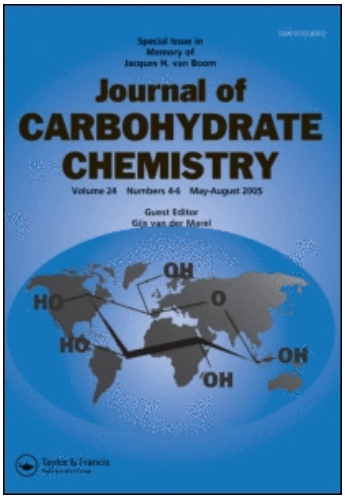

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NEW HETEROCYCLIC ANALOGUES OF ANTHRACYCLINE ANTIBIOTICS

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ABSTRACT

Synthetic approaches to anthracycline antibiotic analogues in which the nitrogen atom of the carbohydrate portion is incorporated into a 1,2,3-triazolyl moiety were investigated. By using methyl 6-azido-2,6-dideoxy-β-D--arabino-hexopyranoside and methyl 3-azido-2,3,6-trideoxy--α-L-arabino-hexopyranoside, the corresponding glycosides (16 a,b - 18 a,b) of carminomycinone and daunomycinone were prepared. The desired heterocyclic system was developed directly with the C-3' and C-6' azido anthracyclines by means of a cycloaddition process to give 7-O-[6'-(4,5--dicarboethoxy-1,2,3-triazolyl)-2',6'-dideoxy-β-D-arabino--hexopyranosyl]-carminomycinone (23) and -daunomycinone (22), and 3'-(4,5-dicarboethoxy-1,2,3-triazolyl)-4'-epi-daunomycin (24).

INTRODUCTION

With a goal of reducing the undesired side effects of the clinically used anthracycline glycoside antibiotics many structural transformations thereof have been accomplished. Of the numerous semisynthetic analogues, currently available in the market, 3'-deamino-(3-cyano-4-morpholinyl)-doxorubicin[1] (1), 4'-epidaunomycin[2] (2) and farmorubicin[2] (3) are those with the advantageous pharmacological properties. These three derivatives were prepared essentially by means of two types of structural modifications, involving either the inclusion of the amino group of the carbohydrate moiety[3] into a piperidinyl[4] and morpholinyl[5,6] ring system, or the change of the L-lyxo configuration of daunosamine into L-arabino[7].

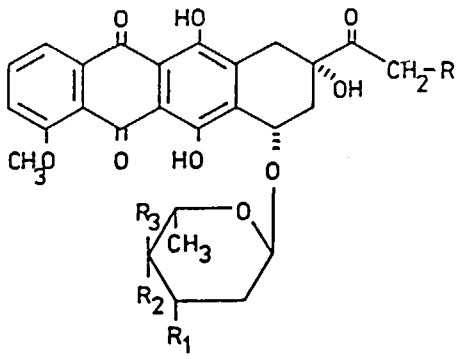
RESULTS AND DISCUSSION

The present paper describes the synthesis of three novel heterocyclic anthracycline glycoside analogues (22-24), for the production of which both of the above modification strategies have been applied; the D- and L-arabino-hexopyranosyl portion of these glycosides carries a 1,2,3-triazolyl heterocyclic moiety.

We have previously reported the preparation of the anthracycline-glycoside derivatives 4-6 containing azido groups in the sugar skeleton,[8,9] and during the present studies several additional azido anthracyclines (16 a,b - 21 a,b) were synthesized.
These azido glycosides were found suitable for the development of the triazolyl heterocyclic ring-system.

The 1,3-dipolar cycloaddition reactions of organic azides with activated unsaturated compounds are well-demonstrated,[10] and such a methodology was first used in the field of carbohydrates by Baddiley et al.[11] for obtaining 1,2,3-triazolyl-nucleosides. Most recently bis-homonucleosides were similarly prepared by Kuszmann et al.[12]

The cycloaddition reaction of diethyl acetylenedicarboxylate on either of the C-6 primary and C-3 sec-

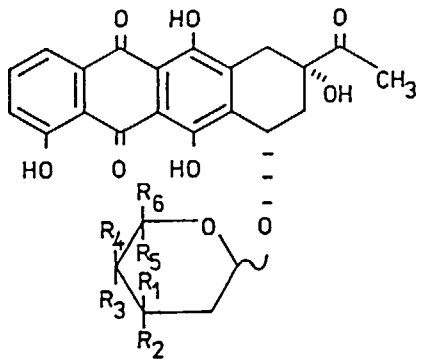


1 R = R_2 = OH ; R_3 = H ; R_1 = –N(CN)–O

2 R = R_2 = H ; R_3 = OH ; R_1 = NH_2

3 R = R_3 = OH ; R_2 = H ; R_1 = NH_2

Fig. 1.



