3′-HYDROXYESORUBICIN

SYNTHESIS AND ANTITUMOR ACTIVITY

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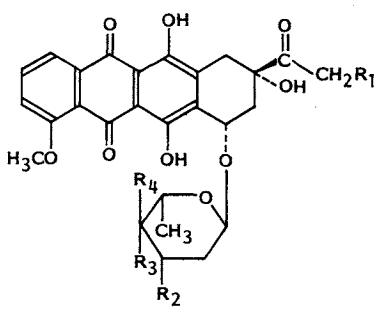
A novel route to 4′-deoxy anthracycline analogues has been developed starting from previously unavailable, optically active 4,6-dideoxy-hex-1-enitol **9**. Coupling of daunomycinone (**11**) or 14-*O*-*tert*-butyldimethylsilyladriamycinone (**12**) with glycosyl chloride **10** in Koenigs-Knorr condition gave mainly α anomers, which were successfully deblocked to final 3′-deamino-4′-deoxy-3′-hydroxydaunorubicin (**7**) and 3′-deamino-3′-hydroxyesorubicin (**8**). Analogues were evaluated *in vitro* against P388 and L1210 leukemia and M5076 cells and *in vivo* against P388 leukemia. Compared with doxorubicin (**1**), 3′-hydroxyesorubicin (**8**) showed *in vitro* similar cytotoxic potential and *in vivo* higher antitumor activity.

Earlier reports on the synthesis and activity of 3′-hydroxydoxorubicin (**5**)[1] and 3′-hydroxyepirubicin (**6**)[2] showed that the replacement of doxorubicin (**1**) or epirubicin (**2**) 3′-amino group by hydroxyl led to highly active analogues. Similar observation was made for deaminated rhodomycin[3], carminomycin[4,5], pyrromycin[4,5] and daunorubicin (**4**)[6]. However, the activity was lower than that observed for the doxorubicin series. It was, therefore, interesting to synthesize and evaluate biologically deaminated versions of other clinically important anthracyclines. Such an approach should confirm the generality of the deamination effect on cytotoxicity and contribute to the assessment of the effects of modifications at C-4′ of 3′-deaminated anthracyclines on biological activity.



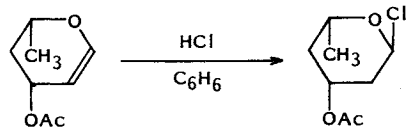
1	R_1=OH	R_2=NH_2	R_3=OH	R_4=H
2	R_1=OH	R_2=NH_2	R_3=H	R_4=OH
3	R_1=OH	R_2=NH_2	R_3=H	R_4=H
4	R_1=H	R_2=NH_2	R_3=OH	R_4=H
5	R_1=OH	R_2=OH	R_3=OH	R_4=H
6	R_1=OH	R_2=OH	R_3=H	R_4=OH
7	R_1=H	R_2=OH	R_3=H	R_4=H
8	R_1=OH	R_2=OH	R_3=H	R_4=H

Table 1. *In vivo* antitumor activity of esorubicin analogues against ascitic P388 leukemia.

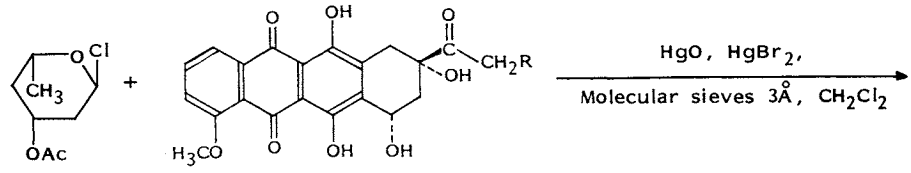
Compound	Dose (mg/kg)	%T/C (animals alive day 60)
7	25	109 (0/5)
	50	127 (0/5)
	100	154 (0/5); 250 (0/5)
8	12.5	136 (0/5)
	25	163 (0/5)
	50	418 (0/5)
	100	>600 (5/5); >600 (4/5)
13	25	100 (0/5)
	50	100 (0/5)
	100	100 (0/5)
Doxorubicin (**1**)	10	172 (0/5); 310 (1/5)

Table 2. *In vitro* cytotoxic activity of esorubicin analogues against murine tumor cells.

