Published in final edited form as:

Angew Chem Int Ed Engl. 2009 ; 48(29): 5372–5375. doi:10.1002/anie.200902338.

A Symmetry-based, Concise Formal Synthesis of Platencin, a Novel Lead against ‘Superbugs’**

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Abstract

The quick access: A concise and efficient formal synthesis of platencin has been accomplished in 9 steps from a commercially available starting material. The synthesis utilized only one protecting group. The base catalyzed Michael cyclization of precursor **1** afforded the key diketone **2**, which was converted to the desired core structure **4** via the radical intermediate **3**.

Keywords

antibiotics; natural products; radical cyclization; Michael cyclization; total synthesis

Antibiotic synthesis

Penicillin was discovered by Alexander Fleming over 65 years ago. Since then, penicillin and its derivatives have been routinely prescribed by physicians for 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 called “superbugs” has led to treatment failure and significantly increased morbidity and mortality for patients. Most currently available antibiotics are ineffective against these drug-resistant bacteria, particularly against methicillin-resistant staphylococcus aureus or MRSA.^[1] Given this major medical crisis, development of new class of antibiotics effective against these drug-resistant bacteria is a top medical priority. Particularly, development of antibiotics with a novel mechanism of action is critical to fight MRSA and other resistant bacteria. Unfortunately, the discovery of novel antibiotics from natural products has been quite limited for more than 40 years until a seminal discovery in 2006. 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* (Figure 1). 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 *Staphylococcus aureus*, vancomycin-resistant *Staphylococcus aureus*, and vancomycin-resistant *Enterococcus faecium*.

In addition to excellent bioactivity, this novel mechanism of action possessed by both compounds is even more exciting. Unlike traditional antibiotics, which break down bacterial cell wall, platensimycin and platencin inhibit the bacterial fatty acid biosynthesis. Both compounds can efficiently inhibit the elongation condensing enzyme, β -ketoacyl-(acyl-carrier-protein) synthase FabF.

** Financial support of this work was provided in part by the National Institutes of Health and Purdue University.

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Moreover, platencin can also inhibit the initiation condensing enzyme FabH, which makes it a superior lead compound. Targeting 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 inhibitory property makes it a more promising lead compound for 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, eleven total and formal syntheses^[6] and four analog 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, Maier and co-workers^[8k] reported a practical route to platencin 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. In 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 a 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 which will be amenable to scale up. Our strategic bond disconnection of 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** via a Michael reaction. Enone **6** can be derived from the 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 methyl vinyl ketone (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** using LDA and 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 the secondary alcohol followed by treatment of the crude product with 3M 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 Lewis acid (Table 1, entry 1).^[10] However, compound **5** could not be isolated using these conditions. We then examined the base catalyzed reaction conditions. Treatment of **6** with *t*-BuOK in a 1:1 mixture of *tert*-butanol and THF at low temperature (entry 2) afforded only trace amount of diketone **5**. The major product was alcohol **10**, which was formed from enolization of enone moiety followed by nucleophilic addition to the side chain methyl ketone. We presume that the formation of **10** is reversible, and therefore, heating the reaction may generate the thermodynamically more stable diketone **5**. Thus, treatment of a dilute solution of **6** with *t*-BuOK as a catalyst (entry 3) in THF at reflux, provided diketone **5** in 76% yield. Changing base to sodium hydride (entry 4) afforded **5** in 50% yield. Lithium bis(trimethylsilyl)amide

(LHMDS) in THF (entry 5) resulted in a sluggish reaction and very poor isolated yield. The ^1H - and ^{13}C -NMR analysis supported the symmetrical structure of diketone **5**.

With the 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 ketoalcohol is critical for the success of the subsequent key radical cyclization step. For 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 lithium tris-*tert*-butoxyaluminum hydride provided an alcohol **11** as a 7:1 mixture of diastereomers in 83% isolated yield (92% based on recovered **5**). We carried out the next step with this mixture since both can be converted to 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 hydroxyl group to a radical precursor using thiocarbonyl derivatives proceeded smoothly. However, subsequent tin hydride reduction and radical cyclization provided only a very small amount of the desired cyclized product **14** (14% yield). The hydroxyl group was then converted to iodide **12**. It was subjected to a radical cyclization reaction by heating a dilute solution of the mixture of iodide **12** and AIBN, followed by slow addition of *n*Bu₃SnH using a syringe pump. This resulted in formation of the desired product **14** as the major product along with a by-product **13** resulting from the direct reduction of iodide to the corresponding alkane. It turns 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% isolated yield for **14** using xylene as a solvent. Synthesis of platencin core **14** constitutes a formal synthesis of platencin as this carbon skeleton has been converted to platencin previously.^[8g] Our synthesis features 8 steps with an unoptimized overall yield of 19% (21% based on recovered diketone **5**) 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 suggests that a hindered strong base may provide selective deprotonation at the C2 carbon. This would result in regioselective enolate formation. Interestingly, treatment of **14** with LHMDS and subsequent reaction with phenylselenenyl chloride followed by oxidation of the resulting selenide afforded a 5:6 mixture of enone regioisomers favoring the enone olefin at the C9–C10 position. However, using KHMDS as the base furnished a >10:1 (by ^1H -NMR analysis of the crude product) mixture of regioisomers favoring 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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Figure 1.
Structures of platensimycin (1) and platencin (2).

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°C to 23°C , 1 h, 89%; d) DIBAL-H (1.5 equiv), toluene, CH_2Cl_2 , -78°C , 1 h, then 3M 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; PPTS = pyridinium *p*-toluenesulfonate.

Scheme 3.

Synthesis of the core **3** via a radical cyclization key step. a) $\text{LiAlH}(\text{t-BuO})_3$ (1.1 equiv), THF, $-78\text{ }^\circ\text{C}$, 30 min, 83% (92%, based on recovered starting material); b) imidazole (3 equiv), PPh_3 (2 equiv), I_2 (2 equiv), THF, $23\text{ }^\circ\text{C}$, 79%; c) AIBN (0.25 equiv), nBu_3SnH (2.5 equiv), xylenes, reflux, 6 h, 21% (**13**), 69% (**14**); d) KHMDS (1.2 equiv), THF, $-78\text{ }^\circ\text{C}$, 30 min, PhSeBr (1.3 equiv), $-78\text{ }^\circ\text{C}$ to $23\text{ }^\circ\text{C}$, 30 min, then NaIO_4 (4 equiv), THF- H_2O , $23\text{ }^\circ\text{C}$, 2 h, 45% (51% based on recovered starting material). AIBN = azobisisobutyronitrile; KHMDS = potassium bis(trimethylsilyl)amide.

Table 1Optimization of the Michael cyclization of compound **6**.

Entry ^[a]	Reagent	Solvent	Temp.	Yield of 5
1	BF ₃ .OEt ₂	CH ₂ Cl ₂	23 °C	0%
2	<i>t</i> -BuOK	<i>t</i> -BuOH & THF	0 °C	trace ^[c]
3	0.1 eq. <i>t</i> -BuOK ^[b]	THF	reflux	76%
4	0.1eq. NaH ^[b]	THF	reflux	50%
5	0.2 eq. LHMDs	THF	reflux	<10%

^[a]Reactions were carried out in 0.01M concentration and the reaction time ranged from 30 min to 2 h.

^[b]The bases were added at 23 °C.

^[c]The major product is compound **10**.