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Synthetic study of aquayamycin. Part 1: Synthesis of 3-(phenylsulfonyl)phthalides possessing a β-*C*-olivoside

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Abstract

An efficient synthetic route to 3-(phenylsulfonyl)phthalides possessing a β-*C*-olivoside was developed by exploiting the regioselective [2+2] cycloaddition of benzyne with ketene silyl acetal. The compounds are useful in the total synthesis of the angucyclines, including aquayamycin.

Among the angucycline class of antibiotics,[1] aquayamycin (**1**)[2] holds a special status because of two salient structural features: (1) the *C*-glycoside at C9, and (2) the hydroxy groups at the A/B ring junction. Since the structure elucidation of **1** in 1970, the congeners that share these two structural features are increasing in number, thereby now constituting the largest subclass, *the aquayamycin-type angucyclines*.[1]

However, no total synthesis of an aquayamycin-type compound has appeared, in contrast to those of the structurally simpler *non-aquayamycin-type* compounds lacking the angular oxygens, such as urdamycinone B and C104 (Fig. 1).[3,4] We now wish to record the first total synthesis of aquayamycin (**1**) in three consecutive papers.[5]

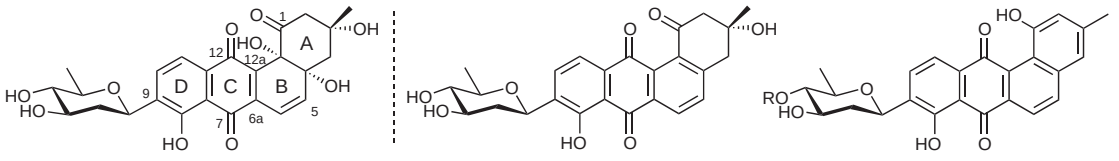

Figure 1.

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In planning the synthesis of **1**, we envisioned the Hauser reaction between the phthalide anion **I** and a cyclohexenone **II**, followed by cyclizing the A ring (Fig. 2).[5b,6,7]

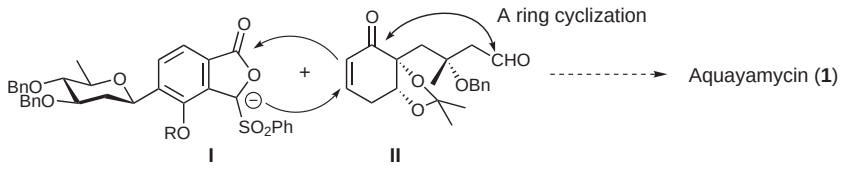
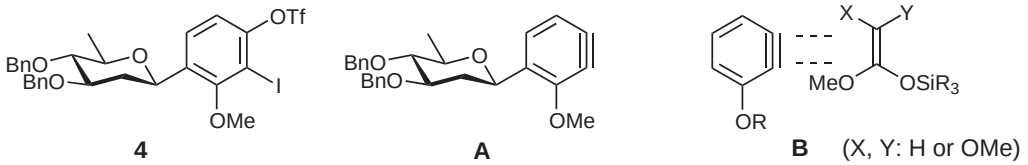


Figure 2.

Along these lines, described herein is the synthesis of the phthalide **2** (Scheme 1) by utilizing the [2+2] cycloaddition of benzyne and ketene silyl acetal (KSA) followed by the Baeyer–Villiger oxidation. The method is flexible enough to allow also the synthesis of the regioisomeric phthalide **3**.

The β-*C*-olivoside **4**, previously reported,[8] served as the common starting material for these regioisomeric phthalides. The [2+2] cycloaddition of the benzyne **A**, generated from **4**, with KSAs proceeded in a regiospecific manner as we previously found for the simple α-alkoxybenzynes (see **B**).[9,10] The regiospecific conversion of the benzocyclobutenone via the Baeyer–Villiger oxidation gave the corresponding phthalide.[11]

