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Total Synthesis and Antibiotic Activity of Dehydrohomoplatencin

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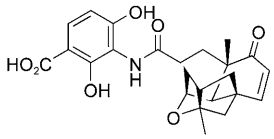
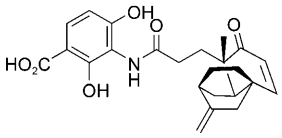
The emergence of resistant pathogens is a rapidly increasing concern to society and has been identified by the World Health Organization (WHO) as one of the three greatest threats to human health. Unfortunately, the pressing need for new classes of antibiotics is still poorly met by the pharmaceutical industry,[1] as illustrated by the recent call by the Infectious Diseases Society of America (IDSA) for a global commitment to develop ten new antibiotics by 2020.[2] In this respect, the recent discovery of two new antibiotics, platensimycin[3] (**1**) and platencin[4] (**2**), represented a potential breakthrough in antibiotic research.

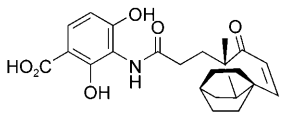


1: platensimycin

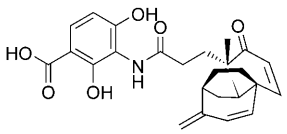


2: platencin

Both compounds are potent inhibitors of the fatty acid synthesis in Gram-positive bacteria and even eradicate notoriously resistant bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus faecalis* (VREF). Interestingly, the validity of this target and hence the in vivo efficacy of **1** and **2** is still under debate.[5] The valuable properties of these natural products immediately caught the attention of the synthetic community, which has culminated in an impressive number of formal and total syntheses given the relatively short time frame.[6] In contrast to **1**, the synthesis of platencin derivatives has received little attention. Norplatencin (**3**),[7] and very recently isoplatencin[8] and derivatives thereof, are the only closely related synthetic analogues of platencin that have been reported. Of these derivatives only isoplatencin demonstrated potent antibiotic activity. Herein, we report a concise total synthesis of dehydrohomoplatencin (**4**) of which the core structure can be synthesized in enantiopure form in two exceedingly simple steps. Furthermore, we will demonstrate that this analogue displays potent antibacterial activity.

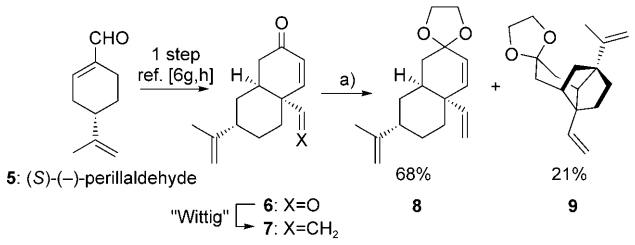


3: norplatencin



4: dehydrohomoplatencin

In our research toward a formal total synthesis of platencin (**2**),[6h] we isolated an unexpected side product in the reaction of alkene **7** with TsOH and ethylene glycol in refluxing benzene (Scheme 1). Extensive 2D NMR spectroscopy studies eventually revealed structure **9**, which might be formed by initial acid-mediated isomerization of the isopropenyl group to an isopropylidene group followed by attack



Scheme 1. Unexpected formation of acetal **9** in the protection of ketone **7**. a) TsOH, ethylene glycol, benzene, reflux, 16 h. Ts = *para*-toluenesulfonyl.

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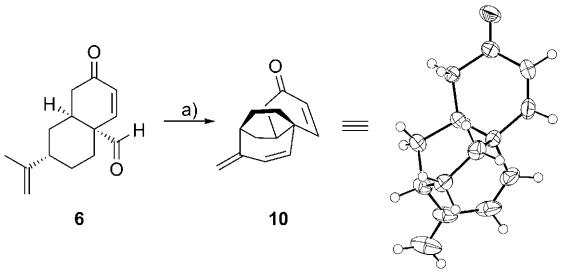
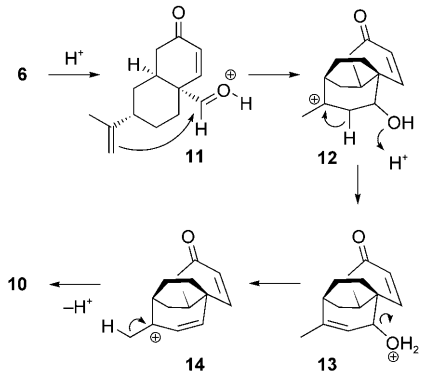
of this double bond in a 1,4-manner to the protonated unsaturated ketone. Loss of a proton from the resulting cation reformed the isopropenyl group. Subsequent protection of the ketone then afforded tricyclic acetal **9**.[9]

Intrigued by this mechanism, we attempted to reproduce the reaction with the precursor of alkene **7**, aldehyde **6**, in the absence of ethylene glycol and with more TsOH (0.5 equiv) to accelerate the reaction (Scheme 2). To our surprise, a completely different reaction occurred to afford diene **10** in 48% yield. By shortening the reaction time to 30 min the yield of diene **10** was increased to 67%.



