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# Synthetic study of aquayamycin. Part 3: First total synthesis

Takashi Matsumoto, Hiroki Yamaguchi, Mitsujiro Tanabe, Yoshizumi Yasui and Keisuke Suzuki*

*Department of Chemistry, Tokyo Institute of Technology, and CREST, Japan Science and Technology Corporation (JST), O-okayama, Tokyo 152-8551, Japan*

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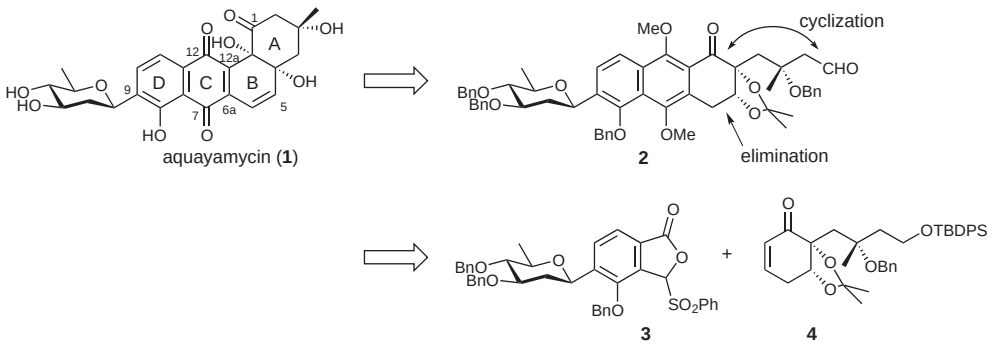
**Abstract**

The first total synthesis of aquayamycin (**1**) has been accomplished. The crucial steps include (1) the Hauser reaction between 3-(phenylsulfonyl)phthalide **3** and cyclohexenone **4** to make up the linear BCD tricycle, and (2) the intramolecular pinacol coupling of keto aldehyde **7** to the full tetracyclic framework.


We report here the first total synthesis of aquayamycin (**1**),[1] the first angucycline antibiotic with a *C*-glycoside structure.[2–4] The main challenge of the synthesis stemmed from the characteristic, highly oxygenated AB ring system, which is prone to rearrange or aromatize under acidic, basic and also photo-irradiation conditions.[1]

Our synthetic plan relied on constructing the unstable A ring in the last stage by the pinacol cyclization of the tricyclic keto aldehyde **2** followed by unsaturation at C(5)–C(6). Compound **2**, in turn, would be accessible via Hauser reaction[5] with the *C*-olivosylated phthalide **3**[6] and the cyclohexenone **4** (Scheme 1).[7]




Scheme 1.

* Corresponding author.

