3′-HYDROXYESORUBICIN HALOGENATED AT C-2′

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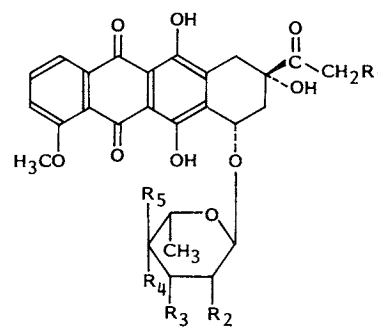
New 3′-deamino-3′-hydroxy-2′-iodoesorubicin analogues were synthesized using optically active 4,6-dideoxyhex-1-enitol (**7**) as starting material. Direct coupling of daunomycinone (**8**) and 14-*O*-*tert*-butyldimethylsilyladriamycinone (**9**) with glycal **7** in the presence of *N*-iodosuccinimide gave 2′-iodo analogues **10** and **12**. Deprotection of compounds **10** and **12** led to compounds **11** and **14**, the 2′-iodinated, fully unblocked 4′-deoxy-3′-hydroxy congeners of daunorubicin (**2**) and doxorubicin (**1**). 2′-Iodo-3′-hydroxyesorubicin (**14**) showed cytotoxic activity similar to that of doxorubicin *in vitro* and higher antitumor activity against L-1210 leukemia than doxorubicin *in vivo*.

The toxic side effects of doxorubicin (**1**), an important anticancer agent, are the factors limiting clinical use of this drug. Therefore, substantial efforts have been directed toward synthesis of novel anthracycline antibiotics exhibiting reduced cardiotoxicity and broader spectrum of activity.

Glycosidic cleavage is an important metabolic process for this group of compounds. An interesting concept that proposes stabilization of the glycosidic bond by utilizing inductive effects of substituents at C-2′ in the sugar portion was put forth and led to the synthesis of 2′-iodo-, 2′-bromo-, and 2′-chloro-anthracyclines[1~4]. Such studies clearly indicated that only analogues with axially oriented halogens at C-2′ showed activity. The usefulness of this approach and the observed effect of configuration at C-2′ on activity were confirmed by synthesis and detailed biological evaluation of 2′-fluoroanthracyclines and their derivatives[5~7], as well as the synthesis of other 2′-iodoanthracyclines modified at the aglycon portion[8]. Our previous studies showed convincingly that anthracyclines (**4**) with an α-L-*manno* configuration were consistently more active than analogues (**5**) with an α-L-*talo* configuration[1~3]. This observation, and the fact that esorubicin[9] is a highly active doxorubicin analogue deoxygenated at C-4′ which is currently under clinical evaluation[10,11], prompted our interest in the synthesis of 2′-halogenated anthracyclines modified at C-4′. Our previous work on 3′-hydroxyesorubicin (**3**)[12] warranted easy access to 2′-halo-analogues deoxygenated at C-4′ and offered the possibility of direct comparison with 2′-unsubstituted congeners. The primary purpose of this work is the synthesis and preliminary biological evaluation of 3′-deamino-4′-*epi*-2′-iodo esorubicin analogues.



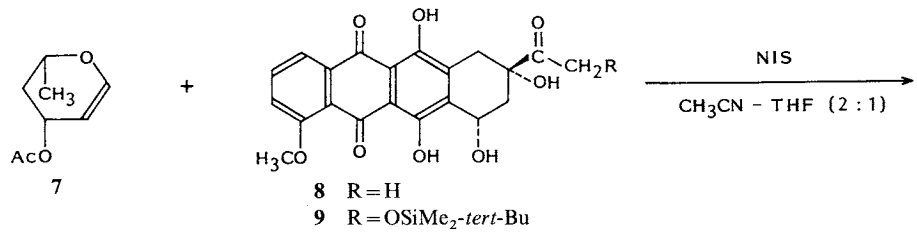
1	R_1=OH	R_2=H	R_3=NH_2	R_4=OH	R_5=H
2	R_1=H	R_2=H	R_3=NH_2	R_4=OH	R_5=H
3	R_1=OH	R_2=H	R_3=OH	R_4=H	R_5=H
4	R_1=H	R_2=I	R_3=OAc	R_4=H	R_5=OAc
5	R_1=H	R_2=I	R_3=OAc	R_4=OAc	R_5=H
6	R_1=H	R_2=F	R_3=OAc	R_4=OAc	R_5=H

