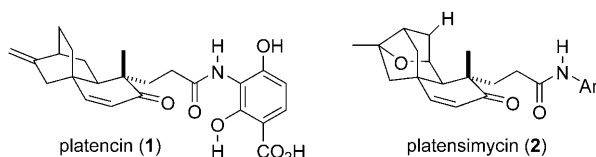


Formal Total Synthesis of Platencin**

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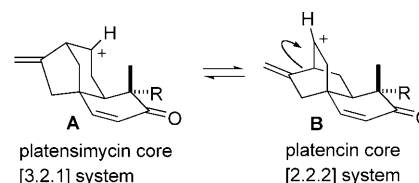
The increasing appearance of bacterial resistance has stimulated a resumption of the search for novel antibiotics. Not only various depsipeptides but also structurally novel polycyclic polyketide and terpene derivatives with antibiotic activity have been discovered.^[1,2] The two closely related antibiotics platencin^[3] and platensimycin^[4] were described by a research group from Merck. Platencin (**1**), the most recently



discovered of the two, was isolated from a strain of *Streptomyces platensis*, MA7339. Like platensimycin (**2**; the aryl group Ar is the same as that in **1**), platencin (**1**) shows potent antimicrobial activity against a broad spectrum of Gram-positive bacteria. In particular, it inhibits key antibiotic-resistant pathogens, such as methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococci*, and *Streptococcus pneumoniae*.

The screening assay was targeted against bacterial fatty-acid biosynthesis; thus, both **1** and **2** inhibit this process.^[5] In contrast to **2**, platencin (**1**) blocks two condensing enzymes, namely, β -ketoacyl synthase (KAS) II and III. Both compounds contain a highly substituted 3-amino-2,4-dihydroxybenzoic acid moiety and a rather hydrophobic polycyclic enone-acid unit. Biosynthetic studies revealed that the terpene moiety in both cases originates from the non-mevalonate MEP pathway^[6,7] (MEP = methylerythritol phosphate) and is formed via the diterpene copalyl pyrophosphate (see the Supporting Information).^[8] Alternatively, a late-stage interconversion of the two ring systems could be possible, as shown by the carbenium-ion structures **A** and **B** (Scheme 1).^[3b]

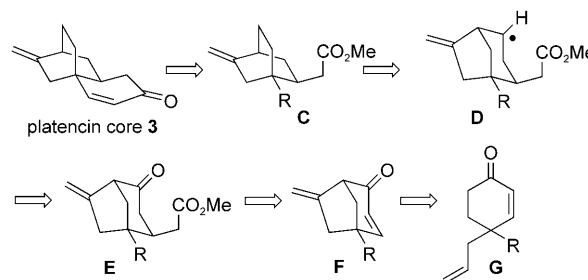
The potent in vivo activities and novel intriguing structures of these compounds prompted a number of attempts at their synthesis. Since platensimycin was first described in



Scheme 1. Possible late-stage interconversion of the platensimycin core into the platencin system.

2006, 10 total or formal total syntheses have been reported.^[9,10] The year 2008 saw the publication of seven platencin syntheses.^[11] We also became interested in the synthesis of platencin and conceived a unique route to the advanced intermediate **3** (Scheme 2). Our approach was inspired by the bicyclo[3.2.1]octane–bicyclo[2.2.2]octane interconversion that is evident from the two natural products. Two prominent methods are known for such transformations: A pinacol rearrangement of bicyclo[2.2.2]octane systems, which can be formed through a Diels–Alder reaction, offers an entry to [3.2.1] systems;^[12,13] on the other hand, the homoallyl–homoallyl radical rearrangement, which might proceed through a cyclopropylcarbinyl radical, was used by the research group of Ihara to convert a [3.2.1] system into a [2.2.2] system.^[14,15] In fact, this skeleton-interconversion strategy was also used by Nicolaou and co-workers^[11a] and Lee and co-workers^[11c] in their syntheses of platencin. We conceived a related strategy independently (Scheme 2) but encountered problems with the rearrangement of **D** into **C**.^[16] According to this synthetic plan, compound **E** might be synthesized by conjugate addition to a bicyclic enone **F**, which could be prepared by the method of Toyota and co-workers^[14,17] by the palladium-catalyzed oxidative cyclization of an allylcyclohexenone **G**. This substrate, in turn, could be constructed by the alkylation and reduction of a 3-alkoxy cyclohex-2-en-1-one.

