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Synthetic Approaches to the Angucycline Antibiotics: Synthesis of the *C*-Glycosidic CD Ring System.

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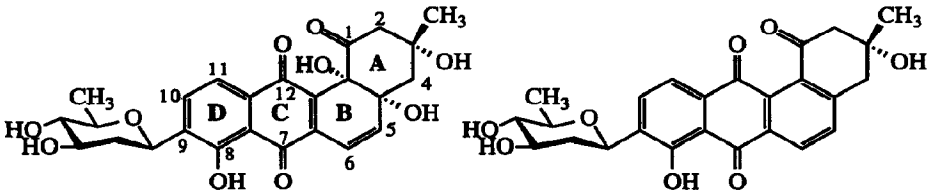
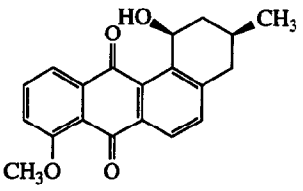
Abstract: *The syntheses of the protected C-glycosyl substituted CD ring system of the angucycline antibiotics and analogues thereof are reported. The key step in their preparation was the C-glycosylation reaction of 5-hydroxy-1,4-dimethoxynaphthalene and a series of 1-O-acyl-2-deoxy and 1-O-acyl-2, 6-dideoxy sugar electrophiles promoted by boron trifluoride etherate. The use of the participating solvent, acetonitrile, was essential for the success of the reaction.*

The angucycline antibiotics are of current interest due to their antibacterial, enzyme inhibitory, and antitumor properties.[1] A common structural feature among many members of this group is a benz[*a*]anthraquinone nucleus bearing an aryl ß-*C*-glycosidic linkage at C-9 to D-olivose. Representatives of this group include vineomycin A1[2], saquayamycins A-D[3], and urdamycins A, C, D, and G[4] which all bear the common aglycone moiety, aquayamycin (**1**). Another member, urdamycin B, lacking the angular hydroxyl functionality at the C-4a and C-12b positions, on mild acid treatment yields the aglycone urdamycinone B (**2**).[5] To date, of all the *C*-glycosidic angucyclines, only the total synthesis of the enantiomer of (**2**) using a biomimetic approach has been reported.[6]



(**1**) (**2**)

We have recently reported the stereoselective syntheses of the racemic forms of the angucyclinones, rubiginone B1 (**3**), and its C-1 epimer, using the Diels-Alder reaction of 5-hydroxynaphthoquinone (**4**) and dienes (**5**) and (**6**) as the pivotal step in the construction of the benz[*a*]anthraquinone ring system.[7,8] A similar approach directed towards the synthesis of SF 2315B, using the Diels-Alder reaction of 5-acetoxy-2-bromo-1,4-naphthoquinone and 3-[(tert-butyldimethylsilyl)oxy]-1-vinylcyclohexene has been reported by Sulikowski and coworkers[9]. As an extension of our programme it was envisaged that the use of 6-*C*-glycosyl derivatives of 5-hydroxynaphthoquinone would facilitate the synthesis of complex *C*-glycosidic angucycline antibiotics such as (**1**) and (**2**). Unfortunately, even though the synthesis of aryl *C*- glycosides has received much attention in recent times[10], the synthesis of *C*-glycosidic naphthoquinones has yet to be achieved.



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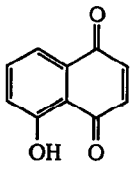

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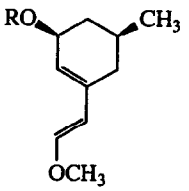
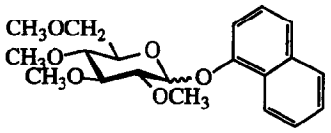


(5) R = H
(6) R = Ac

Our initial approach focussed on work reported by Kometani *et al.*[11] who found that the aryl *O*-glycoside (7) rearranged smoothly to the ß-*C*-glycoside (8) on treatment with boron trifluoride etherate. In the present study it was envisaged that aryl *O*-2-deoxyglycosides would be readily accessed by triphenylphosphine hydrogen bromide catalysed additions of phenols to glycal derivatives[12]. Subsequent treatment with boron trifluoride etherate would furnish the corresponding aryl ß-*C*-glycosides. The use of 1,4-dimethoxy-5-hydroxynaphthalene (9)[13] in such a sequence would provide an intermediate which could be converted into a *C*-glycosidic naphthoquinone.



