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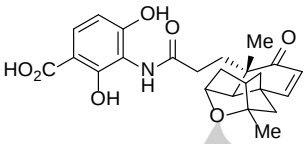
Enantioselective Synthesis of the Platensimycin Core by Silver(I)-Promoted Cyclization of Δ^6-α-Iodoketone

Milos Trajkovic,[a] Zorana Ferjancic,[a] Radomir N. Saicic* [a,b] and Filip Bihelovic* [a]

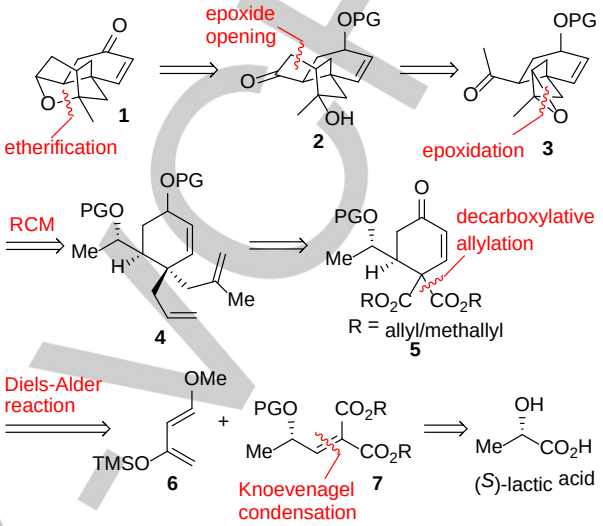
Abstract: A chiral pool based synthesis of the platensimycin core was achieved using (*S*)-lactic acid as an inexpensive starting material. The cyclohexenone ring was closed in a Mukaiyama-Michael domino sequence, while the quaternary stereocenter was created by a highly stereoselective decarboxylative allylation. The spirobicyclic skeleton was constructed by RCM reaction. A new silver(I)-promoted cyclization reaction of Δ^6- and Δ^7-α-iodoketones was developed and applied for the pivotal carbon-carbon bond formation. The scope and limitations of this methodology are also presented.

The development of bacterial resistance to first-line antibiotic drugs[1] urged scientific community to search for new drug candidates.[2] These efforts involved, *inter alia*, the synthesis of new antibiotic compounds, as well as structural modifications of the existing ones.[3] Consequently, new synthetic strategies are constantly emerging, aiming at more efficient and flexible syntheses necessary for SAR studies (of the analogues).[4] In 2006, platensimycin was isolated from a *Streptomyces platensis* strain, showing strong *in vitro* antibacterial activity toward broad-spectrum Gram-positive bacteria, including methicillin-resistant *Staphylococcus Aureus* (MRSA), vancomycin-intermediate *S. aureus* (VISA), and vancomycin-resistant *Enterococci* (VRE).[5] More importantly, it shows *in vivo* activity without toxicity, especially when administered directly into cells.[6] However, due to a high rate of its clearance in the body, its pharmacokinetic properties have to be improved,[7] which calls for the development of a flexible strategy for the synthesis of platensimycin analogues.



(-)-Platensimycin

For this reason and due to the complex and intricate structure of the platensimycin core, a number of enantioselective and racemic (total and formal) syntheses have been reported so far.[8] We set out to develop an alternative and flexible synthesis of the platenismycin core relying on a chiral pool strategy, thus potentially enabling the synthesis of its analogues by simply changing the structures of the reactants.



Scheme 1. Retrosynthetic analysis of the platensimycin core

Our retrosynthetic analysis of the platensimycin core is shown in Scheme 1. It started with the C-O bond disconnection of the tetrahydrofuran ring in **1** through the etherification transform. The formation of the tricyclic skeleton **2** was considered to be one of the key steps in the synthesis and this was planned to be achieved through epoxide **3** opening by a ketone enolate. This spirobicyclic system would be a product of the ring closing metathesis reaction of diene **4**, potentially obtainable by stereoselective decarboxylative allylation of allyl/methallyl diester **5**. Cyclohexenone **5** could be synthesized by Diels Alder reaction of Danishefsky's diene **6** and chiral alkylidenemalonate **7** – a product of the Knoevenegel condensation of malonic ester with the optically pure (*S*)-lactic acid derivative. We believed that the absolute configuration of the chiral dienophile could dictate the absolute configuration of the newly-created stereogenic centre via the diastereoselective Diels Alder reaction, while all other stereocenters could be established in the course of the synthesis through the substrate control.