Initially, we performed some model studies on the palladium(II)-catalyzed cycloalkenylation of silyl enol ether **7** (Scheme 3). The original plan was to convert the desired

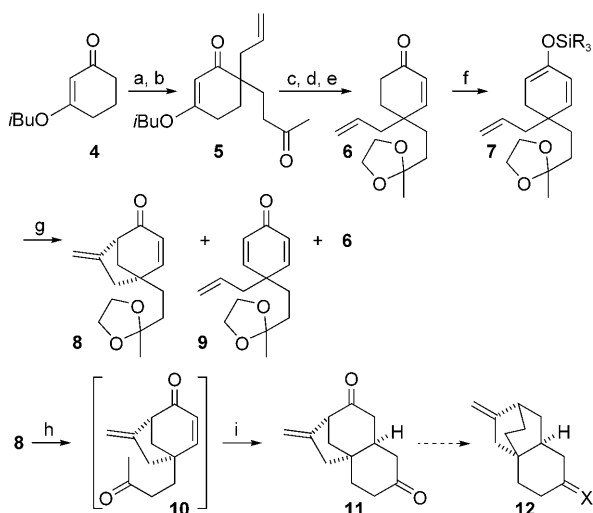


Scheme 2. Synthetic plan for the platencin core structure **3**.

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Scheme 3. Synthesis and oxidative palladium-catalyzed transformation of silyl enol ether **7**: a) LDA (1.1 equiv), THF, -80°C , 1 h, then allyl bromide (1.3 equiv), $-80^{\circ}\text{C} \rightarrow \text{RT}$, 12 h, 90%; b) LDA (1.1 equiv), THF, -80°C , 1 h, then methyl vinyl ketone (1 equiv), -80°C , 0.5 h, 84%; c) $(\text{CH}_2\text{OH})_2$ (20 equiv), PPTS (0.4 equiv), benzene, reflux, 2–12 h; d) DIBAL-H (1.5 equiv), THF, $-80 \rightarrow -60^{\circ}\text{C}$, 1 h; e) $p\text{-TsOH} \cdot \text{H}_2\text{O}$ (0.04 equiv), $\text{Et}_2\text{O}/\text{H}_2\text{O}$ (100:1), 20°C , 0.5 h, 80% from **5**; f) LDA (1.5 equiv), THF, -80°C , 1 h, then R_3SiCl (2 equiv), HMPA (1.5 equiv), room temperature, 1.5 h, approximately 90%; g) $\text{Pd}(\text{OAc})_2$ (cat.), DMSO, O_2 , 85% (see Table 1); h) $p\text{-TsOH} \cdot \text{H}_2\text{O}$ (1 equiv), acetone, 20°C , 40 min; i) KOtBu , THF, $t\text{BuOH}$ (2:1), -80°C , 2.5 h, 88% from **8**; ketone **10** was used without purification. $\text{R}_3\text{Si} = \text{Me}_3\text{Si}$, $i\text{Pr}_3\text{Si}$, or $t\text{BuMe}_2\text{Si}$; DIBAL-H = diisobutylaluminum hydride, DMSO = dimethyl sulfoxide, HMPA = hexamethylphosphoramide, LDA = lithium diisopropylamide, PPTS = pyridinium p -toluenesulfonate, Ts = p -toluenesulfonyl.

bicyclic product into the decalin derivative **11** and then to perform the key skeletal rearrangement on a tricyclic system derived from **11**. However, with our model system **6**, which was prepared by the Stork alkylation strategy^[18] from 3-isobutoxycyclohex-2-en-1-one^[19] (**4**) under the conditions reported by Toyota et al.,^[17] the cyclization resulted in the formation of a mixture of three products (Scheme 3, Table 1).

