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C-DAUNOSAMINYL DERIVATIVES BY THE WITTIG REACTION

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ABSTRACT

C-Glycosylation of a 2-deoxypyranose has been achieved for the first time by conversion of 4-*O*-*p*-nitrobenzoyl-*N*-trifluoroacetyldaunosamine in a Wittig reaction into the corresponding derivative of ethyl 2-(daunosaminyl)acetate. The product was predominantly (54%) in the desired α-L configuration (separated from the β-L anomer, 15%) required for further elaboration of *C*-daunosaminyl derivatives. Conversion into the corresponding derivatives of 2-(α-L-daunosaminyl)acetaldehyde and 2-(α-L-daunosaminyl)ethanol was also achieved.

INTRODUCTION

Daunosamine[1], the sugar that occurs in the clinically important antitumor drugs daunorubicin (**1**, R = H) and doxorubicin (Adriamycin; **1**, R = OH)[2], is 3-amino-2,3,6-trideoxy-L-*lyxo*-hexopyranose. As the *N*,*N*-dimethyl derivative, rhodosamine, it also occurs in several related antitumor anthracyclines, such as aclacinomycin A[3] and marcellomycin[4]. Methods for the chain elongation of daunosamine, starting from C-1, are of interest for the synthesis of *C*-glycosyl analogs of **1** (R = H or OH). Such isosteres as **2**, in which the glycosidic oxygen atom is replaced by CH_2, would be resistant to the rapid metabolic deactivation of **1** that occurs by reductive cleavage of the sugar[5]. The isosteres **2** might also be incapable of generating alkylating activity at the 7-position, one mechanism of action proposed[6] as following ejection of the sugar from **1**. On the other hand, **2** should retain the DNA-binding properties[2] of the anthracyclines and the free-radical generating properties from cyclic reduction and reoxidation of the quinone[7,8]. The *C*-glycosyl derivative **2** should thus give a good test of proposed mechanisms of action, and if the pattern of biological effects is favorably altered, it might prove to be a superior drug.

Synthetic routes to *C*-glycopyranosyl derivatives having the requisite 1,5-*trans** configuration for **2** have been described as particularly elusive[9], as compared with the more widely studied *C*-glycofuranosyl derivatives that have been encountered in syntheses of *C*-nucleosides[10]. Furthermore, the chemistry of 2-deoxy sugars is often difficult. The conventional synthesis of a glycosyl cyanide* from a glycosyl

*The *C*-glycosyl derivatives are here referred to as 1-substituted sugars in preference to the systematic nomenclature as anhydro sugars, in order to emphasize the analogy with *O*-glycosides.

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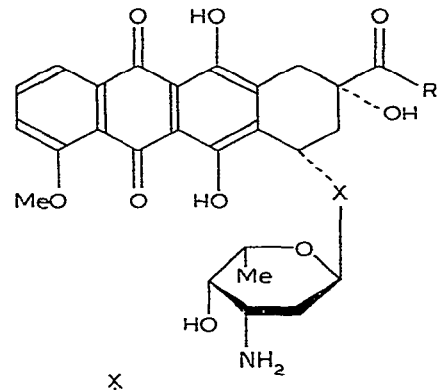
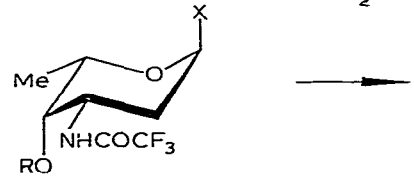
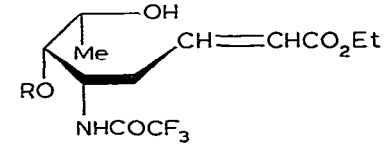


