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Synthesis of Labdane Diterpenes Galanal A and B from (+)-Sclareolide

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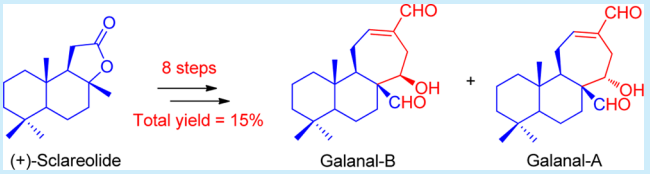
Supporting Information

ABSTRACT: The first chemical synthesis of galanal A and B was achieved by a concise and highly efficient pathway starting from commercially available (+)-sclareolide and features a Wittig reaction and a titanocene-mediated radical cyclization as the key steps.



Galanal A (**1**) and B (**2**) are diterpenes that were first isolated by H. Itokawa et al. in 1986[1] from Zingiberaceae (*Alpinia galanga*) seeds with (+)-labdadienedial (**3**) and miogadial (**4**). The structures of galanal A and B were clearly established on the basis of spectroscopic and chemical evidence. The latter studies[2] of diterpenoids and miogatrial (**5**), based on the pungent principle of Myoga (*Zingiber mioga* Roscoe), have further demonstrated the antifungal[3] and antimicrobial[4] activities and the inhibition of human platelet aggregation and human 5-lipoxygenase.[5] Although synthetic approaches to (+)-labdadienedial (**3**)[6] and miogadial (**4**)[7] have been reported by several groups, there is no synthetic precedent for galanal A and B. The novel galanal motif contains labdane-type A and B six-membered rings and a seven-membered C ring bearing an unsaturated aldehyde and a secondary hydroxyl group with a *trans* configuration. The location of the aldehyde functionality at the junction of the *trans* B/C fused ring would add another dimension of complexity when planning a synthetic strategy. Herein, we report the first chemical synthesis of galanal A and B from commercially available (+)-sclareolide (**6**).

To design a possible synthetic route that addresses the intricate stereochemistry, we sought inspiration from the biochemical pathway used by nature for a potential bioinspired strategy. The large superfamily of labdane-type diterpenoids is now understood to originate from protonation-initiated cyclization of (*E*,*E*,*E*)-geranylgeranyl diphosphate by diterpene cyclase (Figure 1),[8] and the product from this reaction, labdadienyl diphosphate, is then elaborated into diverse labdane-type diterpenoids. Interestingly, labdadienedial (**3**), miogadial (**4**), and miogatrial (**5**) are secondary metabolites resulting from labdadienyl diphosphate via double bond migration and oxidation. Moreover, the coexistence of galanal A and galanal B with substances such as **3**, **4**, and **5** in plants clearly suggests the existence of a common biosynthetic pathway. For these reasons, we speculated that galanal A and B are downstream products of labdadienyl diphosphate in their natural biosynthetic pathway (Scheme 1) and that synthesis of the "C" ring involves cyclization of an intermediate derived from miogadial, miogatrial, or oxidized labdadienyl diphosphate.

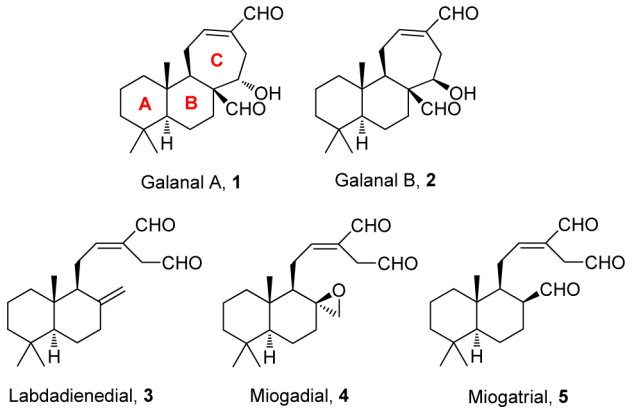


Figure 1. Major labdane-type diterpenes (**1**−**5**) found in *A. galanga* and *Zingiber mioga* Roscoe.

The information obtained from nature and a series of literature searches resulted in the retrosynthetic analysis depicted in Scheme 2. Construction of the all-carbon quaternary center of the key intermediate **I** could be achieved through an intramolecular radical reaction of epoxide **III**. A Lewis acid single electron-transfer reagent would bind to the oxygen atom of the epoxide and trigger the formation of radical intermediate **II**. The radical carbon center would rapidly invert, and the intramolecular equatorial addition of this β-oxy radical to an unsaturated group, such as a nitrile or carbonyl, would avoid the 1,3-diaxial interaction with the methyl group at the bridgehead during the axial addition, leading to a stereoselective 7-*exo*-*dig* cyclization process. The 6−6−7 tricyclic product **I** could then be readily converted to the target compounds galanal A and B.