4 R_1 = R_4 = R_5 = H ; R_3 = OH ; R_2 = N_3 ; R_6 = CH_2Br

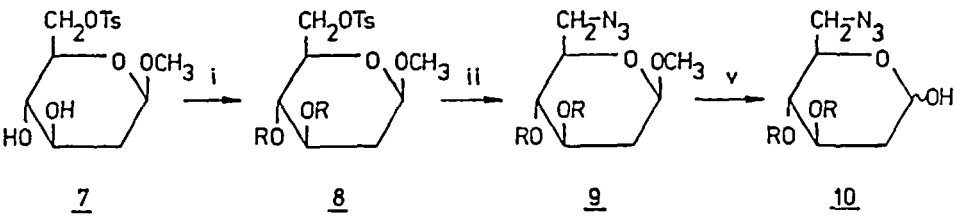
5 R_1 = R_4 = R_5 = H ; R_3 = OH ; R_2 = N_3 ; R_6 = CH_2N_3

6 R_2 = R_3 = R_6 = H ; R_1 = N_3 ; R_4 = OH ; R_5 = CH_3

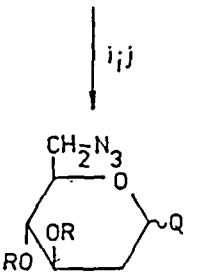
Fig. 2.

ondary azido group of methyl azidodeoxy hexopyranosides was found to be suitable for the development of the required triazolyl function. In addition, this ring closure process worked well also on the above azidodeoxy hexopyranosyl anthracyclinones bearing 6-azido-2,6-dideoxy-D-arabino- and 3-azido-2,3,6-trideoxy-L-arabino-hexopyranose as the glycosidic moieties.

The preparation of the glycosyl chlorides, required for the glycosylation reactions, was carried out as follows. The chloride 13 was prepared on the basis of a reported procedure[13] and compound 12 was synthesized according to literature analogies. Methyl 2-deoxy-6-O-p-toluenesulfonyl-β-D-arabino



7 8 9 10



Ts = p-$CH_3C_6H_4SO_2$

R = p-$NO_2C_6H_4CO$

i RCl ; Py ; 20°C ; 24h

ii NaN_3;DMFA ; 80°C ; 10h

v CH_3COOH – 1 N HCl 2:1 ½;90°C;90'

j anhyd. CH_2Cl_2;HCl ; 0°C ; 60'

11 Q = p-$NO_2C_6H_4COO$

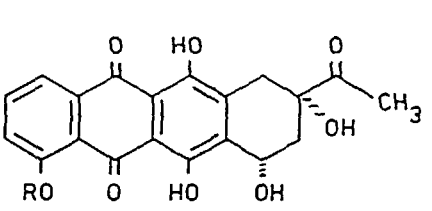
12 Q = Cl

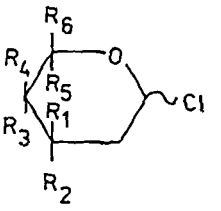
Scheme 1.

-hexopyranoside (7), obtained from D-glucose in a multistep way,[14-16] was first converted into the 3,4-di-O-p-nitrobenzoate 8. Then the nucleophilic displacement of the sulfonyloxy function with sodium azide gave the crystalline 6-azidoglycoside 9. Hydrolysis of the glycosidic bond of 9 was carried out by heating in a 2:1 mixture of acetic acid and 1 N hydrochloric acid to obtain the syrupy free reducing sugar 10.

Both the mutarotation observed for 10, and the band at 3410 cm^{-1} in its IR spectrum clearly indicated the development of the free glycosidic hydroxy function. Para-nitrobenzoylation of 10 afforded the crystalline triester 11, from which the glycosyl chloride 12 was obtained in nearly quantitative yield.

