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SYNTHESIS OF D-RISTOSAMINE AND ITS DERIVATIVES*

ISTVÁN PELYVÁS, FERENC SZTARICSKAI, LÁSZLÓ SZILÁGYI, REZSÖ BOGNÁR,
Research Group for Antibiotics, Hungarian Academy of Sciences, and Institute of Organic Chemistry, L. Kossuth University, H-4010 Debrecen (Hungary)

AND JÓZSEF TAMÁS
Central Chemical Research Institute, Hungarian Academy of Sciences, H-1088 Budapest (Hungary)

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ABSTRACT

A convenient preparative route involving eleven steps starting from D-glucose is described for the synthesis of D-ristosamine (**15**) hydrochloride. Methyl 2-deoxy-β-D-*arabino*-hexopyranoside, prepared from 3,4,6-tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol, was benzylidenated, and the product mesylated to give methyl 4,6-*O*-benzylidene-2-deoxy-3-*O*-methylsulfonyl-β-D-*arabino*-hexopyranoside. Azidolysis of this compound and subsequent opening of the 1,3-dioxane ring with *N*-bromosuccinimide gave methyl 3-azido-4-*O*-benzoyl-6-bromo-2,3,6-trideoxy-β-D-*ribo*-hexopyranoside. Simultaneous reduction of the azido and bromo groups gave a mixture that was benzoylated to give methyl *N*,*O*-dibenzoyl-β-D-ristosaminide and then hydrolyzed to **15** hydrochloride (3-amino-2,3,6-trideoxy-D-*ribo*-hexopyranose hydrochloride).

INTRODUCTION

The anthracycline glycoside-type antibiotics daunomycin, adriamycin, and carminomycins are clinically useful as cancer chemotherapeutic agents. In order to prepare new semisynthetic analogs having greater efficacy, broader spectrum of activity, and decreased toxicity, detailed examinations have been carried out recently. Several analogs[1] of daunomycin and adriamycin, containing structurally or stereochemically modified L-aminodeoxy sugars instead of the probably cardiotoxic L-daunosamine residue[2], have been synthesized. However, analogs having 3-amino-2,3,6-trideoxyhexose constituents and belonging to the D-series have not been prepared hitherto. An interesting group of such analogs would be one in which L-daunosamine is replaced by a 3-amino-2,3,6-trideoxyhexose having the D-*ribo* configuration.

*Dedicated to Professor Kurt Heyns on the occasion of his 70th birthday.

Recently, we reported an investigation of the structure[3] and the synthesis[4] of L-ristosamine (3-amino-2,3,6-trideoxy-L-*ribo*-hexopyranose), the amino sugar constituent[5] of the antibiotic ristomycin-A. Three other research groups[6–8] have also prepared this sugar, and Arcamone *et al.*[7] synthesized a new semisynthetic daunomycin analog *via* glycosylation of daunomycinone with L-ristosamine.

D-Ristosamine (**15**) was first synthesized by Horton and Weckerle[9] in 1976. At the beginning of 1977, we also reported[10] the preparation of some derivatives of D-ristosamine prepared by a method different from that described by Horton and Weckerle[9]. Later, Baer and Georges[11] also synthesized **15** by applying exactly the same method reported by us, and elaborated independently of our work. In this communication, a convenient preparative synthesis of **15** and some of its derivatives, suitable for the preparation of new, semisynthetic anthracycline glycosides, is described.

RESULTS AND DISCUSSION

Methyl 3,4,6-tri-*O*-acetyl-2-deoxy-β-D-*arabino*-hexopyranoside (**2**) was prepared from 3,4,6-tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol (**1**) by addition of dry hydrochloric acid in benzene, followed by methanolysis in the presence of silver carbonate. Hydrolysis of **2** gave methyl 2-deoxy-β-D-*arabino*-hexopyranoside (**3**) in 42% (calc. from **1**) overall yield. Benzylidenation of **3** led to methyl 4,6-*O*-benzylidene-2-deoxy-β-D-*arabino*-hexopyranoside (**4**), which was mesylated to give the corresponding 3-mesylate **5**. Treatment of **5** with sodium azide in hexamethylphosphoric triamide at 100° resulted in 92% of methyl 3-azido-4,6-*O*-benzylidene-2,3-dideoxy-β-D-*ribo*-hexopyranoside (**6**). An analogous reaction of the α anomer of **5** using the method of Kovár *et al.*[12] gave only 25% of the corresponding methyl 3-azido-3-deoxy-α-glycoside because of a β-trans-axial effect[13] involving the axial glycosidic methoxyl group.

