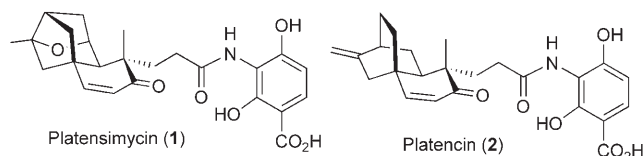


## Natural Products

## Concise Synthesis of the Tricyclic Core of Platencin\*\*

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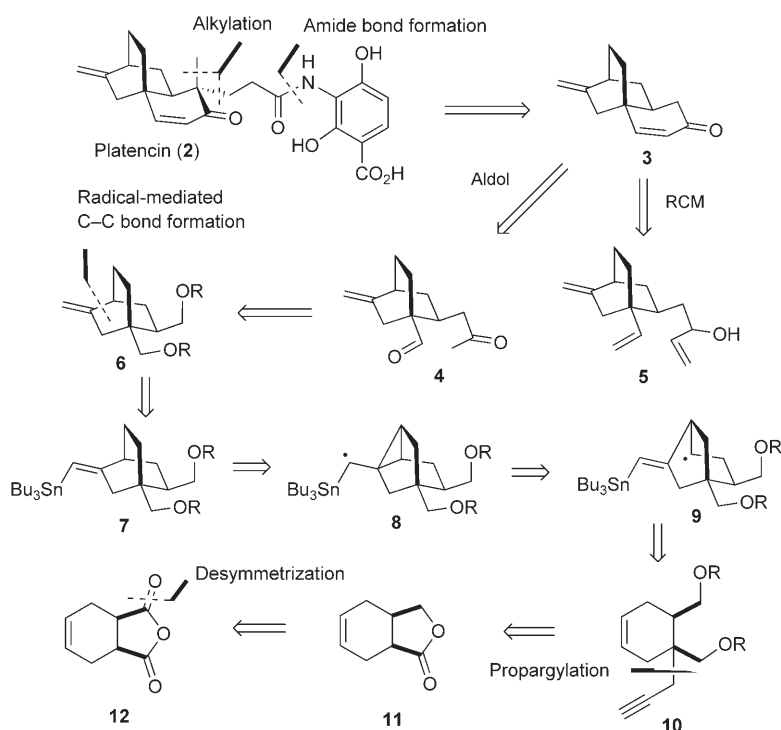
Platensimycin (**1**)<sup>[1]</sup> and platencin (**2**)<sup>[2]</sup> which are structurally related antibiotics, were recently discovered through a systematic target-based whole-cell high-throughput screen-



ing. These novel bacterial metabolites show potent Gram-positive antibacterial activity against antibiotic-resistant pathogens.<sup>[3]</sup> Platencin (**2**), isolated from a new strain of *Streptomyces platensis* MA 7339 found in a soil sample collected in Spain, exhibits MIC values in the range 0.14–9.4  $\mu\text{M}$  against *S. aureus*, MRSA, vancomycin-resistant enterococci, and *Streptococcus pneumoniae*. Further biochemical assays identified **2** as a potent and dual inhibitor of the fatty acid biosynthesis condensing enzymes  $\beta$ -ketoacyl-(acyl-carrier-protein) synthase II (FabF) and III (FabH), with  $\text{IC}_{50}$  values of 1.95 and 3.91  $\mu\text{g mL}^{-1}$ , respectively.<sup>[2]</sup> As a result of the promising antibacterial activities and novel structures of **1** and **2**, many insightful synthetic approaches have been developed since the first total synthesis of platensimycin by Nicolaou et al.<sup>[4,5]</sup> Recently, Nicolaou et al. also reported the first total synthesis of platencin (**2**).<sup>[6]</sup> Herein, we report a concise synthetic route to the tricyclic core of platencin which relies on a radical-mediated construction of the central bicyclo[2.2.2]octane moiety as the key feature.<sup>[7]</sup>

Our retrosynthetic plan for platencin (**2**) is depicted in Scheme 1. Synthesis of the natural product is expected to be completed by the final-stage elaboration of the core **3** through a

three-carbon homologation followed by formation of an amide bond with 3-amino-2,4-dihydroxybenzoic acid.<sup>[6]</sup> An intramolecular aldol reaction or ring-closing metathesis (RCM) reaction is envisioned for the formation of cyclohexenone moiety of **3** starting from ketoaldehyde **4** or from an appropriate diene RCM precursor **5**. These precursors would be elaborated from **6** by a two-carbon homologation. A skeletal rearrangement of the initially formed radical intermediate **9** to the required bicyclo[2.2.2]octane **7** would be initiated by the addition of a tributylstannyl radical to the pendant alkyne moiety of precursor **10**.<sup>[7]</sup> The cyclohexene-



Scheme 1. Retrosynthetic analysis of platencin (**2**).

