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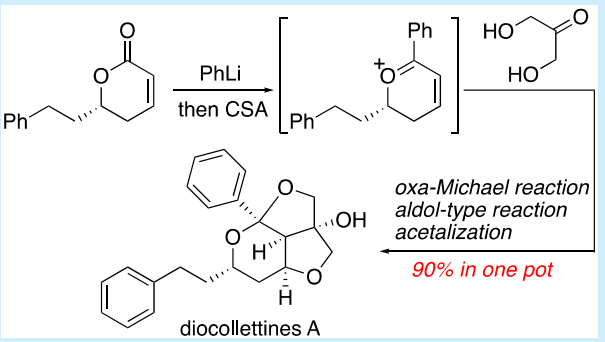
Total Synthesis of Diocollettines A via an Acid-Promoted Oxa-Michael−Aldol−Acetalization Cascade

Misaki Kawamoto, Shuntaro Sato, Masaru Enomoto, Yusuke Ogura, and Shigefumi Kuwahara*

Laboratory of Applied Bioorganic Chemistry, Graduate School of Agricultural Science, Tohoku University, 468-1 Aramaki-Aza-Aoba, Aoba-ku, Sendai 980-0845, Japan

Supporting Information

ABSTRACT: A diastereo- and enantioselective total synthesis of diocollettines A with an unusual oxygen-containing tricyclic ring system has been achieved in 63% overall yield from commercially available 3-phenylpropanal via four steps. The key feature of the present synthesis is an exclusively diastereoselective cascade sequence composed of a *trans*-selective oxa-Michael addition of 1,3-dihydroxyacetone to a 2,3-dihydropyrylium ion intermediate, intramolecular aldol-type reaction, and intramolecular acetalization.



In the course of searching for novel bioactive substances from plants of the genus *Dioscorea* (Dioscoreaceae), Gao and co-workers discovered diocollettines A (**1**) in the extract of rhizomes of the perennial vine *D. collettii* (Figure 1).[1] They

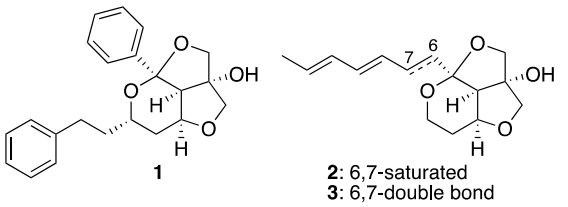
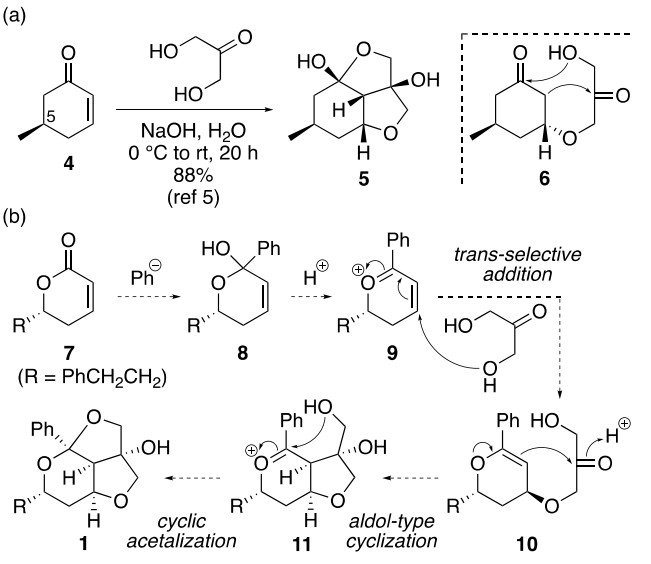


Figure 1. Structures of diocollettines A (**1**) and related natural products.

