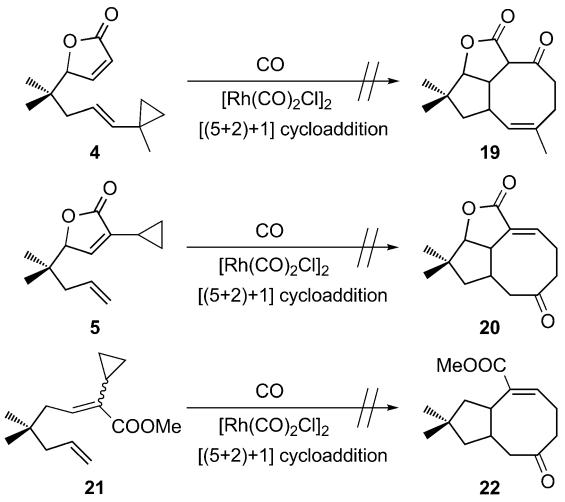
*Test of Strategies **III** and **IV***

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). Retrosynthetically, intermediate **17** could be derived from two different [(5+2)+1] reaction precursors (**4** and **5**; Scheme 6). The challenge of this design was whether electron-deficient cyclic olefins could be compatible in the rhodium(I)-catalyzed [(5+2)+1] reaction or not. We synthesized ene-VCPs **4** and **5** in 7 and 3 steps, respectively.[13] Then, we tried the key rhodium(I)-catalyzed [(5+2)+1] cycloaddition reactions under various conditions. To our disappointment, both substrates **4** and **5** failed to give the target cycloadducts (Scheme 7). A further test of the [(5+2)+1] reaction of acyclic olefin **21** with an electron-withdrawing group in the VCP moiety was also unsuccessful (Scheme 7), thereby suggesting that electron-deficient alkenes are not compatible in the [(5+2)+1] cycloaddition.



Scheme 6. Retrosynthetic analysis of strategies **III** and **IV**.

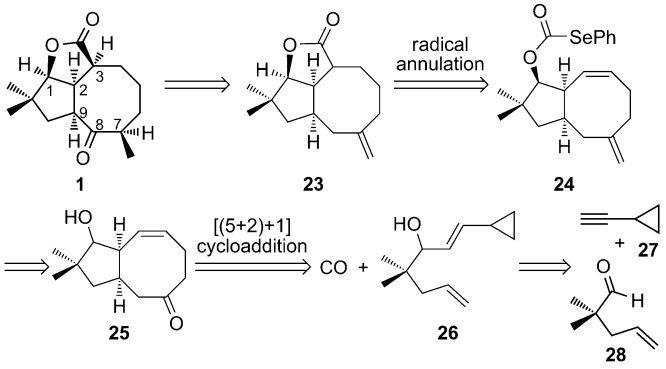
All of these unsuccessful tests of strategies **I**–**IV** for the one-step construction of the tricyclic core of asteriscanolide (described above) show that electron-withdrawing groups, such as esters, cannot be introduced as the chain tether or the substituent of the alkene, and that the ene-VCP substrates with alkenes in pre-existing five-membered rings are not suitable for the rhodium(I)-catalyzed [(5+2)+1] reaction.



Scheme 7. Test of strategies **III** and **IV**.

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

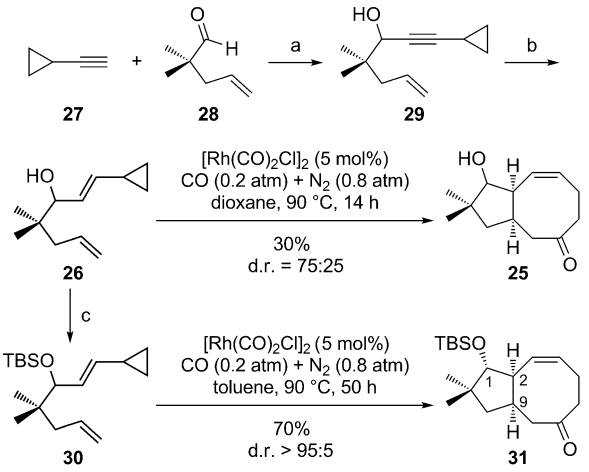


Scheme 8. Retrosynthetic analysis of first-generation strategy **V**.

ring could be constructed through the free-radical-annulation of selenocarbonate **24**,[15] and the [6.3.0] carbocyclic system could be achieved by the rhodium(I)-catalyzed [(5+2)+1] reaction of ene-VCP **26** 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 alkoxycarbonyl-radical-cyclization reaction to construct a bridged ring system,[16] 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-



Scheme 9. Reagents and conditions: a) *n*BuLi, THF, −78 °C to RT; b) Red-Al, THF, 40 °C, 93% over two steps; c) TBSCl, imidazole, DMAP, DMF, 40 °C, 96%. THF = tetrahydrofuran, Red-Al = sodium bis(2-methoxyethoxy)aluminumhydride, TBS = *tert*-butyldimethylsilyl, DMAP = 4-dimethylaminopyridine, DMF = *N*,*N*-dimethylformamide.

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.[17] Therefore, we transformed allylic alcohol **26** into TBS-protected **30** 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 **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 **1**.

