Carbohydrate Research, 58 (1977) 125–138

PREPARATION OF 3-AMINO-2,3,6-TRIDEOXY-D-*arabino*-HEXOSE HYDROCHLORIDE AND ITS *N*-TRIFLUOROACETYL DERIVATIVE*

DEREK HORTON, RODERICK J SORENSON, AND WOLFGANG WECKERLE
Department of Chemistry, The Ohio State University, Columbus, Ohio 43210 (U. S. A.)
(Received December 11th, 1976, accepted for publication, January 11th, 1977)

ABSTRACT

Methyl 3-acetamido-4,6-*O*-benzylidene-2,3-dideoxy-α-D-*arabino*-hexopyranoside (**5**) was converted by treatment with *N*-bromosuccinimide into the 4-*O*-benzoyl-6-bromo derivative **6**. Reduction with Raney nickel followed by catalytic transesterification of the resultant 4-benzoate **7** afforded methyl 3-acetamido-2,3,6-trideoxy-α-D-*arabino*-hexopyranoside (**8**), which could readily be converted into the 4-acetate **11**. *N*-Deacetylation of **7** and subsequent acid hydrolysis furnished 3-amino-2,3,6-trideoxy-D-*arabino*-hexose hydrochloride (**9**), the D enantiomorph of acosamine. The 3-benzamido analog (**12**) of **8** was prepared from **8** by *N*-deacetylation and subsequent benzoylation. Hydrolysis of **8** and **12** gave the 3-acetamido (**10**) and 3-benzamido (**13**) analogs of **9**, which crystallized in the α anomeric form. 2,3,6-Trideoxy-3-trifluoroacetamido-α-D-*arabino*-hexopyranose (**15**), a key intermediate for the synthesis of glycosidically coupled derivatives of **9**, was obtained from **7** by saponification with barium hydroxide followed by *N*-trifluoroacetylation of the resultant glycoside **14** and subsequent, selective hydrolysis.

INTRODUCTION

Daunosamine (3-amino-2,3,6-trideoxy-L-*lyxo*-hexose), the sugar constituent of the important, antitumor antibiotics daunorubicin[2,3], adriamycin[3,4], and carminomycin[5], is the best known of the 3-amino-2,3,6-trideoxyhexoses. These amino sugars have received much attention during the past few years because of the occurrence[6–8] of some of them in several antibiotics and because of interest in structural analogs[9–16] of daunosamine. Such analogs may be coupled[13,16] to an appropriate aglycon in order to obtain new, structurally related compounds, possibly having better therapeutic indices than daunorubicin and adriamycin, which exhibit certain undesirable side-effects, especially a cumulative, dose-related cardiotoxicity[17]. Thus, semisynthetic daunorubicin analogs having the L-*arabino*[16], 6-hydroxy-L-*arabino*[18], and

*For a preliminary report, see ref. 1.

L-*ribo*[13] stereochemistry in the amino sugar moiety have already been prepared, and some of these appear to display significant antitumor activity and/or less toxicity than the parent antibiotics.

Accordingly, the development of convenient, high-yielding routes to structural analogs of daunosamine was considered a desirable objective after a simple, preparative route to daunosamine itself had been developed[10]. A recent report from this laboratory had described[14] a sequence of reactions for converting methyl α-D-mannopyranoside into the 5-epimeric 3-amino-2,3,6-trideoxy-D-*ribo*-hexose[14], and a similar route with methyl α-L-rhamnopyranoside as the starting compound was demonstrated[15] to offer excellent potential for preparations of 3-amino-2,3,6-trideoxy-L-*ribo*-hexose (ristosamine[7]) and its L-*arabino* epimer (acosamine[6]). We now report a facile synthesis of 3-amino-2,3,6-trideoxy-D-*arabino*-hexose (D-acosamine) hydrochloride and its *N*-trifluoroacetyl derivative, the latter constituting a key intermediate in the synthesis of new, possibly antitumor, anthracycline analogs having the D-*arabino* configuration in the carbohydrate residue.

DISCUSSION

The starting point for the synthesis was methyl 3-acetamido-4,6-*O*-benzylidene-2,3-dideoxy-α-D-*arabino*-hexopyranoside (**5**), obtained[19] (Route A) as a side-product in the synthesis of daunosamine[19] and its D-*ribo* analog[14] at the step when the amino group was introduced at C-3. Reduction of the oxime of the 3-ketose **1** with lithium aluminum hydride in ether, followed by acetylation, afforded a 7:1 mixture of the syrupy D-*ribo* product **4** and the crystalline D-*arabino* diastereoisomer **5**; these were separated quantitatively, without recourse to chromatography, by exploiting the very low solubility of **5** in toluene[19]. In order to produce **5** in larger quantities, a different route (Route B) was later adopted, involving[20] reduction of the ketone **1** by lithium aluminum hydride to the corresponding diastereoisomeric alcohols **2** and **3**. In our hands, reduction of the ketone as described by Overend and co-workers[20], but with a procedural modification (see Experimental) for large-scale operations, proved to be less stereospecific, but still strongly in favor of the desired D-*ribo* product **2** (~ 10:1, as compared[20] to 19:1). Mesylation of **2**, and azide exchange[21,22] with concurrent inversion at C-3, followed[21] by reduction and acetylation, afforded **5** in 40% overall yield from **1**, as compared with 10% by route A.

The benzylidene glycoside **5** in carbon tetrachloride reacted readily with *N*-bromosuccinimide, by the general procedure of Hanessian[23], to give the 4-*O*-benzoyl-6-bromo-6-deoxy analog **6**. This compound was isolated crude in high yield, but it proved somewhat difficult to recrystallize. In the p.m.r. spectrum of **6** (see Table I), the low-field location of the H-4 resonance (as compared with that of the precursor **5**) is a characteristic feature, and is attributable to the deshielding effect of the benzoyl group introduced. The well-resolved spectrum indicates the presence of four consecutive, *trans*-diaxial protons (on C-2–C-5), and unequivocally establishes that **6** has the *arabino* configuration in the $^4C_1$ (D) conformation. Elemental com-