unambiguously determined its structure, including the absolute configuration, on the basis of NMR experiments, X-ray crystallography, and ECD spectral analysis and revealed its moderate cytotoxicity against human lung cancer NHL-H460 cell lines (IC_{50} 20.15 μM). Diocollettines A (**1**) features an oxygen-containing tricyclic molecular architecture composed probably of a diarylheptanoid derivative and a three-carbon unit.[2] Although two secondary metabolites **2** and **3** (streptoglycerides A and B, respectively) of actinomycete origin were recently reported to share the same tricyclic core,[3] the 6/5/5 heterocyclic scaffold incorporated in **1** is quite rare in natural products. The unique structural characteristics of **1** attracted the interest of synthetic chemists, which most recently led to the first total synthesis of **1** by Ito and co-workers.[4] Their synthesis was successfully achieved in 7 steps from a known aldehyde but required HPLC separation of diastereomers generated with modest diastereoselectivity by an intermolecular aldol reaction employed as the key step. We describe herein an exclusively diastereoselective single-step synthesis of **1** via a cascade sequence in 90% yield from a known chiral lactone, which in turn was prepared in ca. 70% yield through 3 steps from the same starting aldehyde as used in the first synthesis.

Our synthetic plan for **1** (Scheme 1b) is based on Riss's observation that 5-methyl-2-cyclohexenone **4**, when treated

Scheme 1. (a) Example of the Construction of an Analogous Tricyclic Ring System and (b) Synthetic Plan for 1



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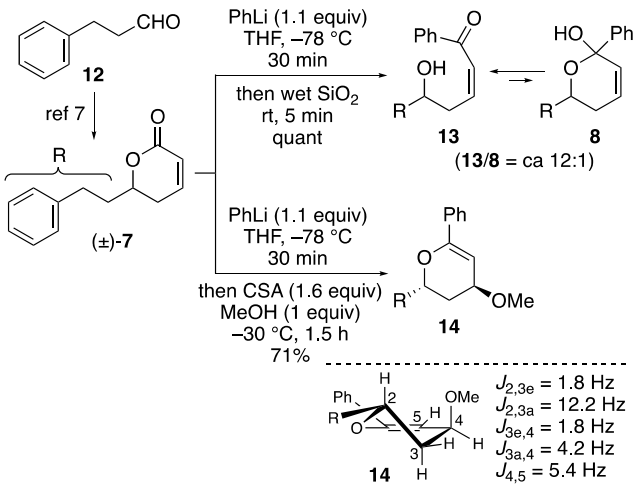
with 1,3-dihydroxyacetone (DHA) under basic conditions, gave tricyclic product **5** diastereoselectively in an excellent yield of 88% (Scheme 1a).[5,6] This transformation can be rationalized by assuming the following three consecutive reactions: (1) oxa-Michael addition of DHA to enone **4**, which proceeds trans to the C5 methyl group; (2) intramolecular aldol reaction of the resulting adduct **6**; and finally (3) intramolecular hemiacetalization to furnish the tricycle **5**. Inspired by this precedent, in which the cyclohexenone derivative **4** served as the Michael acceptor, we envisaged a cascade sequence involving the 2,3-dihydropyrylium ion **9** as the pivotal intermediate. The cyclic oxocarbenium ion **9** would possibly undergo the oxa-Michael addition of DHA to give keto enol ether **10**, which would then lead to bicyclic oxonium ion **11** via an intramolecular aldol-type reaction under acidic conditions. Finally, acetal formation from the hydroxy oxonium ion **11** should afford **1**. The generation of the key transient intermediate **9** would be possible by treating cyclic hemiacetal **8** with an appropriate acid, and the hemiacetal **8**, in turn, would readily be obtained by the addition of a phenyl anion species to known chiral lactone **7**. Since the reactions from **8** to **9** and from **10** to **11** were both considered to be promoted by acid, we expected that the conversion of **8** into **1** could be realized in a cascade manner.

To preliminarily assess the diastereoselectivity of the oxa-Michael addition reaction between **9** and DHA, we first conducted a model experiment using (±)-7, prepared from **12** by a known three-step sequence,[7] and methanol as the nucleophile (Scheme 2). Addition of PhLi to (±)-7 and