Scheme 2. Synthesis and ORTEP plot of diene **10** derived from X-ray crystallographic analysis (non-hydrogen atoms are shown with ellipsoids at 50% probability). a) TsOH, benzene, 80°C, 0.5 h, 67%. Ts = *para*-toluenesulfonyl.

Most likely, the formation of diene **10** proceeds through an acid-mediated Prins cyclization[10] of aldehyde **6** to give the tertiary cation **12** (Scheme 3). Molecular modeling (MM2) indicates that formation of the endo double bond is



Scheme 3. Proposed reaction mechanism for the formation of diene **10**.

energetically favored, giving rise to allylic alcohol **13** as the thermodynamic product. Subsequent protonation and elimination of the alcohol will lead to the highly stabilized allylic cation **14**, which after elimination affords diene **10**. Although a carbonyl ene[11] pathway would also be possible, this seems less likely, since in the high-pressure Diels–Alder reaction leading to aldehyde **6** no carbonyl ene products are observed.[6h] It is interesting to note that examples of seven-membered ring formation through a Prins cyclization are rather rare and to the best of our knowledge none have been reported that yield a diene.

The unique structure of diene **10** was unambiguously confirmed by X-ray crystallographic analysis (Scheme 2) and shows great similarity to the core structure of **2**.[12] An overlay of ketones **10** and **15** clearly shows that the increased ring size of diene **10** does not alter the overall shape of the molecule compared to core structure **15** and only seems to affect the orientation of the exocyclic double bond (Figure 1).

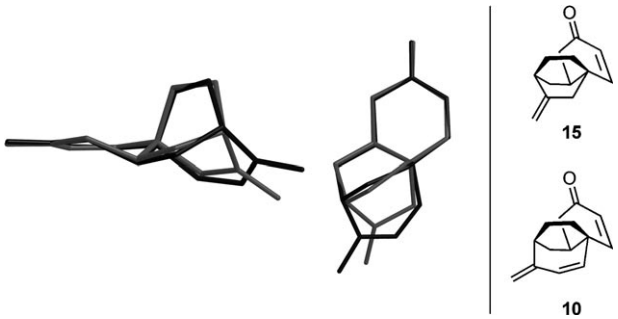
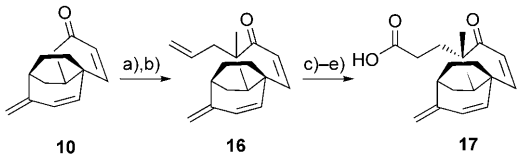


Figure 1. Overlay of the core structure of platencin (**15**) and diene **10**. Energies of conformations and overlap were minimized (MM2).

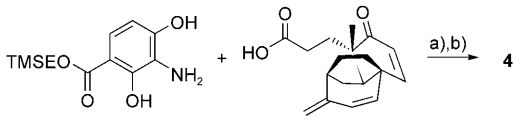
The significant structural resemblance of core structures **10** and **15**, and the exceptionally short synthesis of diene **10** sparked our interest in the antibiotic properties of a platencin analogue incorporating core structure **10**.

According to the methodology developed by Nicolaou and co-workers,[6d,13] diene **10** was methylated by using KHMDS and MeI in 93% yield and in an inconsequential diastereomeric ratio (d.r.) of 1:7 (Scheme 4). Subsequent allylation with allyl iodide proceeded smoothly and afforded alkene **16** in 76% yield and a d.r. of 3:10. The inseparable diastereomeric mixture was reacted in a cross-metathesis reaction with vinylboronic acid pinacol ester. The reaction returned a mixture of *E* and *Z* isomers that was treated with trimethylamine-*N*-oxide in THF at reflux to afford the corresponding aldehyde in 35% yield over two steps based on the 3:10 diastereomeric ratio of alkene **16**. Finally, oxidation of the aldehyde was achieved by a Pinnick oxidation to give carboxylic acid **17** in 91% yield.



Scheme 4. a) KHMDS, THF, −78°C, 45 min, then HMPA, MeI, 1 h, 93%, d.r. 1:7; b) KHMDS, THF, −78°C, 45 min, then HMPA, allyl iodide, 30 min, 76%, d.r. 3:10; c) Vinylboronic acid pinacol ester, Grubbs 2nd generation cat., benzene, 80°C, 1 h; d) Me_3NO, THF, 70°C, 1.5 h, 35% (2 steps); e) 2-methyl-2-butene, NaH_2PO_4, $NaClO_2$, H_2O, *t*BuOH, RT, 15 min, 91%. KHMDS = potassium bis(trimethylsilyl)amide, HMPA = hexamethylphosphoramide.