The synthesis commenced with the preparation of the optically pure diallyl alkylidene malonate **10a**[9] – a reactive partner for the Yb-catalyzed Diels Alder reaction with Danishefsky's diene **6** (Scheme 2).[10] Indeed, the reaction of **10a** with **6** provided cyclohexenone **11a** as a single isomer, but this transformation turn out to proceed by a different mechanism. The product **11a** was actually formed by the Mukaiyama-Michael tandem reaction:[11] the corresponding acyclic intermediate could be isolated when the reaction was performed at ambient temperature. Notably, the reaction proceeded with a complete diastereoselectivity, and the chiral information was successfully transferred from the starting (*S*)-lactic acid to the product, which was crucial for the enantioselective synthesis.

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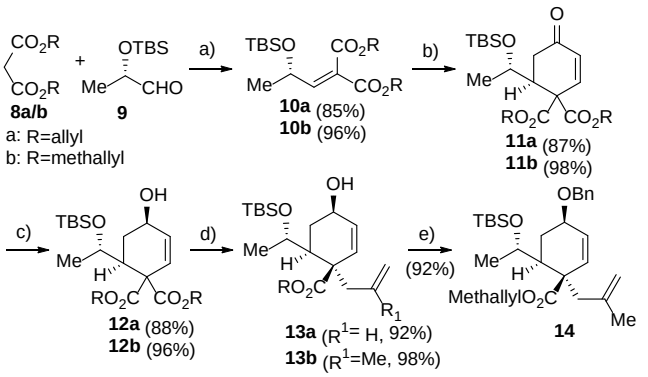
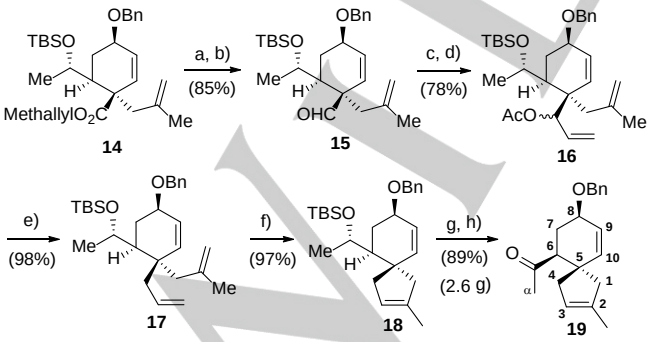


Scheme 2. Synthesis of the cyclohexene ring and diastereoselective decarboxylative allylation. Reagents and conditions: a) $TiCl_4$, Pyr, THF, 0 °C to rt; b) Danishefsky's diene **6**, $Yb(OTf)_3$, PhMe, rt to 120 °C; c) $NaBH_4$, MeOH, 0 °C (dr = 19:1); d) $[Pd(PPh_3)_4]$, CH_2Cl_2, rt; e) NaH, BnBr, TBAI, THF.

The next task in the synthesis was Pd-catalyzed decarboxylative allylation,[12] which was initially tested on cyclohexenone **11a**. However, a complex mixture of products resulted under different reaction conditions, and after extensive experimentation we found that it was necessary to lower the substrate reactivity by the carbonyl group reduction. Free allylic alcohol **12a** turned out to be an excellent substrate for this transformation and after treatment with $[Pd(PPh_3)_4]$ the wanted product **13a** was isolated in 92% yield, as a single diastereoisomer. The remarkable level of stereoselectivity is most probably a consequence of a steric environment on the neighboring carbon atom, bearing a bulky substituent. Encouraged by the completely diastereoselective formation of the new quaternary stereocenter, the whole sequence was repeated with bismethallyl homologue **10b**. This proceeded uneventfully, and free allylic alcohol **13b** was then protected as benzyl ether: the entire sequence was performed on a large scale, supplying us with 6 g of benzyl ether **14** in 77% overall yield (after 5 steps, from dimethallylmalonate **8b**).

