Natural Products

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Concise Synthesis of the Tricyclic Core of Platencin**

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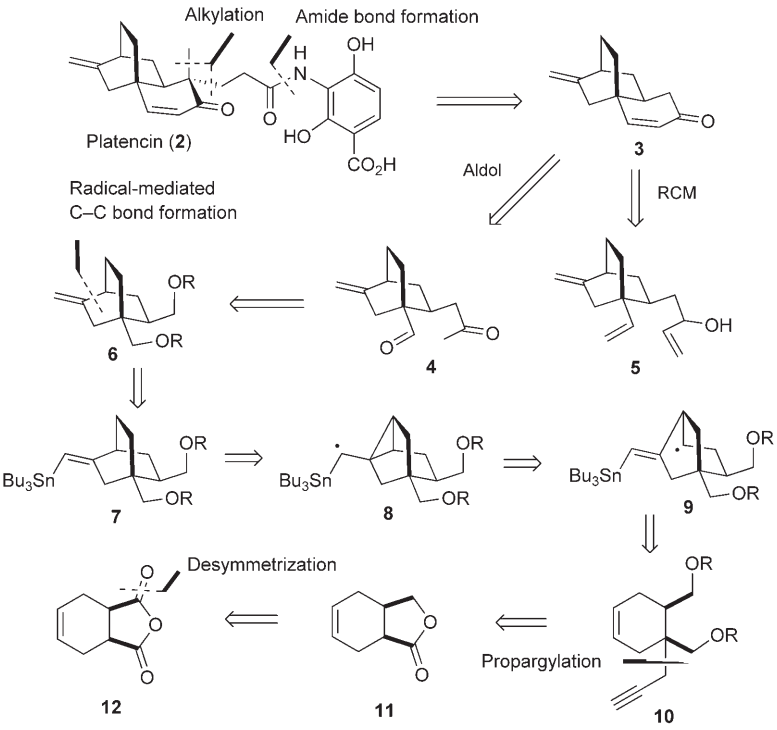
Platensimycin (**1**)[1] and platencin (**2**),[2] which are structurally related antibiotics, were recently discovered through a systematic target-based whole-cell high-throughput screening. These novel bacterial metabolites show potent Gram-positive antibacterial activity against antibiotic-resistant pathogens.[3] 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 μM against *S. aureus*, MRSA, vancomycin-resistant enterococci, and *Steptococcus pneumoniae*. Further biochemical assays identified **2** as a potent and dual inhibitor of the fatty acid biosynthesis condensing enzymes β-ketoacyl-(acyl-carrier-protein) synthase II (FabF) and III (FabH), with IC_{50} values of 1.95 and 3.91 $\mu g\,mL^{-1}$, respectively.[2] 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.[4,5] Recently, Nicolaou et al. also reported the first total synthesis of platencin (**2**).[6] 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.[7]

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.[6] 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**.[7] The cyclohexene-based 1,6-enyne **10**, in turn, could be prepared by desymmetrization of *meso*-anhydride **12** to form lactone **11** followed by propargylation.



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

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.[8] Compound **13** was converted into acid chloride **14** and subsequently reduced then lactonized to give **11**.[9] Propargylation of **11** (LDA, propargyl bromide) formed **15**, which was subsequently

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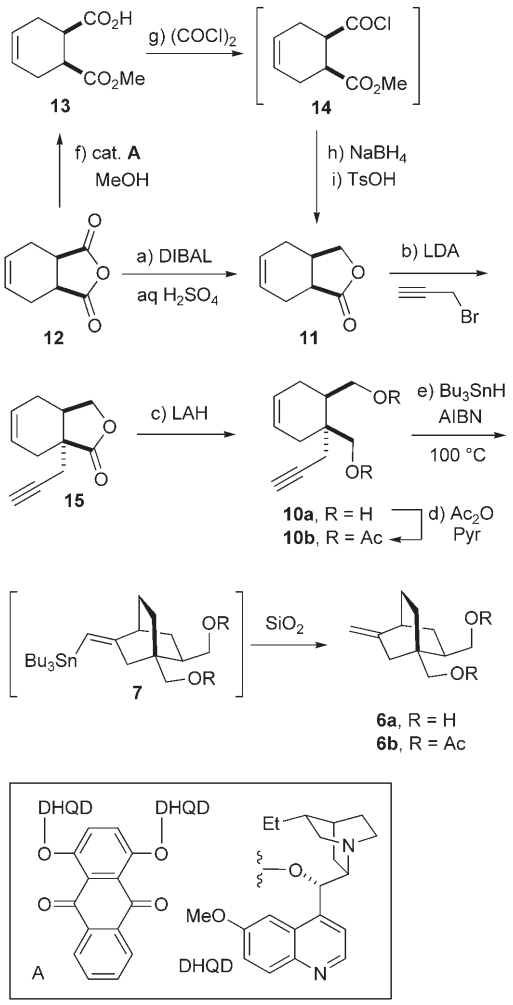
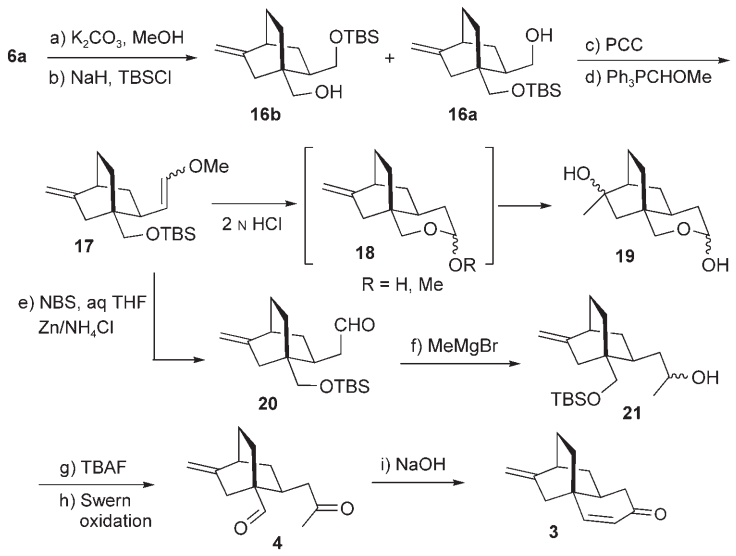


