3′-DEAMINO-4′-EPI-3′-HYDROXY-DAUNORUBICIN AND -DOXORUBICIN

SYNTHESIS AND ANTITUMOR ACTIVITY

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3′-Deamino-4′-epi-3′-hydroxy-daunorubicin (**11**) and -doxorubicin (**14**) have been synthesized. In the *in vivo* murine P-388 lymphocytic leukemia assay, these two compounds were more active than daunorubicin (**1**) and doxorubicin (**2**), respectively. Comparative studies in the P-388 assay indicated 3′-deamino-3′-hydroxydoxorubicin (**3**) to be more active than its 4′-epimer **14**.

Previous studies[1,2] from this laboratory have demonstrated that replacement of the amino group in daunorubicin[3] (**1**) and doxorubicin[3] (**2**) by a hydroxyl or acetoxyl group generates analogs[1,2] having greater *in vivo* activity in animal screens than is shown by the parent antibiotics. The recently synthesized 3′-deamino-3′-hydroxydoxorubicin (**3**) showed high activity and increased potency in the murine P-388 test[2]. This fact, together with the knowledge that epimerization at C-4′ often causes significant changes in activity[1,3], prompted the synthesis of 3′-deamino-4′-epi-3′-hydroxy-daunorubicin (**11**) and -doxorubicin (**14**).

Chemical Synthesis

Compounds **11** and **14** were prepared* by using a modified version of the KOENIGS-KNORR conditions for coupling of the glycosyl chloride[5] **7** with the aglycons **4** and **6**. Glycosidic coupling using silver trifluoromethanesulfonate led to a substantial proportion of the 2,3-unsaturated derivative[1] **9**, and compound **8** was isolated in only 14% yield. The configuration of **8** was assigned on the basis of ^{1}H NMR data. The values of $J_{1',2'_{ax}}$ and $J_{1',2'_{eq}}$ of 4.3 and 1.0 Hz, respectively, clearly confirmed that compound **8** is, as expected, the α-anomer; its ^{13}C NMR spectrum provides further full support of the proposed structure.

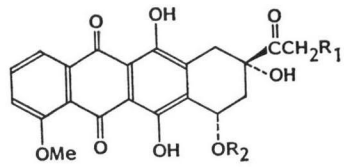
Use of the coupling procedure employing mercuric bromide, yellow mercuric oxide, and 4 Å molecular sieves gave in 77% yield a mixture **10** containing the α- and β-anomers in 3:1 ratio. The same ratio was observed in the mixture (**12**) obtained when 14-*O*-*tert*-butyldimethylsilyladriamycinone (**6**) was the anthracyclinone aglycon employed in the reaction. This result is in contrast to the behavior of 3,4-di-*O*-acetyl-2,6-dideoxy-α-L-*lyxo*-hexopyranosyl chloride in glycosidation reactions with a range of aglycons, when only the α-anomeric products were isolated[1,2]. The different level of anomeric stereocontrol in reactions of the glycosyl chlorides having the α-L-*arabino* (**7**), and α-L-*lyxo* configurations may be attributed to the orientation of the acetyl group at C-4, which is equatorial in **7** but axial in the *lyxo* isomer; attack of the aglycon from below the molecular plane is strongly inhibited in the latter.

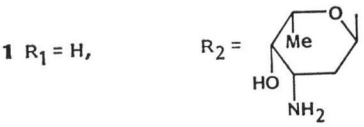
The anomeric mixture **10** was deacetylated with sodium methoxide and the anomers separated in this

* After completion of this work, a patent[4] appeared in which compounds **11** and **14** were reported.

stage to furnish the anomer **11** in 23% yield.