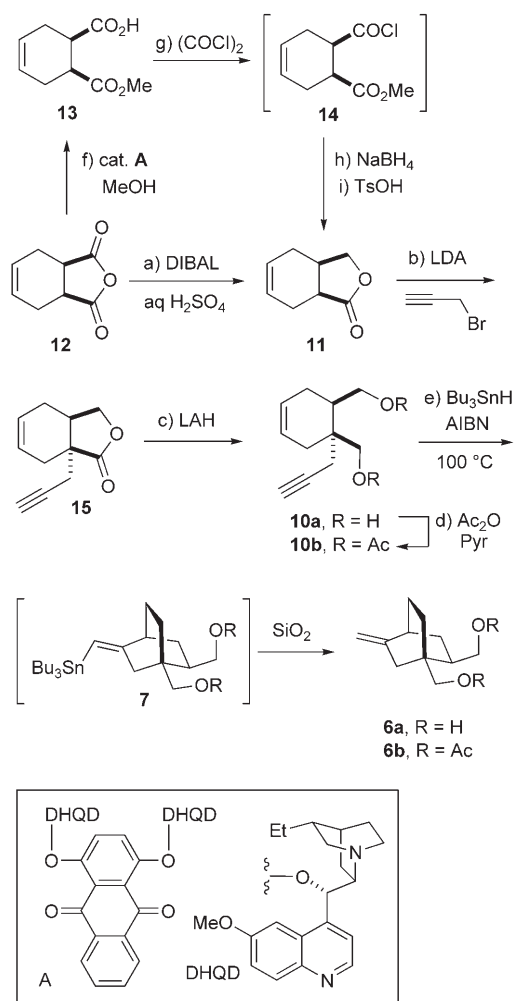
based 1,6-enyne **10**, in turn, could be prepared by desymmetrization of *meso*-anhydride **12** to form lactone **11** followed by propargylation.

The preparation of radical ring-closure precursor **10** commenced with the conversion of cyclic anhydride **12** into lactone **11** by reduction with DIBAL followed by treatment with acid (Scheme 2). For the asymmetric synthesis, **12** was desymmetrized to form the carboxylic acid half ester **13** by using the procedure of Deng and co-workers.<sup>[8]</sup> Compound **13** was converted into acid chloride **14** and subsequently reduced then lactonized to give **11**.<sup>[9]</sup> Propargylation of **11** (LDA, propargyl bromide) formed **15**, which was subsequently

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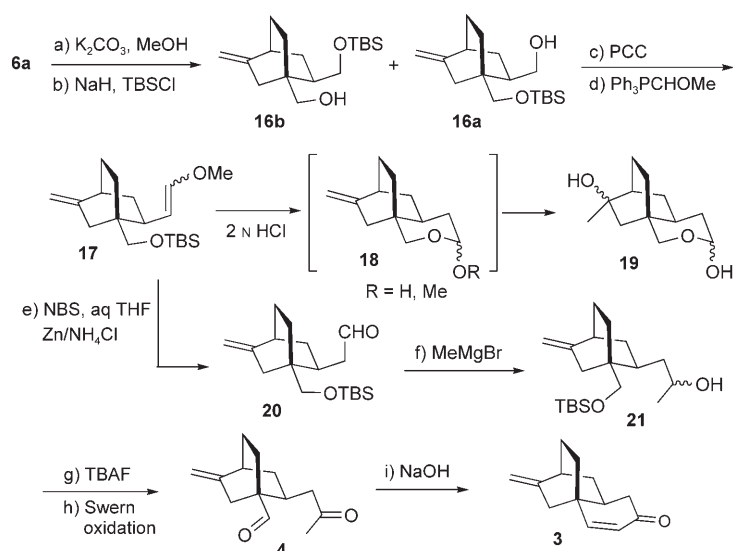
Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/ange.200801587>.