Chemical Synthesis

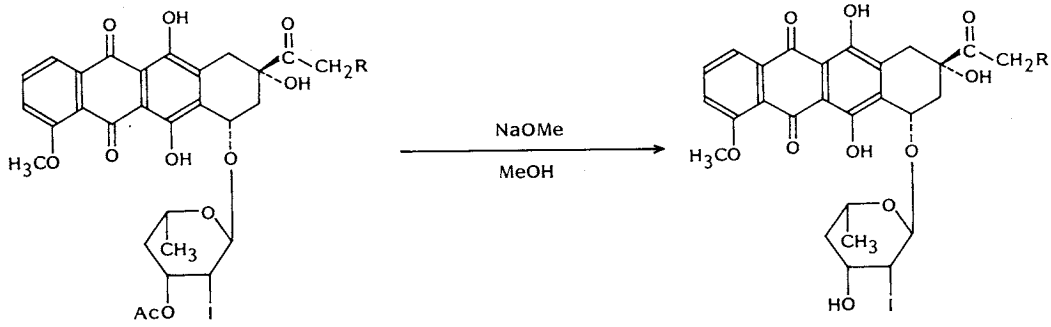
The most convenient route to 2′-iodoglycosides utilizes the electrophilic addition of *N*-iodosuccinimide (NIS)/alcohol to double bonds of hex-1-

enitols[13]. The glycal **7**, used previously in the synthesis of 3'-hydroxyesorubicin[12] was considered by us to be the most suitable substrate for synthesis of 2'-iodo-4'-deoxy analogues. The 3-*O*-acetyl-4-deoxy-L-rhamnal (**7**)[14] prepared in six steps from 3,4-di-*O*-acetyl-L-rhamnal was reacted with daunomycinone (**8**) and NIS in acetonitrile - oxolane (2 : 1) to give two products, as judged by thin-layer chromatography (TLC). The main product (**10**) was isolated by column chromatography with 75% yield. ^{1}H nuclear magnetic resonance (NMR) data analysis revealed the values of coupling constant $J_{1',2'}=0.3$ Hz and $J_{2',3'}=3.9$ Hz, which clearly indicated equatorial orientation of 1'-H and 2'-H protons. Based on these data, the α-L-*lyxo* configuration was assigned for compound **10**. The ^{13}C NMR further confirmed the proposed structure for **10**. 4'-Deoxy-2'-iodo-3'-acetoxydaunorubicin (**10**) was then deacetylated with sodium methoxide to more polar 4-deoxy-2'-iodo-3'-hydroxydaunorubicin (**11**), which showed lack of acetyl group signal in ^{1}H NMR.

2'-Iodo-3'-hydroxyesorubicin analogues were prepared by coupling glycal **7** with 14-*O*-*tert*-butyldimethylsilyladriamycinone (**9**). Reaction of **7** with aglycone **9** in the presence of NIS gave fully

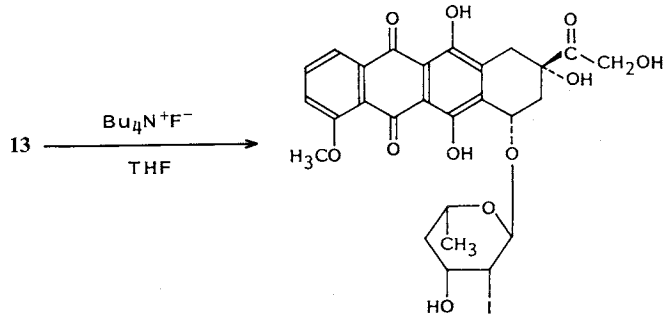


7 + **8** R=H; **9** R=OSiMe$_2$-*tert*-Bu



10 R=H; **12** R=OSiMe$_2$-*tert*-Bu

11 R=H; **13** R=OSiMe$_2$-*tert*-Bu



14

blocked 2′-iodo analogue **12** with a yield of 86%. The observed cou ling constants were similar to that of compound **10**, indicating α-L-*lyxo* configuration of the sugar portion Routine deacetylation of compound **12** with sodium methoxide was carried with 79% yield to 3′-hydroxy compound **13**. The *tert*-butyldimethylsilyl group was then removed by treatment of com ound **13** with tetrabutylammonium fluoride. The desired 2′-iodo-3′-hydroxyesorubicin (**14**) was obtained, ith 70% yield. This step was closely monitored by TLC (toluene-acetone, 4:1). The extension of the rea ion time beyond the end point led to partial decomposition of product **14**. Table 3 shows ^{1}H NMR da of compounds **10**~**14**.