TABLE I

100-MHz N.M.R.-SPECTRAL DATA FOR COMPOUNDS 6–8 AND 10–15

Compound[a]	Chemical shifts (δ)[b] (First-order couplings, Hz, in parentheses)												
	H-1 ($J_{1,2a}$)	H-2e ($J_{1,2e}$)	($J_{2e,2a}$)	H-2a ($J_{2a,3}$)	H-3 ($J_{2e,3}$)	H-4 ($J_{3,4}$)	H-5 ($J_{4,5}$)	H-6 ($J_{5,6}$)	Aryl	NH[c] ($J_{3,NH}$)	OR-1[d] ($J_{1,OH}$)	NAc	OH-4[e] ($J_{4,OH}$)
6[e]	4.83dd (3.5)	2.23m (1.0)	(13.8)	1.76m (11.5)	4.65m (4.8)	5.04t (9.8)	4.18m (9.8)	3.50m (3.2)	8.16–7.30m	6.40d (8.5)	3.39s	1.76s	
7	4.73dd (3.5)	2.26m (1.3)	(13.8)	1.69m (11.2)	4.57m (4.5)	4.80t (10.0)	4.05dq (9.0)	1.19d (6.4)	8.15–7.30m	6.19d (7.8)	3.34s	1.78s	
8	4.73dd (3.0)	2.07m (1.5)	(12.5)	1.64m (12.5)	4.17m	3.09m (9.0)	3.69m (9.0)	1.27d (6.5)		6.66d (7.2)	3.33s	1.99s	4.58d (4.0)
10[f,g]	α 5.05m (4.0)	←— 1.80–1.20m —→ (2.0)			3.73m	2.86m (9.5)	3.22m (9.5)	1.07d (6.0)		7.68d (8.0)	6.10d (3.5)	1.78s	4.78d (5.0)
	β 4.85m (8.5)	←— 1.80–1.20m —→ (3.0)						1.12d (6.0)		7.79d (8.0)	6.47d (6.5)		4.95d (5.0)
11[h]	4.69dd (3.0)	2.19m (1.0)	(13.5)	1.58m (11.5)	←4.20–4.67m→ (3.0)		3.88m (9.0)	1.15d (6.5)		5.86d (7.0)	3.31s	1.88s	
12[f]	4.67dd (3.5)	1.94m (1.0)	(13.5)	1.75m (12.0)	4.16m (5.0)	3.15m (10.0)	3.57m (10.0)	1.16d (6.0)	8.00–7.30m	8.15d (8.0)	3.25s		4.94d (6.0)
13[f,i]	α 5.13m (3.0)	←— 2.10–1.40m —→ (1.0)		(11.5)	4.30m	3.16m	3.85dq	1.12d (6.0)	8.00–7.20m	8.13d (8.0)	6.16d (3.5)		4.88d (5.5)
	β 4.73m (8.0)	←— 2.10–1.40m —→ (3.0)			(4.5)	(9.5)	(9.5)	1.18d (6.0)		8.26d (8.0)	6.53d (6.5)		4.92d (5.5)
14[f,j]	5.03s[c] (W_H 7)	←— 2.35–1.98m —→			4.37m	3.45dt (9.5)	3.89dq (9.5)	1.51d (6.0)		9.48d (8.8)	3.61s		5.45d (6.5)
15[f,k]	5.46d[c]	←— 2.25–1.85m —→			4.47m	3.42dt (9.6)	4.15dq (9.6)	1.48d (6.0)		9.44d (8.8)	6.56d (3.5)		5.38d (6.3)

[a] In chloroform-*d*, unless otherwise stated. [b] Signal multiplicities: d, doublet; m, multiplet; q, quartet; s, singlet; t, triplet. [c] Broadened signal. [d] R = Me for glycosides, and R = H for reducing sugars. [e] The signals for H-6 and H-6′ partly overlap and form a complex, second-order pattern; $J_{5,6}$ 5.5 Hz. [f] In methyl sulfoxide-d_6. [g] About 55% of α and 45% of β anomer present. [h] Signal for OAc at δ 2.03 s. [i] About 77% of α and 23% of β anomer present. [j] Compare the spectrum for the L enantiomer depicted in ref. 29. [k] Only the α-D anomer present.

TABLE II

MASS-SPECTRAL DATA FOR COMPOUNDS 6-8 AND 10-15

m/e *of principal fragments*[a] (% *of base peak*)										*Assignment*[b]
Compound 6	7	8	10	11	12	13	14	15		
387 (0.1)	308 (0.1)	204 (0.3)	190 (0.2)	246 (0.2)	266 (0.11)	252 (0.12)	258 (–)	244 (–)		M + 1
386 (0.1)	307 (0.3)	203 (0.5)	189 (0.3)	245 (0.5)	265 (0.3)	251 (0.26)	257 (0.02)	243 (0.05)		M·
385 (0.1)	306 (0.03)	202 (0.1)	188 (0.2)	244 (0.08)	264 (0.08)	250 (–)	256 (0.02)	242 (0.1)		M – 1
354 (1.1)	275[1] (0.3)	171 (8)	171 (4.4)	213[1] (2.1)	233 (6)	233[1] (4.1)	225 (1.05)	225 (2.5)		A_1
232 (0.2)	153[2] (8)	153 (3.5)	153 (2.5)	153[1,2] (19)	215 (2.7)	215 (4.5)	207[1] (0.3)	207[1] (0.82)		A_2
138 (6)	138[1] (1.9)	138 (1.7)	138 (3.2)	138[1] (4.1)	200 (1.6)	200[1] (6.2)	192 (0.6)	192 (0.9)		A_3
263 (4)	185 (8)	185 (0.9)	171 (4.4)	185[1] (12)	247 (1.3)	233 (4.1)	239 (0.22)	225 (2.5)		B_1
205 (1.1)	142[1] (6)	142 (1.8)	128 (4.5)	142[1] (22)	142 (2.3)	128 (1)	142 (0.22)	128 (0.5)		B_2
355 (0.2)	276 (2)	172 (9)	172 (3.6)	214 (9)	234 (3.6)	234 (–)	226 (5)	226 (0.48)		C_1
296 (0.1)	217[1] (0.7)	113[1] (12)	113 (2.9)	155[1] (2.2)	113 (5)	113 (0.13)	113[1] (15)	113[1] (2.7)		C_2
174 (0.2)	95[1] (9)	95[1] (5)	95 (2.2)	95 (32)	95[1] (2.2)	95 (0.25)	95 (1.8)	95 (1)		C_3
263 (4)	263 (1.1)	159 (3)	145[1] (4.3)	201 (2.5)	221 (1.2)	207 (3.1)	213 (1.6)	199 (3.3)		D_1
205 (1.1)	205[1] (3)	101[1] (80)	101[1,2] (41)	143[1] (25)	163 (24)	163 (6.1)	155[2] (31)	155[2] (42)		D_2
163 (0.1)	163 (1.8)	59[1] (100)	59[1] (78)	101[1] (68)	—	—	—	—		D_3
328 (0.02)	249 (0.05)	145 (0.28)	145[1] (4.3)	187 (0.26)	207 (0.22)	207 (3.1)	199 (2.2)	199 (3.3)		E_1^2
58 (9)	58 (2.6)	58 (23)	44 (67)	58 (15)	58 (8)	44 (1.2)	58 (39)	44 (24)		E_1^1
129 (0.3)	129 (0.23)	129 (46)	115 (34)	129 (4.2)	191[1] (20)	177 (7.3)	183 (4.5)	169[1] (28)		F_1^1
114 (0.3)	114[1] (0.5)	114[1] (8)	—	114[1] (4.5)	176[1] (2.7)	—	168 (1.7)	—		F_2^1
128 (26)	128 (11)	128 (2.6)	114 (23)	128 (35)	190 (3.2)	176 (3.9)	182 (1)	168[1] (5)		F_1^2
86 (12)	86 (5)	86 (14)	86 (35)	86 (34)	148 (2.4)	148 (4.8)	140 (3.5)	140 (29)		G_1^1
72 (6)	72 (2)	72 (23)	72 (61)	72 (11)	134[1] (0.43)	134 (0.19)	126 (0.8)	126 (2.4)		G_1^2
—	—	86 (14)	86 (35)	—	148 (2.4)	148 (4.8)	140 (3.5)	140 (29)		H_1
105 (100)	105 (100)	—	—	—	105 (100)	105 (100)	—	—		$PhCO^+$
77[3] (39)	77[3] (21)	—	—	—	77[3] (25)	77[3] (31)	—	—		Ph^+
43 (42)	43 (17)	43 (61)	43 (100)	43 (16)	—	—	—	—		Ac^+
—	—	60 (18)[c]	60 (100)[c]	[d]	122 (12)[e]	122 (24)[e]	[f,g]	[f,h]		other