**Scheme 2.** Construction of the bicyclo[2.2.2]octane moiety: a) DIBAL (2.1 equiv), THF,  $-78^{\circ}\text{C}$  to RT over 1 h; 50% aq  $\text{H}_2\text{SO}_4$ ,  $0^{\circ}\text{C}$ , 4 h, 92%; b) LDA (1.1 equiv), THF,  $-78^{\circ}\text{C}$ ;  $\text{C}_3\text{H}_7\text{Br}$ ,  $-78^{\circ}\text{C}$  to RT over 1 h, 89%; c) LAH (1.5 equiv), THF,  $0^{\circ}\text{C}$ , 1 h, 95%; d)  $\text{Ac}_2\text{O}$  (2.2 equiv), Pyr, DMAP,  $\text{CH}_2\text{Cl}_2$ , 30 min, 99%; e)  $\text{Bu}_3\text{SnH}$  (1.5 equiv), AIBN, toluene,  $100^{\circ}\text{C}$ , 1 h;  $\text{SiO}_2$ ,  $100^{\circ}\text{C}$ , 30 min, 51% ( $\text{R}=\text{H}$ ), 67% ( $\text{R}=\text{Ac}$ ); f)  $(\text{DHQD})_2\text{AQN}$  (**A**; 8 mol%), MeOH (10 equiv),  $\text{Et}_2\text{O}$ ,  $-20^{\circ}\text{C}$ , 72 h, 99%; g)  $(\text{COCl})_2$  (6 equiv),  $\text{CH}_2\text{Cl}_2$ ,  $-78^{\circ}\text{C}$ , 30 min; h)  $\text{NaBH}_4$  (2 equiv), MeOH, THF,  $-78^{\circ}\text{C}$ , 30 min; i)  $\text{TsOH}$  (12 mol%), toluene,  $100^{\circ}\text{C}$ , 8 h, 89% (over 3 steps). AIBN = azobisisobutyronitrile;  $(\text{DHQD})_2\text{AQN}$  = bis(dihydroquinidine) anthraquinone; DIBAL = diisobutylaluminum hydride; DMAP = 4-(dimethylamino)pyridine; LDA = lithium diisopropylamide; LAH = lithium aluminum hydride; Pyr = pyridine; Ts = *para*-toluenesulfonyl.

reduced and afforded **10a**. An initial attempt at radical-mediated cyclization of **10a** provided bicyclo[2.2.2]octane **6a** in marginal yield (51%). The corresponding diacetate **10b** gave a slightly improved yield of **6b** (67%) under the same reaction conditions ( $\text{Bu}_3\text{SnH}$ , AIBN, toluene,  $100^{\circ}\text{C}$ ; then  $\text{SiO}_2$ ).<sup>[10]</sup> The destannylation of **7** was efficiently achieved by adding silica gel after completion of the reaction but before cooling.

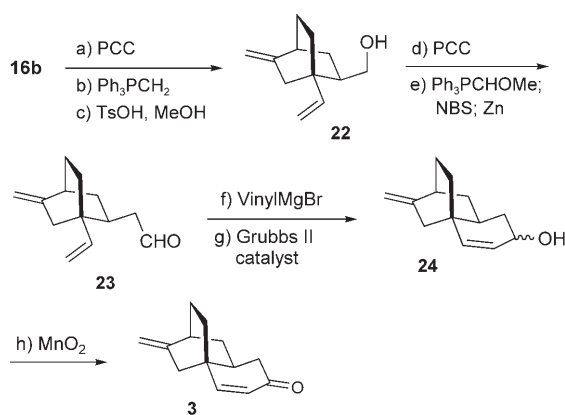
The final steps for the synthesis of enone **3** began with mono protection of diol **6a** (Scheme 3). Diacetate **6b** was converted into diol **6a** ( $\text{K}_2\text{CO}_3$ , MeOH, 96%), which was then treated with sodium hydride (2 equiv, THF) and TBSCl



**Scheme 3.** The intramolecular aldol approach: a)  $\text{K}_2\text{CO}_3$  (2.5 equiv), MeOH, 1 h, 96%; b)  $\text{NaH}$  (2 equiv), TBSCl (1 equiv), THF,  $-78^{\circ}\text{C}$  to RT over 30 min, 90%; c) PCC (2 equiv), 4-Å M.S.,  $\text{CH}_2\text{Cl}_2$ , 40 min; d)  $\text{Ph}_3\text{PCH}_2\text{OMeCl}$  (2 equiv),  $n\text{BuLi}$ , THF,  $-78^{\circ}\text{C}$  to  $-20^{\circ}\text{C}$  over 30 min; then  $-20^{\circ}\text{C}$  to RT over 30 min; e) NBS (1 equiv), THF/ $\text{H}_2\text{O}$  (10:1),  $0^{\circ}\text{C}$ , 1 h; aq  $\text{NH}_4\text{Cl}$ , Zn (3 equiv); f)  $\text{MeMgBr}$  (1.5 equiv), THF,  $0^{\circ}\text{C}$ , 30 min, 45% (ca. 1:1 mixture of diastereomers; over 4 steps); g) TBAF (1.1 equiv), THF,  $0^{\circ}\text{C}$ , 30 min, 85%; h)  $(\text{COCl})_2$  (3 equiv), DMSO (6 equiv),  $\text{CH}_2\text{Cl}_2$ ,  $\text{Et}_3\text{N}$  (6 equiv),  $-78^{\circ}\text{C}$ ; i)  $\text{NaOH}$  (5 equiv), EtOH, 24 h, 60% (over 2 steps). DMSO = dimethyl sulfoxide; M.S. = molecular sieves; NBS = *N*-bromosuccinimide; PCC = pyridinium chlorochromate; TBAF = tetrabutylammonium fluoride; TBS = *tert*-butyldimethylsilyl.

