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A NOVEL METHOD FOR REGIO- AND STEREOSELECTIVE HYDROXYLATION OF ANTHRACYCLINE GLYCOSIDES

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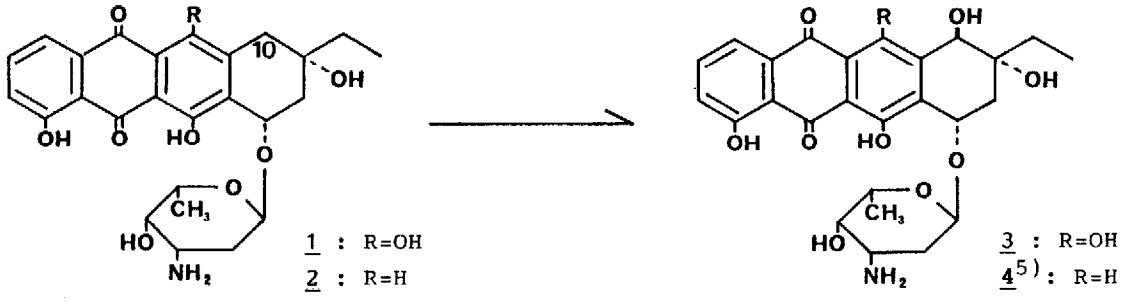
Summary: Hydroxylation at C-10 position of anthracycline glycoside proceeds stereoselectively with trimethylamine-N-oxide in DMF.

The efficient introduction of the hydroxyl group at the C-10 position of anthracyclines is one of main problems for their total synthesis or for their chemical modification[1]. Known hydroxylation methods[1] require multisteps and could not be applied to anthracycline glycosides because of their unstable glycoside linkage. We have recently reported that the reaction of 13-deoxocarminomycin 1 with bis(2-iodoethyl)ether and triethylamine in DMF gave a 10-hydroxylated by-product[2]. This fact prompted us to develop the direct hydroxylation of anthracycline glycosides. After many attempts, a satisfactory method for our preparative or industrial purpose was found out. We here report a novel and concise method for regio- and stereoselective hydroxylation at the C-10 position of anthracycline glycosides.



The compound 1 was converted to 13-deoxo-10-hydroxycarminomycin (oxaunomycin)[3] 3 stereoselectively with trimethylamine-N-oxide (TNO) under a mild condition in good yield. A ratio (>100:1) of 3 and its 10-epi-isomer[4]

Table. Hydroxylation at C-10 position of anthracycline glycosides (room temperature, 40 hr.)

Substrate	Reagent	Eq	Solvent	Product	% Yield
1	TNO	2	DMF	3	82
1	TNO	2	acetone	3	53
1	TNO	2	CH_3CN	3	42
1	TNO	2	CH_2Cl_2	no reaction	
1	NMO	2	DMF	3	31
1	PO	2	DMF	no reaction	
1	Et_3N	38	DMF	3	56
2	TNO	2	DMF	4	34
2	Et_3N	38	DMF	4	14

PO : Pyridine-N-oxide.

was determined by HPLC analysis[2]. As summarized in Table, this reaction proceeded also with N-methylmorpholine-N-oxide (NMO) as well as with a large excess of triethylamine. The existence of a trace amount of triethylamine-N-oxide in triethylamine is suspected in the latter case. The best result was obtained when DMF was used as a solvent.

A typical procedure for 3 is as follows.

To a solution of 1 (40.0mg) in DMF (12ml) was added trimethylamine-N-oxide·$2H_2O$ (16.8mg). The mixture was stirred at room temperature for 40 hr and then evaporated. The product was purified with preparative TLC. Crystallization from MeOH-diethyl ether gave 2 (34.0mg, 82% yield) as a red powder.

Further studies on the mechanism, scope, and limitation of this reaction is in progress and will be reported in our subsequent paper.

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