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Synthesis and Antibacterial Properties of (−)-*nor*-Platencin

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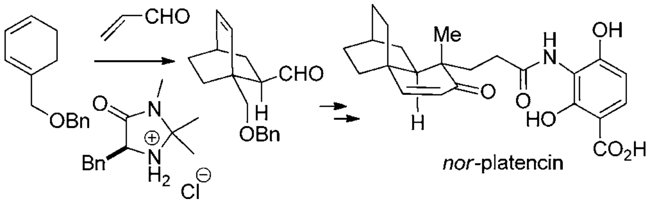
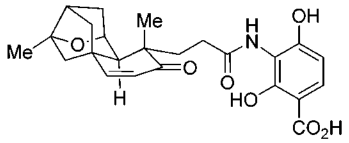
ABSTRACT

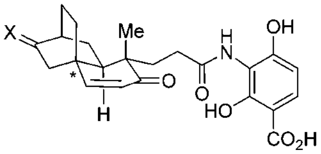


An asymmetric Diels–Alder reaction between acrolein and 1-benzyloxymethyl-1,3-cyclohexadiene affords a bicyclic aldehyde that was elaborated in 11 steps to *nor*-platencin. *nor*-Platencin is 4–16 times less active than platencin against several resistant strains of *Staphylococcus aureus*, macrolide-resistant *Enterococcus faecalis*, and vancomycin-resistant *Enterococcus faecium*.

Scientists at Merck recently isolated the novel antibiotics platensimycin (**1**)[1,2] and platencin (**2**)[3] (see Figure 1). These compounds are the first potent inhibitors of bacterial fatty acid biosynthesis (Fab), which is needed for the survival of bacterial pathogens. This pathway is highly conserved among bacteria and is distinct from the mammalian pathway.



platensimycin (**1**)



platencin, X = CH_2 (**2**)
nor-platencin, X = H_2 (**3**)

Figure 1. Structures of platensimycin (**1**), platencin (**2**), and *nor*-platencin (**3**).

Platensimycin blocks the fatty acid condensing enzyme β-ketoacyl-[acyl carrier protein] synthase II (FabF) selectively, whereas platencin inhibits both enzymes FabF and β-ketoacyl-[acyl carrier protein] synthase III (FabH) with IC_{50} values of 1.95 and 3.91 μg/mL in *Staphylococcus aureus*. These antibiotics do not exhibit cross-resistance to key antibiotic resistant strains, including methicillin-resistant S. aureus, vancomycin-intermediate *S. aureus* and vancomycin-

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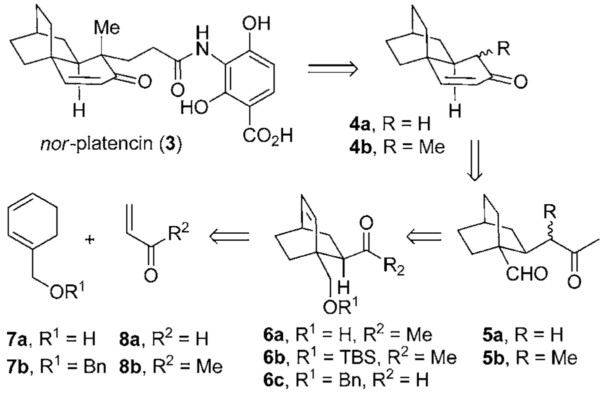
resistant *Enterococcus faecium*. Platencin shows potent in vivo efficacy without any observed toxicity.

As expected from the novel structures and potent antibacterial activity, both platensimycin (**1**)[4,5] and platencin (**2**)[6] have been the object of intense synthetic interest. Numerous analogues of platensimycin have also been prepared, establishing that the aromatic moiety is crucial for activity, but that there is some room for structural modification of the tricyclic diterpenoid moiety.[7] No close analogues of platencin have been prepared. We speculated that the exo-methylene group of platencin is not needed for biological activity but is present simply because it is a structural feature of the terpenoid precursor. The exo-methylene group is acid-sensitive and may also decrease the metabolic stability of platencin. Finally, the exo-methylene group complicates the synthesis by introducing both reactive functionality and an additional chiral center at the carbon marked by an asterisk. Our goal therefore was to develop a short synthesis of *nor*-platencin (**3**), which lacks the exo-methylene group of platencin (**2**).

