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An Expedient Enantioselective Strategy for the Oxatetracyclic Core of Platensimycin

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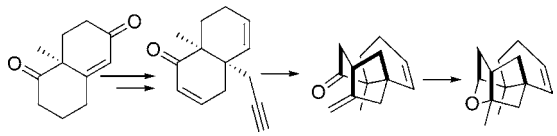
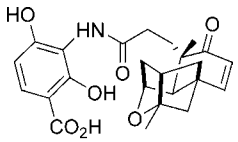
ABSTRACT



An enantioselective route for the synthesis of oxatetracyclic core of platensimycin is reported for the first time using a 5-*exo*-trig cyclization followed by intramolecular etherification as key reactions. The requisite dienynone for the radical cyclization is synthesized in eight steps from the Wieland–Miescher ketone employing a Claisen rearrangement.

Bacterial infection is a widespread problem around the globe and, of late, it is being considered as a serious threat to society owing to the resistance developed by bacteria over the existing several classes of antibiotics. This necessitates the discovery of new classes of antibiotics that can act by different mechanisms and on new targets. In connection to this, it is significant to mention the discovery of a novel class of antibiotic, platensimycin **1**[1] (Figure 1), a small molecule



1: Platensimycin

Figure 1.

isolated from the strain of *Streptomyces platensis* by the Merck research group through a systematic screening of about 250 000 natural product extracts.

Platensimycin is considered as the most powerful and selective inhibitor of condensing enzyme FabF to date. The initiation and elongation condensing enzymes such as FabH and FabF/B are involved in the synthesis of fatty acids which are essential for the survival of bacteria. The inhibition of these enzymes eventually stops the growth of bacteria and hence, these enzymes have been intensively examined as possible novel targets for the last two decades. Prior to the isolation of platensimycin, only two poor inhibitors, cerulenin and thiolactomycin, were known. Now, the discovery of platensimycin came out as a boon for those having the nightmare of multiresistant super bugs.[2]

Platensimycin **1** possesses a rare oxatetracyclic core and an unusual polar 3-amino-2,4-dihydroxybenzoic acid side chain. The structure elucidation was achieved by 2D-NMR which was further confirmed by single X-ray crystallography. The importance of this molecule was immediately recognized

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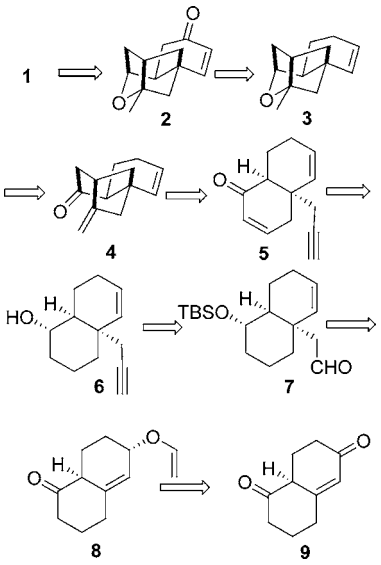
by the first racemic and later asymmetric total syntheses by Nicolaou's group.[3]

As part of our interest in the synthesis of antibiotic natural products,[4] and our quest to develop an efficient enantioselective synthesis of platensimycin, we devised the retrosynthetic strategy as shown in Scheme 1. Our approach involves

Scheme 1. Retrosynthetic Analysis of Platensimycin

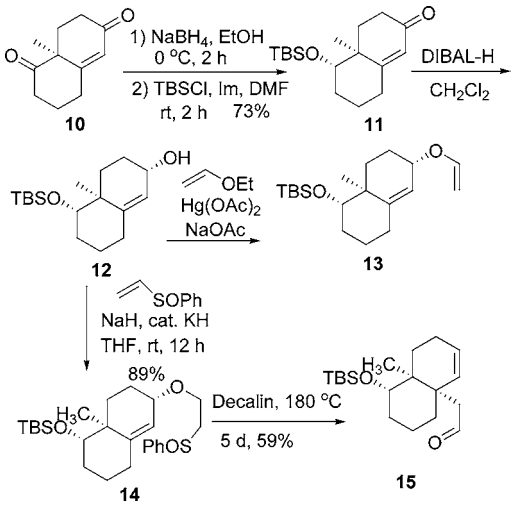


a 5-*exo*-trig radical cyclization as an important key step for the synthesis of the oxatetracyclic core of platensimycin.[5] When we were near to the completion of our model study (vide infra), a couple of formal syntheses of racemic platensimysin were published[6] using a similar radical cyclization reaction as the key step; this has prompted us to disclose our initial results toward the synthesis of platensimycin.

