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First Total Syntheses of (±)-Penicillones A and B

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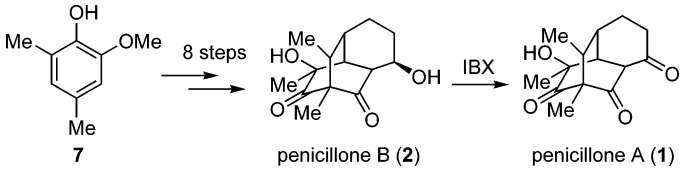
ABSTRACT



The first total syntheses of (±)-penicillones A (1) and B (2) have been accomplished from 2-methoxy-4,6-dimethylphenol (7) in 9 and 8 synthetic steps, respectively. Intramolecular Diels–Alder reaction of masked *o*-benzoquinone 8 and aqueous acid-catalyzed intramolecular aldol reaction are the key steps.

Recent synthetic efforts in our laboratory were focused on the utilization of masked *o*-benzoquinones (MOBs) and demonstrated that MOBs are valuable intermediates in organic synthesis.[1] Among these, we have developed several strategies to construct various natural product skeletons, including *cis*-decalins,[2,3] bicyclo[4.2.2]decenones,[2a,4] iridoids,[5] and triquinanes.[6] In this paper, we report a new strategy to construct a tricyclo[5.3.1.$0^{3,8}$]undecane skeleton employing our MOB strategy and apply to the total syntheses of penicillones A (**1**) and B (**2**).

Penicillones A (**1**) and B (**2**) have been isolated recently from a fungus *Penicillium terrestre* obtained from the marine sediment in Jiaozhou Bay of Qingdao,[7] which possess a novel tricyclo[5.3.1.$0^{3,8}$]undecane skeleton. Compound **1** showed cytotoxicity against P-388 and A-549 cancer cell lines, while **2** was inactive against P-388. Penicillone contains a bicyclo-[2.2.2]octane core structure, which can be easily constructed from MOB through the Diels−Alder reaction with an appropriate dienophile. Retrosynthetically, we envisaged the hydrolysis of acetal **3** followed by intramolecular aldol reaction to be a potential synthetic sequence to acquire requisite penicillone B (**2**), which could be further oxidized into penicillone A (**1**) (Scheme 1). The aldol precursor **3** could be generated from aldehyde **4**, and the triol moiety **5** would be obtained from tricyclic β,γ-enone **6**. Access to this cycloadduct was to be gained from 2-methoxy-4,6-dimethylphenol (**7**) and *trans*-crotyl alcohol via intramolecular Diels−Alder cycloaddition of in situ generated MOB **8**.

The tricyclic β,γ-enone **6**[8] was obtained in 87% yield via intramolecular Diels−Alder reaction of MOB **8**, produced in situ from oxidative addition of *trans*-crotyl alcohol to 2-methoxy-4,6-dimethylphenol (**7**)[9] in the presence of diacetoxyiodobenzene (DAIB) (Scheme 2).[10] Reduction of ketone **6** with samarium diiodide[11] in THF in the presence

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(8) All new compounds were satisfactorily characterized by IR, ^{1}H (600 MHz), ^{13}C (150 MHz) NMR, DEPT, and low- and high-resolution MS analyses.

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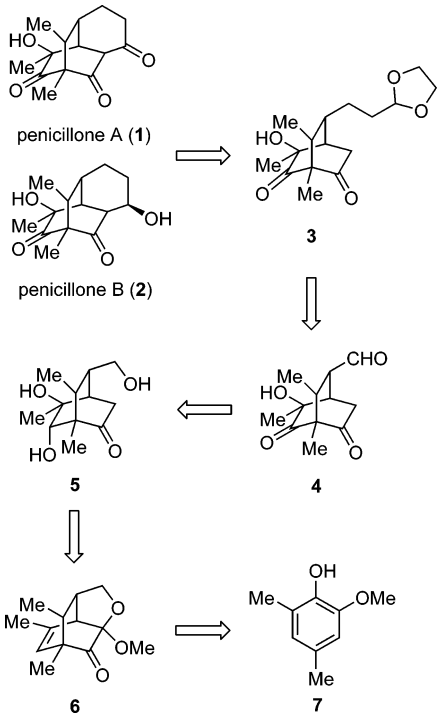
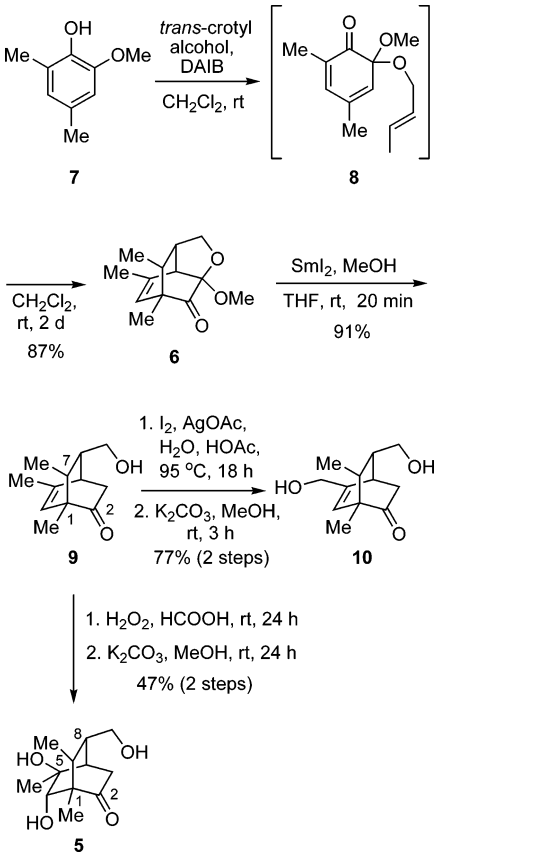
Scheme 1. Retrosynthetic Analysis