Glycosylation of the anthracyclinones 14 and 15 with the glycosyl chlorides 12 and 13 under modified Koenigs-





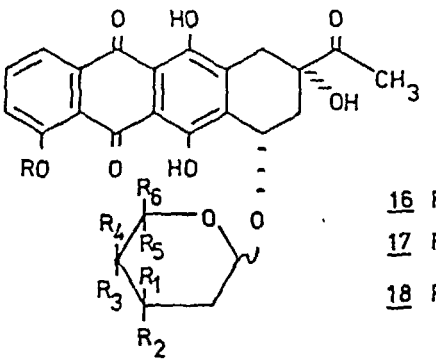
14 R = H
15 R = CH_3

g

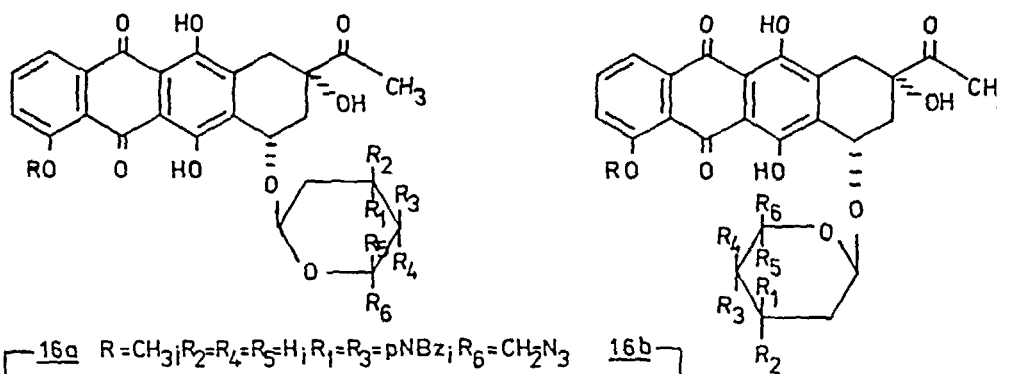
12 R_2=R_4=R_5=H; R_1=R_3=pNBz; R_6=CH_2N_3
13 R_1=R_3=R_6=H; R_2=N_3; R_4=pNBz; R_5=CH_3

pNBz = p-$NO_2C_6H_4COO$

g $HgBr_2$; $Hg(CN)_2$; anhyd. CH_2Cl_2



16 R=CH_3; R_2=R_4=R_5=H; R_1=R_3=pNBz; R_6=CH_2N_3
17 R=R_2=R_4=R_5=H; R_1=R_3=pNBz; R_6=CH_2N_3
18 R=R_5=CH_3; R_1=R_3=R_6=H; R_2=N_3; R_4=pNBz



16a R=CH_3; R_2=R_4=R_5=H; R_1=R_3=pNBz; R_6=CH_2N_3 — 16b
19a R=CH_3; R_2=R_4=R_5=H; R_1=R_3=OH; R_6=CH_2N_3 — 19b

17a R=R_2=R_4=R_5=H; R_1=R_3=pNBz; R_6=CH_2N_3 — 17b
20a R=R_2=R_4=R_5=H; R_1=R_3=OH; R_6=CH_2N_3 — 20b

18b R=R_5=CH_3; R_1=R_3=R_6=H; R_2=N_3; R_4=pNBz — 18a
21b R=R_5=CH_3; R_1=R_3=R_6=H; R_2=N_3; R_4=OH — 21a

Scheme 2.

TABLE I. ^{1}H NMR spectral data of compounds 16a,b-18a,b, 22, 23 and 24

Compound	Chemical shifts (ppm)+ in $CDCl_3$, 200 MHz									ester		
	H-1'	H-2'e	H-2'a	H-3'	H-4'	H-5'	H-6'	CH_3-5'	H-7	CH_3	CH_2	Others
16a	5.37	2.09	1.84	3.91	3.51	4.29	3.61		5.51			2.42 Ac; 4.12 OMe
16b	5.65	2.12	1.82	4.01	3.48	4.75	3.66		5.56			2.42 Ac; 4.10 OMe
17a	5.50	2.25	1.86	3.96	3.43	4.14	3.50		5.41			2.36 Ac
17b	5.58	2.18	1.85	4.10	3.50	4.71	3.51		5.50			2.41 Ac
18a	5.52	2.35	1.87	3.87	4.97	4.17		1.25	5.28			2.40 Ac; 4.03 OMe
18b	5.15	2.37	1.83	3.71	4.82	3.56		0.99	5.61			2.44 Ac; 4.08 OMe
22*	4.93	2.24	1.56	3.65	3.22	3.81	5.15/4.92		4.88	1.29	4.38	2.42 Ac; 4.12 OMe
23*	4.98	2.32	1.61	3.62	3.26	3.82	5.11/4.89		4.82	1.31	4.31	2.38 Ac
24*	5.58	2.48	2.62	5.02	3.68	4.15		1 37	5.21	1.22	4.25	2.29 Ac; 3.95 OMe

