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Synthesis Study toward Mayamycin†

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Natural product mayamycin is the first example in the angucycline class featuring a *C*-glycoside linkage at the C5-position of the benz[*a*]anthracenone core with remarkable biological activities. We successfully synthesized the two retrosynthetic fragments, but found that the final *C*-glycosylation did not occur. Alternatively, an A-ring saturated aglycon was prepared, but the proposed *C*-glycosylation still did not proceed. Finally, a simplified substrate was used and the subsequent *C*-glycosylation went through smoothly, giving a two-ring less analogue of mayamycin.

Keywords natural product, angucycline, mayamycin, total synthesis, *C*-glycosilation

Introduction

Angucycline antibiotics, structurally represent a unique class of polycyclic aromatic polyketides exhibiting diverse biological activities including antibacterial, anti-viral, anticancer, as well as platelet aggregation and enzyme inhibitory properties.[1] Very recently, Imhoff *et al*[2] isolated a novel angucycline antibiotic, named mayamycin, from the marine sponge *Halichondria panacea* by variation of the culture condition. Different from the majority of *O*-glycosidic analogues in the angucycline family,[3,4] mayamycin features a *C*-glycoside linkage connecting to an aminosugar moiety at the C5 aromatic position of the benz[*a*]anthracenone core. Examples of angucyclines bearing an aminosugar fragment are rare, and at this particular site, no other C5-glycosidic bound sugar has been reported so far (Figure 1). In addition, mayamycin was reported[2] showing potent *in vitro* cytotoxicity against eight human cancer cell line with IC_{50} values ranging between 0.13 −0.33 μmol/L. Further, it was also cytotoxic toward the mouse fibroblast cell line NIH-3T3 with an IC_{50} value of 0.22 μmol/L, which is 100-fold more potent than the clinical drug tamoxifen (23.7 μmol/L). The unusual structural architecture along with the remarkable antibacterial and antitumor activities made mayamycin an ideal target for both total synthesis study and subsequent structural modification and drug profiling.

As shown in Figure 1, mayamycin can be structurally dissected to tetracyclic phenol **1** and aminosugar component **2**, with the formation of C5−C1' *C*-glycosidic bond as the key step. The tetracyclic network **1** could be accessed from another natural product **3** (hatomarubigin) that has been synthesized by several groups[4-6] including ours.[7] The C5−C1' *C*-glycosidic bond could be constructed by a Lewis acid-initiated glycosilation reaction from **1** and aminosugar **2** or its precursor **4**. Herein, in this report we describe our synthesis of fragments **1** and **2**, and further efforts on the assembly of natural product mayamycin.

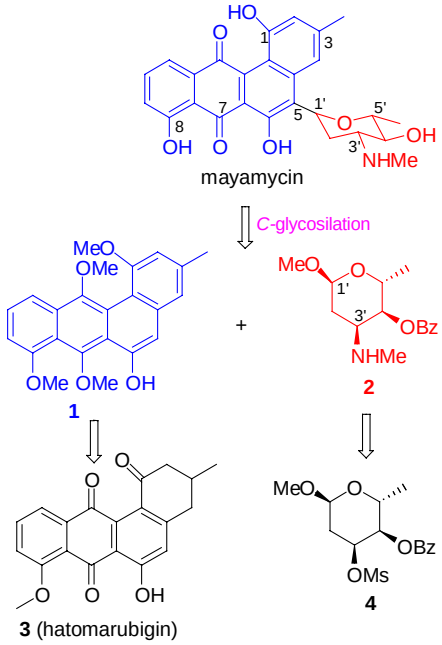

Figure 1 Chemical structure of mayamycin and its retrosythetic analysis.

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† Dedicated to the Memory of Professor Weishan Zhou.

Experimental

Reactions were performed under a nitrogen atmosphere in dry glassware with magnetic stirring. The solvents were purified and dried according to the standard methods prior to use. Commercially available reagents were used without further purification. ^{1}H NMR spectral data were recorded on Varian Mercury 300 MHz NMR spectrometer and ^{13}C NMR data were recorded on Varian Mercury 400 MHz NMR spectrometer using tetramethylsilane as an internal reference. Analytical thin-layer chromatography (TLC) was carried out on 0.2 mm Kieselgel 60F 254 silica gel plastic sheets (EM Science, Newark). Column chromatography was used for the routine purification of reaction products. The column output was monitored with TLC.

