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Total Syntheses of Aturanosides A and B

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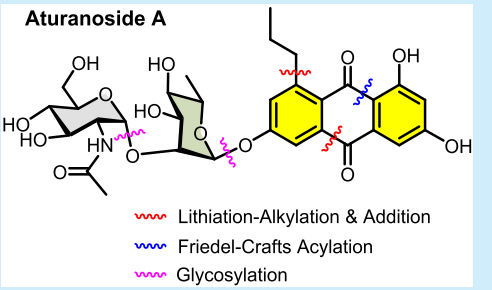
ABSTRACT: Total syntheses of aturanosides A and B, two antiangiogenic anthraquinone glycosides, have been achieved in an expeditious manner, highlighting anthraquinone synthesis, phenol glycosylation, α-D-glucosaminoside installation, and judicious use of protecting groups.



Aturanosides A and B [**1** and **2**, respectively (Figure 1)], two novel anthraquinone glycosides, were isolated from soil-derived *Streptomyces* sp. RK88-1441 by Ahn and co-workers in 2018.[1] The aglycone of aturanosides, named R1128 A (**3**), together with three congeners bearing various alkyl groups at C8, has already been identified from *Streptomyces* sp. No. 1128 by Hori et al. in 1993.[2,3] The *N*-acetyl-α-D-glucosamino-(1→2)-α-L-rhamnoside fragment in **1** has never been found in secondary metabolites; nevertheless, it occurs in a few exopolysaccharides of bacteria.[4−9] Interestingly, the glycosides (**1** and **2**) showed no cytotoxicity against human umbilical vein endothelial cells (HUVECs) but significantly suppressed vascular endothelial growth factor (VEGF)-induced tube formation and invasion of HUVECs,[1] and the aglycone (**3**) significantly inhibited the binding of estrogen to its receptor with IC_{50} values of ∼0.1 μM.[3,10] In 2012, Iwao et al. reported the synthesis of R1128 A (**3**) and its congeners, using iterative *ortho* lithiation of 2-(4-methoxyphenyl)-4,4-dimethyloxazoline as the key reactions.[11] To study in depth the antiangiogenic activity of the glycosides (**1** and **2**) and the nonsteroidal estrogen receptor antagonistic activity of the aglycone (**3**), both relevant to the antitumor activities, we embarked on the synthesis of the anthraquinone and its glycosides. Here, we report an efficient approach to the synthesis of aturanosides A and B (**1** and **2**, respectively).

A collective synthesis of the glycosides called for a linear strategy to install the sugar residues on the aglycone.[12] Thus, anthraquinone derivative **A**, rhamnose donor **B**, and glucosamine donor **C** became requisite building blocks (Figure 1), in which the judicious choice of the protecting groups was necessary to ensure regioselective glycosylation at the anthraquinone C6-OH and stereoselective glycosylations to furnish the 1,2-*trans*-α-L-rhamnoside and 1,2-*cis*-α-D-glucosaminoside linkages. It is known that the glycosylation of electron-deficient phenols is always associated with specific problems, due to the low nucleophilicity of the hydroxyl group

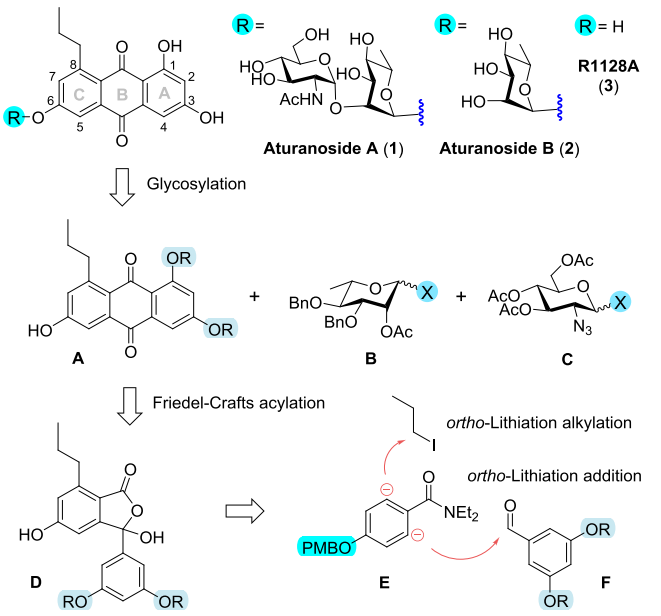


Figure 1. Aturanosides A (**1**) and B (**2**) and R1128 A (**3**) and the retrosynthetic plan.

