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CARMINOMYCINE ANALOGS CONTAINING AMINODEOXY-L-*lyxo*-HEXOFURANOSYL DERIVATIVES AT O-7

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ABSTRACT

The synthesis of two carminomycine analogs respectively containing the 3-azido-2,3,6-trideoxy-5-*O*-methyl-α-L-*lyxo*-hexofuranosyl and the 3,5-diamino-2,3,5,6-tetradeoxy-α-L-*lyxo*-hexofuranosyl (derivative **27**) unit at O-7 is described. For the synthesis of the first compound, methyl 2,3-anhydro-6-deoxy-α-L-gulofuranoside (**1**) and for the second, methyl 2,3-anhydro-β-D-mannofuranoside, was used as the starting material, the latter being an intermediate in the synthesis of **1**, starting from D-glucose. The anomeric configuration of the 2-deoxy-L-*lyxo*-hexofuranosides was established by ^{1}H-n.m.r. spectroscopy. In biological testing, the diamino derivative **27** showed a more favorable therapeutic index than carminomycine.

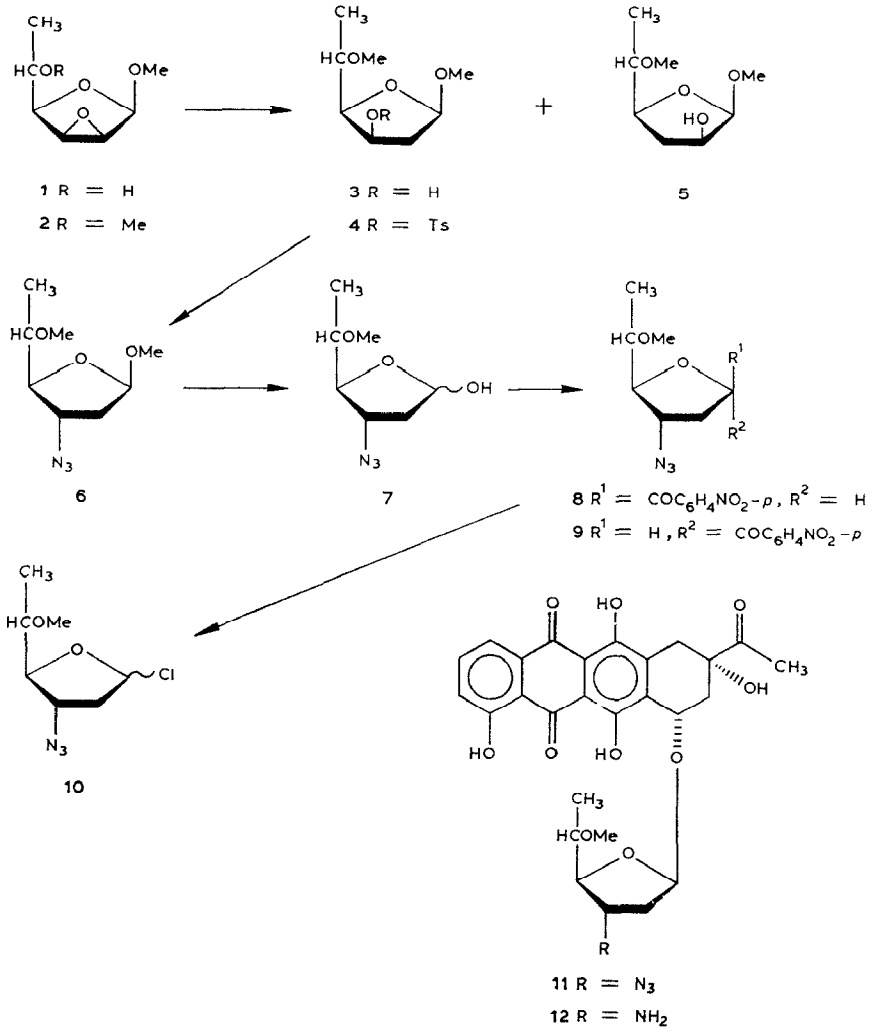
INTRODUCTION

The well documented, cytostatic activity of anthracycline antibiotics[1] has triggered extensive research aimed at the synthesis of analogs that possess a less pronounced cardiotoxic side-effect. Daunosamine, the sugar component of these antibiotics, has been replaced by other aminodeoxy[2–5], as well as by neutral, sugars[6–8], all in their pyranoid form. Recently, the first furanoid analogs, containing a 3-amino-3,5-dideoxy-β-D-ribofuranosyl unit at O-7 was described by Israel *et al.*[9]. Daunosamine itself was converted by El Khadem and Matsuura[10] into its protected, furanoside derivative, but no coupling reaction with anthracyclinones was reported. We now describe the synthesis of a carminomycine analog containing an aminodeoxyhexofuranosyl group at O-7.

DISCUSSION

For studying the synthetic possibilities leading to anthracycline furanosides, the synthesis of the 5-*O*-methylfuranoside analog (**12**) of carminomycine was first attempted. Our original strategy was to link the aglycon with the azidohexofuranose, and to introduce the amino function later, *via* reduction of the azido group. A similar strategy was applied by Staricskai *et al.*[11] for the synthesis of the corresponding hexopyranosyl analogs.

