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Stereocontrolled Formal Synthesis of (±)-Platensimycin

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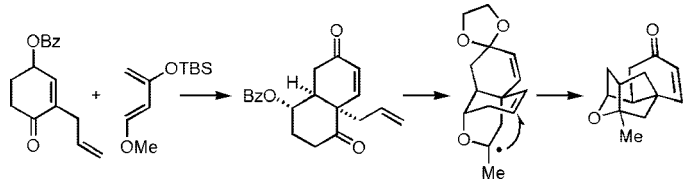
ABSTRACT

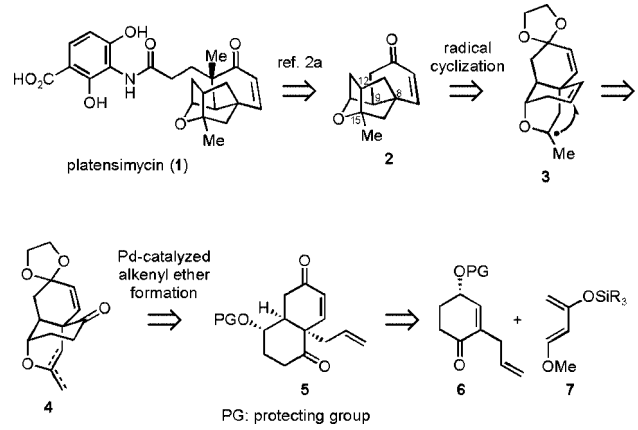


The caged structure of platensimycin, known as Nicolaou's key intermediate for total synthesis of platensimycin, was synthesized stereoselectively by using the following key steps: (i) diastereoselective Diels−Alder reaction between γ-benzoyloxy enone and *tert*-butyldimethylsiloxydiene, (ii) formation of a dihydropyran ring by intramolecular catalytic oxypalladation, and (iii) transannular radical cyclization of monothioacetal with tributyltin hydride and AIBN.

Platensimycin (**1**), which was isolated from *Streptomyces platensis* by Merck's research group in 2006, has potent, broad-spectrum Gram-positive antibacterial activity and exhibits no cross-resistance to antibiotic-resistant bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), and linezolid-resistant and macrolide-resistant pathogens.[1] Platensimycin (**1**) selectively inhibits FabF, an elongation condensing enzyme of fatty-acid biosynthesis, which is highly conserved among key pathogens. In addition to the novelty in the biological activity of **1**, the characteristic caged structure of **1** has attracted the interest of organic chemists, and several research groups have reported total and formal synthesis of **1**.[2,3]

We planned a stereocontrolled synthesis of **2**, a key intermediate in Nicolaou's total synthesis of **1**,[2a] as shown in Scheme 1. We expected that the C12−C15 bond of **2** would be formed by transannular radical cyclization[4] of α-alkoxy radical[5] **3** and that a six-membered cyclic ether ring of **3** would be constructed by palladium-catalyzed intramolecular alkenyl ether formation from **5** to **4**. We

Scheme 1. Retrosynthesis of **2**



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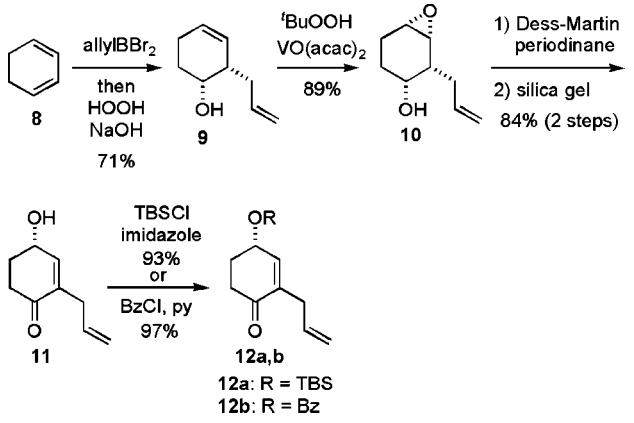
envisioned that compound **5** would be accessible by diastereoselective Diels−Alder reaction of enone **6** and siloxydiene **7**.[6] The key feature of our plan is that all stereocenters in **2** are controlled by the stereochemistry presented in **6**. Thus, stereochemistries at C8 and C9 are controlled by the diastereoselective Diels−Alder reaction, while those at C12 and C15 are determined inevitably by the transannular cyclization.