and the poor solubility of the substrate in common glycosylation solvents.[13] Therefore, rhamnose donors (**B**) bearing a variety of leaving groups were planned to be used in the synthesis. Anthraquinone aglycone **A**, bearing protecting

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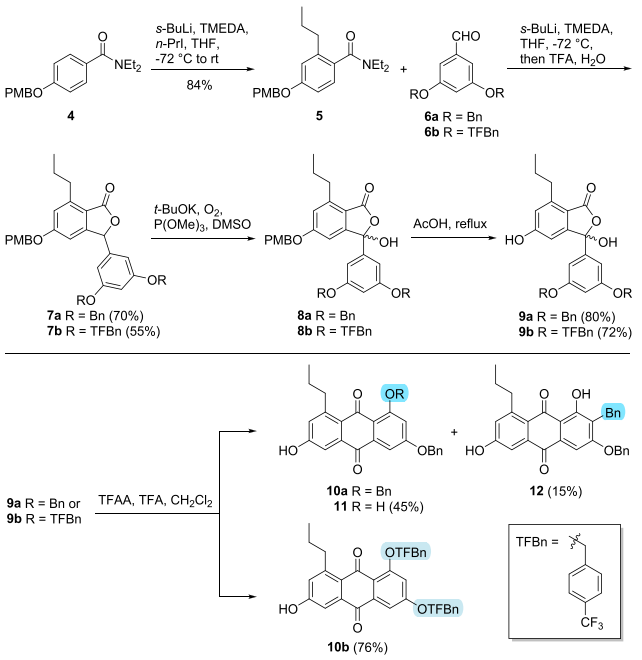
groups at C1-OH and C3-OH, could be prepared by an intramolecular Friedel−Crafts acylation of hydroxyphthalide **D**, which could be accessed from *N,N*-diethylbenzamide **E** via iterative *ortho* lithiation followed by alkylation with 1-iodopropane and addition with aldehyde **F**.

Our synthesis commenced with alkylation of 4-(4-methoxybenzyloxy)benzamide **4** (Scheme 1), which was

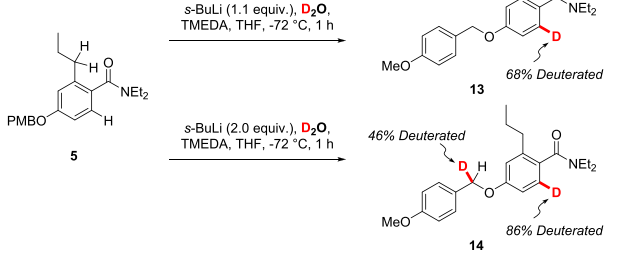
Scheme 1. Construction of Anthraquinone Aglycone 10b



readily prepared from the inexpensive industrial material methyl 4-hydroxybenzoate (see the Supporting Information). Directed by the *N,N*-diethylamide group,[14] *ortho* lithiation took place in the presence of *sec*-BuLi (1.5 equiv) and tetramethylethylenediamine (TMEDA) in THF at −72 °C; subsequent addition of 1-iodopropane delivered the desired alkylation product **5** in good yield.

It was reported that the *ortho* lithiation conditions could lead to lateral lithiation at benzylic positions in the presence of an *o*-alkyl substituent (such as in **5**), and the regioselectivity could be effected by variation of the directing group, solvents, and additives.[15−18] Thus, we performed deuterium labeling experiments on benzamide **5** (Scheme 2) to examine whether the *N,N*-diethylamide directing group and the 4-methoxybenzyl (PMB) protecting group are compatible with the next *ortho* lithiation−addition reaction (i.e., **5** + **6** → **7**). Indeed, the

Scheme 2. Deuterium Labeling Experiments on Amide 5



lithiation directed by the *N,N*-diethylamide group took place preferentially at the *o*-phenyl carbon in **5** rather than the benzylic carbons in the presence of *sec*-BuLi (1.1 equiv), resulting in a 68% yield of monodeuterated derivative **13**. Further lithiation at the benzylic carbon of the PMB residue occurred in the presence of excess *sec*-BuLi (2.0 equiv) to give **14**; nevertheless, deuteration at the lateral alkyl carbon was not observed.