Biological Activity

In Vitro Cytotoxic Activity against Murine Tumor Cells

Table 1 shows the results of the *in vitro* cytotoxic activity of con ounds **10**, **11**, **14**, and doxorubicin against P-388, L-1210, and M-5076 cells. Compound **10** was the least otent of the three tested, with 50% inhibition dose (ID_{50}) values 4- to 5-fold higher than those of compour **11**, compound **14**, and doxorubicin in all cell line systems used. Compound **14** was slightly more cytotox than compound **11** against all cell lines (ID_{50} against P-388 0.41 vs. 0.66 μg/ml, against L-1210 0.55 vs 0.75 μg/ml, and against M-5076 1.3 vs. 1.6 μg/ml). The cytotoxicities of compound **14** and doxorubicin re not significantly different (ID_{50} against P-388 0.41 vs. 0.35 μg/ml, against L-1210 0.55 vs. 0.53 μg/ml, a d against M-5076 1.3 vs. 1.8 μg/ml).

In Vivo Antitumor Activity against P-388 and L-1210 Leukemia

Table 2 shows the results of the *in vivo* antitumor activity studies against P-388 and L-1210 leukemia. Compounds **11** and **14** were tested against both tumor models. Against P-388 leukemia, both compounds had similar and dose-related antitumor activity (median survival time expressed as a percentage of control (% T/C) at a dose of 100 mg/kg: 287 and 250, respectively). Doxorubicin, at the optimal dose of 10 mg/kg, resulted in a % T/C of 241. Compounds **11** and **14** appeared to be also less toxic than doxorubicin since no toxicity was observed at doses up to 100 mg/kg, whereas doxorubicin was toxic at a dose of 15 mg/kg (Table 2). Compound **10** was only tested against P-388 leukemia and did not show any antitumor

Table 1. *In vitro* cytotoxic activity of 4′-deoxy-3′-hydroxy-2′-iodo-anthracyclines against murine tumor cells[a].

Compound	ID_{50}[b] (μg/ml)		
	P-388	L-1210	M-5076
10	2.36±0.51	2.35±0.15	9.10±0.10
11	0.66±0.05	0.75±0.15	1.6 ±0.20
14	0.41±0.10	0.55±0.06	1.3 ±0.60
Doxorubicin	0.35±0.07	0.53±0.04	1.8 ±1.00

[a] MTT, reduction assay; 10,000 cells/well; drug incubation: 72 hours (P-388, L-1210), 24 hours (M-5076).
[b] ID_{50}, 50% inhibition dose (mean value from at least 3 experiments±SD).

Table 2. *In vivo* antitumor activity of 4′-deoxy-3′-hydroxy-2′-iodo-anthracyclines against experimental murine leukemias.

Drug	Dose (mg/kg)	(%) T/C[a]	
		P-388[b]	L-1210[b]
10	25.0	100	
	50.0	100	
	100.0	112	
11	6.25		128
	12.5		142
	25.0	150	142
	50.0	162	
	100.0	287	
14	6.25		185
	12.5		214
	25.0	160	>300
	50.0	190	
	100.0	250	
Doxorubicin	10.0	241	200
	15.0	Toxic	Toxic

[a] % T/C, median survival time expressed as percent of control.
[b] Treatment ip on day 1.

activity up to a dose of 100 mg/kg, whereas, 3′,4′-di-*O*-acetoxy-4′-*epi*-2′-iodo-daunorubicin (**4**) has been shown to be more active than doxorubicin[3]. The α-L-*talo* isomer of 2′-iodo-daunorubicin analogue **5** tested previously showed activity similar to daunorubicin (**2**)[3]. Compound **14** seemed to be less active *in vivo* against P388 leukemia than its non-halogenated analogue **3** (3′-hydroxy-esorubicin)[12]. These findings suggest that for the daunorubicin series of 2′-halogenated analogues, activity is enhanced by the presence of the hydroxy or acetoxy group in preferable equatorial orientation, *trans* to the substituent at C-2′. Similar structural requirements might be important for the activity of doxorubicin congeners. However, further studies including more detailed biological evaluation should be done to confirm these propositions.