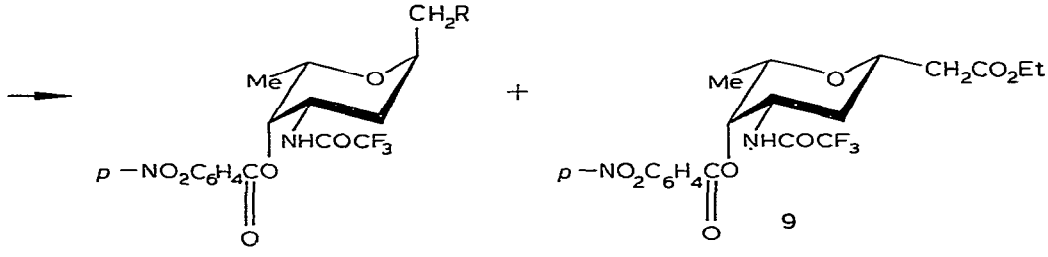
1, X = O
2, X = CH_2





3, X = Cl, R = $p-NO_2C_6H_4CO$
4, X = OMe, R = H
5, X = OMe, R = $p-NO_2C_6H_4CO$
6, X = OH, R = $p-NO_2C_6H_4CO$

7, R = $p-NO_2C_6H_4CO$



8, R = CO_2Et
10, R = CHO
11, R = CH_2OH
12, R = CO_2Me
13, R = CO_2H

chloride could be extended to 2-deoxy-*erythro*-pentofuranosyl chloride only after study and modification[11] of the normal reaction-conditions with use of inorganic cyanide. Conversions of 2-deoxypyranoses into *C*-glycosyl derivatives are virtually unknown, except for such rather remote examples as the preparation of tetrahydropyran-2-acetic acid by alkylating malonic ester with 2-chlorotetrahydropyran[12]. Our initial attempts to convert 4-*O*-*p*-nitrobenzoyl-3-*N*-trifluoroacetyldaunosaminyl chloride[13] (3) into the 1-cyanide gave little or no reaction, except for hydrolysis of the chloride, and that may have occurred during isolation. We now report the

successful *C*-glycosylation of 4-*O*-*p*-nitrobenzoyl-3-*N*-trifluoroacetyldaunosamine (**6**) by the Wittig reaction[14-16] with (ethoxycarbonylmethylene)triphenylphosphorane[9,17-20].

The 1-hydroxy sugar **6** was obtained from methyl 2,3,6-trideoxy-3-trifluoroacetamido-α-L-*lyxo*-hexopyranoside[21] (**4**) by conversion into the 4-*p*-nitrobenzoate **5** and hydrolysis of the methyl glycoside with 80% trifluoroacetic acid at room temperature. Presumably the latent aldehydo function of **6** reacted with the phosphorane to give the intermediate Wittig-reaction product **7**. Heating for 2 days at 110° in *N*,*N*-dimethylformamide solution, with monitoring of the reaction by t.l.c. of aliquots on silica gel in 1:1 ethyl acetate–hexane, was required for conversion of **6** (R_F 0.5) into the products **8** and **9** (unresolved, R_F 0.8). The alkenic intermediate **7** (R_F 0.6) could be isolated, and identified by the presence of vinyl protons in the ^{1}H-n.m.r. spectrum of incompletely reacted mixtures, but was apparently cyclized by this treatment. In an initial experiment, the product was isolated by preparative t.l.c. from trace contaminants and such by-products as triphenylphosphine oxide. It was then reanalyzed on silica gel with 91:10:5 chloroform–toluene–ethanol and found to consist of two components, R_F 0.75 (preponderant) and 0.65, later identified as the isomers **8** and **9**, respectively. On a larger scale, the initial purification was done by dry-column chromatography with elution of the product mixture, and **8** and **9** were resolved by preparative, high-performance liquid chromatography (l.c.). Reviews have indicated[22] that use of *N*,*N*-dimethylformamide is important for achieving ring closure in such reactions; when we attempted the condensation in refluxing oxolane (tetrahydrofuran)[20] solution, we observed no reaction at all.

After separation of the isomers by l.c., the preponderant (54% yield), more-mobile one showed $[\alpha]_D$ −38° in chloroform, whereas the minor (15% yield), less-mobile one had $[\alpha]_D$ +13°. Based on Hudson's rules, the desired α-L configuration (see footnote, p. 235) of structure **8** was assigned to the preponderant isomer*. Hudson's rules have been found applicable to *C*-glycosyl derivatives by a number of investigators[9,10,23,24]. Only one exception was observed in a series of *C*-glycofuranosyl derivatives[19]. Generally, the assignments have been supported by n.m.r. studies. As shown in Table I, the spectra of **8** and **9** were very similar in both the ^{1}H- and ^{13}C-n.m.r., consistent with the fact they are isomers. Assignment of the protons and determination of the proton coupling-constants were completed by addition of Eu(fod)$_3$ shift reagent[25,26] and use of decoupling techniques. Small differences between **8** and **9** in the coupling constants of the C-2 protons were observed that support the configurational assignment based on Hudson's rules. The $J_{1,2}$ values for the preponderant isomer, 7.4 and 7.9 Hz, were consistent[27-30] with the eq–eq and eq–ax interactions† of the α-L structure **8** in the probable $^1C_4$ (L) conformation depicted, even though the couplings were surprisingly identical and at the upper end of the accepted range. The minor isomer showed one $J_{1,2}$ coupling of 5.7 Hz, but the other,

*That the more levorotatory isomer should be *C*-α-L-glycosyl derivative follows from the rule that α-D anomers are more dextrorotatory than the β-D.