A change in the trialkylsilyl group of the silyl enol ether **7** from Me_3Si to $t\text{BuMe}_2\text{Si}$ led to a decrease in the amount of the desilylated cyclohexenone **6** formed but not to a decrease in the formation of cyclohexadienone **9**, which results from oxidative desilylation.^[20] Finally, a solution to this problem was found in the slow addition of the catalyst to the reaction mixture (Table 1, entry 6). Thus, the addition of the catalyst solution over 4 h to a 0.05 M solution of silyl enol ether **7** ($\text{R} = t\text{BuMe}_2\text{Si}$) in DMSO resulted in the clean formation of the desired product **8** in 85% yield. Enone **8** was then converted into the tricyclic diketone **11** in two steps (Scheme 3). Unfortunately, the radical rearrangement of tricyclic derivatives of **11** did not give the desired products.^[21]

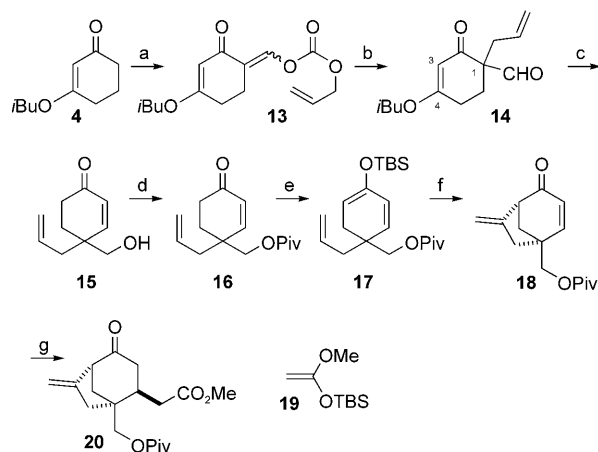
After the optimization of this cycloalkenylation reaction we focused on the synthesis of a functionalized 7-methylenebicyclo[3.2.1]octan-2-one, such as **18**. This approach would enable the formation of the cyclohexenone ring of platencin after the rearrangement of the bicyclic substructure. The racemic synthesis began with the vinylogous

Table 1: Optimization of the palladium-catalyzed alkene–silyl enol ether cyclization.^[a]

Entry	R_3Si	T	Conc.	Pd [mol %]	Ratio 8 / 9 / 6 ^[b]
1	TMS	RT	0.05 M	10	40:50:trace
2	TMS	45°C	0.2 M	10	33:17:50
3	TIPS	45°C	0.3 M	1	38:trace:60
4	TBS	RT	0.1 M	10	80:20:trace
5	TBS	45°C	0.1 M	10	80:20:3
6	TBS	45°C	0.05 M	5 ^[c]	> 95:trace:trace

[a] Reactions were carried out with 0.5 mmol of the substrate **7** in DMSO under oxygen (1 atm) for 24–48 h. [b] The product ratio was determined by ^1H NMR spectroscopy. [c] The catalyst was added slowly (over 4 h). TBS = *tert*-butyldimethylsilyl, TIPS = triisopropylsilyl, TMS = trimethylsilyl.

ester **4**^[19] (Scheme 4). Thus, the formylation of **4** with isobutyl formate, followed by the addition of allyl chloroformate, gave an *E/Z* mixture of enol carbonates **13**, which underwent isomerization upon flash chromatography to form mostly the *Z* isomer, the structure of which was assigned by NMR spectroscopy, in 89% yield. This enol carbonate underwent a rapid decarboxylative allylation^[22,23] under $\text{Pd}(\text{OAc})_2/\text{PPh}_3$ catalysis with the formation of a quaternary center to give the 2-oxocyclohex-3-ene carbaldehyde **14** in high yield. In the next step, the enone as well as the aldehyde functionality were reduced with NaBH_4 and CeCl_3 in MeOH to give cyclohexenone **15**. Surprisingly, the vinylogous ester functionality was also reduced under these conditions; the use of expensive reducing agents, such as DIBAL-H, was thus avoided. The crude hydroxyketone **15** was then subjected to pivaloylation to afford pivalate **16** in 94% yield from aldehyde **14**. Enone **16** was converted into silyl enol ether **17**, which underwent cyclization under our optimized conditions to give the 7-methylenebicyclo[3.2.1]oct-3-en-2-one **18**. A subsequent

