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Natural Products

Short Formal Synthesis of (−)-Platencin**

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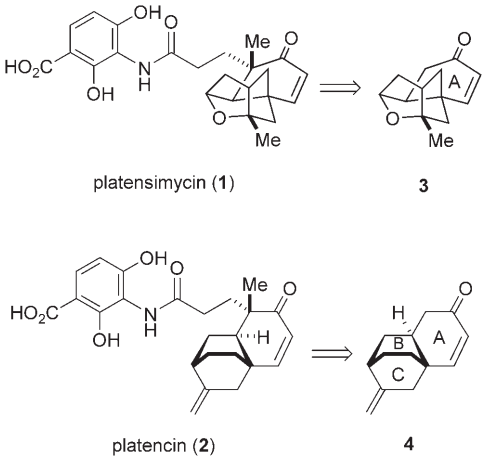
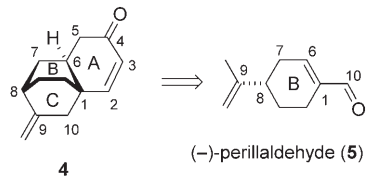
The recent discovery of platensimycin (**1**),[1] a metabolite of *Streptomyces platensis*, by Wang and co-workers has been hailed as a breakthrough in antibiotic research. Even more thrilling was the isolation of a second potent antibiotic named platencin[2] (**2**) from the same microorganism. Compounds **1** and **2** block the condensing enzymes FabH and/or FabF of the bacterial fatty-acid biosynthesis. Platencin (**2**) exhibits broad-spectrum activity against many pathogens that show resistance to current antibiotics, including methycillin-, macrolide-, and linezolid-resistant *S. aureus*, vancomycin-resistant enterococci, and *Streptococcus pneumoniae*.[2]

Structurally, **1** and **2** are relatively similar; they feature the same hydrophilic "western" appendage. The polycyclic lipophilic core systems **3** and **4** are also related and contain the same cyclohexenone A ring (Scheme 1). A large number of synthetic approaches have been reported for **3**,[3] although only one synthesis of **1** has been completed.[3b] Recently, the first synthesis of **2** was reported by Nicolaou et al.[4] Their approach features an enantioselective catalytic Diels–Alder reaction as the key step and requires fifteen steps to the core fragment **4**, which is then converted into **2** by a procedure developed previously for the transformation of **3** into **1**.[3b]



Scheme 1. Structures of platensimycin (**1**) and platencin (**2**), and their polycyclic core fragments.

Herein we report a five-step protecting-group-free synthesis of **4**. Our retrosynthetic analysis led to commercially available (−)-perillaldehyde (**5**) as a promising starting material, as **5** already contains ring B with suitable appendages at C8 and C1 (Scheme 2). The *ee* value of **5** was



Scheme 2. Retrosynthetic correlation between **4** and **5**.

determined by reduction to the alcohol and Mosher analysis to be greater than 92%. The synthetic plan involved the construction of ring A through a Diels–Alder reaction and the construction of ring C by ring-closing metathesis (RCM) followed by transposition of the endocyclic double bond to the exocyclic position.

The Diels–Alder reaction between **5** and the Rawal diene[5] (1-(dimethylamino)-3-(*tert*-butyldimethylsiloxy)-1,3-butadiene) furnished aldehyde **6** in a 20:1 diastereomeric ratio after acidic hydrolysis (Scheme 3). With all stereogenic centers already set correctly, we initiated the closure of ring C by RCM. Thus, ketoaldehyde **6** was monomethylenated under standard Wittig conditions to give triene **7** in good yield. Exposure to the Grubbs second-generation catalyst[6] led to the clean conversion of **7** into tricycle **8**. For the isomerization of the endocyclic double bond to the exocyclic position, we developed a two-step procedure consisting of allylic bromination and chromium(II)-mediated reduction.[7] The allylic bromination of **8** was performed by adding NBS and *t*BuOH to the cooled (0 °C) RCM reaction mixture, which was then warmed to room temperature. The bromoalkene **9** was obtained as an inconsequential mixture of C10 epimers (d.r. ≈3:1). The use of less bulky alcohols, such as MeOH[7] or 2-propanol, led to considerable amounts of the bromoethers, presumably through addition to the bromonium intermediate **10**. In the absence of an alcohol additive, no reaction was observed. The treatment of crude **9** with $CrCl_2$ in THF/DMF led to a separable 3:1 mixture of **4** (whose analytical data, except for the optical rotation value,[8] were in agreement with those reported)[4] and (fully recyclable) **8**.

