

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

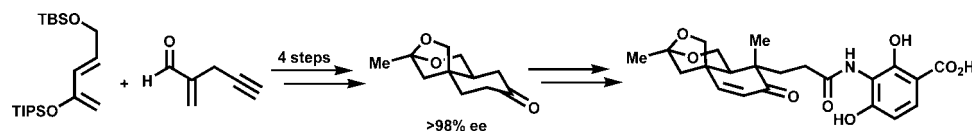
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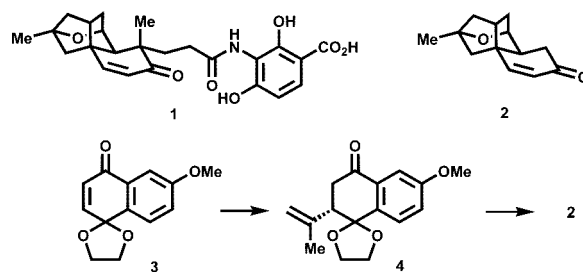
ABSTRACT



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

Scheme 1



of the carbons of **2** are generated in the early intermediate **4** which was produced enantioselectively from the achiral precursor **3**.

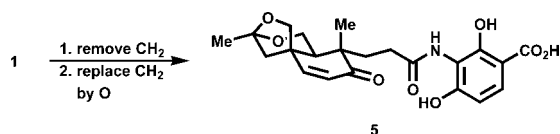
In this paper, we describe a totally new and exceedingly simple synthesis of platensimycin analogue **5**, a compound

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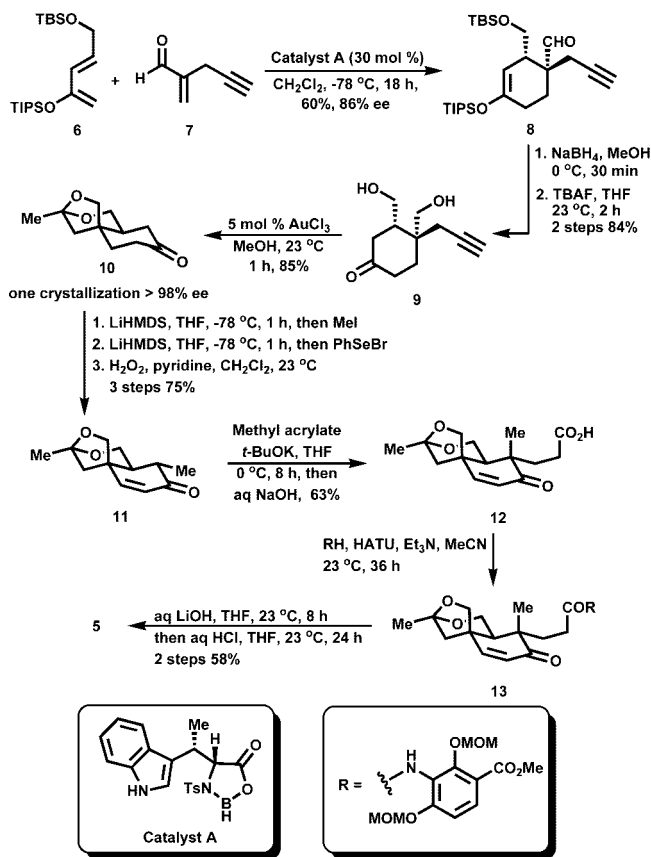
that differs from platensimycin only in the replacement of one of the methylene bridges by oxygen and the excision of the other methylene bridge.



The O—CH₂ 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** to the enynal **7**

Scheme 2



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 AuCl₃ 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 H₂O₂–pyridine in CH₂Cl₂ 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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(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 CH₂Cl₂ 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 MnO₂ in CH₂Cl₂ at 23 °C for 8 h.

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

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(10) The similarity of optical rotation of **5** ([α]_D²³ –68.5, *c* = 0.2, acetone) and the natural platensimycin (**1**) ([α]_D²³ –51.1, *c* = 0.1, MeOH) confirmed the absolute configuration of **5**, which also corresponds to that expected from previous studies with catalyst **A** (see ref 7).