Antibiotic Synthesis

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A Symmetry-Based Concise Formal Synthesis of Platencin, a Novel Lead against "Superbugs"**

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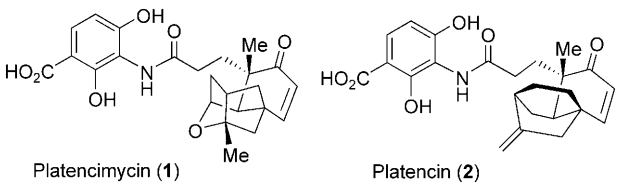
Penicillin was discovered by Alexander Fleming over 65 years ago. Since then, penicillin and its derivatives have been routinely prescribed by physicians for the treatment of ailments from pneumonia to scarlet fever. More recently, however, antibiotic resistance has become a serious medical concern. The emergence of a new breed of drug-resistant bacteria known as "superbugs" has led to treatment failure and has significantly increased morbidity and mortality for patients. Most currently available antibiotics are ineffective against these drug-resistant bacteria, particularly against methicillin-resistant *Staphylococcus aureus* (MRSA).[1] Given this major medical crisis, the development of new classes of antibiotics effective against these drug-resistant bacteria is a top medical priority. Particularly, the development of antibiotics with a novel mechanism of action is critical to fight MRSA and other drug-resistant bacteria. Unfortunately, the discovery of novel antibiotics from natural products was quite limited for more than 40 years, until a seminal discovery in 2006.[2] Singh and co-workers at Merck isolated two novel and closely related natural products, platensimycin (**1**)[3] and platencin (**2**),[4] from a strain of *Streptomyces platensis*. Both compounds exhibited potent



antibacterial activity against a broad range of Gram-positive organisms. Most importantly, both are capable of inhibiting several key antibiotic-resistant strains, including methicillin-resistant *S. aureus*, vancomycin-resistant *S. aureus*, and vancomycin-resistant *Enterococcus faecium*.

In addition to the excellent bioactivity, the novel mechanism of action possessed by both compounds is even more exciting. Unlike traditional antibiotics, which break down the bacterial cell wall, platensimycin and platencin inhibit bacterial fatty acid biosynthesis. Both compounds can efficiently inhibit the elongation condensing enzyme β-ketoacyl-(acyl-carrier-protein) synthase (FabF). Moreover, platencin can also inhibit the initiation condensing enzyme FabH, which makes it a superior lead compound. The targeting of two essential proteins increases the chances of avoiding bacterial resistance. Platencin and platensimycin share the same hydrophilic 3-amino-2,4-dihydroxybenzoic acid polar domain. Although each compound has a cyclohexenone ring on its hydrophobic core, platencin's core structure is less complex. In addition, platencin's dual-inhibition property makes it a more promising lead compound for the development of novel antibiotic drugs.

Due to their important biological activities and intriguing structures, platensimycin and platencin have become popular targets for many synthetic chemists over the last three years.[5] To date, 11 total and formal syntheses[6] and 4 analogue syntheses[7] of platensimycin have appeared in the literature. Since the discovery of platencin was published in 2007, a number of total or formal syntheses of this molecule have been reported.[8] Recently, Varseev and Maier[8i] reported a practical route to platencin by using an oxygen-mediated palladium-catalyzed cycloalkenylation reaction as the key step. Some relevance to this work has prompted us to disclose our preliminary results for the synthesis of platencin. As part of our continuing interest in the chemistry and biology of novel targets, we recently reported the synthesis of the platensimycin's core structure,[9] followed by a total synthesis of platensimycin.[6k] Herein, we report a concise formal synthesis of platencin. Our work provides quick and efficient access to the important hydrophobic core structure **3**.

Our strategy toward the synthesis of platencin core **3** is outlined in Scheme 1. Our plan is to synthesize the complex tricyclic core from a structurally simple precursor that will be amenable to scale up. Our strategic bond disconnection between C6 and C7 provides radical intermediate **4**, which can be formed from the simple symmetric *cis*-bicyclic 1,5-diketone **5**. Diketone **5** can be synthesized from an enone precursor **6** with a Michael reaction. Enone **6** can be derived from commercially available 3-isobutoxy-2-cyclohexen-1-one (**7**).