Methyl 2,3-anhydro-6-deoxy-α-L-gulofuranoside (**1**), readily obtainable from D-glucose in seven steps[12], was 5-*O*-methylated to give **2**, and the oxirane ring in **2** was split reductively with lithium aluminum hydride to afford a 17:3 mixture of the 2-deoxy (**3**) and 3-deoxy derivative (**5**) as a syrup*. As separation of these isomers remained unsuccessful, the mixture was tosylated, yielding the 2-deoxy-3-*O*-tosyl derivative (**4**) in crystalline state. The tosyloxy group of **4** was replaced by azide, with inversion of configuration, yielding the 3-azido-L-*lyxo* derivative **6**. The methyl glycoside **6** could be readily hydrolyzed with aqueous acetic acid, giving the free sugar as an anomeric mixture (**7**). On treatment with 4-nitrobenzoyl chloride in pyridine, this



*In the case of the corresponding 5-*O*-benzyl analogs, the 3-deoxy isomer was formed only in traces under similar conditions[12].

was converted into an ~1:1 mixture of the corresponding α- and β-D-hexosyl 4-nitrobenzoates (**8** and **9**), which could be separated by column chromatography. By treatment with dry HCl, the crystalline β anomer **9** was converted into its chloride **10**, which, without isolation, was coupled, in the presence of mercuric oxide, mercuric bromide, and molecular sieve 3A, with carminomycinone, to give, after two-fold chromatography, the crystalline 3-azido-2,3,5-trideoxy-α-L-*lyxo*-hexofuranoside **11**. All attempts to convert **11** into **12** *via* reduction of the azido group remained unsuccessful, as, on hydrogenation in the presence of palladium, the deep-purple solution immediately became colorless, indicating the reduction of the aglycon moiety. The azido group of **11** remained unchanged on treatment with hydrogen sulfide in aqueous pyridine, which readily reduces terminal azido groups[13].

Taking into account these results, a different strategy had to be planned for the synthesis of the diaminoglycoside **27**. As the starting material, we used methyl 2,3-anhydro-β-D-mannofuranoside (**13**), which is an intermediate in the synthesis of **1** starting from D-glucose[12]. Compound **13** was partially tosylated, and the 6-*O*-tosyl derivative **14** obtained was converted into diepoxide **15** with sodium methoxide. The terminal oxirane ring in **15** was selectively reduced with borohydride[12], furnishing methyl 2,3-anhydro-6-deoxy-β-D-mannofuranoside (**16**). Tosylation of **16** gave the 5-tosylate **17**, the oxirane ring of which was reduced with lithium aluminum hydride at −10°, yielding the rather unstable, syrupy 3-hydroxy compound **18**. This was converted into the 3-mesylate **19**, and this mixed ester was immediately treated with sodium azide in *N*,*N*-dimethylformamide, to give, with inversion at C-3,5, the expected methyl 3,5-diazido-2,3,5,6-tetradeoxy-α-L-*lyxo*-hexofuranoside (**20**). Reduction of the azido groups in the presence of palladium as the catalyst afforded the diamine **21**, which was isolated as the crystalline bis(*N*-trifluoroacetate) **22**. The glycosidic bond in **22** was readily hydrolyzed by aqueous acetic acid, and, after column chromatography, the free, *N*-protected diamino sugar **23** was obtained in crystalline state. On treatment with 4-nitrobenzoyl chloride in pyridine, the latter gave crystalline 1-(4-nitrobenzoate) **24**. The α anomeric configuration of both **23** and **24** was established by ^{1}H-n.m.r. spectroscopy (see Table I).

A solution of 4-nitrobenzoate **24** in dichloromethane was treated with dry HCl, and the resulting glycosyl chloride **25** was used, without purification, for the coupling reaction with carminomycinone in the presence of mercuric bromide, mercuric oxide, and molecular sieve 3A. According to t.l.c., two main components were formed, in the ratio of ~1:1. After column chromatography, the faster-moving, α anomer **26** was obtained in crystalline state, whereas the β anomer **28** could not be crystallized, and it decomposed slowly on storage at room temperature.

Deprotection of **26** was achieved with aqueous sodium hydroxide, and, after de-ionization with ion-exchange resins, and freeze-drying of the solution, the diamino furanoside **27** was obtained as an amorphous material.

The anomeric configuration of the 2-deoxy-L-*lyxo*-hexofuranosides was determined by ^{1}H-n.m.r. spectroscopy, taking into consideration the following. In both anomers, the oxolane ring most probably adopts the $^3T_2$ conformation[14], wherein