[a]Prominent, metastable fragments observed in the spectra are indicated by superscript numbers at the daughter ion of the process involved; number 1 refers to a process within a single series, and number 2 to either $E_1^2 \rightarrow D_2$ or $B_1 \rightarrow A_2$ (see Scheme 1); number 3 is used for the decomposition of 105→77. Deviations between observed and calculated values are less than ±0.1 mass units. [b]By adaptation to fragmentation pathways proposed by Vigevani *et al.* for daunosamine derivatives (see ref. 26). [c]$H_3CCONH_3^+$. [d]*m/e* 59[1] (20%; D_3 – ketene); 44[1] (8%; G_1^1 – ketene). [e]$PhCONH_3^+$. [f]*m/e* 69 (intensities for **14**/**15**: 10/21%; CF_3^+); 86[1] (17/100%; $D_2 - F_3C\cdot$); 58[1] (39/22%, $D_2 - F_3CCO\cdot$). [g]*m/e* 59 (100%; *O*-methyloxiranyl cation; *cf.* ref. 26) [h]*m/e* 45 (27%; oxiranyl cation, *cf.*, ref. 26)

position, and i.r. and mass spectroscopic data (see Table II), are in full agreement with the structure indicated.

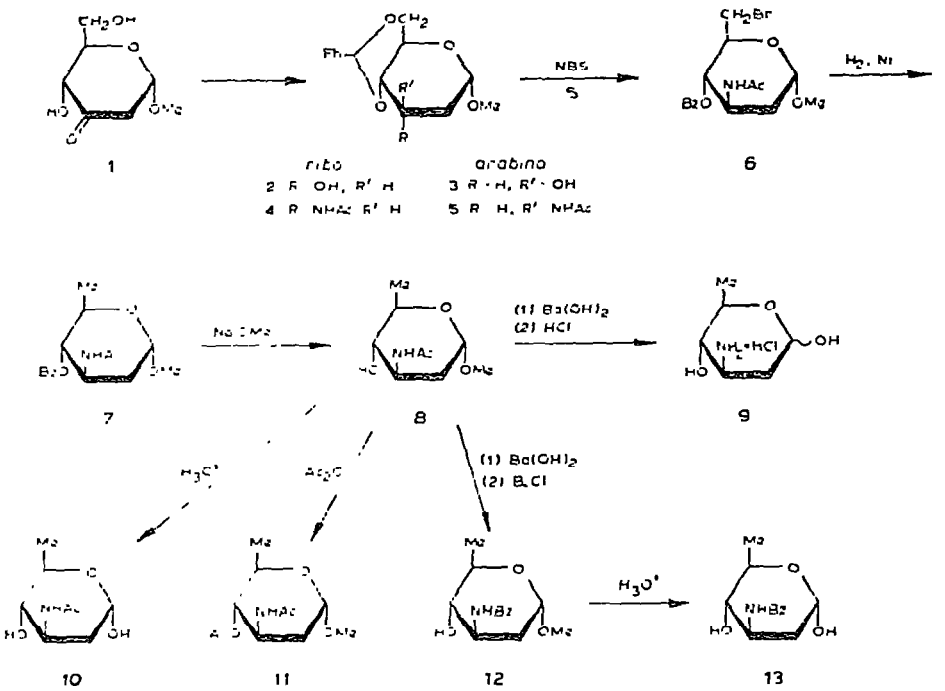
Reductive dehalogenation of **6** with Raney nickel in the presence of triethylamine furnished a quantitative yield of the 6-deoxy derivative **7**, which displayed in its p.m.r. spectrum (see Table I) the anticipated 3-proton doublet at high field (δ 1.19) for the 5-*C*-methyl group. Removal of the benzoyl group by catalytic transesterification led to methyl 3-acetamido-2,3,6-trideoxy-α-D-*arabino*-hexopyranoside (**8**), whose physical constants are in excellent agreement with those reported by Richardson[21] for this product obtained by an independent route. The L enantiomorph of **8** was first[6] prepared from acosamine, the carbohydrate constituent of the antibiotic actinoidin, and has since been synthesized by two independent laboratories[10,11].

Removal of the *N*-acetyl group of **8** with aqueous barium hydroxide, and subsequent cleavage of the glycosidic bond under mildly acidic conditions afforded 3-amino-2,3,6-trideoxy-D-*arabino*-hexose, isolated as its crystalline hydrochloride salt **9** in 94% yield. The latter melted at 172–174°, and showed a complex mutarotation that reached $[\alpha]_D$ +94° at equilibrium in water; these values are in fair agreement with data reported by Baer *et al.*[12] for this compound. No physical data were given[6] for the L enantiomorph (acosamine) of **9**, isolated from the natural source, but the synthetic product was reported[10] to have $[\alpha]_D$ −18.3° in water; no melting point was given[10].

The foregoing synthesis affords the amino sugar **9** in 8 and 33% overall yields, respectively, from the 2-deoxyglycosid-3-ulose **1**, according to whether route A or B is selected for the preparation of the acetamido glycoside **5**. All intermediates were isolated crystalline, and no step requires purification of the product by chromatography.

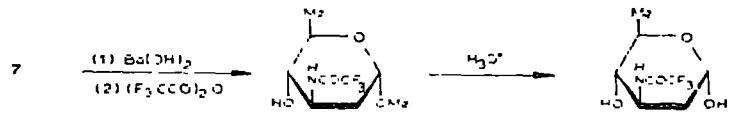
For further characterization, and comparison with literature data, a number of additional derivatives were also prepared. The glycoside **8** was converted by mild, acid hydrolysis into 3-acetamido-2,3,6-trideoxy-D-*arabino*-hexose (**10**), which crystallized in the α-D anomeric form as indicated by its downward mutarotation. The melting point and final optical rotation showed fair agreement with data recorded by Baer and co-workers[12] for this compound. In methyl sulfoxide solution, compound **10** existed in the $^4C_1$(D) pyranose form as a mixture of anomers with the α anomer preponderant (55%), as evidenced by its p.m.r. spectrum (see Table I) which displayed two sets of signals for H-1, H-6, and NH-3, as well as for the hydroxyl groups on C-1 and C-4 (all assignments were verified by double irradiation).