+ chemical shifts are from TMS (internal standard)

* in acetone-d_6

TABLE II. ^1H NMR Coupling constants for compounds 16a,b-18a,b, 22, 23 and 24

Compound	Spin-spin coupling constants ($J_{H,H}$ in Hz) ($CDCl_3$, 200 MHz)							
	$J_{1',2'a}$	$J_{1',2'e}$	$J_{2'a,3'}$	$J_{2'e,3'}$	$J_{2'e,2'a}$	$J_{3',4'}$	$J_{4',5'}$	$J_{5',6'}$
16a	3.7		12.1	5.1	12.2	9.5	9.6	6.1
16b	9.8	1.7	12.2	5.2	12.1	9.5	9.5	6.2
17a	3.9		12.3	5.2	12.1	9.4	9.5	6.3
17b	9.9	1.8	12.1	5.3	12.3	9.6	9.6	6.1
18a	4.1		12.1	5.3	12.1	9.3	9.4	6.3
18b	9.9	1.8	12.2	5.1	12.1	9.5	9.5	6.2
22**	9.8	1.8	12.2	5.3	12.2	9.5	9.6	9.6/3.0
23**	9.9	1.7	12.2	5.2	12.1	9.6	9.7	9.7/3.1
24**	3.9		12.3	5.1	12.3	9.6	9.7	6.3

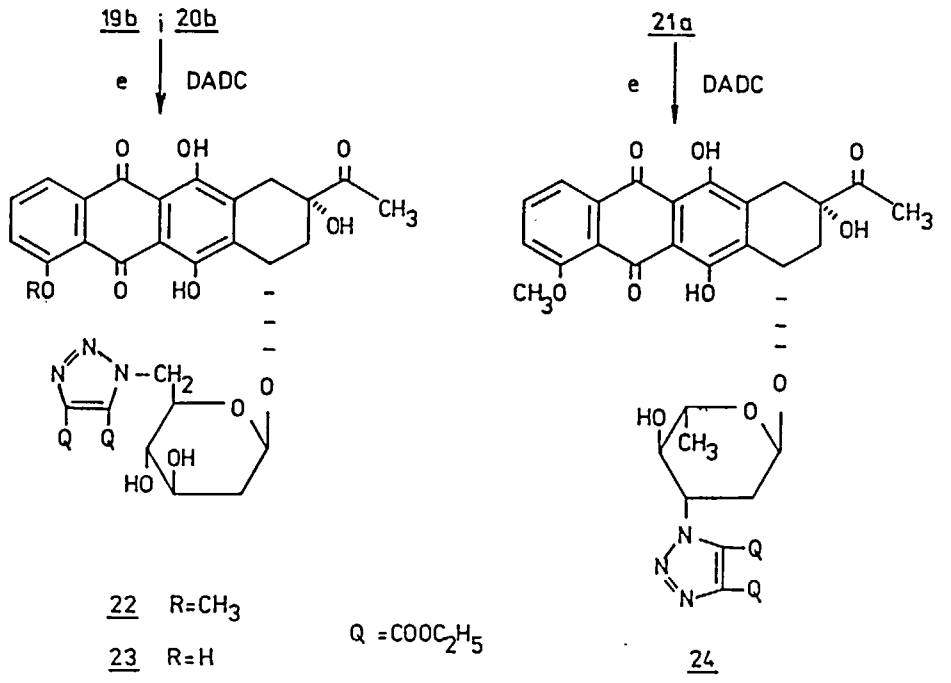
** in acetone-d_6

-Knorr conditions (mercuric cyanide, mercuric bromide in dichloromethane for 24 h at 25 °C) gave anomeric mixtures of the glycosides 16-18, which were purified by means of column chromatography on silica gel 40. The α : β anomeric ratio in the case of the D-arabino-derivatives (16 and 17) was 1:2, whereas for the L-arabino glycoside 18 the ratio was 1.7:1. Separation and isolation of the pure anomers were performed by means of preparative layer chromatography.