6-(Benzyloxy)-8-methoxy-3-methyl-3,4-dihydrotetraphene-1,7,12(2*H*)-trione (6) To a solution of hatomarubigin **3**[4,7] (600 mg, 1.78 mmol) and potassium carbonate (738 mg, 5.34 mmol) in DMF (30 mL), benzylbromide (457 mg, 2.67 mmol) was added. The suspension was stirred at r.t. for 7 h then quenched with water (50 mL) and extracted with Et_2O (100 mL×3). The combined organic phase was washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. Purification on silica gel column (CH_2Cl_2/EA=30/1) gave compound **6** (554 mg, 73% yield) as light yellow powder. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.62−7.62 (m, 4H), 7.43−7.38 (m, 3H), 7.32−7.25 (m, 1H), 6.91 (s, 1H), 5.33 (s, 2H), 3.98 (s, 3H), 2.90−2.82 (m, 2H), 2.62−2.39 (m, 3H), 1.14 (d, J=6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 197.6, 186.3, 181.3, 159.7, 158.6, 150.3, 139.5, 136.9, 135.8, 134.2, 128.7, 128.0, 127.3, 126.7, 124.4, 123.4, 118.3, 116.9, 116.0, 70.9, 56.4, 47.4, 38.8, 30.5, 21.3; EI-MS *m/z*: 426 (M^+); HRMS calcd for $C_{27}H_{22}O_5$ [M^+]: 426.1467, found 426.1460.

6-(Benzyloxy)-1-hydroxy-8-methoxy-3-methyltetraphene-7,12-dione (7) To a solution of compoud **6** (554 mg, 1.30 mmol) and TEA (263 mg, 2.60 mmol) in dry CH_2Cl_2 (20 mL), TMSOTf (433 mg, 1.95 mmol) was added dropwise in ice bath. The mixture was stirred for 30 min, quenched with saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (50 mL×3). The organic phase was combined, washed with brine and dried over anhydrous sodium sulfate. After evaporation of the solvents under reduced pressure, the residue was purified by silica gel column chromatography (EA/PE=5/1) to give trimethylsilyl ether in 76% yield. A solution of the resulting trimethylsilyl ether (100 mg, 0.20 mmol), $Pd(OAc)_2$ (22.4 mg, 0.11 mmol) and *p*-benzenquinone (10.8 mg, 0.11 mmol) was stirred in dry acetonitrile (15 mL) at r.t. under an atmosphere of nitrogen for 3 h and quenched with 10% diluted chlohydric acid. The mixture was extracted with CH_2Cl_2 (50 mL×3). The combined organic phase was washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification on silica gel column chromatography (CH_2Cl_2/PE=2/1) gave compound **7** (84 mg, 82% yield) as red solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 10.95 (s, 1H), 7.76 (d, J=7.2 Hz, 1H), 7.65−7.60 (m, 3H), 7.49 (s, 1H), 7.40−7.38 (m, 2H), 7.29−7.25 (m, 2H), 7.00 (s, 1H), 6.92 (s, 1H), 5.34 (s, 2H), 4.01 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 191.3, 183.1, 157.9, 154.5, 153.0, 141.1, 138.8, 136.5, 136.4, 134.1, 132.4, 131.3, 128.6, 127.8, 126.9, 122.7, 120.0, 119.6, 119.4, 117.9, 117.4, 115.3, 71.2, 56.6, 21.2; EI-MS *m/z*: 424 (M^+); HRMS calcd for $C_{27}H_{20}O_5$ [M^+]: 424.1311, found 424.1311.

6-(Benzyloxy)-1,7,8,12-tetramethoxy-3-methyltetraphene (8) To a solution of compound **7** (84 mg, 0.19 mmol) and KOH (42 mg) in THF (15 mL), CH_3I (106 mg, 1.14 mmol) was added. The mixture was allowed to stir for 7 h and filtered. The filtrate was concentrated under vacuum. To a solution of the resulting residue (62 mg) and catalytic amount of tetrabutylammonium bromide in 10 mL of THF under an atmosphere of nitrogen, sodium dithionite (195 mg, 1.12 mmol) dissolved in water (2 mL) was added. The mixture was allowed to stir for 30 min and then potassium hydroxide (168 mg, 3 mmol) solution in 2 mL of water was added. Dimethyl sulfate (0.113 mL) was added dropwise. The mixture was then stirred for 18 h at r.t. until the starting material was completely consumed. The mixture was poured into 20 mL of saturated NH_4Cl solution and extracted with ethyl acetate (25 mL×3). The combined organic layers were washed with brine and dried over Na_2SO_4. After evaporation of the solvents under reduced pressure the residue was purified by silica gel column chromatography (PE/EA=15/1) to give compound **8** (50 mg, 61% yield for two steps) as light yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.97 (d, J=8.4 Hz, 1H), 7.57 (d, J=7.2 Hz, 2H), 7.39−7.35 (m, 4H), 6.95 (s, 1H), 6.84 (d, J=7.8 Hz, 1H), 6.70 (s, 1H), 6.64 (s, 1H), 5.21 (s, 2H), 3.96 (s, 3H), 3.88 (s, 3H), 3.74 (s, 3H), 3.42 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.7, 157.1, 154.8, 150.7, 149.0, 138.3, 137.2, 134.5, 129.8, 128.4, 127.7, 126.2, 119.7, 119.0, 119.0, 117.7, 115.1, 112.8, 108.7, 105.6, 103.9, 71.2, 63.9, 60.8, 56.3, 56.1, 21.7; EI-MS *m/z*: 468 (M^+); HRMS calcd for $C_{30}H_{28}O_5$ [M^+]: 468.1937, found 468.1930.