We applied DFT calculations to investigate the origin of the high diastereoselectivity observed for the [(5+2)+1] reaction of compound **30**.[14,18] 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.[1a] In principle, four stereoisomers could be generated from the irreversible alkene-insertion step in the reaction of compound **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*$_{1,2}$-*cis*$_{2,9}$**, which leads to the observed product, compound **31**. The other three transition states are all 3–5 kcal mol^{-1} higher than **TS-*trans*$_{1,2}$-*cis*$_{2,9}$** 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*$_{1,2}$-*trans*$_{2,9}$** and **TS-*cis*$_{1,2}$-*trans*$_{2,9}$**, the O-C1-C11-C12 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*$_{1,2}$-*cis*$_{2,9}$**, 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*$_{1,2}$-*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 **31**, followed by deprotection of the TBS group, gave alcohol **33** with the opposite configuration at the C1 position with respect to that in compound **1** (Scheme 10). To invert this configuration, compound **33** was converted into ketone **34** by Dess–Martin oxidation. Then using the bulky reducing reagent DIBAl-H at −78 °C, the desired alcohol **35** with correct configuration at the C1 position was generated (Scheme 10). After alcohol **35** was converted into selenocarbonate **36**, we conducted the radical cyclization of compound **36** in the presence of AIBN and nBu$_3$SnH.[15] Gratifyingly, the tricyclic compound **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 **1**.

Next, we performed DFT calculations to better understand the diastereoselectivity of this radical process.[19] When compound **36** underwent the radical annulation reaction, the *trans*-radical-addition transition state **TS-*trans*-37** was 1.6 kcal mol^{-1} lower in terms of Gibbs free energy than the *cis*-radical-addition transition state **TS-*cis*-38** (in benzene; Figure 2a), thereby suggesting that the radical addition greatly favors the *trans* product **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*-38**, the alkoxycarbonyl radical and

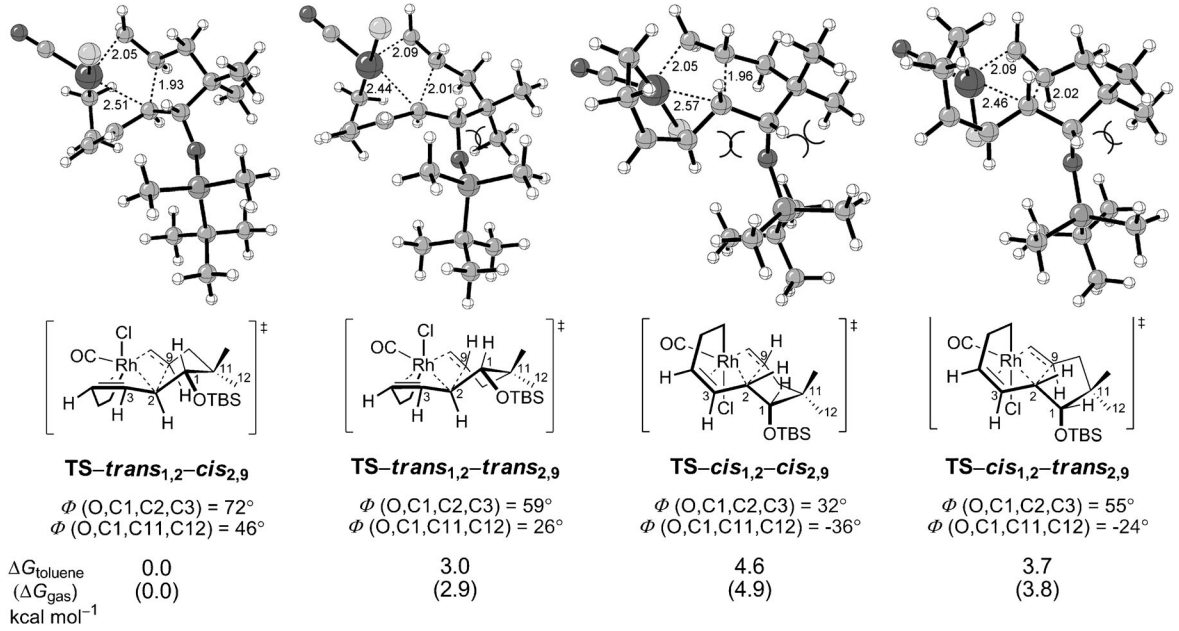
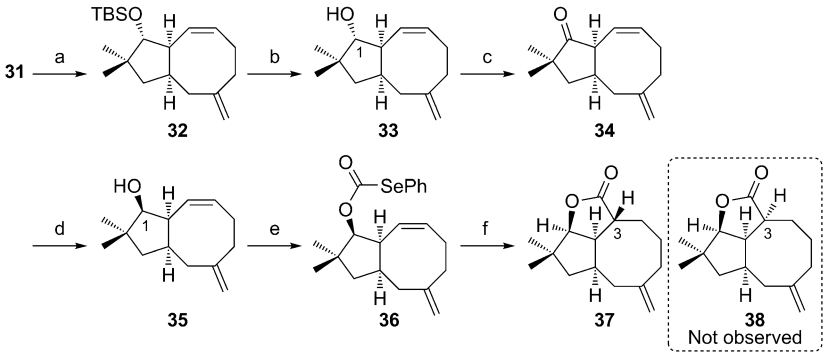


Figure 1. DFT-computed structures and Gibbs free energies of alkene-insertion transition states in the rhodium(I)-catalyzed [(5+2)+1] cycloaddition reaction (distances are given in Å, $G_{toluene}$ = Gibbs free energy in toluene, G_{gas} = Gibbs free energy in the gas phase).



