ORGANIC LETTERS

2013
Vol. 15, No. 14
3782–3785

# Short Route to Platencin

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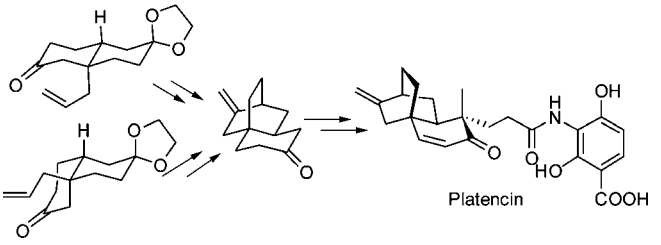
**Received June 21, 2013**

## ABSTRACT




**The synthesis of the complex tricyclic core of the terpenoid antibiotic platencin is achieved in a concise, protecting group-free and stereoselective manner. A flexible approach that highlights the intramolecular aldol reaction as the key step toward the construction of the bicyclo[2,2,2]octane ring from an angular allyl decalone in both the *trans*-fused and the *cis*-fused forms is demonstrated.**

Antibiotics are precious resources in the fight to combat bacterial infections caused by pathogenic organisms. Although the discovery of penicillin[1] represents a milestone in modern medicine followed by the development of antibiotics in the 20th century, the effectiveness of available antibiotics has been decreasing steadily as bacteria have evolved mechanisms to foil them. This growing prevalence of multidrug-resistant (MDR) bacteria represents a major threat to human health and makes the identification and development of new classes of antibiotics imperative. As part of an ongoing and global campaign to identify the next generation of antibiotics, Singh and coworkers based at Merck discovered two new superbug leads: platensimycin[2] **1** and platencin[3] **2** (Figure 1) isolated from strains of *Streptomyces platensis* MA7327 and *Streptomyces platensis* MA7339, respectively.

Platensimycin with nanomolar potency ($IC_{50}$ 48 nM) is active against methicillin-resistant *Staphylococcus aureus* (MRSA) and acts by blocking an enzyme, FabF, a selective inhibitor of fatty acid acyl carrier protein synthase-II, in which bacteria are required for the assembly of their cell membranes. Platencin is a balanced dual inhibitor of both fatty acid acyl carrier protein synthases II (FabF) and III (FabH). As a consequence, it shows broad-spectrum and potent antibacterial activity against all key pathogens harboring resistance to current antibiotics. More specifically, these compounds bind to the malonyl CoA binding site and uniquely inhibit an acyl-enzyme intermediate.

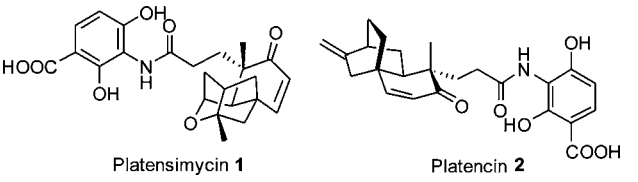



**Figure 1.** Structures of platensimycin **1** and platencin **2**.

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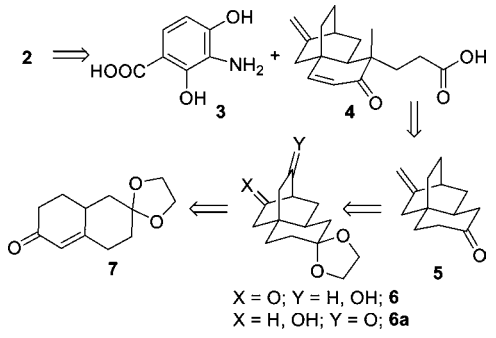
10.1021/ol401760e 
**Published on Web 07/08/2013**

The promising therapeutic potential and intriguing molecular architecture of platencin have attracted great interest from the scientific community, leading to more than 15 total and formal syntheses of platencin during the last five years. The tricyclic core of platencin is comprised of a bicyclic octane ring fused with a cyclohexenone, with an *exo*-cyclic double bond and enone functionalities. The various approaches previously used to construct typical bicyclooctanes comprise of homoallyl−homoallyl radical rearrangement of bicyclo[3.2.1]octane to bicyclo[2.2.2]octane,[4−8] intramolecular Diels-Alder reaction,[9−11] intramolecular Michael addition,[12] Michael addition followed by aldol condensation,[13] ring closing metathesis reaction,[14] Pinacol coupling reaction[15] and radical cyclization reactions.[16−18] In the present context, we have exploited an intramolecular aldol reaction for the construction of bicyclooctane skeleton.