TABLE I

COMPARISON OF N.M.R. DATA OF **8** AND **9** (IN CHLOROFORM-*d*, Me_4Si INTERNAL REFERENCE)

^1H (at 60 MHz)[a]						*^{13}C (at 100 MHz)*[b]		
Group	*Chemical shifts, δ*		*Coupling*	*Coupling constants, Hz*		*Group*	*Chemical shifts, δ*	
	8	**9**		**8**	**9**		**8**	**9**
CO_2Et	1.23t	1.23t	J'_{1,CH_2CO_2R}	4.7	4.5	CH_3(Et)	14.106	14.151
6-H_3	1.43d	1.40d	J''_{1,CH_2CO_2R}	5.1	7.7	CH_3(C6)	16.259	15.866
H-2eq	2.02 qxd	2.13m	$J_{1eq,2eq}$	7.4	5.7	CH_2CO_2R	36.346	38.197
H-2ax	2.60 txd		$J_{1eq,2ax}$	7.9	8.8	C-2	38.732	40.156
CH_2CO_2R	2.79m	2.65m	J_{2gem}	14.0	13.2	C-3	52.538	52.011
H-4	4.05q	4.00t				CH_2(Et)	61.028	60.886
CO_2Et	4.16q	4.12q	$J_{2eq,3ax}$	5.1	3.0	C-5	71.252	71.595
			$J_{2ax,3ax}$	7.9	8.8			
H-1, H-3	4.3–4.75m	4.3–4.7m				C-1	74.804	75.006
H-5	5.30 quintet	5.32 sextet	$J_{3,4}$	3.3	4.7	C-4	86.687	85.487
aryl H-2′, H-6′	8.20d	8.19d	$J_{4,5}$	6.3	4.8			
aryl H-3′, H-5′	8.30d	8.30d				aryl	123.616	123.635
							130.616	130.847
			$J_{5,6}$	6.3	6.5			
			aryl J_{AB}	9.0	9.0	CF_3	not assigned	
						C=O	not assigned	

[a]Varian EM390 spectrometer. Complete analysis of the spectrum was achieved by use of $Eu(fod)_3$ shift reagent (Alfa Products), added as the solid in incremental amounts without special drying precautions until resolution of signals was achieved; at each step the spectrum was recorded, and decoupling techniques were applied as needed; a total of 20 mol% of $Eu(fod)_3$ was required for **8** and 50% for **9**, based on integration of the *tert*-butyl signal introduced. [b]Varian XL-100 spectrometer, with proton-noise decoupling of the spectrum.

8.8 Hz, must indicate[27-30] an ax–ax relationship† that in the $^1C_4$ conformation could occur only in the β-L structure **9**. Furthermore, the difference in $J_{2a,2e}$ between the major (14.0 Hz) and minor (13.2 Hz) isomers may be significant. In cases where the adjacent substituent is an electronegative group, it was found that the geminal coupling is smaller when the substituent is oriented between the protons (that is, is equatorial) than when it is oriented externally to the protons (namely, axial); values of 13.8 Hz (adjacent axial OR) and 12.4 Hz (adjacent equatorial OR) were given in an example[31]. If this applies at C-2 of **8** and **9** when the adjacent substituent is CH_2CO_2R (in place of OR), assignment of the α-L configuration **8** to the major isomer and β-L **9** to the minor isomer is consistent with $J_{2a,2e}$ values of 14.0 and 13.2 Hz, respectively. Assignment of **8** as the major isomer is further supported by the significant chemical-shift differences between H-2e and H-2a (δ 2.02 and 2.60, respectively), which reflects the fact that any interaction with the axial C-1 substituent can only be with H-2e and not with H-2a in the antiparallel orientation. On the other hand, H-2a and H-2e for **9** are indistinguishable (δ 2.13 m), consistent with their equal possibilities for interaction with the equatorial C-1 substituent.

