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An Effective Enantioselective Route to the Platensimycin Core

Gojko Lalic and E. J. Corey*

Department of Chemistry and Chemical Biology, Harvard University, Cambridge, Massachusetts 02138

corey@chemistry.harvard.edu

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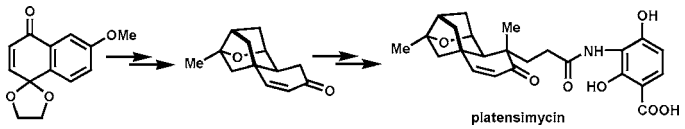
ABSTRACT



An efficient enantiocontrolled synthetic pathway to platensimycin has been developed.

High-throughput screening of 250 000 microbial extracts against the bacterial fatty acid synthesizing enzymes FabF/B and FabH led a Merck group to identify the inhibitor platensimycin (**1**), a product of *Streptomyces platensis*.[1] This new natural product is remarkable because it possesses a totally novel structure, nanomolar potency in Fab binding assays, and high antibiotic activity against *Staphylococcus aureus*, including strains that are resistant to β-lactam antibiotics and vancomycin. Although platensimycin appears unsuitable for human use, it is an important lead compound for the development of more effective antibiotics. Not surprisingly, there has been intense interest in the development of chemical pathways for the synthesis of the platensimycin core which can serve as a platform for explorations in this area. Within a few months of the publication of the structure of platensimycin, a synthesis of the racemic form was reported.[2] This work has been followed by the disclosure of another synthesis of the racemic core[3] and five other approaches to the chiral natural product.[4] Described herein is a highly enantioselective route to the core of **1** in which the correct absolute stereochemistry is established by a chiral catalyst with high efficiency (30:1 selectivity). The process is concise, and the individual steps proceed well. The pathway of synthesis is summarized in Scheme 1.

The tetracyclic α,β-enone **11** (Scheme 1) is a key intermediate for the synthesis of platensimycin or analogues thereof.[2−4] The point of departure for the construction of this molecule was 6-methoxy-1,4-naphthoquinone-4-ethylene ketal **3** which was conveniently prepared from the known methoxy α-naphthol **2**[5a] by oxidative ketalization with bis-trifluoroacetoxyiodobenzene and ethylene glycol in acetonitrile at 0 °C.[5b] Enantioselective conjugate addition of the 2-propenyl group to **3** occurred cleanly and enantioselectively using potassium 2-propenyl trifluoroborate (**4**), a Rh−BINAP BF_4 catalyst (2 mol %) in 4:1 toluene−water containing 4 equiv of triethylamine at 23 °C for 24 h.[6,7] This critical step produced the chiral ketone **5** and established the absolute

(1) (a) Wang, J.; Soisson, S. M.; Young, K.; Shoop, W.; Kodali, S.; Galgoci, A.; Painter, R.; Parthasarathy, G.; Tang, Y. S.; Cummings, R.; Ha, S.; Dorso, K.; Motyl, M.; Jayasuriya, H.; Ondeyka, J.; Herath, K.; Zhang, C.; Hernandez, L.; Allocco, J.; Basilio, A.; Tormo, J. R.; Genilloud, O.; Vicente, F.; Pelaez, F.; Colwell, L.; Lee, S. H.; Michael, B.; Felcetto, T.; Gill, C.; Silver, L. L.; Hermes, J. D.; Bartizal, K.; Barrett, J.; Schmatz, D.; Becker, J. W.; Cully, D.; Singh, S. B. *Nature* **2006**, *441*, 358−361. (b) Singh, S. B.; Jayasuriya, H.; Ondeyka, J. G.; Herath, K. B.; Zhang, C.; Zink, D. L.; Tsou, N. N.; Ball, R. G.; Basilio, A.; Genilloud, O.; Diez, M. T.; Vicente, F.; Pelaez, F.; Young, K.; Wang, J. *J. Am. Chem. Soc*. **2006**, *128*, 11916−11920. (c) Häbich, D.; von Nussbaum, F. *Chem. Med. Chem.* **2006**, *1*, 951−954.

(2) Nicolaou, K. C.; Li, A.; Edmonds, D. J. *Angew. Chem., Int. Ed*. **2006**, *45*, 7086−7090.

(3) Zou, Y.; Chen, C-H.; Taylor, C. D.; Snider, B. B.

(4) (a) Nicolaou, K. C.; Edmonds, D. J.; Li, A.; Tria, G. S. *Angew. Chem., Int. Ed.* **2007**, *46*, 3942−3945. (b) Li, P.; Payette, J. N.; Yamamoto, H. *J. Am. Chem. Soc*. **2007**, *129*, 9534−9535. (c) Kaliappan, K. P.; Ravikumar, V. *Org. Lett*. **2007**, *9*, 2417−2419. (d) Mulzer, J.; Tiefenbacher, K. *Angew. Chem., Int. Ed*. **2007**, *46*, early view. (e) Ghosh, A. K.; Xi, K. *Org. Lett.* **2007**, *9*, 4013−4016.

