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Improved total synthesis of (±)-Tetragocarbone A

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ABSTRACT

Stereoselective total synthesis of (±)-tetragocarbone A isolated from the propolis of an Australian stingless bee, *Tetragonula carbonaria*, has been developed by focusing on the latent symmetry of **1**. The requisite 1*R**, 3*R**, 6*S** stereogenic centers were selectively installed by hydroxy group directing reactions including the late stage desymmetrization of the 1,3-diketone. The target natural product was successfully prepared in 12 steps from phloroglucinol on 300 mg.

1. Introduction

Tetragocarbone A (**1**) was isolated from the propolis of an Australian stingless bee, *Tetragonula carbonaria*.[1] Among several highly substituted cyclic polyketides that have been isolated, such as **2**~**5**, **1** features a highly complex cyclohexanone skeleton with eight substituents and a cinnamic acid ester (Fig. 1).[2,3] The relative structure of **1** was proposed by NMR analysis and the first total synthesis of **1**. The absolute stereochemistry of **1** was elucidated by X-ray structure analysis of the key synthetic intermediates and comparison of the chiral HPLC profiles of the synthetic and naturally occurring **1**.[1]

The first total synthesis of **1** was achieved in 13 steps starting from phloroglucinol (**6**) in 1.9% overall yield (Scheme 1).[1] Although the first synthesis contributed to the structure elucidation, it suffered from low stereoselectivities in the following steps: (i) $LiAlH_4$ reduction of **7** (dr = 10:3), (ii) esterification of diol **8** to give a mixture of mono- and diesters, and (iii) dihydroxylation of **10** to give **11** (dr = 1:1). These results suggested that the above intermolecular reactions would not be suitable for the practical synthesis of **1**.

2. Results and discussion

In this paper, we would like to report a stereoselective total synthesis of (±)-**1** focusing on the latent symmetry of the natural product (Scheme 2).[4] Tetragocarbone (**1**) was initially divided into the cinnamic acid and the cyclohexanone core **12** in a retrosynthetic manner. The molecular complexity of **12** was thought to be reduced to **13** and **14** possessing symmetrical elements. We set hydroxyl-directing reactions: the late stage desymmetrization of **13** and dihydroxylation of **15**, for the introduction of the requisite stereocenters. Alcohol **15** would be elaborated by the stereoselective reduction of enone **16**.

The synthesis commenced with the stereoselective synthesis of acetate **15**. Alcohol **7** was prepared from phloroglucinol (**6**) according to the literature (Scheme 3).[1] Alcohol **7** was smoothly reduced using $NaBH_4$ in MeOH to give (1*R**,3*S**)-**17** in a stereoselective manner. On the other hand, switching to $LiAlH_4$ afforded a 10:3 mixture of (1*R**,3*R**)-**8** and (1*R**,3*S**)-**17**.[1] Reduction of acetate **16** with $NaBH_4$ in MeOH gave (1*R**,5*S**)-**15** as a single isomer. The stereochemistry of **15** was unambiguously determined by the total synthesis of **1** from **15**.

Proposed reaction mechanism for the stereoselective reductions of **7** and **16** is depicted in Scheme 4. Senda et al. reported that reduction of ketone **18** with $LiAlH_4$ or $NaBH_4$ to give **19a** in a stereoselective manner (eq. (1)).[5,6] The stereochemical outcomes were rationalized by the Cieplak effect in which the orbital interaction between the axial carbon-carbon bond and the carbonyl π-orbital plays an important role in the selective hydride approach.[7] We assumed that the Cieplak effect would be adopted to the stereoselective reduction of **7** and **16** (eqs. (2) and (3), model A and B). On the other hand, reduction with $LiAlH_4$ instead of $NaBH_4$ afforded

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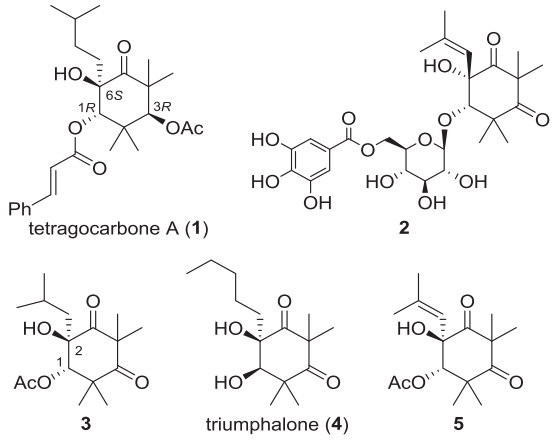
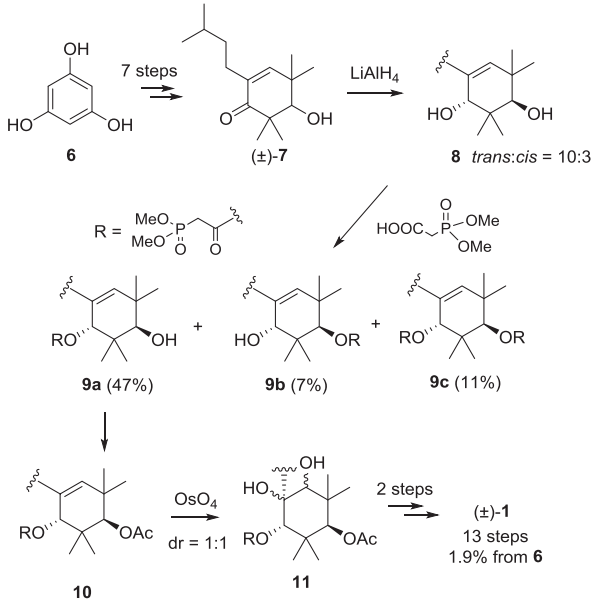


Fig. 1. Structures of cyclic polyketides sharing a tetra-methylcyclohexanone skeleton. No names are given for **2**, **3**, and **5**.



