



Synthetic study of aquayamycin. Part 3: First total synthesis

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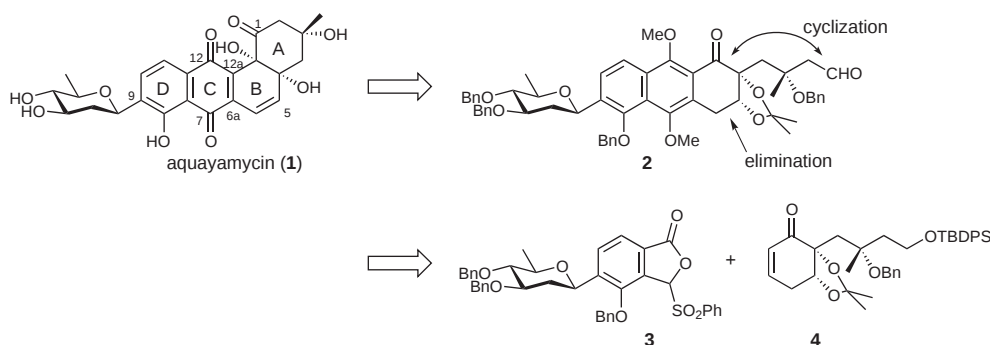
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Abstract

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.
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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

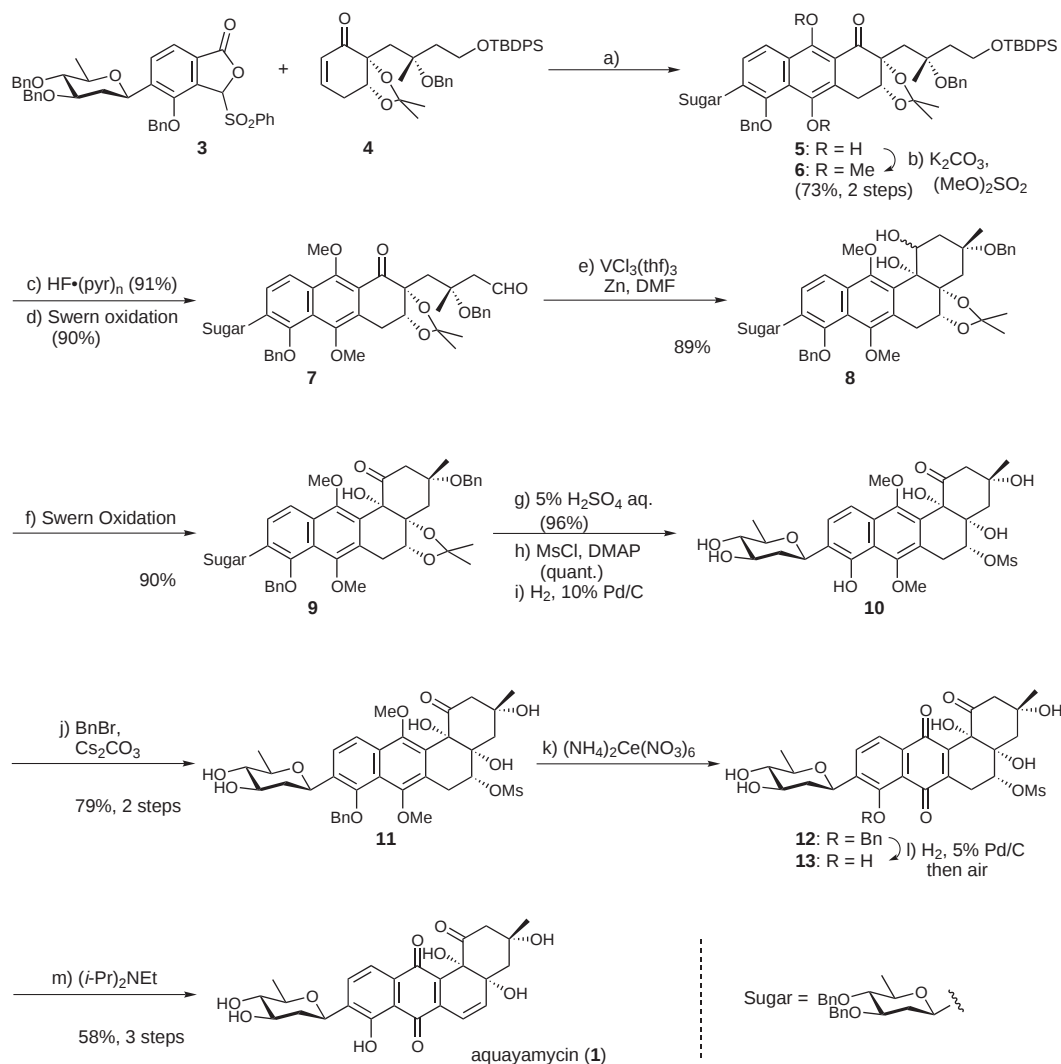
Our synthetic plan relied on constructing the unstable A ring in the last stage by the pinacol cyclization of the tricyclic keto aldehyde **2** followed by unsaturation at C(5)–C(6). Compound **2**, in turn, would be accessible via Hauser reaction⁵ with the C-olivosylated phthalide **3**⁶ and the cyclohexenone **4** (Scheme 1).⁷



Scheme 1.

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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 $(\text{MeO})_2\text{SO}_2$ and K_2CO_3 to give the dimethyl ether **6** in 73% yield (Scheme 2).



Scheme 2. (a) **3**, $t\text{-BuOLi}$, 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) $(\text{COCl})_2$, DMSO, CH_2Cl_2 , -78°C ; then Et_3N , warm up to 0°C . (e) CH_2Cl_2 , rt, 30 min. (f) $(\text{COCl})_2$, 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 $\text{HF}\cdot(\text{pyr})_n$ 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 $\text{VCl}_3\cdot(\text{thf})_3$ 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.

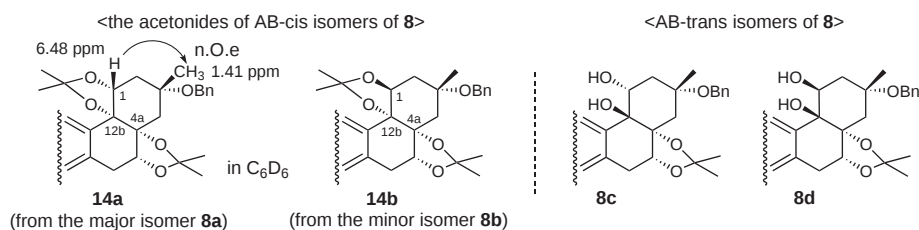
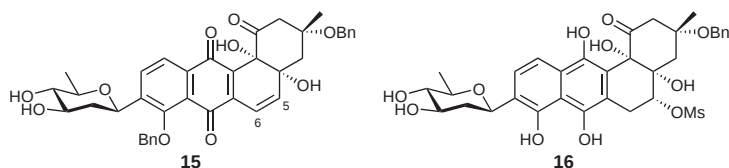


Figure 1.

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 debenzoylation 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*-Pr₂NEt 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 ¹³C 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**.

Acknowledgements

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