Compound	ID_{50} (μg/ml)		
	L1210	M5076	P388
7	>10.0	>10.0	>25.0
8	0.59±0.10	1.35±0.77	0.42±0.13
13	18.5	4.6	14.6
Doxorubicin (**1**)	0.53±0.04	1.82±0.99	0.35±0.07

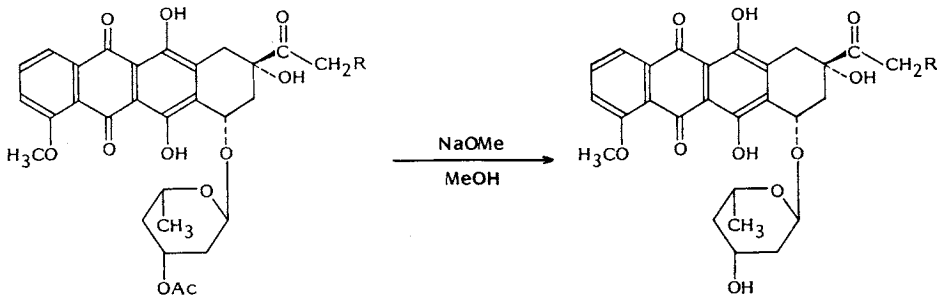


9 **10**



10

11 R=H
12 R=OSiMe$_2$*tert*-Bu



13 R=H
14 R=OSiMe$_2$*tert*-Bu

7 R=H
16 R=OSiMe$_2$*tert*-Bu
8 R=OH

The initial target for modification has been esorubicin (**3**, 4′-deoxydoxorubicin)[7], whose properties have been extensively studied (currently under clinical evaluation)[8,9] and 4′-deoxydaunorubicin. The syntheses starting from glycal **9** and proper aglycons (**11** and **12**) gave 3′-acetoxy-4′-deoxydaunorubicin (**13**)[10] and 14-*O*-silylated compound **14** which after purification and deblocking led to 3′-hydroxy-4′-deoxy-daunorubicin (**7**)[10] and 3′-hydroxyesorubicin (**8**)[10]. Daunorubicin analogue **7** showed *in vivo* significant activity, despite low potency (at 100 mg/kg T/C 154 and 250, in two separate experiments, respectively). The 3′-deamino-3′-hydroxyesorubicin (**8**) appeared to be a highly active compound, especially *in vivo* against P388 leukemia (Table 1). The highest observed T/C was >600 at the dose of 100 mg/kg, with all animals alive on day 60. *In vitro* cytotoxicity of 3′-hydroxyesorubicin (**8**) against three cell lines (P388, L1210 and M5076) was similar to doxorubicin (Table 2).

Chemical Synthesis

The synthetic approach has been based on using previously unreported 4-deoxy-glycals as starting material. Our efforts toward preparation of these substrates by applying free radical deoxygenation in the key step resulted in the development of novel routes to optically active 4,6-dideoxy-glycals[11]. The 3-*O*-acetyl-4-deoxy-L-rhamnal (**9**) was prepared by this method in six steps, with high yield from

Table 3. ^{1}H NMR data for compounds **7**, **8**, **13**, **14**, and **16**.