(5) (a) Ziegler, T.; Layh, M.; Effenberger, F. *Chem. Ber.* **1987**, *120*, 1347−1355. (b) Breuning, M.; Corey, E. J. *Org. Lett*. **2001**, *3*, 1559−1562.

(6) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829−2844.

(7) (a) Pucheault, M.; Darses, S.; Genet, J.-P. *Eur. J. Org. Chem.* **2002**, 3552−3557. (b) Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275−286.

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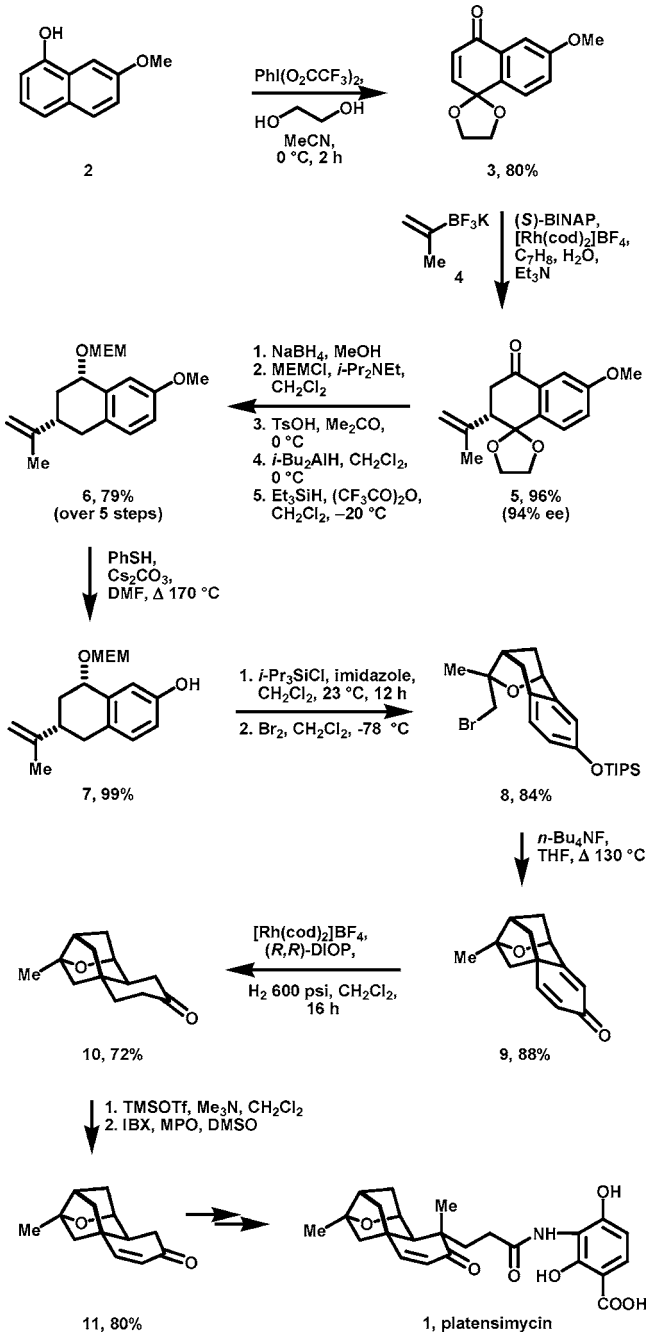
Scheme 1



stereochemistry required for further molecular elaboration of the naturally occurring form of platensimycin.

The successful conversion of **3** to **5** depended critically on the use of triethylamine, which is an essential participant in the reaction since in its absence *no* reaction occurs at 23 °C. Acceleration of the conjugate addition by triethylamine is especially important because, at the higher temperatures generally used for Rh-catalyzed conjugate additions (ca. 100 °C), the intermediate 2-propenylrhodium is unstable and undergoes reversible β-H elimination that eventually generates the 1-propenyl conjugate adduct. We believe that the strong catalysis by triethylamine may be due to its ability to convert a dimeric $Rh_2(I)^{2+}$ species to $Et_3N^+-Rh(BINAP)$-BF_4^- which could be the active catalyst. It is possible that the remarkable acceleration by triethylamine will prove to be generally useful and allow the realization of high enantioselectivities at ambient temperature; this point is under investigation.

The next stage of the synthesis involving reduction of the carbonyl group of **5**, hydroxyl protection, and reductive cleavage of the ethylene ketal subunit was accomplished very efficiently without purification of intermediates and provided the chiral *cis*-tetralin **6**, as detailed in Scheme 1. Demethylation of the methoxy group of **6** occurred quantitatively to form the corresponding phenol **7** which was then converted to the phenolic triisopropylsilyl (TIPS) ether. Reaction of this silyl ether with Br_2 in CH_2Cl_2 at −78 °C was remarkably clean and diastereoselective and led to a predominant (>10:1 ratio) bromoether, **8** (84% overall from **7**). The assignment of relative configuration at the quaternary stereocenter in **8** followed from ^{1}H NMR NOE experiments (Figure 1) and

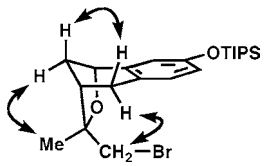
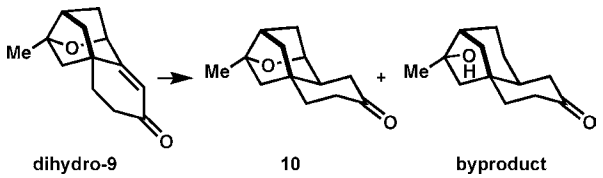


Figure 1. Observed NOE interactions for bromoether **8**.

also from the clean conversion to the tetracyclic dienone **9** in a single step by heating with tetra-*n*-butylammonium fluoride in THF at 130 °C (88% isolated yield).