According to our retrosynthetic analysis, the bicyclic intermediate should be synthesized by a ring closing metathesis. To this end, ester **14** was transformed to the corresponding aldehyde **15** in two-steps (Scheme 3).

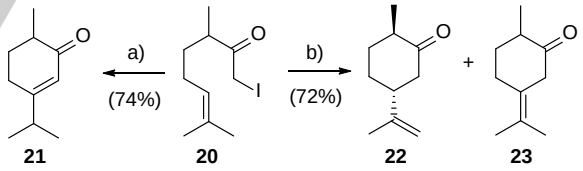


Scheme 3. Synthesis of the spirobicyclic key intermediate **19**. Reagents and conditions: a) Dibal-H, Et_2O, -50 °C; b) DMP, CH_2Cl_2; c) CH_2=CHMgBr, Et_2O; d) Ac_2O, Et_3N, DMAP, CH_2Cl_2; e) $Pd(OAc)_2$, Ph_3P, Et_3N, HCO_2H, THF; f) 2nd generation Grubbs catalyst, CH_2Cl_2; g) HF·Pyr, THF; h) DMP, CH_2Cl_2.

The addition of vinylmagnesium bromide afforded a diastereomeric mixture of allylic alcohols, which were subsequently acetylated (**16**). The deoxygenation of allylic acetate **16** proceeded in almost quantitative yield,[13] leading to the formation of the metathesis precursor **17**. The second generation Grubbs catalyst effected this spirocyclization with high efficiency.[14] Finally, the TBS group in **18** was removed and the free alcohol was oxidized to yield methylketone **19** in 56% overall yield (over 8 steps, starting from diester **14**).

With gram quantities of the key bicyclic intermediate **19** in hand, the stage was set for the crucial C_α-C_3 bond formation. However, we were unable to accomplish the intramolecular epoxide opening by ketone enolate on the **3**-like substrates, even in the presence of Lewis acids.[15]

Another complementary strategy relied on radical cyclizations: the functionalization of methyl ketone **19** in the α-position afforded the corresponding xanthate (or iodide) which, under either thermal or photochemical conditions, cyclized only sluggishly, yielding an equimolar mixture of the two regioisomers (C_α-C_3 and C_α-C_2). Encouraged with these initial results, we wanted to test whether the yield as well as the regioselectivity of the addition could be improved by switching the neutral radical conditions for the ionic ones. To this end, we prepared Δ^6-α-iodoketone **20** (Scheme 4) as a model substrate, assuming that silver(I) salts could promote the desired cyclization. Much to our pleasure, the reaction indeed worked and, after optimization of the reaction conditions, we found that the highest yield of the cyclized product could be obtained with silver(I) trifluoromethanesulfonate in CH_2Cl_2. This unprecedented cyclization can be perfomed either in the absence or in the presence of 2,6-lutidine, resulting in the formation of conjugated cyclohexenone (**21**), or cyclohexanone (**22** and **23**), respectively.



Scheme 4. Silver(I)-promoted cyclization of Δ^6-α-iodoketone **20**. Reagents and conditions: a) AgOTf, CH_2Cl_2, rt, 30 min; b) AgOTf, 2,6-lutidine, CH_2Cl_2, rt, 15 min (**22**:**23** = 1:1).

The scope of the reaction was tested on several substrates, and the representative results are summarized in Table 1. The reaction allowed for the smooth synthesis of cyclohexanone (entries 1-5) and cycloheptanone (entry 6) derivatives in good to excellent yields, without formation of any side product, thus simplifying the purification/isolation steps.