The construction of diketone **5** is outlined in Scheme 2. Treatment of commercially available cyclohexenone **7** with LDA followed by addition of MVK furnished the corresponding Michael addition product in 92% yield. Chemoselective protection of the ketone with ethylene glycol in the presence of a catalytic amount of PPTS afforded ketal **8** in 75% yield. Alkylation of compound **8** by using LDA and

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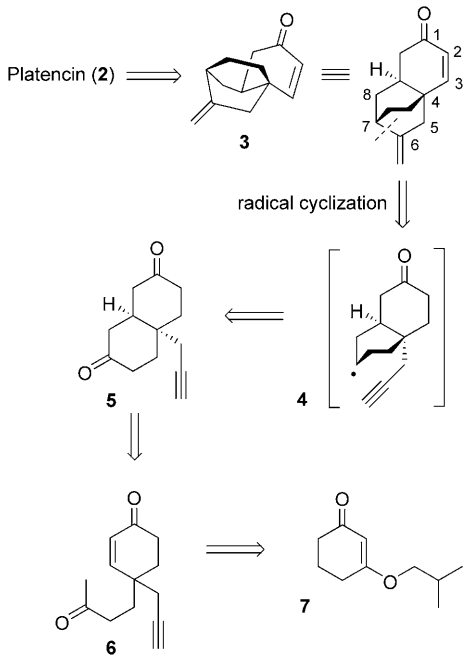
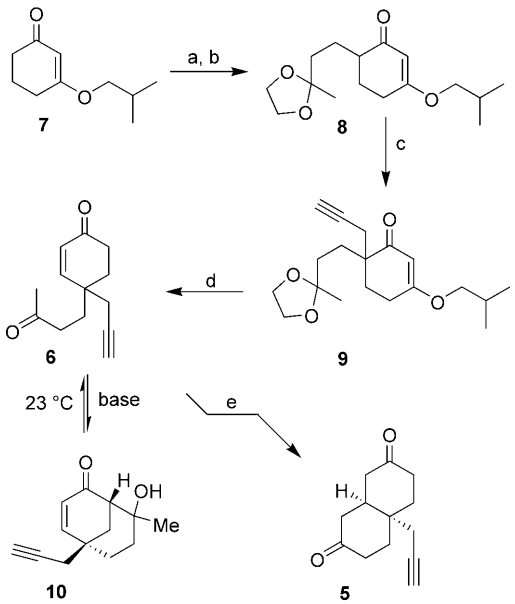


Scheme 1. Retrosynthetic analysis of the platencin core **3**.



Scheme 2. Synthesis of the symmetric diketone **5**. a) LDA (1.2 equiv), THF, −78 °C, 40 min, then MVK (1.05 equiv), −78 °C, 1 h, 92%; b) ethylene glycol (20 equiv), PPTS (0.4 equiv), benzene, reflux, 1 h, 75%; c) LDA (1.5 equiv), THF, −78 °C, 30 min, then propargyl bromide (3 equiv), −78→23 °C, 1 h, 89%; d) DIBAL-H (1.5 equiv), CH_2Cl_2, −78 °C, 1 h, then 3 M HCl (8 equiv), THF, 23 °C, 30 min, 88%; e) *t*BuOK (0.1 equiv), THF (0.01 M), reflux, 30 min, 76%. DIBAL-H: diisobutylaluminum hydride; LDA: lithium diisopropylamide; MVK: methyl vinyl ketone; PPTS: pyridinium *p*-toluenesulfonate; THF: tetrahydrofuran.

propargyl bromide provided alkylated product **9** in 89% yield. An alternative strategy involving alkylation of **7** with propargyl bromide followed by Michael addition with MVK provided the corresponding ketone in poor yield (<10%). Reduction of the carbonyl group in **9** with DIBAL-H to form the secondary alcohol followed by treatment of the crude product with 3 M aqueous HCl furnished the new enone moiety after rearrangement. The cyclic ketal protecting group was removed concomitantly under these reaction conditions. The desired enone **6** was isolated in 88% yield.

We initially tested the Michael cyclization promoted by a Lewis acid (Table 1, entry 1).[10] However, compound **5** could not be isolated under these conditions. We then examined the base-catalyzed reaction. Treatment of **6** with *t*BuOK in a 1:1 mixture of *tert*-butyl alcohol and THF at low temperature (Table 1, entry 2) afforded only a trace amount of diketone **5**. The major product was alcohol **10**, which was formed from enolization of the enone moiety followed by nucleophilic addition to the side-chain methyl ketone. We presume that the formation of **10** is reversible and, therefore, heating of the reaction may generate the thermodynamically more stable diketone **5**. Thus, a dilute solution of **6** with *t*BuOK as a catalyst (Table 1, entry 3) in THF was heated at reflux to provide diketone **5** in 76% yield. A change of base to sodium hydride (Table 1, entry 4) afforded **5** in 50% yield. LHMDS in THF (Table 1, entry 5) resulted in a sluggish reaction and a very poor yield of isolated product. The ^1H and ^{13}C NMR analysis supported the symmetrical structure of diketone **5**.