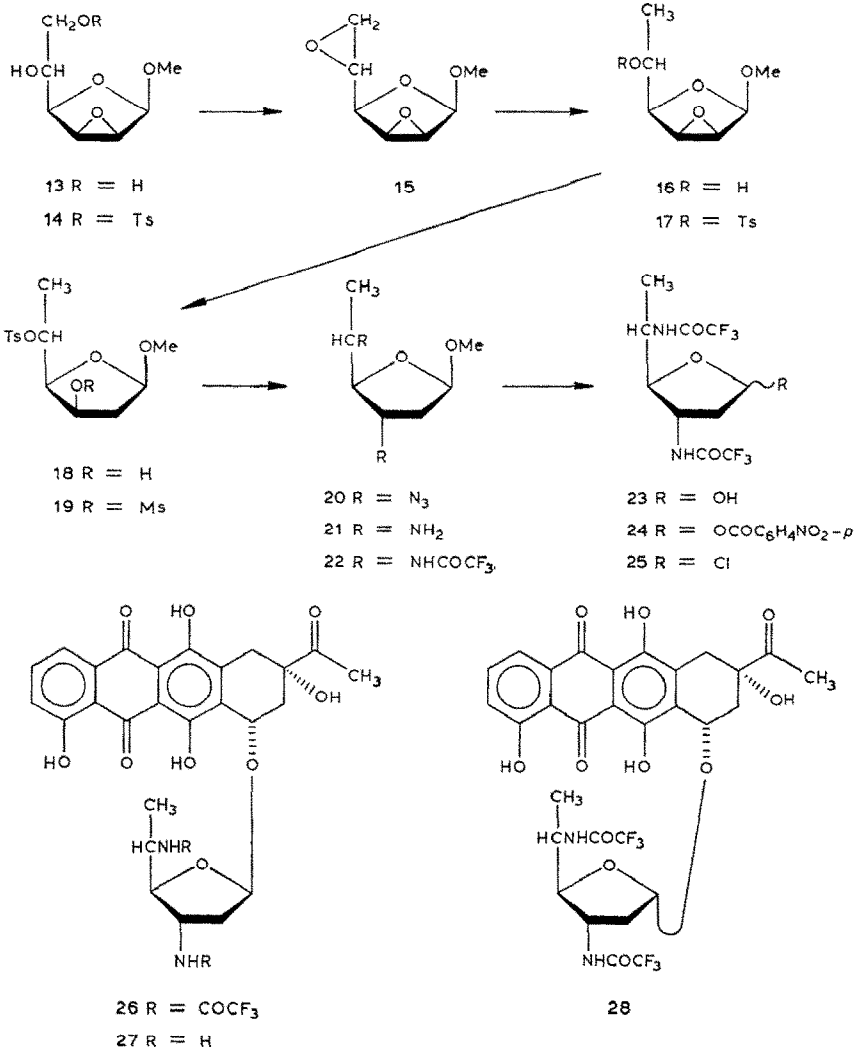
TABLE I

^{1}H-N.M.R. DATA[a] FOR COMPOUNDS **1–9**, **11**, **13–17**, **20**, **22–24**, **26**, AND **28**

Compound	*H-1*	*H-2*	*H-3*	*H-4*	*H-5*	*H-5′*	*1-OMe*	*5-OMe*	*Other*	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	*Other*
1[b]	5.00*s*	3.50*d*	3.69*d*	3.66*d*	4.03*p*	1.28*d*	3.50*s*	—		0.0	2.5	0.0	6.0	6.0	
2[b]	5.03*s*	3.5*m*	3.5*m*	3.5*m*	3.71*dq*	1.27*d*	3.44*s*	3.53*s*		0.0			~1	6.0	
3[b]	5.06*d*	2.11*d*	4.13*m*	3.5*m*	3.5*m*	1.25*d*	3.46*s*	3.39*s*	3.0 (3-OH)	2.5 ~0	~0			6.0	
4[b]	5.01*t*	2.07*t*	5.03*q*	3.82*dd*	3.52*dq*	1.12*d*	3.42*s*	3.33*s*	2.44 (Ts-Me)	3.5	3.5	3.5	8.0	6.0	
5[b]	4.73*d*		2.08*dd*			1.09*d*				4.5				6.0	
6[c]	4.90*dd*	2.19*ddd* ~ 1.93*ddd*	~3.4	3.76*dd*	4.03*dq*	1.13*d*	3.48*s*	3.28*s*		4.5 2.0	7.5 7.5	5.5	6.5	6.0	$J_{2,2'}$ 12.5
7[b,d]	5.53*dd* 5.46*dd*	~2.1*m*	~3.45*m*	~3.9*m*	~3.9*m*	1.16*d* 1.25*d*	—	3.40*s* 3.36s	4.4 (1-OH)	4.5 2.0 4.0 3.0				6.0 6.0	
8[b]	6.52*dd*	2.58*ddd* 2.31*ddd*	4.36*dt*	3.98*dd*	3.52*qd*	1.21*d*	—	3.36*s*		4.0 2.0	9.0 7.5	7.5	4.0	6.0	
9[b+e]	6.62*d*	2.60*ddd* ~ 2.29*dd*	~4.2*m*	~4.2*m*	3.52*qd*	1.21*d*	—	3.37*s*		5.5 ~0	~1 1.5		4.0	6.0	
11[b]	5.64*d*		4.23*td*	3.72*dd*	3.42*qd*	1.33*d*	—	3.42*s*		4.5 ~0	9.0 ~0	7.5	2.5	6.0	
13[b]	4.99*s*	3.98*d*	3.72*d*				3.48*s*	—		0.0	2.5	0.0			