The analysis of the ^{1}H-n.m.r. spectra of **4**, **5**, and **6** proved to be difficult because of the similarity or accidental concordance of the values of chemical shifts and coupling constants (for example $J_{3,4} \approx J_{4,5} \approx J_{5,6'} \approx 2\ J_{5,6}$ for **5**; see Table I).

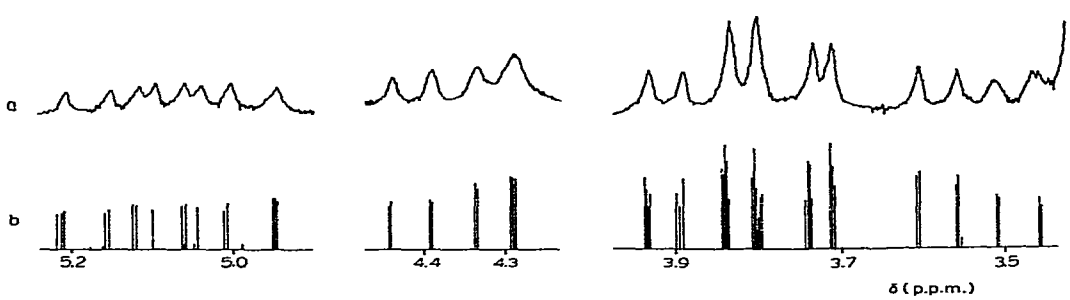


Fig. 1. (a) A part of the observed ^{1}H-n.m.r. spectrum of **5** in pyridine-d_5 solution; (b) simulated (LAOCN-3) spectrum of **5** using first-order parameters.

To confirm the assignments, spin-decoupling experiments, and for **4** and **5**, the simulation (LAOCN-3 method)[14] of the spectra were effected. Fig. 1 shows the observed and simulated ^{1}H-n.m.r. spectra of **5**. The coupling constants (Table I) indicate the strongly favored chair conformation of both pyranoside and 1,3-dioxane rings of the benzylidene derivatives **4**, **5**, and **6**.

TABLE I

^{1}H-N.M.R. SPECTRAL DATA AT 100MHz FOR SOLUTIONS IN $CDCl_3$ OF **4–9**, **11**, **12**, AND **14**

Compd.	*Chemical shifts* (δ)									
	H-1	*H-2e*	*H-2a*	*H-3*	*H-4*	*H-5*	*H-6*	*H-6'*	*CH_3-5*	*Others*
4	4.39	2.26	1.61	3.74	3.74	3.23	4.28	3.36		3.46, OMe; 3.0, OH
5	4.54	2.52	1.91	4.79	3.70	3.39	4.36	3.82		3.49, OMe; 3.10, OMs; 5.55, PhC*H*
5[a]	4.55	2.59	2.00	5.08	3.80	3.50	4.36	3.84		3.41, OMe; 3.10, OMs; 5.68, PhC*H*
6	4.68	2.04	1.74	4.15			4.33			3.48, OMe; 5.54, PhC*H*
6[b]	4.49	1.75	1.46	3.82			4.16			3.21, OMe; 5.25, PhC*H*
7	4.75	2.15	1.89	4.3	5.15	4.2		3.5		3.51, OMe
8	4.68	2.16	1.81	4.09		3.51–3.85				3.51, OMe
9	4.67	2.25	1.85	4.54	3.62	3.83			1.37	3.43, OMe 6.6, NH
11	4.55	2.04	2.29	5.0	5.16	4.19			1.47	3.45, OMe
12	4.81	1.87	2.43	4.66	3.56–3.90		4.0–4.2			3.40, OMe
14[c]	5.03	2.09	2.42	3.88	5.77		4.78			3.42, OMe