Compound solvent	1-H ($J_{1,2}$) ($J_{1,3}$)	2-H ($J_{2,3}$)	3-H	1′-H ($J_{1',2'_{ax}}$) ($J_{1',2'_{eq}}$)	7-H	3′-H ($J_{2'_{ax},3'}$) ($J_{2'_{eq},3'}$)	9-OH	14-H	5′-H ($J_{4'_{ax},5'}$) ($J_{4'_{eq},5'}$)	OMe	OAc	6-OH, 11-OH
13	7.96	7.44	7.35	5.58	5.23	4.95	4.57	2.42	4.15	4.07	1.98	13.18, 13.92
($CDCl_3$)	(7.6)	(8.5)		(3.62)		(12.1)			(11.50)			
	(0.9)			(<1.0)		(4.11)	s	s	m	s	s	s, s
	dd	t	dd	br d	s	m						
7	7.96	7.74	7.33	5.58	5.24	3.95	4.76	2.41	4.10	4.05		13.19, 13.92
($CDCl_3$)	(7.8)	(8.6)		(3.60)		(11.43)			(11.05)			
	(1.0)			(1.0)		(3.98)			(4.58)			
	dd	t	dd	br d	s	m	s	s	m	s	s	s, s
14	7.97	7.74	7.36	5.57	5.21	4.99	4.50	4.90	4.08	4.08	1.98	13.11, 13.89
($CDCl_3$)	(7.8)	(8.4)		(3.86)		(12.05)			(11.59)			
	(0.9)			(1.0)		(4.43)			(4.61)			
	dd	t	dd	br d	s	m	s	s	m	s	s	s, s
16	8.02	7.68	7.38	5.83	5.40	4.43	6.57	5.34	4.50	3.92	—	13.54, 14.56
(C_5D_5N)	(7.7)	(8.5)		(3.80)		(12.07)			(11.5)			
	(0.9)			(<1.0)		(4.07)			(3.55)			
	dd	t	dd	br d	m	m	s	s	m	s		s, s
8	8.05	7.76	7.45	5.81	5.38	4.40	5.30	4.50	3.99			
(C_5D_5N)	(7.6)	(8.5)		(3.88)		(12.54)			(11.55)	—	—	—
	(0.9)			(<1.0)		(4.43)			(4.03)			
	dd	t	dd	br d	m	m	s	m	s			

Table 3. (Continued)

Compound (solvent)	10-H_{eq} ($J_{8_{eq},10_{eq}}$)	10-H_{ax} ($J_{10_{eq},10_{ax}}$)	8-H_{eq} ($J_{8_{eq},8_{ax}}$)	8-H_{ax} ($J_{7,8_{ax}}$)	2'-H_{eq}	2'-H_{ax} ($J_{2'_{eq},2'_{ax}}$) ($J_{4'_{eq},3'}$)	4'-H_{eq} ($J_{4'_{eq},4'_{ax}}$)	4'-H_{ax} ($J_{3',4'_{ax}}$)	6'-H ($J_{5',6'}$)	$SiCMe_3$	$SiMe_2$
13	3.17	2.81	2.35	2.13	2.08	1.67	2.07	1.34	1.26	—	—
($CDCl_3$)	(1.50)	(18.91)	(14.78)	(4.05)		(12.50)	(12.21) (4.7)	(11.5)	(6.24)		
	dd	d	dt	br d	m	ddd	m	ddd	d		
7	3.19	2.88	2.35	2.13	2.08	1.58	2.03	1.33	1.28		
($CDCl_3$)	(1.51)	(18.94)	(14.78)	(4.00)		(12.75)	(11.6) (4.58)	(11.59)	(6.22)	—	—
	dd	d	dt	br d	m	ddd	m	ddd	d		
14	3.11	2.80	2.35	2.20	2.11	1.66	2.10	1.35	1.28	0.98	0.16
($CDCl_3$)	(1.50)	(18.92)	(14.86)	(3.97)		(12.4)	(12.1) (4.61)	(11.59)	(6.2)		
	br d	d	dt	br d	m	ddd	m	ddd	d	s	s
16	3.51	3.35	2.78	2.41	2.58	1.92	2.2	1.60	1.32	1.00	0.19
(C_5D_5N)	(18.54)		(14.48)	(4.85)		(12.70)	(12.42) (4.33)		(11.8)	(6.27)	
	br d	d	dt	dd	dd	ddd	dt	ddd	d	s	s
8	3.49		2.80	2.46	2.58	1.92	2.19	1.59	1.23		
(C_5D_5N)	(14.58)		(5.07)		(12.71)	(12.82)	(11.82) (4.03)		(6.25)	—	—
	dd		dd	dd	dddd	dt	ddd				

δ ppm, J = Hz.

3,4-di-*O*-acetyl-L-rhamnal[11]. The 4-deoxy-glycal **9** treated with dry hydrogen chloride gave glycosyl chloride **10**, which was used immediately for coupling with proper aglycone.

