Stereoselective Synthesis of 1,4,5-Tri-cis-guaiane Sesquiterpene: First Total Synthesis of (−)-Dendroside C Aglycon

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Supporting Information

ABSTRACT: The first total synthesis of (−)-dendroside C aglycon, consisting of a 1,4,5-tri-cis-guaiane skeleton, from a versatile hydroazulene intermediate has been accomplished. The key features of the syntheses include the stereoselective preparation of the unusual cis-hydroazulene core via a sequence of a unique Dieckmann condensation of the bicyclic lactone system, which was concisely prepared by the tandem conjugate addition and intramolecular allylic alkylation of a butenolide precursor, and construction of the characteristic tricyclic skeleton by a carbene-mediated cyclopropanation.

Recently, the target-oriented synthesis of complex natural products has been remarkably advanced via the discovery of useful catalytic reactions, the development of efficient bond formations, and innovative synthetic planning by eminent organic chemists.1 Despite these improvements, extensive syntheses of architecturally complex natural products, which co-occur in biological pathways, are still not easily achievable on a substantial scale. Thus, the syntheses of structurally or biologically unique natural products from a pluripotent synthetic intermediate have drawn much attention from organic and medicinal chemists.2

Guaianes belong to a family of naturally occurring sesquiterpenes that have recently received considerable attention owing to their unique skeletal features and broad range of biological activities.3 They are characterized by a 5,7-fused hydroazulene framework which usually contains abundant stereogenic centers. Although the syntheses of numerous biologically relevant guaianes, such as arglabin,4 englerin A,5 cladantholide,6 and chinesiolide B,7 have been achieved through enormous efforts, a unified synthetic strategy toward their congeners has not been well established. In particular, synthetic studies toward the 1,4,5-tri-cis-guaiane skeleton have been limited partly due to the highly congested core structure. In pursuit of a synthetic strategy for structurally constrained guaianes possessing potential biological activities, we herein report the first stereoselective total synthesis of dendroside C,8 which consists of an unusual 5/7/3 cis-fused tricyclic system, contiguous seven stereogenic centers, and a unique cyclopropane unit. (Figure 1)

Our synthetic strategy for alloaromadendrane-type guaiane sesquiterpenes is depicted in Scheme 1. We envisioned that the targeted dendroside C aglycon (2) could be accessed by the final

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intermolecular cyclopropanations of the bicyclic intermediate 3, which possesses the requisite carbon skeleton and functionalities for the diverse guaiane natural products. The key intermediate 3 could be obtained through a chemo- and diastereoselective dihydroxylation of hydroazulene 4. The highly formidable 1,4,5-tri-cis-hydroazulene structure could be prepared via an intramolecular C-acyl transfer of bicyclic lactone 5. We anticipated that a tandem conjugate addition/intramolecular allylic alkylation of butenolide 6 would stereoselectively produce the pivotal cyclopentane core 5 of the hydroazulene system as well as three adjacent stereogenic centers. Butenolide 6 could be efficiently prepared by the convergent assembly of readily available phenylsulfonyl acetate 7, epoxide 8, and olefin 9.

Our synthesis commenced with the convergent synthesis of butenolide 6, as shown in Scheme 2. The convergent assembly of three components, as our first task to prepare lactone 11 with a trisubstituted olefin, was essential for our unique strategy. We employed Robinson’s CM protocol recently reported for the synthesis of a sterically demanding olefin unit. Cross metathesis of the germinal dimethyl olefin 10 and the sterically hindered olefin 9 provided intermediate 11 as a mixture of E and Z isomers in a viable chemical yield. The gem-dimethyl olefin 10 was readily prepared by the nucleophilic epoxide opening of (R)-8 with an anion of sulfone 7 followed by spontaneous transesterification. Finally, a sequence of selenylation/selenoxide elimination of 11 furnished butenolide 6.

We next focused on the stereoselective and concise preparation of the cyclopentane core of the guaiane skeleton. Inspired by a tandem conjugate addition/alkylation based on our intramolecular allylic alkylation protocol, we envisaged that enolate 6a resulting from the conjugate addition of an organocuprate to butenolide 6 could be involved in the Pd(0)-assisted intramolecular allylic alkylation. Ultimately, the C4-stereochemistry would control the newly generated three contiguous stereogenic centers of bicyclic lactone 5. The initial attempt for the Cu-catalytic conjugate addition with organozinc, organoaluminum, and a Grignard reagent gave a complex mixture with no desired product (entries 1–3). The in situ generated lithium dimethylcuprate in diethyl ether underwent conjugate addition but did not undergo intramolecular allylic alkylation (entry 4). However, the facile intramolecular allylic alkylation of enolate 6a proceeded in THF to afford the desired bicyclic lactone 5 with nearly complete diasterecontrol (dr = 30:1, entry 5) in 82% yield. The high diastereoselectivity is likely due to the preference of the Pd−π-allyl complex with a less steric interaction. The hydroazulene cores of the guaiane natural products are generally constructed via cycloisomerization or RCM after allylation of cyclopentanecarbaldehyde. However, the highly congested 1,4,5-tri-cis-guaiane systems are not accessible by these synthetic methods. As shown in Scheme 3, we investigated the intramolecular O−C-acyl transfer reactions of 5 to efficiently construct tri-cis-fused guaiane sesquiterpenes after appropriate manipulation of the terminal alkoxy moiety.

