Natural Product Synthesis

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High-Pressure Entry into Platencin**

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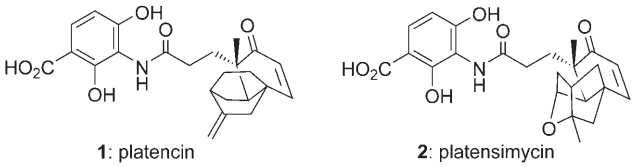
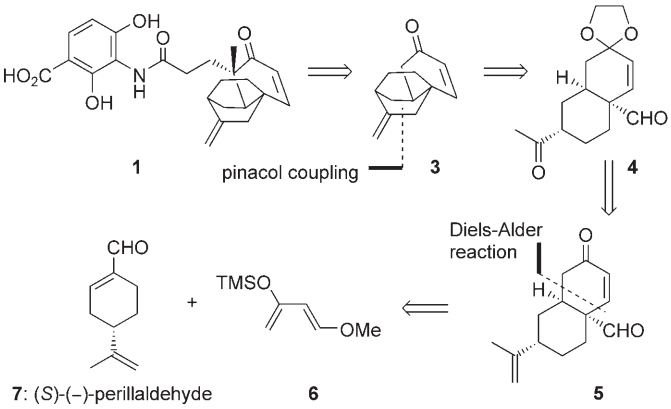
Nature's answers to even our latest antibiotics force scientists to continuously search for new leads in combating bacterial resistance.[1] However, over the last two decades these efforts have been met with little success, whilst the threat of resistant pathogens steadily increased. The recent discovery of two new potent antibiotics, platencin (**1**)[2] and platensimycin (**2**; Scheme 1),[3] which both act through an unprecedented



Scheme 1. Structures of platencin (**1**) and platensimycin (**2**).



Scheme 2. Retrosynthetic analysis of platencin (**1**). TMS = trimethylsilyl.

mechanism, is therefore considered a potential breakthrough by scientists. The unique properties and intriguing structures of platencin and platensimycin immediately caught the attention of the synthetic community. In 2006, Nicolaou et al.[4a] were the first to report the total synthesis of platensimycin, thereby paving the way for nine formal syntheses.[4] To date, only two total syntheses and one formal synthesis of platencin have been reported.[5]

Herein, we report a highly efficient synthesis of core enone **3** in an enantiopure form starting from (*S*)-(−)-perillaldehyde (**7**; Scheme 2), which is an inexpensive and commercially available flavoring agent. The construction of **3** was envisioned through a SmI_2-mediated pinacol cyclization of **4**, which can be accessed by a simple protection and oxidation sequence from **5**. Finally, a diastereoselective Diels–Alder reaction of (*S*)-(−)-perillaldehyde (**7**) with Danishefsky's diene **6** would deliver key intermediate **5**.

Initially, we had to address the challenge posed by activated cyclohexenes, which are notoriously unreactive towards Diels–Alder reactions with Danishefsky's diene **6**.[6] Thermal activation requires a large excess of **6** and long reaction times, while Lewis acid catalysis is not applicable because of the acid lability of **6** and the preference for a competitive hetero-Diels–Alder reaction.[7] Inspired by previous work from our research group,[8] we envisioned that high-pressure activation could be a key approach in tackling these problems.[9] To our delight, performing the Diels–Alder reaction of (*S*)-(−)-perillaldehyde (**7**) and Danishefsky's diene **6** at 15 kbar, followed by Lewis acidic workup with $Yb(OTf)_3$,[10] afforded aldehyde **5** in an excellent yield of 81% (Scheme 3). With all carbon atoms and stereocenters of the platencin core installed in the first step, aldehyde **5** was selectively protected through a Wittig reaction in 86% yield. Protection of the unsaturated ketone with ethylene glycol and subsequent twofold oxidative cleavage with ozone in the presence of pyridine yielded ketone **4** in 91% over two steps.

The construction of the bicyclo[2.2.2]octane core was then realized through a diastereo- and *syn*-selective SmI_2-mediated pinacol coupling.[11] The protecting groups were cleanly removed from the crude product by using a catalytic amount of TsOH in wet dichloromethane to give diol **8** in a yield of 85%. X-ray crystallographic analysis confirmed the desired relative stereochemistry of **8** (Figure 1).[12] Selective protection of the secondary alcohol with Ac_2O and a catalytic amount of DMAP proceeded quantitatively. Subsequent dehydration with freshly prepared Burgess reagent[13] afforded allylic actetate **9** in a moderate yield of 48%. This acetate is ideally equipped to undergo a palladium-mediated hydrogenolysis as developed by Tsuji et al.[14] Thus, treatment of **9** with $[Pd_2(dba)_3]$ and PBu_3 in the presence of Et_3N/HCO_2H (1:1) delivered the target compound **3** in 60% yield.