Initially, glycosyl chloride **10** was coupled with daunomycinone (**11**) in methylene dichloride solution in the presence of mercuric bromide, yellow mercuric oxide and molecular sieves 3Å. Compound **13** was isolated as a major product; however, other compounds were also present in the reaction mixture. No further attempts were made to purify and identify these byproducts. The low values of $J_{1',2'_{eq}}$ and $J_{1',2'_{ax}}$ (<1.0 and 3.6 Hz, respectively) indicate an equatorial orientation of proton 1-H, therefore, an α configuration of analogue **13** (Table 3). 3'-Acetoxy-4'-deoxydaunorubicin **13** was then deacetylated in standard conditions with sodium methoxide in methanol to 3'-deamino-4'-deoxy-3-hydroxydaunorubicin **7**.

In order to prepare 3'-hydroxyesorubicin (**8**), 14-*O*-*tert*-butyldimethylsilyladriamycinone (**12**) was reacted with glycosyl chloride **10** in conditions similar to that described above. The main product of the reaction was isolated with 51% yield after column chromatography. NMR data (Table 3) clearly indicate α anomeric orientation of the aglycone and confirm the proposed structure. The deacetylation with sodium methoxide gave 3'-hydroxy-14-*O*-*tert*-butyldimethylsilyl anthracycline **16**, which was confirmed by disappearance of acetyl group signals in ^1H and ^{13}C NMR. Intermediate **16** was finally desilylated with

Table 4. ^{13}C NMR data for compounds **7**, **8**, **13**, **14**, and **16**.

C-Atom	Compound				
	13	**7**	**14**	**16**	**8**
1	119.76	119.39	119.73	119.64	119.67
2	135.56	135.28	135.52	135.80	135.72
3	118.45	118.12	118.48	119.48	119.55
4	161.05	160.64	161.01	161.52	161.58
6	156.42	156.14	156.29	156.95	156.97
11	155.85	155.36	155.70	155.71	155.78
5	186.87	186.13	186.79	186.98	187.09
12	186.54	185.85	186.45	186.92	187.03
4a	121.04	120.35	120.90	121.21	121.36
5a	111.42	110.91	111.38	111.85	111.93
11a	111.26	110.72	111.25	111.54	111.62
6a	135.51	134.95	135.46	135.62	135.64
10a	134.57	134.14	134.11	135.01	135.01
12a	134.21	134.14	133.89	134.52	134.65
7	69.95	69.90	70.01	70.69	70.56
8	35.16	33.05	35.79	37.20	37.22
9	76.77	76.77	77.11	77.13	76.96
10	33.45	30.72	31.53	33.89	33.94
13	211.96	211.79	211.08	211.75	214.39
14	24.68	24.58	66.61	66.69	65.66
OMe	56.63	56.31	56.62	56.66	56.69
1'	101.62	101.95	101.75	102.87	102.69
2'	35.35	39.03	33.93	40.64	40.62
3'	66.68	63.46	66.55	63.25	63.28
4'	38.77	42.29	38.75	43.98	43.96
5'	64.90	65.33	64.91	65.65	65.63
6'	21.07	21.19	21.06	21.74	21.62
OAC	21.16		21.19		
C=O	169.97		169.99		
CSi			14.01	18.77	
Me_3CSi			25.88	26.11	
$SiMe_2$			−5.32, −5.38	−5.00, −5.06	

tetrabutylammonium fluoride in dichloromethane solution to 7-*O*-(2,4,6-trideoxy-α-L-*threo*-hexopyranosyl)adriamycinone (**8**, 3'-deamino-3'-hydroxyesorubicin). The proposed structures for all compounds were confirmed by ^1H and ^{13}C NMR data presented in Tables 3 and 4.

Biological Activity

In Vivo Antitumor Activity against P388 Leukemia

Table 1 shows the results of the *in vivo* antitumor activity studies against P388 leukemia in two different experiments. The optimal dose of compounds **7** and **8** was 100 mg/kg. At this dose, the %T/C obtained with **7** was 154 and 250; the %T/C obtained with **8** was >600 in both experiments with 5/5 animals alive on day 60 in Experiment 1 and 4/5 alive in Experiment 2. A dose of 125 mg/kg was toxic for both drugs. Lower doses of compound **8** showed significant activity (%T/C 163 at 25 mg/kg and 418 at 50 mg/kg). Compound **13** was inactive up to a dose of 100 mg/kg. In the same experiments, doxorubicin, at a dose of 10 mg/kg, resulted in a %T/C of 172 and 310 in Experiments 1 and 2, respectively.