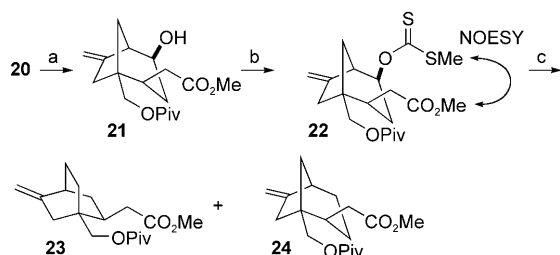


Scheme 4. Synthesis of the bicyclic ketoester **20**: a) NaH , HCO_2iBu , 24 h, 0°C , then $\text{ClCO}_2\text{allyl}$, KH (cat.), THF, 0°C , 1 h; b) $\text{Pd}(\text{OAc})_2$ (1.3 mol %), PPh_3 , THF, 20°C , 1 h, 92% from **4**; c) NaBH_4 , $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$, MeOH, 0°C , 0.5 h, then $p\text{-TsOH}$, $\text{H}_2\text{O}/\text{Et}_2\text{O}$, room temperature, 0.5 h; d) PivCl (2 equiv), pyridine (4 equiv), DMAP (0.05 equiv), CH_2Cl_2 , room temperature, 48 h, 94% from **14**; e) LDA (1.5 equiv), TBSCl (2 equiv), HMPA (1 equiv), THF, $-80^{\circ}\text{C} \rightarrow \text{RT}$, overnight, 88%; f) O_2 , $\text{Pd}(\text{OAc})_2$ (0.058 equiv), DMSO, 85%; g) $\text{H}_2\text{C}=\text{C}(\text{OMe})\text{OTBS}$ (**19**; 1.5 equiv), TiCl_4 (1.2 equiv), CH_2Cl_2 , -80°C , 12 h, 88%. DMAP = 4-dimethylaminopyridine.

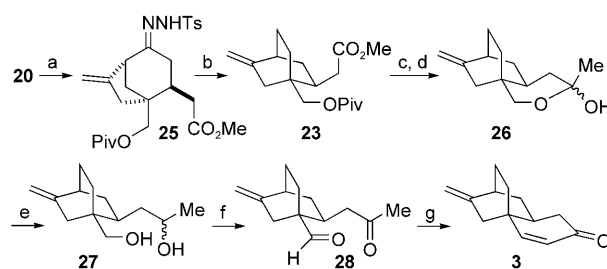
Mukaiyama-type Michael addition^[24] of the silyl ketene acetal^[25] **19** to enone **18** in the presence of TiCl_4 (1.2 equiv) gave only the desired diastereomer **20**. Thus, the nucleophile attacks the enone *syn* to the one-carbon-atom methylene bridge.

In preparation for the intended skeletal rearrangement, the keto functionality of **20** was reduced under various conditions (Scheme 5). The use of sodium borohydride, zinc borohydride, or Meerwein–Ponndorf–Verley conditions (aluminum isopropoxide/2-propanol) always gave a mixture of alcohols, at best in a 3:1 ratio. Finally, we discovered that the reaction of **20** with Et_3SiH and TiCl_4 proceeded with exclusive formation of the alcohol diastereomer **21**. The configuration of the OH-bearing stereocenter could be determined from NOESY experiments. Alcohol **21** was then converted into xanthate **22**. However, the radical rearrangement of xanthate ester **22** did not proceed under the conditions reported for the first total synthesis of platencin by Nicolaou et al. (AIBN, Bu_3SnH , toluene, 100°C).^[11a,26] With a methoxymethyl or acetyl protecting group instead of the pivalate group, this reaction gave the desired rearrangement product, but in very poor yield together with large amounts of by-products.^[21] Better results were obtained when the reaction was carried out under conditions reported by Park et al., namely, with a combination of tetrabutylammonium peroxydisulfate and sodium formate.^[27] An 82:18 mixture of the rearranged product **23** and the simple deoxygenation product **24** was obtained in 38% yield under these conditions in DMSO. In DMF, the reaction afforded the same product mixture in 25% yield.

In our search for conditions that would provide a better yield and better selectivity in the key radical rearrangement to form the bicyclo[2.2.2]octane core, we eventually found that the desired deoxygenative rearrangement occurred upon heating a solution of the hydrazone **25** in methanol in the presence of NaCNBH_3 and ZnCl_2 to give the methylenebicyclo[2.2.2]octane **23** in 60% yield (Scheme 6).^[14b] Although the product **23** was still contaminated with 8 mol % of the by-product **24**, this impurity could be removed by flash chromatography of the diol derivative **27**. This diol was obtained in pure form through a very efficient three-step sequence from **23**. Thus, the conversion of ester **23** into the corresponding Weinreb amide, treatment with MeLi (6 equiv), and reduction of the resulting hemiketal **26** with LiAlH_4 furnished diol **27** in 85% yield from **23**. The oxidation of hemiketal **26** with tetrapropylammonium perruthenate/*N*-



