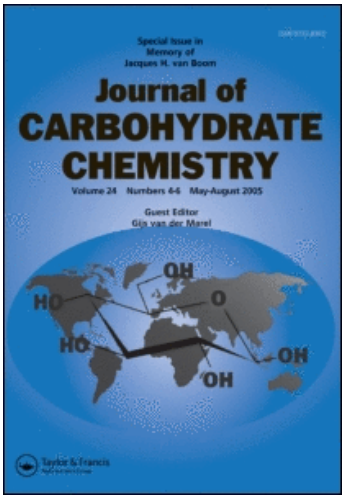

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COMMUNICATION

SYNTHESIS OF 11-METHOXY ANTHRACYCLINES

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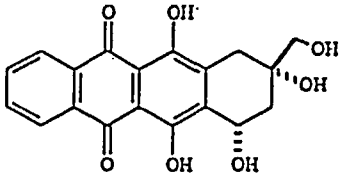
Doxorubicin and daunorubicin are clinically important antitumor antibiotics but their use is restricted, especially for long-term treatment by their toxicity.[1] Hence the cardiotoxic side effects associated with these drugs have stimulated the search for analogues with lower cardiotoxicity, improved antitumor activity and lack of cross-resistance.

In a recent paper[2] we reported the synthesis of several new anthracycline glycosides, derived from 4-demethoxy-9-deacetyl-9-hydroxymethyldaunomycinone (**1**), and such glycosides display substantial antitumor activity. One of the routes[3,4] we used for preparing **1** involved the formation of intermediate **2** which possesses one of the two phenol groups of ring B as a methyl ether. In order to establish structure-activity relationships in this novel series of anthracyclines, we decided to synthesize several glycosides from the 11-methoxyanthracyclinone **3** which resulted from selective deprotection of **2**, and to test their <u>in vitro</u> activity against L 1210 leukemia. Daunosamine but also 3-deamino-3-hydroxy-2,6-dideoxy-L-hexoses such as 2-deoxy-L-fucose, 2-deoxy-L-rhamnose or 2,6-dideoxy-2-iodo-L-mannose were chosen as sugar moieties owing to the fact that their

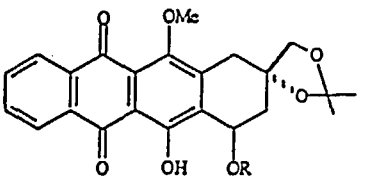
corresponding glycosides previously obtained from **1** showed high antitumor activity.[2]

Several studies have shown that the cardiotoxicity of anthracyclines is probably related[5] to the redox activity of the quinone moiety leading to production of reactive oxygen species and concomitant lipid peroxidation. Thus, analogues modified at the quinone would be important, for example, Acton *et al.*[6] reported that the 5-imino derivatives of daunorubicin and doxorubicin retain antitumor activity and are significantly less cardiotoxic than the parent compounds. This may be attributed to the fact that 5-imino analogs do not generate oxygen radicals, and this suggests that a separation of cytotoxic and cardiotoxic effects is possible by appropriate structural modifications. For this reason, but also as the result of a one electron reduction study that we had previously undertaken with variously substituted imino-anthraquinones[7] (redox models of anthracyclines), a 4-demethoxy-5-imino-11-methoxyanthracycline derivative was prepared and tested. Indeed the life-time of the radical anion of the corresponding anthraquinone was shorter compared to other models.

