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SYNTHESIS OF NOVEL ANALOGUES OF ANTHRACYCLINE ANTIBIOTICS CONTAINING A BRANCHED-CHAIN SUGAR 4-EPI-L-VANCOSAMINE

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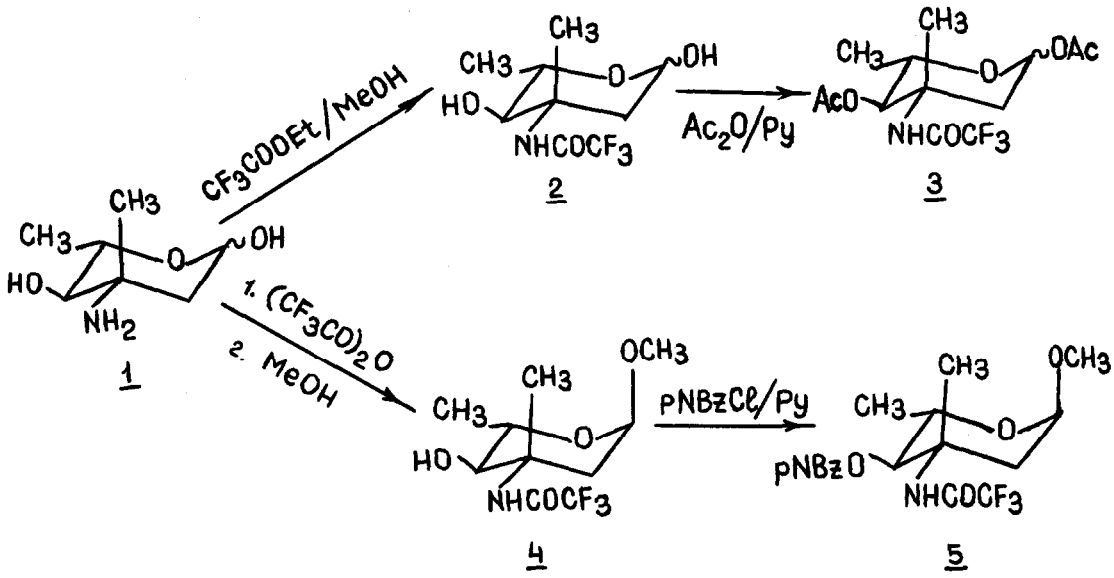
Abstract: Novel semisynthetic analogues of anthracycline antibiotics containing a branched aminosugar 4-epi-L-vancosamine have been prepared.

Several anthracycline-glycoside antibiotics are clinically useful antineoplastic agents. The goal of chemical modification of these compounds is enhancement of their therapeutic activity and reduction of toxic effects [1,2]. Glycosylation has widely been employed to prepare analogues of anthracycline antibiotics though the involvement of branched-chain sugars is documented rather scarcely [1]

Here we present data on synthesis of novel analogues of anthracycline antibiotics based on glycosylation of natural and semisynthetic anthracyclinones with a derivative of 4-epi-L-vancosamine (L-eremosamine) 1. This C-3-branched aminosugar, 2,3,6-trideoxy-3-amino-3-C-methyl-L-arabino-hexose, was obtained by hydrolysis of new antibacterial antibiotic eremomycine [3,4] (antibiotic A 82846) [5] which belongs to a glycopeptide group. This sugar 1 was also found in antibiotic orienticin [6]. Its synthesis is described [7].

The sugar 1 was converted into glycosyl-donor 3 by sequential trifluoroacetylation into 2 (CF_3COOEt/MeOH, yield 50%) and acetylation (Ac_2O/Py, yield 40%,$\alpha:\beta$=1:2; Ac_2O/Py/DMAP, yield 60%,$\alpha:\beta$=1:4), ^1H NMR ($CDCl_3$)δ ppm: 6.13 (dd, $J_{1e,2a}$4.5 Hz, $J_{1e,2e}$1.0 Hz, H - 1α); 5.80 (dd, $J_{1a,2a}$12.5 Hz, $J_{1a,2e}$2.2 Hz, H - 1α). Attempted, conventional N-trifluoroacetylation /$(CF_3CO)_2O$, CH_2Cl_2, then MeOH (cf.[8])/ resulted instead of 2, in methyl glycoside 4 characterized as p-nitrobenzoate 5, ^1H NMR ($CDCl_3$)δ ppm: 8.29(2d, $J_{2,3}=J_{3,2}$5.0 Hz,p-$NO_2C_6H_4CO$), 4.79 (d,$J_{1e,2a}$4.5 Hz,H - 1α), 3.38 (s,OCH_3).