Acetylation of the glycoside **8** with acetic anhydride–pyridine provided the peracetylated glycoside **11** as needles. The optical rotations (+173° in chloroform and +184° in methanol) of **11** correspond well with those of the synthetic, L enantiomorph of **11**, whereas contamination with the β anomer would account for the smaller values given by Baer *et al.*[12] for the same product (+142° in chloroform) and by Lomakina *et al.*[6] for a compound (−84° in methanol) derived from the natural L-acosamine.



N-Deacetylation of **8** with barium hydroxide, followed by *N*-benzoylation with benzoyl chloride in buffered aqueous solution, led to methyl 3-benzamido-2,3,6-trideoxy-α-D-*arabino*-hexopyranoside (**12**), a compound that had previously been prepared in the L series[11]. Mild, acid hydrolysis converted **12** into the reducing sugar **13**, which was obtained crystalline as its α anomer, as deduced from the downward mutarotation observed. It is noteworthy that **13** is very sparingly soluble in water, despite the presence of two hydroxyl groups. In methyl sulfoxide solution, compound **13** adopts an anomeric equilibrium having the α anomer strongly favored (77%), as indicated by its p.m.r. spectrum (see Table I).

In order to obtain semisynthetic analogs of daunorubicin possessing the D-*arabino* configuration for the amino sugar residue, a derivative of **9** had to be prepared that would be suitably protected[13,16,24] for the coupling reaction with the aglycon derivative. Therefore, the amino glycoside **7** was converted into the trifluoroacetamido derivative **14** by consecutive treatment with aqueous barium hydroxide and trifluoroacetic anhydride. Glycoside **14** was then hydrolyzed to the reducing sugar **15** by use of dilute acetic acid. The physical constants for both **14** and **15** agreed well with those reported[16] for the corresponding L enantiomorphs. The reducing sugar **15** crystallized as the α-D anomer, as evidenced by its downward mutarotation, and by its p.m.r. spectrum recorded in methyl sulfoxide solution (see Table I), which displayed only one signal for the anomeric proton (doublet of broad singlets at δ 5.46) and a hydroxyl group (doublet at δ 6.56).



14 15

Detailed characterization and biological evaluation of the products of coupling of **15** to daunomycinone will be reported separately[25].

The amino sugar derivatives described in this paper were examined by electron-impact mass spectrometry, and the principal fragments, together with their relative intensities, are summarized in Table II. As mass spectra are, in general, little influenced by changes of stereochemical configuration, it is not surprising that these compounds follow fragmentation pathways (see Scheme 1) similar to those described by Vigevani *et al.*[26] for daunosamine derivatives.

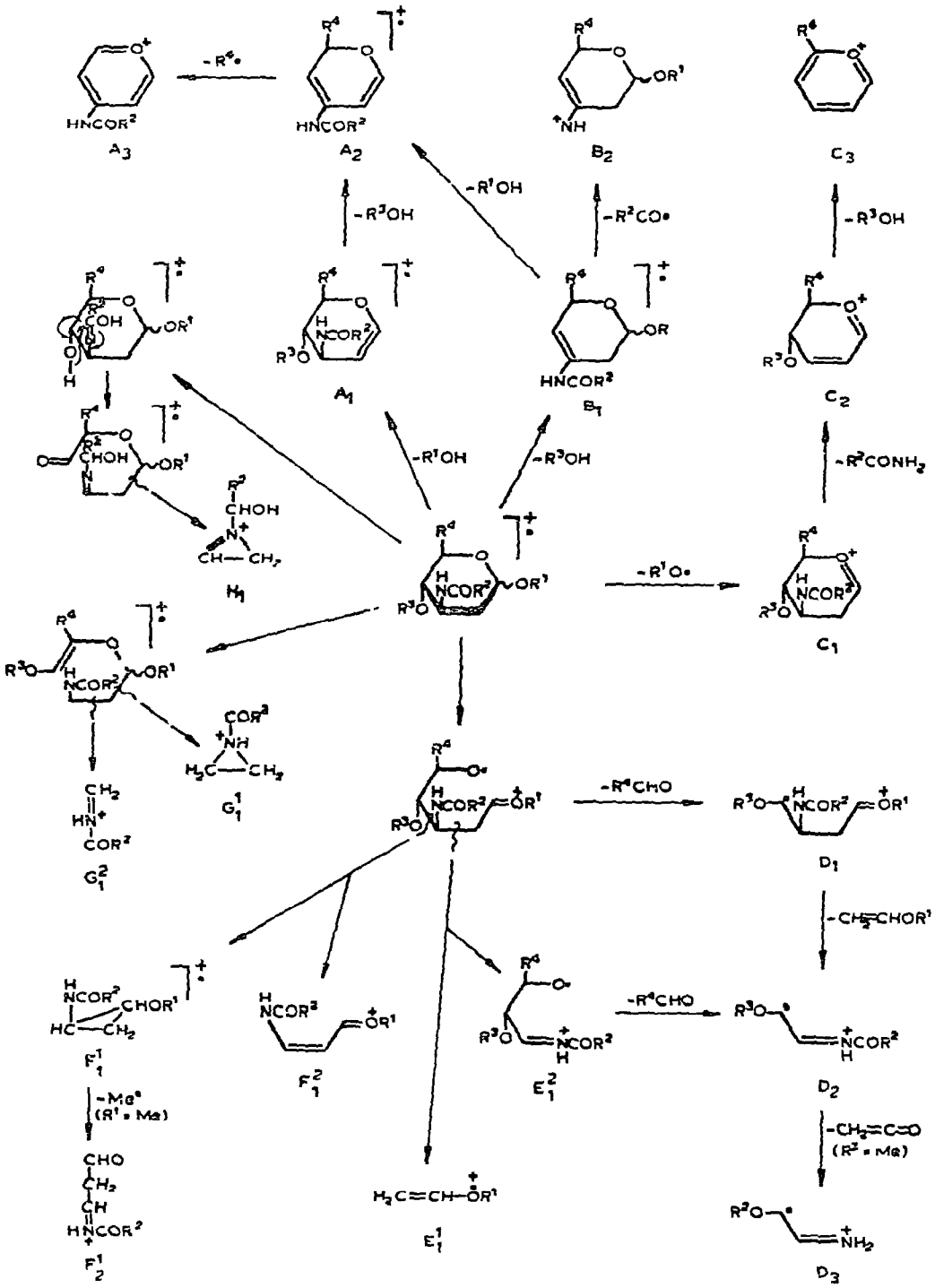
Processes leading to ions of the A and B series are both initiated by cleavage of the glycosidic bond. Sequential loss of two more groups attached to the pyranose ring then gives rise to the substituted pyrylium ions A_3 and C_3. Fragments of the B series evidently arise through expulsion of the substituent at C-4 of the molecular ion to give B_1, which then decomposes to B_2 or A_2 by departure of either the *N*-acyl group or the anomeric group. Rupture of the pyranose ring between C-1–O-5 leads to ions of the D, E, and F series by subsequent cleavage of a second ring-bond between C-4–C-5, C-2–C-3, and C-3–C-4, respectively. The H_1 ion can only be formed by derivatives bearing a free hydroxyl group at C-4 (**8**, **10**, **12**, **13**, **14**, and **15**), as its hydrogen atom is involved in the proposed rearrangement-fragmentation process. Finally, ions of the G series arise through initial opening of the pyranose ring between C-3 and C-4, with subsequent scission of either the C-1–C-2 or the C-2–C-3 bond, to afford G_1^1 and G_1^2. In addition to these modes of fragmentation, peaks characteristic of certain substituents (such as acetates and benzoates) were found in the spectra of the corresponding, substituted compounds (see Table II).