Aglycon **3** : [mp 185 °C (hexane), $[\alpha]_D^{20}$ + 81° (*c* 0.04, $CHCl_3$)], was prepared in 60% yield by desilylation of **2** with Bu_4NF in THF at room temperature for 2.5 h. Coupling of the 1,4-bis-(*O*-*p*-nitrobenzoate) of *N*-trifluoroacetyl daunosamine[8] with **3** was then carried out in dry acetonitrile in the presence of *p*-toluenesulfonic acid at 40 °C for 5 h. Use of a three-fold excess of the sugar with respect to aglycon led to 40% of glycosides (based on aglycon used). Chromatography on silica gel (hexane-EtOAc, 1:1) allowed isolation of less than 10% of the 7,13-bis-glycoside derivative and 30% of α-L-glycoside (**4**) [amorphous solid, $[\alpha]_D^{20}$ - 148° (*c* 0.02, $CHCl_3$), DCI/NH_3[9] m/z 762 $(M+18)^+$, 745 $(M+1)^+$]. *O*-deacylation of **4** under standard conditions with 0.25 N aqueous NaOH in a mixture of THF and MeOH (20 min, 0 °C) afforded **5** [70% yield, amorphous solid, $[\alpha]_D^{20}$ -15° (*c* 0.02, THF)], whose ^1H NMR and IR spectra showed the ester group signal to be absent. Anthracycline **6** was obtained by stirring **5** in ammonia-saturated MeOH at 0 °C for 1 h and at 4 °C for 26 h. Column chromatography (silica gel, MeOH-CH_2Cl_2, 85:15) gave **6** [50% yield, amorphous solid, $[\alpha]_D^{20}$ - 100° (*c* 0.026, dioxane), m/z 392 $(M+1)^+$].

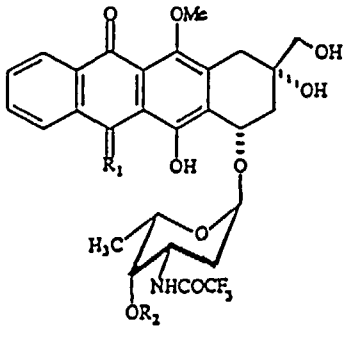


1



2 R=TBDMS

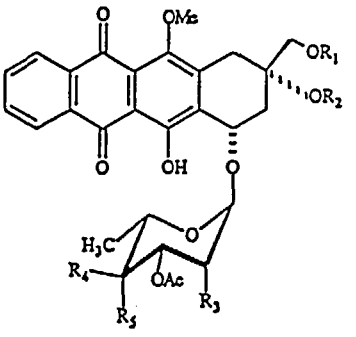
3 R=H



4 R_1=O; R_2=pNBz

5 R_1=O; R_2=H

6 R_1=NH; R_2=H



	R_1	R_2	R_3	R_4	R_5
7	$C(CH_3)_2$		H	H	OAc
8	H	H	H	H	OAc
9	$C(CH_3)_2$		I	OAc	H
10	H	H	I	OAc	H

Glycosidation of 3 with 3,4-di-O-acetyl-2,6-dideoxy-α-L-lyxo-hexopyranosyl bromide[10] in the presence of yellow HgO, mercuric bromide and molecular sieves 4 Å for 24 h at room temperature (two fold excess of sugar derivative) gave the fully protected analogue 7 [amorphous solid, $[\alpha]_D^{20}$ – 20° (c 0.04, $CHCl_3$), m/z 642 $(M+18)^+$, 625 $(M+1)^+$]. Upon mild acid hydrolysis [0.1 N HCl in a mixture of MeOH-H_2O-THF (50:2:1)], compound 7 gave anthracycline 8 [36% yield, $[\alpha]_D^{20}$ + 14° (c 0.06, $CHCl_3$), mz 602 $(M+18)^+$, 585 $(M+1)^+$], along with 58 % of recovered starting material 7.

L-Rhamnal diacetate[11] reacted with 3 in the presence of N-iodosuccinimide[12] to afford mainly in 75% yield, the α-L-manno glycoside 9 [$[\alpha]_D^{20}$ – 27° (c 0.04, $CHCl_3$), m/z 768 $(M+18)^+$, and 751

$(M+1)^+$]. Finally selective deprotection of the acetal ring as present in the aglycon moiety of **9** by stirring for 18 h at room temperature in the presence of AcOH and H_2O (1:1) afforded **10** [50% yield, $[\alpha]_D^{20}$ – 180° (c 0.55, $CHCl_3$); m/z 728 $(M+18)^+$], whereas 20% of starting material **9** was recovered.

The novel anthracyclines **5**, **8** and **10** displayed *in vitro* a reduced cytotoxicity (IC_{50} > 1 µg/mL) *versus* doxorubicine (IC_{50} ≈ 0.02 µg/mL). These data show that, as in daunorubicin–doxorubicin related anthracyclines[13], methylation of the 11–hydroxy group resulted in a practically complete loss of cytotoxicity, even in the presence of a 5–imino group.

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