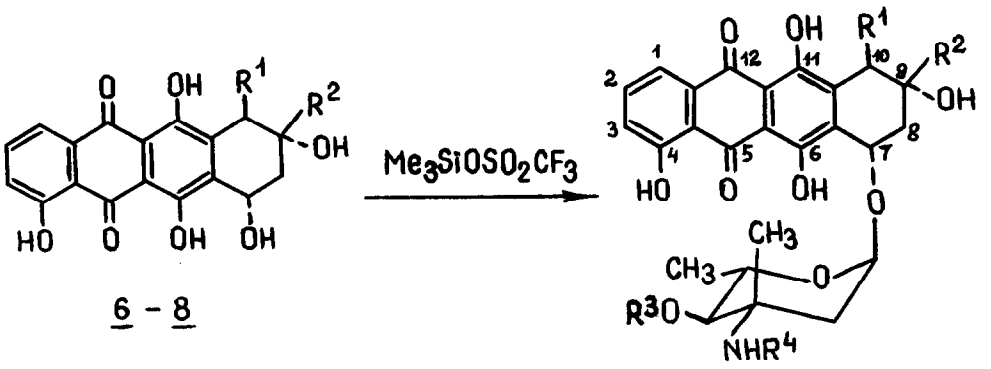


The glycosyl-acceptors used were the natural ε-rhodomycinone 6 and carminomycinone 7, isolated from carminomycine complex [9], as well as a semisynthetic anthracyclinone, 14-acetoxycarminomycinone 8 [10].

Glycosylation of 6 with 3 (α:β=1:2) was performed in dichloromethane in the presence of trimethylsilyl trifluoromethanesulfonate and molecular sieves 4Å (-10 ÷ -15°C, 15 min, Ar) [11]. Column chromatography yielded 10 (38%) and 9 (9%), the recovery of 6 being 38%. That the glycosidic bond in 10 was α followed from ^{1}H NMR data: ($CDCl_3$) δ ppm, 5.40 (d, $J_{1e,2a}$ 4.7 Hz). Condensation of 3 with 6 (α:β=1:2) under the above conditions gave 60% of 10, while addition of p-dioxane (20%) to the reaction mixture raised the yield of the glycoside to 73%.

Under the latter conditions (p-dioxane:dicloromethane, 1:4), glycosylation of 7 and 8 with 3 (α:β=1:2) afforded 11 (70%) and 12 (31%). The low yield in the latter case may be accounted for by instability of the anthracyclinone moiety. ^{1}H NMR spectra evidenced to α-configuration of the glycocydic bond in 11 and 12 ($CDCl_3$) δ ppm: 11, 5.50 (d, $J_{1e,2a}$ 5.0 Hz, H - 1α); 12, 5.48 (d, $J_{1e,2a}$ 5.0 Hz, H - 1α).

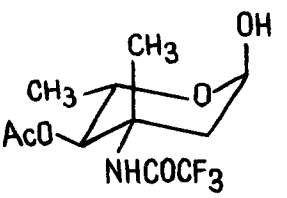
Deprotection of 10 and 11 was performed stepwise. O-Deacetylation (0.005 M KOH in aq.MeOH, 30 min) afforded 13 and 14. Under these conditions 12 underwent degradation. Removal of N-trifluoroacetyl group from 13 and 14 (0.1 M KOH, aq.p-dioxane, 1 h) gave the free glycosides 15 and 16 [12] with yields on the deblocking steps 60 and 40% respectively.