The aforementioned assignments are based on plausible mechanistic steps (*cf.*, ref. 26), and are in many instances supported by metastable fragments observed in the spectra (as indicated in Table II), but the possibility of isomeric structures is not precluded.

EXPERIMENTAL

General methods. — See preceeding papers in this series[14,15,19].

Methyl 4,6-O-benzylidene-2-deoxy-α-D-ribo-hexopyranoside (**2**). — In a 2-liter, round-bottomed flask equipped with a magnetic stirrer, a Soxhlet extractor, and a reflux condenser was placed lithium aluminum hydride (7.2 g, 190 mmoles) in ether (1200 ml), and in the extractor thimble was placed the ketone **1** (20 g, 75.6 mmoles). The contents of the flask were stirred and boiled under reflux for 24 h, after which time the unreacted reducing agent was decomposed by the conventional procedure[27].



Scheme 1

Concentration of the ether solution afforded a crystalline mixture (19.5 g, 97%) of the title compound **2** and its D-*arabino* diastereoisomer **3**, as indicated through comparison with authentic samples[21,28] by t.l.c. (4:1 ether–petroleum ether), the ratio being ~10:1 in favor of **2** (optical rotation, p.m.r.). Recrystallization of the mixture from isopropyl ether provided the pure D-*ribo* isomer **2**; yield 14.2 g (70.5%), m.p. 127–128° (unchanged on admixture with an authentic sample), $[\alpha]_D^{20}$ +146° (*c* 0.98, chloroform) (lit.[20] m.p. 124–125°, $[\alpha]_D$ +145° in chloroform, and[21] 127–129°, $[\alpha]_D$ +140° in chloroform).

Methyl 3-acetamido-4-O-benzoyl-6-bromo-2,3,6-trideoxy-α-D-arabino-*hexopyranoside* (**6**). — To a solution of compound[18] **5** (4 g, 13.03 mmoles) in dry carbon tetrachloride (100 ml) were added *N*-bromosuccinimide (2.75 g, 15.5 mmoles) and barium carbonate (4 g). The mixture was boiled under reflux for 2 h under normal, room illumination, during which time the mixture, originally colorless, became successively yellow, red, and, finally, faintly yellow. The solvent was evaporated, and the residue was extracted with chloroform (100 ml). The resultant, clear extract was washed successively with 5% aqueous sodium hydrogensulfite and aqueous sodium hydrogencarbonate, dried (magnesium sulfate), and evaporated, to give **6** as a chromatographically homogeneous glass that crystallized upon addition of ether; yield 5 g (99%). For analytical purposes, a sample was recrystallized from isopropyl alcohol; m.p. 154–155°, $[\alpha]_D^{22}$ +116.7° (*c* 1, chloroform); ν_{max}^{KBr} 3280 (NH), 1720 (ester C=O), 1650 and 1548 (amide), 1600 and 1580 cm^{-1} (monosubstituted phenyl); X-ray powder diffraction data: 9.30 s (2), 7.69 m, 6.41 m, 5.77 w, 5.40 m (3), 4.67 vs (1), 4.44 m, 4.20 m, and 3.98 w.

Anal. Calc. for $C_{16}H_{20}BrNO_5$ (386.250): C, 49.76; H, 5.22; Br, 20.78; N, 3.63. Found: C, 49.52; H, 5.17; Br, 20.69; N, 3.78.

Methyl 3-acetamido-4-O-benzoyl-2,3,6-trideoxy-α-D-arabino-*hexopyranoside* (**7**). — A mixture of **6** (6.4 g, 16.7 mmoles), Raney nickel (~12 g) and triethylamine (2.4 ml) in methanol (200 ml) was shaken under hydrogen (50 lb.in.$^{-2}$) for 8 h at ~25°. T.l.c. [2:3 (v/v) benzene–acetone] then indicated that the reaction was complete. The catalyst was filtered off, and the filtrate was evaporated. The semicrystalline residue (~6 g) was dissolved in chloroform (200 ml), and the solution was washed twice with water to remove triethylammonium bromide, dried (magnesium sulfate), and evaporated. The resultant, crystalline residue was recrystallized from ether (300 ml), to give (in two crops) analytically pure **7**; yield 5.1 g (99%), m.p. 133–134°, $[\alpha]_D^{22}$ +137.8° (*c* 1, chloroform); ν_{max}^{KBr} 3300 (NH), 1720 (ester C=O), 1640 and 1545 (amide), 1600 and 1580 cm^{-1} (monosubstituted phenyl); X-ray powder diffraction data: 8.54 vs (1), 6.46 m, 4.99 w, 4.70 m (3), 4.67 w, 4.36 s (2,2), 4.20 s (2,2), 3.87 vw, and 3.74 w.

Anal. Calc. for $C_{16}H_{21}NO_5$ (307.349): C, 62.53; H, 6.89; N, 4.56. Found: C, 62.43; H, 7.08; N, 4.86.

Methyl 3-acetamido-2,3,6-trideoxy-α-D-arabino-*hexopyranoside* (**8**). — To a solution of compound **7** (4.5 g, 14.6 mmoles) in abs. methanol (40 ml) was added M sodium methoxide (0.7 ml), and the mixture was kept for ~12 h at ~25°, whereupon

t.l.c. [2:3 (v/v) benzene–acetone] indicated that the saponification was complete. The solvent was evaporated, and the crystalline residue (4 g, 100%) recrystallized from isopropyl ether, to give pure **8** as fine, white needles; yield 2.4 g (80%), m.p. 155–156°, $[\alpha]_D^{25}$ +193° (*c* 1, chloroform) and +139° (*c* 1, methanol); ν_{max}^{KBr} 3410, 3300 (OH, NH), 1640 and 1560 cm^{-1} (amide); X-ray powder diffraction data: 10.64 s (1), 8.72 m, 6.55 m, 5.26 s (3), 4.77 w, 4.44 s (2), 4.23 m, 4.06 m, 3.61 w, and 3.44 w.