Thus, treatment of amide **5** with *sec*-BuLi (1.2 equiv) and TMEDA in THF at −72 °C, followed by addition of 3,5-dibenzyloxybenzaldehyde **6a**, led to the desired adduct, which underwent lactonization under the action of aqueous CF_3COOH to provide phthalide **7a** in a satisfactory 70% yield.[11,14] Attempts at reductive ring opening of the lactone in **7a** led to preferential cleavage of the phenolic benzyl ethers. Gratifyingly, phthalide **7a** could be smoothly oxidized to hydroxyphthalide **8a** in the presence of oxygen under basic conditions;[19] subsequent treatment with AcOH under reflux led to selective removal of the PMB group,[20] which gave **9a** in good yield (80% for two steps). This rise of the oxidation state would allow intramolecular Friedel−Crafts acylation to furnish the desired anthraquinone (i.e., **10a**). However, subjecting **9a** (or **8a**) to various Friedel−Crafts conditions resulted in mixtures. A relatively clean reaction of **9a** was realized under the action of TFAA (20 equiv) and TFA in CH_2Cl_2 at rt, leading to two major products identified as **11** (45%) and **12** (15%), in which the C1-*O*-benzyl group was cleaved and migrated to C2, respectively.[21] In fact, the cleavage and O → C migration (via the resultant benzyl cation) of phenolic benzyl groups have been well appreciated.[22−25] To avoid these side reactions, we replaced the benzyl groups with 4-trifluoromethylbenzyl (TFBn) groups;[26] the electron-withdrawing *para*-substituted trifluoromethyl group would destabilize the corresponding benzyl cation and thus disfavor the cleavage and subsequent Friedel−Crafts alkylation reaction. Thus, hydroxyphthalide **9b** was prepared from benzamide **5** and benzaldehyde **6b** following the previous procedure for the preparation of **9a** (from **5** and **6a**), in a slightly lower yield (40% vs 56% yield for four steps). To our delight, the desired intramolecular Friedel−Crafts acylation of **9b** took place smoothly under the action of TFAA and TFA (CH_2Cl_2, rt), providing anthraquinone **10b** in a decent 76% yield without detection of the side products derived from cleavage and rearrangement of the TFBn groups.

With anthraquinone **10b** being available in quantity (2 g scale), we set out to explore the glycosylation of phenol **10b** with a panel of 2-*O*-acetyl-3,4-di-*O*-benzyl-L-rhamnopyranosyl donors (i.e., **15**−**19**) under various conditions (Table 1). First, we examined the Mitsunobu glycosylation, which has been found to be particularly useful for the glycosylation of phenols;[27] however, the reaction of **10b** and lactol **15** did not take place under the conventional Mitsunobu conditions (entries 1 and 2). The gold(I)-catalyzed glycosylation with *o*-alkynylbenzoate donors (e.g., **16**) has been successfully applied to the glycosylation of a wide variety of nucleophiles,[28] including electron-deficient phenols.[29,30] Unfortunately, the glycosylation of **10b** with donor **16** proceeded sluggishly in the presence of PPh_3AuNTf_2 (entry 3), leading to coupled α-rhamnoside **20** in only 42% yield even with heating (1 equiv of PPh_3AuNTf_2, CH_2Cl_2, 45 °C; entry 4). This result testified to the poor nucleophilicity of anthraquinone phenol **10b**, resulting in decomposition of the donor before glycosylation. Trichloroacetimidate donor **17** was also found to be ineffective

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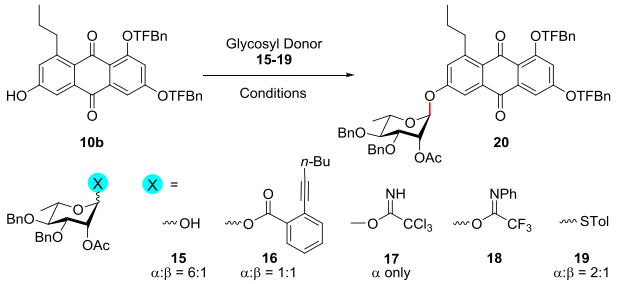
Table 1. Optimization of the Rhamnosylation on Anthraquinone 10b



entry	donor	conditions	yield of **20** (%)[a]
1	**15** (3 equiv)	PPh_3, DEAD, DMF, rt	NR
2	**15** (3 equiv)	PPh_3, DEAD, THF, rt	NR
3	**16** (2 equiv)	PPh_3AuNTf_2 (0.2 equiv), 4 Å MS, CH_2Cl_2, rt	28
4	**16** (3 equiv)	PPh_3AuNTf_2 (1 equiv), 4 Å MS, CH_2Cl_2, 45 °C	42
5	**17** (3 equiv)	$BF_3{\cdot}Et_2O$ (0.5 equiv), 4 Å MS, CH_2Cl_2, 0 °C to rt	49
6	**17** (3 equiv)	TMSOTf (0.5 equiv), 4 Å MS, CH_2Cl_2, 0 °C to rt	22
7	**18** (3 equiv)	$BF_3{\cdot}Et_2O$ (0.5 equiv), 4 Å MS, CH_2Cl_2, rt	92
8	**18** (3 equiv)	TMSOTf (0.5 equiv), 4 Å MS, CH_2Cl_2, rt	92
9	**19** (3 equiv)	NIS (3.6 equiv), TfOH, 4 Å MS, CH_2Cl_2, rt	0
10	**19** (3 equiv)	MeOTf (9 equiv), 4 Å MS, CH_2Cl_2, rt	58
11	**19** (3 equiv)	MeOTf (5 equiv), 4 Å MS, CH_2Cl_2, 45 °C	95