14[b]	4.91*s*	3.83*d*	3.69*d*	3.78*d*	~4.0*m*	~4.2*m*	3.39*s*	—	3.21 (5-OH)	0.0	2.5	0.0	5.5	5.0	$J_{OH,H}$ 4.5
15[b]	4.82*s*	3.53*d*	3.61*dd*	3.30*dd*	3.00*ddd*	2.66*dd* 2.48*dd*	3.30*s*	—		0.0	2.5	1.0	7.0	4.0 2.5	$J_{5,5'}$ 5
16[b]	4.93*s*	3.79*d*	3.66*d*	3.61*d*	3.97*p*	1.30*d*	3.48*s*	—	3.18 (5-OH)	0.0	2.5	0.0	6.0	6.0	
17[b]	4.92*s*	3.49*d*	3.60*d*	3.74*d*	4.71*dq*	1.32*d*	3.42*s*	—	2.42 (Ts-Me)	0.0	2.5	0.0	8.0	6.0	
20[b]	5.04*dd*	2.32*ddd* 2.09*ddd*	4.05*dt*	3.69*t*	3.39*p*	1.31*d*	3.40*s*	—		1.5 4.5	7.5 9.5	6.0	6.0	6.0	
22[b]	5.11*dd*	2.31*dd*	~4.3*m*	~4.3*m*	~4.3*m*	1.30*d*	3.42*s*	—	7.72*d* 7.61*d* (2 NH)	5.0 ~0	8.5 ~0			6.0	$J_{NH,H}$ 7; 7
23[e]	5.44*dd*	2.10*dd*	~4.0*m*	~4.0*m*	~4.39*m*	1.17*d*	—	—	9.69*d* 9.01*d* (2 NH)	3.0 ~0	9.0 ~0			6.0	$J_{NH,H}$ 9; 7
24[b+e]	6.48*d*	2.47*dd*	~4.2*m*	~4.2*m*	~4.2*m*	1.20*d*	—	—	9.47 9.10 (2 NH)	3.0 ~0	9.0 ~0			6.0	$J_{NH,H}$ 5; 9
26[f]	5.79*d*		~4.4*m*	~4.4*m*	~4.4*m*	1.35*d*	—	—	8.22*d* 8.07*d* (2 NH)	4.2 ~0				6.0	$J_{NH,H}$ 7.5; 6.5
28[f]	5.72*t*		~4.4*m*	~4.4*m*	~4.4*m*	1.32*d*			8.75 8.30*d* (2 NH)	~4				6.0	$J_{NH,H}$ 6.5; 7.5

[a]On the δ scale. [b]Chloroform-*d* solution; Me_4Si as the standard. [c]CCl_4 solution; Me_4Si as the standard. [d]1:1 anomeric mixture. [e]Me_2SO-d_6 solution; sodium 4,4-dimethyl-4-silapentane-1-sulfonate as the standard. [f]Me_2CO-d_6 solution; Me_4Si as the standard.



the bulky groups at C-3 and C-4 are quasi-equatorially oriented, and only the α anomer contains one quasi-axial group, at C-1. It may be seen from Fig. 1, in which the $^2T_3$ and $^3T_2$ conformations of both anomers, as well as the "Newman" projection along the C-2–C-1 bond, are depicted, that the dihedral angle between the anomeric proton (H-1) and the two diastereomeric protons at C-2 (H_c and H_t)* is $\sim 30°$ and $\sim 90°$, respectively, in the preponderant conformer of the α anomer, but $\sim 30°$ and $\sim 150°$ for the β anomer. That means that, according to the Karplus equation[15], the relation $J_{1,2c} > J_{1,2t} = \sim 0$ can be expected for the α anomer, but two roughly equal values, $J_{1,2c} \approx J_{1,2t}$, for the β anomer. The data obtained for compounds

*H_c and H_t refer to the protons in *cis* and *trans* relationship to H-1.

