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Formal synthesis of (–)-platensimycin†

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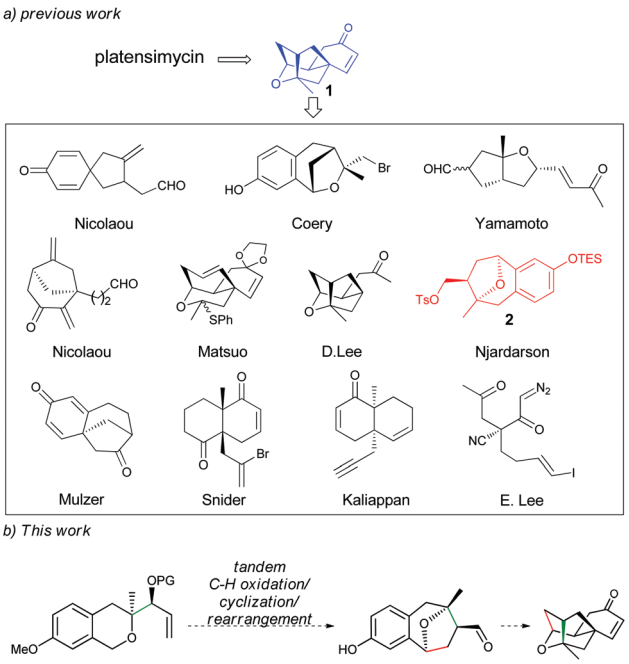
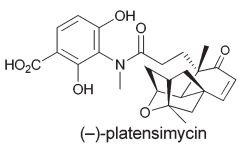
A formal synthesis of (–)-platensimycin has been successfully carried out using a tandem C–H oxidation/C–C coupling (cyclization)/rearrangement as the key step.

Exploring new antibiotics is an evergreen topic in the field of drug discovery because of the continuous emergence of multi-resistant bacteria.[1] Among the antibiotics developed/discovered in the past several years, (–)-platensimycin (Fig. 1), as a potential antibiotic drug candidate, was firstly isolated from a strain of *Streptomyces platensis* by Merck scientists in 2006.[2] Subsequent biological activity test of such a polycyclic natural product showed that it could selectively inhibit FabF, a key enzyme in the fatty acid synthetic pathway in bacteria, in the 48–160 nM range.

Due to its special bioactivity and structural molecular skeleton, this molecule has been an ideal target for total synthesis. Right after its isolation, Nicolaou's group reported the first total synthesis of platensimycin in its racemic form.[3a] Since then, a number of research groups have also attempted the synthesis of the molecule. Most of them take compound **1** as the key intermediate to develop the corresponding synthetic strategies (Scheme 1).[3,4] Among them, the strategy reported by Njardarson and co-workers, who used compound **2** with a benzoxa[3.2.1]octane skeleton to afford precursor **1**,[3o] has drawn our attention as such type of an intermediate might be readily obtained through a tandem C–H oxidation/C–C coupling (cyclization)/rearrangement of isochroman-derived allylic silylether, which has been recently developed by our group and has been applied to the asymmetric total syntheses of (–)-brussonol and (–)-przewalskine *E*.[5,6] Based on the above information and combined with our long interest in α-C–H bond functionalization of oxygen atoms[7] and synthesis of bioactive natural products,[8] we proposed a strategy toward the synthesis of (–)-platensimycin (Scheme 1). In this study, we present our results of the formal synthesis of (–)-platensimycin using the above-mentioned tandem reaction as the key step.



Scheme 1 Key intermediates used for the synthesis of core structure **1**.



(–)-platensimycin

Fig. 1 The structure of (–)-platensimycin.

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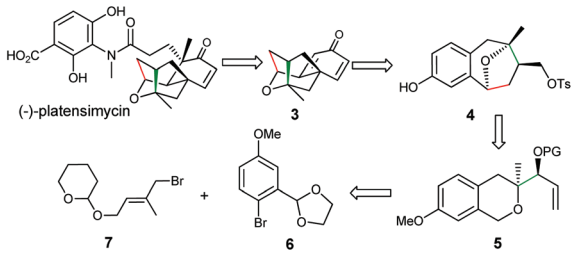
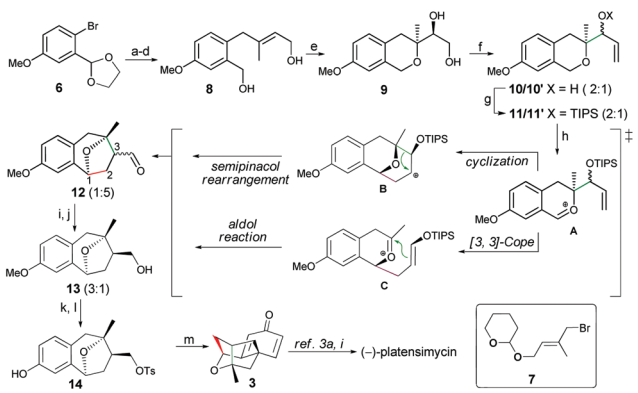