Other confirmatory evidence was obtained by comparison of the ^{13}C-n.m.r. spectra. The greatest differences were in the chemical shifts of C-2 and of the CH_2CO_2R methylene carbon atom, 36.346 (major isomer) and 38.197 (minor isomer). The upfield signal (36.346 p.p.m.) was assigned to the axially oriented 1-CH_2CO_2R group present in structure **8**. The upfield shift of the axial CH_2 group was attributed to the steric proximity of the axial H-3 and H-5, based on observations with a series of methylcyclohexanes[32]. The downfield signal was consequently assigned to the equatorial 1-CH_2CO_2R group in **9**. (The eq–ax difference of the methyl groups in 1,1,3-trimethylcyclohexane as an example[32] was greater because the effect could not be relieved by conformational mobility.) Likewise, the chemical shift of C-2 in **8** upfield relative to the corresponding signal in **9** may be explained by the presence of an axial rather than an equatorial substituent at C-1. These differences in the ^{13}C-n.m.r. spectra are smaller than those cited[32], and they are used here as additional confirmation. Because of the agreement in applying the varied criteria given here, including those developed for *O*-glycosides, we consider that the anomeric configurations of **8** and **9** are correctly assigned.

For subsequent synthetic use and elaboration of the carbon chain, an intermediate of even greater utility than the ester **8** is the aldehyde **10**. In principle, **10** should be obtainable directly from **6** in a Wittig process analogous to that used for **8**. However, reaction of **6** with formylmethylenetriphenylphosphorane or the ylide derived from 1,3-dioxolan-2-yl-methyltriphenylphosphonium bromide[33] failed to provide any identifiable Wittig products. This caused us to explore the chemical modification of **8**.

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†Narrower ranges of coupling constants than those given in ref. 27 ($J_{ax,ax}$ 8–14, $J_{ax,eq}$ and $J_{eq,eq}$ 1–7 Hz) have been presented[28] ($J_{ax,ax}$ 8.6–11.5, $J_{ax,eq}$ 1.5–5.8, and $J_{eq,eq}$ 0.6–3.5 Hz), but with the proviso that larger coupling constants (such as we observed with **8**) tend to occur in pyranoid ring derivatives bearing a carbon atom at C-1.

Our initial efforts to further elaborate **8** were focused on conversion into the aldehyde **10**. Treatment of **8** with diisobutylaluminum hydride (DIBAL) or sodium bis(2-methoxyethoxy)aluminum hydride in oxolane at −78° afforded only unreacted **8** or mixtures of **8** and the alcohol **11**, with no detectable (t.l.c., n.m.r.) amounts of **10**. The methyl ester **12**, obtained in 93% yield by transesterification of **8** catalyzed by methanesulfonic acid, gave similar results with the foregoing reagents. Esters **8** and **12** failed to provide carboxylic acid **13** upon reaction with iodotrimethylsilane formed *in situ* from chloromethylsilane and sodium iodide[34], thus precluding synthesis of **10** *via* reduction of the acid chloride. However, alcohol **11** could be obtained by reaction of **8** in 3.5 equivalents of DIBAL in oxolane at 0°. The successful reduction of the ester group was accompanied by partial cleavage of the *N*-trifluoroacetyl group. This side-reaction required that the basic fraction from the mixture be subjected to reacylation with trifluoroacetic anhydride and hydrolysis with aqueous sodium hydrogencarbonate, to afford the alcohol **11** in 88% overall yield. Cleavage of *N*-trifluoroacetyl groups under basic conditions has previously been observed[35].

Two-phase oxidation of **11** with potassium dichromate in aqueous sulfuric acid–dichloromethane[36] was capricious, affording mixtures of **10** and unreacted **11** or the carboxylic acid **13**. The best yield of **10** was 41%. Oxidation of **11** with pyridinium chlorochromate[37], pyridinium dichromate[38], and dimethyl sulfoxide–*N*,*N*-dicyclohexylcarbodiimide[39] were all unsatisfactory, affording only mediocre (30–40%) yields of **10**. We found that the oxidation of **11** could best be achieved by the Swern[40] procedure using dimethyl sulfoxide–oxalyl chloride at −60°. This route afforded **10** in 73% isolated yield.

The synthetic availability of the esters **8** and **12**, the aldehyde **10**, and the alcohol **11** provides a versatile series of intermediates for further elaboration of *C*-daunosaminyl derivatives.