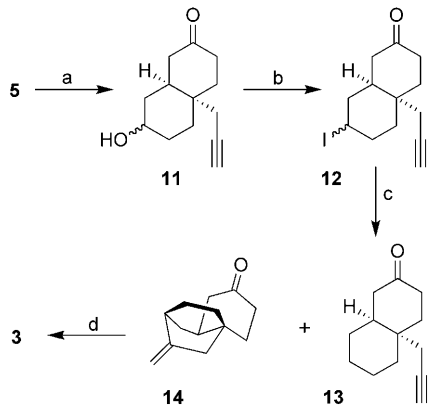
Table 1: Optimization of the Michael cyclization of compound **6**.[a]

Entry	Reagent	Solvent	*T*	Yield of **5**
1	$BF_3{\cdot}OEt_2$	CH_2Cl_2	23 °C	0%
2	*t*BuOK	*t*BuOH/THF	0 °C	trace[d]
3	*t*BuOK[b] (0.1 equiv)	THF	reflux	76%
4	NaH[b] (0.1 equiv)	THF	reflux	50%
5	LHMDS[c] (0.2 equiv)	THF	reflux	<10%

[a] Reactions were carried out at 0.01 M concentrations and the reaction times ranged from 30 min to 2 h. [b] The bases were added at 23 °C. [c] LHMDS: lithium bis(trimethylsilyl)amide. [d] The major product is compound **10**.

With diketone **5** in hand, we next examined the key radical cyclization step (Scheme 3). Selective reduction of one of the two carbonyl groups in diketone **5** to form the ketoalcohol is critical for the success of the subsequent key radical cyclization step. For the selective reduction, we examined a range of reducing agents and found that the bulky hydride donor, lithium tris-*tert*-butoxyaluminum hydride is most effective for monoreduction of ketone **5**. Treatment of diketone **5** with this hydride provided alcohol **11** as a 7:1 mixture of diastereomers in 83% yield (92% based on recovered **5**). We carried out the next step with this mixture because both diastereomers can be converted into the same radical intermediate **4**. Presumably, an enzymatic enantioselective monoreduction[11] or a resolution of the corresponding alcohol[12] would potentially provide access to the radical precursor in optically active form.

Our direct conversion of the hydroxy group to a radical precursor by using a thiocarbonyl derivative proceeded smoothly. However, the subsequent tin hydride reduction and radical cyclization only provided a very small amount of the desired cyclized product **14** (14% yield). The hydroxy



Scheme 3. Synthesis of core **3** by a key radical cyclization step. a) $LiAlH(tBuO)_3$ (1.1 equiv), THF, −78 °C, 30 min, 83% (92% based on recovered starting material); b) imidazole (3 equiv), PPh_3 (2 equiv), I_2 (2 equiv), THF, 23 °C, 79%; c) AIBN (0.25 equiv), nBu_3SnH (2.5 equiv), xylene, reflux, 6 h, 21% (**13**), 69% (**14**); d) KHMDS (1.2 equiv), THF, −78 °C, 30 min, then PhSeBr (1.3 equiv), −78→23 °C, 30 min, then $NaIO_4$ (4 equiv), THF/H_2O, 23 °C, 2 h, 45% (51% based on recovered starting material). AIBN: azobisisobutyronitrile; KHMDS: potassium bis(trimethylsilyl)amide.

group was therefore converted to form iodide **12**. This was subjected to a radical cyclization reaction by heating a dilute solution of iodide **12** and AIBN, followed by slow addition of nBu_3SnH with a syringe pump. This resulted in the formation of **14** as the desired major product, along with by-product **13**, which results from the direct reduction of the iodide to the corresponding alkane. It turned out that the solvent plays an important role. When benzene was used as the solvent, the major product was **13** and the ratio of **14** to **13** was 2:3. This can be improved to 10:3 with a 69% yield of isolated **14** by using xylene as the solvent. Synthesis of platencin core **14** constitutes a formal synthesis of platencin because this carbon skeleton has been converted into platencin previously.[8g] Our synthesis features eight steps with an unoptimized overall yield of 19% (21% based on recovered diketone **5**) by using commercially available starting material **7**.

The installation of the conjugated olefin moiety on ketone **14** has been reported with marginal (3:1) regioselectivity.[8g] Although both ketone α positions have methylene groups, the steric congestion around the β carbon atom suggests that a hindered strong base may provide selective deprotonation at the C2 carbon atom. This would result in regioselective enolate formation. Interestingly, treatment of **14** with LHMDS and subsequent reaction with phenylselenyl bromide followed by oxidation of the resulting selenide afforded a 5:6 mixture of enone regioisomers, with the enone olefin at the C9–C10 position being favored. However, use of KHMDS as the base furnished a $>10:1$ (by ^1H NMR analysis of the crude product) mixture of regioisomers in favor of the desired product **3**.

In summary, we have completed the formal synthesis of platencin by synthesizing the platencin core structure **3** in nine steps. Our synthetic route is concise, efficient, and involved only a single ketal protecting group. The synthesis features a base-catalyzed Michael cyclization to produce the *cis*-bicyclic 1,5-diketone **5** and a key radical cyclization step to furnish the core structure. Further investigation of the chemistry and biology of platencin is currently underway in our laboratories.

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