Natural Products Synthesis

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Formal Total Synthesis of Platencin**

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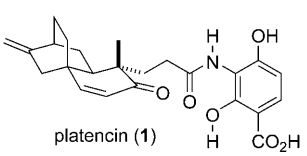
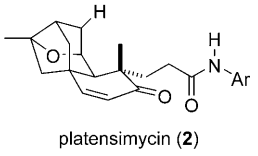
The increasing appearance of bacterial resistance has stimulated a resumption of the search for novel antibiotics. Not only various depsipeptides but also structurally novel polycyclic polyketide and terpene derivatives with antibiotic activity have been discovered.[1,2] The two closely related antibiotics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

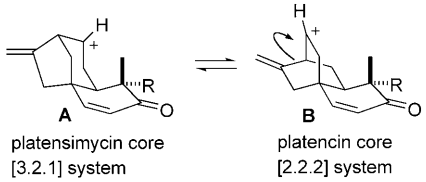




discovered of the two, was isolated from a strain of *Streptomyces platensis*, MA7339. Like platensimycin (**2**; the aryl group Ar is the same as that in **1**), platencin (**1**) shows potent antimicrobial activity against a broad spectrum of Gram-positive bacteria. In particular, it inhibits key antibiotic-resistant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

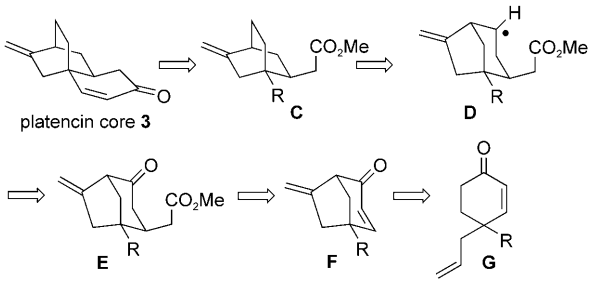
The potent in vivo activities and novel intriguing structures of these compounds prompted a number of attempts at their synthesis. Since platensimycin was first described in



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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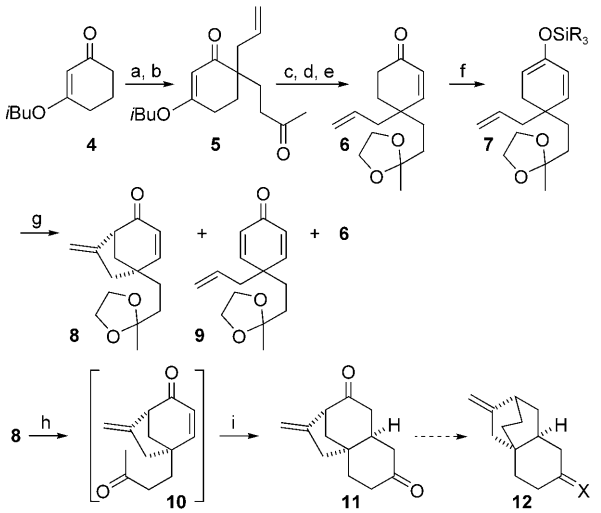


Scheme 3. Synthesis and oxidative palladium-catalyzed transformation of silyl enol ether **7**: a) LDA (1.1 equiv), THF, −80 °C, 1 h, then allyl bromide (1.3 equiv), −80 °C→RT, 12 h, 90%; b) LDA (1.1 equiv), THF, −80 °C, 1 h, then methyl vinyl ketone (1 equiv), −80 °C, 0.5 h, 84%; c) $(CH_2OH)_2$ (20 equiv), PPTS (0.4 equiv), benzene, reflux, 2–12 h; d) DIBAL-H (1.5 equiv), THF, −80→−60 °C, 1 h; e) *p*-TsOH·H_2O (0.04 equiv), Et_2O/H_2O (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) $Pd(OAc)_2$ (cat.), DMSO, O_2, 85% (see Table 1); h) *p*-TsOH·H_2O (1 equiv), acetone, 20 °C, 40 min; i) KO*t*Bu, THF, *t*BuOH (2:1), −80 °C, 2.5 h, 88% from **8**; ketoenone **10** was used without purification. R_3Si = Me_3Si, iPr_3Si, or $tBuMe_2Si$; 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 $tBuMe_2Si$ 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** (R = $tBuMe_2Si$) 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]