Showing behavior similar to that of 3'-deamino-3'-hydroxy- and 3'-acetoxy-daunorubicin[6], compounds **10** and **11** could not be effectively brominated at C-14. To obtain the doxorubicin analogs, the general approach earlier[2] found effective was therefore employed, starting from the 14-*O*-silylated adriamycinone **6**. This aglycon was coupled with the glycosyl chloride **7** in the presence of mercuric salts to afford a 3:1 mixture (**12**) of α- and β-anomers, which was deacetylated to give a separable mixture that yielded the α-anomer **13** in 46% yield by column chromatography. The values of the coupling constants between vicinal protons at C-1' and C-2' (4.0 and <1.0 Hz) indicate the α-configuration at the anomeric center. The absence of acetoxyl group signals in the ^1H and ^{13}C NMR spectra of **13** confirmed the deprotection of the sugar portion.





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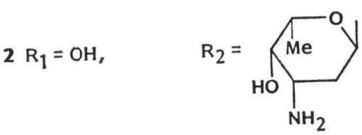
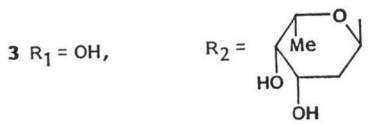


2 R_1 = OH, R_2 =



3 R_1 = OH, R_2 =

4 R_1 = H, R_2 = H

5 R_1 = OH, R_2 = H

6 R_1 = $OSiMe_2Bu^t$, R_2 = H

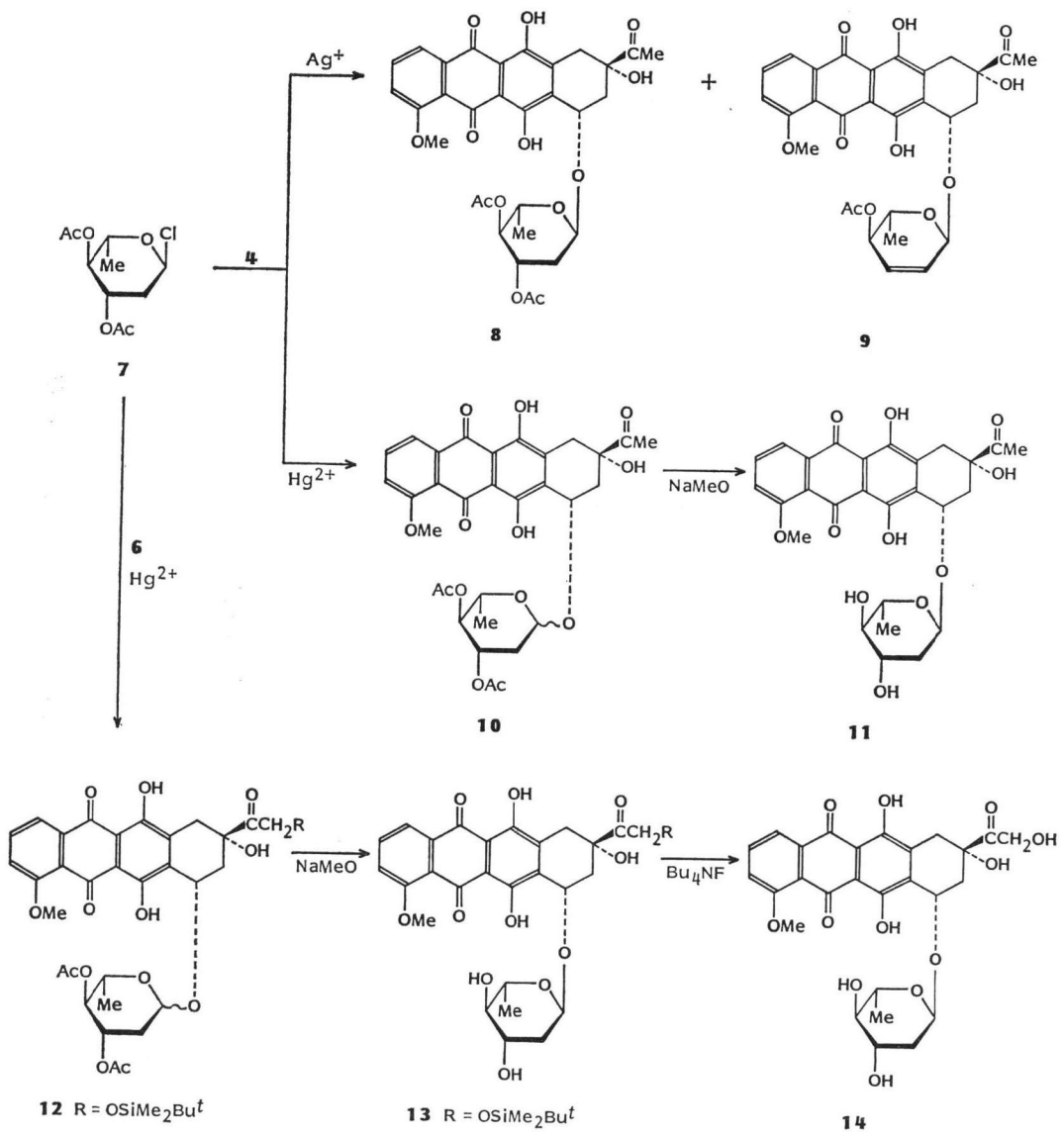
Compound **13** was then desilylated with tetrabutylammonium fluoride to give in 68% yield the fully deprotected 3'-hydroxy-4'-epi analog **14**. The ^1H NMR data showed absence of the *tert*-butyldimethylsilyl group. The coupling constants that could be read on a first-order basis were very close to those for compound **13**.