EXPERIMENTAL

General methods. — Solutions in organic solvents were dried over magnesium sulfate and filtered. Evaporations were carried out *in vacuo* on a rotary evaporator. Melting points are uncorrected. *N*,*N*-Dimethylformamide solvent was dried over calcium hydride and decanted prior to use. Oxolane(tetrahydrofuran) solvent was dried by distillation from lithium aluminum hydride immediately prior to use. Dimethyl sulfoxide and triethylamine were dried by distillation from calcium hydride immediately prior to use. I.r. spectra were determined on the solid products in Nujol mull. N.m.r. (^{1}H and ^{13}C) spectra were determined with solutions in $CDCl_3$, unless otherwise noted (Me_4Si internal reference, δ 0.0) with Varian EM390, and XL-100 spectrometers; signals are designated as s (singlet), d (doublet), t (triplet), q (quartet), or m (multiplet). We thank Mr. L. W. Cary for the ^{13}C spectra. Mass spectra were recorded with an LKB Model 9000 spectrometer at 12 eV or, for high resolution, with a CEC double-focusing spectrometer. We thank Dr. D. W. Thomas for the spectra and interpretations. Optical rotations, $[\alpha]_D$, were determined for 1% solutions

by using a Perkin–Elmer Model 141 polarimeter or Rudolph Research Model Autopol III automatic polarimeter. T.l.c. was conducted on 2 × 8 in. glass plates precoated with 0.25-mm layers of silica gel GF. Analytical high-performance liquid chromatography (l.c.) was performed with a Spectra-Physics Model 3500 liquid chromatograph by using a Waters 0.39 × 30 cm column (P/N 27477) of 10-μm silica gel. Preparative l.c. was performed with a Waters Associates Prep LC/system 500 instrument, a Prep Pak-500/silica cartridge column, and a refractive-index detector.

*Methyl 2,3,6-trideoxy-4-*O-p-*nitrobenzoyl-3-trifluoroacetamido-*α-L-lyxo-*hexopyranoside* (**5**). — A solution of 13.8 g (53.7 mmol) of methyl 2,3,6-trideoxy-3-trifluoroacetamido-α-L-*lyxo*-hexopyranoside (**4**, m.p. 112–113° with sublimation beginning at 108°, lit[21] m.p. 108–109°) in 400 mL of pyridine was cooled to 0°, stirred, and treated with 18 g (97 mmol) of *p*-nitrobenzoyl chloride. After 16 h, 20 mL of water was added, and stirring and cooling were continued for 1 h. The mixture was diluted with 500 mL of water and extracted with two 300-mL portions of chloroform. The combined chloroform solution was washed with 1.5M sulfuric acid (two, 600-mL portions), water (600 mL), saturated aqueous sodium hydrogencarbonate (three, 1-L portions), and water (500 mL). The dried chloroform solution was evaporated to give 23 g of residual oil that was crystallized from 50 mL of 2-propanol with gradual chilling to 0° to yield 21.5 g (98%) of **5**, m.p. 71–73°, $[\alpha]_D^{21}$ −200° (chloroform); λ_{max} 3.0 (NH), 5.79 and 5.82 shoulder (C=O), and 8.60 μm (CF_3); ^{1}H n.m.r. δ 8.23s (ArH), 5.40d (H-4, $J_{3,4}$ 2.4 Hz), 4.94 broad s (H-1), 4.58m (H-3), 4.18q (H-5, $J_{4,5}$ ~0.9, $J_{5,6}$ 6.6 Hz), 3.41s (OCH_3), and 1.19d (6-H_3).

Anal. Calc. for $C_{16}H_{17}F_3N_2O_7$: C, 47.3; H, 4.22; N, 6.89. Found: C, 47.3; H, 4.24; N, 6.70.

