to a stirred, near boiling solution of 7.35 g (0.03 mol) of 1-(5-phenyl-4-oxo-2-oxazolin-2-yl)piperazine and 3.34 g (0.033 mol) of Et_3N in 250 ml of C_6H_6. The mixture was refluxed for 1 h and, after cooling, the solid was filtered and washed with H_2O. The C_6H_6 filtrate was evaporated in vacuo leaving a solid residue. The combined solids were purified by recrystallization.

1-(Phenylcarbamoyl)-4-(5-phenyl-4-oxo-2-oxazolin-2-yl)piperazine (4d). A solution of 2.38 g (0.02 mol) of phenyl isocyanate in 5 ml of dioxane was added dropwise to a stirred, hot solution of 4.9 g (0.02 mol) of 1-(5-phenyl-4-oxo-2-oxazolin-2-yl)piperazine in 150 ml of dioxane. The mixture was refluxed with stirring for 1 h and evaporated to dryness in vacuo and the residue was recrystallized. Compounds **4e** and **4f** were similarly prepared.

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Communications to the Editor

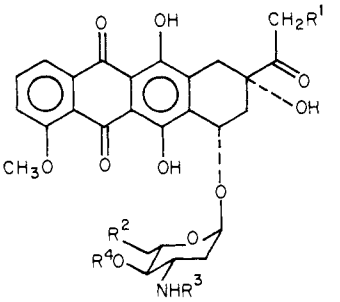
Stereocontrolled Glycosidation of Daunomycinone. Synthesis and Biological Evaluation of 6-Hydroxy-L-arabino Analogues of Antitumor Anthracyclines

Sir:

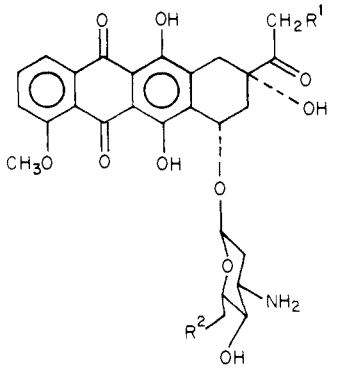
Daunorubicin and adriamycin are anthracycline glycosides which are clinically useful chemotherapeutic agents against cancer.[1] The synthesis of analogues in which the carbohydrate component is functionally and/or configurationally altered is of great biochemical and practical interest, particularly with the finding[2,3] that the semisynthetic analogues 1 and **2**, possessing an inverted configuration at C-4', display high activity against experimental tumors in mice. It is also of interest in this connection that the β anomers **6** and **7** have a much lower biological activity than the α anomers.[2,3] It is apparent, therefore, that the stereospecific synthesis of glycosides in this class of compounds is of paramount importance. To date, all glycosidations in this series have been carried out by the classical Koenigs–Knorr procedure and have led to anomeric mixtures that necessitated separation.[3]

We report herein on the stereocontrolled synthesis of 7-*O*-(3-amino-2,3-dideoxy-α-L-*arabino*-hexopyranosyl)-daunomycinone (**4**), via an acid-catalyzed glycosidation of a glycal intermediate, and the chemical conversion of **4** into the corresponding adriamycin analogue **5**.

The key intermediate for the stereocontrolled glycosidation of daunomycinone, 1,2,3-trideoxy-4,6-di-*O*-*p*-nitrobenzoyl-3-trifluoroacetamido-L-*arabino*-hex-1-enopyranose (**10**), was prepared from methyl 4,6-*O*-benzylidene-2-deoxy-α-L-*ribo*-hexopyranoside, following procedures available in the literature for the D series,[4] via methyl 3-amino-4,6-*O*-benzylidene-2,3-dideoxy-α-L-*arabino*-hexopyranoside. The latter compound was converted to methyl 3-amino-2,3-dideoxy-α-L-*arabino*-hexopyranoside, mp 120° dec, $[\alpha]^{20}D$ −92° (*c* 0.4, H_2O),[5] upon treatment with methanolic hydrogen chloride. This compound was hydrolyzed (1 N HCl for 5 h at 95°) to the free amino sugar, mp 155–157° dec, $[\alpha]^{20}D$ −55° (*c* 0.5, H_2O), previously unknown in the L series, and the latter was converted to the trifluoroacetyl derivative **9**, mp 177°, $[\alpha]^{20}D$ −58° (*c* 0.5, dioxane), by treatment with trifluoroacetic anhydride in dichloromethane (25°, 20 h) and hydrolysis of the 1,6-di-*O*-trifluoroacetyl groups with methanol (25°, 20 h). *p*-Nitrobenzoylation of **9** with *p*-nitrobenzoyl chloride in pyridine followed by treatment with aqueous sodium bicarbonate afforded 1,2,3-trideoxy-4,6-di-*O*-*p*-nitrobenzoyl-3-trifluoroacetamido-L-*arabino*-hex-1-enopyranose (**10**), mp 214–215°, $[\alpha]^{20}D$ −117° (*c* 0.5, $CHCl_3$). The overall yield of **10** from methyl 3-amino-4,6-*O*-benzylidene-2,3-dideoxy-α-*arabino*-hexopyranoside was 70%.