Our proposed retrosynthetic analysis is delineated in Scheme 1. We envisaged that the total synthesis of platensimycin would be achieved by dialkylation of the enone **2** and subsequent attachment of the aromatic portion. The enone **2** could then be obtained by allylic oxidation of alkene **3**, which, in turn, could be easily synthesized by an intramolecular etherification of dienone **4**, as employed by Nicolaou.[3] The dienone **4** could be derived from the dienynone **5** by a 5-*exo*-trig radical cyclization. Enone **5** could be made from the corresponding alcohol **6**, which could be obtained from the aldehyde **7** in a couple of steps. Aldehyde **7** could be traced back to the enedione **9** via the vinyl ether **8** using Claisen rearrangement[7] as a key step.

Before executing the proposed sequence of reactions starting from the diketone **9** as depicted in the Scheme 1, we decided to weigh the feasibility of these reactions using the well-known chiral Wieland−Miescher ketone **10**.[8] Accordingly, we began a model study for the enantioselective synthesis of the oxatetracyclic core of platensimycin (Scheme 2) with the preparation of enone **11** by a regio- and

Scheme 2. Synthesis of Aldehyde **15**



stereoselective reduction of Wieland−Miescher ketone **10** with $NaBH_4$ in EtOH at 0 °C.[9] The resultant *sec*-alcohol was protected as its TBS-ether to yield **11** in 73% yield for two steps. The reduction of ketone **11** with DIBAL-H yielded the allylic alcohol **12** along with its epimer in 96:4 ratio as an inseparable diastereomeric mixture.[10] The stereochemistry of this alcohol was very crucial for the subsequent transposition step to obtain the *cis*-fused decalin derivative. After preparing the known allylic alcohol **12**, our next task was to convert this alcohol to aldehyde **15**. Toward this end, we needed to prepare the allyl−vinyl ether **13**, required for the Claisen rearrangement, and to our dismay, treatment of allylic alcohol **12** with ethylvinylether and $Hg(OAc)_2$ in the presence of NaOAc gave **13** in poor yield. Alternatively, when the Johnson−Claisen rearrangement[11] and the Ireland−Claisen rearrangement[12] were attempted on the alcohol **12**, yet again, these reactions did not lead to the required products.

Finally we were relieved to see that the protocol developed by Mandai[13] worked very well for this transformation.

(3) (a) Nicolaou, K. C.; Li, A.; Edmonds, D. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 7086−7090. (b) Nicolaou, K. C.; Edmonds, D. J.; Li, A. *Angew. Chem., Int. Ed.* **2007**, *46*, DOI: 10.1002/anie200700586.

(4) Kaliappan, K. P.; Ravikumar, V. *Synlett* **2007**, 977−979.

(5) For selected examples of similar 5-*exo*-trig cyclization, see: (a) Stork, G.; Tang, P. C.; Casey, M.; Goodman, B.; Toyota, M. *J. Am. Chem. Soc.* **2005**, *127*, 16255−16262. (b) Janardhanam, S.; Shanmugam, P.; Rajagopalan, K. *J. Org. Chem.* **1993**, *58*, 7782−7788.

(6) (a) Zou, Y.; Chen, C. -H.; Taylor, C. D.; Foxman, B. M.; Snider, B. B. *Org. Lett.* **2007**, *9*, 1825−1828. (b) Nicolaou, K. C.; Tang, Y.; Wang. *Chem. Commun.* **2007**, DOI: 10.1039/b704589a

(7) (a) Claisen, L. *Ber. Dtsch. Chem. Ges.* **1912**, *45*, 3157. (b) Burgstahler, A. W.; Nordin, I. C. *J. Am. Chem. Soc.* **1961**, *83*, 198−206.

(8) Harada, N.; Sugioka, T.; Uda, H.; Kuriki, T. *Synthesis* **1990**, 53−56.

(9) Yeo, S. -K.; Hatae, N.; Seki, M.; Kanematsu, K. *Tetrahedron* **1995**, *51*, 3499−3506.

