Studies Toward the Total Synthesis of Schinortriterpenoids Bearing an All-*Cis* Cyclopropane: Diastereoselective Synthesis of the Left-hand Fragment

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Abstract: Schinortriterpenoids, such as pre-schisanartanin A and arisanlactone C, are complex and highly oxygenated polycyclic terpenes. In this study, the left-hand fragment of this class terpenes, which possesses oxygen-functionality at C19, was synthesized through [3+2] cycloaddition with excellent diastereoselectivity. This stereoselectivity was investigated by computational studies. Further selective transformation provided a tricyclic skeleton with the desired stereochemistry.

Schinortriterpenoids are highly oxygenated polycyclic terpenes isolated from fruits of the Schisandraceae family.[1] These natural products are assumed to be biosynthetically produced from a cycloartane skeleton through complicated rearrangements. In these rearrangements, biosynthetic intermediates containing a three-membered ring structure are proposed. Additionally, natural products containing this structure, such as pre-schisanartanins,[2a] arisanlactones,[2b] spiroschincarins,[2c] and schincarins,[2d] have been isolated from the same species (Figure 1). Their structures, as determined by HR-ESI-MS, NMR, and single-crystal X-ray diffraction analysis, were characterized as polycyclic skeletons containing a 5/5/7-membered tricyclic ring system and an all-*cis*-substituted cyclopropane, along with more than 10 stereocenters. Schinortriterpenoids exhibit various biological activities, including anti-cancer and anti-HIV activities, while pre-schisanartanin A shows anti-HIV-1 activity (EC_{50}, 13.81 μg/mL). 2β-Hydroxyarisanlactone C and spiroschincarins demonstrate a mild anti-inflammatory effect and weak immunosuppressive activity in vitro, respectively.

Owing to their complicated and unique structure, and important biological activities, schinortriterpenoids have attracted the attention of researchers developing strategies for total synthesis.[3,4] Among natural products containing an all-*cis*-substituted cyclopropane, Yang and coworkers recently reported the first total synthesis of pre-schisanartanin C using Au-catalyzed intramolecular cyclopropanation to construct a bicyclo[6.1.0]nonane skeleton.[4m] We previously reported a strategy for the construction of all-*cis*-substituted cyclopropanes.[5] Using this synthetic method, we have initiated a synthetic project to clarify the relationship between the three-membered ring structure and biological activity of schinortriterpenoids.

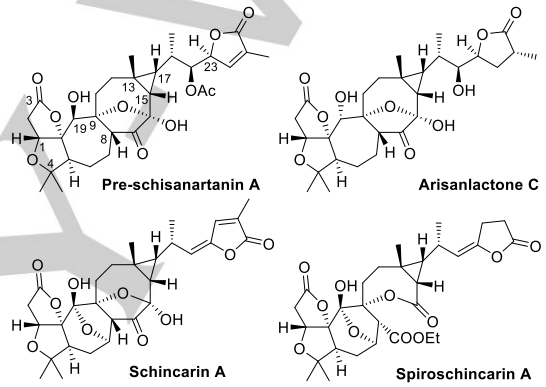
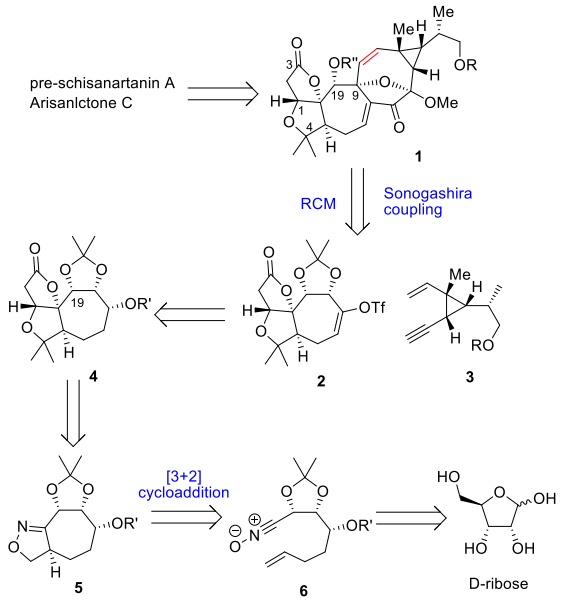


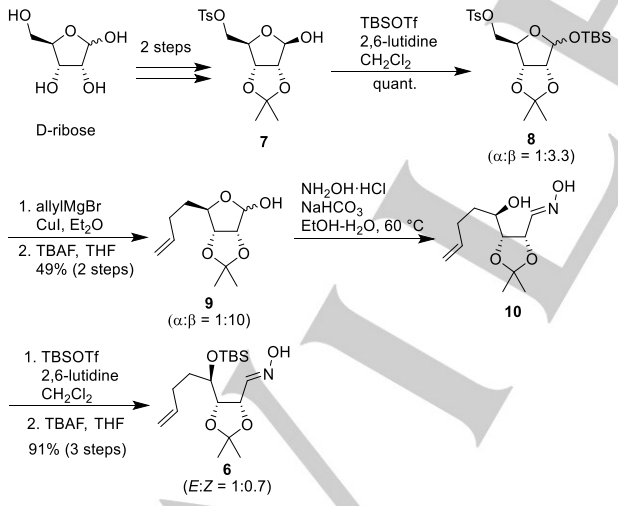
Figure 1. Schinortriterpenoids containing an all-*cis*-substituted cyclopropane.