In summary, we have developed a five-step, protecting-group-free, formal synthesis of (−)-platencin (overall yield of compound **4**: 26%) from a chiral-pool starting material. The

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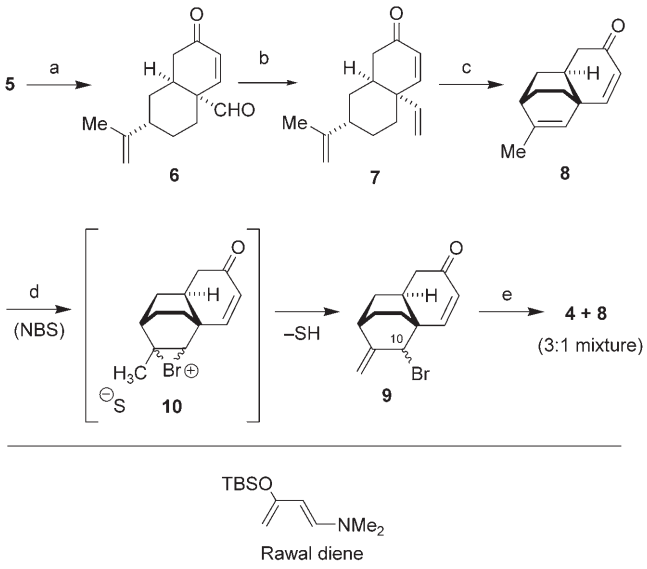

Scheme 3. Synthesis of the core fragment **4** of platencin: a) Rawal diene,[5] toluene, reflux, 4.5 h, then HCl (1.2 M), THF, room temperature, 16 h, 68% (d.r. 20:1); b) Ph_3PMeBr, *t*BuOK, THF, 0°C, 25 min, 80%; c) Grubbs second-generation catalyst, CH_2Cl_2, reflux, 36 h; d) NBS, *t*BuOH, room temperature; e) $CrCl_3$, $LiAlH_4$, THF, DMF, 2-propanol, room temperature, 48% (3 steps; analytically pure **4**). DMF = *N*,*N*-dimethylformamide, NBS = *N*-bromosuccinimide, SH = succinimide.

overall procedure is simple, as the conversion of **7** into **9** is performed as a one-pot operation, and for the reduction to **4**/**8**, the crude bromide **9** can be used.[9]

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[8] Our value of $[\alpha]_D^{35} = +22.2\ deg\,cm^2\,g^{-1}$ ($c = 0.68\ g\,dL^{-1}$, $CHCl_3$) differs from the reported value of $[\alpha]_D^{35} = +6.3\ deg\,cm^2\,g^{-1}$ ($c = 0.46\ g\,dL^{-1}$, $CHCl_3$). Prof. Nicolaou and Dr. Edmonds informed us that more recently they measured values of $+17.4\ deg\,cm^2\,g^{-1}$ ($c = 2.25\ g\,dL^{-1}$, $CHCl_3$) and $+17.8\ deg\,cm^2\,g^{-1}$ ($c = 0.49\ g\,dL^{-1}$, $CHCl_3$) for a sample of **4** with 85% *ee*.

[9] Note added in proof: In the meantime two additional syntheses of platencin were published: a) J. Hayashida, V. H. Rawal, *Angew. Chem.* **2008**, *120*, 4445; *Angew. Chem. Int. Ed.* **2008**, *47*, 4373; b) S. Y. Yun, J.-C. Zheng, D. Lee, *Angew. Chem.*, DOI: 10.1002/ange.200801587; *Angew. Chem. Int. Ed.*, DOI: 10.1002/anie.200801587.