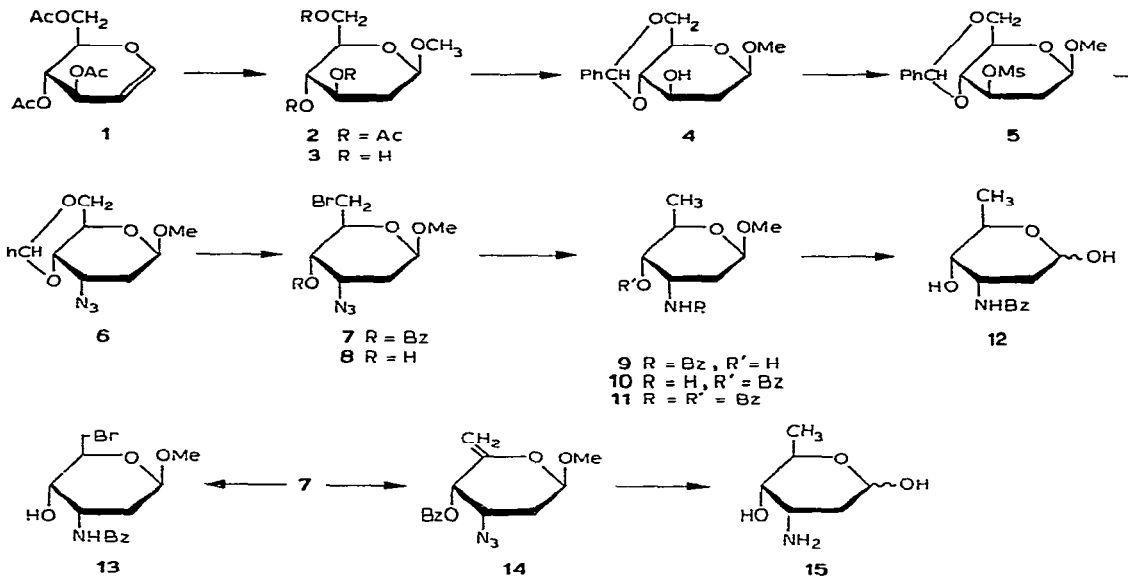
Compd.	*Spin–spin coupling constants* ($J_{H,H}$ *in Hz*)										
	$J_{1,2e}$	$J_{1,2a}$	$J_{2e,3}$	$J_{2a,3}$	$J_{2e,2a}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$	*Others*
4	2.3	9.6	5.0	11.4	13.0	10.4					
5	2.3	9.5	5.5	11.5	13.0	9.2	9.2	4.7	9.4	10.3	
5[a]	2.4	9.3	5.7	11.4	12.8	9.4	9.0	4.6	9.0	9.0	
6	2.7	9.4	3.3	3.3	14.2	3.5		3.5			
6[b]	2.6	9.0	3.6	3.6	14.4					9.0	
7	2.8	8.5	4.1	3.7	13.6	3.3	9.0				
8	2.5	8.8	4.0	3.5	14.0						
9	2.9	6.2	6.8	4.5	13.2	3.7	6.4	6.4			$J_{CH,NH}$ 6.0
11	3.3	4.4	5.0	9.0	13.0	3.5	4.6	7.0			$J_{CH,NH}$ 6.0
12	5.5	3.0	4.4	8.0	3.0						
14[c]	3.4	2.0	4.8	11.8	13.2	3.5					$J_{2e,4}$ ~1.0

[a]Recorded in pyridine-d_5. [b]Recorded in C_6D_6. [c]The values do not change even at 60°.

Reaction of **6** with *N*-bromosuccinimide in carbon tetrachloride under reflux in the presence of barium carbonate[15] gave crystalline methyl 3-azido-4-*O*-benzoyl-6-bromo-2,3,6-trideoxy-β-D-*ribo*-hexopyranoside (**7**) in 90% yield. *O*-Debenzoylation

of **7** was quantitatively effected by Zemplén's method to give crystalline methyl 3-azido-6-bromo-2,3,6-trideoxy-β-D-*ribo*-hexopyranoside (**8**).

Conversion in one step of N_3-3 and CH_2Br-5 of **7** or **8** into NH_2-3 and CH_3-5, respectively, was attempted. Hydrogenation of **7** or **8** at atmospheric pressure in the presence of palladium-on-carbon, palladium-on-barium sulfate, or Raney nickel catalysts and triethylamine failed to give a homogeneous product. When **7** was hydrogenated in methanol under reflux in the presence of Raney nickel and triethylamine for 8 h, methyl 3-benzamido-6-bromo-2,3,6-trideoxy-β-D-*ribo*-hexopyranoside[11] (**13**) was isolated in 50% yield. Applying the same conditions but prolonging the reaction time (25–30 h) an ~ 4:1 mixture of methyl 3-benzamido-2,3,6-trideoxy-β-D-*ribo*-hexopyranoside (**9**) and the corresponding 4-monobenzoate **10** was obtained. Due to the slight difference in the chromatographic mobilities of **9** and **10** in a number of solvent systems, only **9** (the main product with lower R_F value) could be isolated for i.r. and mass-spectrometric investigations. The mass-spectrometric fragmentation[16] (see Experimental), as well as the amide and hydroxyl bands in the i.r. spectrum unequivocally prove the *N*-benzoyl structure **9** of the main product. Thus, the



4-*O*-benzoyl group of the initially formed **10** migrated to the adjacent *cis* amino group under alkaline conditions (O → N acyl migration[17]).