Diastereoselective hydrogenation of **9** over the catalyst Rh(COD)$_2$BF$_4$−(*R*,*R*)-DIOP ((4*R*,5*R*)-(−)-*O*-isopropylidine-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane) (Strem Chemicals) produced the tetrahydro derivative **10** in 72% isolated yield along with a small amount of the diastereomer at the carbon β to the carbonyl function. Although the same product could be produced stereospecifically by the reduction of dihydro-**9** with Li in liquid NH_3−THF at −78 °C, this reduction proceeded with concomitant formation of a byproduct from reductive cleavage of the bond between the ether oxygen and the carbon γ to the carbonyl group.



The saturated ketone **10** was transformed into the corresponding α,β-enone **11** using the 2-iodoxybenzoic acid (IBX) sequence of Nicolaou and co-workers.[8] Specifically, the ketone **9** was treated with excess trimethylamine[9] and

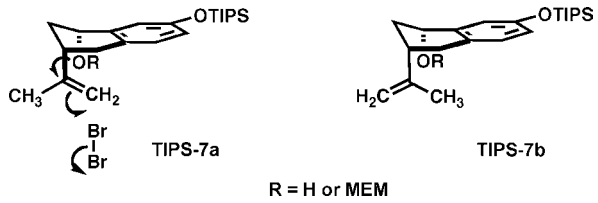
(8) (a) Nicolaou, K. C.; Gray, D. L. F.; Montagnon, T.; Harrison, S. T. *Angew. Chem., Int. Ed.* **2002**, *41*, 996−1000. (b) Nicolaou, K. C.; Zhong, Y.-L.; Baran, P. S. *J. Am. Chem. Soc.* **2000**, *122*, 7596−7597.

trimethylsilyl triflate at 0 to 23 °C to form a TMS enol ether which when oxidized by 1.5 equiv of IBX and 1.5 equiv of 4-methoxypyridine *N*-oxide in dimethylsulfoxide (DMSO) at 23 °C gave the tricyclic α,β-enone **11**. The spectroscopic data for our sample of synthetic **11** were completely identical with those previously reported.[2−4]

There are a number of noteworthy steps in the synthetic pathway to the chiral tricyclic core of platensimycin, which is outlined in Scheme 1. These may be summarized as follows: (1) the highly enantioselective, triethylamine-accelerated, catalytic conjugate addition of 2-propenyl group of **4** to the α,β-enone **3**; (2) the stereospecific reduction of the carbonyl group of **3** and the subsequent smooth reductive removal of the ethylene ketal subunit; (3) the diastereoselective formation of the bromoether **8**; (4) the one-step desilylation and cyclization to form **9**; (5) the diastereoselective reduction of **9** to form **10**; and (6) the regioselective conversion of **10** to the α,β-enone **11**.

An interesting mechanistic question arising from our synthetic route to **1** via **11** concerns the highly diastereoselective formation of the bromoether **8** by reaction of bromine (and possibly trace HBr) with TIPS-**7** (in CH_2Cl_2 at −78 °C).

That selectivity would be very difficult to explain were the attack of bromine on TIPS-**7** to occur in a conformation in which the 2-propenyl appendage is equatorial on the half-chair six-membered ring. On the other hand, a straightforward explanation is possible if the formation of **8** takes place



by a concerted pathway involving simultaneous attack of bromine and the neighboring oxygen on a conformation (TIPS-**7a**) in which the 2-propenyl group is axial on the six-membered ring. Since TIPS-**7a** is expected to be more stable than conformation TIPS-**7b** by ca. 1.5 kcal/mol,[10] and the transition state is likely an early one due to the high exothermicity of the reaction, it is reasonable that reaction would occur via TIPS-**7a** rather than TIPS-**7b** and that the product would be bromoether **8** rather than the diastereomer.

Note Added after ASAP Publication. Scheme 1 was corrected. The corrected version was published ASAP October 25, 2007.

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

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(9) The required intermediate silyl enol ether was generated more selectively by trimethylamine than by other tertiary amines.

(10) The differential interactions involving the 2-propenyl group in TIPS-**7a** and TIPS-**7b** resemble those of CH_3/CH_2 anti and CH_3/CH_2 syn in 1-butene. The former conformation of 1-butene is more stable than the latter by ca. 1.5 kcal/mol; see: Hemelrijk, D. V.; Enden, L. V. D.; Geise, J. J.; Sellers, H. L.; Scafer, L. *J. Am. Chem. Soc.* **1980**, *102*, 2189−2194.