Scheme 10. Reagents and conditions: a) methyltriphenylphosphonium bromide, *t*BuOK, C_6H_6, 40 °C; b) TBAF, THF, 40 °C, 77 % over two steps; c) DMP, $NaHCO_3$, CH_2Cl_2, RT; d) DIBAl-H, CH_2Cl_2, −78 °C, 88 % over two steps; e) (1) Py, DMAP, THF, triphosgene, C_6H_6, RT, (2) PhSeH, 40 °C; f) nBu_3SnH, AIBN, C_6H_6, reflux, 78 % over two steps. TBAF = tetrabutylammonium fluoride, DMP = Dess–Martin periodinane, DIBAl-H = diisobutylaluminum hydride, Py = pyridine, AIBN = azobisisobutyronitrile.

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).

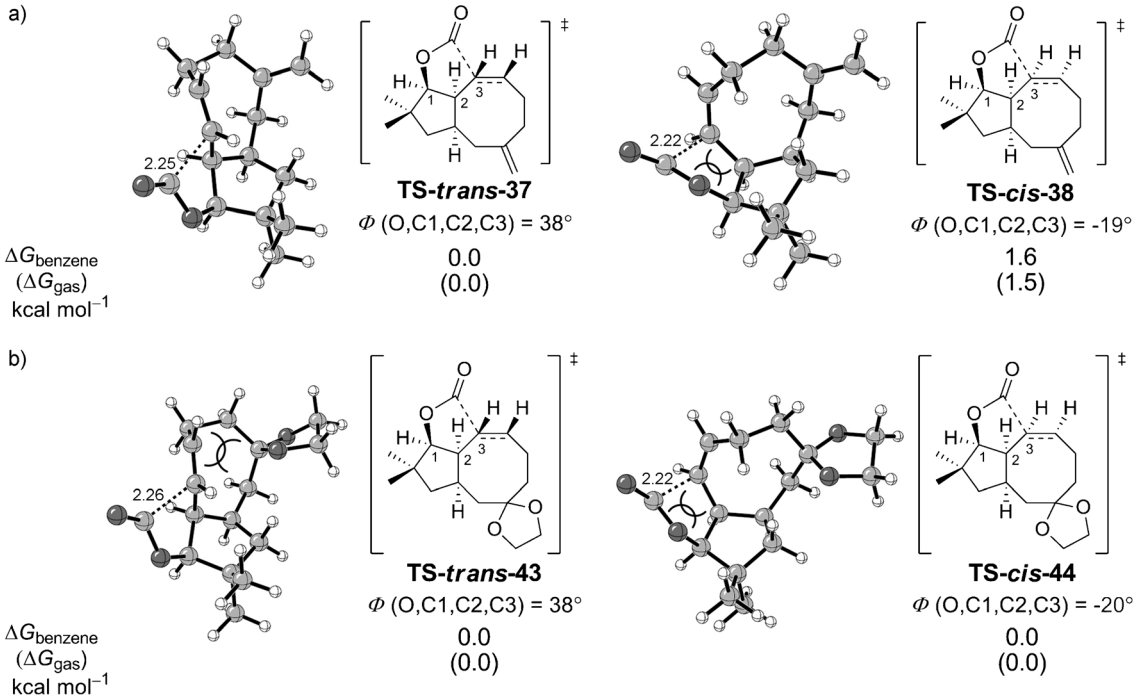


Figure 2. DFT-computed structures and Gibbs free energies of radical addition transition states in the radical annulations (distances are given in Å, $G_{benzene}$ = Gibbs free energy in benzene, G_{gas} = Gibbs free energy in the gas phase).

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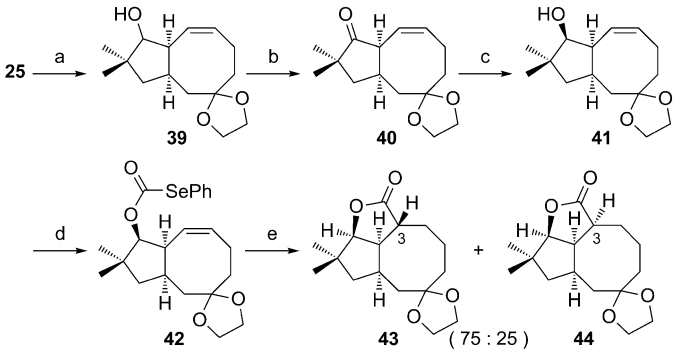
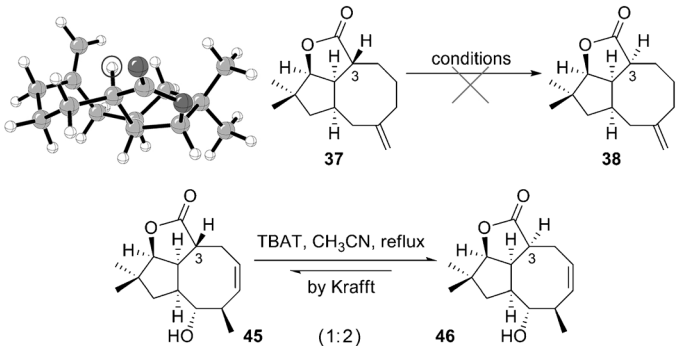