The ^{1}H NMR spectral data from the separated glycosides 16a-18a showed that the anomeric proton of these compounds is disposed equatorially (δ 5.5 $J_{1',2'}$ = 2.0 Hz), and thus these glycosides are α-anomers. The chemical shift and coupling constant values (δ 5.1 $J_{1'a,2'a}$ = 9.9 Hz, $J_{1'a,2'e}$ = = 1.7 Hz) observed for compounds 16b-18b indicated the β-glycosidic linkage (axial anomeric proton) of these glycosides. Assignment of the ^{1}H NMR spectra was carried out by means of the COSY analysis[17] of the proton-proton correlation maps. The spectral data are summarized in Table I and II.

Removal of the O-p-nitrobenzoyl groups of glycosides 16 a,b - 18 a,b with the Zemplén method resulted in the azidodeoxy anthracyclines 19 a,b - 21 a,b of which 21a is the azido analogue of 4'-epidaunomycin.

Treatment of the glycosides 19b, 20b and 21a with diethyl acetylenedicarboxylate resulted in the formation of the corresponding disubstituted 1,2,3-triazolyl derivatives 22, 23 and 24. The ^{1}H NMR resonances between δ = 1.22-1.31 ppm and in the range δ = 4.25-4.38 ppm, obtained for these latter three compounds were assigned to the ethyl groups of the carboxylic esters located on the triazole ring. Together with the analytical and mass spectral data this clearly indicated the incorporation of the heterocycle with the nitrogen function of the carbohydrate moiety. The biological effects of these novel anthracyclines will be published elsewhere.



e acetone ; 60°C ; 5h
DADC : diethyl acetylenedicarboxylate

Scheme 3.

EXPERIMENTAL

General Procedures

The IR spectra were determined with a Perkin-Elmer 283 B, and the UV spectra were obtained with a UNICAN SP 800 instrument. ^{1}H NMR spectra were recorded at 200 MHz on a Bruker WP 200 SY spectrometer. Optical rotations were measured with Perkin-Elmer 241 and Haensch-Schmidt polarimeters. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Column chromatography was carried out on silica gel 40 (Merck). For preparative layer chromatography 2 mm thick precoated Kieselgel 60 F_{254} sheets (Merck) were applied.

Methyl 2-Deoxy-3,4-di-O-p-nitrobenzoyl-6-O-p-toluenesulfonyl-β-D-arabino-hexopyranoside (8). To a cold solution of 7 (5.8 g, 17.4 mmol) in anhydrous pyridine p-nitrobenzoyl chloride (9.0 g, 48.5 mmol) was added and the mixture was kept at room temperature for 10 h. It was then poured into a mixture of crushed ice and sodium hydrogen carbonate, the precipitate was filtered off and washed until neutral on the filter. The crude product was crystallized from ethanol to give 6.85 g (63 %) of 8, mp 137-138 °C; $[\alpha]_D^{20}$ - 86.5° (c 0.52, chloroform); IR (KBr) 1737 (C=O ester), 1529, 1350 cm^{-1} (NO_2);

Anal. Calcd for $C_{28}H_{26}O_{13}N_2S$: C, 53.33; H, 4.13; N, 4.44; S, 5.08. Found: C, 53.26; H, 4.22; N, 4.16; S, 4.99.

Methyl 6-Azido-2,6-dideoxy-3,4-di-O-p-nitrobenzoyl-β-D-arabino-hexopyranoside (9). A mixture of compound 8 (6.8 g, 13.7 mmol) and sodium azide (5.3 g, 82.2 mmol) in anhydrous N,N-dimethylformamide (200 mL) was intensively stirred at 80 °C for 10 h. The solvent was then distilled off at diminished pressure and the residue was taken up with a 1:1 mixture of chloroform and water. The organic layer was washed with water, dried and concentrated to give crystalline 9 (4.7 g, 87 %), mp 195-197 °C; $[\alpha]_D^{20}$ - 133.8° (c 0.76, chloroform); IR (KBr) 2110 (N_3), 1730 (C=O ester), 1525 and 1348 cm^{-1} (NO_2);

Anal. Calcd for $C_{21}H_{19}O_{10}N_5$: C, 50.3; H, 3.79; N, 13.97. Found: C, 50.28; H, 3.70; N, 13.94.