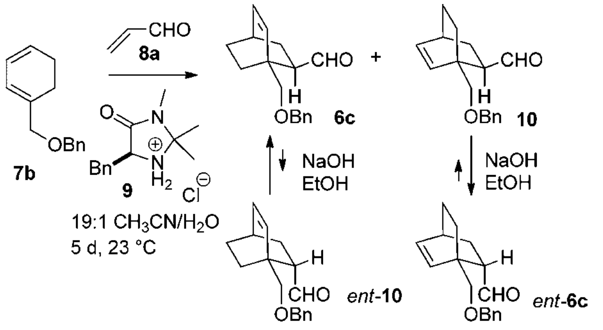
Our retrosynthesis is outlined in Scheme 1. We planned to prepare *nor*-platencin (**3**) from enone **4**, R = H or Me, using methods developed for the synthesis of platencin (**2**). Enone **4** will be prepared by an intramolecular aldol reaction of keto aldehyde **5**, R = H or Me, which can be prepared by homologation of Diels−Alder adduct **6**, which will be synthesized from the readily available 1,3-cyclohexadienemethanol (**7a**, R = H)[8] and acrolein (**8a**, R = H) or methyl vinyl ketone (**8b**, R = Me). Use of methyl vinyl ketone would introduce the methyl group early in the synthesis. Use of acrolein would require methylation of **4a**, as in the platencin syntheses.[7]

Scheme 1. Retrosynthesis of *nor*-Platencin (**3**)



The Diels−Alder reaction of **7a**, R^1 = H, with methyl vinyl ketone (**8b**) proceeded poorly either thermally or with Lewis acid catalysis but gave a reasonable yield of racemic Diels−Alder adduct **6a** and stereo- and regioisomers by reaction "on water".[9] Unfortunately, the Diels−Alder adducts were difficult to work with because they exist as a mixture of open and hemiketal tautomers. We were able to prepare **6b**, R^1 = TBS and R^2 = Me, but all attempts to homologate this by a Wittig reaction resulted in enolization of the hindered methyl ketone. For these reasons we turned to acrolein (**8a**) as the dienophile and readily available 1,3-cyclohexadienylmethyl benzyl ether (**7b**)[10] as the diene. The protecting group will prevent formation of hemiacetals and will be removed without an additional step during hydrogenation of the double bond. Enolization should not occur during homologation of **6c** because the carbonyl group is an aldehyde rather than a methyl ketone.

Scheme 2. Diels−Alder Reaction of **7b** and **8a**



In the reaction of **7b** with acrolein (**8a**) as the dienophile, we were able to take advantage of MacMillan's asymmetric Diels−Alder reaction using 10% of imidazolidinone **9**[11] as the catalyst in 19:1 CH_3CN/H_2O for 5 days (see Scheme 2). This afforded a 9:1 mixture of the desired endo adduct **6c** and exo adduct **10**, from which **6c** (32%) and **10** (4%) were