Biological Activity

The 3,4-di-*O*-acetylated daunorubicin analog **8** showed no activity up to 25 mg/kg in the *in vivo* murine P-388 lymphocytic leukemia system with a single injection ip on the first day of the test. *O*-Deacetylation led to the active 4'-epi-3',4'-dihydroxydaunorubicin analog **11** (T/C 165 at 16.7 mg/kg). As anticipated, hydroxylation at C-14 caused a significant increase in activity and potency; the fully deprotected doxorubicin analog **14** showed T/C 223 at 6.25 mg/kg. However, as shown by comparative tests (Table 2) between 3'-deamino-3'-hydroxydoxorubicin (**3**) and its 4'-epimer (**14**) that is the subject of the present report, the epimerization at C-4' led to some net decrease of activity, although there was some increase in potency. This behavior is in contrast to that reported for 4'-epidoxorubicin[3] and certain other 4'-epi analogs[1], which are more active than the respective drugs having the natural (L-*lyxo*) configuration, and indicates the need for caution in making generalizations in predicting the effect of configurational changes on biological activity in these anthracycline analogs.

Compound **14** manifested toxicity at doses higher than 25 mg/kg, whereas 3'-hydroxydoxorubicin (**3**) retained high activity at doses up to 100 mg/kg*. Both compounds showed better activity and higher potency than doxorubicin. This work on compound **14** and the previous report[2] on compound **3** thus establish that replacement of the 3'-amino group in doxorubicin and its 4'-epimer by a hydroxyl

* Other, comparative assays are in progress and will be reported at a later date.



group gives analogs more active than doxorubicin in the murine P-388 assay.

Experimental

TLC was performed on precoated plastic sheets (0.22 mm) and glass plates (0.25 mm) of Silica gel 60F-254 (E. Merck, Darmstadt, G.F.R.); zones of colorless compounds were detected by UV light and by spraying the plates with 0.1 M ceric sulfate in 2 M sulfuric acid, with subsequent heating. Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer 141 polarimeter. IR spectra were recorded with a Perkin-Elmer 457 grating spectrophotometer. ^{1}H and ^{13}C NMR spectra were determined by Mr. P. BHATÉ at 200 and 50 MHz, respectively, with a Bruker WP-200 spectrometer. Chemical shifts refer to an internal standard of tetramethylsilane (δ 0.00). Elemental analysis were performed by Atlantic Microlab, Inc., Atlanta, Georgia.

Table 1. ^{1}H NMR data for compounds **8**, **11**, **12**, **13** and **14**.