Retrosynthetic simplification of platencin **2** is depicted in Scheme 1. The target synthesis was expected to be completed by the final stage elaboration of the core **5** to get **4** followed by coupling with aniline **3** (3-amino-2,4-dihydroxybenzoic acid) to form the amide bond realizing **2**. We envisaged **5** as an advanced key intermediate that can be obtained from two tetracyclic compounds **6** and **6a** through three-step functional group manipulations. The compounds **6** or **6a** in turn are easily accessible from tricyclic enone **7** through a four step sequence using an intramolecular aldol reaction as the key step (*vide infra*).

**Scheme 1.** Retrosynthetic Analysis of Platencin **2**




Our approach relied on a prominent and flexible method, an intramolecular aldol reaction for the construction of the bicyclo[2.2.2]octane moiety through decalone **8** or **8a** (Figure 2). The selection of ketone or alcohol functionality in adducts **6** or **6a** for proceeding further depends on the stereochemistry of decalone **8** (*trans*-fused) and **8a** (*cis*-fused). Thus, if the decalone is *trans*-fused (**8**), the hydroxyl group of adduct (**6**) would be dehydroxylated first and the carbonyl group will be converted to *exo*-methylene group. Simultaneously, if the decalone is *cis*-fused (**8a**), the carbonyl group in the adduct (**6a**) will be deoxygenated first and the hydroxyl group would be oxidized and transformed to *exo*-methylene group to obtain the target motif with desired stereochemistry.

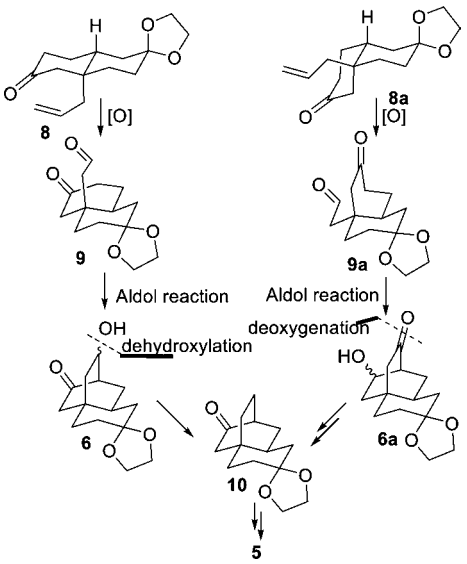



**Figure 2.** Possibility of elaboration of both *trans*- and *cis*-decalones **8** and **8a** to common intermediate **5**.

Accordingly, our journey began with the Robinson annulation reaction of ketone **11** with methyl vinyl ketone. The major problem in Robinson reaction with MVK is anionic polymerization, and polyalkylation which led to poor yields.[18] We optimized this reaction with a new procedure which produced excellent yield for Robinson product (Scheme 2). The cyclohexanone **11** was treated with methyl vinyl ketone in the presence of a catalytic amount of *t*-BuOK and anhydrous $Na_2SO_4$ in dry *t*-BuOH at room temperature to provide the tricyclic enone **7** in 90% yield. $Na_2SO_4$ proved to be a critical additive and was found to be more effective than molecular sieves and

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$K_2CO_3$ (see Table 1). It was observed that these reagents accelerate the rate of reaction by removing the water that is produced during the condensation reaction.