To synthesize schinortriterpenoids containing an all-*cis*-substituted cyclopropane, a convergent synthesis involving coupling a 5/5/7-membered tricyclic ring fragment (left-hand fragment) and an all-*cis*-substituted cyclopropane (right-hand fragment) would be desirable. Pre-schisanartanin A and arisanlactone C were envisaged to be accessed from triflate **2** and alkyne **3** via a Sonogashira coupling,[6] ring-closing metathesis (RCM),[7] and functional group manipulations via **1** (Scheme 1). Left-hand fragment **2** would be prepared from stable tricyclic compound **4** bearing C19 oxygen functionality and six contiguous stereocenters. The seven-membered ring, which is a key structure of tricyclic ring system **4**, would be constructed by the [3+2] cycloaddition of nitrile oxide **6**. Resultant isoxazoline **5** would be converted into **4** by the formation of five-membered ether and lactone rings. The intramolecular [3+2] cycloaddition of nitrile oxides to alkenes is a powerful reaction for isoxazoline formation that is widely employed for the synthesis of heterocycles and natural products.[8,9] The synthesis of a 7-membered ring with a fused isoxazoline through [3+2] cycloaddition of a nitrile oxide was expected to proceed with high diastereoselectivity considering its transition states.[10] Nitrile oxide **6** would be readily prepared from D-ribose. Herein, we report a stereoselective synthesis of left-hand fragment containing a seven-membered ring with six contiguous stereocenters.



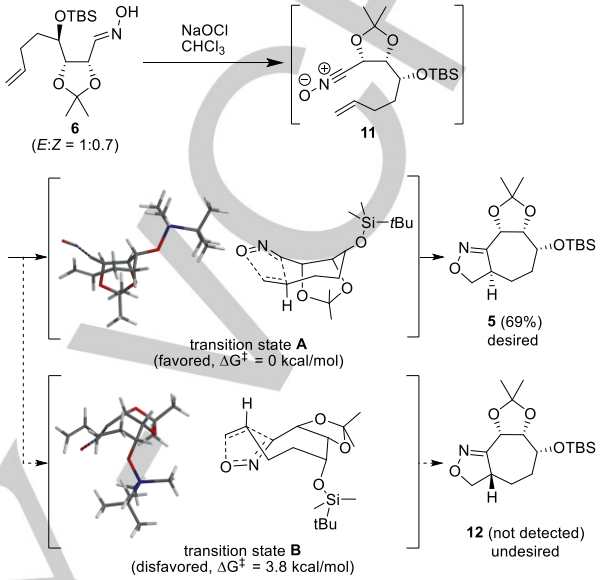
Scheme 1. Retrosynthesis of pre-schisanartanin A and arisanlactone C.

The synthesis started with the silylation of known compound **7**,[11] which was prepared from D-ribose in two steps (Scheme 2). The obtained anomeric mixture of **8** was coupled with allyl magnesium bromide in the presence of CuI, and the resultant products were treated with tetrabutylammonium fluoride (TBAF) to give hemiacetal **9** as an anomeric mixture (α/β = 1:10) in 49% yield. The formation of oxime **10** was followed by a protecting group manipulation to give cyclization precursor **6** in 91% overall yield from compound **9**.



Scheme 2. Synthesis of cyclization precursor **5**. TBS, *tert*-butyldimethylsilyl; TBAF, tetrabutylammonium fluoride.

With oxime **6** in hand, the [3+2] cyclization reaction was investigated. Treatment of **6** with NaOCl produced nitrile oxide **11**, which immediately cyclized to give isoxazoline **5** in 69% yield with excellent selectivity (Scheme 3). Diastereomer **12** was not observed. The newly generated stereochemistry was confirmed by NOESY experiment, as shown in Figure 2. To rationalize this selectivity, the transition states into both diastereomers **5** and **12** were evaluated using DFT calculations at the B3LYP/6-31G* level of theory. The calculations suggested that transition state **A** toward **5** was more favorable than transition state **B**, which was a boat-like conformation ($\Delta\Delta G^{\ddagger}$ = 3.8 kcal/mol), toward **12**.



Scheme 3. Diastereoselective synthesis of isoxazoline **5**, and transition states of [3+2] cycloaddition based on the B3LYP/6-31G* level of theory (in a vacuum) obtained using Spartan '18.