The Barbier-type reaction of alkyl halide 12a mediated by magnesium, zinc, and samarium diiodide gave a simple protonated product. The Dieckmann condensation of ester 12b provided the desired hydroazulene system 4a. However, the thermodynamically favored trans-hydroazulene was consistently obtained due to facile epimerization at C5 during the thermal decarboxylation of the hydroazulene product. In this connection, the benzenesulfonyl group turned out crucial for our successful transformation. Reductive desulfonylation with SmI2 at −78 °C of the Dieckmann condensation product 4 after alcohol protection provided the cis-hydroazulene intermediate 13 without epimerization at C5. The sulfone precursor 12 was

### Scheme 1. Retrosynthetic Analysis for the Synthesis of Dendroside C Aglycon

![Scheme 1](image)

### Scheme 2. Convergent Synthesis of Butenolide 6

![Scheme 2](image)

### Table 1. Tandem Conjugate Addition/Intramolecular Allylic Alkylation

<table>
<thead>
<tr>
<th>entry</th>
<th>reagents (equiv)</th>
<th>solvent</th>
<th>result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me₂Zn (1.0), CuOTf (0.1), Pd(PPh₃)₄ (0.05)</td>
<td>toluene</td>
<td>complex mixture</td>
</tr>
<tr>
<td>2</td>
<td>Me₂MgBr (1.0), CuOTf (0.1), Pd(PPh₃)₄ (0.05)</td>
<td>toluene</td>
<td>complex mixture</td>
</tr>
<tr>
<td>3</td>
<td>AlMe₃ (1.0), CuOTf (0.1), Pd(PPh₃)₄ (0.05)</td>
<td>toluene</td>
<td>complex mixture</td>
</tr>
<tr>
<td>4</td>
<td>MeLi (2.0), CuCN (1.0), Pd(PPh₃)₄ (0.05)</td>
<td>Et₂O</td>
<td>1,4-addition product</td>
</tr>
<tr>
<td>5</td>
<td>MeLi (2.0), CuCN (1.0, Pd(PPh₃)₄ (0.05)</td>
<td>THF</td>
<td>82% (dr = 30:1)</td>
</tr>
</tbody>
</table>

*aAfter complete addition of the organometallic reagents at −78 °C, the palladium catalyst was added and the reaction mixture was slowly warmed to 70 °C. Similar results were obtained with different solvents. Only a single diastereomer was observed. The poor solubility of the Pd catalyst in Et₂O might hinder the allylic alkylation. Diastereomers produced by the tandem conjugate addition/intramolecular allylic alkylation were separated by flash column chromatography.*
easily acquired from 5 via a sequence of desulfonylation, TBS-deprotection, mesylation, and benzenesulfonylation. The structure of 4, including stereochemistries, was confirmed by X-ray crystallographic analysis of silylenol ether 16 and a NOE study of desulfonylated hydroazulene 13. To avoid facile epimerization at C5, ketone 13 was readily converted to enol phosphonate 14. Phosphate 14 underwent a chemo and diastereoselective dihydroxylation in the presence of OsO4 to give diol 15 as a single isomer. Finally, acetone protection of diol 15 followed by dephosphorylation provided the versatile intermediate 3 (Scheme 3).

With the key intermediate 3 in hand, we turned our attention to the construction of tricyclic skeleton bearing a unique hydroxymethyl cyclopropane unit (Scheme 4). To elaborate the hydroxymethyl cyclopropane possessing a quaternary carbon center, we conducted a Rh-catalyzed intermolecular cyclopropanation of 3 with ethyl 2-diazopropanoate. Following extensive investigation, we finally obtained cyclopropane 17 using a triphenylacetate (TPA) ligand with a high steric effect at −40 °C in 61% yield (BRSM 97%) and with excellent diastereocontrol (>30:1) of all three stereogenic centers. The observed high diastereoselectivity could be rationalized by a concerted asynchronous mechanism in favor of transition state 17b compared to transition state 17a by less steric interaction between the hydroazulene moiety and the rhodium carbenoid (Scheme 5). To the best of our knowledge, our cyclopropanation is the first synthetic application of catalytic and diastereoselective cyclopropanation using alkyl diazoacetate.

Deprotection of TBS-ether and Barton–McCombie deoxygenation of the resulting alcohol 18 successfully afforded ester intermediate 19. However, final removal of the acetone protecting group failed despite numerous attempts, as ester 19 and the corresponding alcohol resulting from DIBAL-H reduction of 19 were consistently degraded under standard deprotection conditions, such as use of HCl, AcOH, TFA, BCl3, and TsOH. After intensive examination of the reaction conditions with various mild Lewis acids, (−)-dendroside C aglycon (2) was finally obtained by assistance of a lanthanum nitrate catalyst in CH3CN. Spectral data of synthesized 2 was all identical with the reported data of natural (−)-dendroside C aglycon. In summary, we accomplished the first total synthesis of the structurally unique alloaromadendrane-type guaiane sesquiterpene (−)-dendroside C aglycon from the versatile hydroazulene intermediate. Facile construction of the challenging 1,4,5-tri-cis-hydroazulene core with the desired stereochemistries. Elaboration of the characteristic 5/7/3 tricyclic backbone was completed by a late-stage carbene-mediated cyclopropanation with high diastereocontrol. Our versatile synthetic strategy is anticipated to be widely utilized for a variety of guaiane sesquiterpenes. Further studies toward collective syntheses of guaiane sesquiterpenes and evaluation of biological activities are currently underway in our laboratory.
ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03701.

Experimental details and procedures, compound characterization data, and 1H and 13C NMR spectra for all new compounds (PDF)

Accession Codes

CCDC 1562116 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(14) The E/Z isomer of 6a could be easily interconverted in the presence of palladium catalyst via π−σ−π isomerization of the π-allylpalladium complex.
(18) The Cs-stereocenter spontaneously underwent facile epimerization during decarboxylation of 4a under thermal reaction conditions, including basic decarboxylation and Krapcho decarboxylation.

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