(1 equiv) at low temperature ( $-78^{\circ}\text{C}$ ) to provide a mixture of **16a** and **16b** (ca. 2:1) in excellent yield (90%).<sup>[11]</sup> Oxidation of the primary alcohol of **16a** followed by treatment with triphenylmethoxymethylphosphorane yielded methyl enol ether **17**. Attempted hydrolysis of **17** ( $2\text{N HCl}$ , THF) proceeded through acid-catalyzed hydration to form **19** via **18**. Gratifyingly, treatment of **17** with NBS in aqueous THF at low temperature gave the  $\alpha$ -bromoaldehyde, which was directly treated with zinc powder to give aldehyde **20**. The addition of methyl Grignard reagent to **20** led to a separable mixture of diastereomeric alcohols **21** (ca. 1:1; 45% overall yield from **16a**). Removal of the TBS group was followed by global oxidation to give the corresponding ketoaldehyde **4**, and a subsequent intramolecular aldol/dehydration<sup>[5g, 6a]</sup> afforded enone **3** in good yield (60% over 2 steps).

Although **16b** could be recycled to form **16a** through a deprotection/reprotection cycle, an RCM-based approach was developed to facilitate the use of **16b**. As shown in Scheme 4, **16b** was elaborated to **22** by a three-step sequence involving oxidation with PCC, a Wittig reaction, and removal of the TBS group (73% over 3 steps). One-carbon homologation of **22** to give the corresponding unstable aldehyde **23** followed by addition of vinyl Grignard reagent set the stage for RCM of the diene,<sup>[12]</sup> which delivered allylic alcohol **24** as an inconsequential mixture (ca. 1:1) upon treatment with the second-generation Grubbs catalyst.<sup>[13]</sup> Manganese dioxide mediated oxidation of **24** afforded enone **3** in 86% yield. The



**Scheme 4.** RCM approach for the construction of enone **3**: a) PCC (2 equiv), 4-Å M.S., CH<sub>2</sub>Cl<sub>2</sub>, 30 min; b) Ph<sub>3</sub>PCH<sub>3</sub>Br (3 equiv), *n*BuLi, −78 to 0°C over 30 min; then 0°C, 30 min; c) TsOH (5 mol%), MeOH, 1 h, 73% (over 3 steps); d) PCC (2 equiv), 4-Å M.S., CH<sub>2</sub>Cl<sub>2</sub>, 30 min; e) Ph<sub>3</sub>PCH<sub>2</sub>OMeCl (2.5 equiv), *n*BuLi, THF, −78 to −20°C over 30 min; then −20°C to RT over 30 min; NBS (1 equiv), THF/H<sub>2</sub>O (10:1), −20 to 0°C over 1 h; then aq NH<sub>4</sub>Cl, Zn (3 equiv); f) VinylMgBr (1.5 equiv), THF, 0°C, 1 h, 39% (ca. 1:1 mixture of diastereomers; over 4 steps); g) Grubbs II catalyst (5 mol%), CH<sub>2</sub>Cl<sub>2</sub>, 40°C, 4 h, 95%; h) MnO<sub>2</sub> (8 equiv), CH<sub>2</sub>Cl<sub>2</sub>, 1 h, 86%.

<sup>1</sup>H and <sup>13</sup>C NMR spectra of **3** are identical to those reported by Nicolaou et al.<sup>[6a]</sup>

In conclusion, we have achieved a concise synthesis (14 steps in the shortest sequence with 10% overall yield) of the bridged tricyclic enone core **3**, a key advanced intermediate in the total synthesis of platencin by Nicolaou et al. Our route highlights the radical-mediated construction of a key building block through a skeletal rearrangement. An intramolecular aldol reaction and an RCM reaction were employed to complete the core cyclohexenone moiety of platencin. A Lewis base catalyzed desymmetrization of a cyclic anhydride was utilized to introduce appropriate chirality. We are currently pursuing the asymmetric total synthesis of both platencin and platensimycin starting from chiral building block **15**.

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