In Vitro Cytotoxic Activity against Murine Tumor Cells

Table 2 shows the results of the *in vitro* cytotoxic activity of the three esorubicin analogues and doxorubicin against P388, L1210 and M5076 cells. Compound **7** did not show significant cytotoxicity at concentrations of up to 10 and 25 μg/ml against any of the three cell types. On the other hand, the cytotoxic potential of compound **8** was similar to that of doxorubicin against the three cell lines tested (ID_{50} against P388: 0.42 *versus* 0.35 μg/ml for doxorubicin; ID_{50} against L1210: 0.59 *versus* 0.53 μg/ml for doxorubicin; ID_{50} against M5076: 1.35 *versus* 1.82 μg/ml for doxorubicin). By contrast, compound **13** was significantly less cytotoxic (ID_{50} 14.6 μg/ml against P388, 18.5 μg/ml against L1210 and 4.6 μg/ml against M5076).

Experimental

TLC was performed on precoated plastic sheets (0.2 mm) of silica gel 60 F-254 (E. Merck AG, Darmstadt, West Germany); compounds were detected by spraying the plates with 10% sulfuric acid with subsequent heating. MP's were determined with an Buchi 530 apparatus and are uncorrected. IR spectra were recorded with a Beckman Microlab 250 MX. NMR spectra were recorded for solution in chloroform-*d* (internal standard Me_4Si) with an IBM-Bruker AFT 200 or Nicolet 300-MHz spectrometer. ^{13}C and ^1H assignments were confirmed by 2D experiments using the standard Bruker microprogram COSY. AU and XHCORR.AU. The COSY spectra were acquired in a (1/2K × 1/4K) block of 128 FIDs and XHCORR in a (1K × 1/2K) block of 256 FIDs. Elemental analysis was performed by Atlantic Microlab Inc. Atlanta, GA, U.S.A.

Preparation of Drug Suspensions for Biological Assays

Because of their lack of solubility in water solutions, drug suspensions were used for all *in vitro* and *in vivo* biological assays. Drugs were initially dissolved in pure DMSO. NaCl solution (0.9%) in water was subsequently added to achieve a drug concentration of 1 mg/ml and the suspension was sonicated for 2 minutes in a water bath sonicator. The final suspension contained 1% DMSO and could be used for *in vivo* injections through a 27-gauge needle. Doxorubicin dissolved in 5% glucose in water at a concentration of 1 mg/ml before usage.

In Vitro Cytotoxic Activity against Murine Tumor Cells

P388 and L1210 leukemia cells were obtained from the Tumor Repository, National Cancer Institute, Frederick, MD, and were kept in culture in RPMI-1640 (Cellgro, Mediatech, Washington, D.C.) and supplemented with 15 and 10% fetal calf serum, respectively. M5076 cells were obtained from the

Department of Cell Biology, The University of Texas M. D. Anderson Cancer Center, Houston, TX, U.S.A., and were kept in culture in RPMI-1640 and supplemented with 15% horse serum.

In vitro drug cytotoxicity against the different cell lines was assessed by using the MTT reduction assay, as previously reported[12]. The MTT dye was obtained from Sigma Chemical Company, St. Louis, MO. Cells were plated in 96-well microassay culture plates (2×10^4 cells/well) and grown for 24 hours at 37°C in a 5%-CO_2 incubator. Drugs were then added to the wells to achieve a final drug concentration, ranging from 0.1 to 25 μg/ml (8 wells were used for each different concentration). The same volume of 0.9% NaCl solution in water with 1% DMSO was added to control wells. Wells containing culture medium alone without cells were used as blanks. The plates were incubated at 37°C in a 5%-CO_2 incubator for 72 hours (P388 and L1210 cells) or 24 hours (M5076 cells). When incubation was complete, 15 μl of stock solution of MTT dye in a 0.9% NaCl solution in water were added to each well to achieve a final dye concentration of 0.5 mg/ml. The plate was incubated at 37°C in a 5%-CO_2 incubator for 4 hours. Subsequently, 100 μl of medium was removed from each well from the upper microwell, layer and 100 μl of DMSO was added to solubilize the MTT formazan. Complete solubilization was achieved by placing the plate in a mechanical shaker for 30 minutes at room temperature. The optical density of each well was then measured with a microplate spectrophotometer at a wavelength of 600 nm. The percentage of cell viability was calculated by the following equation:

$$\% \text{ Cell viability} = \frac{\text{Mean optical density of treated wells}}{\text{Mean optical density of control wells}} \times 100$$

The percentage of viability values obtained were plotted against the drug concentrations used, and the drug concentration resulting in a 50%-cell viability (ID_{50}) was calculated from the curve. Experiments were repeated at least three times.