Anal. Calc. for $C_9H_{17}NO_4$ (203.240): C, 53.19; H, 8.43; N, 6.89. Found: C, 53.36; H, 8.68; N, 6.79.

In scaled-up preparations, the methyl benzoate formed was best removed prior to recrystallization by placing the crude product on a short column of silica gel that was then washed with chloroform. After all of the methyl benzoate had been eluted (t.l.c. monitoring; absorption under u.v. light, negative), compound **8** was recovered by using acetone as the eluant.

For this compound, Richardson reported[21] m.p. 157.5–158° and $[\alpha]_D$ +137° in methanol; for the α-L enantiomorph of **8**, the following constants have been recorded: m.p. 160–162°, $[\alpha]_D$ −90° in methanol[6*]; m.p. 160–161°, $[\alpha]_D$ −146° in methanol[10]; and m.p. 159–160°, $[\alpha]_D$ −148° in methanol[11].

3-Amino-2,3,6-trideoxy-D-arabino-*hexose hydrochloride* (**9**). — A solution of the *N*-acetylated glycoside **8** (800 mg, 3.94 mmoles) and barium hydroxide octahydrate (2.85 g, 9 mmoles) in water (40 ml) was boiled under reflux for 12 h, after which time, t.l.c. [2:3 (v/v) benzene–acetone] indicated saponification to be complete. The pH was then adjusted to 3 by adding 0.5M sulfuric acid, and the mixture was kept for 2 h at 98°. Barium sulfate was removed by filtration with suction through Celite, and the excess of sulfuric acid by treatment with anion-exchange resin (Amberlite IRA-400, OH^-). After addition of M hydrochloric acid to adjust the pH to 5.6, the solution was lyophilized, affording **9** as a solid that was recrystallized from 1-propanol–ether: yield 680 mg (94%), m.p. 172–174° (dec.), $[\alpha]_D^{23}$ +90.8 (2.75 min) → +98.4 (5 min) → +94° (10 min, equil.; *c* 0.7, water). The i.r. spectrum of **9** was found in excellent agreement with data given by Baer and co-workers[12]: ν_{max}^{KBr} 3400–3300 (OH), 3050, 1595 and 1525 (NH_3^+), 1125, 1065, 1010, 975, and 905 cm^{-1}; X-ray powder diffraction data: 13.48 w, 9.25 vw, 6.96 s (1), 5.23 w, 4.58 s (2), 4.14 w, 3.98 m (3), and 3.68 w. The compound retained solvent of recrystallization (compare refs. 10 and 12), even after several days of drying over phosphorus pentaoxide, potassium hydroxide, and paraffin in a desiccator, and this factor may account for the high carbon and hydrogen and the low nitrogen values in the elemental analysis.

Anal. Calc. for $C_6H_{14}ClNO_3$ (183.637; values for $C_6H_{14}ClNO_3 + 0.33\ C_3H_8O$ in parentheses): C, 39.24 (41.28); H, 7.69 (8.25); N, 7.63 (6.88). Found: C, 41.45; H, 8.12; N, 6.16.

Baer *et al.* reported[12] m.p. 168–170° (dec.) and $[\alpha]_D$ +81.7° in water; in their hands, the compound retained almost one mole of 2-propanol per mole. The L

*This product undoubtedly contained some of the β anomer, because of its mode of preparation (see also, note 8 in ref. 10).

enantiomer was described[10] as containing 1/3 mole of water per mole, $[\alpha]_D$ −18.3° in water at equilibrium*; no melting point was given.

3-Acetamido-2,3,6-trideoxy-α-D-arabino-*hexose* (**10**). — A solution of the *N*-acetylated glycoside **8** (510 mg, 2.5 mmoles) in water (20 ml) and acetic acid (4 ml) was boiled for 30 min under reflux, whereupon t.l.c. showed that the **8** had all been converted into the product **10**. The solution was concentrated, and water (three 10-ml portions) was added to the concentrate (~2 ml) and then evaporated, to remove all of the acetic acid. Finally, the solution was evaporated to dryness, to give crystalline **10**; yield 465 mg (98%). For analytical purposes, a sample was recrystallized from ethyl acetate; m.p. 199–201° (dec.), $[\alpha]_D^{22}$ +53 (initial, extrapolated) → +38 (6 min) → +22° (15 min, equil.; *c* 1, water); ν_{max}^{KBr} 3380, 3290 (OH, NH), 1640 and 1560 cm^{-1} (amide); X-ray powder diffraction data: 9.50 s (2), 5.43 m, 4.79 m, 4.31 s (1), 3.57 s (3), 3.37 vw, 3.18 w, 2.88 w, 2.64 w, and 2.41 w.

Anal. Calc. for $C_8H_{15}NO_4$ (189.214): C, 50.78; H, 7.99; N, 7.40. Found: C, 50.94; H, 8.02; N, 7.51.

This compound has been reported by Baer and co-workers to have[12] m.p. 199–201° (dec.) and $[\alpha]_D$ +30.4 → +18.3° in water.

Methyl 3-acetamido-4-O-*acetyl-2,3,6-trideoxy*-α-D-arabino-*hexopyranoside* (**11**). — Compound **8** (1 g, 4.9 mmoles) was treated with 1:3 acetic anhydride–pyridine (20 ml) for 18 h at ~25°. The mixture was poured into ice–water, and the product extracted with dichloromethane; the extract was washed successively with aqueous sodium hydrogencarbonate and water, dried (magnesium sulfate), and evaporated. Pyridine (two 10-ml portions) and toluene (three 10-ml portions) were successively added to and evaporated from the residue. The crystalline product was then recrystallized from isopropyl ether (or hexane) to give **11** as needles; yield 544 mg (45%), m.p. 161–162°, $[\alpha]_D^{24}$ +173° (*c* 1, chloroform) and +184° (*c* 0.9, methanol); ν_{max}^{KBr} 3310 (NH), 1740 (ester CO), 1650 and 1550 (amide), and 1380 cm^{-1} (C-Me); X-ray powder diffraction data: 10.97 s (2), 8.11 s (1), 6.17 w, 5.50 m, 5.23 w, 4.88 m, 4.67 m, 4.49 s (3), 4.27 m, 3.97 s, 3.51 m, 3.32 w, and 3.21 w.

Anal. Calc. for $C_{11}H_{19}NO_5$ (245.278): C, 53.87; H, 7.81; N, 5.71. Found: C, 53.68; H, 7.55; N, 5.60.

The product proved to be substantially water-soluble, and some loss of material evidently occurred during the isolation procedure.