Therefore, commercially available (+)-sclareolide (**6**) was readily converted to olefin **8** in 68% yield using a two-step protocol[9] and subsequently reduced with $LiAlH_4$ to afford aldehyde **9** in 90% yield, as shown in Scheme 3. After

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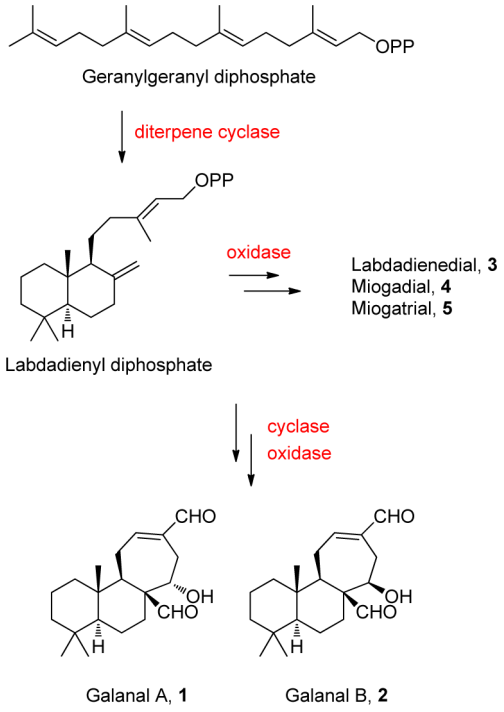
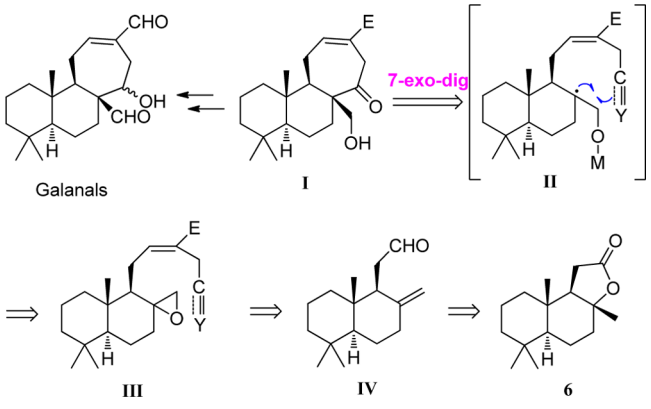
Scheme 1. Hypothetical Biosynthetic Pathway of Galanal A and B



Scheme 2. Retrosynthetic Analysis of Galanal A and B

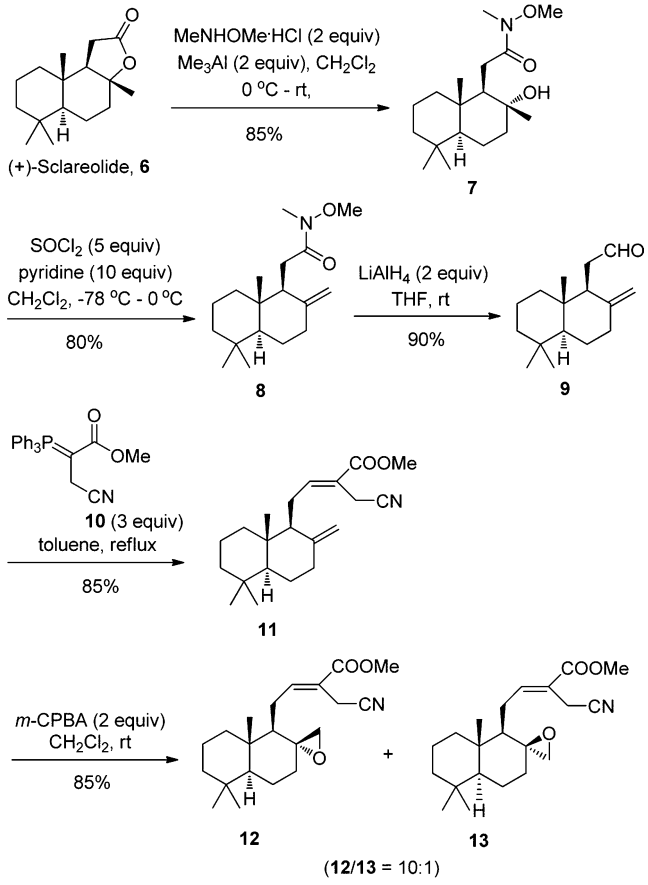


considerable optimization, we were pleased to find that the treatment **9** with a solution of phosphorus ylide **10**[10] in hot toluene efficiently furnished the (*E*)-olefin **11** as a single isomer in 85% yield. The terminal double bond of compound **11** was then selectively epoxidized by *m*-CPBA to afford an inseparable mixture of **12** and **13** in a 10:1 ratio.