1, $R^1 = R^2 = R^3 = R^4 = H$
2, $R^1 = OH$; $R^2 = R^3 = R^4 = H$
3, $R^1 = H$; $R^2 = pNBzO$; $R^3 = COCF_3$; $R^4 = pNBz$
4, $R^1 = R^3 = R^4 = H$; $R^2 = OH$
5, $R^1 = R^2 = OH$; $R^3 = R^4 = H$

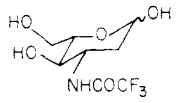


6, $R^1 = R^2 = H$
7, $R^1 = OH$; $R^2 = H$
8, $R^1 = H$; $R^2 = OH$

Table I. Biological Activity of 4'-Epi-6'-hydroxydaunorubicin (4) and 4'-Epi-6'-hydroxyadriamycin (5) in Comparison with Daunorubicin (D) and Adriamycin (A)

Compd	In vitro[a]			In vivo on ascites sarcoma 180 in mice[e]		
	HeLa[b]	MEF[c]	MSV[d]	Dose[f]	AST[g]	LST[h]
4	>10 000	256	100	10	167	
D[i]	13	9	5.5	2	192	11/68
5	1 000	50	25	10	162	2/10
A[i]	110	7	2.5	2	210	30/125

[a] Data are expressed as 50% inhibiting dose (ng/ml). [b] HeLa cells cloning efficiency after 8 h of exposure to drug. [c] Mouse embryo fibroblasts proliferation, treatment for 72 h. [d] Murine sarcoma virus (Moloney) foci formation on MEF, treatment for 72 h. [e] Treatment ip on day 1. [f] Optimal doses, mg/kg of body weight. [g] Average survival time expressed as percent of untreated controls. [h] Long-term (60 days from tumor transplantation) survivors. [i] Average data of several experiments. For experimental details see ref 3. No toxic deaths were observed at the optimal doses indicated.



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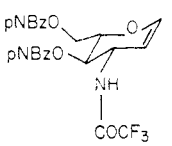

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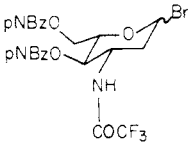

11

pNBz = *p*-nitrobenzoyl

Reaction of **10** with daunomycinone in benzene and in the presence of a catalytic amount of *p*-toluenesulfonic acid for 20 h at 55° gave 7-*O*-(2,3-dideoxy-4,6-di-*O*-*p*-nitrobenzoyl-3-trifluoroacetamido-α-L-*arabino*-hexopyranosyl)daunomycinone (**3**), mp 282°, $[\alpha]^{20}D$ +260° (*c* 0.05, $CHCl_3$). Removal of the protecting groups of **3**, with 0.1 N sodium hydroxide in aqueous dioxane, afforded 7-*O*-(3-amino-2,3-dideoxy-α-L-*arabino*-hexopyranosyl)-daunomycinone (4'-epi-6'-hydroxydaunorubicin, **4**) which was isolated as hydrochloride, mp 199–201°, $[\alpha]^{20}D$ +388° (*c* 0.05, methanol), in 56% yield (from daunomycinone). The α configuration of the glycosidic linkage was assigned on the basis of the C(1')H NMR signal which is a broad singlet ($W_H \sim 7.5$ Hz) at δ 5.30 (Me_2SO-d_6). The corresponding adriamycin analogue **5**, mp 180° dec, $[\alpha]^{20}D$ +216° (*c* 0.01, methanol), was obtained from **4** in 50% yield via the 14-bromo derivative, following a procedure already established in the 6'-deoxy-L-*lyxo* series.[6]

When daunomycinone was allowed to react in methylene chloride and, in the presence of mercuric oxide, mercuric bromide, and molecular sieve, with 2,3-dideoxy-4,6-di-*O*-*p*-nitrobenzoyl-3-trifluoroacetamido-L-*arabino*-hexopyranosyl bromide (**11**), obtained by treatment of the product of the *p*-nitrobenzoylation of **9** with dry hydrogen bromide in methylene chloride, a second condensation product was obtained in addition to **3**. The former after removal of the protecting groups afforded the β-anomer **8** (6%): mp 180–182°; $[\alpha]^{23}D$ +412° (*c* 0.055, methanol). The desired α-anomer **4** was obtained in 15% yield.

The remarkable stereocontrol[7] in the acid-catalyzed glycosidation reaction, particularly with a bulky aglycon, is noteworthy and paves the way to the preparation of the analogues in which the axial orientation[8] of the aglycon is preserved, as in the natural series.

Biological activity of compounds **4** and **5** is lower, on a weight basis, than that of daunorubicin and adriamycin both on cultured cells and on sarcoma 180 ascites in mice (Table I). This lower degree of efficacy could not be known a priori from the available knowledge about the biochemical mode of action of the antitumor anthracyclines.[1] The new analogues are, on the other hand, definitely less toxic than the corresponding 6'-deoxy derivatives with L-arabino configuration which cause toxic deaths in the treated animals at doses higher than 5 mg/kg (treatment ip on day 1).[3]

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