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A Simple, Efficient, and Enantiocontrolled Synthesis of a Near-Structural Mimic of Platensimycin

Ying-Yeung Yeung and E. J. Corey*

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

corey@chemistry.harvard.edu

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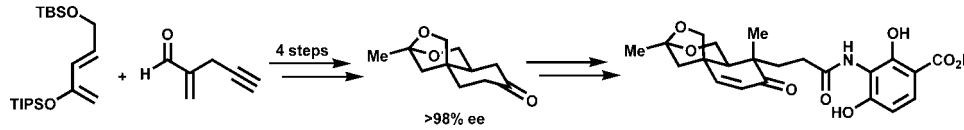
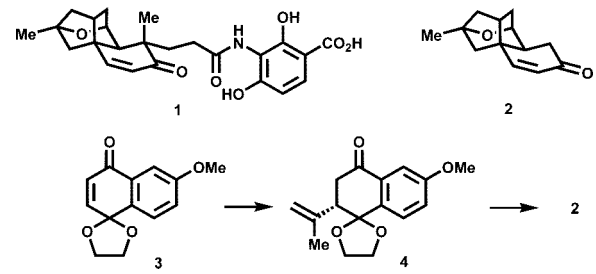
ABSTRACT



A close structural relative of platensimycin was synthesized efficiently in nine steps.

Despite the pressing need for new types of antibiotics to combat the emergence of drug-resistant strains of pathogenic microbes, very few useful naturally produced and novel antimicrobial compounds have been identified in recent years. A rare exception is the discovery by Merck of platensimycin (**1**), a potent inhibitor of microbial fatty acid biosynthesis.[1] That fact and the fascinating structure of **1** have stimulated much recent research on synthetic approaches to platensimycin and related structures. Several quite interesting and diverse synthetic sequences for the synthesis of platensimycin via the key tetracyclic ketone **2** have been described.[2] In our laboratory,[3] the core tetracycle **2** was constructed enantioselectively and expeditiously from the achiral quinone monoketal **3** via the chiral conjugate adduct **4** (Scheme 1).[3] This route is interesting not only because it is short, highly enantioselective, and stereocontrolled but also because all of the carbons of **2** are generated in the early intermediate **4** which was produced enantioselectively from the achiral precursor **3**.

Scheme 1



In this paper, we describe a totally new and exceedingly simple synthesis of platensimycin analogue **5**, a compound

(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. *ChemMedChem* **2006**, *1*, 951–954.

(2) (a) Nicolaou, K. C.; Li, A.; Edmonds, D. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 7086–7090. (b) Nicolaou, K. C.; Tang, Y.; Wang, J. *Chem. Commun.* **2007**, 192–1923. (c) Nicolaou, K. C.; Edmonds, D. J.; Li, A.; Tria, G. S. *Angew. Chem., Int. Ed.* **2007**, *46*, 3942–3945. (d) Li, P.; Payette, J. N.; Yamamoto, H. *J. Am. Chem. Soc.* **2007**, *129*, 9534–9535. (e) Zou, Y.; Chen, C.-H.; Taylor, C. D.; Foxman, B. M.; Snider, B. B. *Org. Lett.* **2007**, *9*, 1825–1828. (f) Ghosh, Q.; Xi, K. *Org. Lett.* **2007**, *9*, 4013–4016. (g) Tiefenbacher, K.; Mulzer, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 2548–2555. (h) Kim, C. H.; Jang, K. P.; Choi, S. Y.; Chung, Y. K.; Lee, E. *Angew. Chem., Int. Ed.* **2008**, *47*, 4009–4011.

(3) Lalic, G.; Corey, E. J. *Org. Lett.* **2007**, *9*, 4921–4923.

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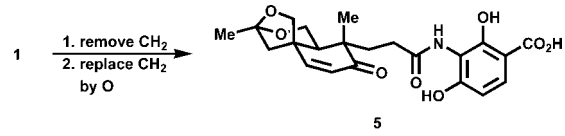
that differs form platensimycin only in the replacement of one of the methylene bridges by oxygen and the excision of the other methylene bridge.



The O−CH_2 bridge across the tetrahydropyran ring of **5** serves to maintain a conformation of the core that is very similar to that for platensimycin. Evidence in the literature suggests that **5** will have excellent antimicrobial activity.[4]

An interesting aspect of our synthesis of **5** is the assembly of all of the carbon atoms of the bridged ring core and also the two initial stereocenters (as a vicinal pair) with excellent diastereo- and enantioselectivity in the very first step (Scheme 2). [4 + 2]-Cycloaddition of the diene **6**[5] to the enynal **7**[6] produced the required key intermediate **8** in 60% yield and with 93:7 enantioselectivity using the Corey−Loh chiral catalyst **A**.[7,8] Reduction of the formyl group of **8** followed by desilylation provided the keto diol **9** in 84% overall yield. Treatment of **9** with a catalytic amount of $AuCl_3$ in MeOH at 23 °C for 1 h afforded the tricyclic core of **5**, ketone **10**, in 85% yield and >98% ee after one crystallization from EtOAc−hexanes, mp 140−142 °C.[9] The structure of **10** was fully confirmed by single-crystal X-ray diffraction analysis.[8] The saturated ketone **10** was then α-methylated and α,*β*-dehydrogenated by the following sequence: (1) treatment with lithium hexamethyldisilazide (LiHMDS) in THF at −78 °C followed by reaction with methyl iodide, (2) α′-deprotonation and conversion to the α′-phenylseleno ether using LiHMDS followed by PhSeBr in THF at −78 °C, and (3) treatment with H_2O_2−pyridine in CH_2Cl_2 at 23 °C to give the α,*β*-enone **11** in 75% overall yield.