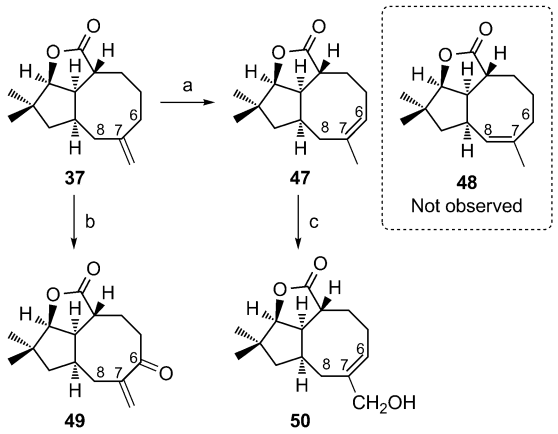
Scheme 11. Reagents and conditions: a) $HOCH_2CH_2OH$, $TsOH{\cdot}H_2O$, C_6H_6, reflux under a Dean–Stark trap; b) DMP, $NaHCO_3$, CH_2Cl_2, RT; c) DIBAl-H, CH_2Cl_2, −78 °C, 58 % over three steps; d) (1) Py, DMAP, THF, triphosgene, C_6H_6, RT, (2) PhSeH, RT; e) nBu_3SnH, AIBN, C_6H_6, reflux, 68 % over two steps. Ts = *para*-toluenesulfonyl.

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,[20] 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.[7] 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.[7] However, in our case, this method was unsuccessful for converting compound **37** into compound **38**.



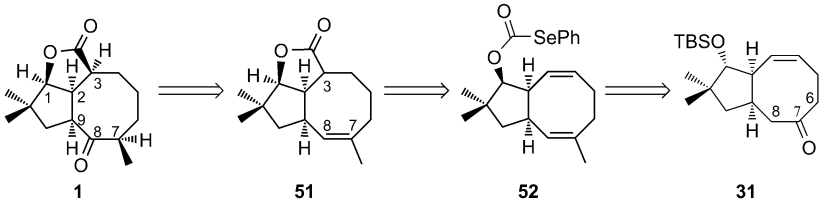
Scheme 12. Attempts at epimerizing the stereocenter at the C3 position.

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 SeO_2/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.

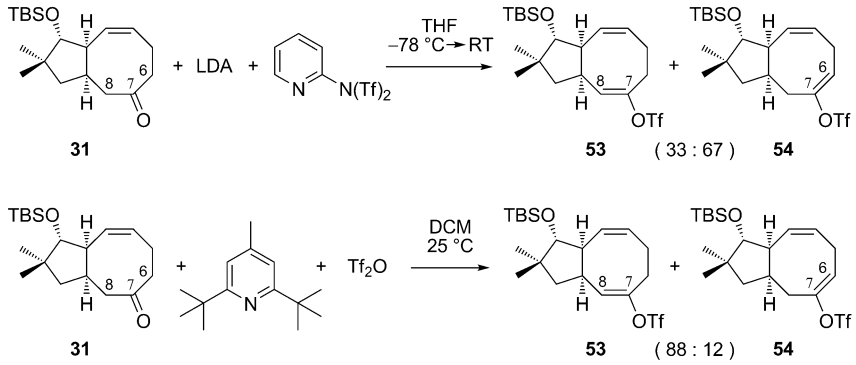


Scheme 13. Reagents and conditions: a) $TsOH{\cdot}H_2O$, $CHCl_3$, 60 °C, 87 %; b) SeO_2, *t*BuOOH, CH_2Cl_2, 25 °C, 90 %; c) SeO_2, *t*BuOOH, CH_2Cl_2, 25 °C, 78 %.

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 ^{1}H NMR spectrum of the crude reaction mixture;



Scheme 14. Retrosynthetic analysis in second-generation strategy **V**.

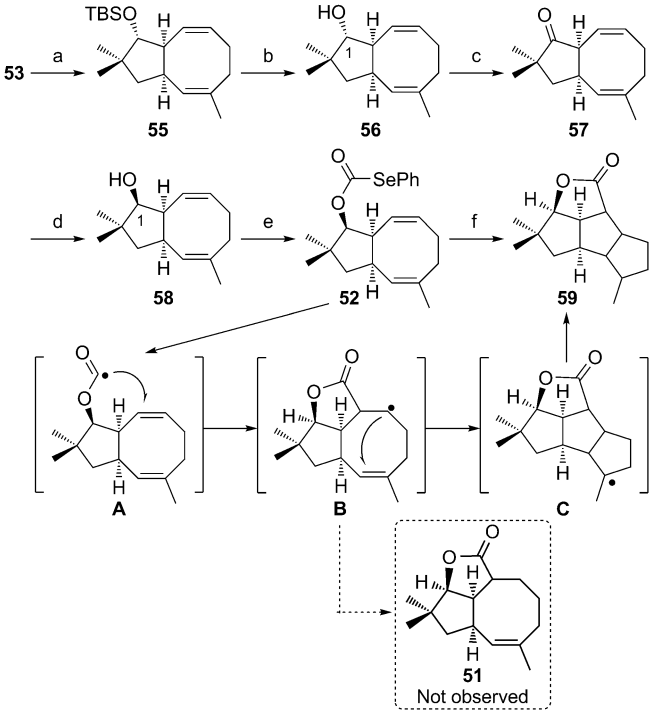


Scheme 15. Regioselectivity in the conversion of the [(5+2)+1] cycloadduct into its enol triflate.