(2*R*,3*S*,4*S*,6*S*)-4-Hydroxy-6-methoxy-2-methyltetrahydro-2*H*-pyran-3-yl benzoate (10) Bromopyranoside **9** (835 mg, 2.4 mmol) was dissolved in 10 mL EtOH, and then excess Raney nickel and triethylamine (492 mg, 4.86mmol) were added. The mixture was stirred under an atomsphere of H_2 overnight. After filtration, the filtrate was concentrated and the resulting residue was purified over silica gel column chromatography (PE/EA=3/1) to give colorless oil **10** (446 mg, 70% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.04 (d, J=8.4 Hz, 2H), 7.53−7.51 (m, 1H), 7.43−7.38 (m, 2H), 5.33 (s, 1H), 4.68 (s, 1H), 4.09 (s, 1H), 3.46 (s, 1H), 3.35 (s, 3H), 2.48 (d, J=6.9 Hz, 1H), 2.25 (d, J=15.3 Hz, 1H), 2.00 (d, J=15.0 Hz, 1H), 1.31 (d, J=6.3 Hz, 3H).

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(2*R*,3*R*,4*S*,6*S*)-6-Methoxy-2-methyl-4-((methylsulfonyl)oxy)tetrahydro-2*H*-pyran-3-yl benzoate (4) To a solution of sugar **10** (520 mg, 1.95 mmol) and trethylamine (395 mg, 3.87 mmol) in 20 mL dry DCM, MsCl (336 mg, 2.9 mmol) was added dropwise under ice bath. The mixture was stirred for 1 h and then the solvent was removed. The resulting residue was purified by silica gel column chromatography (PE/EA＝5/1) to give colorless oil **4** (650 mg, 97% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.08 (d, J＝7.5 Hz, 2H), 7.60 (t, J＝7.5 Hz, 1H) , 7.46 (t, J＝7.5 Hz, 2H) , 5.68 (q, J＝3.0 Hz, 1H), 4.75 (d, J＝4.2 Hz, 1H), 4.57 (dd, J＝9.9, 3.0 Hz, 1H), 4.44－4.32 (m, 1H), 3.39 (s, 3H), 3.02 (s, 3H), 2.26 (dd, J＝15.0, 3.5 Hz, 1H), 2.12 (dt, J＝15.3, 3.9 Hz, 1H), 1.36 (d, J＝6.3 Hz, 3H).

6-Ethoxy-8-methoxy-3-methyl-6-((trimethylsilyl)oxy)-1,3,4,12b-tetrahydrotetraphene-7,12(2*H*,6*H*)-dione (16) *n*-BuLi (2 mL, 1.6 mol/L in hexane, 3.29 mmol) was added slowly to a solution of diisopropylamine (0.5 mL, 3.29 mmol) in dry THF (3 mL) under nitrogen at 0 ℃. The mixture was stirred at 0 ℃ for 30 min and then cool to –78 ℃. HMPA (0.45 mL, 2.63 mmol) was added. After 30 min, a solution of **14**[8-10] (400 mg, 2.19 mmol) in dry THF (2 mL) was added slowly. The mixture was stirred at –78 ℃ for another 2 h before a solution of TBSCl (396 mg, 2.63 mmol) in dry THF (3 mL) was added and moved to room temperature directly. After 1 h, the solution was concentrated at reduced pressure and taken up by pentane and filtrated. The solvent was removed under reduced pressure and the residue containing compound **15** was used directly in the next step. 2-Bromo-5-methoxynaphthalene-1,4-dione (100 mg, 0.749 mmol) was added directly to the residue containing compound **15**. After stirring for 5 min, toluene was added and the mixture was stirred over night. The mixture was concentrated at reduced pressure. The residue was purified by chromatography on silica gel (PE/EA＝10/1) to afford **16** (50 mg). This product was used for further reaction without NMR monitoring.

