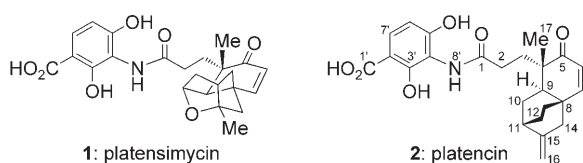


Total Synthesis of Platencin**

K. C. Nicolaou,* G. Scott Tria, and David J. Edmonds

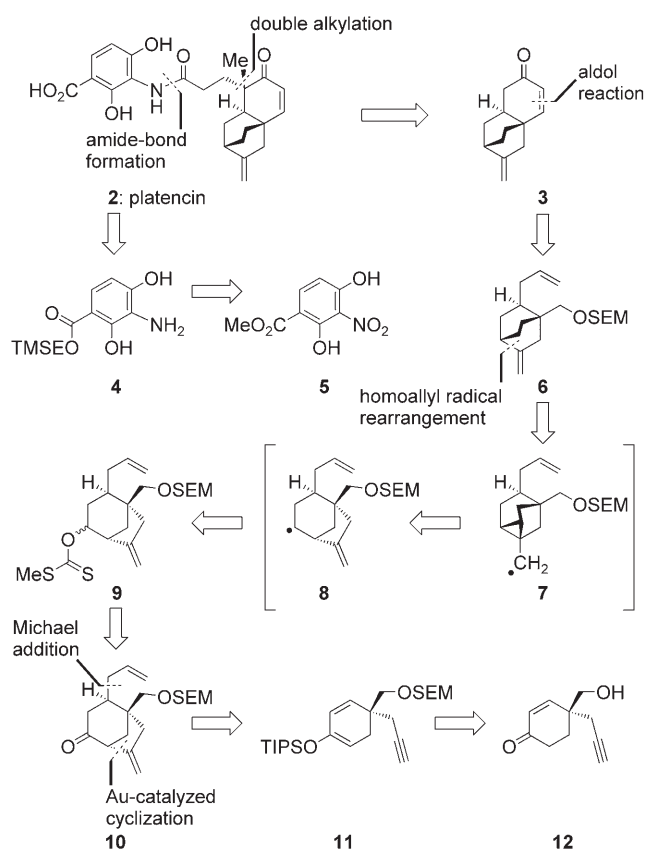
The evolution of bacteria with resistance towards clinically used antibiotics requires constant efforts in the search for new antibacterial compounds to target these menacing strains.^[1] Recent advances in screening technologies allowed a team of scientists at Merck to develop and employ a target-based, whole-cell, high-throughput screening assay for the detection of inhibitors of the condensing enzymes FabH and FabF in the biosynthesis of fatty acids in bacteria.^[2,3] Their efforts were rewarded with the discovery of the much hailed antibiotics platensimycin (**1**)^[2] and platencin (**2**, Scheme 1).^[3] Isolated

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

from a new strain of *Streptomyces platensis* MA7339 found in a soil sample collected in Spain, platencin (**2**) is a potent inhibitor of *Staphylococcus aureus* fatty acid biosynthesis ($IC_{50} = 0.45 \mu M$), SaFabH ($IC_{50} = 9.2 \mu M$), and SaFabF ($IC_{50} = 4.6 \mu M$). Platencin (**2**) exhibits broad-spectrum antibacterial activity against many Gram-positive pathogens that show resistance to current antibiotics ($MIC_{50} \leq 0.06\text{--}4 \mu g mL^{-1}$), including *S. aureus*, methicillin-resistant *S. aureus* (MRSA), macrolide-resistant MRSA, linezolid-resistant MRSA, vancomycin intermediate *S. aureus*, vancomycin-resistant enterococci, and *Streptomyces pneumoniae*.^[3] Impressively, this new antibiotic demonstrated a thousandfold reduction of

S. aureus colony-forming units in an in vivo mouse model compared to an untreated control.^[3] Whereas several syntheses of platensimycin (**1**) and its analogues have been reported,^[4] none for platencin (**2**) has yet appeared in the literature. Herein we report an enantioselective total synthesis of this newly discovered and highly promising antibiotic.