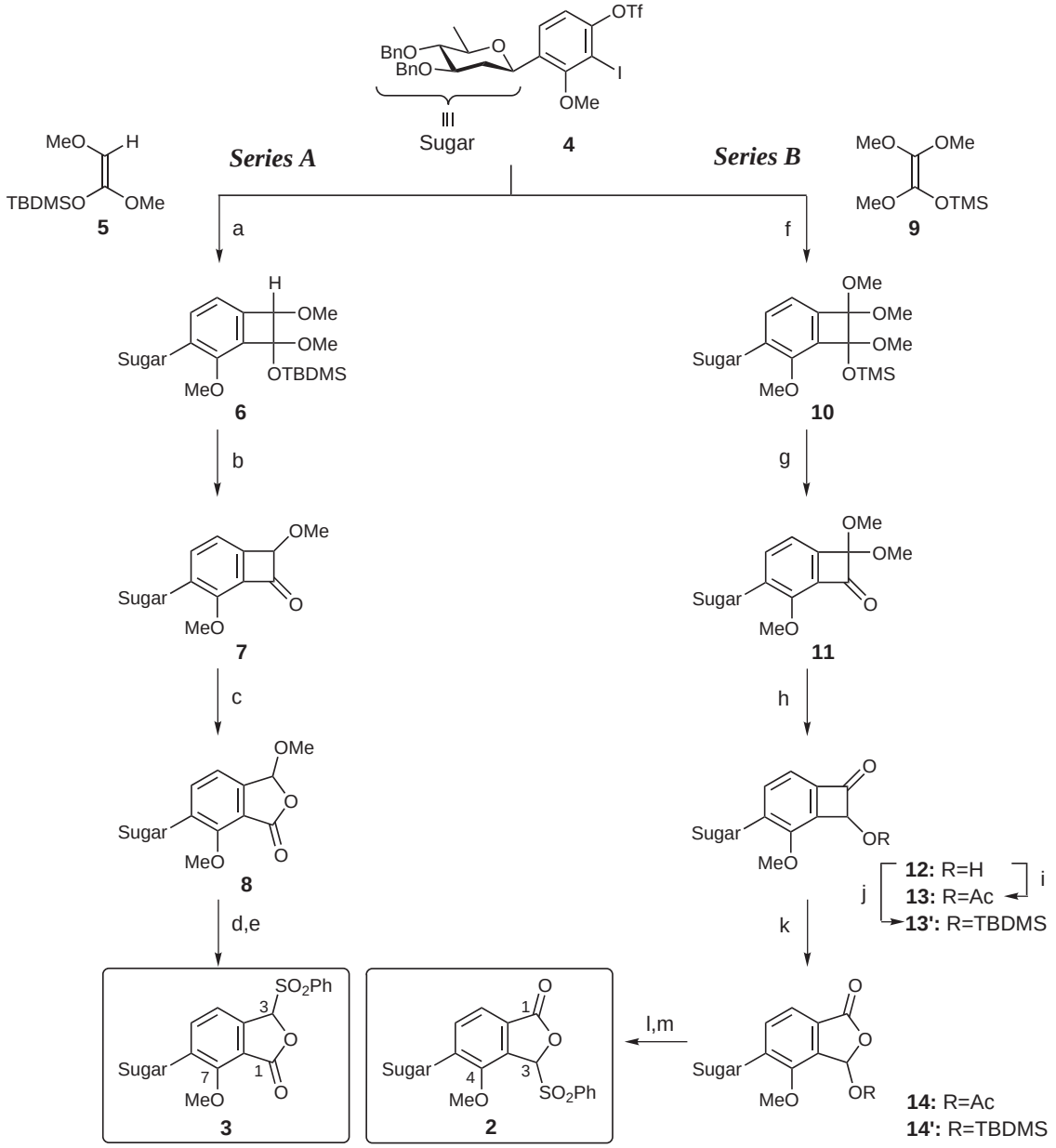


1. Synthesis of phthalide 3 (series A)

A mixture of the triflate **4**[8] (1 equiv.) and the KSA **5** (1.5 equiv.) in THF was treated with *n*-BuLi (1.2 equiv.) at −78°C.[10] The benzyne **A**, thus generated, underwent rapid [2+2] cycloaddition with **5** at this temperature. The cycloadduct **6**, obtained as a single regioisomer as expected, was hydrolyzed with aqueous HF in CH_3CN to give the ketone **7**.[12,13] The Baeyer–Villiger oxidation of **7** with MMPP (magnesium monoperoxyphthalate) in the presence of Na_2HPO_4 gave the phthalide **8** in 93% yield.[11] The regioselectivity was perfect in that the regioisomer, the 2(3*H*)-benzofuranone, was not observed. This was in line with our previous finding that benzocyclobutenones undergo an oxygen insertion at the C1–C2 bond upon Baeyer–Villiger reaction,[11] which proved valid for this more oxidized congener **7**. Treatment of **8** with thiophenol under acidic conditions, followed by oxidation of the resulting sulfide with *m*CPBA, afforded the 3-(phenylsulfonyl)phthalide **3** in high yield.[12,14]

2. Synthesis of phthalide 2 (series B)

The synthesis of the phthalide **2** started with the cycloaddition of the benzyne **A** with the KSA **9**, which has an additional oxygen function. Gratifyingly, the reaction also proceeded regio-