6-Ethoxy-8-methoxy-3-methyl-1,2,3,4-tetrahydrotetraphene-7,12-dione (17) and 6-hydroxy-8-methoxy-3-methyl-1,2,3,4-tetrahydrotetraphene-7,12-dione (18) Catalytic amount of TFA was added to a solution of compound **16** in CH_2Cl_2. The reaction mixture was stirred for 2 h. After removal of the solvent, the residue was purified on silica gel column chromatography (PE/EA＝10/1) to give ether **17** (36%) and phenol **18** (50%) as yellow solid. For ether **17**: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.63 (dd, J＝7.7, 1.1 Hz, 1H), 7.55 (dd, J＝8.2, 7.7 Hz, 1H), 7.18 (d, J＝8.3 Hz, 1H), 6.95 (s, 1H), 4.22－4.10 (m, 2H), 3.96 (d, J＝3.6 Hz, 3H), 3.36－3.24 (m, 1H), 3.17－3.00 (m, 1H), 2.85 (dd, J＝16.9, 3.2 Hz, 1H), 2.45 (dd, J＝17.1, 10.7 Hz, 1H), 2.01－1.77 (m, 3H), 1.50 (t, J＝7.0 Hz, 3H), 1.05 (d, J＝6.5 Hz, 3H). For phenol **18**: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 13.23 (s, 1H), 7.83 (d, J＝7.7 Hz, 1H), 7.68 (t, J＝6.7 Hz, 1H), 7.29 (s, 1H), 6.98 (s, 1H), 4.05 (s, 3H), 3.38 (d, J＝16.6 Hz, 1H), 3.17－3.00 (m, 1H), 2.87 (d, J＝14.5 Hz, 1H), 2.45 (dd, J＝17.7, 11.0 Hz, 1H), 1.89 (d, J＝39.5 Hz, 3H), 1.06 (d, J＝6.5 Hz, 3H).

6-Hydroxy-8-methoxy-3-methyl-3,4-dihydrotetra-*p*-hene-1,7,12(2*H*)-trione (3) Conpound **18** (85 mg, 0.26 mmol) was dissolved in EtOH (6 mL), and the solution was stirred in the open air under sunlight for 3 h. After removal of the solvent, the residue was purified on silica gel column chromatography (PE/EA＝3/1) to give hatomarubigin **3** (72 mg, 85%) as yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 13.02 (s, 1H), 7.76－7.70 (m, 2H), 7.28 (dd, J＝6.7, 2.7 Hz, 1H), 6.95 (s, 1H), 4.05 (s, 3H), 2.96－2.86 (m, 2H), 2.30－2.70 (m 3H), 1.16 (d, J＝6.3 Hz, 3H).

6-(Benzyloxy)-7,8,12-trimethoxy-3-methyl-1,2,3,4-tetrahydrotetraphene (20) To a solution of compound **18** (1450 mg, 4.5 mmol) and potassium carbonate (1244 mg, 9 mmol) in DMF (50 mL), benzylbromide (1154 mg, 6.75 mmol) was added. The suspension was stirred at r.t. overnight and then quenched with water (50 mL) and extracted with Et_2O (100 mL×3). The combined organic phase was washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. Purification on silica gel column (CH_2Cl_2/EA＝250/1) gave the ether intermediate. To a solution of resultant ether (750 mg, 1.818 mmol) and tetrabutylammonium bromide (176 mg, 0.545 mmol) in 15 mL of THF under an atmosphere of nitrogen, sodium dithionite (2532 mg, 14.54 mmol) dissolved in 8 mL water was added. The mixture was allowed to stir for 30 min and then potassium hydroxide (2545 mg, 45.45 mmol) solution in 15 mL of water was added. Dimethyl sulfate (1.7 mL) was added dropwise after 30 min. The mixture was stirred for 2 h at r.t., until the starting material was completely consumed. KOH was added until pH＞7. Water and ethyl acetate were added, and the combined organic layer was washed with brine and then dried over Na_2SO_4. After evaporation of the solvent under reduced pressure the residue was purified by silica gel column chromatography (PE/EA＝50/1) to give compound **20** (260 mg, 56%) as light yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.87 (dd, J＝8.8, 0.9 Hz, 1H), 7.63 (d, J＝7.0 Hz, 2H), 7.47－7.32 (m, 4H), 6.77 (d, J＝7.4 Hz, 1H), 6.55 (s, 1H), 5.21 (s, 2H), 4.03 (s, 3H), 3.79 (d, J＝1.9 Hz, 6H), 3.63－3.51 (m, 1H), 3.38－3.21 (m, 1H), 2.92 (dd, J＝16.6, 6.4 Hz, 1H), 2.53 (dd, J＝17.2, 10.0 Hz, 1H), 2.06－1.93 (m, 2H), 1.35 (dd, J＝12.8, 5.4 Hz, 1H), 1.14 (d, J＝6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.13, 153.87, 150.98, 149.12, 137.63, 134.74, 129.11, 128.49, 127.82, 127.71, 125.86, 123.76, 119.58, 118.70, 114.90, 109.24, 103.87, 71.71, 63.94, 62.88, 56.20, 40.21, 32.54, 29.14, 28.54, 21.98; EI-MS *m/z*: 422 (M^+); HRMS calcd for $C_{29}H_{30}O_4$ [M^+]: 422.2144, found 422.2144.