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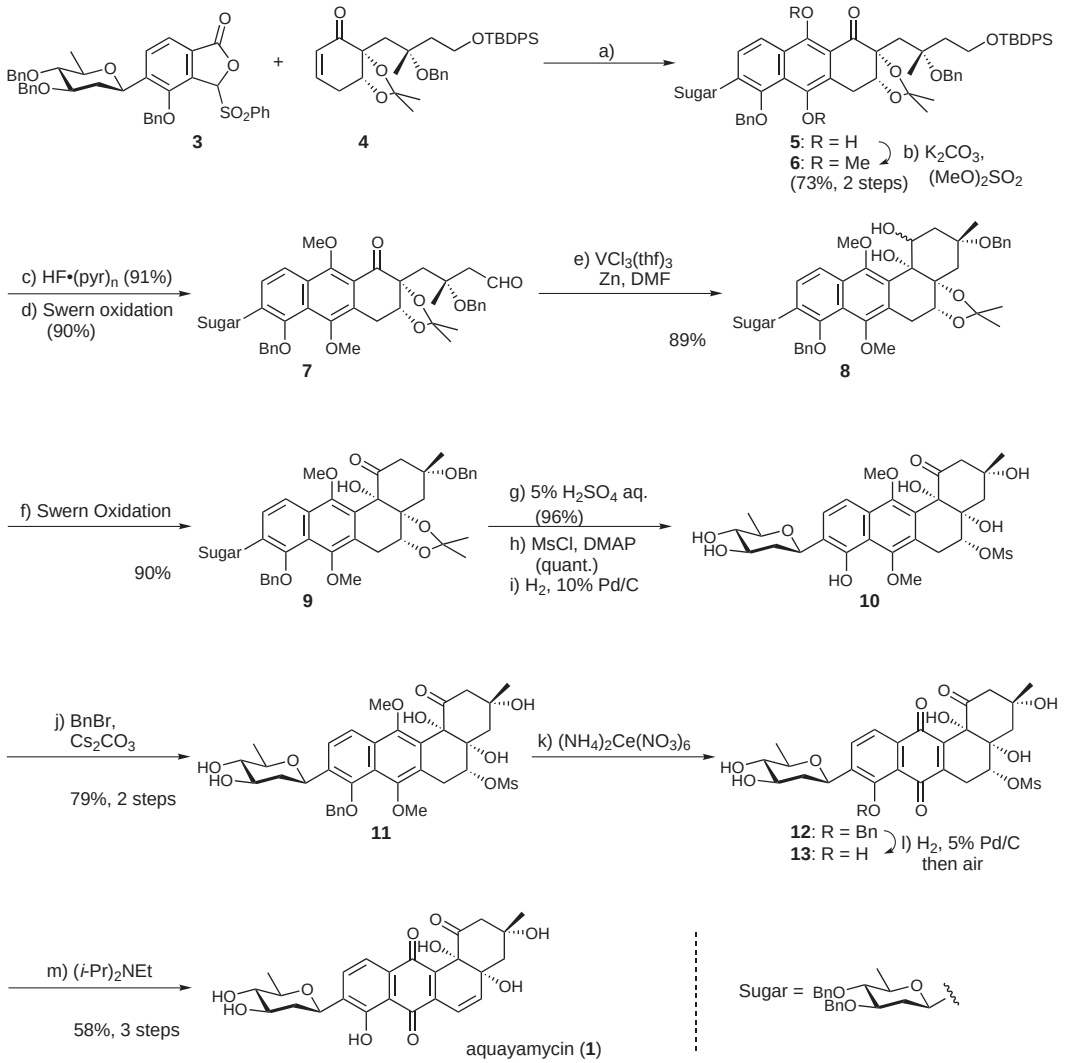
The enone **4** was added to a solution of the lithio anion of the phthalide **3** at −78°C. Upon warm up to 45°C, a clean reaction occurred to give the unstable hydroquinone **5**, which was immediately protected with $(MeO)_2SO_2$ and $K_2CO_3$ to give the dimethyl ether **6** in 73% yield (Scheme 2).




Scheme 2. (a) **3**, *t*-BuOLi, THF, −78°C, 30 min; then **4** at −78°C; warm up to 45°C, for 1 h. (b) Acetone, reflux, 5 h. (c) THF, rt, 7 h. (d) $(COCl)_2$, DMSO, $CH_2Cl_2$, −78°C; then $Et_3N$, warm up to 0°C. (e) $CH_2Cl_2$, rt, 30 min. (f) $(COCl)_2$, DMSO, $CH_2Cl_2$, −78°C; then $Et_3N$, warm up to 0°C. (g) 1,4-Dioxane, 80°C, 2 h. (h) Pyridine, $CH_2Cl_2$, rt, 1 h. (i) EtOAc, MeOH, rt, 9.5 h. (j) DMF, 0°C, 1.5 h. (k) Aq. MeCN, 0°C, 3 min. (l) See text. (m) 1,4-Dioxane, 45°C, 1.5 h

Removal of the TBDPS group in **6** by HF·(pyr)$_n$ followed by Swern oxidation gave the keto aldehyde **7**, which was then subjected to an intramolecular pinacol coupling for the A ring cyclization. Among various methods attempted, the Pedersen procedure by utilizing $VCl_3$·$(thf)_3$ and Zn[8] effected clean cyclization to give the pinacol **8** as a mixture of the C(1)-epimers (**8a**:**8b** = 13:1), which *converged to a single ketone* ***9*** by Swern oxidation in high yield.