6-Azido-2,6-dideoxy-3,4-di-O-p-nitrobenzoyl-D-arabino-hexopyranose (10). A solution of the methyl glycoside 9 (0.3 g, 0.5 mmol) in a mixture of glacial acetic acid (15 mL) and 2 N hydrochloric acid (15 mL) was kept at 90 °C for 90 min. The reaction mixture was then concentrated to dryness, and a solution of the residue in chloroform was washed with water until neutral. After concentration of the organic layer, compound 10 was obtained as a pale yellow syrup (0.25 g, 85 %); $[\alpha]_D^{20}$ - 35° ⟶ - 22° (after 24 h, c 1.27, chloroform); IR (KBr) 3465 (OH), 2100 (N_3), 1730 (C=O ester), 1525 and 1345 cm^{-1} (NO_2).

6-Azido-2,6-dideoxy-1,3,4-tri-O-p-nitrobenzoyl-D--arabino-hexopyranose (11). A mixture of 10 (0.6 g, 1.23 mmol) in dry pyridine (15 mL) was treated with p-nitrobenzoyl chloride (0.6 g, 3.23 mmol) with stirring at room temperature for 4 h. The reaction mixture was poured onto a mixture of crushed ice and sodium hydrogen carbonate, the product was filtered off, washed with water until neutral, dried and crystallized from a 1:7 mixture of benzene and ethanol to give 11 (0.5 g, 64 %); mp 95-97 °C; $[\alpha]_D^{20}$ + 54.2° (c 0.33, benzene); IR (KBr) 2101 (N_3), 1736 (C=O ester), 1527 and 1365 cm^{-1} (NO_2);

Anal. Calcd for $C_{27}H_{20}O_{13}N_6$: C, 50.83; H, 3.38; N, 13.17. Found: C, 50.90; H, 3.29; N, 12.99.

Glycosylation

A solution of compound 11 or 3-azido-1,4-di-O-p--nitrobenzoyl-2,3,6-trideoxy-L-arabino-hexopyranose (0.15 mmol, 100 or 70 mg respectively) in anhyd dichloromethane (20 mL) was treated with dry hydrogen chloride gas at 0 °C for 20 min. In the case of 11 the reaction mixture was kept at +4 °C for 10 h. The precipitated p-nitrobenzoic acid was filtered off, the filtrate concentrated under diminished pressure, and the residual glycosyl chlorides (12 and 13) were used for the glycosylation reactions without further purification. A solution of the glycosyl chloride in anhyd dichloromethane (10 mL) was added to the mixture of the anthracyclinone 14 or 15 (50 mg, 0.13 mmol), mercuric cyanide (170 mg, 0.67 mmol), mercuric bromide (70 mg, 0.19 mmol) and 3 Å molecular sieves (500 mg) in anhyd dichloromethane (20 mL).[18] The reaction mixture was stirred at room temperature for 24 h, filtered and the filtrate was washed with 10 % aqueous potassium iodide solution (100 mL) and with water. After drying the solvent was evaporated and the residue purified by column chromatography, using 100:1 chloroform-methanol (for 16) and 100:3 chloroform-methanol (for 17) as the eluant, to obtain the anomeric mixture of the α- and β-azido-deoxy glycosides.

Separation of the anomeric glycosides

The mixtures of anomers (100 mg) were separated by means of preparative layer chromatography on Kieselgel 60 F_{254} layer and using 9:1 benzene-ethyl acetate for 17, 100:3:1 toluene-2-propanol-methanol for 16 and 10:1 benzene--ether for 18. After UV detection the pure anomers were isolated from the layer by elution with a 5:1 mixture of anhyd chloroform - anhyd methanol. After evaporation of the solvents the products spontaneously crystallized.

O-Deacylation of the azidohexopyranosyl anthracyclinones

To the suspensions of compound 16 a,b, 17 a,b and 18 a,b (100-100 mg) in anhyd methanol (30-40 mL) 0.1 N methanolic sodium methoxide solution was added, and the mixtures were stirred at room temperature for 2 h. The reaction mixtures were neutralized with AG 50 W-X 12 (H^+) cation exchange resin, filtered, and the filtrates concentrated under diminished pressure. The residual products were treated with petroleum ether several times.
(See Table III)

Introduction of the 1,2,3-triazole ring system

To the solutions of 19b, 20b and 21a (100 mg, 0.17 mmol) in acetone (10 mL) diethyl acetylenedicarboxylate (0.14 mL, 0.85 mmol) was added and the mixtures were boiled under reflux for 5 h. The solvent was then evaporated under diminished pressure and the residue purified by means of column chromatography, using ethyl acetate for 22, 6:2 benzene:acetone for 23 and 7:3 dichloromethane-ethyl acetate for 24 as the eluants.