Scheme 2. Preparation of Triol **5**



of MeOH as proton source furnished alcohol **9** in 91% yield. The next step was stereocontrolled installation of the C-5 hydroxyl group. Initial attempts were centered on Woodward's dihydroxylation[12] protocol, which is the best method for the preparation of *cis*-diols with the hydroxyl groups on the more hindered side of the molecule. However, these reaction conditions or other modifications[13] were not successful, only providing the allylic oxidation[14] product **10**. We therefore turned our attention to an *anti*-dihydroxylation strategy; this was achieved via sequential epoxidation, ring-opening of the epoxide, and saponification.[15] The direction of epoxidation was controlled by the C-7 methyl group (more hindered π-face); the epoxide was cleaved by back-side nucleophilic attack. The stereostructure of the triol **5** was determined with ^{1}H NMR nuclear Overhauser enhancement (NOE) experiments (Figure 1).

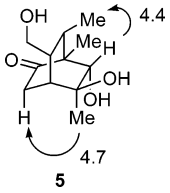


Figure 1. ^{1}H NMR studies of NOE (%) for **5**.

Having secured the stereochemistry of the C-5 hydroxyl, the stage was set for the elongation of the C-8 hydroxymethyl side chain. Toward this end, the primary and secondary alcohols were first oxidized to the aldehyde and ketone simultaneously with *o*-iodoxybenzoic acid (IBX)[16] in 83% yield (Scheme 3). Two-carbon homologation on the aldehyde in **4** was achieved by Wittig reaction with (1,3-dioxolan-2-ylmethyl)triphenylphosphonium bromide[17] and *t*-BuOK[18] to give the unsaturated dioxolane intermediate **11** as an *E*/*Z* mixture (*E*/*Z* = 1:5). Hydrogenation of the unsaturated dioxolane **11** over 5% Rh on alumina, a catalyst that was selected to minimize hydrogenolysis of the allylic acetal,[19] afforded the aldol precursor **3** in 76% yield. Aqueous acid-catalyzed hydrolysis and aldol reaction were carried out in refluxing THF with 2 M H_2SO_4 to generate the desired product penicillone B (**2**) as the only epimer. The reason for formation of a single *endo*-epimer is presumably due to

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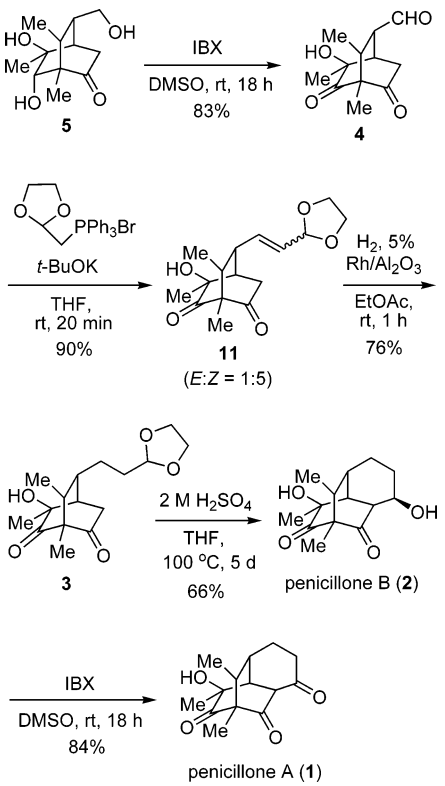
Scheme 3. Complete the Total Synthesis of Penicillones A (**1**) and B (**2**)



the 1,3-diaxial interaction present in the *exo*-epimer **12** (Figure 2).[20] Finally, oxidation of penicillone B (**2**) with IBX furnished penicillone A (**1**). The spectra of the synthetic materials were fully consistent with the literature data.[7]

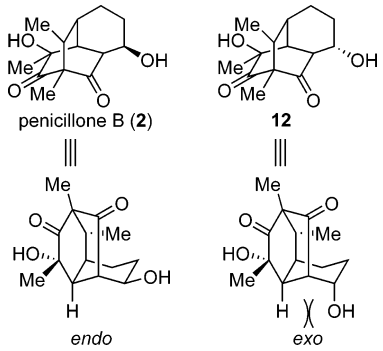


Figure 2. Structures of penicillone B (**2**) and **12**.

In conclusion, we have accomplished the total syntheses of penicillones A (**1**) and B (**2**) from 2-methoxy-4,6-dimethylphenol (**7**) in 9 and 8 synthetic steps, respectively, using the MOB strategy.

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

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