Two-step synthesis of *C*-glycosyl juglones from unprotected sugars: a novel approach to angucycline antibiotics

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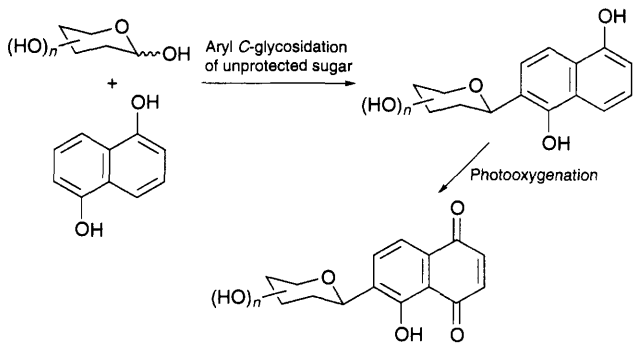
The two-step synthesis of *C*-glycosyl juglones, versatile synthetic intermediates for angucycline antibiotics, has been developed by the *C*-glycosidation of naphthalene-1,5-diol with an unprotected sugar and the subsequent regioselective photooxygenation of the resultant *C*-glycosyl naphthalenediol.

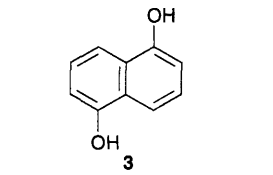
C-Glycosyl juglone, a 5-hydroxy-1,4-naphthoquinone bearing a *C*-glycoside at C6, is a common structural feature among the many members of angucycline antibiotics such as aquayamycin **1** and urdamycinone B **2** which show a variety of biological activity including antitumour activity.[1] *C*-Glycosyl juglone is also a promising synthetic intermediate for this class of antibiotics. Therefore, several approaches to *C*-glycosyl juglone have been developed[2] and the syntheses of angucycline antibiotics *via* the *C*-glycosyl juglone have also been reported.[3,4] Herein we report a novel and efficient approach to *C*-glycosyl juglones in two steps involving the *C*-glycosidation of naphthalene-1,5-diol with an unprotected sugar to form the aryl *C*-glycosidic linkage and the subsequent regioselective photooxygenation of the resultant *C*-glycosyl naphthalenediol to construct the juglone skeleton (Scheme 1). To the best of our knowledge, this is the first protocol for the synthesis of *C*-glycosyl juglones without any protecting groups on the aglycon or glycon moieties.

The first step is the *C*-glycosidations[5] of naphthalene-1,5-diol **3** with several unprotected sugars **4**–**7**. The results are summarized in Table 1. D-Olivose **4** is the most representative sugar that appeared in many angucycline antibiotics. The *C*-glycosidation of **3** (2.0 equiv.) and **4** (1.0 equiv.) using trimethylsilyl trifluoromethanesulfonate (Me_3SiOTf) (0.2 equiv.)[6] in MeCN at 25 °C for 1 h proceeded smoothly to give the unprotected aryl β-*C*-glycoside **8**† in 65% yield as a single isomer (entry 1 in Table 1). Unprotected methyl D-olivoside **5** was also coupled with **3** under similar conditions to afford **8** in good yield (entry 2 in Table 1). To enhance the synthetic utility of this reaction, we further examined the *C*-glycosidations of other unprotected 2,6-dideoxy sugars **6** and **7** with **3** mediated by a catalytic amount of Me_3SiOTf. It was found that these *C*-glycosidations also proceeded easily to furnish the unprotected aryl β-*C*-glycosides **9**† and **10**† in 61 and 65% yields, respectively (entries 3 and 4 in Table 1).

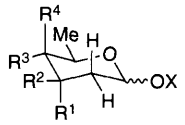
With the unprotected *C*-glycosyl naphthalenediols in hand, the second step, the oxygenation to the *C*-glycosyl juglones, was carried out. We first examined the oxygenation of **8** using ammonium cerium(IV) nitrate (CAN),[7] potassium nitrosodisulfonate (Fremy's salt)[8] and thallium(III) nitrate trihydrate (TTN)[9] as the oxygenating agents, which are widely used for



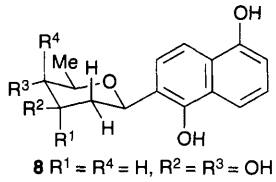
Scheme 1



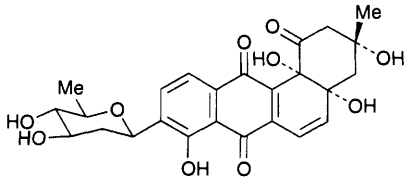
3



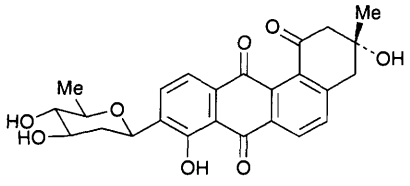
4 X = R^1 = R^4 = H, R^2 = R^3 = OH
5 X = Me, R^1 = R^4 = H, R^2 = R^3 = OH
6 X = R^2 = R^4 = H, R^1 = R^3 = OH
7 X = R^1 = R^3 = H, R^2 = R^4 = OH