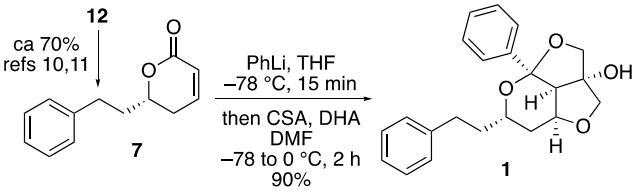
Scheme 2. Addition of Phenyllithium to (±)-7 Followed by Treatment with Wet SiO_2 or CSA/MeOH



quenching of the resulting mixture with sat. aq NH_4Cl to obtain **8** (the precursor of **9**) gave unexpectedly a considerably complex mixture, probably due to the acidic nature of the reaction medium after quenching, which might have induced some additional reactions. Fortunately, when the reaction was quenched with wet silica gel, the clean and nearly quantitative formation of an equilibrium mixture consisting of the cyclic hemiacetal **8** (produced as a single diastereomer) and its ring-opened form **13** (*Z*-form) was observed by ^{1}H NMR analysis of the crude reaction product, which showed the latter to be significantly predominant (**13**/**8** = ca. 12:1).[8] Upon exposure to prolonged silica gel column chromatography, the mixture gradually changed into a more complicated product mixture, which made us decide to treat the mixture of **13** and **8** in situ with acidic methanol to bring about the oxa-Michael reaction. Thus, a reaction mixture prepared by the addition of PhLi (1.1 equiv) to (±)-7 in THF at −78 °C followed by 30 min of stirring was treated, without extraction, with CSA (1.6 equiv) and MeOH (1 equiv) successively, and the resulting mixture was stirred at −30 °C for 1.5 h. This one-pot process afforded, as expected, the desired cyclic enol ether **14** in an exclusively *trans*-selective manner in 71% yield.[9] The relative stereochemistry of **14** was assigned on the basis of the ^{1}H NMR coupling constants depicted in Scheme 2.

Having established the desirable *trans*-selective formation of **14**, we applied the protocol to the one-pot synthesis of **1** from **7** using DHA instead of methanol (Scheme 3). The optically

Scheme 3. One-Pot Synthesis of 1 from 7 via an Oxa-Michael−Aldol−Acetalization Cascade



active form of **7** (96% ee) was prepared from **12** in ca. 70% yield by a three-step sequence comprising an asymmetric allylation,[10] esterification of the resulting homoallylic alcohol with acryloyl chloride, and ring-closing metathesis using Grubbs first-generation catalyst.[11] After exposing the *α,β*-unsaturated lactone **7** to PhLi in THF, the resulting mixture was successively treated with CSA, DHA (dimer), and DMF, providing **1** as a single diastereomer in an excellent yield of 90%; the addition of DMF was necessary to dissolve the crystalline DHA dimer. The ^{1}H and ^{13}C NMR spectra of **1** obtained as a colorless crystalline solid (mp 127.3−128.8 °C) were in good agreement with those of natural diocollettines A. The specific rotation of **1** ($[\alpha]^{20}_D$ −130 (*c* 0.19, toluene); $[\alpha]^{20}_D$ −150 (*c* 0.10, MeOH)) also matched the value reported for the natural product ($[\alpha]^{20}_D$ −126.82 (*c* 0.104, MeOH)).[1a,12]

In conclusion, the enantio- and diastereoselective total synthesis of diocollettines A (**1**) was accomplished in a surprisingly excellent yield of 90% from the known *α,β*-unsaturated lactone **7** by a one-pot transformation consisting of the addition of PhLi to **7** (**7** → **8**), acid-promoted dehydration of **8** to give the 2,3-dihydropyrylium ion **9**, and the oxa-Michael−intramolecular aldol−intramolecular acetalization cascade (**9** → **10** → **11** → **1**). The overall yield of **1** obtained in 4 steps from the commercially available aldehyde **12** amounted to 63%. Our efforts toward the total synthesis of the related natural products streptoglycerides A and B (**2** and **3**) are now underway and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04074.

Experimental procedures, characterization data, and NMR spectra for new compounds (PDF)

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AUTHOR INFORMATION

Corresponding Author

*E-mail: shigefumi.kuwahara.e1@tohoku.ac.jp.

ORCID

Masaru Enomoto: 0000-0001-6342-217X
Yusuke Ogura: 0000-0002-8646-9322
Shigefumi Kuwahara: 0000-0002-5839-6875

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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(12) The specific rotation of **1**, when measured as a methanol solution, sometimes varied over time. This mutarotation would be probably due to adventitious contamination of **1** with a minute amount of acidic impurity, which would promote the cleavage of the acetal moiety.

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