In Vivo Antitumor Activity against P388 Leukemia

BDF_1 male mice weighing between 18 and 22 g were obatined from Harlan, Indianapolis, IN. P388 Cells for *in vivo* experiments were obtained from the Tumor Repository, National Cancer Institute, and kept as an ascitic tumor in BDF_1 mice with weekly transplants. P388 Cells (1×10^6) were inoculated ip on day 0. Treatment was administered ip on day 1 in volumes ranging from 0.1 to 0.8 ml. Groups of five animals each were used. Animals were monitored on a daily basis, and the median survivals for each group were recorded. A wide dose range was used in the initial experiments to identify the dose levels that resulted in an optimal activity without toxic deaths. All animal experiments were approved by the Institutional Committee for Animal Use and Care.

7-*O*-(3-*O*-Acetyl-2,4,6-trideoxy-α-L-*threo*-hexopyranosyl)daunomycinone (**13**)

A solution of 3-*O*-acetyl-1,5-anhydro-2,4,6-trideoxy-L-*threo*-hex-1-enitol (**9**, 235 mg, 1.51 mmol) in dry bezene was treated with dry hydrogen chloride gas for 5 minutes until a more polar product **10** (TLC: Hexane-ethyl acetate, 4:1; Rf 0.1) was formed. Benzene was removed and dichloromethane (10 ml) was added. The solution was poured into a suspension of daunomycinone (**11**, 300 mg, 0.75 mmol), 3Å molecular sieves (3.0 g), mercuric bromide (45 mg) and yellow mercuric oxide (600 mg) in dichloromethane (50 ml). The resulting mixture was stirred for 60 minutes after which an additional 1.0 equiv of glycosyl chloride (**10**, 1.51 mmol) was added, and stirring was continued for 2 more hours until the substrate disappeared. Salts were filtered off, and the filtrate was diluted with dichloromethane (100 ml) and extracted with 10% aqueous potassium iodide (50 ml × 2) and water (50 ml × 2). The organic extract was dried over sodium sulfate and evaporated. The residue showed, on TLC, a major product at Rf 0.37 in toluene-acetone (8:1). The mixture was immediately chromatographed on silica gel (toluene-acetone, 20:1) to give after crystallization (dichloromethane-hexane) **13** (225 mg, 54%); mp 150~155°C; IR ν_{max} (KBr) cm^{-1} 3487 (OH), 1737 and 1718 (CO), 1617 and 1578 (H-bonded quinone), 1411, 1370, 1285, 1236, 1206, 1121, 1032 and 979.

Anal Calcd for $C_{29}H_{30}O_{11} \cdot \frac{1}{2}H_2O$ (554.56): C 61.81, H 5.54.
Found: C 61.46, H 5.49.

7-*O*-(2,4,6-Trideoxy-α-L-*threo*-hexopyranosyl)daunomycinone (**7**)

A solution of **13** (120 mg, 0.22 mmol) in methanol (10 ml) was treated with 0.5 M solution of sodium

methoxide in methanol (0.5 ml). After 90 minutes of stirring at room temperature, the reaction was completed. Dry ice was added and the mixture was diluted with dichloromethane (100 ml) and washed with water (40 ml × 3), dried over sodium sulfate, filtered and evaporated. TLC showed one spot with Rf 0.11 (toluene - acetone, 8 : 1). The product was crystallized from dichloromethane and hexane; yield 83 mg (75%); mp 143 ~ 148°C; IR ν_{max} (KBr) cm^{-1} 3470 (OH), 1713 (CO), 1616 and 1579 (H-bonded quinone), 1411, 1350, 1285, 1207, 1123, 1087, 1031, 991 and 976.

Anal Calcd for $C_{27}H_{28}O_{10} \cdot \frac{1}{2}H_2O$ (512.52): C 62.18, H 5.60.
Found: C 61.79, H 5.40.