(2*R*,3*R*,4*S*,6*R*)-6-(2-Hydroxynaphthalen-1-yl)-2-methyl-4-((methylsulfonyl)oxy)tetrahydro-2*H*-pyran-3-yl benzoate (21) To a stirred solution of 2-naphthol (9 mg, 0.033 mmol), sugar mesylate **4** (11 mg, 0.028

mmol) and $AgClO_4$ (6.8 mg, 0.033 mmol) in 1.2 mL of CH_2Cl_2, TMSOTf (7.326 mg, 0.033 mmol) was added via a syringe. The mixture was stirred for 5 min at 0 ℃ and then the temperature was gradually increased to r.t. during 40 min. The reaction was quenched with saturated sodium bicarbonate and the mixture was extracted with CH_2Cl_2. The organic phase was dried with sodium sulfate and concentrated to give **21** (12 mg, 65%) as white solid after column chromatography (PE/EA=2/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.68 (s, 1H), 8.25 (d, J=8.4 Hz, 2H), 7.77−7.68 (m, 3H), 7.62−7.53 (m, 3H), 7.35−7.25 (m, 2H), 7.14 (d, J=9.3 Hz, 1H), 6.02−5.99 (m, 2H), 4.82 (d, J=9.6 Hz, 1H), 4.41 (d, J=2.9 Hz, 1H), 3.12 (s. 3H), 2.43−2.41 (m, 2H), 1.56 (d, J=6.3 Hz, 3H).

(2*R*,3*R*,4*S*,6*R*)-3-Hydroxy-6-(2-hydroxynaphthalen-1-yl)-2-methyltetrahydro-2*H*-pyran-4-yl-methanesulfonate (22) To a solution of glycoside **21** (456 mg, 1 mmol) in MeOH (15 mL), K_2CO_3 (138 mg, 1 mmol) was added. The mixture was allowed to stir at r.t. overnight and filtered. The resulting filtrtate was evaperated to give the residue which was further purified on column chromatography ($CHCl_3$/MeOH=100/1) to afford **22** (345 mg, 90%) as white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.75 (s, 1H), 7.77−7.68 (m, 3H), 7.49 (t, J=6.3 Hz, 1H), 7.43 (t, J=6.0 Hz, 1H), 7.13 (d, J=9.3 Hz, 1H), 6.00 (d, J=9.3 Hz, 1H), 4.61−4.58 (m, 2H), 4.40−4.30 (m, 1H), 3.21 (s, 1H), 3.17 (s, 3H), 2.40−2.20 (m, 2H), 1.46 (d, J=6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.6, 130.7, 129.9, 128.8, 128.6, 126.9, 122.1, 120.4, 119.7, 113.3, 81.9, 71.7, 70.5, 66.3, 38.8, 37.2, 18.1.

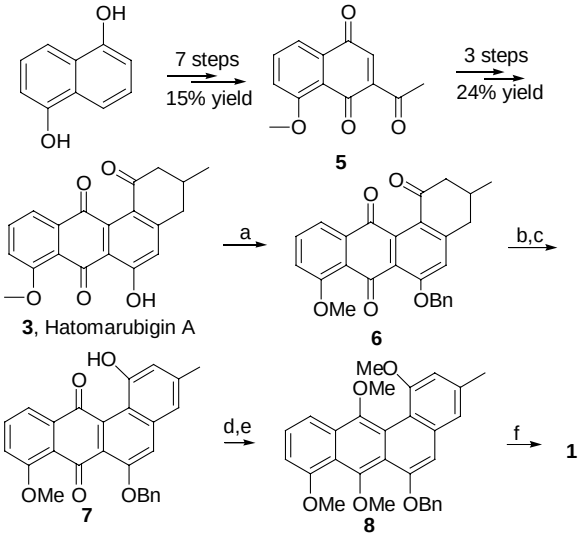
(2*S*,3*R*,4*S*,6*R*)-6-(2-Hydroxynaphthalen-1-yl)-2-methyl-4-(methylamino)tetrahydro-2*H*-pyran-3-ol (23) Compound **22** (97 mg, 0.25 mmol) was dissolved in 30% methylamine alcoholic solution (30 mL) in sealed tube. The mixture was stirred under 70 ℃ for 2 h and the solvent was evaporated. The residue was purified on column chromatography ($CHCl_3$/MeOH=30/1) to give **23** (120 mg, 45%) as white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.87 (d, J=8.7 Hz, 1H), 7.75−7.64 (m, 2H), 7.44−7.38 (m, 1H), 7.30−7.25 (m, 1H), 7.08 (d, J=8.7 Hz, 1H), 4.92−4.90 (m, 1H), 4.58 (s, 1H), 4.10 (s, 1H), 2.71 (s, 1H), 2.51 (s, 3H), 2.27−2.17 (m, 3H), 1.40 (d, J=6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.3, 132.6, 129.4, 128.7 128.3, 126.5, 122.5, 120.8, 118.4, 112.9, 80.4, 70.7, 66.0, 65.8, 65.5, 40.7, 39.9. EI-MS *m/z*: 287 (M^+).