[a]Isolated yields are given. The β anomer was not detected.

in the glycosylation presented here, which underwent decomposition faster than glycosylation, furnishing α-rhamnoside **20** in 49% yield in the presence of $BF_3{\cdot}Et_2O$ (0.5 equiv) and in 22% yield with TMSOTf (0.5 equiv) at 0 °C (entries 5 and 6, respectively).[31,32] Gratifyingly, the glycosylation with *N*-phenyltrifluoroacetimidate donor **18**, which is less vulnerable than the trichloroacetimidate counterpart, was successful, providing α-rhamnoside **20** in a high 92% yield in the presence of either $BF_3{\cdot}Et_2O$ (0.5 equiv) or TMSOTf (0.5 equiv) at the expense of 3 equiv of the donor (entries 7 and 8). We also tried the glycosylation with thioglycoside **19**. It was not surprising that the thioglycoside underwent decomposition quickly in the presence of a strong promoter (i.e., NIS/TfOH) with no evidence of glycosylation (entry 9). Excitingly, under a mild promoter, i.e., MeOTf,[33] the rate of activation on the thioglycoside could match the rate of glycosylation with phenol **10b**, leading to the desired **20** in 58% yield (entry 10), and the yield was increased to 95% (at a gram scale) with a slight decrease in the amount of MeOTf (from 9.0 to 5.0 equiv) and an increase in the temperature (from rt to 45 °C; entry 11).

Subsequent removal of the 2-*O*-acetyl group in rhamnoside **20** with NaOMe in methanol gave **21** (95%) smoothly (Scheme 3); installation of the α-glucosamine residue was then examined (Table 2). 3,4,6-Tri-*O*-acetyl-2-azido-2-deoxy-gluco-

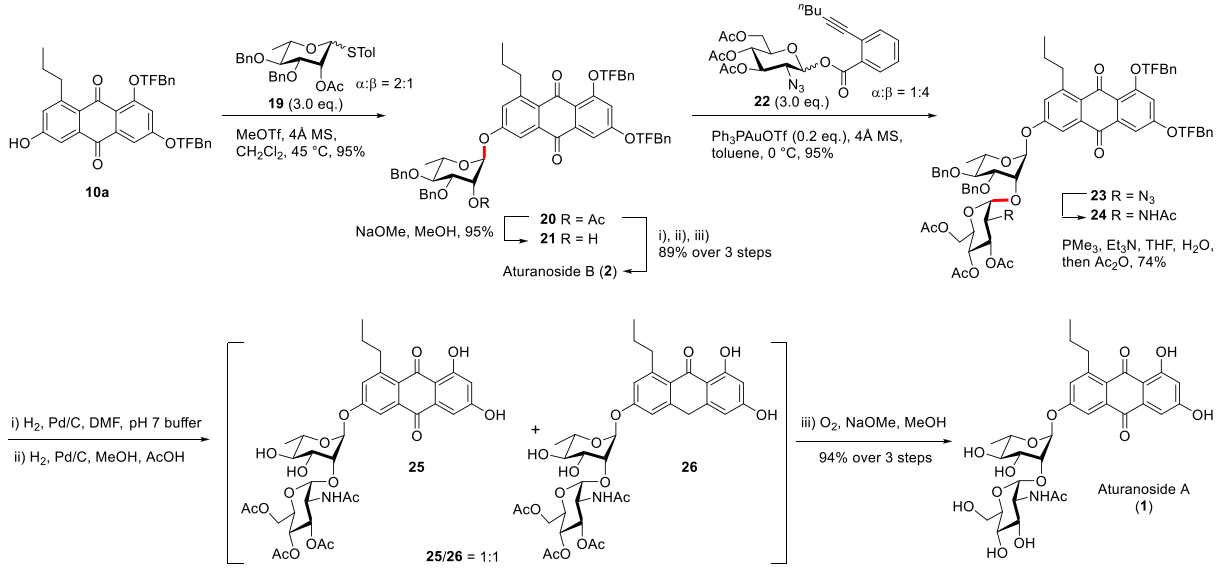
Table 2. Optimization of the Gold-Catalyzed Glycosylation of 21 with Donor 22