The molecular structure of platencin (**2**) resembles that of platensimycin (**1**) in that they both contain an identical domain (comprising $C_1\text{--}C_9$, C_{17} , $C_{18}\text{--}C_{20}\text{--}N_1$) but they differ significantly in their $C_8\text{--}C_{16}$ core domains (Scheme 1). As such, a distinctly different approach from those employed to synthesize platensimycin (**1**) is required to construct the “right-hand” core structure of the molecule (enone **3**), while the rest of the pathway to platencin (**2**) should, in principle, follow that already charted for platensimycin (**1**).^[4a] Scheme 2 outlines, in retrosynthetic format, the devised strategy for the synthesis of platencin (**2**), which defines enone **3** as the key precursor to the target molecule and requires amide coupling

Scheme 2. Retrosynthetic analysis of platencin (**2**). TMSE = 2-(trimethylsilyl)ethyl, SEM = 2-(trimethylsilyl)ethoxymethyl, TIPS = triisopropylsilyl.

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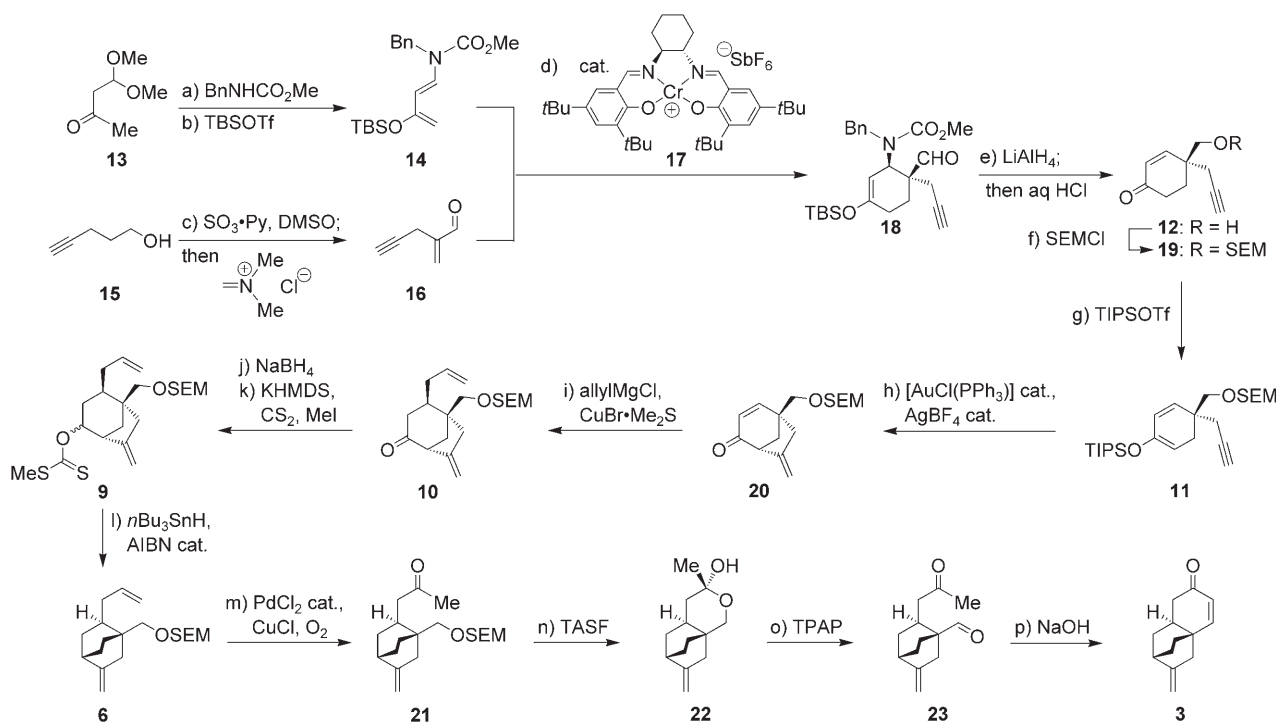
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with aniline derivative **4** (which traces back to nitroarene **5**^[5]) and final deprotection. In our previous work on platensimycin (**1**), we employed an aniline derivative bearing a methyl ester group and methoxymethyl (MOM) ethers to mask its carboxylic acid and phenolic moieties, respectively.^[4a] The MOM groups dictated the use of acidic hydrolysis conditions for their removal in the final step. In this case, to ensure the survival of the molecule under the deprotection conditions, we chose the TMSE ester as the obligatory protecting group for the carboxylic acid and decided to leave the phenolic groups unprotected. This modification has the extra advantage of shortening the sequence by a number of steps, as compared to the route used for the total synthesis of platensimycin (**1**), as a result of easier access to the aniline fragment and the avoidance of any deprotection of the phenolic groups. Enone **3** was envisioned to be derived through an aldol condensation of the corresponding ketoaldehyde, which could, in turn, be obtained from diene **6** by Wacker oxidation. A homoallyl radical rearrangement^[6] was then envisioned as a means to connect bicyclo[2.2.2] diene **6** to bicyclo[3.2.1] ketone **10** (through radical species **8** and **7**,

Scheme 2). A retro gold-catalyzed cyclization^[7] revealed acetylenic TIPS enol ether **11** as a possible precursor. The synthesis of **11** from enone **12** was envisioned, with **12** potentially being available through an asymmetric Diels–Alder reaction.