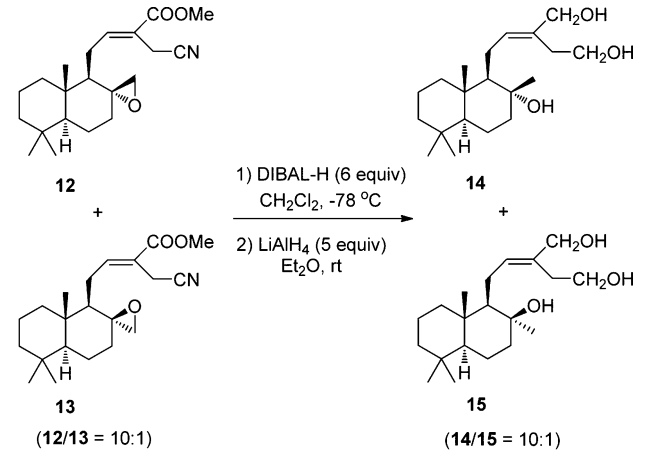
To determine the relative configuration of the epoxide, the 10:1 mixture of **12** and **13** was reduced sequentially with DIBAL-H and $LiAlH_4$ to afford triols **14** and **15** (Scheme 4) in the same ratio. The NMR spectra of the minor product **15** is consistent with the data reported by J. D. Connolly.[11]

Of Lewis acidic electron-transfer reagents, titanocene complexes are the most promising.[12] When the mixture of epoxides **12** and **13** was treated with Cp_2TiCl_2 and Zn metal, the Ti(III) species generated in situ reacted with the oxirane moiety to effect homolytic cleavage of the most substituted C–O bond, to give the more stable tertiary radical intermediate. Subsequent equatorial addition of the β-titanoxyl radical to the nitrile resulted in the generation of an iminyl radical, which

Scheme 3. Synthesis of 12 and 13, Precursors for the 7-*exo-dig* Radical Cyclization



Scheme 4. Conversion of Epoxides 12 and 13 to Triols 14 and 15 for Structural Elucidation



afforded the corresponding ketone after work-up. As predicted, compound **16** with the hydroxymethyl group in an axial position, 1,3 with respect to an angular methyl group, was obtained exclusively in 60% yield (Scheme 5) with trace amounts of side products resulting from ring-opening of the oxirane. The structural connectivity of **16** was confirmed by single-crystal X-ray diffraction analysis, as shown in Figure 2. DIBAL-H reduction of **16** followed by selective oxidation of the primary alcohol with TEMPO[13] gave a 1:5 ratio of galanal A and galanal B. The two final products were separated by

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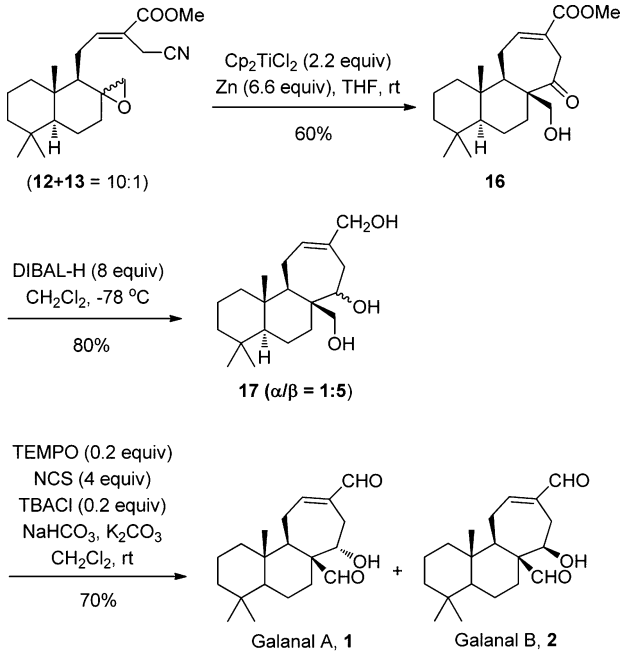
Scheme 5. Synthesis of Galanals through Titanocene-Mediated Radical Cyclization



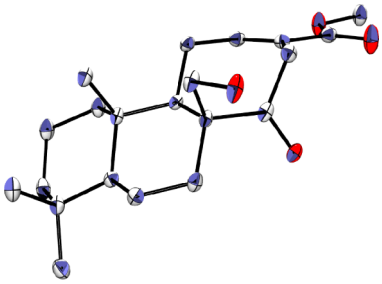


Figure 2. ORTEP diagram from the X-ray crystal analysis of **16** (hydrogen atoms omitted for clarity).

column chromatography and were identical in all respects to authentic samples isolated from Myoga and matched the previously reported data.

In conclusion, novel diterpenes galanal A and B were synthesized in eight steps with a total yield of 15% starting from commercially available (+)-sclareolide. This method shows the importance of a bioinspired strategy in constructing the complex "C" ring that is embedded in the galanals with a minimal number of laborious steps. Gram scale syntheses of galanal B have been achieved for biological investigations.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, X-ray crystallographic data of compound **16**, and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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