*2,3,6-Trideoxy-4-*O-p-*nitrobenzoyl-3-trifluoroacetamido-*α-L-lyxo-*hexopyranose* (**6**). — A solution of 21.5 g (52.9 mmol) of **5** in 100 mL of 80% trifluoroacetic acid was stored at 25° and monitored by t.l.c. analysis with 1:1 hexane–ethyl acetate. After 18 h there was 70–80% conversion into **6**, R_F 0.5, with 20–30% unreacted **5** at R_F 0.9. The solution was evaporated without heating, and the residue (dissolved in ethyl acetate) was resolved by preparative l.c. with 2:1 hexane–ethyl acetate as eluent. Fractions (200 mL) were monitored by t.l.c. The unreacted **5** containing unknown impurities was recovered from the first 2.4 L of eluate. An additional 2.6 L was collected and evaporated. The residual **6** crystallized from 20:10:1 hexane–ethyl ether–acetone with chilling to 10° to yield 8.0 g (38%) of **6**, m.p. 208–210°. The mother liquors were evaporated, and the residue was combined with the fraction of unreacted **5**, treated with 80% trifluoroacetic acid, and processed to yield an additional 3.2 g, m.p. 132–135°. After a third treatment, the total yield of **6** was 13.5 g (65%), R_F 0.24 by t.l.c. with 19:1 chloroform–methanol, $[\alpha]_D^{21}$ −210° (methanol); λ_{max} 2.89, 3.00 (NH, OH), and 5.88 μm (C=O); ^{1}H-n.m.r. (acetone-d_6) δ 8.35s (ArH), 5.44 broad s ($\nu_{1/2}$ 6 Hz, H-1), and 1.05d (CCH_3, J 6 Hz); m/z 375 (M^+ − OH, 12) and 348 (M^+ − CH_3CHO, 2.8). A sample recrystallized for analysis melted at 198–203°

but was identical by ^{1}H-n.m.r. with the sample melting at 134–138°; both were homogeneous by t.l.c.

Anal. Calc. for $C_{15}H_{15}F_3N_2O_7 \cdot 0.2\ H_2O$: C, 45.5; H, 3.92; N, 7.08. Found: C, 45.6; H, 3.92; N, 6.97.

Further processing and chromatography of the mother liquors afforded an isomer identified as the β-L anomer of **6**, m.p. 182–183°, R_F 0.33, $[\alpha]_D^{20}$ +3.5° (methanol); λ_{max} 2.90, 3.00 (OH, NH), 5.75, and 5.82 (C=O); ^{1}H-n.m.r. (acetone-d_6) δ 8.32s (ArH), 5.63dd (*J* 2 and 9 Hz, H-1)*, and 1.41d (CCH_3, *J* 6 Hz); *m/z* 375 (M^+ — OH, 3), 224 (30).

Anal. Calc. for $C_{15}H_{15}F_3N_2O_7 \cdot 0.5\ H_2O$: C, 44.9; H, 4.01; N, 6.98. Found: C, 45.15; H, 3.81; N, 6.75.

*Ethyl 2-(2,3,6-trideoxy-4-O-*p*-nitrobenzoyl-3-trifluoroacetamido-α- and β-*L*-lyxo-hexopyranosyl)acetate* (**8** and **9**). — A mixture of 5.50 g (14.0 mmol) of **6** and 5.50 g (15.8 mmol) of (ethoxycarbonylmethylene)triphenylphosphorane (Pfaltz and Bauer, Inc.) in 100 mL of dry *N,N*-dimethylformamide was refluxed under nitrogen, and aliquots were monitored by t.l.c. in 1:1 ethyl acetate–hexane. After two days, **6** (R_F 0.5) was completely converted into the products **8** and **9** (unresolved, R_F 0.8). Impurities of R_F 0.1 (presumably triphenylphosphine oxide) and R_F 0.2 were also observed. At intermediate stages of reaction, a component (R_F 0.6) was observed that was identified as the uncyclized alkene **7** from the appearance of vinylic protons (δ 7.2–6.7m and 6.0–5.85m) in the ^{1}H-n.m.r. spectrum when a sample was partly purified by preparative t.l.c., but after 2 days it was also gone. The mixture on completion of reaction was poured into 500 mL of ice and water, and the solution was extracted with three, 150-mL portions of ethyl ether. The combined ether solutions were washed with 300 mL of saturated aqueous sodium hydrogencarbonate and 300 mL of saturated aqueous sodium chloride solution, dried, and evaporated in the presence of ~100 mL of ICN dry-column silica gel (activity III) for dry-column chromatography. The impregnated silica gel was added to another 200 mL of dry silica gel in a column that was then eluted with 3 L of 5:1 hexane–ethyl acetate. Fractions (15 mL) were monitored by t.l.c. The triphenylphosphine oxide was retained on the column. Fractions 40–150 were combined and evaporated to yield 5.5 g (84%) of a mixture of **8** and **9**. The isomers were separated by preparative l.c. with 9:1 chloroform (reagent grade, 1% ethanol)–toluene. After the solvent front, **8** was eluted in a series of fractions (250 mL) totaling 2.25 L, one 250-mL fraction contained a mixture of **8** and **9**, and **9** was eluted in a volume of 3.7 L.