Baer and co-workers reported[12] m.p. 162–163°, $[\alpha]_D$ +142° in chloroform for a product that was contaminated by the β anomer. For the L enantiomorph, the following data have been reported: m.p. 163–164°, $[\alpha]_D$ −191° in methanol[10], and m.p. 158–163°, $[\alpha]_D$ −84° in methanol[6] **.

Methyl 3-benzamido-2,3,6-trideoxy-α-D-arabino-*hexopyranoside* (**12**). — A solution of compound **8** (1 g, 4.9 mmoles) and barium hydroxide octahydrate (3.2 g,

*This figure might be a typographical error, and should possibly read −81.3°.

**This product undoubtedly contained some of the β anomer, because of its mode of preparation (see also, note 8 in ref. 10).

10.1 mmoles) in water (35 ml) was boiled under reflux for 21 h, whereupon t.l.c. [2:3 (v/v) benzene–acetone] indicated saponification to be complete. Solid carbon dioxide was added, and the resultant precipitate of barium carbonate was filtered off with suction. To the filtrate was added potassium hydrogencarbonate (6 g), and the solution was cooled to 0°. A cold solution of benzoyl chloride (2.5 ml, 21.7 mmoles) in acetone (30 ml) was added, and the mixture was stirred for 3 h at 0° and then for 18 h at ~20°. The inorganic material was removed by filtration with suction, the acetone was evaporated off, and the aqueous solution remaining was extracted with chloroform (60-, 35-, and 35-ml portions). The extract was washed with aqueous sodium hydrogencarbonate, dried (magnesium sulfate), and evaporated, to give **12**, which was recrystallized from ethanol, affording white, cotton-like crystals; yield 1.05 g (81%), m.p. 203–205°, $[\alpha]_D^{23}$ +104° (*c* 1, methanol); ν_{max}^{KBr} 3310 (OH), 3290 (NH), 1630 and 1545 (amide), 1600 and 1580 cm^{-1} (monosubstituted phenyl); X-ray powder diffraction data: 12.62 s (2), 8.62 w, 5.68 s (1.1), 4.90 w, 4.57 s (1.1), 4.10 m, 4.04 m, 3.91 m, 3.67 s (3), 3.42 m, 3.27 m, and 3.02 m.

Anal. Calc. for $C_{14}H_{16}NO_4$ (265.312): C, 63.38; H, 7.22; N, 5.28. Found: C, 63.22; H, 7.28; N, 5.51.

For the α-L enantiomorph of **12**, Gupta reported[11] m.p. 204–206° and $[\alpha]_D$ −92° in methanol.

3-Benzamido-2,3,6-trideoxy-α-D-arabino-*hexose* (**13**). — A solution of the glycoside **12** (500 mg, 1.89 mmoles) in acetic acid (4 ml) and water (20 ml) was boiled for 30 min under reflux, after which time, t.l.c. [2:3 (v/v) benzene–acetone] indicated that hydrolysis of the glycoside was complete. Most of the solvent was evaporated off, and water (10 ml) was added to the concentrated solution, which was then evaporated. This evaporation step was repeated twice more, in order to remove all of the acetic acid before the solution was evaporated to dryness. The residue was recrystallized from ethyl acetate, to give compound **13**; yield 350 mg (74%), m.p. 212–213°, $[\alpha]_D^{23}$ +39.1 (initial, extrapolated) → +35.1 (10 min) → +12.3° (5 h, equil.; *c* 0.98, methanol); ν_{max}^{KBr} 3395 (OH), 3290 (NH), 1630 and 1545 (amide), 1600 and 1575 cm^{-1} (monosubstituted phenyl); X-ray powder diffraction data: 12.27 s (2), 9.93 m, 8.18 m, 6.63 s (1), 6.23 w, 5.40 m, 4.41 s (3), 4.23 m, 3.95 m, 3.64 m, and 3.48 w.

Anal. Calc. for $C_{13}H_{17}NO_4$ (251.285): C, 62.14; H, 6.82; N, 5.57. Found: C, 62.31; H, 6.62; N, 5.70.

Methyl 2,3,6-trideoxy-3-trifluoroacetamido-α-D-arabino-*hexopyranoside* (**14**). — A mixture of the fully protected amino glycoside **7** (4.66 g, 15.15 mmoles) and barium hydroxide octahydrate (18 g, 57 mmoles) in water (20 ml) was stirred magnetically, and boiled for 17 h under reflux, after which time, t.l.c. (2:3 benzene–acetone) indicated that all of compound **7** had reacted. Solid carbon dioxide was added, the inorganic precipitate was filtered off, and the solution was treated with anion-exchange resin (Amberlite IRA-400, OH^-; 60 ml) and then evaporated. To the white, solid residue were added dry ether (50 ml) and trifluoroacetic anhydride (14 ml, 98.7 mmoles) with cooling. After 15 min at 0°, and 3 h at ~25°, the clear solution was evaporated, to give a white, featherlike residue that was dissolved in dry methanol

(100 ml) to remove the 4-*O*-trifluoroacetyl group. After 18 h at ~25°, the solvent was evaporated off, and the residue was recrystallized from acetone–hexane, to afford pure **14** as needles; yield 3.56 g (91.4%), m.p. 194–196° (subl.), $[\alpha]_D^{21}$ +115.8° (*c* 0.38, methanol) and +125.3° (*c* 0.44, chloroform); ν_{max}^{KBr} 3450, 3300 (OH, NH), 1695 and 1560 cm^{-1} (amide); X-ray powder diffraction data: 10.80 m, 8.58 w, 5.71 m (2,2), 5.47 w, 5.12 m (2,2), 4.55 s (1), 4.32 m, 4.06 m, 3.83 m (3), 4.69 w, and 3.41 m.

Anal. Calc. for $C_9H_{14}F_3NO_4$ (257.212): C, 42.03; H, 5.49; N, 5.45. Found: C, 42.08; H, 5.32; N, 5.12.

For the L enantiomer of **14**, Arcamone *et al.* recorded[16] m.p. 195–197°, $[\alpha]_D$ −110° in methanol and −123° in chloroform.

2,3,6-Trideoxy-3-trifluoroacetamido-α-D-arabino-*hexose* (**15**). — A solution of the methyl glycoside **14** (1.6 g, 6.22 mmoles) in aqueous acetic acid (25%, 80 ml) was heated for 4 h at 100°, after which time, t.l.c. (2:3 benzene–acetone or 4:1 ether–petroleum ether) showed that the hydrolysis was complete. The solution was evaporated to dryness, and the residue was recrystallized from methanol–dichloromethane, to give **15** as white, fluffy crystals; yield 1.19 g (78.6%), m.p. 206° (dec.), $[\alpha]_D^{21}$ +53.5 (initial, extrapolated) → +51.3 (50 min) → +46.4 (3.5 h) → +34 (20 h, equil.; *c* 0.78, 1,4-dioxane); ν_{max}^{KBr} 3370, 3280 (OH, NH), 1690 and 1560 cm^{-1} (amide); X-ray powder diffraction data: 5.69 m (3), 4.95 vw, 4.84 vw, 4.40 s (1), 3.73 m (2), and 3.19 w.