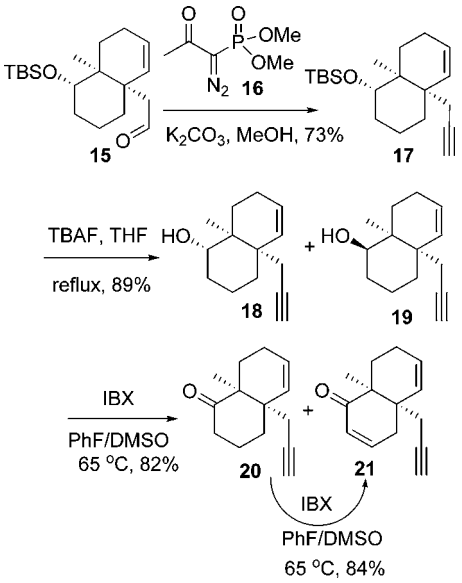
(10) Boyer, F. -D.; Ducrot, P. -H. *Synthesis* **2000**, 1868−1877.

(11) (a) Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.-t.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741−743. (b) Johnson, W. S.; Brocksom, T. J.; Loew, P.; Rich, D. H.; Werthemann, L.; Arnold, R. A.; Li, T.-t.; Faulkner, D. J. *J. Am. Chem. Soc.* **1970**, *92*, 4463−4464.

(12) Ireland, R. E.; Mueller, R. H. *J. Am. Chem. Soc.* **1972**, *94*, 5897−5898.

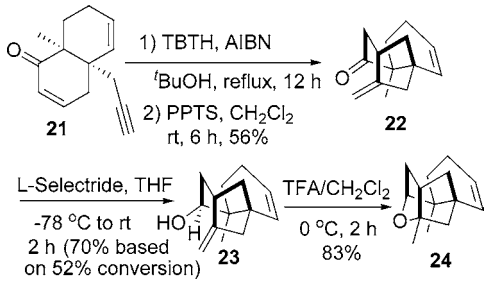
Accordingly, the allylic alcohol **12** was reacted with phenylvinyl sulfoxide[14] in the presence of NaH and a catalytic amount of KH to afford the sulfoxide **14** in 89% yield (Scheme 2). The sulfoxide on heating with decalin at 180 °C for 5 days yielded the aldehyde **15** in 59% yield. The aldehyde **15** on treatment with Ohira−Bestmann reagent **16** and K_2CO_3 in MeOH provided the enyne **17**.[15] However, removal of the TBS group from **17** was not as easy as we thought; even after stirring for 5 days with TBAF the reaction was incomplete. Finally, it was successfully removed by treatment with TBAF in refluxing THF which afforded the alcohol **18** in 89% yield along with a trace amount of its epimer **19**, which could be separated at this stage. Nevertheless, separation was not necessary as the next step was to oxidize both the epimers to the ketone and subsequently introduce a double bond. These two reactions were carried out in a single step following Nicolaou's protocol.[16] Accordingly, when the mixture of alcohols was treated with IBX at 65 °C for 36 h, the desired enone **21** was obtained in 39% yield along with the ketone **20** in 43% yield. The ketone **20** was separated and on further treatment with IBX furnished the enone in 84% yield based on 52% conversion (Scheme 3).

Scheme 3. Synthesis of Dienynone **21**



The synthesis of enone **21** set the stage for the pivotal 5-*exo*-trig radical cyclization. Initially, when we attempted the crucial radical cyclization reaction with TBTH and AIBN in benzene at reflux for 1h followed by destannation, a mixture of several products along with the required product was obtained in 23% yield. However, this reaction proceeded smoothly when ^{t}BuOH was used as the solvent, and only the requisite vinyl stannane (Scheme 4)[5a] was obtained as a single product. After concentrating the reaction mixture, the crude product was treated with PTSA in CH_2Cl_2 for 6 h at room temperature to afford the unsaturated ketone **22** in 56% yield for two steps.[5b] Our initital attempts to reduce ketone **22** with DIBAL-H furnished the undesired stereoisomer as the major product. However, the reduction of ketone **22** using L-Selectride, as reported,[6] afforded the desired alcohol **23** in 70% yield based on 52% conversion as a major isomer in 20:1 ratio which was confirmed by ^{1}H NMR spectroscopy. Subsequently, intramolecular etherification was successfully accomplished with TFA to obtain the oxatetracyclic core structure of platensimycin in 83% yield.

Scheme 4. Synthesis of Oxatetracyclic Core **24**



In conclusion, an enantioselective route for the synthesis of the oxatetracyclic core of platensimycin has been accomplished employing Claisen rearrangement, 5-*exo*-trig cyclization and intramolecular etherification as key reactions. Efforts are underway to extend this strategy for the enantioselective total synthesis of platensimycin.

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Supporting Information Available: Experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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