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Synthetic study of aquayamycin. Part 2: Synthesis of the AB ring fragment

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Abstract

A highly oxygen-functionalized cyclohexenone **2**, the AB ring fragment for the aquayamycin synthesis, was efficiently synthesized via stereoselective addition of allylzinc bromide to ketone **3a** which, in turn, was available from the optically pure cyclohexane 1,2,3-triol derivative **5**.

In the preceding paper,[1a] we described an access to the left-half fragment for the synthesis of aquayamycin (**1**).[2] The present paper describes the synthesis of the corresponding right-half (AB ring) fragment, i.e. the cyclohexenone **2** with many oxygen functions.

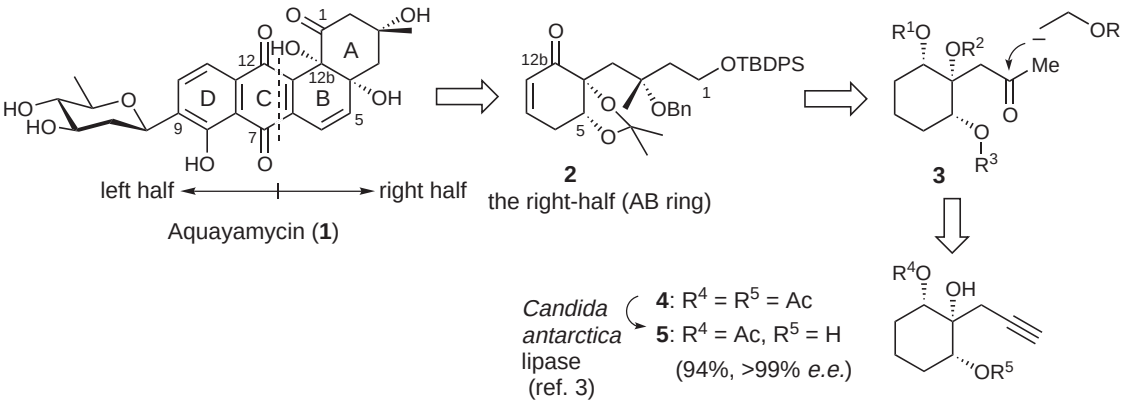

Figure 1.

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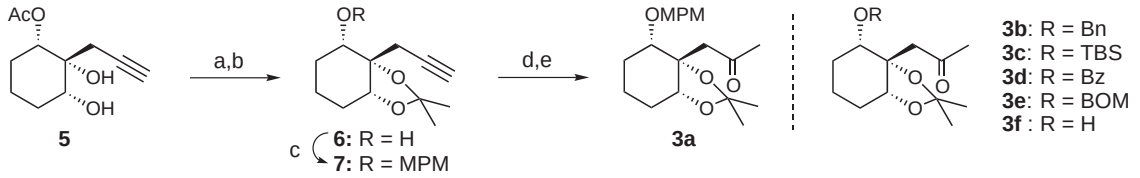
The key to the synthesis of **2** was the stereocontrolled construction of the chiral tertiary alcohols. As shown retrosynthetically in Fig. 1, we envisioned the ketone **3** as the precursor to **2**. We hoped that a suitable choice of the protecting groups (R^1–R^3) would allow the stereoselective addition of a β-alkoxyethyl anion equivalent. Furthermore, the ketone **3** could be easily obtained from the diol **5**, which is available in an optically pure form by the enzymatic hydrolysis of the *meso*-acetate **4**.[3]

Along these lines, the methyl ketones **3a**–**f** were synthesized from the diol **5**.[3] Scheme 1 shows the synthesis of the *p*-methoxybenzyl (MPM) ether **3a**.[4]



Scheme 1. (a) CH_2=C(OMe)Me, TsOH, benzene, 30 min. (b) K_2CO_3, MeOH, 45 min (97%, two steps). (c) MPMCl, NaH, DMF, 0°C, 2 h (92%). (d) H_2, quinoline, Lindlar's catalyst, hexane, 70 min (97%). (e) $Hg(OAc)_2$, MeOH, 1 h; then $PdCl_2$, LiCl, $CuCl_2$, 30 min (80%)