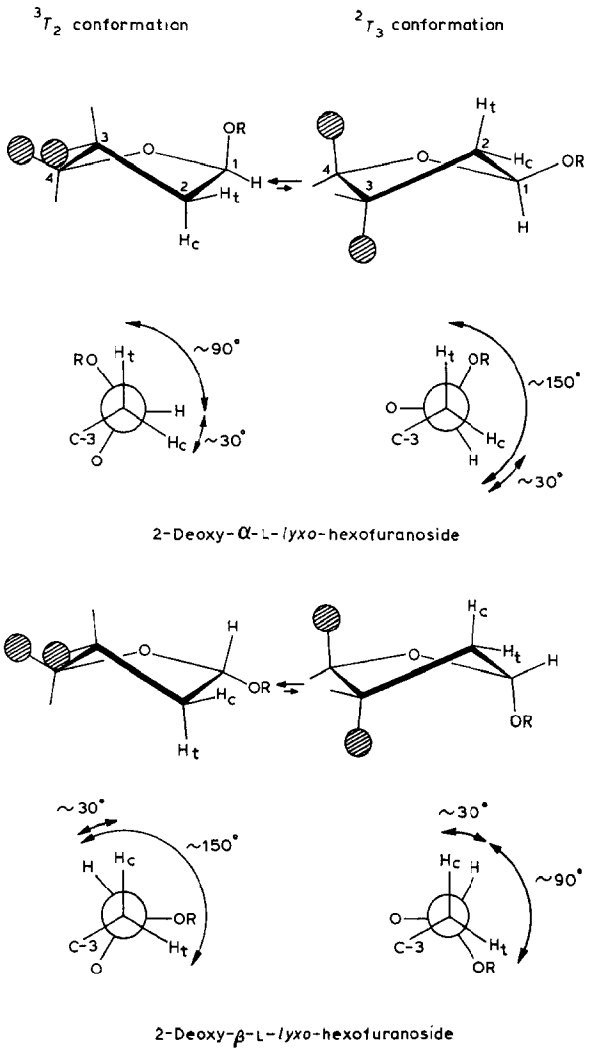


Fig. 1. $^3T_2$ and $^2T_3$ conformations, as well as "Newman" projections along the C-2–C-1 bond, of 2-deoxy-α- and -β-L-*lyxo*-hexofuranosides.

having known anomeric configurations (*e.g.*, **6**, **20**, and **22**), as well as from the spectrum of the anomeric mixture **7**, confirmed the data predicted (see Table I), and made determination of the chirality of the anomeric centers in compounds **11**, **26**, and **28** possible*.

The biological activity of the α-glycosides **11** and **27** was determined against P-388 lymphocytic leukemia in mice. The azide **11** showed no activity, whereas the

*From among the anomeric 1-(4-nitrobenzoates), **8** showed the splitting of the H-1 signal that is characteristic for α-glycosides, but **9** showed an unexpected splitting, which might indicate the presence of a different, preponderant conformation.

TABLE II

BIOLOGICAL ACTIVITY OF COMPOUND **27** AND CARMINOMYCINE ON P388 LYMPHOCYTIC LEUKEMIA IN MICE[a]

Compound **27**		*Carminomycine*	
Dose[b] *(mg/kg)*	*T/C (%)*	*Dose*[b] *(mg/kg)*	*T/C (%)*
0.03	118	0.03	156
0.1	141	0.1	196
0.3	153	0.3	213
1.0	170	1.0	toxic
3.0	180	3.0	toxic

[a]BD_2F_1 mice were injected i.p. with 10^6 P388 lymphocytic leukemia cells on day 0. [b]Treatment was performed i.p., on days 1, 2, 3, and 4, with the drug dose specified.

diamine **27**, although less active than carminomycine (see Table II), was also much less toxic (LD_{50} > 50 mg/kg), and consequently, the therapeutic index (ED_{50}/LD_{50}) of **27** was more favorable than that of carminomycine.

EXPERIMENTAL

General methods. — After organic solutions had been dried with sodium sulfate, all evaporations were conducted in a rotary evaporator under diminished pressure. Melting points are uncorrected. Light petroleum had b.p. 60–80°. Optical rotations were determined in chloroform (*c* 1), if not stated otherwise. T.l.c. was effected on Kieselgel G with (*A*) ethyl acetate, (*B*) 2:1, (*C*) 1:1, (*D*) 1:2, and (*E*) 1:3 ethyl acetate–carbon tetrachloride, (*F*) 1:1 ethyl acetate–ethanol, and (*G*) 10:5:2 chloroform–benzene–methanol. For detection, 1:1 0.1M potassium permanganate–M sulfuric acid was used at 105°. Column chromatography was performed on Kieselgel 40 (62–200 μm). ^{1}H-N.m.r. spectra (90 MHz) were recorded at room temperature with a Varian EM-390 spectrometer. Coupling constants are given in Hz.

*Methyl 2,3-anhydro-6-deoxy-5-*O*-methyl-α-*L*-gulofuranoside* (**2**). — To a stirred solution of epoxide[9] **1** (3.2 g) in *N*,*N*-dimethylformamide (60 mL) were simultaneously added methyl iodide (3 mL) and powdered potassium hydroxide (20 g) in small portions during 30 min at 30–35°. The mixture was stirred for 1 h at this temperature, and then filtered, and the filtrate was evaporated. The residue was dissolved in chloroform, and the solution was washed with water, dried, and evaporated. After column chromatography (solvent *A*), the fractions having R_F 0.8 gave, on evaporation, pure **2** as a colorless syrup (2.3 g, 66%); $[\alpha]_D^{20}$ −103°.

Anal. Calc. for $C_8H_{14}O_4$: C, 55.16; H, 8.10. Found: C, 55.02; H, 8.16.

*Methyl 2,6-dideoxy-5-*O*-methyl-α-*L*-xylo-hexofuranoside* (**3**) *and methyl 3,6-dideoxy-5-*O*-methyl-α-*L*-xylo-hexofuranoside* (**5**). — To a stirred solution of epoxide

2 (4.5 g) in dry ether (120 mL) was added lithium aluminum hydride (2 g) at −20°, and stirring was continued for 30 min at −10°. Thereafter, the temperature was raised to 0°, and, after 30 min, the excess of hydride was decomposed by gradually adding, first, ethyl acetate (8 mL), and then water (2 mL), 15% aqueous sodium hydroxide (2 mL), and water (6 mL). The inorganic salts were filtered off, and washed with ethyl acetate, and the filtrate and washings were combined, and evaporated, to yield a 17:3 mixture of **3** and **5** (determined by ^{1}H-n.m.r. spectroscopy) as a colorless syrup (4.3 g, 94.5%); $[\alpha]_D^{20}$ −121°; R_F 0.7 (*A*).