O-TBS and *O*-benzoyl-protected enones **12a**,**b** were prepared from 1,3-cyclohexadiene (**8**) as shown in Scheme 2. Allylboration of **8** with allyldibromoborane[7] gave **9** in

Scheme 2. Preparation of Enone **12a**,**b**



71% yield after oxidative workup. The homoallylic double bond of **9** was selectively oxidized with $VO(acac)_2$ and *tert*-butyl hydroperoxide[8] to afford epoxide **10** in 89% yield. Oxidation of the hydroxy group of **10** with Dess−Martin periodinane[9] gave the corresponding β,γ-epoxy ketone and successive isomerization to γ-hydroxy enone **11** took place readily in the presence of silica gel.[10] Other oxidation methods such as Swern oxidation[11] and PDC[12] gave inferior results because of the lability of formed β,γ-epoxy ketone under the reaction conditions. Protection of the hydroxy group of **11** with TBSCl and benzoyl chloride gave **12a** and **12b**, respectively.

Next, the Diels−Alder reaction of thus-prepared dienophiles **12a**,**b** with siloxydienes **13a**,**b** was investigated (Table 1).[13] The Diels−Alder reaction between TBS-protected enone **12a** and trimethylsiloxydiene **13a** in the presence of pyridine and 2,6-di-*tert*-butyl-4-methylphenol (BHT) at 200 °C (in toluene, sealed tube) gave the corresponding Diels−Alder adducts (**14a** and **15a**) in 32% yield with low diastereoselectivity (**14a**:**15a** = 4:1) after acidic treatment (entry 1). The yield and selectivity were improved by employing benzoyl-protected enone **12b** instead of **12a**, presumably due to the lower LUMO level of **12b** (entry 2). After screening various reaction conditions, it was found that the Diels−Alder reaction between **12b** and *tert*-butyldimethylsiloxydiene **13b** at 180 °C without any solvents gave the desired Diels−Alder adduct **14b** and its diastereomer **15b** in 83% combined yield in a ratio of **14b**:**15b** = 11:1 after treatment with trifluoroacetic acid (entry 3). This further improvement of chemical yield and diastereoselectivity might be explained by better thermal stability of **13b** than that of **13a** and by effective steric repulsion between the benzoyloxy group of **12b** and TBS group of **13b** in the transition state of the Diels−Alder reaction. The mixture of two diastereomers (**14b** and **15b**) was employed in the next step because of difficulty in separation at this stage.

Selective protection of the less-hindered carbonyl group by Noyori's procedure[14] followed by hydrolysis of the benzoyl group and separation of diastereomers gave **16** in 80% yield as a single diastereomer. Catalytic oxypalladation of **16** by using a catalytic amount of palladium(II) chloride and copper(II) acetate under oxygen atmosphere in dimethylacetamide[15] gave **17a** and **17b** in 73% combined yield (**17a**:**17b** = 10:1).[16] The mixture of isomers was employed in the following steps.

To form a carbon−carbon bond between C12 and C15 by radical cyclization, we needed to prepare alkene **19** from ketone **17**. Reduction of the keto group of **17** followed by dehydration of the resulting alcohol via mesylate did not give **19**. It was found that vinyl triflate **18**, which was prepared from **17** with KHMDS and *N*-(5-chloro-2-pyridyl)trifimide,[17]

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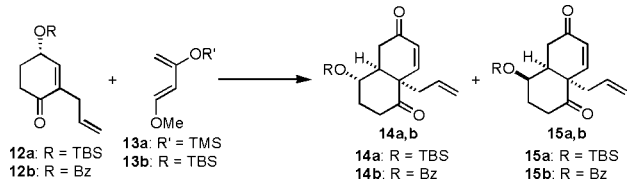
Table 1. The Diels–Alder Reaction Between **12a**,**b** and **13a**,**b**