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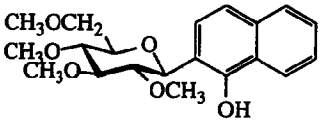

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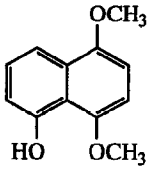
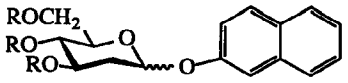
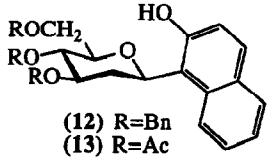


(9)



(10) R=Ac
(11) R=Bn



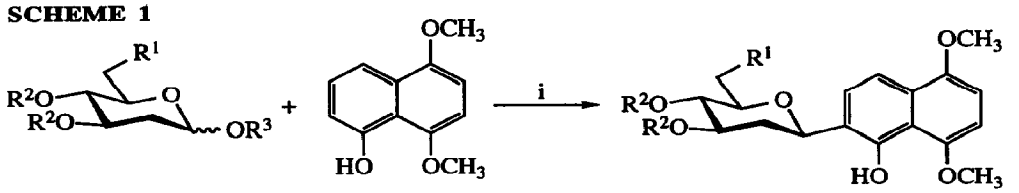
(12) R=Bn
(13) R=Ac

In a preliminary study, the reaction of 2-naphthol with tri-*O*-acetyl- and tri-*O*-benzyl-D-glucal in dichloromethane using 10mol% triphenylphoshine hydrogen bromide gave the corresponding *O*-glycosides (10) and (11) in 15 and 25% yields respectively. The poor conversion to (10) was attributed to the deactivating nature of the C-3 acetate group of tri-*O*-acetyl-D-glucal. However, compound (11) proved extremely labile and the low yield was due to rapid decomposition during purification. To circumvent this problem, the crude reaction product was used and subsequent treatment of a dichloromethane solution of (11) with boron trifluoride etherate (5 equivalents) resulted in a smooth rearrangement to the ß-*C*-glycoside (12)[14] in 71% yield. Unfortunately, the naphthol (9) proved unreactive to both tri-*O*-acetyl- and tri-*O*-benzyl-D-glucal under similar conditions.

An alternative strategy would employ the methodology of Suzuki and coworkers[16] who have developed a direct synthetic route to *ortho* aryl *C*-glycosides by the Lewis acid promoted reaction of 1-*O*-acetyl-2-deoxysugars with phenols. In a trial reaction, treatment of a dichloromethane solution of 2-naphthol and 1,3,4,6-tetra-*O*-acetyl-D-glucopyranose (14) at room temperature with boron trifluoride etherate gave the ß-*C*-glycoside (13)[15] in 83% yield. Unfortunately, reaction of the naphthol (9) under similar conditions gave complex mixtures of products. The use of alternative promoters such as $SnCl_4$ and Cp_2HfCl_2-$AgClO_4$[16] was also unsuccessful.

The problem was overcome by use of dry acetonitrile as the solvent[17]. Treatment of a mixture of naphthol (**9**) and a variety of 1-*O*-acetyl and 1-*O*-trifluoroacetyl-2-deoxyglycopyranoses in acetonitrile with boron trifluoride etherate gave good yields of the corresponding aryl *C*-glycosides (scheme 1). The yields of the products (**17**) to (**19**) (entries 1 to 4, table 1) were obtained after purification by silica-gel column chromatography and crystallisation from diethyl ether and hexanes.

SCHEME 1



(14) - (16) **(9)** **(17) - (19)**

Reagents: i; $BF_3.Et_2O$, 0°C, CH_3CN.

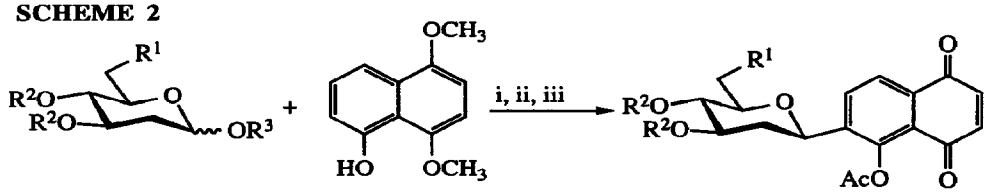
TABLE 1

Entry	Sugar Electrophile	Product	% Yield§	$[\alpha]_D$†
1.	(14) R^1=OAc, R^2=R^3=Ac	(17)	94	+17.3°
2.	(15) R^1=OBn, R^2=Bn ,R^3=$COCF_3$	(18)¶	81	+33.3°
3.	(16) R^1=H, R^2=Ac, R^3=Ac	(19)[19]	75	+29.4°
4.	*ent*-(16)	*ent*-(19)	72	-29.9°

† Solvent; CH_2Cl_2, temperature 22 °C. § isolated yields. ¶ Compound (**18**) was a syrup.