Compound (solvent)	H-1 ($J_{1,2}$) ($J_{1,3}$)	H-2	H-3 ($J_{2,3}$)	H-1′ ($J_{1',2'ax}$) ($J_{1',2'eq}$)	H-7	H-4′ ($J_{3',4'}$)	H-3′ ($J_{2'ax,3'}$) ($J_{2'eq,3'}$)	9-OH	H-14A ($J_{14A,14B}$)	H-14B	H-5′ ($J_{4',5'}$)
8	8.04	7.78	7.39	5.53	5.27	4.78	5.06	4.38	2.44	—	4.06
($CDCl_3$)	(7.7)		(8.1)	(4.3)		(9.4)	(11.6)		(14-CH_3)		(9.5)
	(0.8)			(~1.0)			(5.4)				
11	8.05	7.79	7.40	5.52	5.29	3.18	3.75	4.60	2.42	—	3.86
($CDCl_3$)	(7.7)		(8.5)	(4.3)		(9.2)	(11.6)		(14-CH_3)		(9.2)
	(0.8)						(5.5)				
12[a]	8.03	7.77	7.39	5.51	5.26	4.78	5.04	4.37	4.98	4.87	4.02
($CDCl_3$)	(7.7)		(8.4)	(3.4)		(9.3)			(19.7)		(9.2)
	(1.0)										
13	8.02	7.68	7.38	5.76	5.40	3.63	4.45	4.05	5.32	5.21	4.53
(C_5D_5N)	(7.7)		(8.1)	(4.0)		(9.1)	(12.0)		(19.7)		(9.2)
	(0.9)			(<1.0)			(5.1)				
14	7.98	7.72	7.41	5.68	5.36	3.59	4.38	—	←——~5.22——→		4.47
(C_5D_5N	(7.6)		(8.1)			(9.0)	(12.0)				
$+D_2O$)							(5.1)				

	H-10eq ($J_{8eq,10eq}$)	H-10ax ($J_{10ax,10eq}$)	H-8eq ($J_{8eq,8ax}$)	H-8ax ($J_{7,8ax}$)	H-2′eq	H-2′ax ($J_{2'eq,2'ax}$)	H-6′ ($J_{5',6'}$)	6-OH, 11-OH	OMe	OAc	$SiCMe_3$	$SiMe_2$
8	3.25	2.92	←—— 2.42~2.02 ——		→	1.83	1.24	14.00, 13.27	4.08	2.06,	—	—
	(1.5)	(18.9)				(13.3)	(6.2)			1.96		
11	3.25	2.96	←—— 2.42~2.04 ——		→	1.70	1.36	14.02, 13.30	4.09	—	—	—
	(1.7)	(18.9)				(13.3)	(6.2)					
12[a]	3.25	3.00	←—— 2.50~2.00 ——		→	1.86	1.24	13.98, 13.25	4.08	2.06,	0.96	0.15
	(1.5)	(18.9)					(6.2)			1.96		
13	3.46	3.34	2.80	2.43	2.63	2.14	1.68	14.49, 13.49	3.94	—	0.99	0.19
	(1.5)	(18.4)	(14.5)	(4.9)		(13.0)	(6.2)					
14	←——3.39——→		2.75	2.45	2.55	2.09	1.55	—	3.96	—	—	—
			(14.6)	(5.1)		(12.8)	(6.2)					

[a] Data for the α-anomer of **12**.

7-*O*-(3,4-Di-*O*-acetyl-2,6-dideoxy-α-L-*arabino*-hexopyranosyl)daunomycinone (**8**)

Compound **8** was prepared under two sets of conditions employing two different catalysts for glycosidic coupling.