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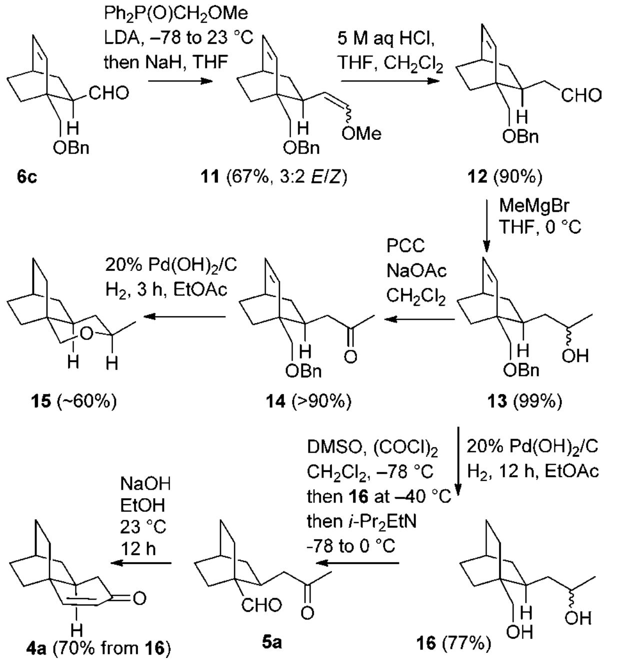
isolated in pure form along with an additional 10% of impure **6c**. Other conditions, including MeOH/H_2O and CH_3NO_2/H_2O, were less successful. Chiral HPLC established that the ee of the major product **6c** is 87%. Our yield does not compare favorably with that reported by MacMillan for the reaction of 1,3-cyclohexadiene with **8a** catalyzed by 5% of **9**, which gave a 14:1 mixture of endo and exo isomers in 82% yield with 94% ee for the endo isomer.[11a] However, in his synthesis of hapalaindole Q, Kerr carefully optimized the Diels−Alder reaction of 1,3-dimethyl-1,3-cyclohexadiene with 3-(3-(*N*-tosyl)indolyl)acrolein catalyzed by 40% of **9** to obtain a maximum yield of 35% with 85:15 endo/exo selectivity and 93% ee for the endo isomer.[11c] As Kerr also noted in his synthesis,[11c] the rapid and enantioselective assembly of the key intermediate **6c** makes this route attractive despite the modest yield.

The lower ee in our case could result from an uncatalyzed background reaction. Reaction of **7b** and **8a** for 5 days without catalyst **9** afforded Diels−Alder adducts in 10% yield. The background reaction will be much less significant in the presence of catalyst **9** because the diene is consumed in the more rapid catalyzed reaction. The ee can probably be improved somewhat by increasing the catalyst loading. Equilibration of both **6c** and **10** with aqueous NaOH in EtOH afforded the identical 3:1 mixture of **6c** and **10**. The catalyst controls the stereochemistry adjacent to the aldehyde center so that epimerization of exo adduct **10** will give *ent*-**6c**, providing another possible explanation for the lower ee. However, the isolation of a 9:1 mixture of endo isomer **6c** and exo isomer **10** suggests that epimerization is not a major issue.

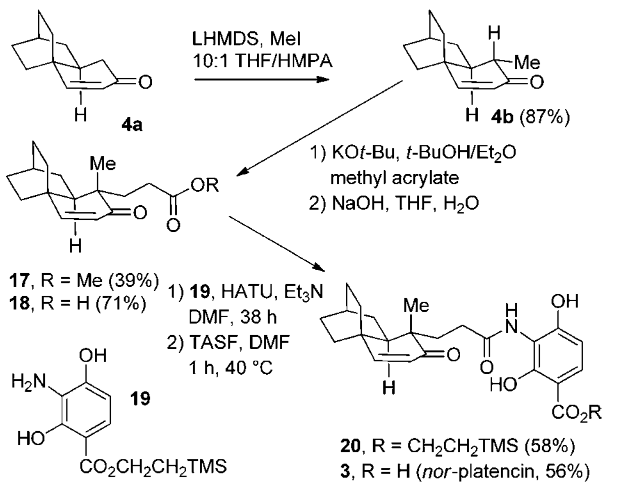
Homologation of **6c** by a Horner−Wittig reaction[12] now proceeded smoothly to give **11** as a 3:2 mixture of stereoisomers in 67% yield (see Scheme 3). Hydrolysis of **11** in a two-phase system[13] with aqueous HCl in CH_2Cl_2 and THF provided the homologated aldehyde **12** in 90% yield. Addition of MeMgBr to **12** afforded secondary alcohol **13** in 99% yield as a mixture of stereoisomers. Buffered PCC oxidation of **13** gave ketone **14** in >90% yield. To our surprise, hydrogenation of **14** afforded mainly tetrahydropyran **15**. Hydrogenation and hydrogenolysis provided the desired saturated hydroxy ketone, which cyclized to form the hemiketal. Further reduction, probably by dehydration to the enol ether and hydrogenation, afforded **15**.