Scheme 1. *Series A* (synthesis of **3**): (a) **5**, *n*-BuLi, THF, –78°C, 20 min; (b) HF aq., MeCN, 2 h, 93% (two steps from **4**); (c) MMPP, Na_2HPO_4, DMF, H_2O, 40°C, 2 h, 93%; (d) PhSH, *p*-TsOH, benzene, reflux, 3 h, 78%; (e) *m*CPBA, CH_2Cl_2, 7 h, 90%. *Series B* (synthesis of **2**): (f) **9**, *n*-BuLi, Et_2O, –78°C, 15 min; (g) KF aq., $(n\text{-}Bu)_4NCl$, MeCN, 40 min, 73% (two steps from **4**); (h) $NaBH_4$, MeOH, THF, 0°C, 15 min; then 4 M HCl aq., 2 h, 98%; (i) Ac_2O, DMAP, pyridine, 0°C, 15 min, 93%; (j) TBDMSCl, imidazole, DMF, 1.5 h, 98%; (k) (for **13**) *m*CPBA, Na_2HPO_4, CH_2Cl_2, 0°C, 15 min, 95%; (for **13′**) *m*CPBA, Na_2HPO_4, CH_2Cl_2, 2 h, 88%; (l) (for **14**) PhSH, *p*-TsOH, benzene, reflux, 1 h, 97%; (m) *m*CPBA, CH_2Cl_2, 0°C, 2 h, 93%

specifically to give the adduct **10**,[10c,13] which was treated with aqueous KF in the presence of (n-Bu)$_4$NCl in CH_3CN to give the ketone **11** as a single product.[10c,12] Reduction of the ketone **11** with $NaBH_4$ followed by acid hydrolysis gave the hydroxy ketone **12**[12,13] in quantitative yield, which was converted to the corresponding acetate **13** and the *tert*-butyldimethylsilyl ether **13′**. Significantly, the Baeyer–Villiger oxidation again proceeded with rigorous regioselectivity for both compounds, **13** and **13′**. For these cases, *m*CPBA (1.2 equiv.) was the oxidant of choice, thereby giving a better yield of the phthalide, **14** and **14′**, respectively.[11] Unfortunately, replacement of the *tert*-butyldimethylsiloxy group in the phthalide **14′** by a phenylthio group proved to be very slow under the conventional conditions (PhSH, *p*-TsOH, benzene, reflux), and was not reproducible (the yield <65%) because of a competing deprotection at the sugar hydroxy group(s). On the other hand, the reaction of the phthalide **14** proceeded smoothly under similar conditions, and oxidation of the resulting sulfide with *m*CPBA afforded the 3-(phenylsulfonyl)phthalide **2** in high yield.[12,14]

In summary, an isomeric pair of 3-(phenylsulfonyl)phthalides possessing a β-*C*-olivoside, **2** and **3**, was synthesized in a divergent manner. Based on these findings, we successfully accomplished the first total synthesis of aquayamycin (**1**), which will be described in the following papers.

Acknowledgements

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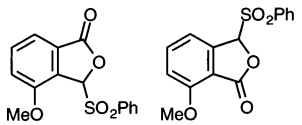
12. The regioisomers were assigned by the comparison of the ^{13}C NMR spectra with those of the congeners lacking the sugar moiety, whose structures have been unambiguously determined. The chemical shifts of the carbonyl carbons (δ, $CDCl_3$) are shown for compounds **2**, **3**, **7**, **11**, **12**, and **15**–**22** in the table below.

2*: 166.8, 166.9	**3***: 165.2, 165.3	**7***: 185.7, 186.0	**11**: 185.5	**12**: 191.2
15: 167.6	**16**: 165.4	**17**: 186.1	**19**: 185.8	**21**: 187.2
		18: 190.6	**20**: 191.5	**22**: 191.7

*The chemical shift for each stereoisomers.



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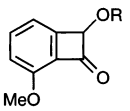
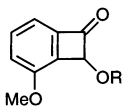
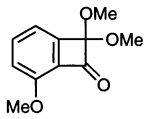


17 (R = Me)
21 (R = H)



18 (R = Me)
22 (R = H)



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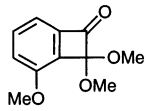

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13. The sugar moiety, not surprisingly, induced virtually no stereochemical bias on the reaction, thereby giving a ca. 1:1 mixture of the diastereomers. We used the diastereomer mixture in the following reaction, although the separation was possible by careful chromatography.
14. The phthalide **3** underwent facile partial epimerization at C3 during the silica-gel chromatography, which was not the case for **2**.