**Scheme 2.** Preparation of Enone **7** and Studies for 1,4-Addition

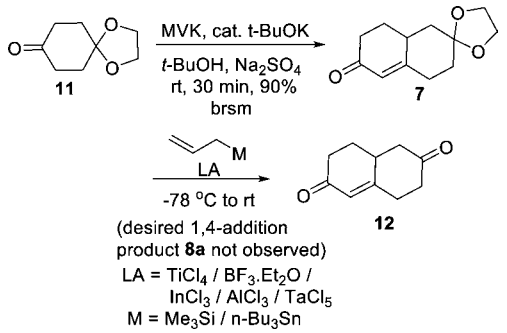



**Table 1.** Reaction Conditions for Reaction of Ketone **11** with Methyl Vinyl Ketone

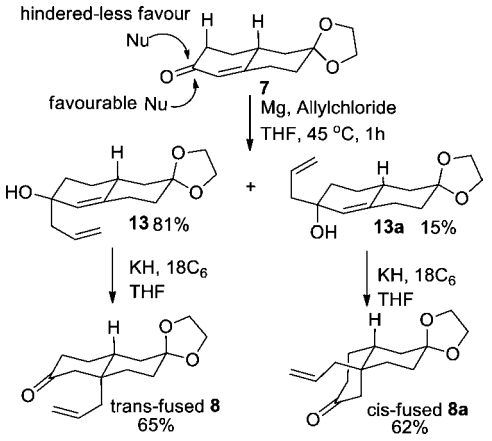
| entry | reaction conditions | yield (%)[a] |
|---|---|---|
| 1 | cat. *t*-BuOK in *t*-BuOH/THF (1:1), 0 °C to rt, 6 h | 72% |
| 2 | cat. *t*-BuOK in *t*-BuOH, rt, 8 h | 77% |
| 3 | cat. *t*-BuOK in *t*-BuOH, 4 Å MS, rt, 18 h | 30% |
| 4 | cat. *t*-BuOK in *t*-BuOH, $K_2CO_3$, rt, 30 min | 87% |
| 5 | cat. *t*-BuOK in *t*-BuOH, $Na_2SO_4$, rt, 30 min | 90% |

[a] Yields calculated based on recovery of starting materials.

Our next task was to install the allyl group at the angular position. This was anticipated in two routes by either a direct 1,4-addition, which would result in a *cis*-decalone **8a** or a 1,2-addition followed by Cope rearrangement. The *cis*-stereochemistry was expected as nucleophilic addition should occur from the convex outer face of the enone.[19] However, our initial attempts following the Hosomi-Sakurai reaction[19d] (for 1,4-conjugate addition reaction) using $TiCl_4$ and allyltrimethylsilane were not successful and resulted in a product **12** with simple ketal deprotection. Even when other Lewis acids such as $AlCl_3$, $BF_3 \cdot Et_2O$, $InCl_3$ and $TaCl_5$ in the presence of allyltributylstannane or allyltrimethylsilane reagents were explored under different solvent conditions, we could observe the formation of the undesired diketone **12** as the only product without any success for the formation of the allylated product (Scheme 2). Thus, we were left with an only option to adopt a two-step procedure wherein a enone **7** could be subjected to Grignard reaction with allylmagnesium chloride and the resulting product would then undergo a [3,3]-sigmatropic rearrangement to provide the desired 1,4-addition product.

Thus, enone **7** was subjected to a Grignard reaction with allylmagnesium chloride in THF to provide dienol **13** and **13a** as an 81:15 diastereomeric mixture in 96% overall yield. The stereochemical outcome of the Grignard addition was predicted based on analysis of molecular models with the approach of the nucleophile coming from the least-hindered face to produce the major diastereomer **13**. Both the diastereomers **13** and **13a** were separated by column chromatography and each was further subjected to oxy-Cope rearrangement. At first the dienol **13** in the presence of KH and 18-Crown-6 in THF at reflux temperature underwent oxy-Cope rearrangement to provide angular allyl product **8** (white solid) as the exclusive diastereomer in 65% yield.[20] The structure of decalone **8** was confirmed as the *trans*-fused system by X-ray crystallography (ORTEP structure showed in Supporting Information).[21] Formation of the *trans*-decalone also suggests that the 1,2-addition of allyl group to the enone **7** occurred from the less hindered side and the subsequent [3,3]-sigmatropic rearrangement proceeded in a stereocontrolled manner through a six membered transition state **14** as depicted in Figure 3. In similar way the minor isomer **13a** was subjected to oxy-Cope rearrangement to produce **8a** (colorless thick liquid) in 62% yield (Scheme 3). This rearrangement was expected to take place through the transition state **14a** (Figure 3).