Against L-1210 leukemia, the highest dose tested for compounds **11** and **14** was 25 mg/kg. At this dose, compound **14** was significantly more active than compound **11** and doxorubicin (% T/C >300 vs. 142 vs. 200).

Experimental

TLC was performed on precoated plastic sheets (0.2 mm) of Silica gel 60 F254 (E. Merck AG, Darmstadt, West Germany); compounds were detected by first spraying with 10% sulfuric acid and subsequently heating the plates. Melting points were determined with a Buchi 530 apparatus and are uncorrected. Infrared (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 ^{1}H assignments were confirmed by two-dimensional (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. Mass spectral determinations were performed by the Midwest Center for Mass Spectrometry, a National Science Foundation Regional Instrumentation Facility (Grant No. CHE 8620177). The samples were analyzed by FAB on a Kratos-MS-50 Triple Analyzer mass spectrometer. 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 dimethyl sulfoxide (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 (Adria Laboratories) was dissolved in 5% glucose in water at a concentration of 1 mg/ml before usage.

In Vitro Cytotoxic Activity against Murine Tumor Cells

P-388 and L-1210 leukemia cells were obtained from the Tumor Repository, National Cancer Institute, Frederick, MD, and were kept in culture in RPMI-1640 medium (Cellgro, Mediatech, Washington, D.C.) and supplemented with 15 and 10% fetal calf serum, respectively. M-5076 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 16% horse serum.

In vitro drug cytotoxicity against the different cell lines was assessed by using the MTT reduction assay, as previously reported[15]. The MTT dye was obtained from Sigma Chemical Company, St. Louis, MO, U.S.A. Cells were plated in 96-well microassay culture plates (1×10^4 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 (P-388 and L-1210 cells) or 24 hours (M-5076 cells). When incubation was complete,

Table 3. ^{1}H NMR data for compounds **10**~**14**.

Compound (solvent)	1-H ($J_{1,2}$)	2-H	3-H ($J_{2,3}$)	1′-H	7-H	2′-H ($J_{2',3'}$)	3′-H	9-OH	14-H	5′-H	OMe
10	8.03	7.79	7.39	5.79	5.23	4.53	4.19	4.19	2.42	4.19	4.09
($CDCl_3$)	(7.6)		(8.6)			(3.87)					
	(0.7)										
	dd	t	dd	br s	m	dd	m	s	s	m	s
11	8.03	7.80	7.41	5.84	5.25	4.56	2.93	4.26	2.42	4.15	4.10
($CDCl_3$)	(7.7)		(8.5)								
	(1.0)										
	dd	t	dd	br s	dd	m	m	s	s	m	s
12	8.02	7.79	7.40	5.79	5.21	4.52	4.17	4.17	4.89	4.17	4.12
($CDCl_3$)	(7.6)		(8.5)			(3.89)					
	(0.9)										
	dd	t	dd	br s	m	d	m	s	m	m	s
13	8.02	7.80	7.40	5.82	5.22	4.57	2.92	4.23	4.89	4.18	4.10
($CDCl_3$)	(7.8)		(8.5)			(3.21)					
	(0.9)										
	dd	t	dd	br s	m	dd	m	s	m	m	s
14	8.02	7.68	7.38	6.21	5.36	3.90	4.70	5.05	5.15	3.65	3.96
(C_5D_5N)	(7.4)		(8.3)			(4.48)					
	(0.6)										
	dd	dt	dd	br s	m	d	m	s	m	m	s