The synthesis of dehydrohomoplatencin (**4**) was efficiently completed by the coupling of carboxylic acid **17** to aniline **18**[6d] and subsequent deprotection of the TMSE ester with TASF (Scheme 5).



18 **17**

Scheme 5. a) HATU, Et_3N, DMF, RT, 70%; b) TASF, DMF, RT→40°C, 57%. TMSE = 2-(trimethylsilyl)ethyl, HATU = *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate, TASF = tris(dimethylamino)sulfonium difluorotrimethylsilicate.

With derivative **4** in hand, we could determine its antibiotic profile. Much to our delight, dehydrohomoplatencin (**4**) proved virtually equipotent to **2** and only lacked activity against *Streptococcus pneumoniae* (Table 1).[14]

Table 1. Minimum inhibitory concentration ($\mu g\,mL^{-1}$) of dehydrohomoplatencin (**4**) compared to the reported values for platensimycin (**1**) and platencin (**2**).

Organism and resistance	**4**	**2**[a]	**1**[a]
S. aureus (MSSA)	0.5	0.5	0.5
S. aureus (MRSA)	1	1	0.5
S. aureus (MRSA, Macrolid)	1	1	0.5
E. faecalis	2	2	1
E. faecium (vancomycin)	0.12	<0.06	0.1
CNS (MRSE)	0.12	ND[b]	ND[b]
S. pneumoniae	>16	4	1

[a] Values taken from literature.[3,4a] [b] ND = not determined.

In conclusion, we have developed an exceedingly short enantiopure synthesis to core structure **10** using a novel Prins cyclization as the key step. By this easy two-step protocol using commercially available starting materials, we are now able to routinely synthesize diene **10** on a multigram scale. This structure was elaborated to derivative **4**, which proved to be virtually equipotent to **2**. Currently, we are exploiting the concise synthesis of diene **10** to quickly assemble a library of derivatives with modified aromatic fragments for structure–activity relationship (SAR) studies.

Experimental Section

Diene 10: TsOH (0.789 g, 4.58 mmol) was added in one portion to a solution of aldehyde **6** (2.00 g, 9.16 mmol) in benzene (70 mL) under an argon atmosphere. The reaction flask was placed in a preheated oil bath at 80°C and stirred for 30 min. At that time TLC analysis showed complete consumption of aldehyde **6** and the reaction mixture was cooled to RT using a water bath. The reaction mixture was diluted with diethyl ether (40 mL) and washed with water (80 mL). The water layer was extracted with diethyl ether (2×40 mL) and the combined organic layers were washed with saturated aqueous $NaHCO_3$ (40 mL) and brine (40 mL), dried over Na_2SO_4, and the solvent was evaporated in vacuo. The crude product was purified by flash chromatography (silica gel, EtOAc/heptane 1:20 to 1:5) to give diene **10** as a pale yellow oil that solidified upon storage in the freezer (1.22 g, 67%). A sample for X-ray crystallographic analysis was obtained by dissolving diene **10** in heptane and subsequent slow evaporation of most of the solvent. The remaining mother liquor was removed by pipette and the process was repeated again to give diene **10** as colorless rodlike crystals. $[\alpha]_D^{20} = -42.4$ (*c* 1.07, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 6.67$ (d, $J = 10.1$ Hz, 1H), 6.14 (dd, $J = 1.6$, 10.8 Hz, 1H), 5.91 (dd, $J = 1.0$, 10.1 Hz, 1H), 5.73 (d, $J = 10.8$ Hz, 1H), 4.82 (m, 1H), 4.77 (m, 1H), 2,60–2.65 (m, 1H), 2.48–2.57 (m, 1H), 2.39 (ddd, $J = 0.8$, 5.1, 16.2 Hz, 1H), 2.30 (dd, $J = 13.7$, 16.2 Hz, 1H), 2.12 (tdd, $J = 2.4$, 9.4, 13.9 Hz, 1H), 1.76–1.94 (m, 4H), 1.43 ppm (ddd, $J = 4.4$, 7.3, 13.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 199.6$, 157.4, 153.2, 139.0, 132.8, 126.6, 112.8, 43.1, 40.0, 39.3, 38.6, 35.6, 28.4, 26.4 ppm; IR (neat): $\tilde{\nu} = 3076$, 3018, 2930, 2858, 1679, 1635, 1620, 1592 cm^{-1}; HRMS (EI^+): *m*/*z* calcd for $C_{14}H_{16}O$: 200.1201 $[M]^+$; found: 200.1204.

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Keywords: antibiotics · medicinal chemistry · platencin · Prins reaction · total synthesis

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[9] A scheme of the proposed reaction mechanism has been included in the Supporting Information.

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[12] CCDC-783495 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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[14] See the Supporting Information for a full overview of MIC values of derivative **4**.

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