(a) The glycosyl chloride **7**, generated by passing hydrogen chloride gas through a solution of L-rhamnal diacetate (0.26 g, 1.2 mmol) in benzene, for 3 minutes at 5°C, was dissolved in dichloromethane (10 ml) and poured into a solution of daunomycinone (**4**, 0.28 g, 0.7 mmol) in dichloromethane (100 ml) containing 4 Å molecular sieves (5 g). To this suspension, silver trifluoromethanesulfonate (0.334 g, 1.13 mmol) in oxolane (2 ml) was added dropwise (20 minutes) and, after 30 minutes, the salts were filtered off. The filtrate was diluted with dichloromethane (200 ml) and extracted successively with saturated, aqueous sodium hydrogencarbonate (60 ml) and water (60 ml×2), dried (magnesium sulfate), and evaporated. The residue showed in TLC two compounds migrating faster than daunomycinone and having Rf 0.58 and 0.48 (toluene - acetone, 3: 1). The mixture was resolved by column chromatography (toluene - ether - dichloromethane, 2: 1: 1). The first fractions from the column afforded 7-*O*-(4-*O*-acetyl-2,3,6-trideoxy-α-L-*erythro*-hex-2-enopyranosyl)daunomycinone[1] (**9**, 112 mg, 29%). Fractions containing the product having Rf 0.48 were pooled and evaporated. Hexane was added to a solution of the residue in dichloromethane to precipitate 7-*O*-(3,4-di-*O*-acetyl-2,6-dideoxy-α-L-*arabino*-hexopyranosyl)daunomycinone (**8**, 60 mg, 14%); mp 139~142°C; $[\alpha]_D^{25}$ +80° (*c* 0.03, $CHCl_3$); IR ν_{max} (KBr) 3460 (OH), 1740, 1720 (CO), 1615 and 1575 cm^{-1} (H-bonded quinone); ^{13}C NMR ($CDCl_3$) δ 211.8 (C-13), 187.1, 186.7 (C-5,12), 170.1, 169.9 (AcO), 161.1 (C-4), 156.4, 155.8 (C-6, 11), 135.6 (C-2), 134.5, 133.8 (C-6a,10a,12a), 121.1 (C-4a), 119.8 (C-1), 118.5 (C-3), 111.6, 111.4 (C-5a,11a), 100.3 (C-1′), 76.7 (C-9), 74.5, 70.2, 68.8, 67.0 (C-3′,4′,5′,7), 56.7 (OMe), 35.2, 33.5 (C-2′,8,10), 24.7 (C-14), 20.9, 20.8 (AcO) and 17.5 (C-6′).

Anal Calcd for $C_{31}H_{32}O_{13}$ (612.59): C 60.78, H 5.27.
Found: C 60.80, H 5.27.

Table 2. Comparison of antitumor activity of 3′-deamino-3′-hydroxydoxorubicin (**3**) and its 4′-epimer (**14**) in the murine P-388 lymphocytic leukemia system.

Dose (mg/kg)	Compound	
	14[a]	**3**[a]
100.0		342
50.0		>420
25.0	91	243
12.5	173	203
6.25	223	178
3.12	193	
1.56	168	

[a] Activity of doxorubicin in this test is T/C 193 at 12.5 mg/kg.

(b) The glycosyl halide **7**, prepared from 3,4-di-*O*-acetyl-L-rhamnal (1.07 g, 5 mmol) as described in part (a), was dissolved in dichloromethane (20 ml) and the solution was poured into a suspension of daunomycinone (**4**, 1.0 g, 2.5 mmol), mercuric bromide (0.15 g), yellow mercuric oxide (2.0 g), and 4 Å molecular sieves (10 g) in dichloromethane (200 ml). The mixture was vigorously stirred for 16 hours. The salts were filtered off and the filtrate was diluted with dichloromethane (200 ml) and extracted with 10% aqueous potassium iodide (100 ml×2) and water (100 ml). The organic extract was dried (magnesium sulfate) and evaporated. The residue showed in TLC two very close spots having Rf 0.45 and 0.42 (toluene - dichloromethane - ether, 1: 1: 1), in 3: 1 ratio as judged by NMR data. Chromatographic purification with toluene - dichloromethane - ether, 2: 1: 1 as eluant led to only partial separation. Fractions containing the product having Rf 0.45 were evaporated and compound **8** was obtained as a red solid by dissolution in dichloromethane and precipitation with hexane; yield 0.19 g (12%). It showed the same properties as the α-glycoside **8** described in part (a). Later fractions from the column consisted of an anomeric mixture (**10**); yield 0.98 g; overall yield of both anomers, 1.17 g (76.5%).