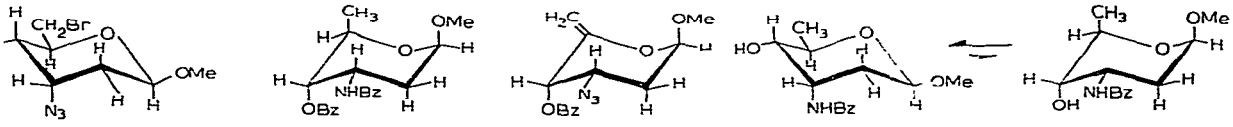
Benzoylation of the crude mixture of **9** and **10** gave methyl 3-benzamido-4-*O*-benzoyl-2,3,6-trideoxy-β-D-*ribo*-hexopyranoside (**11**) in 90% yield. *O*-Debenzoylation of **11** resulted in methyl 3-benzamido-2,3,6-trideoxy-β-D-*ribo*-hexopyranoside (**9**), the mass and i.r. spectra of which were completely identical with those of **9** obtained directly from **7**. The H-3 signal in the ^{1}H-n.m.r. spectrum of **9** (Table I) is shifted to

lower field by ~0.25 p.p.m., whereas the H-4 signal is shifted towards the higher field by ~1.5 p.p.m., as compared to that of **7**, indicating the presence of the benzoyl group at the C-3 substituant. Simultaneous generation of CH_3-5 and NH_2-3 in 3-amino-di- or -trideoxyhexoses has not been reported hitherto.

Saponification of **9** with barium hydroxide, followed by acid hydrolysis, gave the hydrochloride of **15** (D-ristosamine hydrochloride), while mild acid hydrolysis of **9** resulted in *N*-benzoyl-D-ristosamine (**12**). The physical data of **12** and **15** are in good agreement with those reported for the corresponding enantiomers[2–4] and with those described earlier by Horton and Weckerle[9] for D-ristosamine hydrochloride and *N*-benzoyl-D-ristosamine.

To synthesize L-daunosamine (3-amino-2,3,6-trideoxy-L-*lyxo*-hexopyranose) from **7**, it was converted into methyl 3-azido-4-*O*-benzoyl-2,3,6-trideoxy-β-D-*erythro*-hex-5-enopyranoside (**14**). However, as shown by t.l.c., saponification of **14**, followed by hydrogenolysis, and subsequent acid hydrolysis resulted mainly in D-ristosamine (**15**) hydrochloride, and only traces of L-daunosamine could be detected. Contrary to this result, Horton and Weckerle[18] prepared L-daunosamine in good yield by the hydrogenolysis of methyl 3-acetamido-2,3,6-trideoxy-α-D-*erythro*-hex-5-enopyranoside, followed by removal of the *N*-acetyl and methyl glycosidic groups.

The easy conversion of **14** into **15** provides, for the preparation of D-ristosamine derivatives, an additional route that avoids step **7**→**9**+**10**, associated with unfavorable O→N acyl migration.



7 **11** **14** **9**

The high value (9 Hz) of $J_{4,5}$ observed in the ^{1}H-n.m.r. spectrum of **7** (Table I) indicates the $^4C_1$(D) conformation of this derivative. On the other hand, the observed coupling constants for the corresponding 5-enopyranoside **14** clearly show that the $^1C_4$(D) conformation is strongly favored in this case, even at 60°. This conformation is also confirmed by the observation of a long-range coupling ($J_{2,4}$ ~1 Hz) between H-4 and H-2e.

The values (6.2 and 6.4 Hz) of $J_{1,2a}$ and $J_{4,5}$ for **9** indicate a $^4C_1$(D) ⇌ $^1C_4$(D) equilibrium, strongly shifted towards the $^4C_1$(D) conformation, whereas the low value (4.6 Hz) of $J_{4,5}$ shows that the $^1C_4$(D) conformation is strongly favored for **11**.

In the case of **11**, **13**, and **14**, H-2e appears at higher field than H-2a (Table I). This observation can be attributed to the anisotropic shielding-effect of the *N*-benzoyl and azido groups, respectively, at C-3. A similar effect is probably operative in the $^1C_4$(D) conformer of **9**, as well, but it is obscured by the $^4C_1$(D) ⇌ $^1C_4$(D) equilibrium.

EXPERIMENTAL

General methods. — Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Optical rotations were measured with Schmidt–Haensch and Bendix NPL polarimeters. ^{1}H-n.m.r. spectra were recorded at 100 MHz with a Jeol MH-100 instrument in $CDCl_3$ solutions, tetramethylsilane being the internal standard. Mass spectra were recorded with an AEI MS-902 high-resolution spectrometer (70 eV) and i.r. spectra with a Unicam SP-200 G instrument. T.l.c. and column chromatography were performed on Kieselgel G (Merck) adsorbent with the following solvent and eluent systems (all v/v): (*A*) 9:1 abs. benzene–abs. methanol; (*B*) 19:1 abs. benzene–abs. ethanol; (*C*) 17:3 abs. benzene–abs. methanol; (*D*) 4:1 benzene–ethyl acetate; (*E*) 6:2:1 2-propanol–25% ammonium hydroxide–water; and (*F*) abs. benzene. Evaporations were carried out under diminished pressure at 35–40°