It was surprising to witness the inertness of Δ^5-α-iodoketones toward cyclization,[16] or even toward decomposition of the starting material after prolonged reaction time (48 h). Moreover, it proved necessary for all the substrates to possess a trisubstituted double bond. The stability of Δ^5-α-iodoketones under the reaction conditions ruled out a formation of the energy-rich α-acylcarbenium ions intermediates,[17] as its irreversible formation (AgI precipitation) would result in the

disappearance of the starting material. Therefore, we believe that the reaction might proceed via a reversible silver(I) complexation to the double bond, with a simultaneous formation of the C-C bond and AgI.

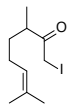
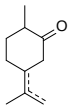
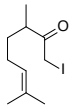
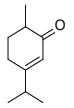
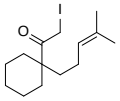
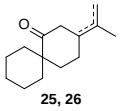
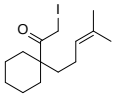
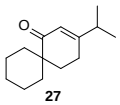
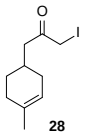
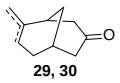
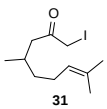
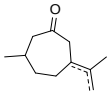
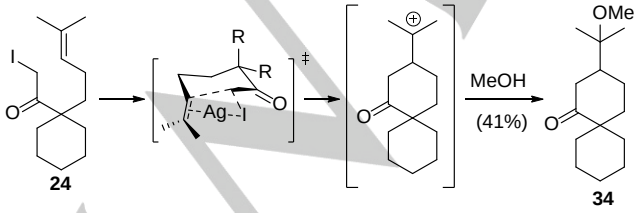
Entry	Substrate	Product	Reaction Conditions	Isolated Yields
1	 20	 22, 23	AgOTf (1.5 eq) 2,6-lutidine (1.2 eq), 15 min, rt	72%
2	 20	 21	AgOTf (1.5 eq), 30 min, rt	74%
3	 24	 25, 26	AgOTf (1.2 eq) 2,6-lutidine (1.3 eq), 2 h, rt	89%
4	 24	 27	AgOTf (1.2 eq), 30 min, rt	90%
5	 28	 29, 30	AgOTf (1.5 eq) 2,6-lutidine (1.7 eq), overnight, rt	88%
6	 31	 32, 33	AgOTf (1.5 eq) 2,6-lutidine (1.2 eq), 7 h, rt	67%

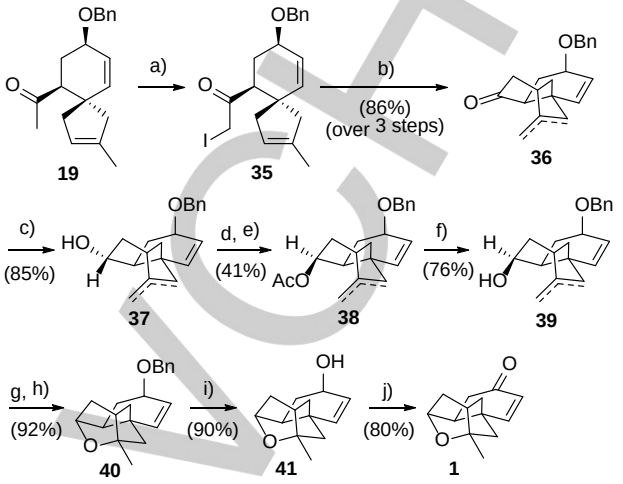
Table 1: Representative examples of AgOTf promoted cyclization of Δ^6- and Δ^7-α-iodoketones

The reaction proceeds via the carbocationic intermediate, as demonstrated by its trapping with methanol (Scheme 5). While Δ^6- and Δ^7-α-iodoketones can attain a geometrically favorable transition state conformation, Δ^5-α-iodoketones most probably cannot. Intramolecular carbocation trapping by either the OH group or by another suitably positioned double bond could lead to more complex polycyclic products, and the results of this study will be published in due course.



Scheme 5. A plausable mechanistic pathway for Ag(I)-promoted cyclization of Δ^6- and Δ^7-α-iodoketones

We then applied the optimized cyclization conditions to α-iodoketone **35**, and much to our delight a smooth cyclization occurred within minutes, affording the key tricyclic product **36** in almost quantitative yield (Scheme 6).