**Scheme 3.** Preparation of *trans*- and *cis*-Fused Decalones **8** and **8a**



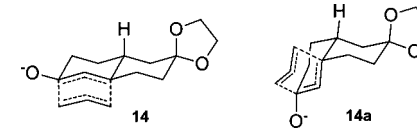




**Figure 3.** Transition state structures of anionic oxy-Cope rearrangement.

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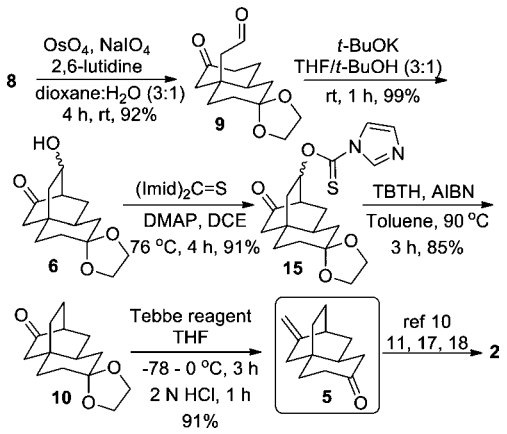
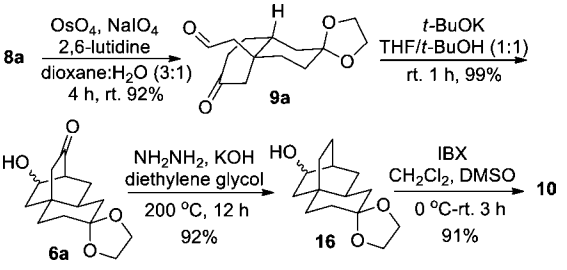
**Scheme 4.** Synthesis of Advanced Key Intermediate **5** of Platencin




With both decalones in hand, we further proceeded to achieve the target tricyclic core **5** in two distinct pathways via an intramolecular aldol reaction. Initially, the terminal double bond in compound **8** was converted to aldehyde in one pot by oxidation with $OsO_4$ in the presence of 2,6-lutidine followed by degradation with $NaIO_4$ to produce compound **9** in 92% yield.[22] The dicarbonyl compound **9** was then subjected to crucial intramolecular aldol reaction in the presence of *t*-BuOK in *tert*-butanol and THF to afford the tetracyclic core **6** as diastereomeric mixture in 99% yield.[23] As we mentioned earlier the hydroxyl functional group in **6** was deoxygenated under Borton-McCombie reaction condition after converting the alcohol to thiocarbamate **15** followed by treatment with tri-*n*-butyltin hydride (TBTH) in the presence of AIBN as the radical initiator to yield tetracyclic ketone **10**.[24] Our initial attempts to convert the ketone **10** to *exo*-methylene (olefination) by a Wittig reaction resulted in formation of an unidentified byproduct.[25] However, this challenge was easily overcame by proceeding the olefination using Tebbe reagent to provide the olefin, which subsequently exposed to 2 *N* HCl provided the required key intermediate enone **5** in 91% yield (Scheme 4). Spectral data of the resulted olefin was compared and found to be identical to that of the previously reported data.[10,11,17,18] Thus, the synthesis of **5** constituted a formal synthesis of platencin **2** as this carbon skeleton has been converted to platencin previously by other groups.[10,11,17,18]

In our next attempt (Scheme 5), we tried to convert the minor isomer *cis*-decolone (**8a**) to the tetracyclic ketone **10** which was achieved from *trans*-decalone and elaborated to the target enone **5**. Accordingly compound **8a** was converted to aldol adduct **6a** followed by the similar two step procedure (as used for the **6**), i.e., oxidative cleavage of olefin to aldehyde followed by an intramolecular aldol reaction.[23] As discussed earlier the ketone **6a** was reduced under Wolff–Kishner reduction conditions. Consequently compound **6a** was treated with hydrazine and potassium hydroxide in diethylene glycol to furnish compound **16** in 92% yield.[23,26] The alcohol **16** was oxidized with IBX to provide tetracyclic ketone **10** in 91% yield. The spectral data of this compound is well matched with the ketone **10** obtained from decalone **8** (Scheme 4).

**Scheme 5.** Elaboration of *cis*-Decalone **8a** to Tetracyclic Ketone **10**




In conclusion, we have achieved a concise (8 step), protecting group-free and stereoselective synthesis of the bridged polycyclic core, a key advanced intermediate in the total synthesis of platencin. Our approach is more flexible and it highlights the intramolecular aldol reaction as a key step to attain the bicyclo[2.2.2]octane moiety. We demonstrated that both the *cis*-fused and *trans*-fused decalone systems were converted to the target tricyclic moiety. We also developed a good procedure for the Robinson annulation reaction with methyl vinyl ketone to achieve better yields.

**Acknowledgment.** Dedicated to Prof. Goverdhan Mehta on the occasion of his 70th birthday. G.R. thanks CSIR, New Delhi for the award of research fellowship. J.S.Y. thanks CSIR, New Delhi for Bhatnagar Fellowship.

**Supporting Information Available.** Experimental details, characterization data of products, $^1H$ and $^{13}C$ NMR spectra of products, and X-ray crystallography data for **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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