entry	conditions[a]	yield of **23** (%)[b]
1	$Ph_3PAuNTf_2$, 4 Å MS, CH_2Cl_2, rt	5
2	$Ph_3PAuOTf$, 4 Å MS, CH_2Cl_2, rt	8
3	$Ph_3PAuNTf_2$, 4 Å MS, toluene, rt	26
4	$Ph_3PAuOTf$, 4 Å MS, toluene, rt	19
5	$Ph_3PAuNTf_2$, 4 Å MS, toluene, 40 °C	17
6	$Ph_3PAuOTf$, 4 Å MS, toluene, 40 °C	12
7	$Ph_3PAuNTf_2$, 4 Å MS, toluene, 0 °C	20
8	$Ph_3PAuOTf$, 4 Å MS, toluene, 0 °C	83 (95)[c]

[a]Reactions were performed with glycosyl donor **22** (0.03 mmol), acceptor **21** (0.01 mmol), and a gold catalyst (2.5 μmol). [b]Isolated yield on a 0.01 mmol scale (c = 5.0 mM). The β-anomer was not detected. [c]Isolated yield on a 0.05 mmol scale (c = 20 mM).

pyranosyl *o*-hexynylbenzoate **22** was chosen as the donor, which has been found to be effective in highly α-selective glycosylation under the action of PPh_3AuOTf.[34] However, in the presence of either PPh_3AuOTf or $Ph_3PAuNTf_2$ (0.25

Scheme 3. Completion of the Syntheses of Aturanosides A (1) and B (2)



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equiv), the glycosylation of **21** with donor **22** hardly took place in CH_2Cl_2 at rt (entries 1 and 2). When the CH_2Cl_2 was replaced with toluene, the glycosylations improved slightly, leading to the desired disaccharide **23** in <30% yields (entries 3 and 4). Increasing the temperature from rt to 40 °C led to lower yields of coupled product **23** and faster decomposition of the donor (entries 5 and 6). When the reaction temperature was decreased to 0 °C, the glycosylation in the presence of $Ph_3PAuNTf_2$ did not improve much (entry 7), but under the action of $Ph_3PAuOTf$, the reaction proceeded smoothly, leading to **23** in 83% yield (entry 8); the yield was further enhanced to 95% when the reaction was carried out at a higher concentration (from 5.0 to 20 mM).

The azido group in disaccharide **23** could be reduced into the requisite amino group under the hydrogenolysis conditions for removal of the benzyl protecting groups. However, subjecting **23** to a variety of hydrogenolysis conditions led to complex mixtures. Thus, the azido group in **23** was selectively reduced via Staudinger reduction with trimethylphosphine; subsequent acetylation with acetic anhydride provided *N*-acetylglucosamine derivative **24** in 74% yield. Simultaneous cleavage of the TFBn and Bn groups in **24** via hydrogenolysis was also not successful. Nevertheless, the phenolic TFBn ethers were selectively cleaved via hydrogenolysis with 10% Pd/C in DMF in the presence of a phosphate buffer solution (pH 7.0), with the benzyl groups remaining unaffected.[35,36] In the absence of the TFBn ether, cleavage of the benzyl groups occurred smoothly under the action of H_2 over 10% Pd/C in methanol in the presence of acetic acid, providing a mixture of anthraquinone **25** and over-reduced anthrone **26** (1:1 **25**/**26**). Colorless anthrone **26** was autoxidized completely to afford yellow anthraquinone **25** in acetone-d_6 in an NMR tube overnight. In fact, treatment of the resultant mixture of anthraquinone **25** and anthrone **26** with NaOMe (0.05 M) in methanol in an oxygen atmosphere led to removal of the acetyl groups and concomitant oxidation of **26**, furnishing aturanoside A (**1**) in an excellent 94% yield over three steps. By the same token, aturanoside B (**2**) was synthesized from anthraquinone rhamnoside **20** (89% over three steps). The analytic data of synthetic **1** and **2** are identical to those reported for natural aturanosides A and B.

In summary, total syntheses of aturanosides A and B, two anthraquinone glycosides with promising antitumor activities, have been achieved. The synthesis of the disaccharide aturanoside A takes the longest path with linear 12 steps in 14% overall yield, while the synthesis of the monosaccharide congener aturanoside B proceeds in nine steps in 21% overall yield. The expeditious synthetic approach presented here would allow easy access to analogues of these rare natural products and thus facilitate in-depth studies of their biological activities.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c02244.

Experimental details and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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