Scheme 6. Synthesis of the tetracyclic platensimycin core **1**. Reagents and conditions: a) TMSOTf, DIPEA, CH_2Cl_2, 0 °C, then NIS, CH_2Cl_2, -78 °C; b) AgOTf, 2,6-lutidine, CH_2Cl_2, rt; c) $NaBH_4$, $CeCl_3$, MeOH, -78 °C; d) $ClCH_2SO_2Cl$, Pyr, DMAP, CH_2Cl_2; e) CsOAc, 18-crown-6, PhH; f) K_2CO_3, MeOH, H_2O; g) NBS, CH_2Cl_2, -40 °C; h) TBTH, AIBN, PhH, hν (Xenophot); i) Li-naphthalenide, THF, -25 °C; j) DMP, CH_2Cl_2.

It was necessary to perform the reaction in the presence of 2,6-lutidine: in its absence the starting material/product decomposed quickly due to the release of triflic acid. In the next step of the synthesis, the reduction of the carbonyl group could not be achieved with a satisfying level of diastereoselectivity, as the unwanted diastereomer was obtained either as a major or as a single product, under various reduction conditions. Therefore, we relied on a two-step strategy comprising the inversion of configuration of the opposite alcohol diastereomer **37**, obtained almost exclusively by the Luche reduction of **36**. Unfortunately, this inversion could not be performed by the standard Mitsunobu protocol, probably due to considerable steric hindrance of the OH-group in the starting alcohol. As an alternative, the alcohol **37** was first converted to the corresponding chloromesylate which was treated with CsOAc/18-crown-6,[18] to afford the inverted acetate **38**. After the hydrolysis of acetate **38**, the fourth (tetrahydrofuran) ring remains to be closed. Contrary to the results of the other groups, this etherification could not be catalyzed by acids due to the liability of the allylic fragment. However, bromoetherification/radical debromination strategy allowed for the formation of tetracycle **40** in 92% yield. Debenzylation of **40** with lithium naphthalenide,[19] followed by DMP oxidation of allylic alcohol **41**,[20] afforded the target platensimycin core **1**, with all physical and spectral characteristics identical to those previously reported in the literature.[5a]

In summary, we exploited a chiral pool strategy for the enantioselective synthesis of the platensimycin core. The Mukaiyama-Michael domino reaction successfully transferred the chiral information from the (*S*)-lactic acid derivative to the cyclohexenone product. A palladium-catalyzed decarboxylative

allylation enabled the proper stereochemistry of the quaternary stereocenter to be set. The crucial C-C bond was formed efficiently, under mild reaction conditions by a newly-developed method for the cyclization of Δ^6- and Δ^7-α-iodoketones with silver(I) salts, which is complementary to radical methodology, and may have general applicability.

Acknowledgements

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Keywords: antibiotics • natural products • total synthesis • cyclization • silver

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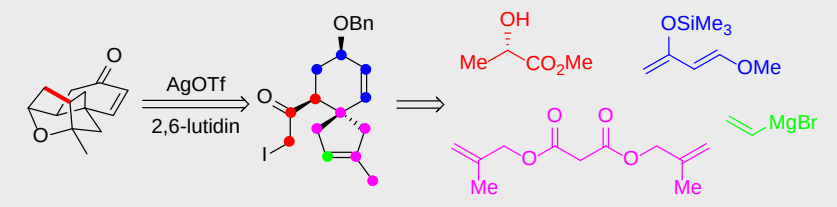

Enantioselective synthesis of the platensimycin core was achieved, relying on a chiral pool strategy. The Mukaiyama-Michael domino sequence enabled cyclohexenone ring to be closed diastereoselectively, while the quaternary stereocenter was created by a highly stereoselective decarboxylative allylation. The crucial C-C bond was formed by using a newly developed method for silver(I)-promoted cyclizations of Δ^6- and Δ^7-α-iodoketones.

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