Scheme 5. Rearrangement of xanthate **22**: a) Et_3SiH (4 equiv), TiCl_4 (1.2 equiv), CH_2Cl_2 , -40°C , 15 min, 89%; b) NaH (3 equiv), CS_2 (3 equiv), 0°C , 0.5 h, MeI (3 equiv), THF, $0^\circ\text{C} \rightarrow \text{RT}$, 1 h, 83%; c) $(\text{Bu}_4\text{N})_2\text{S}_2\text{O}_8$, HCO_2Na , DMSO, 45°C , 12 h, 38%, **23/24** = 82:18.

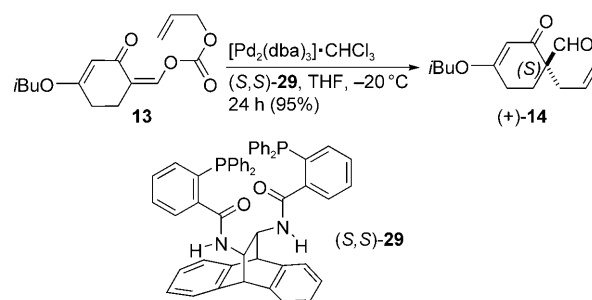


Scheme 6. Efficient conversion of ketoester **20** into the bicyclo[2.2.2]octane system **23**, and the transformation of **23** into the core structure **3** of platencin: a) TsNHNH_2 (1.3 equiv), MeOH , 60°C , 5 h, 95%; b) NaCNBH_3 , ZnCl_2 , MeOH , 60°C , 3 h, 60%; the one-pot preparation of **23** from **20** gave **23** in 54% yield; c) $\text{HCl}\cdot\text{NH}(\text{OMe})\text{Me}$ (6 equiv), Me_3Al (5 equiv), CH_2Cl_2 , 0°C , overnight; d) MeLi (6 equiv), Et_2O , $-80 \rightarrow -30^\circ\text{C}$, overnight; e) LiAlH_4 (1 equiv), Et_2O , $-80 \rightarrow 0^\circ\text{C}$, 2 h, 85% from **23**; f) $(\text{COCl})_2$ (5.8 equiv), DMSO (9 equiv), -80°C , 3 h, Et_3N , 2 h, 73%; g) NaOH (6.5 equiv), EtOH , 20°C , 20 h, 87%. Compound **25** and the Weinreb amide derived from **23** were used without purification.

methylmorpholine *N*-oxide by a previously reported procedure^[11a] afforded the desired ketoaldehyde **28** in poor yield (<25%). On the other hand, Swern oxidation of diol **27** led to **28** in good yield. A final aldol condensation of **28** upon treatment with NaOH in EtOH gave the advanced intermediate **3** in 87% yield. The overall yield of the platencin tricyclic core structure **3** from the commercially available starting material **4** was 17.5% (13 steps).

We also studied an enantioselective approach to **3**. Asymmetry could be introduced by an enantioselective palladium-catalyzed decarboxylative allylation^[23] of the allyl enol carbonate **13** with a chiral phosphine ligand. According to the results of Trost and co-workers, the use of the ligand (*S,S*)-**29** should result in (*S*)-**14** (Scheme 7).^[28,29] Indeed, when this decarboxylative allylation was performed in the presence of ligand (*S,S*)-**29** at 0°C in THF, (+)-**14** was formed with 78% *ee*. When the temperature was lowered to -20°C , (+)-**14** was obtained with an improved *ee* value of 87%. The use of optically active **14** should lead to the optically enriched platencin core structure **3**.

In summary, we have developed an efficient formal synthesis of platencin. The tricyclic advanced intermediate **3** was prepared in 13 steps and 17.5% overall yield from the commercially available starting material **4**. Our approach is based on original key reactions, namely, an asymmetric decarboxylative allylation of the allyl enol carbonate **13**, an



Scheme 7. Asymmetric approach to platencin (**1**). dba = dibenzylidene-neoacetone.

optimized palladium-catalyzed cycloalkenylation of **7**, a highly diastereoselective Mukaiyama Michael addition of the silyl ketene acetal **19** to the bicyclic enone **18**, and a radical-mediated reductive rearrangement of the tosylhydrazone **25** to construct the bicyclo[2.2.2]octane core of platenicin.

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