Results and Discussion

Since the tetracyclic angucyclinone framework (*e.g.* **1**, **3**) is a common glycosilation acceptor in the synthesis of angucycline antibiotics,[11a-11c] various strategies have been developed, including Au-catalyzed ring closure,[11d] Diels-Alder reaction,[12-22] Co^{2+}-mediated [2+2+2] cycloadditions[23-25] and Michael-type cyclization.[26] The skeleton of angucyclinone **1** has been reported by us and others earlier through an Aldol-Michael addition process, however, preparation of **1** with selective protection of the 1,8-dihydroxys and leaving 6-OH free for introduction of the *C*-glycosilation is challenging.

As described in Scheme 1, our synthesis commenced from hatomarubigin A (**3**), which was prepared in 24% overall yield from acetyl naphthoquinone **5** through Michael addition with 5-methyl-1,3-cyclohexan-dione followed by intramolecular Aldol condensation.[4] In turn, compound **5** was prepared in seven steps from 1,5-binaphthol in 15% overall yield.[4] Although compound **3** could be used to the glycosilation reaction with aminosugar **2** followed by aromatization of the tetracyclic A-ring to furnish target compound mayamycin, however, electron-deficient phenols generally are poor substrates (sugar acceptors) in *C*-glycosilation reactions.[27] Accordingly, ketone **3** was converted to electron-rich aglycone **1**. Protection of **3** with benzyl group provided ether **6** whose A ring was efficiently aromatized *via* enol etherization combined with $Pd(OAc)_2$-mediated oxidation to afford phenol **7** in 60% overall yield.[5] Protection of phenol **7** with MeI provided corresponding ether in 75% yield, which was then treated with sodium hyposulfite followed by dimethyl sulfate delivering anisole **8** in 81% yield.[28,29] Subsequent debenzylation of anisole **8** with Pd/C afforded electron-rich phenol **1** in 85% yield. Compound **1** was found highly unstable and readily shifted back to its quinone version during storage. Therefore, phenol **1** has to be prepared from **8** *in situ* for subsequent *C*-glycosilation (Scheme 1).

Scheme 1 Synthesis of the phenol **1**



Reagents and conditions: (a) K_2CO_3, BnBr, DMF, 73%; (b) TMSOTf, TEA, −40 ℃, 76%; (c) $Pd(OAc)_2$, MeCN, 82%; (d) MeI, KOH, THF; (e) $Na_2S_2O_4$, TBAB, Me_2SO_4, KOH, 61% for two steps; (f) H_2, Pd/C, THF, 85%.

With glycosyl receptor **1** in hand, we then set out to prepare aminosugar **2**. In the synthesis of C2-glycosylation natural products benzanthrins, Parker and co-

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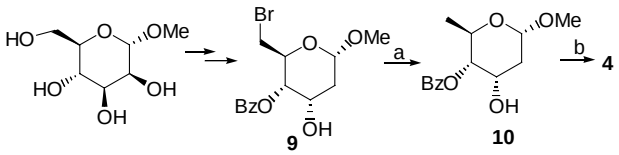
workers[5] reported that the existence of a basic amino group in the sugar component was unfavorable for subsequent Lewis acid-catalyzed glycosylation, therefore we decided to prepare its precursor **4** and explore its reaction with phenol **1**. As shown in Scheme 2, bromide **9** was prepared from *α-D*-mannopyranoside in 4 steps,[30-32] and subjected to debromination with Raney Ni-directed hydrogenation providing **10** in 70% yield. Subsequent mesylation of **10** using a typical procedure (MsCl, TEA) led to 3-sulfonate sugar **4** in 97% yield.