In conclusion, a short synthesis (9 steps, 15.5% overall yield) of enantiopure **3** has been reported, which is a key intermediate in total syntheses of platencin.[5a,b] Our approach commenced with an unprecedented diastereoselective high-

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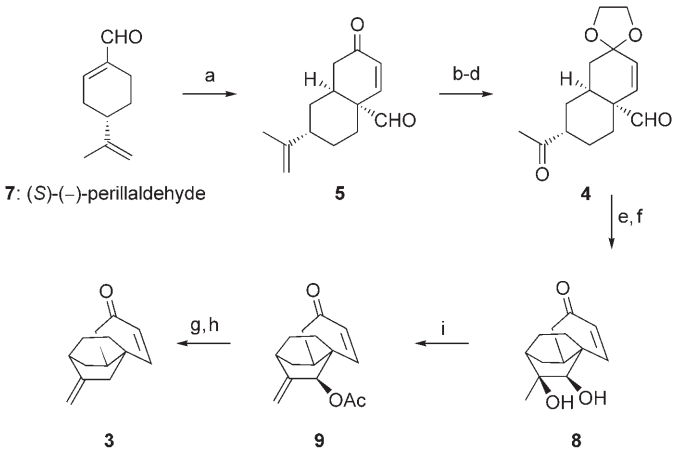

Scheme 3. Asymmetric synthesis of the platencin core **3**. Reagents and conditions: a) Danishefsky's diene (**6**; 1.1 equiv), MeCN, 15 kbar, RT to 50 °C, 16 h; then $Yb(OTf)_3$ (0.03 equiv), MeOTMS (0.10 equiv), toluene, 0 °C, 6 h, 81 %; b) Ph_3PMeBr (1.30 equiv), KO*t*Bu (1.10 equiv), THF, 0 °C, 30 min, 86 %; c) ethylene glycol (10.0 equiv), PPTS (0.25 equiv), benzene, reflux, 16 h; d) O_3, pyridine (4.0 equiv), CH_2Cl_2/MeOH (1:1), −78 °C; then Ph_3P (3.0 equiv), −78 °C to RT, 1.5 h, 91 % (over 2 steps); e) SmI_2 (0.1 M in THF, 5.0 equiv), MeOH (5.2 equiv), THF, RT, 10 min; f) TsOH, wet CH_2Cl_2, RT, 30 min, 85 % (over 2 steps); g) Ac_2O (5.0 equiv), DMAP, CH_2Cl_2/pyridine (20:1), 0 °C to RT, 1.5 h, quant.; h) Burgess reagent (2.0 equiv), toluene, 70 °C, 15 min, 48 %; i) $[Pd_2(dba)_3]$ (0.1 equiv), PBu_3 (0.2 equiv), Et_3N (6.0 equiv), HCO_2H (6.0 equiv), THF, reflux, 18 h, 60 %. dba = *trans,trans*-dibenzylideneacetone; DMAP = 4-dimethylaminopyridine; PPTS = pyridinium *para*-toluenesulfonate; Tf = trifluoromethanesulfonyl; Ts = *para*-toluenesulfonyl.

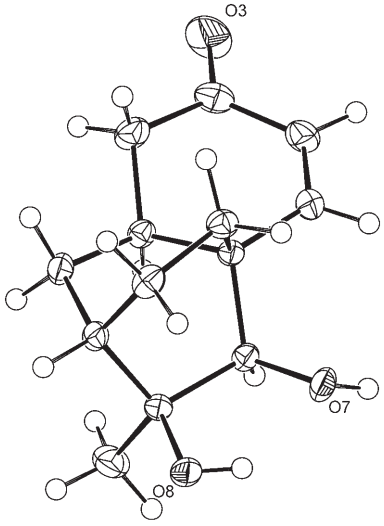

Figure 1. ORTEP plot of diol **8** derived from X-ray crystallographic analysis (non-hydrogen atoms are shown with ellipsoids at 50 % probability).

pressure Diels–Alder reaction of (*S*)-(−)-perillaldehyde (**7**). This single transformation led to the incorporation of the unsaturated ketone motif and all three stereocenters within the first step of the rection sequence. In addition, the bicyclo[2.2.2]octane core was efficiently accessed through a SmI_2-mediated pinacol coupling reaction. Currently, we are using this strategy for the succinct synthesis of analogues of platencin.

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[12] CCDC 691947 (**8**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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