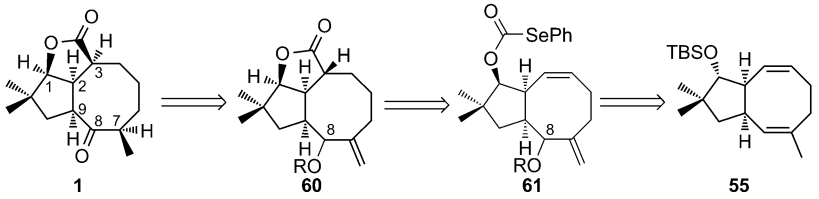
Scheme 15). However, to our delight, ketone **31** was converted into enol triflate **53** using trifluoromethanesulfonic anhydride and 2,6-di-*tert*-butyl-4-methylpyridine with good regioselectivity (**53**/**54** = 88:12; Scheme 15).[22]

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,[15] 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 nBu$_3$SnH 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 *m*CPBA 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 nBu$_3$SnH.[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 condi-



Scheme 16. Reagents and conditions: a) [Fe(acac)$_3$], 1-methyl-2-pyrrolidinone, MeMgBr, THF, −10 °C, 58% over two steps from compound **31**; b) TBAF, THF, 40 °C, 98%; c) DMP, $NaHCO_3$, CH_2Cl_2, RT; d) DIBAl-H, CH_2Cl_2, −78 °C, 48% over two steps; e) (1) Py, DMAP, THF, triphosgene, C_6H_6, 28 °C, (2) PhSeH, 28 °C; f) nBu$_3$SnH, AIBN, benzene, reflux, 70% over two steps. acac = acetylacetonyl.



Scheme 17. Retrosynthetic analysis of third-generation strategy **V**.

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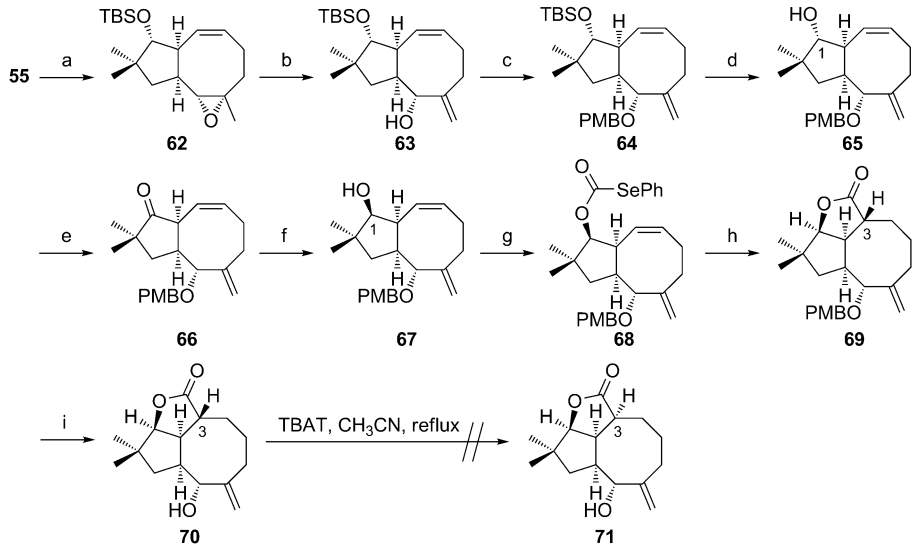
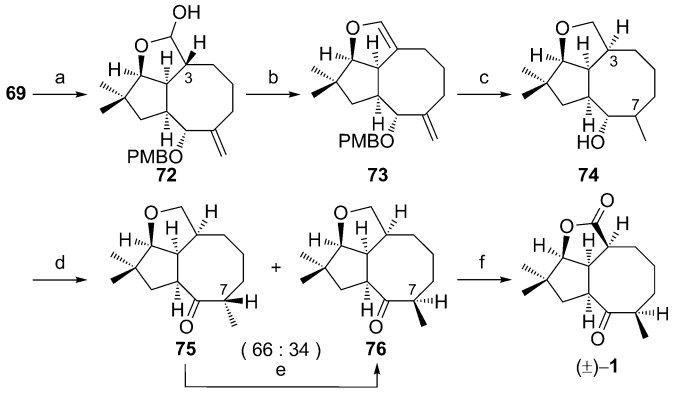


Scheme 18. Reagents and conditions: a) *m*CPBA, EtOAc, 0 °C; b) 2,2,6,6-tetramethylpiperidine, *n*BuLi, Me_2AlCl, C_6H_6, 0 °C, 86 % over two steps; c) NaH, PMBCl, DMF, 50 °C, 82 %; d) TBAF, THF, 40 °C, 90 %; e) DMP, $NaHCO_3$, CH_2Cl_2, RT; f) DIBAl-H, CH_2Cl_2, −78 °C, 84 % over two steps; g) (1) Py, DMAP, THF, triphosgene, C_6H_6, 30 °C, (2) PhSeH, 30 °C; h) nBu_3SnH, AIBN, C_6H_6, reflux, 95 % over two steps; i) DDQ, CH_2Cl_2/H_2O (4:1), RT, 89 %. *m*CPBA = *meta*-chloroperbenzoic acid, PMB = *para*-methoxybenzyl, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

tions (Scheme 18). Therefore, the next challenging problem was to efficiently convert the inside–outside tricycle 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



Scheme 19. Reagents and conditions: a) DIBAl-H, CH_2Cl_2, −78 °C; b) CH_3SO_2Cl, Et_3N, CH_2Cl_2, 25 °C, 85 % over two steps; c) H_2, Pd/C, EtOH, 60 °C; d) DMP, $NaHCO_3$, CH_2Cl_2, 25 °C, 46 % (**75**) and 24 % (**76**) over two steps; e) (1) TMSOTf, 2,6-lutidine, CH_2Cl_2, 25 °C, (2) 1 M HCl, Et_2O, 25 °C, 48 % brsm; f) $RuCl_3$, $NaIO_4$, $CH_3CN/CCl_4/H_2O$ (1:1:1), 25 °C, 59 %. TMS = trimethylsilyl, Tf = trifluoromethanesulfonyl, brsm = based on recovered starting material.