Anal. Calc. for $C_8H_{16}O_4$: C, 54.53; H, 9.15. Found: C, 54.40; H, 9.32.

*Methyl 2,6-dideoxy-5-*O*-methyl-3-*O*-p-tolylsulfonyl-α-*L*-xylo-hexofuranoside* (**4**). — To a solution of the mixture containing compound **3** and **5** (8.6 g), just described, in pyridine (50 mL) was added tosyl chloride (13.5 g), and the mixture was kept for 2 days at room temperature. Thereafter, it was poured into water, and the precipitate was filtered off, washed with water, dried, and recrystallized from ethanol, to give **4** (10.6 g, 66%); m.p. 100–103°, $[\alpha]_D^{20}$ −114.7°; R_F 0.85 (*A*).

Anal. Calc. for $C_{15}H_{22}O_6S$: C, 54.53; H, 6.71; S, 9.71. Found: C, 54.45; H, 6.55; S, 9.62.

*Methyl 3-azido-2,3,6-trideoxy-5-*O*-methyl-α-*L*-lyxo-hexofuranoside* (**6**). — To a stirred solution of tosylate **4** (10.3 g) in *N,N*-dimethylformamide (100 mL) was added sodium azide (3 g), and the mixture was heated for 30 min at 120°. Thereafter, it was evaporated, the residue obtained was dissolved in chloroform, and the solution was washed with water, dried, and evaporated, to give pure **6** as a pale-yellow syrup (5.2 g, 83%); $[\alpha]_D^{20}$ −93°; R_F 0.8 (*E*).

Anal. Calc. for $C_8H_{15}N_3O_3$: C, 47.75; H, 7.51; N, 20.88. Found: C, 47.62; H, 7.58; N, 20.71.

*3-Azido-2,3,6-trideoxy-5-*O*-methyl-*L*-lyxo-hexofuranose* (**7**). — A solution of methyl glycoside **6** (4.7 g) in 75% aqueous acetic acid was heated on a steam bath for 1 h. The solution was cooled, diluted with water, extracted with chloroform, and the extract successively washed with 5% aqueous solution of sodium hydrogencarbonate and water, dried, and evaporated; the residue was purified by column chromatography, first using solvent *E*, and after elution of the byproduct (R_F 0.8), with solvent *C*. On evaporation, the fractions having R_F 0.3 (*E*) gave **7** as a colorless syrup (2.0 g, 46.5%); $[\alpha]_D^{20}$ +83° (water; no mutarotation observed).

Anal. Calc. for $C_7H_{13}N_3O_3$: C, 44.91; H, 7.00; N, 22.45. Found: C, 44.80; H, 6.85; N, 22.12.

*3-Azido-2,3,6-trideoxy-5-*O*-methyl-1-*O*-(4-nitrobenzoyl)-α-*L*-lyxo-hexofuranose* (**8**) *and -β-*L*-lyxo-hexofuranose* (**9**). — To a stirred solution of compound **5** (3.4 g) in pyridine (50 mL) was added 4-nitrobenzoyl chloride (5 × 1 g, successively) during 2 h. The mixture was stirred for 20 h at room temperature, and then poured onto ice. The precipitated oil was dissolved in chloroform to give, after the usual processing, a crude mixture of the anomers, which were separated by column chromatography (*E*). On evaporation, the fractions having R_F 0.8 gave the α anomer **8** as a syrup (2 g, 33%); $[\alpha]_D^{20}$ −49.4°.

Evaporation of the fractions having R_F 0.7 gave, after recrystallization from carbon tetrachloride–hexane, pure β anomer **9** (2.15 g, 35%); m.p. 78–80°, $[\alpha]_D^{20}$ −113.5°.

Anal. Calc. for $C_{14}H_{16}N_4O_6$: C, 50.00; H, 4.80; N, 16.66. Found, for **8**: C, 49.72; H, 4.85; N, 16.32. Found, for **9**: C, 50.05; H, 4.80; N, 16.85.

7-O-(3-Azido-2,3,6-trideoxy-5-O-methyl-α-L-lyxo-hexofuranosyl)carminomycinone (**11**). — Through a cooled solution of the crystalline 1-(4-nitrobenzoate) **9** (2 g) in dry dichloromethane (20 mL) was passed a stream of dry hydrogen chloride until no more 4-nitrobenzoic acid was precipitated; then the slurry was filtered, the filtrate evaporated, and dry dichloromethane (20 mL) was added to, and evaporated from, the residue. A solution of this crude chloride **10** in dichloromethane (20 mL) was added to a stirred slurry of carminomycinone (2.4 g), mercuric oxide (1.2 g), mercuric bromide (2 g), and molecule sieve 3A (15 g) in dichloromethane (200 mL). Stirring was continued for 20 h, the slurry was filtered, and the filtrate was washed successively with water, 5% aqueous potassium iodide, and water, dried, and evaporated, to yield a crude mixture containing, besides **11** (R_F 0.9), unreacted aglycon (R_F 0.4) and its decomposition products. Despite the great difference in these R_F values, purification of **11** proved to be very difficult, and could be achieved only after two-fold, column chromatography using solvent *G* for elution. After evaporation, and recrystallization of the residue from dichloromethane–carbon tetrachloride or ethyl acetate–carbon tetrachloride, pure α-glycoside **11** was obtained (650 mg, 19.4% calculated on the aglycon); m.p. 195–197°, $[\alpha]_D^{20}$ +331°.