Anal. Calc. for $C_8H_{12}F_3NO_4$ (243.185): C, 39.51; H, 4.97; N, 5.76. Found: C, 39.59; H, 5.15; N, 5.56.

The L enantiomer of **15** was reported[16] to have m.p. 202° (dec.) and $[\alpha]_D$ −51 → −33.4° (2 h) in 1,4-dioxane.

ACKNOWLEDGMENT

This work was supported by Contract No. N01-CM-57015 (The Ohio State University Research Foundation Project 4226-A1) from the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Department of Health, Education, and Welfare, Bethesda, Md. 20014.

REFERENCES

1 D. HORTON AND W. WECKERLE, *Abstr. Pap. Am. Chem. Soc. Meet.*, 171 (1976) CARB 3; *Am Chem. Soc., Symp. Ser.*, 39 (1976), 22–35
2 F. ARCAMONE, G. CASSINELLI, G. FRANCESCHI, R. MONDELLI, P. OREZZI, AND S. PENCO, *Gazz. Chim. Ital.*, 100 (1970) 949–989; R. B LIVINGSTON AND S K CARTER, "Daunomycin", *Chemother. Fact Sheet*, National Cancer Institute, Bethesda Md., 1970
3 A. DI MARCO, F. ARCAMONE, AND F. ZUNINO, in J. W. CORCORAN AND F. E. HAHN (Eds.), *Antibiotics*, Vol. III, Springer Verlag, New York, 1975, pp. 101–128.
4 F. ARCAMONE, G. FRANCESCHI, S. PENCO, AND A SELVA, *Tetrahedron Lett.*, (1969) 1007–1010; S. K. CARTER, A. DI MARCO, M. GHIONE, J. H KRAKOFF, AND G MATHE (Eds.), *Proceedings of the International Symposium on Adriamycin*, Springer Verlag, Berlin, 1972
5 M. G. BRAZHNIKOVA, V. B. ZBARSKY, V. L. PONOMARENKO, AND N. P. POTAPOVA, *J. Antibiot.*, 27 (1974) 254–259; G. F. GAUSE, M G. BRAZHNIKOVA, AND V. A. SHORIN, *Cancer Chemother Rep.*, 58 (1974) 255–256.

6 N. N. LOMAKINA, I. A. SPIRIDONOVA, YU. N. SHEINKER, AND T. F. VLASOVA, *Khim. Prir. Soedin.*, 9 (1973) 101–107; *Chem. Abstr.*, 78 (1973) 148,170 *m*.
7 N. N. LOMAKINA, I. A. SZPIRIDONOVA, R. BOGNÁR, M. PUSKÁS, AND F. SZTARICSKAI, *Antibiotiki (Moscow)*, 13 (1968) 975–978; R. BOGNÁR, F. SZTARICSKAI, M. E. MUNK, AND J. TAMÁS, *J. Org. Chem.*, 39 (1974) 2971–2974.
8 S. HANESSIAN AND T. H. HASKELL, in W. PIGMAN AND D. HORTON (Eds.), *The Carbohydrates*, Vol. IIA, Academic Press, New York, 1970, pp. 139–211.
9 W. W. LEE, H. Y. WU, J. J. MARSH, JR., C. W. MOSHER, E. M. ACTON, L. GOODMAN, AND D. W. HENRY, *J. Med. Chem.*, 18 (1975) 767–768.
10 W. W. LEE, H. Y. WU, J. E. CHRISTENSEN, L. GOODMAN, AND D. W. HENRY, *J. Med. Chem.*, 18 (1975) 768–769.
11 S. K. GUPTA, *Carbohydr. Res.*, 37 (1974) 381–383.
12 H. H. BAER, K. ČAPEK, AND M. C. COOK, *Can. J. Chem.*, 47 (1969) 89–97.
13 F. ARCAMONE, A. BARGIOTTI, G. CASSINELLI, S. PENCO, AND S. HANESSIAN, *Carbohydr. Res.*, 46 (1976) C3–C5.
14 D. HORTON AND W. WECKERLE, *Carbohydr. Res.*, 46 (1976) 227–235.
15 D. M. CLODE, D. HORTON, AND W. WECKERLE, *Carbohydr. Res.*, 49 (1976) 305–314.
16 F. ARCAMONE, S. PENCO, A. VIGEVANI, S. REDAELLI, G. FRANCHI, A. DI MARCO, A. M. CASAZZA, T. DASDIA, F. FORMELLI, A. NECCO, AND C. SORANZO, *J. Med. Chem.*, 18 (1975) 703–707.
17 R. H. BLUM AND S. K. CARTER, *Ann. Intern. Med.*, 80 (1974) 249–259; J. J. RINEHART, R. P. LEWIS, AND S. P. BALCERZAK, *ibid.*, 81 (1974) 475–478; E. A. LEFRAK, J. PITHA, S. ROSENHEIM, AND J. A. GOTTLIEB, *Cancer*, 32 (1973) 302–314.
18 F. ARCAMONE, A. BARGIOTTI, G. CASSINELLI, S. REDAELLI, S. HANESSIAN, A. DI MARCO, A. M. CASAZZA, T. DASDIA, A. NECCO, P. REGGIANI, AND R. SUPINO, *J. Med. Chem.*, 19 (1976) 733–734.
19 D. HORTON AND W. WECKERLE, *Carbohydr. Res.*, 44 (1975) 227–240.
20 P. J. BEYNON, P. M. COLLINS, AND W. G. OVEREND, *J. Chem. Soc., C*, (1969) 272–281.
21 A. C. RICHARDSON, *Carbohydr. Res.*, 4 (1967) 422–428.
22 R. D. GUTHRIE AND D. MURPHY, *J. Chem. Soc.*, (1965) 6956–6960.
23 S. HANESSIAN, *Carbohydr. Res.*, 2 (1966) 86–88.
24 E. M. ACTON, A. N. FUJIWARA, AND D. W. HENRY, *J. Med. Chem.*, 17 (1974) 659–660.
25 D. HORTON, T.-M. CHEUNG, R. J. SORENSON, W. WECKERLE, AND B. WINTER, *Abstr. Pap. Chem. Inst. Can., Am. Chem. Soc. Joint Conf.*, 2nd (1977) CARB-39.
26 A. VIGEVANI, B. GIOIA, AND G. CASSINELLI, *Carbohydr. Res.*, 32 (1974) 321–330.
27 L. F. FIESER AND M. FIESER, *Reagents for Organic Synthesis*, Wiley, New York, 1967, pp. 583–584.
28 G. R. INGLIS, J. C. P. SCHWARZ, AND L. MCLAREN, *J. Chem. Soc.*, (1962) 1014–1019.
29 F. ARCAMONE, S. PENCO, AND A. VIGEVANI, *Cancer Chemother. Rep., Part 3*, 6 (1975) 123–129.