*Methyl 3,4,6-tri-*O*-acetyl-2-deoxy-β-*D-arabino-*hexopyranoside* (**2**). — A solution of 3,4,6-tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol (**1**) (9 g, 33 mmol) in abs. benzene (90 ml) was cooled to 0 to −5° and saturated with dry hydrogen chloride. The mixture was kept at −5° for an additional 30 min, and then evaporated to dryness. The remaining water was co-evaporated with abs. benzene (3 × 20 ml), and to the syrupy product abs. methanol (90 ml), freshly prepared silver carbonate (36 g), and "Klinosorb" (10 g) were immediately added. The mixture was boiled for 30 min and cooled, silver salts were filtered off, and the filtrate was concentrated. The residue was dissolved in chloroform, the solution was decolorized with Celite and evaporated to dryness to give a thick syrupy mixture (7.6 g, 75.5%) of **2** and the corresponding α- anomer. After several days, **2** spontaneously crystallized; it was filtered off, washed with cold 1:2 methanol–water, and recrystallized from water (4.15 g, 41.2%), m.p. 95–97°, $[\alpha]_D^{25}$ −22° (*c* 1.0, chloroform); R_F (*A*) 0.69; lit.[19] m.p. 96–98°, $[\alpha]_D^{22}$ −24° (*c* 1.0, chloroform); ^{1}H-n.m.r.: δ 1.95–2.05 (3 OAc), 3.44 (s, 3 H, OCH_3), and 4.42 (dd, 1 H, $J_{1,2e}$ ~2.5 Hz, $J_{1,2a}$ ~10 Hz, H-1).

*Methyl 2-deoxy-β-*D-arabino-*hexopyranoside* (**3**). — To a solution of **2** (8.1 g, 27 mmol) in abs. methanol (40 ml) was added 0.1M sodium methoxide in abs. methanol (0.9 ml). After being kept for 2 h at room temperature, the solution was neutralized with AG 50W-X12 (H^+) ion-exchange resin and evaporated. The crystalline residue was recrystallized from acetone (4.64 g, 96.7%), m.p. 119–120°, $[\alpha]_D^{25}$ −48° (*c* 0.52, water); R_F (*A*) 0.25; lit.[19] m.p. 121–122°, $[\alpha]_D^{20}$ −48° (*c* 1.0, water).

*Methyl 4,6-*O*-benzylidene-2-deoxy-β-*D-arabino-*hexopyranoside* (**4**). — A mixture of **3** (4.6 g, 25.8 mmol), benzaldehyde (12.2 g, 115 mmol), and freshly fused zinc chloride (3.5 g, 25.8 mmol) was shaken for 20 h. The reaction mixture was treated with 1:1 water–petroleum ether (30 ml), and the resulting solid material was filtered off, washed with water, petroleum ether, and finally 1:2 ether–petroleum ether. The product was recrystallized from abs. ethanol (5.16 g, 75%), m.p. 155–57°, $[\alpha]_D^{25}$ −75° (*c* 0.8, chloroform); R_F (*A*) 0.65; lit.[20] m.p. 155–156° $[\alpha]_D$ −67°.

Anal. Calc. for $C_{14}H_{18}O_5$: C, 63.14; H, 6.80. Found: C, 63.32; H, 6.61.

*Methyl 4,6-O-benzylidene-2-deoxy-3-O-methylsulfonyl-β-*D-arabino*-hexopyranoside* (**5**). — Compound **4** (2.25 g, 8.5 mmol) was dissolved in dry pyridine (7.5 ml) and treated with methanesulfonyl chloride (1.62 g, 14.2 mmol) for 6 h at 0°. The reaction mixture was diluted with cold water, and precipitated **5** was filtered off and washed with water (2.8 g, 96.2%), m.p. 143–145° (dec. in capillary tube), $[\alpha]_D^{25}$ −59.5° (*c* 1.0, chloroform); R_F (*A*) 0.86.

Anal. Calc. for $C_{15}H_{20}O_7S$: C, 52.31; H, 5.85; S, 9.31. Found: C, 52.58; H, 5.85; S, 9.34.