The construction of enone **3** (Scheme 3) started from the known diene **14** (available from ketone **13** by literature procedures)^[8] and the rather volatile dienophile **16**, prepared from acetylenic alcohol **15** in a one-pot procedure involving oxidation ($\text{SO}_3 \cdot \text{Py}$, DMSO, Et_3N , 0°C) followed by addition of Eschenmoser's salt^[9] (53% yield). A Rawal asymmetric Diels–Alder reaction^[8,10] between **14** and **16** in the presence of Cr^{III} -salen catalyst **17**^[11] furnished cyclohexene **18** in 92% yield. Reduction of **18** with lithium aluminum hydride followed by exposure to aqueous HCl led to hydroxy enone **12** in 63% yield and 93% *ee*.^[12] Formation of the SEM ether **19** (SEMCl, Et_3N , THF, 70°C , 94% yield) and its subsequent exposure to TIPSOTf (Et_3N , CH_2Cl_2 , $-78 \rightarrow 0^\circ\text{C}$, 97% yield) gave acetylenic diene **11**. Treatment of **11** with the catalyst derived from $[\text{AuCl}(\text{PPh}_3)]$ (2 mol %) and AgBF_4 (2 mol %) induced the desired cyclization,^[7] thereby generating the



Scheme 3. Asymmetric synthesis of the core enone (**3**) of platencin. Reagents and conditions: a) *N*-benzyl methyl carbamate (1.0 equiv), **13** (2.0 equiv), TsOH (0.05 equiv), CHCl_3 , reflux, 24 h, 89%; b) TBSOTf (1.1 equiv), Et_3N (3.0 equiv), Et_2O , $-78 \rightarrow 0^\circ\text{C}$, 1 h, 87%; c) $\text{SO}_3 \cdot \text{Py}$ (2.0 equiv), DMSO (5.0 equiv), Et_3N (5.0 equiv), CH_2Cl_2 , 25°C , 2 h; then $\text{Me}_2\text{NCH}_2\text{Cl}$ (1.5 equiv), 25°C , 12 h, 53%; d) **16** (1.0 equiv), **14** (1.7 equiv), **17** (0.05 equiv), 4-Å M.S., CH_2Cl_2 , -60°C , 60 h, 92%; e) LiAlH_4 (1.5 equiv), Et_2O , $-78 \rightarrow -40^\circ\text{C}$, 2 h; then HCl (2 M in MeOH, 10 equiv), 25°C , 16 h, 63%; f) SEMCl (1.2 equiv), Et_3N (4.0 equiv), DMAP (0.1 equiv), THF, reflux, 16 h, 94%; g) TIPSOTf (1.5 equiv), Et_3N (3.0 equiv), $-78 \rightarrow 0^\circ\text{C}$, 1 h, 97%; h) $[\text{AuCl}(\text{PPh}_3)]$ (0.02 equiv), AgBF_4 (0.02 equiv), toluene/MeOH (10:1), 25°C , 30 min, 94%; i) allylmagnesium chloride (4.0 equiv), $\text{CuBr} \cdot \text{Me}_2\text{S}$ (2.0 equiv), THF, -78°C , 1.5 h, 74%; j) NaBH_4 (2.5 equiv), MeOH, $-5^\circ\text{C} \rightarrow 25^\circ\text{C}$, 1 h, 97%; k) CS_2 (10 equiv), KHMDS (5.0 equiv), MeI (5.0 equiv), THF, $-78^\circ\text{C} \rightarrow 25^\circ\text{C}$, 1.5 h, 100%; l) $n\text{Bu}_3\text{SnH}$ (2.0 equiv), AIBN (0.08 equiv), toluene, 100°C , 20 min; m) PdCl_2 (0.25 equiv), CuCl (1.5 equiv), O_2 (balloon), DMF/ H_2O (6.6:1), 25°C , 24 h, 50% (2 steps); n) TASf (10 equiv), DMPU, 85°C , 1.5 h, 80% (based on recovered starting material); o) TPAP (0.03 equiv), NMO (6.5 equiv), CH_2Cl_2 , 25°C , 4 h, 54%; p) NaOH (6.0 equiv), EtOH, 25°C , 19 h, 99%. Bn = benzyl, Ts = *p*-toluene sulfonyl, TBS = *tert*-butyldimethylsilyl, Tf = trifluoromethanesulfonyl, Py = pyridine, DMSO = dimethyl sulfoxide, M.S. = molecular sieves, DMAP = 4-dimethylaminopyridine, THF = tetrahydrofuran, HMDS = hexamethyldisilazide, AIBN = 2,2'-azobis(isobutyronitrile), DMF = *N,N*-dimethylformamide, TASf = tris(dimethylamino)sulfonium difluorotrimethylsilicate, DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone, TPAP = tetra-*n*-propylammonium perruthenate, NMO = 4-methylmorpholine *N*-oxide.