6 - 8

10 - 16

	R^1	R^2	R^3	R^4
6	$COOCH_3$	CH_2CH_3	-	-
7	H	$COCH_3$	-	-
8	H	$COCH_2OOCCH_3$	-	-
10	$COOCH_3$	CH_2CH_3	Ac	$COCF_3$
11	H	$COCH_3$	Ac	$COCF_3$
12	H	$COCH_2OOCCH_3$	Ac	$COCF_3$
13	$COOCH_3$	CH_2CH_3	OH	$COCF_3$
14	H	$COCH_3$	OH	$COCF_3$
15	$COOCH_3$	CH_2CH_3	OH	H
16	H	$COCH_3$	OH	H



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Compound 15 is an analogue of the antibiotic 11-hydroxyaklavine [1], wherein rhodosamine is substituted for 4-epi-L-vancosamine. Compound 16 is an analogue of the antibiotic carminomycine with 4-epi-L-vancosamine instead of daunosamine.

Compounds 15 and 16 were 10-fold less cytotoxic in vitro (NK/Ly) than carminomycine.

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12. 15 - 7-O-(4-Epi-α-L-vancosaminyl)-ε-rhodomycinone. $C_{29}H_{33}NO_{11}\cdot HCl$. MS, m/z: 572 $(M+H)^+$. ^1H NMR (base, $CDCl_3$) δ ppm (J,Hz): 7.86 (1H, dd, $J_{1,2}$7.5, $J_{1,3}$1.2, H-1), 7.70 (1H,t,$J_{2,1}=J_{2,3}$7.5, H-2), 7.31 (1H,dd, $J_{3,2}$7.5, $J_{3,1}$1.2, H-3), 5.44 (1H,d,$J_{1'e,2'a}$5.0, H-1'), 5.17 (1H,dd, $J_{7e,8a}$2.0, H-7), 4.30 (1H,s, H-10), 3.90 (1H,dq,$J_{5'a,4'a}$10.0, $J_{5'a,6'}$ 6.2, H-5'), 3.72 (3H,s, $COOCH_3$), 3.16 (1H,d,$J_{4'a,5'a}$10.0, H-4'), 2.38 (1H,d,J_{gem}15.0, H-8), 2.24 (1H,dd,J_{gem}15.0, $J_{8a,7e}$4.5,H-8), 2.01 (1H,d,J_{gem}14.0, H-2'), 1.81 (1H,dd,J_{gem}14.0, $J_{2'a,1'e}$5.0, H-2'), 1.83 and 1.44 (2H,dq,J_{gem}14.5, $J_{13,14}$7.5, H-13A and H-13B), 1.37 (3H,d, $J_{6,5a}$6.25, 3H-6'), 1.26 (3H,s, CH_3-3'), 1.13 (3H,t,$J_{14,13}$7.5,3H-14).
16 - 7-O-(4-Epi-α-L-vancosaminyl)-carminomycinone. $C_{27}H_{29}NO_{10}\cdot HCl$. MS, m/z: 528 $(M+H)^+$. ^1H NMR (base, $CDCl_3$:CD_3OD, 1:1) δ ppm (J,Hz) : 7.80 (1H,d,$J_{1,2}$7.5, H-1), 7.64 (1H,t,$J_{2,1}=J_{2,3}$7.5, H-2), 7.23 (1H, d,$J_{3,2}$7.5, H-3), 5.36 (1H,d,$J_{1'e,2'a}$5.0, H-1'), 5.11 (1H,m, H-7), 3.80 (1H,dq,$J_{5'a,4'a}$10.0, $J_{5'a,6'}$ 6.5, H-5'), 3.05 (1H,d,$J_{4'a,5'a}$10.0, H-4'), 3.13 and 2.92 (2H,2d,J_{gem}18.0, H-10A and H-10B), 2.34 (3H,s,14-CH_3), 2.28 (1H,d,J_{gem}17.0, H-8), 2.03 (1H,dd,J_{gem}17.0,$J_{8a,7e}$5.0,H-8), 1.87 (1H,d,J_{gem}14.0, H-2'), 1.72 (1H,dd,J_{gem}14.0,$J_{2'a,1'e}$5.0, H-2'), 1.27 (3H,d,$J_{6',5'a}$6.5, 3H-6'), 1.12 (3H,s, CH_3-3').

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