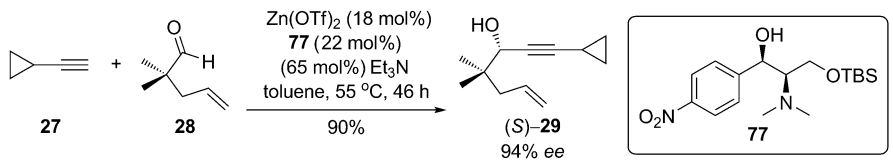
the enol ether successfully installed the hydrogen atom at the C3 position with correct configuration. Meanwhile, the PMB group was removed, and the *exo* C=C double bond was also hydrogenated with 66:34 diastereoselectivity. The resulting alcohols **74** were formed as a mixture of two inseparable diastereomers. 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).[6b]

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.



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

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 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, 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.

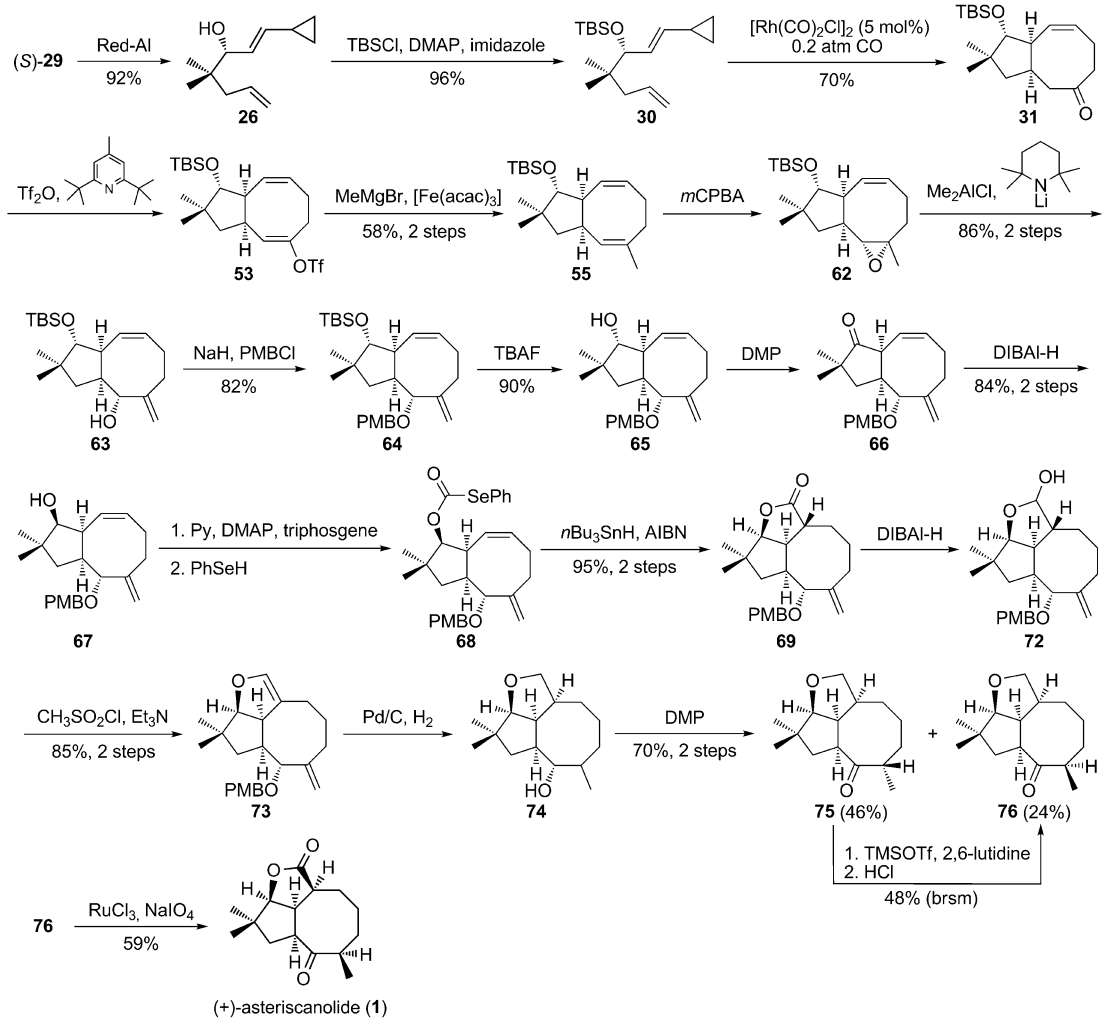
Experimental Section

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_6H_5Me (310 mL) was degassed by bubbling CO/N_2 (balloon, pressurized mix of CO and N_2 gas, 1:4 V V^{-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



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** (1.15 g, 70%) as a pale-yellow oil: $R_f = 0.19$ (petroleum ether/EtOAc = 20:1); $[\alpha]_D^{20} = -45.3$ ($c = 1.18$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = -0.02$ (s, 3H), 0.02 (s, 3H), 0.86 (s, 9H), 0.93 (s, 3H), 1.01 (s, 3H), 1.10 (t, $J = 12.4$ Hz, 1H), 1.54–1.63 (m, 1H), 2.01–2.30 (m, 3H), 2.34–2.56 (m, 4H), 2.61–2.70 (m, 1H), 3.63 (d, $J = 4.4$ Hz, 1H), 5.44–5.51 (m, 1H), 5.87–5.96 ppm (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = -4.9$, −4.2, 18.0, 22.0, 23.8, 25.8, 28.4, 36.9, 41.7, 44.6, 44.7, 46.7, 47.8, 89.2, 130.0, 133.9, 213.9 ppm; IR: $\tilde{\nu} = 1255$, 1367, 1464, 1706, 2957 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{34}NaO_2Si$: 345.2220; found: 345.2221.