Evidence for the *cis* stereochemistry of the A/B ring junction was provided by separation of the epimers of **8** followed by forming the bis-acetonides **14a** (from the major isomer) and **14b** (from the minor isomer) [2-methoxypropene, cat. *p*-TsOH, benzene] (Fig. 1)—if *trans*, one of the isomers, **8c**, would fail to give the corresponding bis-acetonide because of the topological reason. The NOE experiments on the bis-acetal **14a** proved that the orientation of the C(1) hydroxy group is α in the major epimer of **8**, i.e. **8a**. The *cis* selectivity for the AB ring junction can be attributed to the C–C bond formation on the convex face of the *cis*-fused 5–6 ring system of the dioxolane and the B ring.

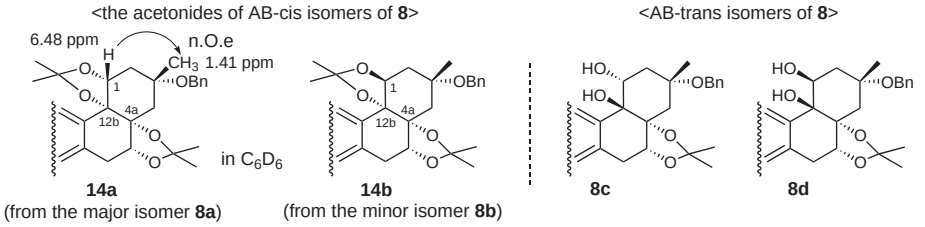
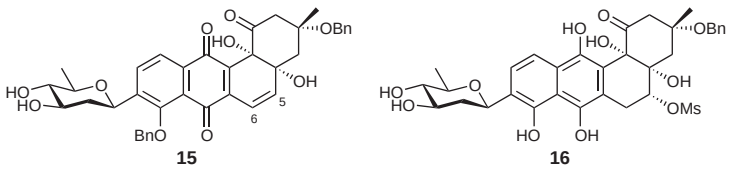



Figure 1.

The ketone **9** was converted to the hexol **10** in high yield via three steps: (1) removal of the acetonide, (2) selective mesylation of the C(5) hydroxy group and (3) hydrogenolysis of all four benzyl ethers. Attempted oxidation of the hexol **10** with CAN to the corresponding *para*-quinone was unsuccessful under various conditions, giving many unidentified products. Fortunately, however, clean oxidation could be effected when the C(8) phenol was selectively re-protected by a benzyl group by using $Cs_2CO_3$.[9]




The quinone **12** underwent elimination of a methanesulfonic acid during the chromatographic purification on silica gel to give compound **15**, i.e. the benzyl ether of aquayamycin. Unfortunately, however, all attempts to convert **15** into **1** failed so long as the reductive debenzylation was employed, because the C(5)–C(6) double bond was concomitantly saturated.[10] After considerable experimentation, a solution to this issue was provided by the following sequence of reactions. The quinone **12**, without purification, was subjected to a quick catalytic hydrogenolysis (1 min) over 5% Pd/C in EtOAc, which effected reduction of the C ring to the corresponding hydroquinone and removal of the benzyl group. The resulting hydroquinone **16** underwent spontaneous oxidation upon exposure to air to give the quinone **13**, which was treated with *i*-$Pr_2NEt$ in 1,4-dioxane at 45°C (1.5 h) to effect clean elimination of a methanesulfonic acid to give aquayamycin (**1**) in high yield. The synthetic material proved to be identical with the natural product in all respects (mp, $[\alpha]_D$, IR, $^1H$ and $^{13}C$ NMR).[11]

In summary, the first total synthesis of aquayamycin (**1**), the prototypical and synthetically most challenging member among the angucycline antibiotics, was achieved in 13 steps (21% overall yield) from the phthalide **3** and the cyclohexenone **4**.

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