*Methyl 3-azido-4,6-*O*-benzylidene-2,3-dideoxy-β-*D-ribo*-hexopyranoside* (**6**). — A mixture of **5** (4.7 g) and sodium azide (4.7 g) in hexamethylphosphoric triamide (25 ml) was stirred for 10 h at 100°. After being cooled, the reaction mixture was diluted with cold water, and the crystalline product was filtered off, washed with cold water, and recrystallized from methanol (3.56 g, 92%), m.p. 101–102°, $[\alpha]_D^{25}$ −104° (*c* 1.0, chloroform); R_F (*B*) 0.78; ν_{max}^{KBr} 2100 cm^{-1} (C–N azide); m.s. (I%): *m/e* 291 (2), 290 (3), 263 (1), 262 (0.5), 260 (0.1), 259 (0.2), 248 (1.5), 190 (1), 189 (2), 177 (13), 159 (3), 157 (2), 149 (60), 142 (100), 121 (8), 119 (5), 113 (15), 105 (90), 99 (70), 91 (70), 87 (30), 86 (60), and 77 (50).

Anal. Calc. for $C_{14}H_{17}N_3O_4$: C, 57.72; H, 5.88; N, 14.42. Found: C, 57.68; H, 5.74; N, 14.53.

*Methyl 3-azido-4-*O*-benzoyl-6-bromo-2,3,6-trideoxy-β-*D-ribo*-hexopyranoside* (**7**). — To a solution of **6** (2.5 g, 8.6 mmol) in carbon tetrachloride (40 ml) were added barium carbonate (3 g) and *N*-bromosuccinimide (1.73 g, 9.72 mmol), and the mixture was boiled for 4.5 h under reflux; during this period the **6** disappeared (t.l.c., *B*). After being cooled, the mixture was evaporated to dryness, the residue was dissolved in abs. ether, the solution was filtered, and the filtrate was washed with 3% aqueous sodium hydrogencarbonate and then cold water. After being dried (magnesium sulfate), the solution was evaporated and the residue treated with cold abs. methanol to give colorless, crystalline **7**. This was filtered off, washed with ice-cold abs. methanol, and recrystallized from methanol (2.88 g, 90%), m.p. 64.5–65°, $[\alpha]_D^{25}$ −110° (*c* 0.69, chloroform); R_F (*B*) 0.92; ν_{max}^{KBr} 2100 (C–N azide) and 1762 cm^{-1} (C=O ester); m.s. (I%): *m/e* 370 (0.1), 368 (0.1), 340 (0.2), 276 (0.2), 269 (5), 267.0023 (5) ($C_{12}H_{12}{}^{79}BrO_2$), 262.1080 (1) ($C_{14}H_{16}NO_4$), 248.0940 (4) ($C_{13}H_{14}NO_4$), 207 (1), 204.9922 (1) ($C_5H_8N_3{}^{79}BrO$), 189.0532 (3) ($C_9H_7N_3O_2$), 161.0607 (3) ($C_{10}H_9O_2$), 146 (4), 122.0370 (3) ($C_7H_6O_2$), 114 (6), 105 (100), and 77 (30).

Anal. Calc. for $C_{14}H_{16}BrN_3O_4$: C, 45.42; H, 4.36; Br, 21.59; N, 11.35. Found: C, 45.71; H, 4.44; Br, 21.70; N, 11.36.

*Methyl 3-azido-6-bromo-2,3,6-trideoxy-β-*D-ribo*-hexopyranoside* (**8**). — Saponification of **7** in methanol (15 ml) with 0.1M methanolic sodium methoxide (0.3 ml) gave **8** (384 mg, 78%), m.p. 88–88.5°, $[\alpha]_D^{25}$ −56.2° (*c* 0.34, methanol); R_F (*B*) 0.35.

Anal. Calc. for $C_7H_{12}BrN_3O_3$: Br, 30.03; N, 15.79. Found: Br, 30.20; N, 15.67.

Hydrogenolysis of **7**. — Hydrogen gas was passed for 25–30 h through a mixture of **7** (973 mg, 2.63 mmol), triethylamine (270 mg, 2.67 mmol), and Raney nickel (2 g) in boiling abs. methanol (15 ml) under reflux. The mixture was then cooled, the

catalyst was filtered off, and the filtrate was evaporated to dryness to give 640 mg (92%) of crude syrupy product, which was chromatographed on Kieselgel G (20 g, Merck) with the eluent system *C* to give a mixture (~4:1) [t.l.c. (*C*): R_F 0.64 and 0.67; ^{1}H-n.m.r.] of **9** and **10** (450 mg, 64.5%), $[\alpha]_D^{23}$ −49° (*c* 1.1, chloroform) and pure syrupy **9** (8 mg), R_F (*C*) 0.64; ν_{max}^{film} 3410 cm^{-1} (OH), 3300 (NH), 1530 (Amide II), and 1360 cm (Amide I); m.s. (I%): *m/e* 247 (0.3), 233 (3), 215 (2), 191 (10), 190 (2), 176 (2), 163 (16), 142.0869 (10) ($C_7H_{12}NO_2$), 122.0600 (7) [$(C_6H_5CONH_3)^+$], 113.0605 (2) ($C_6H_9O_2$), 105 (100), and 77 (20).