The residue from evaporation of the fractions containing **8** was crystallized from toluene in 2 crops to yield 3.6 g (54%) of **8**, m.p. 130–131°, $[\alpha]_D^{21}$ −38° (chloroform); λ_{max} 3.02 (NH), 5.78, 5.90 (C=O), 8.58 (CF_3), 11.98, and 14.0 μm.

Anal. Calc. for $C_{19}H_{21}F_3N_2O_8$: C, 49.4; H, 4.58; N, 6.06. Found: C, 49.2; H, 4.42; N, 5.93.

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*Assignments for the α- and β-anomeric configurations for **6** were based on the coupling constants of H-1 as previously used[21] in the assignment of anomeric configuration of daunosamine derivatives.

The residue from evaporation of the fractions containing **9** was crystallized from 20:1 cyclohexane–ethyl acetate to give 1.0 g (15.4%) of **9**, m.p. 124–126°, $[\alpha]_D^{21}$ +13° (chloroform); λ_{max} 3.02 (NH), 5.78, 5.90 (C=O), 8.60 shoulder $(CF)_3$, 11.78, and 13.85 μm.

Anal. Found: C, 49.3; H, 4.83; N, 5.95.

*Methyl (2,3,6-trideoxy-4-*O*-p-nitrobenzoyl-3-trifluoroacetamido-α-*L*-lyxo-hexopyranosyl)acetate* (**12**). — The ethyl ester (**8**, 504.4 mg, 1.092 mmol) and methanesulfonic acid (72 μL) were dissolved in methanol and boiled for 16 h under reflux. The solution was allowed to cool, diluted with chloroform (100 mL), washed with saturated aqueous sodium hydrogencarbonate (2 × 20 mL) and saturated sodium chloride (20 mL), dried, and evaporated. The residue contained two components by t.l.c. (19:1 chloroform–methanol). The minor and more-polar component was identified in an earlier experiment as the *N*-deacylated product, methyl (3-amino-2,3,6-trideoxy-4-*O*-*p*-nitrobenzoyl-α-L-*lyxo*-hexopyranosyl)acetate, by its n.m.r. spectrum; ^{1}H-n.m.r. δ 8.19 m (ArH), 5.25 m (H-5), 4.42 m (H-1, H-4), 3.62 s (CO_2CH_3) 3.40 m (H-3), 2.3–2.7 m (CH_2CO and H-2eq), 1.55–2.00 m (H-2ax and NH_2, becomes 1H m on addition of D_2O), and 1.40 d (6-H_3). The residue was dissolved in oxolane (12 mL) and cooled to 0°. Trifluoroacetic anhydride (2.0 mL) was added and the solution stirred for 4 h at 23°. The solution was evaporated and the residue crystallized from ether–hexane to afford 454.4 mg (93%) of **12**, m.p. 118°; λ_{max} 3.05 (NH), 5.76, and 5.88 μm (C=O); ^{1}H-n.m.r. δ 8.20 m (NH and ArH), 5.28 quintet (H-5), 4.50 m (H-1, H-4), 4.02 m (H-3), 3.68 s (CO_2CH_3), 2.5–2.8 m (H-2eq and CH_2CO), 1.8–2.2 m (H-2ax), and 1.43 d (6-H_3).

Anal. Calc. for $C_{18}H_{19}F_3N_2O_8$: C, 48.2; H, 4.28; N, 6.25. Found: C, 48.2; H, 4.20; N, 6.14.

*2-(2,3,6-Trideoxy-4-*O*-p-nitrobenzoyl-3-trifluoroacetamido-α-*L*-lyxo-hexopyranosyl)ethanol* (**11**). — To a solution of the ethyl ester **8** (2.70 g, 5.84 mmol) in dry oxolane (81 mL) under nitrogen at 0° was added DIBAL (13.5 mL of a 1.52M solution in toluene, 20.5 mmol; Aldrich) dropwise. The solution was stirred for 3 h at 0°, methanol (75 mL) was added, and the mixture was stirred for 1.5 h at 23°. The mixture was filtered through Celite, and the Celite pad was washed with 50 mL of 19:1 chloroform–methanol and with two, 50-mL portions of ethyl acetate. The filtrate and washings were combined and evaporated. The residue was dissolved in ethyl acetate (75 mL). The solution was extracted with 0.5M citric acid (3 × 25 mL), washed with saturated aqueous sodium hydrogencarbonate (10 mL), and saturated sodium chloride (10 mL), dried, and evaporated. The residue was crystallized from ethyl acetate–hexane to afford 1.08 g of **11**; m.p. 144–146°; λ_{max} 2.80, 3.05 (OH, NH), 5.79, and 5.88 μm (C=O); ^{1}H-n.m.r. δ 8.37 d (*J* 9 Hz, aryl H-3′ and H-5′), 8.21 d (*J* 9 Hz, aryl H-2′ and H-6′), 5.37 quintet (H-5), 4.48 m (H-3, H-4), 4.04 m (H-1), 3.82 m (CH_2OH), 2.62 m (H-2eq), 1.88 m (H-2ax and CH_2CH_2OH), and 1.48 d (6-H_3).