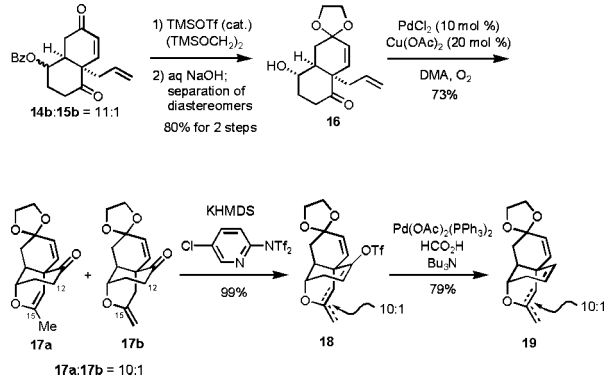


entry	enone	diene (equiv)	conditions	yield (%)[a]	**14**:**15**
1	**12a**	**13a** (4.0)	(1) py (1.0 equiv), BHT[b] (cat.), toluene, 200 °C, 34 h (2) 0.01 N aq HCl	32	**14a**:**15a** = 4:1
2	**12b**	**13a** (4.0)	(1) py (1.0 equiv), BHT[b] (cat.), toluene, 180 °C, 25 h (2) 0.01 N aq HCl	60	**14b**:**15b** = 8:1
3	**12b**	**13b** (2.5)	(1) neat, 180 °C (2) TFA, CH_2Cl_2	83	**14b**:**15b** = 11:1

[a] Combined yield of **14** and **15**. [b] 2,6-Di-*tert*-butyl-4-methylphenol.

was reduced to **19** in good yield by using a palladium catalyst, formic acid, and tributylamine (Scheme 3).[18]

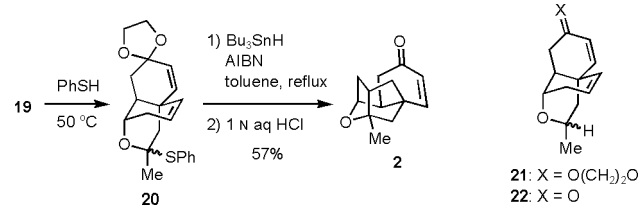
Scheme 3. Preparation of **19** by Palladium-Catalyzed Alkenyl Ether Formation



Reduction of vinyl triflate **18** by the use of tributyltin hydride and palladium(0)[19] gave alkene **19** in only 37% yield.

Monothioacetal **20**, a precursor for radical cyclization, was prepared by reaction of alkenyl ether **19** and benzenethiol at 50 °C without any solvents (Scheme 4).[20] Transannular radical cyclization of monothioacetal **20**[21] was accomplished by using tributyltin hydride in the presence of AIBN in refluxing toluene. Subsequent deprotection of the acetal group gave **2** in 57% yield in two steps along with compound **22** (18% yield), which was formed by reduction of α-alkoxy radical intermediate with tributyltin hydride followed by acid

Scheme 4. Transannular Radical Cyclization of **20** to **2**



hydrolysis. It was also observed by TLC analysis that elimination of the phenylthio group of **20** to **19** proceeded in refluxing toluene. Tributyltin hydride was found to be a better hydrogen source in this transannular radical cyclization than tris(trimethylsilyl)silane and triphenyltin hydride. At the outset, we tried to prepare the phenylselenoacetal for radical cyclization.[22] However, the preparation of the phenylselenoacetal by the reaction of **19** with benzeneselenol[23] gave compound **21**, which might be formed by reductive cleavage of a tentatively introduced benzeneselenyl group.[24]

In summary, we have established a stereocontrolled synthesis of the platensimycin core **2** with the following key findings. (1) Diastereoselective Diels–Alder reaction proceeded efficiently by the combination of enone **12b** and siloxydiene **13b**. The steric and electronic factors of the benzoyl group of **12b** and TBS group of **13b** significantly affected the Diels–Alder reaction. (2) Intramolecular alkenyl ether formation to construct a dihydropyran ring was performed by oxypalladation with a catalytic amount of

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palladium(II) chloride and copper(II) acetate under oxygen atmosphere. (3) The caged structure was constructed by transannular radical cyclization of conformationally rigid monothioacetal **20** by using tributyltin hydride and AIBN in refluxing toluene with minimization of the elimination of benzenethiol from **20** to **19** and reduction of **20** to **21**. This convergent synthesis of **2** will be useful for the synthesis of platensimycin analogues which might improve the pharmacokinetic properties[25] of **1**.

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

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