Exposure of the enone **11** to potassium *tert*-butoxide and methyl acrylate in THF effected Michael addition to form a keto methyl ester which upon saponification yielded the keto acid **12** (63% overall yield). The acid **12** was coupled to the amino group of the bis-methoxymethyl ether of methyl 2,4-dihydroxy-3-aminobenzoate after carbonyl activation using 2-(1*H*-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU) to give the amide ester **13** which after saponification gave the required platensimycin analogue **5** in 58% overall yield from **12**.[10]

We have also used the carboxylic acid **12** to synthesize a number of other carboxamido benzoic analogues of **5**. The antibiotic activities of **5** and these new analogues relative to platensimycin are now under study. Initial results indicate that **5** is a potent antibiotic.

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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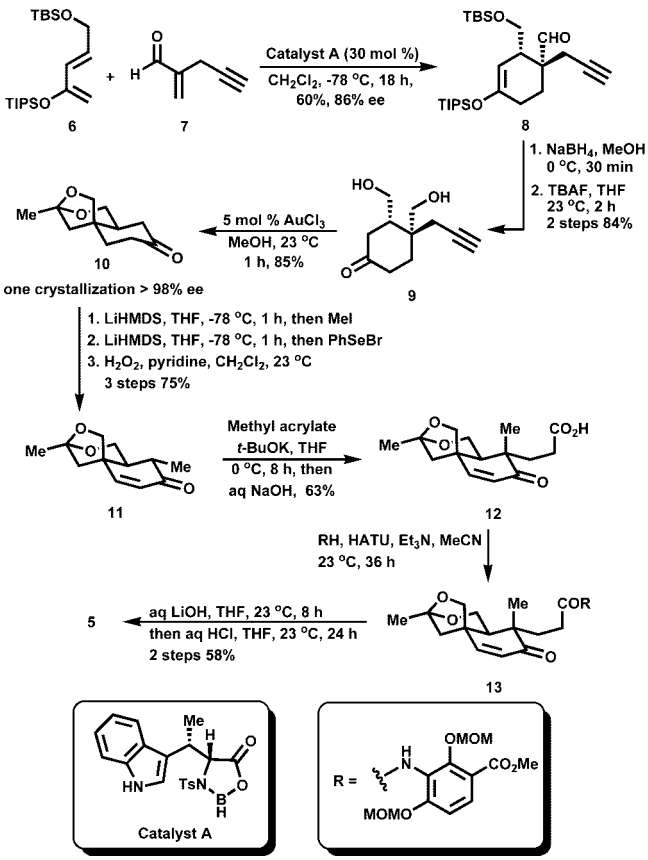
Scheme 2



(4) (a) Nicolaou, K. C.; Tang, Y.; Wang, Y.; Stepan, A. F.; Li, A.; Montero, A. *J. Am. Chem. Soc.* **2007**, *129*, 14850–14851. (b) Nicolaou, K. C.; Lister, T.; Denton, R. M.; Montero, A.; Edmonds, D. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 4712–4714.

(5) This diene was prepared in 92% yield from 5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-4-penten-2-one (see Piggott, M. J.; Wege, D. *Aust. J. Chem.* **2003**, *56*, 691–702.) by reaction with triisopropylsilyl triflate and triethylamine in CH_2Cl_2 at −78 °C for 1 h and then 0 °C for 12 h.

(6) The aldehyde **7** was made from 2-methylenyl-4-pentyn-1-ol (see Mesnard, D.; Miginiac, L. *J. Organomet. Chem.* **1991**, *420*, 163–170.) by oxidation with activated MnO_2 in CH_2Cl_2 at 23 °C for 8 h.

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(8) Experimental details and analytical and physical data are given in the Supporting Information.

(9) (a) Antoniotti, S.; Genin, E.; Michelet, V.; Genet, J.-P. *J. Am. Chem. Soc.* **2005**, *127*, 9976–9977. (b) Barluenga, J.; Diéguez, A.; Fernández, A.; Rodríguez, Fañanás, F. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 2091–2093.

(10) The similarity of optical rotation of **5** ($[\alpha]^{23}_D$ −68.5, c = 0.2, acetone) and the natural platensimycin **(1)** ($[\alpha]^{23}_D$ −51.1, c = 0.1, MeOH) confirmed the absolute configuraton of **5**, which also corresponds to that expected from previous studies with catalyst **A** (see ref 7).