Scheme 2. Construction of the bicyclo[2.2.2]octane moiety: a) DIBAL (2.1 equiv), THF, −78 °C to RT over 1 h; 50% aq H_2SO_4, 0 °C, 4 h, 92%; b) LDA (1.1 equiv), THF, −78 °C; C_3H_3Br, −78 °C to RT over 1 h, 89%; c) LAH (1.5 equiv), THF, 0 °C, 1 h, 95%; d) Ac_2O (2.2 equiv), Pyr, DMAP, CH_2Cl_2, 30 min, 99%; e) Bu_3SnH (1.5 equiv), AIBN, toluene, 100 °C, 1 h; SiO_2, 100 °C, 30 min, 51% (R = H), 67% (R = Ac); f) $(DHQD)_2AQN$ (**A**; 8 mol%), MeOH (10 equiv), Et_2O, −20 °C, 72 h, 99%; g) $(COCl)_2$ (6 equiv), CH_2Cl_2, −78 °C, 30 min; h) $NaBH_4$ (2 equiv), MeOH, THF, −78 °C, 30 min; i) TsOH (12 mol%), toluene, 100 °C, 8 h, 89% (over 3 steps). AIBN = azobisisobutyronitrile; $(DHQD)_2AQN$ = bis(dihydroquinidine) anthraquinone; DIBAL = diisobutylaluminum hydride; DMAP = 4-(dimethylamino)pyridine; LDA = lithium diisopropylamide; LAH = lithium aluminum hydride; Pyr = pyridine; Ts = *para*-toluenesulfonyl.

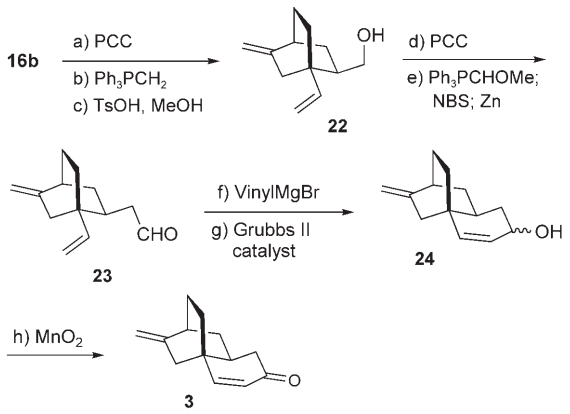


Scheme 3. The intramolecular aldol approach: a) K_2CO_3 (2.5 equiv), MeOH, 1 h, 96%; b) NaH (2 equiv), TBSCl (1 equiv), THF, −78 to RT over 30 min, 90%; c) PCC (2 equiv), 4-Å M.S., CH_2Cl_2, 40 min; d) Ph_3PCH_2OMeCl (2 equiv), *n*BuLi, THF, −78 to −20 °C over 30 min; then −20 °C to RT over 30 min; e) NBS (1 equiv), THF/H_2O (10:1), 0 °C, 1 h; aq NH_4Cl, Zn (3 equiv); f) MeMgBr (1.5 equiv), THF, 0 °C, 30 min, 45% (ca. 1:1 mixture of diastereomers; over 4 steps); g) TBAF (1.1 equiv), THF, 0 °C, 30 min, 85%; h) $(COCl)_2$ (3 equiv), DMSO (6 equiv), CH_2Cl_2, Et_3N (6 equiv), −78 °C; i) 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.

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 (Bu_3SnH, AIBN, toluene, 100 °C; then SiO_2).[10] 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** (K_2CO_3, MeOH, 96%), which was then treated with sodium hydride (2 equiv, THF) and TBSCl (1 equiv) at low temperature (−78 °C) to provide a mixture of **16a** and **16b** (ca. 2:1) in excellent yield (90%).[11] Oxidation of the primary alcohol of **16a** followed by treatment with triphenylmethoxymethylphophorane yielded methyl enol ether **17**. Attempted hydrolysis of **17** (2N 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 α-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[5g,6a] 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,[12] which delivered allylic alcohol **24** as an inconsequential mixture (ca. 1:1) upon treatment with the second-generation Grubbs catalyst.[13] 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_2Cl_2, 30 min; b) Ph_3PCH_3Br (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_2Cl_2, 30 min; e) Ph_3PCH_2OMeCl (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_2O (10:1), −20 to 0 °C over 1 h; then aq NH_4Cl, 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_2Cl_2, 40 °C, 4 h, 95 %; h) MnO_2 (8 equiv), CH_2Cl_2, 1 h, 86 %.

^{1}H and ^{13}C NMR spectra of **3** are identical to those reported by Nicolaou et al.[6a]

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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