*tert-Butyldimethyl((1R,3aR,4Z,8Z,9aS)-2,2,5-trimethyl-2,3,3a,6,7,9a-hexahydro-1H-cyclopenta[8]annulen-1-yloxy)silane (**55**)*

To a solution of 2,6-di-*tert*-butyl-4-methylpyridine (1.16 g, 5.67 mmol) in anhydrous CH_2Cl_2 (30 mL) was added sequentially trifluoromethanesulfonic anhydride (1.32 g, 4.68 mmol) and a solution of **31** (890 mg, 2.76 mmol) in anhydrous CH_2Cl_2 (30 mL). The reaction mixture was stirred at 25 °C for 12 h. Afterwards, the solvent was removed by evaporation under reduced pressure, the residue was dissolved in 150 mL Et_2O, washed with 1 M HCl solution and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting brown oil was filtered through a pad of silica gel and the filtrate was concentrated under reduced pressure to give the crude product **53**, which was used in the next step without further purification. A solution of crude **53** in THF (35 mL) was added to a mixture of [Fe(acac)$_3$] (199 mg, 0.56 mmol) and 1-methyl-2-pyrrolidinone (3 mL), and the resulting mixture was cooled to −10 °C. MeMgBr (3.0 M in Et_2O, 3.5 mL, 10.5 mmol) was added dropwise and the reaction mixture was allowed to warm to room temperature and stirred overnight. Then, to the reaction mixture was added saturated NH_4Cl solution and Et_2O, and the aqueous layer was extracted with Et_2O. The combined organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether) to give compound **55** (515 mg, 58% over two steps) as a colorless oil: $R_f = 0.39$ (petroleum ether); $[\alpha]_D^{20} = +13.8$ ($c = 1.00$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.04$ (s, 3H), 0.05 (s, 3H), 0.89 (s, 9H), 0.92 (s, 3H), 0.98 (s, 3H), 1.24 (t, $J = 12.4$ Hz, 1H), 1.66 (s, 3H), 1.73 (dd, $J = 12.4$, 7.6 Hz, 1H), 1.79 (dt, $J = 14.1$, 6.8 Hz, 1H), 2.02–2.12 (m, 1H), 2.39–2.48 (m, 1H), 2.58–2.66 (m, 1H), 2.84–2.92 (m, 1H), 3.14–3.24 (m, 1H), 3.46 (d, $J = 7.7$ Hz, 1H), 5.09 (d, $J = 4.6$ Hz, 1H), 5.41 (ddd, $J = 11.0$, 5.5, 2.4 Hz, 1H), 5.50–5.57 ppm (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = -4.5$, −3.8, 18.2, 21.2, 23.8, 26.0, 26.6, 27.8, 32.0, 38.3, 40.7, 46.0, 50.5, 88.7, 128.6, 128.7, 133.7, 136.4 ppm; IR: $\tilde{\nu} = 1255$, 1363, 1468, 2935 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{36}NaOSi$: 343.2428; found: 343.2431.

*Tricyclic Lactone (**69**)*

To a mixture of **67** (101 mg, 0.29 mmol), DMAP (27 mg, 0.22 mmol), and pyridine (0.88 g, 11.1 mmol) in anhydrous THF (8 mL) was added a solution of triphosgene (145 mg, 0.49 mmol) in anhydrous C_6H_6 (8 mL). After stirring at 30 °C for 3 h, freshly distilled PhSeH (387 mg, 2.46 mmol) was added and the reaction mixture was stirred at 30 °C for 16 h before H_2O (100 mL) and Et_2O (100 mL) were added. The aqueous layer was separated and extracted with Et_2O. The combined organic phase was washed sequentially with 1 M HCl, H_2O, and saturated $NaHCO_3$ solution, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting yellow oil was filtered through a pad of silica gel, and the filtrate was concentrated under reduced pressure to give the crude **68**, which was used in the next step without further purification. To a solution of the crude **68** and AIBN (21 mg, 0.13 mmol) in anhydrous C_6H_6 (60 mL) was added nBu$_3$SnH (360 mg, 1.20 mmol). The resulting mixture was heated to reflux in an oil bath (90 °C) for 3.5 h. The solvent was removed by evaporation under reduced pressure, and the residue was purified by flash column chromatography on silica gel (petroleum ether/EtOAc 50:1 to 10:1) to afford compound **69** (104 mg, 95% over two steps) as a colorless oil: $R_f = 0.35$ (petroleum ether/EtOAc = 5:1); $[\alpha]_D^{20} = +36.0$ ($c = 0.87$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.01$ (s, 3H), 1.05 (s, 3H), 1.34–1.45 (m, 2H), 1.69–1.82 (m, 2H), 1.89–2.02 (m, 1H), 2.08–2.25 (m, 2H), 2.39 (dq, $J = 12.8$, 6.4 Hz, 1H), 2.50–2.63 (m, 2H), 2.77 (dd, $J = 15.4$, 7.8 Hz, 1H), 3.78 (d, $J = 6.9$ Hz, 1H), 3.81 (s, 3H), 4.20 (d, $J = 11.3$ Hz, 1H), 4.30 (d, $J = 7.7$ Hz, 1H), 4.50 (d, $J = 11.3$ Hz, 1H), 5.10 (s, 1H), 5.13 (s, 1H), 6.88 (d, $J = 8.4$ Hz, 2H), 7.23 ppm (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 24.4$, 25.2, 28.8, 29.9, 34.5, 38.1, 40.4, 43.1, 46.0, 46.3, 55.2, 70.4, 81.7, 89.8, 113.8, 113.9, 129.3, 130.3, 148.8, 159.2, 180.0 ppm; IR: $\tilde{\nu} = 1251$, 1520, 1620, 1769, 2939 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{30}NaO_4$: 393.2036; found: 393.2035.