Scheme 2 Synthesis of the sugar fragment **4**



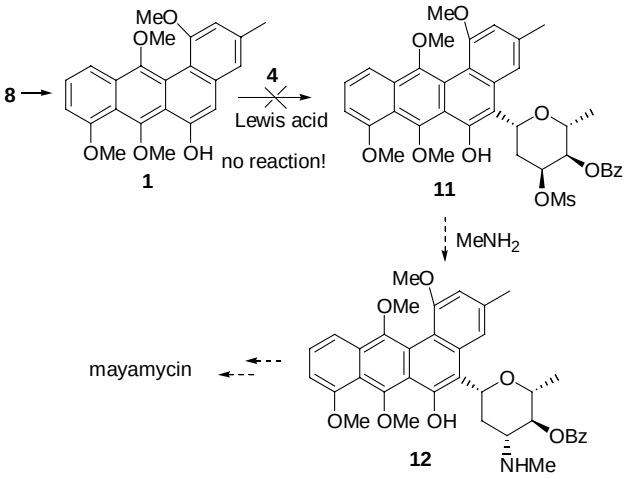
Reagents and conditions: (a) Raney Ni, H_2, 70%; (b) MsCl, TEA, 97%.

With both key fragments **1** and **4** readily synthesized, we decided to explore the optimum condition to assemble the natural product mayamycin. In 1990, Suzuki *et al*[33] reported a similar *C*-glycosydic bond formation through a two-step process including *O*-glycosylation first followed by an *O*- to *C*-glycoside migration in the presence of an appropriate Lewis acid, including $SnCl_4$, BF_3•EtO_2 and Cp_2HfCl_2-$AgClO_4$. Later, Matsumura *et al* also reported this type reaction by employing a mild Lewis acid TMSOTf or a combination of TMSOTf-$AgClO_4$ exclusively affording the corresponding *C*-glycosidic products in high yields.[34] Nevertheless, in the synthesis of kidamycin, another natural product structurally similar to mayamycin, $SnCl_4$ proved to be efficient in the corresponding *C*-glycosylation.[35] In this regard, we initially took advantage of $SnCl_4$ to promote the *C*-glycosylation reaction of sugar moiety **4** with aglycon **1**. As outlined in Scheme 3, aglycon **1** was freshly prepared from benzyl ether **8** by hydrogenation, and then treated with 3-sulfonate sugar **4** equivalently under initiation of excessive $SnCl_4$ (1 mol/L solution in CH_2Cl_2) at −78 ℃, leading to no product, except the decomposition of sugar **4**. Extending reaction time or raising temperature to 0 ℃ or r.t. gave no benefit except producing a dark complex without any major product. Likewise, other reported catalysts, including TMSOTf/$AgClO_4$, Cp_2HfCl_2/$AgClO_4$, or BF_3•EtO_2 were used, and the proposed *C*-glycosylation still did not occur.

Although the exact reason for the failure of *C*-glycosylation reaction was unclear, the instability of aglycon **1** may be one key issue. To avoid the air- and sunlight-sensitivity of the large aromatic system of **1**, we chose to use the more chemo-stable aliphatic A-ring precursor **13** as a replacement.

As described in Scheme 4, phenol **13** was synthesized

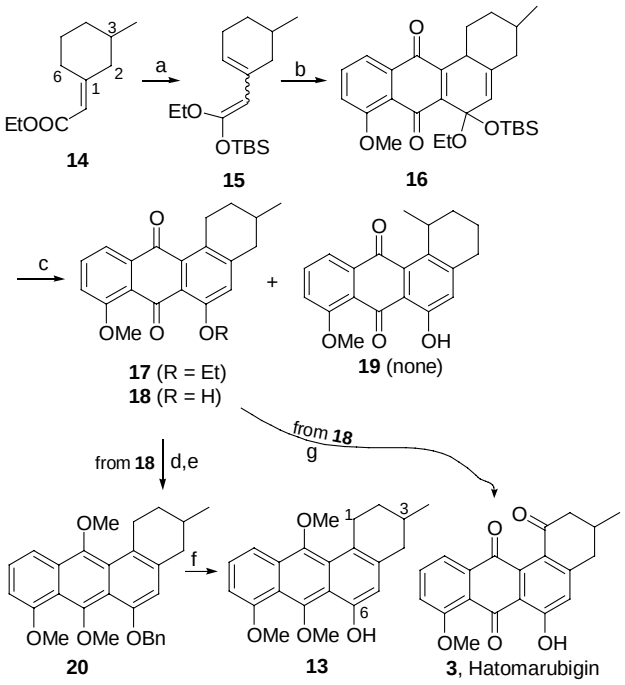
Scheme 3 Glycosilation of phenol **1** with 3-sulfonate sugar **4**