14-*O*-*tert*-Butyldimethylsilyl-7-*O*-(3-*O*-acetyl-2,4,6-trideoxy-α-L-*threo*-hexopyranosyl)adriamycinone (**14**)

A solution of glycosyl chloride **10** in dichloromethane (10 ml), prepared by hydrochlorination of hexenitol **9** (295 mg, 1.89 mmol), was added to a suspension of 14-*O*-*tert*-butyldimethylsilyladriamycinone (**12**, 500 mg, 0.95 mmol), mercuric bromide (50 mg), yellow mercuric oxide (750 mg) and 3Å molecular sieves (3.0 g) in dichloromethane (50 ml). The resulting mixture was actively stirred at room temperature until the substrate disappeared (60 minutes). The salts were filtered off and filtrate was diluted with dichloromethane (150 ml) and extracted with 10% aqueous potassium iodide (50 ml × 2) and water (50 ml × 2). The organic extract was dried over sodium sulfate and evaporated. The residue showed, on TLC, a mixture of two major products, Rf 0.55 and 0.72, and two minor products, Rf 0.53 and 0.70 (toluene - acetone, 8 : 1). The mixture was then chromatographed on silica gel (toluene - acetone, 50 : 1) to give **14** (331 mg, 51%). First crystallization (dichloromethane - hexane) of TLC-pure fractions gave analytically pure **14** (133 mg); mp 175 ~ 180°C; IR ν_{max} (KBr) cm^{-1} 3487 (OH), 1733 (CO), 1617 and 1580 (H-bonded quinone), 1412, 1366, 1285 (SiMe), 1109, 991, 978 and 838 (CSi).

Anal Calcd for $C_{35}H_{44}O_{12}Si$ (684.82): C 61.39, H 6.48.
Found: C 61.31, H 6.50.

14-*O*-*tert*-Butyldimethylsilyl-7-*O*-(2,4,6-trideoxy-α-L-*threo*-hexopyranosyl)adriamycinone (**16**)

To a solution of **14** (150 mg, 0.22 mmol) in methanol (10 ml), sodium methoxide (0.5 M) in methanol (0.5 ml) was added. After 40 minutes reaction was terminated by adding dry ice. The mixture was then diluted with dichloromethane (100 ml), washed with water (50 ml × 3), dried over sodium sulfate, filtered and evaporated. TLC showed one spot having Rf 0.19 (toluene - acetone, 8 : 1). The product was then crystallized from dichloromethane and hexane to give analytically pure **16**; yield 101 mg (73%); mp 220°C; IR ν_{max} (KBr) cm^{-1} 3475 (OH), 1732 (CO), 1618 and 1580 (H-bonded quinone), 1458, 1442, 1430, 1412, 1285 (SiMe), 1207, 1107, 993, 976, 950 and 838 (CSi).

Anal Calcd for $C_{33}H_{42}O_{11}Si$ (642.78) C 61.66, H 6.59.
Found: C 61.58, H 6.59.

7-*O*-(2,4,6-Trideoxy-α-L-*threo*-hexopyranosyl)adriamycinone (**8**, 3'-deamino-3'-hydroxyesorubicin)

To a solution of **16** (100 mg, 0.155 mmol) in oxolane (10 ml), dichloromethane (4 ml) and pyridine (1.0 ml) were added and stirred with tetrabutylammonium fluoride (0.3 ml of a 1-M solution in oxolane). After completion of the reaction (TLC: Toluene - acetone, 3 : 1; Rf 0.25) in 30 minutes, the mixture was diluted with dichloromethane (150 ml) and washed with 0.1 N HCl (40 ml), 5% aqueous $NaHCO_3$ (40 ml) and water (50 ml × 3). The organic layer was dried (sodium sulfate), and the residue, after evaporation was purified by dissolving it in dichloromethane. It was precipitated by adding ethyl ether. The solid was washed with ether and dried to afford pure compound **8**; yield 61 mg (74.4%); mp 160 ~ 163°C; IR ν_{max} (KBr) cm^{-1} 3457 (OH), 1720 (CO), 1618 and 1578 (H-bonded quinone), 1438, 1410, 1208, 1181, 1122, 1019 and 993.

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