bicyclic enone **20** in 94% yield. Reaction of substrate **20** with allylmagnesium chloride/CuBr-Me₂S at low temperature resulted in conjugate addition to the enone moiety to give cyclohexanone derivative **10** in 74% yield. This compound was reduced with NaBH₄ and the resulting mixture of diastereoisomeric alcohols (ca. 2:1) was converted into xanthate **9** by reaction with KHMDS, CS₂, and MeI (ca. 2:1 mixture of diastereoisomers, 97% yield for the two steps).^[13] Treatment of the mixture of xanthates **9** with *n*Bu₃SnH in the presence of catalytic amounts of AIBN at 100 °C^[6] then furnished the desired rearranged product **6** contaminated with about 15% of a by-product, presumed to arise from 5-*exo*-trig cyclization onto the pendant allyl group. The selectivity of this reaction for the desired rearrangement product was dependent on the protecting group residing on the primary alcohol of the substrate, with small unbranched groups favoring the required pathway. Rearrangement of each diastereomerically pure xanthate **9** gave essentially identical results. Wacker oxidation^[14] (PdCl₂ cat., CuCl, O₂) of diene **6** produced methyl ketone **21** (50% yield from **9**). Cleavage of the SEM group in **21** to give the hydroxy ketone was best achieved with TASF in DMPU at 85 °C in 80% yield based on 70% conversion. Interestingly, the hydroxy ketone product presumed to be formed initially in this reaction was found to exist as hemiacetal **22**, which was isolated as a single diastereoisomer. Hemiacetal **22** crystallized from CDCl₃/CH₂Cl₂ (m.p. 115–117 °C) as colorless needles. An X-ray crystallographic analysis of **22** revealed its [2.2.2] bicyclic structural motif (see ORTEP drawing, Figure 1), thus confirming that the radical rearrangement had taken place as anticipated, and that this series of compounds had the required relative configuration.^[15] Oxidation of hemiacetal **22** was achieved with NMO in the presence of catalytic amounts of TPAP,^[16] and led to keto aldehyde **23** (54% yield), whose exposure to ethanolic NaOH furnished the targeted enone **3** in 99% yield through the expected aldol condensation.

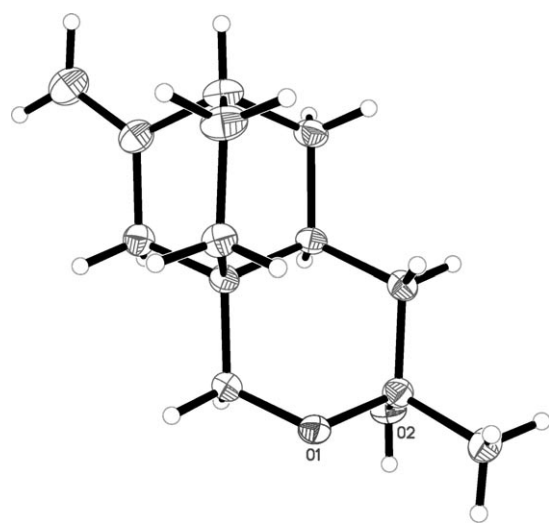
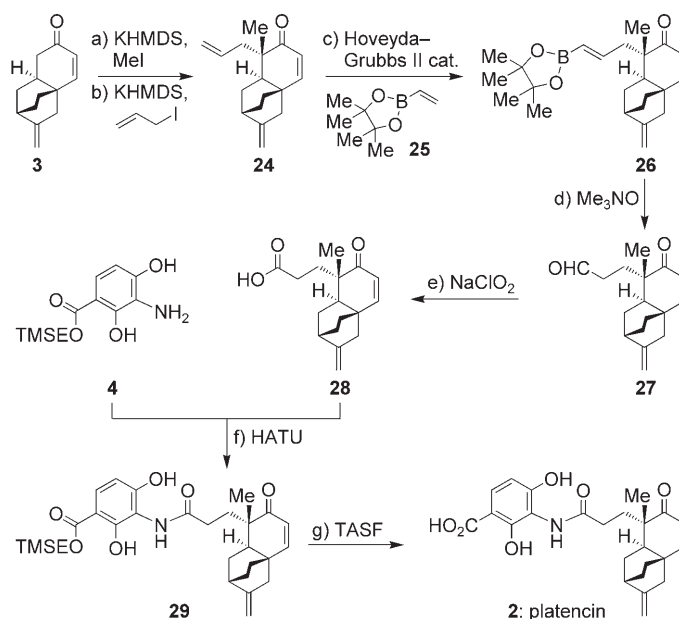