by using a Diels-Alder reaction as the key step. Although D-A reaction[12-22] has been widely used to synthesize polycyclic angucyclinone analogues, however, only a few cases were reported dealing with C6-hydroxyl products. Krohn *et al*[8-10] have ever reported the synthesis of angucyclinone core with a C6-OH by using ketene acetal as diene in the Diels-Alder reaction. Inspired by this pioneer work, we developed a modified procedure to approach our C6-hydroxyl angucyclinone **13**. Deprotonation of ester **14**[8-10] with LDA at C6 or C2 followed by silylation with TBSCl provided the crude regio- and/or *E/Z* mixture of ketene ketals **15**. Diels-Alder reaction of the mixture **15** with 5-methoxynaphthalene-1,4-dione proceeded smoothly, and upon acidification with CF_3COOH provided tetracyclic product **18** as the major product in 50% overall yield, together with another minor product in 36% yield which was originally assumed to be the regioisomer **19**. However, NMR examination of the minor product proved that it was indeed ether **17**. This result in turn confirmed that ketene ketals **15** were only *E/Z* mixture rather than regioisomers, probably due to the methyl steric effect. In Krohn's report,[8-10] they installed a more steric dimethylphenylsilyl group at the C3 of ester **14** to control regioselectivity, while in our case the C3 methyl was sufficient to achieve the same regioselectivity. Phenol **18** was readily oxidized to hatomarubigin **3** in the open air under sunlight in 67% yield after 12 h further confirming the structure of **18**. Similar to the preparation of **1**, electron-deficient phenol **18** was transformed to electron-rich phenol **13** following a set of similar reactions including C6-hydroxy protection, quinoline-reduction, etherization and debenzoylation in 20% overall yield.

Quite disappointingly, the reaction of glycosyl donor **4** with phenol **13** under various Lewis acids as mentioned above did not go through at all, except the recovery of phenol **13**. In view of the fact that mayamycin is the only reported example among both natural and synthetic angucycline analoguess bearing a C-5 glycosydic

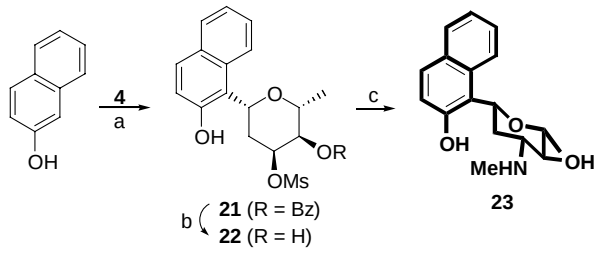
Scheme 4 Synthesis of the phenol **13**



Reagents and conditions: (a) LDA, HMPA, TBSCl, 5 h,; (b) 2-Bromo-5-methoxynaphthalene-1,4-dione, (c) CF_3COOH, for **17**, 36%, and for **18**, 50%; (d) K_2CO_3, BnBr, 12 h, 46%; (e) TBAB, $Na_2S_2O_4$, KOH, Me_2SO_4, 4 h, 56%; (f) Pd/C, H_2, 80%; (g) sunlight, air 85%.

linkage, our failure in reactions of both aglycons **1** and **13** with sugar **4** may reflect the C5 as an unfavorable site for *C*-glycosylation (likely due to steric effect). To confirm our analysis, we decided to use a simplified substrate 2-naphthol as the aminosugar acceptor (Scheme 5). As expected, reaction of 2-naphthol with sugar **4** went through smoothly under several Lewis acid promotion, and high yield of 65% was achieved in the case of combined promoter TMSOTf-$AgClO_4$. Subsequent saponification of benzoate **21** followed by S_N2 substitution with methylamine in refluxing ethanol furnished *C*-glycosidic product **23** in 43% overall yield. This result supported our analysis that C5 position of angucyclinones is not suitable for direct *C*-glycosylation, and other strategies including introduction of the aminosugar moiety in the earlier synthetic process may be more appropriate.

Scheme 5 A model of glycosylation reaction



Reagents and conditions: (a) TMSOTf-$AgClO_4$, DCM, 0 ℃, 65%; (b) K_2CO_3, MeOH, 90%; (c) $MeNH_2$, EtOH, sealed tube, 80 ℃, 45%.

Conclusions

We successfully synthesized the two retrosynthetic fragments of natural product mayamycin, but found that the subsequent *C*-glycosylation did not occur. Alternatively, an A-ring saturated aglycon was prepared through a D-A cycloaddition process. However, the proposed *C*-glycosylation still did not proceed. Finally, a simplified substrate was used and the subsequent *C*-glycosylation went through smoothly. Although a two-ring less analogue of mayamycin was obtained, much more work is needed to access the exact natural product.

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