7-*O*-(2,6-Dideoxy-α-L-*arabino*-hexopyranosyl)daunomycinone (**11**)

Product **10** (a 3: 1 mixture of α- and β-anomers, 0.92 g, 1.5 mmol) was dissolved in methanol (50 ml) and 1 M sodium methoxide in methanol (3.8 ml) was added. After 1 hour, the reaction was terminated by addition of Dry Ice and water (100 ml). The solution was extracted with dichloromethane (150 ml ×3), and the organic layer was washed with water, dried (magnesium sulfate) and evaporated. TLC examination showed two spots having Rf 0.35 and 0.30 (dichloromethane - acetone, 2: 1) corresponding,

respectively, to the α- and β-anomers of deacylated product **10**. A solution of the mixture in oxolane - acetone, 1: 1 was evaporated onto silica gel. The powder was applied to the top of a column of silica gel (100 g) that was eluted with 1: 1 (300 ml) and then oxolane - toluene, 2: 1. The faster-migrating component (Rf 0.35) was isolated and then precipitated from a solution in dichloromethane by addition of ether - hexane to afford 0.19 g (23%) of the anomerically pure compound **11**; mp 180~182°C; $[\alpha]_D^{25}$ +91° (*c* 0.03, $CHCl_3$); IR ν_{max} (KBr) 3400 (broad, OH), 1710 (CO), 1610 and 1578 cm^{-1} (H-bonded quinone).

Anal Calcd for $C_{27}H_{28}O_{11} \cdot H_2O$ (546.54): C 59.34, H 5.53.
Found: C 59.74, H 5.50.

Subsequent fractions from the column consisted of a mixture of the α- and β-anomers of **11** (0.43 g); overall yield 0.62 g (78%).

14-*O*-*tert*-Butyldimethylsilyl-7-*O*-(3,4-di-*O*-acetyl-2,6-dideoxy-α,β-L-*arabino*-hexopyranosyl)adriamycinone (**12**)

A solution in dichloromethane (10 ml) of the glycosyl chloride **7**, prepared by hydrochlorination of 3,4-di-*O*-acetyl-L-rhamnal (0.64 g, 3 mmol) in dry benzene (20 ml), was added to a mixture of 14-*O*-*tert*-butyldimethylsilyladriamycinone[2] (**6**, 1.06 g, 2 mmol), mercuric oxide (1.6 g), mercuric bromide (0.1 g) and 4 Å molecular sieves (3.0 g) in dichloromethane (40 ml). The mixture was vigorously stirred for 16 hours at 25°C and then diluted with dichloromethane (250 ml), and washed with aqueous 10% potassium iodide (60 ml×2) and water (100 ml). The extract was dried (magnesium sulfate) and evaporated. The residue was purified by column chromatography on silica gel (40 g) with toluene - acetone, 10: 1 Compound **12** precipitated from a solution in acetone - ether upon addition of hexane; yield 0.90 g (61%). Although this product showed a single spot in TLC (Rf 0.53, toluene - acetone, 3: 1), the ^1H NMR spectrum demonstrated that product **12** was a 3: 1 α: β anomeric mixture, mp 131~137°C; $[\alpha]_D^{25}$ +264° (*c* 0.02, $CHCl_3$). The ^{13}C NMR spectrum ($CDCl_3$) of the α-anomer was determined by subtraction from that of the mixture: δ 211.0 (C-13), 186.9, 186.6 (C-5,12), 170.0, 169.8 (AcO), 161.0 (C-4), 156.2, 155.6 (C-6,11), 135.6 (C-2), 135.4, 134.1, 133.5 (C-6a,10a,12a), 120.9 (C-4a), 119.7 (C-1), 118.5 (C-3), 111.5, 111.4 (C-5a,11a), 100.3 (C-1′), 77.0 (C-9), 74.4, 70.1, 68.6, 67.0, 66.5 (C-3′,4′,5′,7,14), 56.6 (OMe), 35.8, 35.1, 33.9 (C-2′,8,10), 25.8 (Me_3CSi), 20.8, 20.7 (AcO), 18.5 (Me_3*C*Si), 17.4 (C-6′) and −5.4 ($SiMe_2$).