Compound (solvent)	10-H_{eq} ($J_{8eq,10eq}$)	10-H_{ax} ($J_{10ax,10eq}$)	8-H_{eq} ($J_{8eq,8ax}$)	8-H_{ax} ($J_{7,8ax}$)	4′-H_{eq}; 4′-H_{ax}	6′-H ($J_{5',6'}$)	6-OH, 11-OH	OAc	$SiCMe_3$	$SiMe_2$
10	3.24	2.90	2.3	2.17	1.7~1.9	1.31	13.99, 13.26	2.03		
($CDCl_3$)	(1.5)	(18.9)	(15.1)			(6.3)			—	—
	dd	d	dt	m	m	d	s	s		
11	3.25	2.95	2.35	2.16	1.6~1.8	1.30	14.04, 13.29	—	—	—
($CDCl_3$)	(1.8)	(18.9)	(14.9)	(4.27)		(6.3)				
	dd	d	dt	dd	m	d	s			
12	3.20	2.91	2.35	2.19	1.7~1.9	1.31	13.96, 13.22	2.03	0.96	0.15
($CDCl_3$)	(1.2)	(18.9)	(15.0)			(6.3)				
	dd	d	dt	m	m	d	s	s	s	s
13	3.27	2.95	2.35	2.21	1.7~1.8	1.31	14.0, 13.22	—	0.97	0.14
($CDCl_3$)	(1.3)	(18.9)	(15.0)	(4.10)		(6.2)				
	dd	d	dt	dd	m	d	s		s	s
14		3.30	2.47	2.09	1.7~1.9	1.25	14.61, 13.52	—	—	—
(C_5D_5N)			(14.5)	(5.3)		(6.3)				
		m	br d	m	m	d	s			

15 μl of stock solution of MTT dye in a 0.9% NaCl solution in water was 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 ID_{50} was calculated from the curve. Experiments were repeated at least three times.

In Vivo Antitumor Activity against P-388 Leukemia

BDF1 male mice weighing between 18 and 22 g were obtained from Harlan (Indianapolis, IN., U.S.A.). P-388 cells for *in vivo* experiments were obtained from the Tumor Repository, National Cancer Institute, and kept as an ascitic tumor in BDF1 mice with weekly transplants. P-388 cells (1×10^6) were inoculated intraperitonially (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-iodo-2,4,6-trideoxy-α-L-*lyxo*-hexopyranosyl)daunomycinone (**10**)

N-Iodosuccinimide (83 mg, 0.37 mmol) was added with stirring to a solution of daunomycinone (100 mg, 0.25 mmol) and 3-*O*-acetyl-4-deoxy-L-rhamnal (**11**; 58 mg, 0.37 mmol) in dry acetonitrile (2.0 ml) and oxolane (1 ml) at 0°C. The resulting mixture was stirred for 15 minutes at 0°C; and then, after 12 hours at 25°C, an additional 0.5 of the initial amount of 3-*O*-acetyl-4-deoxy-L-rhamnal (28 mg, 0.18 mmol) and *N*-iodosuccinimide (41 mg, 0.18 mmol) were added, and the mixture was stirred until disappearance of substrate (24 hours) on TLC (toluene - acetone, 4 : 1). Dichloromethane (20 ml) was added and the resulting solution was washed with 10% aqueous sodium thiosulfate (2×15 ml) and then with water (3×20 ml). The extract was dried with sodium sulfate, filtered, and evaporated. Red solid residue was prepurified by crystallization from dichloromethane - hexane. TLC (toluene - acetone, 20 : 1) revealed presence of a major (Rf 0.16) and a minor (Rf 0.24). Major product (**10**) was isolated by column chromatography on silica gel (10 g) with toluene - acetone (20 : 1) and precipitated from a solution of ethyl ether - dichloromethane upon addition of hexane; yield, 130 mg (75%); mp 126~128°C; IR ν_{max} (KBr) cm^{-1} 3480 (OH), 1741 and 1718 (CO), 1618 and 1578 (H-bonded quinone), 1412, 1375, 1282, 1232, 1207, 1116, 1034, and 988. ^{13}C NMR ($CDCl_3$) δ 211.4 (C-13), 187.0, 186.8 (C-5, C-12), 169.6 (AcO), 161.2 (C-4), 156.3, 155.8 (C-6, C-11), 135.7 (C-2), 135.6, 135.5, 134.4 (C-6a, C-10a, C-12a), 120.8 (C-4a), 119.8 (C-1), 118.5 (C-3), 111.6, 111.5 (C-5a, C-11a), 105.9 (C-1'), 76.6 (C-9), 70.8, 66.7, 66.2 (C-7, C-3', C-5'), 56.7 (OMe), 35.3, 35.2, 33.4, 32.5 (C-8, C-4', C-10, C-2'), 24.7 (C-14), 21.0 (C-6', AcO).