8 R^1 = R^4 = H, R^2 = R^3 = OH
9 R^2 = R^4 = H, R^1 = R^3 = OH
10 R^1 = R^3 = H, R^2 = R^4 = OH



Aquayamycin **1**



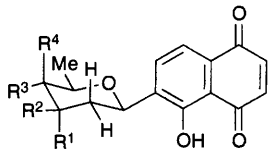
Urdamycinone B **2**

Table 1 *C*-Glycosidations of **3** and the unprotected sugars **4**–**7** to give the β-*C*-glycosides **8**–**10**[a]

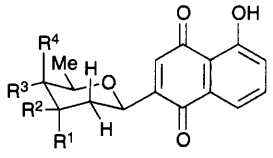
Entry	Sugar	Product	Yield (%)
1	**4**	**8**	65
2	**5**	**8**	64
3	**6**	**9**	61
4	**7**	**10**	65

[a] All reactions were carried out using 2.0 equiv. of **3** with respect to the sugars.

conversion of naphthol to quinone. However, in these cases, the desired *C*-glycosyl juglone **11**‡ was either not detected at all or isolated in a very low yield while the regioisomer **14**‡ was predominantly produced as shown in Table 2. Therefore, our attention next turned to the photooxygenation[10] of **8**. These results are summarized in Table 3. Remarkably, the regioselectivity of the oxygenation of **8** was dramatically changed and the desired *C*-glycosyl juglone **11** was predominantly obtained by choice of the appropriate reaction solvent. Thus, the photooxygenation of **8**, without any reagent, was best effected by irradiating it with sunlight in Bu^{t}OH–$CHCl_3$ (1 : 3, 0.0069 M



11 $R^1 = R^4 = H$, $R^2 = R^3 = OH$
12 $R^2 = R^4 = H$, $R^1 = R^3 = OH$
13 $R^1 = R^3 = H$, $R^2 = R^4 = OH$



14 $R^1 = R^4 = H$, $R^2 = R^3 = OH$
15 $R^2 = R^4 = H$, $R^1 = R^3 = OH$
16 $R^1 = R^3 = H$, $R^2 = R^4 = OH$

Table 2 Oxygenations of **8** at 25 °C to give the *C*-glycosyl juglones **11** and **14**

				Yield (%)	
Entry	Reagent (equiv.)	Solvent	*t*/h	**11**	**14**
1	CAN (2.5)	MeCN–H_2O	0.5	0	25
2	Fremy's salt (3.6)	MeOH	1	10	55
3	TTN (1.8)	MeOH	0.5	1	74

Table 3 Photooxygenations of **8–10** to give the *C*-glycosyl juglones **11–16**

Entry	*C*-Glycosyl naphthalenediol	Solvent[a]	*C*-Glycosyl juglone/ Yield (%)			
1	**8**	MeOH	**11**	7	**14**	12
2	**8**	EtOH	**11**	19	**14**	17
3	**8**	Pr^{i}OH	**11**	30	**14**	17
4	**8**	Bu^{t}OH	**11**	52	**14**	22
5	**8**	Bu^{t}OH–hexane(1 : 1)	**11**	41	**14**	13
6	**8**	Bu^{t}OH–PhH(1 : 1)	**11**	51	**14**	15
7	**8**	Bu^{t}OH–$CHCl_3$(1 : 1)	**11**	52	**14**	14
8	**8**	Bu^{t}OH–$CHCl_3$(1 : 3)	**11**	57	**14**	13
9	**9**	Bu^{t}OH–$CHCl_3$(1 : 1)	**12**	56	**15**	17
10	**10**	Bu^{t}OH–$CHCl_3$(1 : 1)	**13**	55	**16**	18

[a] 0.0069 M for *C*-glycosyl naphthalenediol.

for **8**) under O_2 at room temperature for 12 h to give the *C*-glycosyl juglone **11** in 57% yield along with a 13% yield of **14** (entry 8 in Table 3). Other *C*-glycosyl naphthalenediols **9** and **10** were also found to cleanly convert under similar conditions to the *C*-glycosyl juglones **12** and **13** in 56 and 55% yields, respectively (entries 9 and 10 in Table 3).

A typical experimental procedure for the preparation of **8** *via* *C*-glycosidation of **3** and **4**, followed by photoxygenation to give **11**, is as follows. To a mixture of **3** (183.8 mg, 1.148 mmol) and **4** (85.0 mg, 0.574 mmol) in dry MeCN (5.74 ml) was added Me_3SiOTf (0.022 ml, 0.115 mmol) under ice-cooling conditions. After stirring for 1 h at 25 °C, the reaction was quenched with Et_3N and the resulting mixture was then concentrated *in vacuo*. Purification of the residue by flash column chromatography with 10 : 1 chloroform–methanol gave **8** (108.8 mg, 65.3%, β only) as a white solid. A solution of **8** (108.8 mg, 0.375 mmol) in Bu^{t}OH–$CHCl_3$ (3 : 1, 54.4 ml) was then irradiated with diffuse sunlight (a 75 W xenon lamp, Wacom Sunray Lamp, I-Sunsun) under O_2 for 12 h and then concentrated *in vacuo*. Purification of the residue by flash column chromatography with 2 : 1 hexane–acetone gave **11** (64.4 mg, 56.5%) and **14** (14.8 mg, 13.0%) as an orange solid.

Footnotes

† The β-configuration of *C*-glycoside was evident from the ^1H NMR spectra.
‡ Structure confirmation relies on the NOE experiments.

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