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Enantioselective divergent approaches to both (−)-platensimycin and (−)-platencin

Sho Hirai, Masahisa Nakada *

Department of Chemistry and Biochemistry, ASE Graduate School, Waseda University, 3-4-1 Ohkubo, Shinjuku-ku, Tokyo 169-8555, Japan

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ABSTRACT

Enantioselective divergent approaches to (−)-platencin and (−)-platensimycin have been developed. A rationally designed chiral synthetic intermediate, possessing a useful α,β-unsaturated sulfone functionality, which served as a masked ketone as well as a good Michael acceptor, was successfully prepared via the highly enantioselective catalytic asymmetric intramolecular cyclopropanation (CAIMCP) developed in our laboratory.

1. Introduction

The emerging threat of multi-resistant bacteria, such as methicillinresistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), penicillin-resistant *Streptococcus pneumonia* (PRSP), and so on, has made researchers find new antibiotics having a new mode of action. Under such situation, the research group at Merck isolated new class antibiotics, (−)-platensimycin (**1**)[1] (Fig. 1) and (−)-platencin (**2**)[2] from *Streptomyces platensis* MA 7327 and 7339, respectively. (−)-Platensimycin (**1**) is a potent and selective inhibitor of FabF, the condensing enzyme, which catalyzes elongation in bacterial fatty acid synthesis.[1] (−)-Platencin (**2**) is a moderate inhibitor of both FabF and FabH, the enzyme catalyzing the initial condensation in bacterial fatty acid synthesis.[2] Because of their new modes of action, **1** and **2** show potent, broad-spectrum Gram-positive antibacterial activity, and also exhibit no cross-resistance to antibiotic-resistant bacteria, including MRSA and VRE.[1,2]

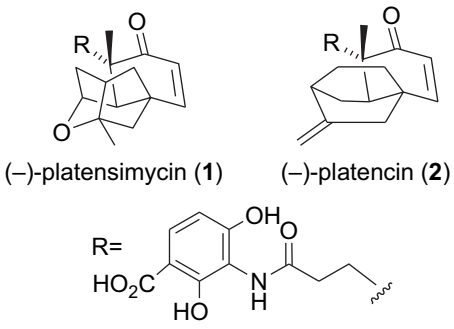

Fig. 1. Structures of (−)-platensimycin (**1**) and (−)-platencin (**2**).

These compounds have a same side-chain including 3-amino-2,4-dihydroxybenzoic acid as the common structure; however, both compounds have unique structural features in their polycyclic moieties. (−)-Platensimycin (**1**) has a tetracyclic framework including a cyclic ether while (−)-platencin (**2**) has a tricyclic framework, which consists of only carbons.

The new modes of action and unique structural features of these new antibiotics **1** and **2** have attracted much interest of synthetic chemists and medicinal scientists, and a number of research groups have reported total syntheses[3–6] and SAR studies.[7] Because of their novelty in the structure and biological activity, we were also interested in the enantioselective total synthesis of compounds **1**, **2**, and their new derivatives. The structural similarities between **1** and **2** led us to develop enantioselective divergent approaches to these antibiotics, and recently, we completed a formal total synthesis of **2**.[5] During the synthesis of **2**,[5] we found that the intermediate in the total synthesis of **2** would be used for the total synthesis of **1**, too. Therefore, we started the total syntheses of **1** via the same key intermediate, and herein report the full detail of the enantioselective formal total synthesis of **2** and a new enantioselective formal total synthesis of **1** via the enantioselective divergent approaches.

* Corresponding author. Tel.: +81352863240; e-mail address: mnakada@waseda.jp (M. Nakada).

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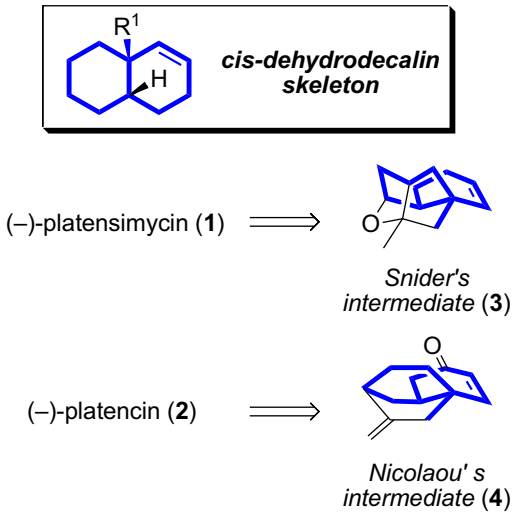
2. Results and discussions

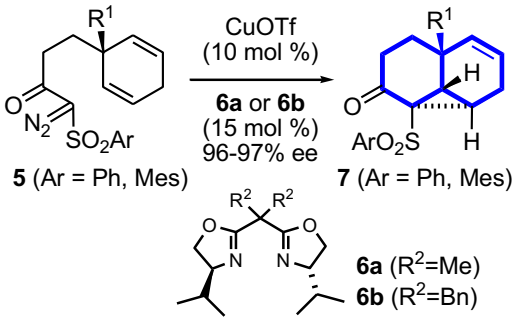
2.1. Retrosynthetic analysis of 1 and 2

In the course of the retrosynthetic analysis of **1** and **2**, we identified a common carbon framework, a *cis*-dehydrodecalin skeleton possessing a bridgehead stereogenic quaternary carbon, which was hidden within their structures (Scheme 1). The *cis*-dehydrodecalin skeleton was also found in intermediates reported earlier by other research groups, including Snider's intermediate **3**[3b] for **1** and Nicolaou's intermediate **4**[4a] for **2**. Therefore, we set **3** and **4** as targets of our formal total synthesis.