Figure 1. ORTEP drawing of **22** derived from X-ray crystallographic analysis (non-hydrogen atoms are shown as 30% ellipsoids).

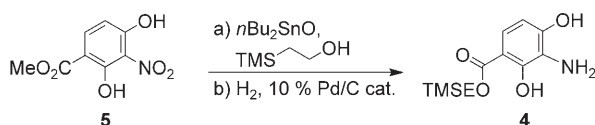
Enone **3** was converted into the required carboxylic acid **28** by a sequence similar to that developed by our research group for the corresponding platensimycin carboxylic acid.^[4a] Thus, as shown in Scheme 4, sequential alkylation of **3**



Scheme 4. Completion of the total synthesis of platencin (**2**). Reagents and conditions: a) KHMDS (1.1 equiv), MeI (8.0 equiv), THF/HMPA (4:1), –78 → 0 °C, 2 h, 68%; b) KHMDS (4.0 equiv), allyl iodide (8.0 equiv), THF/HMPA (4:1), –78 → 0 °C, 3 h, 86%; c) **25** (5.0 equiv), Hoveyda–Grubbs II cat. (0.1 equiv), benzoquinone (0.1 equiv), benzene, 70 °C, 1 h; d) Me₃NO (5.0 equiv), THF, 70 °C, 1 h; e) NaClO₂ (3.0 equiv), NaH₂PO₄ (5.0 equiv), 2-methyl-2-butene (10 equiv), *t*BuOH/H₂O (1:1), 25 °C, 20 min, 39% (3 steps); f) **4** (3.2 equiv), HATU (3.2 equiv), Et₃N (4.2 equiv), DMF, 25 °C, 14 h, 61%; TASF (2.0 equiv), 40 °C, 40 min, 93%. HMPA = hexamethylphosphoramide, HATU = *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate.

[a] KHMDS, MeI, 68% yield; b) KHMDS, allyl iodide, 86% yield] gave triene **24**, which underwent regioselective cross-metathesis with vinyl boronate **25**^[17] in the presence of the second-generation Hoveyda–Grubbs catalyst^[18] and benzoquinone^[19] to afford boronate **26** (*E/Z* ca. 3:1). Oxidation of the so-obtained mixture of boronates with Me₃NO (THF, 70 °C) followed by Pinnick oxidation (NaClO₂) then led to the desired carboxylic acid **28**, via aldehyde **27**, in 39% overall yield from **24**.

The requisite aniline fragment **4** was conveniently prepared from Giannis' nitro ester **5**^[5] through ester exchange (TMSEOH, *n*Bu₂SnO, 61% yield)^[20] and catalytic hydrogenation (10% Pd/C, 100% yield), as shown in Scheme 5. Finally, coupling of the carboxylic acid fragment **28** with aniline fragment **4** was achieved through the action of HATU (Et₃N, DMF, 25 °C, 61% yield, unoptimized) to furnish platencin derivative **29**, from which platencin (**2**) was liberated by treatment with TASF (DMF, 40 °C, 93% yield). Synthetic platencin (**2**) exhibited spectral data consistent with its structure and in accord with those reported^[3] for the natural product.^[21]



Scheme 5. Preparation of aniline fragment **4**. Reagents and conditions: a) TMSEOH (14.8 equiv), $n\text{Bu}_2\text{SnO}$ (1.5 equiv), 70°C , 3 h, 61%; b) H_2 (balloon), 10% Pd/C (0.05 equiv), AcOH (1 equiv), EtOAc/MeOH (5:1), 15 h, 100%. TMS = trimethylsilyl.

The described synthetic strategy allows access to platencin (**2**) in its naturally occurring form and opens the way to the construction of analogues of this newly discovered and valuable lead for drug discovery in the area of infectious diseases. Such studies are anticipated, as are other synthetic routes to the natural substance.

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