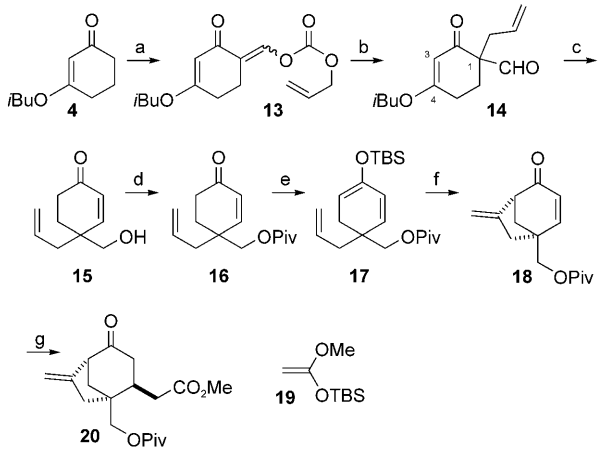
After the optimization of this cycloalkenylation reaction we focused on the synthesis of a functionalized 7-methylenebicyclo[3.2.1]octan-2-one, such as **18**. This approach would enable the formation of the cyclohexenone ring of platencin after the rearrangement of the bicyclic substructure. The racemic 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 $Pd(OAc)_2/PPh_3$ 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

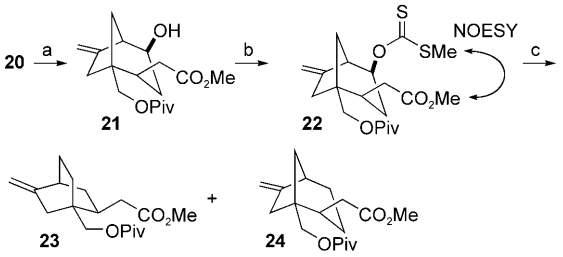


Scheme 4. Synthesis of the bicyclic ketoester **20**: a) NaH, HCO_2iBu, 24 h, 0 °C, then $ClCO_2$allyl, KH (cat.), THF, 0 °C, 1 h; b) $Pd(OAc)_2$ (1.3 mol%), PPh_3, THF, 20 °C, 1 h, 92% from **4**; c) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 0 °C, 0.5 h, then *p*-TsOH, H_2O/Et_2O, room temperature, 0.5 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 °C→RT, overnight, 88%; f) O_2, $Pd(OAc)_2$ (0.058 equiv), DMSO, 85%; g) $H_2C{=}C(OMe)OTBS$ (**19**; 1.5 equiv), $TiCl_4$ (1.2 equiv), CH_2Cl_2, −80 °C, 12 h, 88%. DMAP = 4-dimethylaminopyridine.

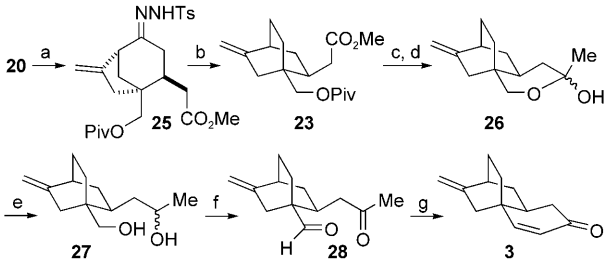
Mukaiyama-type Michael addition[24] of the silyl ketene acetal[25] **19** to enone **18** in the presence of $TiCl_4$ (1.2 equiv) gave only the desired diastereomer **20**. Thus, the nucleophile attacks the enone *syn* to the one-carbon-atom methylene bridge.

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 pivaloate 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*-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).



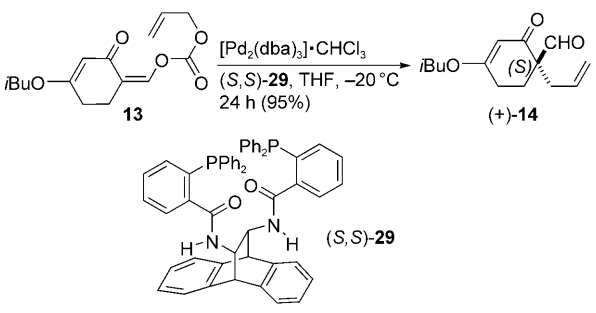
Scheme 5. Rearrangement of xanthate **22**: a) Et_3SiH (4 equiv), $TiCl_4$ (1.2 equiv), CH_2Cl_2, −40 °C, 15 min, 89%; b) NaH (3 equiv), CS_2 (3 equiv), 0 °C, 0.5 h, MeI (3 equiv), THF, 0 °C→RT, 1 h, 83%; c) $(Bu_4N)_2S_2O_8$, HCO_2Na, DMSO, 45 °C, 12 h, 38%, **23**/**24** = 82:18.



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) HCl·NH(OMe)Me (6 equiv), Me_3Al (5 equiv), CH_2Cl_2, 0 °C, overnight; d) MeLi (6 equiv), Et_2O, −80→−30 °C, overnight; e) $LiAlH_4$ (1 equiv), Et_2O, −80→0 °C, 2 h, 85% from **23**; f) $(COCl)_2$ (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.

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 = dibenzylideneacetone.

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 platencin.

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