*Methyl 3-benzamido-4-*O*-benzoyl-2,3,6-trideoxy-β-*D*-ribo-hexopyranoside* (**11**) (*methyl* N,O-*dibenzoyl-β-*D*-ristosaminide*). — The crude syrupy mixture of **9** and **10** (316 mg) obtained by the hydrogenolysis of **7** was benzoylated with benzoyl chloride (181 mg) in abs. pyridine (3 ml) for 24 h to give a single component [R_F (*C*) 0.84]. The mixture was concentrated to 1 ml and diluted with ice-cold water to give crystalline **11**, which was filtered off and washed with cold water. Recrystallization from ethanol–water yielded 396 mg (90%), m.p. 124–126°, $[\alpha]_D^{25}$ −75.1° (*c* 0.73, methanol); R_F (*C*) 0.84; ν_{max}^{KBr} 3362, 3300 (NH), 1719 (C=O) ester, 1638 (Amide I), and 1528 cm^{-1} (Amide II); m.s. (I%): *m/e* 369 (0.1), 368 (0.1), 354 (0.1), 338.1369 (2) ($C_{20}H_{20}NO_4$), 325 (0.2), 309 (0.2), 267 (0.4), 264 (0.8), 247 (10), 215.0938 (12) ($C_{13}H_{13}NO_2$), 204 (4), 200 (2), 190 (7), 188 (5), 174 (2), 172 (1), 163 (1), 142.0865 (20) ($C_7H_{12}NO_2$), 127 (1), 122.0597 (5) (C_7H_8NO), 122.0362 (1) ($C_7H_6O_2$), 117 (3), 105 (100), 95 (7), and 77 (20).

Anal. Calc. for $C_{21}H_{23}NO_5$: C, 68.27; H, 6.27; N, 3.79. Found: C, 67.90; H, 6.33; N, 3.82.

*Methyl 3-benzamido-6-bromo-2,3,6-trideoxy-β-*D*-ribo-hexopyranoside* (**13**). — Hydrogenolysis of **7** (1.2 g) under the conditions described for the preparation of the mixture of **9** and **10** was effected for 8 h. The catalyst was filtered off and the filtrate was concentrated to obtain a mixture of crystalline **13** and syrupy **9** [t.l.c. (*C*) R_F 0.8 and 0.64, respectively]. The crystals were filtered off and washed with cold ether to give pure **15** (560 mg, 51%), m.p. 148–149.5°, $[\alpha]_D^{25}$ −60° (*c* 0.73, chloroform); lit.[11] m.p. 146–147°, $[\alpha]_D$ −53.4° (*c* 0.3, chloroform).

Anal. Calc. for $C_{14}H_{18}BrNO_4$: Br, 23.22. Found: Br, 23.43.

*Methyl 3-benzamido-2,3,6-trideoxy-β-*D*-ribo-hexopyranoside* (**9**) (*methyl* N-*benzoyl-β-*D*-ristosaminide*). — Compound **11** (170 mg) was hydrolyzed with 0.1M methanolic sodium methoxide (0.5 ml) in abs. methanol (12 ml). After being kept for 24 h at room temperature, the solution was neutralized with AG 50W-X12 (H^+) ion-exchange resin and filtered. The filtrate was evaporated to give 120 mg (98%) of chromatographycally homogeneous, syrupy **9**, $[\alpha]_D^{25}$ −38° (*c* 0.5, chloroform); R_F (*C*) 0.64, identical with **9** obtained by hydrogenation of **7**; ν_{max}^{film} 3350 (OH and NH), 1640 (Amide I and C–C aromatic), and 1530 cm^{-1} (Amide II); m.s. identical with that of **9** obtained from **7**.

Anal. Calc. for $C_{14}H_{14}NO_4$: C, 63.29; H, 7.22; N, 5.28. Found: C, 63.18; H, 7.01; N, 5.39.