Anal Calcd for $C_{29}H_{29}IO_{11}$ (680.4): C 51.19, H 4.30, I 18.65.
Found: C 50.95, H 4.36, I 18.55.

7-*O*-(2-Iodo-2,4,6-trideoxy-α-L-*lyxo*-hexopyranosyl)daunomycinone (**11**)

A solution of compound **10** (40 mg, 0.058 mmol) in methanol (5.0 ml) was treated with 0.5 M solution of sodium methoxide in methanol (0.35 ml). After 40 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 (50 ml × 3), dried (sodium sulfate), filtered, and evaporated. TLC (toluene - acetone, 8 : 1) showed one spot having Rf 0.15. The product was crystallized from dichloromethane and ethyl ether: yield, 25 mg (66%); mp 145~148°C; IR ν_{max} (KBr) cm^{-1} 3445 (OH), 1717 (CO), 1618 and 1579 (H-bonded quinone), 1412, 1248, 1233, 1207, 1117, 1033, and 989. ^{13}C NMR ($CDCl_3$) δ 211.1 (C-13), 186.2, 186.0 (C-5, C-12), 160.5 (C-4), 155.8, 155.0 (C-6, C-11), 135.3 (C-2), 134.7, 134.0, 133.5 (C-6a, C-10a, C-12a), 120.2 (C-4a), 119.1

(C-1), 118.2 (C-3), 110.8, 110.6 (C-5a, C-11a), 105.2 (C-1'), 75.8 (C-9), 70.0, 65.9, 62.8 (C-7, C-3', C-5'), 56.1 (OMe), 41.2, 38.2, 34.9, 32.3 (C-8, C-10, C-2', C-4'), 24.0 (C-14), 20.5 (C-6'); FAB-MS *m/z* 661 (M+Na), 639 (M+H), 638 (M, $C_{27}H_{27}IO_{10}$); exact mass calcd for $C_{27}H_{27}IO_{10}$: *m/z* 638.06489; found: *m/z* 638.0656.

7-*O*-(3-*O*-Acetyl-2-iodo-2,4,6-trideoxy-α-L-*lyxo*-hexopyranosyl)-14-*O*-*tert*-butyldimethylsilyladriamycinone (**12**)

N-Iodosuccinimide (160 mg, 0.71 mmol) was added with stirring to a solution of compound **9** (250 mg, 0.473 mmol) and 3-*O*-acetyl-4-deoxy-L-rhamnal (**7**, 110 mg, 0.70 mmol) in dry acetonitrile (4.0 ml) and oxolane (2.0 ml) at 0°C. The resulting mixture was stirred for 15 minutes at 0°C, and, after 12 hours at 25°C, and additional 0.5 of the initial amount of 3-*O*-acetyl-4-deoxy-L-rhamnal (55 mg, 0.35 mmol) and *N*-iodosuccinimide (80 mg, 0.36 mmol) were added, and the mixture was stirred until disappearance of the substrate (24 hours) on TLC (toluene-acetone, 8:1). A work up similar to that for compound **10** gave, after column chromatography (toluene-acetone, 40:1), a major product (**12**): yield, 330 mg, (86%) and a minor fraction 20 mg (5% yield). Further purification of **12** by crystallization afforded 285 mg (74%) of red crystals; mp 145~150°C; IR ν_{max} (KBr) cm^{-1} 3501 (OH), 1736 (CO), 1618 and 1579 (H-bonded quinone), 1459, 1443, 1412, 1376, 1283 (SiMe), 1110, 1025, 989, 974 and 838 (CSi).

Anal Calcd for $C_{35}H_{43}IO_{12}Si \cdot H_2O$ (810.7): C 50.73, H 5.47.
Found: C 50.70, H 5.29.