Anal. Calc. for $C_{27}H_{27}N_3O_{10}$: C, 58.58; H, 4.92; N, 7.59. Found: C, 58.42; H, 4.80; N, 7.45.

Methyl 2,3-anhydro-6-O-p-tolylsulfonyl-β-D-mannofuranoside (**14**). — To a stirred solution of epoxide[12] **13** (95.5 g) in pyridine (500 mL) was added gradually tosyl chloride (124 g) at −10°. The mixture was stirred for 5 h at −5°, and then poured into water. The precipitate was dissolved in chloroform, and processed in the usual way, to give, after evaporation of the chloroform solution, and recrystallization of the residue from ether, crude **14**, which was purified by recrystallization from ethanol (1.5 vol.), giving 105 g (59%) of **14**; m.p. 95–97°, $[\alpha]_D^{20}$ −40°; R_F 0.80 (*A*).

Anal. Calc. for $C_{14}H_{18}O_7S$: C, 50.90; H, 5.49; S, 3.71. Found: C, 50.72; H, 5.60; S, 3.85.

Methyl 2,3:5,6-dianhydro-β-D-mannofuranoside (**15**). — To a vigorously stirred solution of tosylate **14** (105 g) in chloroform (1 L) was added 4M methanolic sodium methoxide (100 mL). The mixture was stirred for a further 30 min at room temperature, and then washed with water (2 × 200 mL). The aqueous washings were re-extracted with chloroform, and the chloroform solutions were combined, dried, and evaporated, to yield diepoxide **15** as a colorless syrup (45 g, 89.5%); $[\alpha]_D^{20}$ −104.4°; R_F 0.7 (*B*).

Anal. Calc. for $C_7H_{10}O_4$: C, 53.16; H, 6.37. Found: C, 53.02; H, 6.45.

Methyl 2,3-anhydro-6-deoxy-β-D-mannofuranoside (**16**). — To a stirred solution of diepoxide **15** (45 g) in water (500 mL) was gradually added sodium borohydride

(25 g), without cooling. The mixture was stirred for 5 h at 55–60°, and then evaporated. The residue was extracted with chloroform, and the extract freed of inorganic salts by filtration, and evaporated. The residue was purified by column chromatography, using solvent *B* for elution. On evaporation, the fractions having R_F 0.4 gave **16** as a colorless syrup (38 g, 83.4%); $[\alpha]_D^{20}$ −115°.

Anal. Calc. for $C_7H_{12}O_4$: C, 52.49; H, 7.55. Found: C, 52.22; H, 7.03.

*Methyl 2,3-anhydro-6-deoxy-5-*O*-p-tolylsulfonyl-β-*D*-mannofuranoside* (**17**). — To a solution of **16** (38 g) in pyridine (200 mL) was added tosyl chloride (60 g), and the mixture was kept for 2 days at room temperature, poured into water, and the precipitated oil extracted with chloroform, to give, after processing in the usual way, **17** as a pale-yellow syrup (66 g, 89%); R_F 0.7 (*C*).

Anal. Calc. for $C_{14}H_{18}O_6S$: C, 53.49; H, 5.77; S, 10.20. Found: C, 53.11; H, 5.82; S, 10.04.

*Methyl 3,5-diazido-2,3,5,6-tetradeoxy-α-*L*-lyxo-hexofuranoside* (**20**). — To a stirred solution of epoxide **17** (38 g) in dry ether (1 L) was added lithium aluminum hydride (15 g) in small portions at −20°. Then, the temperature of the mixture was gradually raised during 30 min to −10°, and stirring was continued for another 30 min at this temperature. The excess of hydride was decomposed at −10°, as described for compound **3**, to yield, after similar processing, the crude 2-deoxy compound **18** as a syrup (R_F 0.65, *C*), which was unstable at room temperature and was therefore immediately mesylated.

To a stirred solution of the foregoing syrup in pyridine (50 mL) was added mesyl chloride (12 mL), while the temperature of the mixture was kept below 20° by gentle cooling. Thereafter, the mixture was kept for 3 h at room temperature, and was then poured into ice–water. The precipitated oil was dissolved in chloroform, to give, after the usual processing, the mixed ester **19** (R_F 0.2, *E*) as an unstable, yellow syrup. This was immediately dissolved in *N,N*-dimethylformamide (300 mL), and sodium azide (20 g) was added. The mixture was stirred for 1 h at 120°, and was then evaporated. The residue was partitioned between ether and water, and the ether layer was washed with water, dried, and evaporated. The residue was purified by column chromatography, using solvent *E* for elution. On evaporation, the fractions having R_F 0.9 gave diazide **20** as a pale-yellow syrup (15.7 g, 61.4%); $[\alpha]_D^{20}$ −4°.