7-O-[6'-(4,5-Diethoxycarbonyl-1,2,3-triazolyl)-2',6'--dideoxy-β-D-arabino-hexopyranosyl]-daunomycinone (22). 84.4 mg (65 %); mp 108-110 °C; $[\alpha]_D^{20}$ + 27.6° (c 0.47, acetone); IR (KBr) 3483 (OH), 1727 (C=O ester + acetyl), 1615, 1585 cm^{-1} (quinone). UV λ_{max}^{MeOH} (nm): 235, 253, 288, 480, 498, 535. MS: 740 $(M+H)^+$.

Anal. Calcd for $C_{35}H_{37}O_{15}N_3$: N, 5.68. Found: N, 5.55.

TABLE III. Physico chemical properties of compounds 16-21b

Compound	Yield %	mp (°C)	$[\alpha]_D^{20}$ in $CDCl_3$	IR (KBr) cm^{-1}					UV $\lambda_{max}^{CHCl_3}$ nm
				ν_{OH}	ν_{N_3}	$\nu_{C=O}$	$\nu_{C=O(quinone)}$	ν_{NO_2}	
16	61.3	152		3502	2095	1729	1614,1576	1525,1346	236,256,482,498,534
17	56.2	150		3498	2100	1736	1608	1529,1349	256,466,484,492,515,528
18	53.4	117		3446	2098	1732	1613,1577	1525,1345	237,254,478,497,532
16a	25.4	145	+ 309°	3417	2097	1729	1613,1580	1529,1350	
16b	55.1	160	+ 136°	3437	2095	1730	1608,1580	1529,1350	
17a	29.0	138	+ 290°	3425	2096	1729	1604	1525,1342	
17b	60.0	152	+ 63°	3430	2098	1729	1608	1520,1349	
18a	50.0	145	+ 121°	3441	2093	1727	1613,1574	1524,1347	
18b	30.5	126	+ 283°	3460	2093	1733	1614,1576	1525,1347	
19a*	86.0	116	+ 250°	3450	2098	1715	1610,1570		237,255,289,473,497,530
19b*	84.2	130	+ 172°	3456	2095	1715	1615,1570		239,250,285,475,493,532
20a*	80.0	120	+ 211°	3428	2100	1708	1605		235,255,293,488,524
20b*	85.4	135	- 20°	3430	2098	1710	1606		237,250,294,486,525
21a*	75.0	95	+ 270°	3440	2100	1710	1612,1580		236,253,287,480,496,534
21b*	70.8	81	+ 198°	3438	2100	1716	1616,1584		238,250,289,482,498,530

* $[\alpha]_D^{20}$ in acetone and UV λ_{max} in methanol

All new compounds gave satisfactory elemental analyses for C, H and N.

7-O-[6'-(4,5-Diethoxycarbonyl-1,2,3-triazolyl)-2'-6'--dideoxy-β-D-arabino-hexopyranosyl]-carminomycinone (23). 76.0 mg (58.2 %); mp 187-189 °C; $[\alpha]_D^{20}$ - 187.5° (c 0.24, acetone); IR (KBr) 3440 (OH), 1725 (C=O ester), 1600, 1550 cm^{-1} (quinone); UV λ_{max}^{MeOH} (nm): 235, 255, 292, 470, 495, 530. MS: 726 $(M+H)^+$.

Anal. Calcd for $C_{34}H_{35}O_{15}N_3$: N, 5.79. Found: N, 5.72.

7-O-[3'-(4,5-Diethoxycarbonyl-1,2,3-triazolyl)-2',3',6'--trideoxy-α-L-arabino-hexopyranosyl]-daunomycinone (24). 100 mg (76.5 %); mp 110-113 °C; $[\alpha]_D^{20}$ + 192.8° (c 0.28, acetone); IR (KBr) 3440 (OH), 1730 (C=O ester), 1617, 1580 cm^{-1} (quinone); UV λ_{max}^{MeOH} (nm): 235, 253, 290, 480, 496, 534. MS: 724 $(M+H)^+$.

Anal. Calcd for $C_{35}H_{37}O_{14}N_3$: N, 5.80. Found: N, 5.85.

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