Anal Calcd for $C_{37}H_{46}O_{14}Si$ (742.86): C 59.82, H 6.24.
Found: C 59.65, H 6.27.

14-*O*-*tert*-Butyldimethylsilyl-7-*O*-(2,6-dideoxy-α-L-*arabino*-hexopyranosyl)adriamycinone (**13**)

A solution of compound **12** (0.74 g, 1.0 mmol) in methanol (30 ml) was treated with 1 M sodium methoxide in methanol (2.5 ml). The reaction was terminated after 1 hour by addition of Dry Ice and the solution was evaporated to ~10 ml. The residue was diluted with dichloromethane (300 ml) and washed with water (100 ml×2), dried (magnesium sulfate), and evaporated. TLC of the residue showed two spots having Rf 0.48 and 0.40 (dichloromethane - acetone, 3: 2), corresponding to a mixture of the fully deacylated product (**13**) and its β-L-anomer. Partial separation was achieved by column chromatography with 4: 1 (80 ml) and then dichloromethane - acetone, 2: 1. The product having Rf 0.48 was isolated pure and precipitated from dichloromethane - acetone - hexane to afford compound **13** (0.30 g, 46%); mp 235°C; $[\alpha]_D^{25}$ +163° (*c* 0.02, $CHCl_3$); IR ν_{max} (KBr) 3480 (OH), 1733 (CO), 1610, 1580 (H-bonded quinone), 1280 (SiMe) and 830 cm^{-1} (CSi); ^{13}C NMR [$(CD_3)_2SO$] δ 211.4 (C-13), 186.3, 186.2 (C-5,12), 160.7 (C-4), 155.9, 154.3 (C-6,11), 136.0 (C-2), 135.2, 134.5, 133.9 (C-6a,10a,12a), 119.9 (C-4a), 119.6 (C-1), 118.9 (C-3), 110.7, 110.6 (C-5a,11a), 100.5 (C-1′), 77.1 (C-9), 75.2, 69.9, 68.4, 67.5, 65.2 (C-3′, 4′,5′,7,14), 56.5 (OMe), 39.0 (C-8), 36.8 (C-10), 32.0 (C-2′), 25.6 (Me_3CSi), 18.0 (Me_3*C*Si), 17.7 (C-6′) and −5.5 (SiMe).

Anal Calcd for $C_{33}H_{42}O_{12}Si$ (658.79): C 60.17, H 6.43.
Found: C 60.19, H 6.45.

Later fractions from the column gave a mixture (0.22 g) of compound **13** and its β-anomer; overall yield 0.52 g (79%).

7-*O*-(2,6-Dideoxy-α-L-*arabino*-hexopyranosyl)adriamycinone (**14**)

Compound **13** (0.18 g, 0.27 mmol) was dissolved in oxolane (10 ml), dichloromethane (5 ml), and pyridine (0.1 ml), and tetrabutylammonium fluoride (0.41 ml of a 1 M solution in oxolane) was added. The mixture was stirred for 1 hour at 25°C, diluted with dichloromethane (300 ml) and washed with 5% hydrochloric acid (50 ml), water (100 ml) and 10% sodium hydrogencarbonate (50 ml). An emulsion was formed during the aqueous washing, and it was necessary to extract this several times with dichloromethane. The organic layer was dried (magnesium sulfate) and evaporated. The residue was dissolved in oxolane - dichloromethane and the product precipitated by addition of ether. The solid was washed with ether and dried to afford pure compound **14** (0.10 g, 68%); mp 152~156°C; $[\alpha]_D^{25}$ +196° (*c* 0.02, $CHCl_3$); IR ν_{max} (KBr) 3470 (broad, OH), 1725 (CO), 1612 and 1580 cm^{-1} (H-bonded quinone).

Anal Calcd for $C_{27}H_{28}O_{12} \cdot H_2O$ (562.54): C 57.65, H 5.38.
Found: C 57.55, H 5.31.

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