Scheme 3. Synthesis of Tricyclic Enone **4a**



We therefore decided to carry out the hydrogenation and hydrogenolysis before formation of the ketone. Hydrogenation of **13** afforded a mixture of 1,5-diols **16** in 77% yield. Swern oxidation appears to be the method of choice for the oxidation of 1,5-diols to keto aldehydes,[14] because other procedures give the δ-lactone as a byproduct.[15] Swern oxidation of **16** using *i*-Pr_2EtN,[16] rather than Et_3N, gave the unstable keto aldehyde **5a**, which was treated with NaOH in EtOH to give the desired cyclohexenone **4a**[17] in 70% overall yield from **16**.

Scheme 4. Completion of the *nor*-Platencin (**3**) Synthesis



Alkylation of **4a** with LHMDS and MeI in 10:1 THF/HMPA afforded 87% of **4b** containing a few percent of the stereoisomer (see Scheme 4).[6b] Elaboration of **4b** to carboxylic acid **18** was carried out using procedures developed by Corey for the preparation of a platensimycin analogue

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and by Mulzer for the synthesis of platencin.[6h,7b] Treatment of **4b** with *t*-BuOK and methyl acrylate in ether/*t*-BuOH for 30 min at 0 °C provided a 5:1 mixture of ester **17** and the diastereomer from which the desired isomer **17** was isolated in 39% yield by preparative HPLC. Hydrolysis of **17** afforded acid **18** in 71% yield. Amide formation was accomplished by reaction of acid **18** with protected aniline **19**[5d,6a,18] using HATU (*O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate) in DMF for 38 h to give trimethylsilylethyl ester **20** (58%), which was hydrolyzed with TASF in DMF to provide (−)-*nor*-platencin (**3**) in 56% yield.

The antibiotic acitivity of *nor*-platencin (**3**) was determined against several resistant strains of *S. aureus*, macrolide-resistant *E. faecalis*, and vancomycin-resistant *Enterococcus faecium*. The minimum inhibitory concentration (MIC) data shown in Table 1 indicate that *nor*-platencin (**3**) is 4−16 times less potent than platencin (**2**) as an antibiotic. As with platencin (**2**), the best activity is shown against vancomycin-resistant *E. faecium*. The reduced potency of **3** indicates that the exo-methylene group of platencin (**2**) contributes modestly to the antibiotic activity.

In conclusion, an asymmetric Diels−Alder reaction between acrolein (**8a**) and 1-benzyloxymethyl-1,3-cyclohexadiene (**7b**) affords bicyclic aldehyde **6c** that was elaborated in 11 steps to *nor*-platencin (**3**). *nor*-Platencin (**3**) is 4−16 times less potent than platencin (**2**) against several bacterial strains, indicating that the exo-methylene group of platencin (**2**) contributes modestly to the antibiotic activity.

Table 1. Antibiotic Activity of Platencin (**2**) and *nor*-Platencin (**3**)

organism and genotype	platencin (**2**) MIC, μg/mL[a]	*nor*-platencin (**3**) MIC, μg/mL[b]
S. aureus (MSSA)	0.5	4
S. aureus (MRSA)	1	4
S. aureus (MRSA) plus serum	8	>32
S. aureus (MRSA macrolide-R and Linezolid-R)	1	4
S. aureus (VISA)	0.5	8
S. aureus (VRSA)	1	16
S. aureus (hVISA)	ND	4
S. aureus (MRSA daptomycin-R)	ND	4
E. faecalis (macrolide-R)	2	16
E. faecium (vancomycin-R)	<0.06	0.25
E. coli	>64	>32

[a] Data from ref 3a. [b] MIC determined according to *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard*, 8th ed.; Document M07-A8; Clinical and Laboratory Standards Institute: Wayne, Pennsylvania, 2008. ND = not determined. R = resistant.

Acknowledgment. We are grateful to the National Institutes of Health (GM-50151) for support of this work.

Supporting Information Available: Complete experimental procedures and copies of ^{1}H and ^{13}C NMR spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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