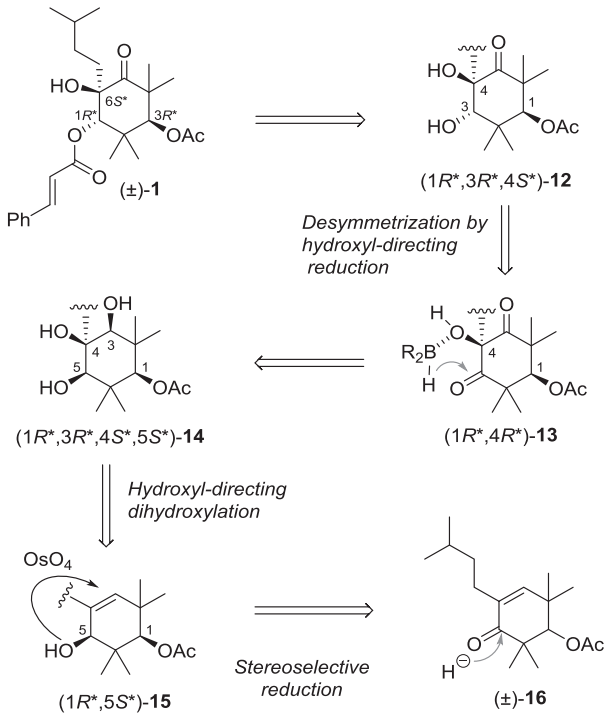
Scheme 1. First total synthesis of **1** from phloroglucinol.

(1*R**,3*R**)-**8** as a major product from **7** (eq. (4)). The selectivity switching would be ascribed to the hydroxyl-directing model C in which the hydride is predominantly transferred in an intramolecular fashion.

With the key intermediate (1*R**,5*S**)-**15** in hand, we next examined stereoselective transformation of **15** to the symmetrical triol **14** (Scheme 5). Dihydroxylation of **15** using a stoichiometric amount of OsO_4 in pyridine was not fruitful to give a mixture of **14**, **20**, and the unexpected ketone **21**. Although the stereochemistry of **21** could not be determined, these results implied that the intermolecular oxidation was not effective. These results led us to examine the hydroxyl-directing dihydroxylation reaction developed by Donohoe et al.[8,9]

Pleasingly, the stereoselectivity was significantly improved by treatment of **15** with OsO_4 in the presence of TMEDA in CH_2Cl_2 at low temperature to provide the desired triol **14** in 81% yield as a single isomer. In addition, the undesired formation of **21** was suppressed under the conditions.

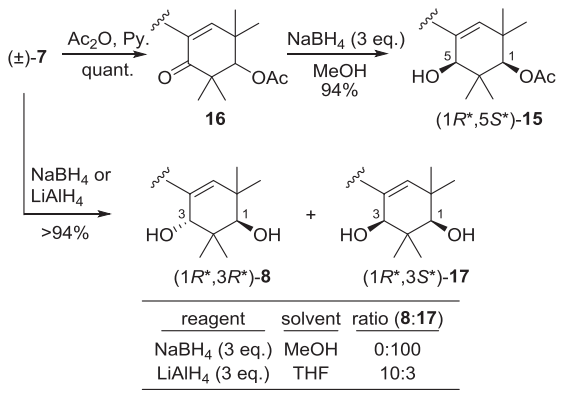
Triol **14** was smoothly converted to the symmetrical 1,3-diketone **13** by AZADO-catalyzed oxidation reaction[10,11] (Scheme 6). The stereoselective reduction of **13** was successfully achieved under the Saksena reduction condition[12] using $NaBH(OAc)_3$ in AcOH to give **12** as a sole product. It is conceivable that the tertiary hydroxy group participates to the directing effect to conduct the preferential intramolecular hydride transfer (model D). *trans*-Diol **12** was found to be labile and immediately employed for the next esterification reaction. Although diol **12** did not react with cinnamic acid under the conventional esterification condition using EDCI, DMAP, and Et_3N, the esterification was significantly promoted by the Shiina's esterification.[13,14] Treatment of **12** with 2-methyl-6-nitrobenzoic anhydride (MNBA) in the presence of DMAP furnish (±)-tetragocarbone A (**1**) in 76% from **14** in 3 steps. Spectroscopic data of the synthetic **1** were identical with those of the authentic data.[1]



Scheme 2. Retrosynthetic analysis.

3. Conclusion

We have developed an efficient stereoselective synthesis of **1**



Scheme 3. Stereoselective reduction of **7** and **16**.