Scheme 1. *cis*-Dehydrodecalin skeleton hidden in **1** and **2**.

We have reported a highly enantioselective catalytic asymmetric intramolecular cyclopropanation (CAIMCP) of α-diazo-β-keto sulfones with CuOTf and bisoxazoline ligand **6**.[8] The cyclopropanes thus prepared have been successfully utilized for the enantioselective total synthesis of some natural products in our laboratory.[9] Indeed, tricyclo[4.4.0.0]decene derivatives **7** have been easily prepared in a highly enantioselective manner from **5** by the CAIMCP (Scheme 2).

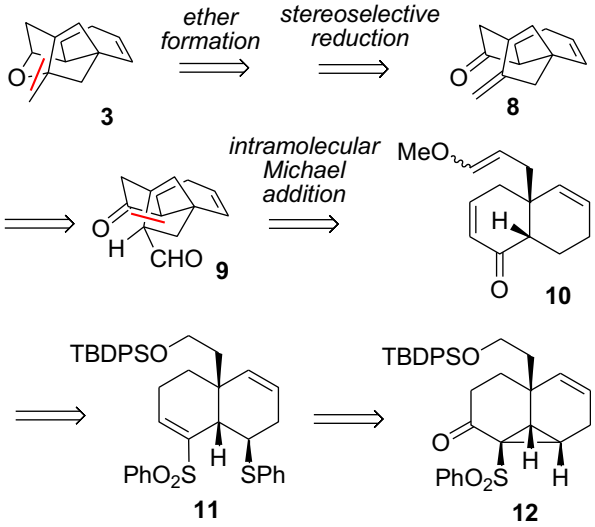


Scheme 2. Preparation of **7** by catalytic asymmetric intramolecular cyclopropanation (CAIMCP).

Compounds **7** can serve as key synthetic intermediates because they possess useful functional groups including a cyclopropane, an alkene, and a ketone. As compounds **7** incorporate the above mentioned *cis*-dehydrodecalin skeleton with a quaternary stereogenic center; hence, we surmised that **7** would be suitable for the synthesis of **3** and **4**, and undertook retrosynthetic analysis of **3** and **4** starting from **7**.

2.2. Retrosynthetic analysis of 3

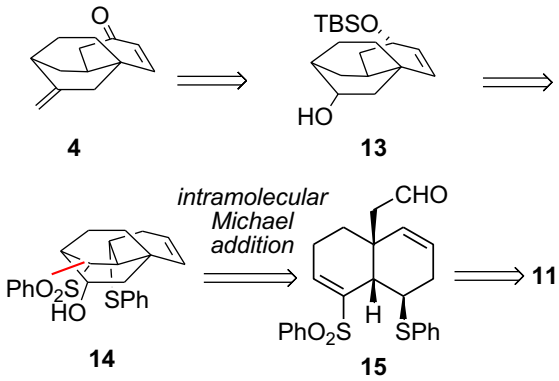
In our retrosynthetic analysis of **3** (Scheme 3), compound **3** would be formed by the acid-catalyzed intramolecular ether formation of the corresponding alcohol, which would be obtained by the stereoselective reduction of ketone **8**. Ketone **8** could be derived from keto-aldehyde **9** by converting the aldehyde group to the *exo*-methylene. We proposed that tricyclic keto-aldehyde **9** could be obtained by the acid-catalyzed intramolecular Michael reaction of ketone **10** or the corresponding aldehyde, which would be obtained from compound **11** since an α,β-unsaturated sulfone can be converted to a ketone and a C-1 elongation of the bridgehead substituent of **11** would furnish the methyl alkenyl ether moiety in **10**. Compound **11** was thought to be prepared via the ring-opening reaction of cyclopropane **12** and following appropriate transformations.



Scheme 3. Retrosynthetic analysis of **3**.

2.3. Retrosynthetic analysis of 4

Our retrosynthetic analysis of **4** is shown in Scheme 4. Compound **4** was thought to be formed from alcohol **13** via oxidation, Wittig olefination, deprotection of the TBS group, and oxidation of the resulting alcohol. Alcohol **13** would be obtained from **14** by reductive removal of all the sulfur-containing functional groups at the same time, followed by allylic oxidation to introduce the hydroxy group, and selective TBS ether formation. As an α,β-unsaturated sulfone is a good Michael acceptor, tricyclic compound **14** could be formed by the intramolecular Michael addition of aldehyde **15**. Finally, aldehyde **15** would be easily prepared from



Scheme 4. Retrosynthetic analysis of **4**.