*Tricyclic Enol Ether (**73**)*

To a solution of **69** (104 mg, 0.28 mmol) in anhydrous CH_2Cl_2 (2.5 mL) at −78 °C was added DIBAl-H (1.0 M in n-hexane, 0.9 mL, 0.9 mmol). After stirred at −78 °C for 3 h, the reaction mixture was diluted with Et_2O (30 mL) and quenched with saturated potassium sodium tartrate solution (30 mL). The aqueous layer was separated and extracted with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product **72**, 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_2Cl_2 (8 mL) was added methanesulfonyl chloride (85 mg, 0.74 mmol). The resulting mixture was stirred at 25 °C for 2 h before it was diluted with Et_2O and washed with saturated $NaHCO_3$ solution and brine. The organic phase was dried over $MgSO_4$, 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); $[\alpha]_D^{20} = +38.6$ ($c = 0.76$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.96$ (s, 3H), 1.07 (s, 3H), 1.40 (t, $J = 12.4$ Hz, 1H), 1.57–1.74 (m, 2H), 1.85 (dd, $J = 12.4$, 5.6 Hz, 1H), 1.95–2.04 (m, 1H), 2.21–2.31 (m, 2H), 2.34–2.52 (m, 2H), 3.17 (t, $J = 8.3$ Hz, 1H), 3.66 (d, $J = 10.2$ Hz, 1H), 3.80 (s, 3H), 4.19 (d, $J = 11.2$ Hz, 1H), 4.37 (d, $J = 8.2$ Hz, 1H), 4.46 (d, $J = 11.2$ Hz, 1H), 5.13 (s, 1H), 5.28 (s, 1H), 6.06 (s, 1H), 6.86 (d, $J = 8.4$ Hz, 2H), 7.23 ppm (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 23.8$, 25.4, 26.8, 27.2, 38.9, 42.3, 42.6, 50.1, 50.3, 55.2, 69.8, 79.3, 96.0, 113.2, 113.7, 114.4, 129.2, 131.0, 142.9, 151.0, 159.0 ppm; IR: $\tilde{\nu} = 1251$, 1516, 1616, 1654, 2928 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{31}O_3$: 355.2268; found: 355.2264.

*(+)-Asteriscanolide (**1**)*

To a mixture of compound **76** (10.5 mg, 0.044 mmol) and sodium periodate (47.0 mg, 0.22 mmol) in $CH_3CN/CCl_4/H_2O$ (3 mL, 1:1:1, $VV^{-1}V^{-1}$) was added ruthenium trichloride (4.7 mg, 0.023 mmol). After stirring at 25 °C for 9 h, the reaction mixture was diluted with CH_2Cl_2, washed with water, dried over $MgSO_4$, 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 **1** (6.6 mg, 59%) as a white solid: $R_f = 0.16$ (petroleum ether/EtOAc = 3:1); m.p. = 155–156 °C (lit. m.p. = 178 °C,[5a] 156–158 °C,[6b] 163–165 °C,[6c] 142–143 °C[7b]); $[\alpha]_D^{20} = +11.8$ ($c = 0.28$, $CHCl_3$; lit. value = +12.1,[5a] +8.5,[6b] +16.6[6c]); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.00$ (s, 3H), 1.13 (d, $J = 6.3$ Hz, 3H), 1.20 (s, 3H), 1.31–1.44 (m, 2H), 1.51–1.62 (m, 1H), 1.76–1.85 (m, 1H), 1.88–2.01 (m, 2H), 2.19 (t, $J = 13.4$ Hz, 1H), 2.36–2.57 (m, 2H), 2.72 (ddd, $J = 12.3$, 9.6, 6.3 Hz, 1H), 3.21 (dt, $J = 11.9$, 6.8 Hz, 1H), 3.73 (dt, $J = 10.5$, 5.3 Hz, 1H), 4.27 ppm (d, $J = 5.2$ Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 13.2$, 22.4, 23.0 (2 C), 24.5, 28.0, 38.4, 40.7, 43.2, 45.66, 45.72, 50.2, 90.9, 177.8, 213.6 ppm; IR: $\tilde{\nu} = 1274$, 1475, 1698, 1769, 2928 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{22}NaO_3$: 273.1461; found: 273.1463.

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[19] The geometry optimizations and frequency calculations were performed at the UB3LYP/6–31G(d)level. Solvent effects were computed using the CPCM model in benzene.

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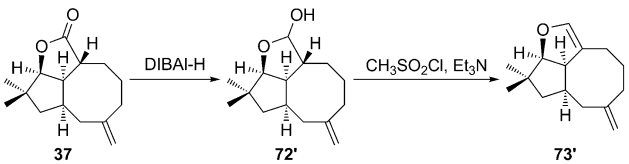

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