Protection of the vicinal diol in **5** (>99% ee) as an acetonide followed by deacetylation gave the alcohol **6**, which was then protected as a *p*-methoxybenzyl ether. The stereochemical integrity of this three-step conversion was proven by the HPLC analysis (no decrease in the ee).[5] After semi-hydrogenation of the triple bond with Lindlar's catalyst, oxidation of the resulting olefin to the methyl ketone was examined. Unfortunately, under the conventional conditions of Wacker-type oxidation ($PdCl_2$, CuCl, O_2/DMF, H_2O, 25°C), the positional selectivity of the carbonyl formation was not satisfactory to give a 5.7/1-mixture of the ketone **3a** and the corresponding aldehyde (92% combined yield). After considerable experimentation, the desired ketone **3a** was selectively obtained by the Hg^{2+}-mediated procedure.[6] The other ketones **3b**–**e** with different protecting groups (R) were similarly synthesized from the alcohol **6**. The ketone **3f** was synthesized by the hydrogenolysis of **3b**.[4]

With these ketones in hand, their reaction with several allylmetal reagents was examined. Among them, allylmagnesium chloride (Et_2O, −78°C) or allylzinc bromide (THF, −78°C) turned out to react in high yields and to give uniformly the (*S*)-alcohol **8** as the major isomer (Table 1).[4,7] Further optimization of the reaction of allylzinc bromide with **3a**, **3b** and **3d**, revealed that Et_2O was the solvent of choice. The highest selectivity (24:1) was achieved in the reaction of **3a** in Et_2O (Table 2).

A possible rationale for the high stereoselectivity is the involvement of the six-membered zinc chelate as **A**, where a methyl on the acetal hinders the top-face approach of the nucleophile as shown. Indeed, much poorer selectivities (2.1:1 in Et_2O, 1.6:1 in THF) resulted for the same reaction with the ketone **3g** without two methyl groups on the acetal center.

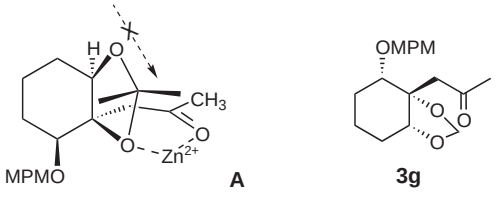
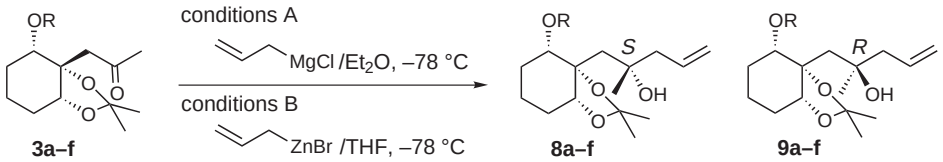


Table 1

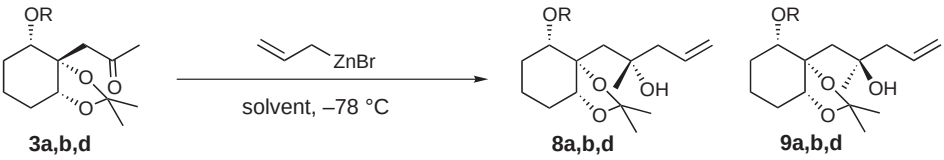


(a: MPM, b: Bn, c: TBDMS, d: Bz, e: BOM, f: H)

Ketone **3**	Conditions **A** **8**:**9** (yield%)[a]	Conditions **B** **8**:**9** (yield%)[a]
R = MPM (**3a**)	3.9:1 (77)	8.0:1 (89)
R = Bn (**3b**)	3.8:1 (81)	8.5:1 (77)
R = TBS (**3c**)	1.5:1 (85)	5.3:1 (77)
R = Bz (**3d**)	3.2:1 (89)	9.6:1 (91)
R = BOM (**3e**)	2.4:1 (85)	3.6:1 (87)
R = H (**3f**)	1.3:1 (68)	3.8:1 (87)

[a] The stereoselectivities were determined by ^{1}H NMR analyses (400 MHz).