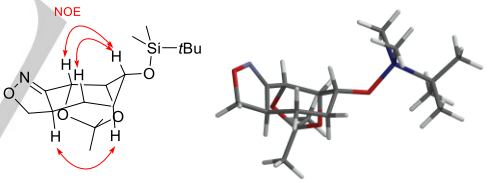
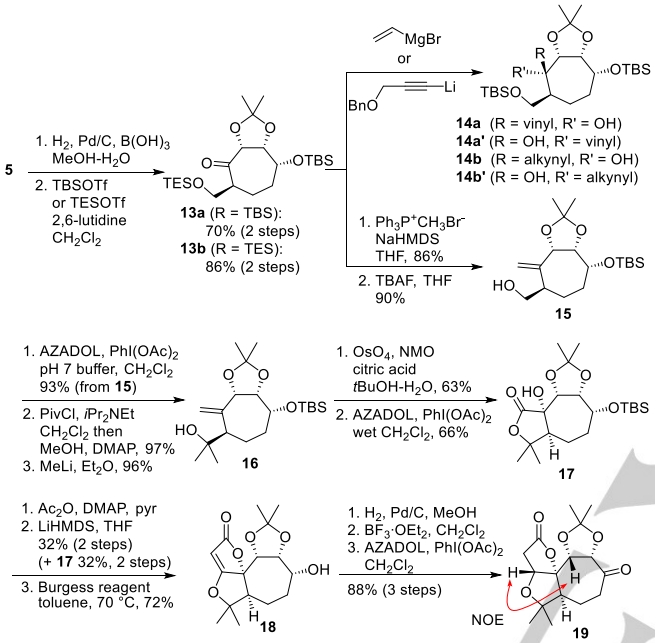


Figure 2. NOESY experiment of isoxazoline **5**, and its calculated stable conformation based on the B3LYP/6-31G* level of theory (in a vacuum) obtained using Spartan '18.

After construction of the seven-membered ring, isoxazoline **5** was reductively cleaved and hydrolyzed to give a hydroxyketone,[12] which was then converted to tert-butyldimethylsilyl (TBS) and triethylsilyl (TES) ethers **13a** and **13b** in 70% and 86% overall yields, respectively (Scheme 4). Initially, nucleophilic additions of vinyl magnesium bromide and a lithiated alkyne were attempted to produce compounds **14a** and **14b**, respectively. However, these nucleophiles unexpectedly approached from the *Si*-face, which is shielded by the silyloxy and acetal groups on the seven-membered ring, to give undesired tertiary alcohols **14a'** and **14b'**. Therefore, **13b** was converted to exo-methylene **15** by Wittig olefination, followed by TES group removal. After AZADO oxidation[13] and esterification, treatment of the resulting ester with methyl lithium gave tertiary alcohol **16**. As expected, dihydroxylation with OsO_4 in the presence of citric acid[14] proceeded with the desired

stereochemistry to give a triol, which was oxidized to lactone **17**. Notably, no reaction occurred in the absence of citric acid. The introduction of an acetyl group was followed by an intramolecular aldol reaction to give a cyclized acetal,[4a] which was dehydrated using Burgess reagent [15] to give tricyclic compound **18**. The obtained olefin was hydrogenated in the presence of Pd/C. TBS group removal and AZADO oxidation gave left-hand fragment **19**, which is a precursor of **2**, in 88% overall yield from **18**. The stereochemistry newly generated in the hydrogenation reaction was determined by NOESY experiment of **19**, as shown in Scheme 3.



Scheme 4. Synthesis of left-hand fragment **19**. TES, triethylsilyl; NaHMDS, sodium bis(trimethylsilyl)amide; AZADOL, 2-azaadamantane-2-ol; Piv, pivaloyl; DMAP, 4-dimethylaminopyridine; LiHMDS, lithium bis(trimethylsilyl)amide; Burgess reagent, (methoxycarbonylsulfamoyl)triethylammonium hydroxide inner salt.

In summary, we synthesized the left-hand fragment of pre-schisanartanin A and arisanlactone C, which possesses oxygen-functionality at C19. The seven-membered ring was constructed with excellent diastereoselectivity by [3+2] cycloaddition. Attempts to synthesize the right-hand fragment for convergent synthesis are now underway in our laboratory. The results will be reported in due course.

Acknowledgements

This work was supported by a Grant-in-Aid from the JSPS KAKENHI (Grant No. JP17H05051, and JP21H02131, CT).

Keywords: terpenoids • cycloaddition • diastereoselectivity • pre-schisanartanin • arisanlactone

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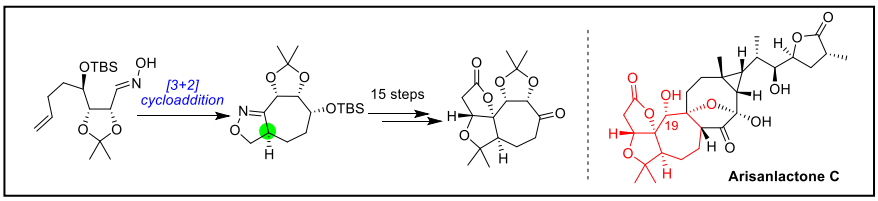

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