3-Amino-2,3,6-trideoxy-D-ribo-*hexopyranose* (**15**) *hydrochloride* (D-*ristosamine hydrochloride*). — Compound **9** (150 mg, 0.6 mmol) was treated with barium hydroxide octahydrate (384 mg, 1.2 mmol) in water (4 ml) for 20 h at 100°. The mixture was cooled and filtered, and the filtrate was saturated with carbon dioxide, filtered again, and evaporated. The residue (91 mg) was chromatographed on a Kieselgel G (Merck) column (20 g) with eluent system *D* and, after evaporation, 33 mg of methyl β-D-ristosaminide, $[\alpha]_D^{26}$ −44.8° (*c* 1.65, methanol); R_F (*E*) 0.8 was obtained. This was hydrolyzed with 0.1M hydrochloric acid (0.3 ml) for 1 h at 100°. The hydrolyzate was evaporated (bath temperature 25°) to give extremely hygroscopic **15** hydrochloride (29 mg), m.p. 127–130° (dec.), $[\alpha]_D^{25}$ +75 → +79.3° (after 40 min, *c* 0.46, water): R_F (*E*) 0.90; lit.[9] m.p. 123–125° (dec.), $[\alpha]_D^{22}$ +85° (equil., *c* 2.7, water); for the L enantiomer, lit.[3] $[\alpha]_D^{21}$ −34.3° (*c* 0.57, water).

3-Benzamido-2,3,6-trideoxy-D-ribo-*hexopyranose* (**12**) (N-*benzoyl*-D-*ristosamine*). — Compound **9** (164 mg) was hydrolyzed with 1:3 acetic acid–water (5 ml) for 35 min at 100°. After being cooled, the solution was evaporated and the residue was dried in a vacuum desiccator in the presence of calcium chloride and potassium hydroxide. After being kept for several days, the syrupy product crystallized to yield **12** (126 mg, 81%), m.p. 128–130°, $[\alpha]_D^{25}$ +37° (equil. after 30 min, *c* 0.57, water); R_F (*C*) 0.26; lit.[9] m.p. 128–129°, $[\alpha]_D^{23}$ +39° (equil., *c* 0.6, water); for the L-enantiomer, lit.[3] m.p. 131–133°, $[\alpha]_D^{20}$ −14 → −11° (equil. after 10 min, *c* 1.0, ethanol); ν_{max}^{KBr} 3355 (OH), 3280 (NH), 1540 and 1365 (Amide) cm^{-1}; m.s. (1%): *m/e* 251 (0.6), 233 (2), 215 (1), 207 (1.5), 206 (2), 189 (5), 177 (7), 176 (2), 163 (6), 161 (2), 148 (4), 146 (1.5), 128 (3), 122 (25), 105 (100), and 77 (30).

Anal. Calc. for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57. Found: C, 62.31; H, 6.94; N, 5.68.

*Methyl 3-azido-4-*O-*benzoyl-2,3,6-trideoxy-β*-D-erythro-*hex-5-enopyranoside* (**14**). — A mixture of **7** (200 mg, 0.54 mmol) and dry silver fluoride (116 mg, 0.91 mmol) was stirred in the dark for 4 days. The dark reaction mixture was poured into ether (10 ml), the silver salts were filtered off, and the filtrate was washed with water and dried (magnesium sulfate). It was then evaporated and the syrupy residue was chromatographed on a Silicagel 40 column (Merck) with the eluent system *F* to give 50.5 mg (32%) of syrupy **14**, $[\alpha]_D^{23}$ −140° (*c* 0.5, chloroform); R_F (*F*) 0.6; ν_{max}^{film} 3040, 2100 (C–N azide), 1720 (C=O ester), 1665, 1450, and 870 cm^{-1}(C=CH_2); m.s. (1%): *m/e* 258.0870 (0.3) ($C_{13}H_{12}N_3O_3$), 247.0970 (12) ($C_{14}H_{15}O_4$), 246 (0.4), 215.0698 (16) ($C_{13}H_{11}O_3$), 214 (0.6), 204 (0.5), 125 (0.7), 122 (2) ($C_7H_6O_2$), 112 (3), 111 (1.5), 105 (100), 84.0443 (4) (C_4H_6NO), 77 (25), 58.0412 (5) (C_3H_6O), and 51 (3); metastables: 247−32 = 215 and 289−42 = 247.

Attempted preparation of L-*daunosamine*. — Compound **14** (45 mg) was hydrolyzed in abs. methanol with sodium methoxide. After 4 h, **14** [R_F (*F*) 0.6] had disappeared and a single spot of the *O*-debenzoylated analog [R_F (*F*) 0.2] had appeared. After being processed in the usual manner, the product (30 mg) was hydrogenated for 1 h in methanol in the presence of palladium-on-barium sulfate catalyst. During this period, reduction was complete and the product, isolated after

filtration of the catalyst and evaporation, proved to be homogeneous on t.l.c. [R_F (*E*) 0.86]. It was then hydrolyzed with 0.1M hydrochloric acid for 1 h at 100°. T.l.c. of the hydrolyzate showed that the main component was D-ristosamine [**15**, R_F (*E*) 0.7] and only traces (<5%) of L-daunosamine [R_F (*E*) 0.6] could be detected.

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