It was evident that decomposition of the products was occurring to some extent after the purification process. To circumvent this problem the crude reaction product was used in the subsequent reaction sequence (scheme 2). The results are summarised in table 2.

SCHEME 2



(14) - (16) **(9)** **(20) - (22)**

Reagents: i. $BF_3.Et_2O$, 0°C, CH_3CN, 15 min; ii. Ac_2O, C_6H_5N; iii. CAN, CH_3CN/H_2O.

TABLE 2

Entry	Sugar Electrophile	Product	% Yield§	$[\alpha]_D$†
5.	(14) R^1=OAc, R^2=R^3=Ac	(20)	63	+18.6°
6.	(15) R^1=OBn, R^2=Bn ,R^3=$COCF_3$	(21)¶	53	+13.3°
7.	(16) R^1=H, R^2=Ac, R^3=Ac	(22)[20]	49	+23.9°
8.	*ent*-(16)	*ent*-(22)	52	-23.2°

† Solvent; CH_2Cl_2, temperature 25 °C. § isolated yields. ¶ Compound (**21**) was a syrup.

Acetylation of the crude *C*-glycosides followed by oxidation with cerium (IV) ammonium nitrate in aqueous acetonitrile[18] gave the *C*-glycosidic quinones (**20**) to (**22**) (entries 5 to 8, table 2).

In summary, the *C*-glycosidic naphthoquinones (**20**) to (**22**) have been prepared in moderate to good overall yields from the naphthol (**9**) and the sugar electrophiles (**14**) to (**16**). It is planned that these compounds will serve as key intermediates in the synthesis of *C*-glycosidic angucycline antibiotics such as (**1**) and (**2**). Both naphthoquinone (**22**), which represents the protected *C*-glycosidic CD ring system of both (**1**) and (**2**), and its enantiomer [*ent*-(**22**)] are available using this approach.

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19. Selected data for (**19**); Found: C, 63.16; H, 6.30%; $C_{22}H_{26}O_8$ requires C, 63.15; and H, 6.26%; δ_H(300 MHz, $CDCl_3$) 1.30 (3 H, d, *J* 6 Hz,6'-H_3), 1.75 (1 H, apparent quartet, *J* 12, 11.5, and 11.5 Hz, 2'-H_{ax}), 2.01 and 2.09 (each 3 H, s, 2 x OAc), 2.49 (1 H, ddd, *J* 12, 5, and 2 Hz, 2'-H_{eq}), 3.70 (1 H, dq, *J* 9.5, 6, 6, and 6 Hz, 5'-H), 3.93 and 4.01 (each 3 H, s, 2 x OCH_3), 4.88 (1 H, t, *J* 9.5 and 9.5 Hz, 4'-H), 5.10 (1 H, dd, *J* 11.5 and 2 Hz, 1'-H), 5.21 (1 H, ddd, *J* 11.5, 9.5, and 9.5 Hz, 3'-H), 6.62 (1 H, d, *J* 8.5 Hz, 2-H)*, 6.68 (1 H, d, *J* 8.5 Hz, 3-H)*, 7.56 (1 H, d, *J* 9 Hz, 8-H), 7.72 (1 H, d, *J* 9 Hz, 7-H), 9.75 (1 H, s, OH) [* assignments may be reversed]; FAB-MS; m/z 419 (MH^+, 100%), 418 (M^+, 81%), 359 (MH^+-AcOH, 51%).
20. Selected data for (**22**); Found: C, 61.55; H, 5.04%; $C_{22}H_{22}O_9$ requires C, 61.39; and H, 5.15%; δ_H(300 MHz, $CDCl_3$) 1.29 (3 H, d, *J* 6 Hz, 6'-H_3), 1.66 (1 H, q, J 11.5, 11.5, and 11.5 Hz, 2'-H_{ax}), 2.02, 2.09, and 2.50 (each 3 H, s, 3 x OAc), 3.66 (1 H, dq, *J* 9.5, 6, 6, and 6 Hz, 5'-H), 4.73 (1 H, m, 1'-H), 4.85 (1 H, t, *J* 9.5 and 9.5 Hz, 4'-H), 5.12 (1 H, ddd, *J* 11.5, 9.5, and 5 Hz, 3'-H), 6.83 (1 H, d, *J* 10.5, 3-H), 6.93 (1 H, d, *J* 10.5 Hz, 2-H), 7.98 (1 H, d, *J* 8 Hz, 8-H), 8.06(1 H, d, *J* 8 Hz, 7-H); FAB-MS; m/z 432 (MH_2^+, 5%), 431 (MH^+, 5%), and 136 (100%).

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