Scheme 2 Retrosynthetic analysis of (–)-platensimycin.

with a benzoxa[3.2.1]octane skeleton could be prepared through our newly developed methodology from precursor **5**, which could be assembled *via* a simple construction of the isochroman moiety from readily available bromide **6**[10] and **7**.[11]

As shown in Scheme 3, our synthesis started with the bromide **6**, which was coupled with segment **7** followed by sequential transformations including acetal-deprotection/reduction/THP-deprotection to provide smoothly the allylic alcohol **8**. Next, we investigated the tandem Sharpless asymmetric epoxidation/epoxy opening reaction of **8**, and careful condition screening showed that the use of the classical Sharpless catalyst (1.5 equiv.) at −50 °C could give the best result (90% yield, 91% ee) of the expected diol **9**. However, when the catalyst loading was less than 1.0 equiv., the reaction gave product **9** with both low yield and poor enantioselectivity. For example, only 33% ee was achieved while a 0.3 equiv. Sharpless catalyst was employed. Cleavage of the diol **9** with $NaIO_4$ followed by the Grignard reaction with excess vinyl magnesium bromide afforded the allylic alcohol **10** as two diastereoisomers (2 : 1), which were protected as TIPS ethers **11** (2 isomers, dr = 2 : 1). To our delight, when **11** (2 isomers) was subjected to the standard conditions of 0.1 eq. $InCl_3$ and 2.0 eq. DDQ., the expected aldehyde **12** with a benzoxa[3.2.1]octane skeleton was obtained as two diastereoisomers (dr = 1 : 5) in moderate 52% yield. As mentioned in our previous report, there are two possible ways to go through after the formation of intermediate A with a benzylic oxacarbenium cation under the oxidative conditions. One is a tandem cyclization/semipinacol rearrangement to give B and the other is a tandem [3,3]-cope rearrangement/aldol reaction.[12]



Scheme 3 Formal synthesis of (–)-platensimycin. Reagents and conditions: (a) *t*-BuLi, Et_2O, −78 °C to −30 °C, then **7**; (b) PTS·H_2O, acetone/H_2O, RT; (c) $NaBH_4$, MeOH, 0 °C; (d) PTS·H_2O, MeOH, RT, 32% yield (4 steps); (e) (+)-DET, Ti(*i*-PrO)$_4$, *t*-BuO_2H, −25 °C to −50 °C, CH_2Cl_2, 90% yield, 91% ee; (f) (i) $NaIO_4$, $NaHCO_3$ (aq.), CH_2Cl_2; (ii) vinylMgBr, THF, (**10'**, 29%; **10**, 59% yield (2 steps)); (g) TIPSOTf, pyridine, CH_2Cl_2, (**11'**, 88% yield; **11**, 86% yield); (h) 4 Å MS, 2, 6-dibromopyridine, $InCl_3$, DDQ, CH_2Cl_2, RT; (i) Na_2CO_3, MeOH, 30 °C; (j) $NaBH_4$, MeOH, 0 °C, 43% (three steps); (k) TsCl, Et_3N, CH_2Cl_2, 98% yield; (l) $AlCl_3$, EtSH, CH_2Cl_2, RT, 80%; (m) TBAF, xylene, 130 °C, 85%.

Although the major isomer of **12** did not possess the desired C-3 configuration, fortunately, a final basification of the reaction system with Na_2CO_3/MeOH could reverse the stereochemistry of aldehyde **12**, which was directly reduced with $NaBH_4$ without purification to give alcohol **13** in 43% yield (dr = 3 : 1).[13] Tosylation of the major isomer of **13** followed by demethylation with $AlCl_3$/EtSH[14] gave precursor **14**. Finally, treatment of **14** with anhydrous TBAF in xylene could initiate the dearomatization/intramolecular cyclization to afford the tetracyclic core **3** in 85% yield. Intermediate **3** showed the identical spectroscopic data (^1H and ^{13}C NMR, IR, HRMS, and optical rotation) with the previously reported compound,[3o] and could be easily converted to (–)-platensimycin by using the methods described by Corey[3i] and Nicolaou.[3a]

Conclusions

In conclusion, the formal synthesis of (–)-platensimycin has been finished through the use of a new strategy, in which a newly developed tandem C–H oxidation/C–C coupling (cyclization)/rearrangement has been used as the key step. These results not only further demonstrate the utility of such a tandem reaction, but also provide additional choice for the construction of molecules with a benzoxa[3.2.1]octane skeleton.

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