Anal. Calc. for $C_{17}H_{19}F_3N_2O_7 \cdot 0.5\ H_2O$: C, 47.6; H, 4.71; N, 6.52. Found: C, 47.3; H, 4.48; N, 6.33.

The mother liquors were evaporated to afford 275.7 mg of **8** (R_F 0.55) contaminated with a small amount (<10%) of *p*-nitrobenzoyl alcohol (R_F 0.36), as determined by t.l.c. with 19:1 chloroform–methanol.

The acid extracts from the foregoing were combined, made neutral with solid sodium hydrogencarbonate, and extracted with chloroform (3 × 25 mL). The extracts were combined, washed with water (10 mL), dried, and evaporated. The residue was dissolved in dichloromethane (40 mL) and cooled to 0°. Trifluoroacetic anhydride (20 mL) was added and the solution stirred for 15 min at 0° and for 4 h at 23°. The solution was evaporated and the residue dissolved in ethyl acetate (20 mL) and stirred with saturated aqueous sodium hydrogencarbonate (30 mL) for 16 h. The organic phase was separated and the aqueous phase extracted with ethyl acetate (20 mL). The organic solutions were combined, washed with water (10 mL), 0.5M citric acid (10 mL), water (10 mL), and saturated sodium chloride (10 mL), dried, and evaporated. The residue was recrystallized 3 times from ethyl acetate–hexane to afford an additional 0.64 g of **11**. The total yield of **11** was 1.72 g (70%, 88% based on unrecovered **8**). The mother liquors from the first 2 recrystallizations were combined to afford an additional 275 mg of **8**.

(*2,3,6-Trideoxy-4-*O-p-*nitrobenzoyl-3-trifluoroacetamido-*α-L-lyxo-*hexopyranosyl)acetaldehyde* (**10**). — Oxalyl chloride (95 mg) in dichloromethane (0.5 mL) was cooled to −70°, dimethyl sulfoxide (150 mg) in dichloromethane (0.2 mL) was added dropwise, and the mixture stirred for 10 min at −70°. A solution (0.4 mL) of alcohol **11** (142 mg, 0.338 mmol) in 1:1 dichloromethane–dimethylsulfoxide was added dropwise during 5 min, and the solution was stirred for 2.5 h at 70–30°. Triethylamine (0.5 mL) was added dropwise during 5 min and the mixture was allowed to warm to 23°. Water (20 mL) was added and the mixture was extracted with dichloromethane (3 × 8 mL). The extracts were combined, washed with water (5 mL), M hydrochloric acid (5 mL), water (5 mL), saturated aqueous sodium hydrogencarbonate (2 × 5 mL), and saturated sodium chloride (10 mL). Drying and evaporation afforded 102 mg (73%) of **10**, homogenous by t.l.c.; R_F 0.43 (1:1 ethyl acetate–hexane) and n.m.r. spectrum. An analytical sample of **10** was prepared by preparative t.l.c. with 19:1 chloroform–methanol and recrystallization from chloroform–hexane; m.p. 140–148°; λ_{max} 3.00 (NH), 5.75, and 5.86 μm (C=O); ^{1}H-n.m.r. δ 9.78 s (CHO), 8.33 d (*J* 9 Hz, aryl H-3 and H-5), 8.19 d (*J* 9 Hz, aryl H-2 and H-6), 5.34 quintet (H-5), 4.56 m (H-3, H-4), 4.04 m (H-1), 2.86 m (CH_2CHO), 2.5–2.8 m (H-2eq), 1.65–2.00 m (H-2ax), and 1.47 d (6-H_3).

Anal. Calc. for $C_{17}H_{17}F_3N_2O_7 \cdot 1.25\ H_2O$: C, 46.5; H, 4.01; N, 6.38. Found: C, 46.5; H, 3.96; N, 6.13.

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