Table 2

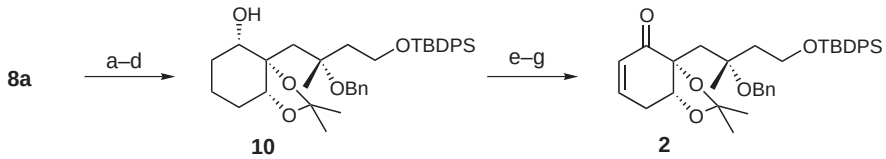


(a: MPM, b: Bn, d: Bz)

Solvent	R = MPM (**3a**) **8a**:**9a**[a] (yield%)	R = Bn (**3b**) **8b**:**9b**[a] (yield%)	R = Bz (**3d**) **8d**:**9d**[a] (yield%)
THF	8.0:1 (89)	8.5:1 (77)	9.6:1 (91)
CH_2Cl_2	4.0:1 (97)	4.5:1 (86)	5.2:1 (97)
Toluene	10:1 (95)	7.7:1 (87)	6.3:1 (95)
Et_2O	24:1 (89)	17:1 (84)	15:1 (91)

[a] The stereoselectivities were determined by ^{1}H NMR analyses (400 MHz).

The alcohol **8a** was converted to the compound **10** in four steps: (1) protection of the tertiary alcohol, (2) ozonolysis of the olefin followed by reduction with $NaBH_4$,[8] (3) silylation and (4) selective removal of the MPM group. Oxidation of **10** followed by dehydrogenation of the resulting ketone via the enol allyl carbonate under the palladium-promoted conditions furnished the enone **2**[9] (Scheme 2).



Scheme 2. (a) BnBr, KH, cat. $(n\text{-Bu})_4NI$, DMF, 0°C, 1.5 h (98%). (b) O_3, MeOH, −78°C; then $NaBH_4$, 0°C, 1 h (78%). (c) TBDPSCl, imidazole, DMF, 25 min (98%). (d) DDQ, CH_2Cl_2, H_2O, 0°C, 30 min (98%). (e) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78→0°C, 50 min (94%). (f) KHMDS, THF, −78→−40°C, 30 min; then CH_2=$CHCH_2OCOCl$, −78°C (quant.). (g) $Pd(OAc)_2$, MeCN, 15 h (82%)

In summary, the cyclohexenone **2**, the key intermediate of the aquayamycin synthesis, was efficiently synthesized from the optically pure diol **5** in a stereoselective manner. The total synthesis of aquayamycin (**1**) will be described in the following paper.[1b]

Acknowledgements

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References

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2. (a) Sezaki, M.; Hara, T.; Ayukawa, S.; Takeuchi, T.; Okami, Y.; Hamada, M.; Nagatsu, T.; Umezawa, H. *J. Antibiot*. **1968**, *21*, 91. Nagatsu, T.; Ayukawa, S.; Umezawa, H. *J. Antibiot*. **1968**, *21*, 91. (b) Sezaki, M.; Kondo, S.; Maeda, K.; Umezawa, H.; Ohno, M. *Tetrahedron* **1970**, *26*, 5171. Also see, (c) Imamura, N.; Kakinuma, K.; Ikekawa, N.; Tanaka, H.; Omura, S. *Chem. Pharm. Bull*. **1981**, *29*, 1788.
3. Matsumoto, T.; Konegawa, T.; Yamaguchi, H.; Nakamura, T.; Sugai, T.; Suzuki, K., submitted for publication.
4. The syntheses of ketones **3b**–**f**, and the reactions of ketones **3a**–**f** with other allylmetal reagents will be detailed in the full paper.
5. Column: CHIRALCEL OD-H (Daicel, Co), 4.6×250 mm; Eluent: hexane-2-propanol (97:3), 0.35 mL/min; retention time: 14.9 min for **7**, 15.5 min for *ent*-**7**.
6. Rodeheaver, G. T.; Hunt, D. F. *J. Chem. Soc., Chem. Commun*. **1971**, 818.
7. The configuration of the newly formed chiral center was eventually confirmed by applying each diastereomer to the synthesis of aquayamycin (**1**) (Ref. 1b). The stereostructures of the adducts from **3b**–**3f** were determined by correlation to the compound **8a**.
8. The diastereomers were easily separated by silica-gel chromatography at this stage.
9. Shimizu, I.; Tsuji, J. *J. Am. Chem. Soc*. **1982**, *104*, 5844.