7-*O*-(2-Iodo-2,4,6-trideoxy-α-L-*lyxo*-hexopyranosyl)-14-*O*-*tert*-butyldimethylsilyladriamycinone (**13**)

To a solution of **12** (200 mg, 0.246 mmol) in methanol (10.0 ml), 0.5 M sodium methoxide in methanol (1.5 ml) was added with stirring. After 90 minutes, the reaction was terminated by adding dry ice. Mixture was then diluted with dichloromethane (100 ml) and washed with water (3×50 ml), dried with sodium sulfate, filtered, and evaporated (170 mg, 89.6%). TLC (toluene-acetone, 8:1) showed one spot having Rf 0.25. Product was then crystallized from dichloromethane and hexane to give analytically pure compound **13**; yield, 150 mg (79%); mp 190~192°C; IR ν_{max} (KBr) cm^{-1} 3510 (OH), 1745 (CO), 1624 and 1585 (H-bonded quinone), 1291 (SiMe), 1120 and 845 (CSi); ^{13}C NMR ($CDCl_3$) δ 210.7 (C-13), 187.6, 186.7 (C-5, C-12), 161.2 (C-4), 156.2, 155.7 (C-6, C-11), 135.7 (C-2), 135.7, 134.1, 133.3 (C-6a, C-10a, C-12a), 119.9 (C-4a), 119.9 (C-1), 118.6 (C-3), 111.7, 111.5 (C-5a, C-11a), 105.6 (C-1'), C-9 (overlap with $CDCl_3$ signals), 70.7, 66.7, 66.5, 64.21 (C-3', C-5', C-7, C-14), 56.7 (OMe), 41.8, 39.2, 35.7, 33.9 (C-4', C-2', C-8, C-10), 25.9 (Me_3CSi), 21.0 (C-6'), 18.6 (Me_3CSi), -5.4, -5.3 ($SiMe_2$); exact mass calcd for $C_{33}H_{41}IO_{11}Si+K$ (M+K): *m/z* 807.11016; found: *m/z* 807.1061.

7-*O*-(2-Iodo-2,4,6-trideoxy-α-L-*lyxo*-hexopyranosyl)adriamycinone (**14**)

Tetrabutylammonium fluoride (0.25 ml of a 1 M solution in oxolane) was added with stirring to a solution of compound **13** (110 mg, 0.143 mmol) in oxolane (10 ml), dichloromethane (4 ml), and pyridine (0.07 ml). After completion of reaction (TLC, toluene-acetone, 4:1) at 20 minutes, mixture was diluted with dichloromethane (150 ml) and washed with 0.1 N HCl (50 ml), 5% aq $NaHCO_3$ (50 ml) and water (3×50 ml). The organic layer was dried (sodium sulfate), and the residue after evaporation was purified by dissolution in oxolane-dichloromethane and precipitation by addition of ethyl ether. The solid was washed with ether and dried to afford pure compound **14**; yield, 62 mg (70%); mp 155~160°C; IR ν_{max} (KBr) cm^{-1} 3459 (OH), 1718 (CO), 1616 and 1578 (H-bonded quinone), 1439, 1427, 1410, 1120, 1018, and 989; ^{13}C NMR ($CDCl_3$) δ 213.5 (C-13), 186.9, 186.7 (C-5, C-12), 161.2 (C-4), 156.0, 155.5 (C-6, C-11), 135.8 (C-2), 135.5, 135.4, 133.0 (C-6a, C-10a, C-12a), 119.9 (C-4a), 119.9 (C-1), 118.6 (C-3), 111.7, 111.6 (C-5a, C-11a), 105.6 (C-1'), 76.6 (C-9), 70.4, 66.9, 65.4, 64.2 (C-7, C-3', C-5', C-14), 56.7 (OMe), 41.5, 39.1, 35.6, 33.9 (C-4', C-2', C-10, C-8), 21.06 (C-6'); FAB-MS *m/z* 676 (M+Na), 655 (M+H), 654 (M, $C_{27}H_{27}IO_{11}$); exact mass calcd for $C_{27}H_{27}IO_{11}$: *m/z* 654.05981; found: *m/z* 654.0621.

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