Anal. Calc. for $C_7H_{12}N_6O_2$: C, 39.62; H, 5.70; N, 39.61. Found: C, 39.75; H, 5.80; N, 39.36.

*Methyl 2,3,5,6-tetradeoxy-3,5-bis(trifluoracetamido)-α-*L*-lyxo-hexofuranoside* (**22**). — A solution of diazide **20** (5 g) in ethanol (50 mL) was hydrogenated in the presence of 10% Pd–C catalyst (2 g) for 2 h at room temperature. According to t.l.c. (*F*), the starting material (R_F 0.95) was converted, *via* a monoamine (R_F 0.5), into the diamine **21** (R_F 0.1). The catalyst was filtered off, the filtrate was evaporated, the residue was dissolved in pyridine (15 mL), and trifluoroacetic anhydride (4 mL) was added dropwise, while the temperature was kept below 20° by ice-cooling. The mixture was kept at room temperature for a further 15 min, and was then poured into ice–water. The precipitated oil was dissolved in chloroform, to give,

after the usual processing, and recrystallization (from ether–petroleum ether) of the residue left on evaporation, pure diamide **22** (6.65 g, 80%); m.p. 102–104°, $[\alpha]_D^{20}$ −69.6°; R_F 0.8 (*C*).

Anal. Calc. for $C_{11}H_{14}F_6N_2O_4$: C, 37.51; H, 4.01; F, 32.36; N, 7.95. Found: C, 37.38; H, 4.20; F, 32.15; N, 7.82.

2,3,5,6-Tetradeoxy-3,5-bis(trifluoracetamido)-L-lyxo-*hexofuranose* (**23**). — A slurry of diamide **22** (6.4 g) in 75% aqueous acetic acid (150 mL) was heated on a steam bath for 5 h, and the solution obtained was evaporated. The residue was purified by column chromatography, using solvent *C* for elution. The fractions having R_F 0.7 gave, on evaporation, and recrystallization of the residue from ether–hexane, pure **23** (3.8 g, 63%); m.p. 143–145°, $[\alpha]_D^{20}$ −32° (pyridine).

Anal. Calc. for $C_{10}H_{12}F_6N_2O_4$: C, 35.51; H, 3.58; F, 33.71; N, 8.28. Found: C, 35.40; H, 3.72; F, 33.58; N, 8.17.

2,3,5,6-Tetradeoxy-1-O-(*4-nitrobenzoyl*)-*3,5-bis(trifluoracetamido)*-L-lyxo-*hexofuranose* (**24**). — To a stirred solution of **23** (2.6 g) in pyridine (20 mL) was added 4-nitrobenzoyl chloride (1.8 g) while the temperature was kept at 20° by gentle cooling. The mixture was kept overnight at room temperature, and was then processed in the usual way, to give, after evaporation of the chloroform solution, crude **24**, which was filtered with the aid of ether (2.5 g, 66.7%); m.p. 160–162°, $[\alpha]_D^{20}$ +26.5° (pyridine); R_F 0.5 (*D*).

Anal. Calc. for $C_{17}H_{15}F_6N_3O_7$: C, 41.90; H, 3.10; F, 23.39; N, 8.62. Found: C, 41.75; H, 3.28; F, 23.20; N, 8.50.

7-O-[*2,3,5,6-Tetradeoxy-3,5-bis(trifluoracetamido)*-α-L-lyxo-*hexofuranosyl*]*carminomycinone* (**26**) *and its β anomer* (**28**). — A solution of 4-nitrobenzoate **24** (2.5 g) in dry dichloromethane was converted into the glycosyl chloride **25**, and the latter was coupled with carminomycinone as described for **11**. The crude mixture of the anomers **26** and **28** was separated by two successive treatments by column chromatography, using solvent *G* for elution. On evaporation, and recrystallization of the residue from dichloromethane–carbon tetrachloride, the fractions having R_F 0.4 gave pure α anomer **26** (570 mg, 15.6%); m.p. 144–146°.

Anal. Calc. for $C_{30}H_{26}F_6N_2O_{11}$: F, 16.18; N, 3.98. Found: F, 16.03; N, 3.78.

The fraction having R_F 0.3 gave, on evaporation, pure β anomer **28** (490 mg, 13.4%), which was unstable, and decomposed on standing at room temperature.

7-O-(*3,5-Diamino-2,3,5,6-tetradeoxy*-α-L-lyxo-*hexofuranosyl*)*carminomycinone dihydrochloride* (**27**). — A solution of diamide **26** (110 mg) in 0.1M sodium hydroxide (15 mL) was stirred for 1.5 h at room temperature. Thereafter, ions were removed by successive treatment with cation- and anion-exchange resins. The suspension was filtered, the filtrate was acidified to pH 3 with M hydrochloric acid, and the solution was freeze-dried, to yield dihydrochloride **27** as an amorphous material (50 mg, 54.7%).

Anal. Calc. for $C_{26}H_{30}Cl_2N_2O_9$: C, 53.34; H, 5.17; Cl, 12.11; N, 4.79. Found: C, 53.20; H, 5.32; Cl, 11.85; N, 4.63.

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