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SYNTHESIS OF *N*-TRIFLUOROACETYL-L-ACOSAMINE, *N*-TRIFLUOROACETYL-L-DAUNOSAMINE, AND THEIR 1-THIO ANALOGS*

ISTVÁN PELYVÁS†, AKIRA HASEGAWA‡, AND ROY L. WHISTLER
Department of Biochemistry, Purdue University, West Lafayette, Indiana 47907 (U.S.A.)
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ABSTRACT

A simple and efficient route to *N*-trifluoroacetyl-L-acosamine (**13**), *N*-trifluoroacetyl-L-daunosamine (**12**), and their 1-thio analogues (**18** and **20**) is described. Stereoselective reduction of oxime **5** with borane, followed by trifluoroacetylation resulted in the *arabino* methyl glycoside (**8**), which, on mild acid hydrolysis gave *N*-trifluoroacetyl-L-acosamine (**13**) in an overall yield of 33%, based on L-rhamnal (**1**). Upon oxidation of the C-4 hydroxyl group and stereoselective reduction of the resulting ketone **11**, compound **8** of L-*arabino* configuration was converted into *N*-trifluoroacetyl-L-daunosamine (**12**) in a one-flask sequence with an overall yield of 28% calculated for **1**. Benzyl 1-thio-*N*-trifluoroacetyl-α-L-acosaminide (**18**) was synthesized from enone **2** on Michael-type addition of phenylmethanethiol, followed by oximation, stereoselective reduction with borane and subsequent trifluoroacetylation. 4-*O*-Acetyl-1-*S*-acetyl-*N*-trifluoroacetyl-1-thio-β-L-daunosamine **20** was prepared from **12** *via* the corresponding glycosyl chloride derivative.

INTRODUCTION

During the past decade substantial effort has been devoted to developing processes for the production of L-daunosamine (3-amino-2,3,6-trideoxy-L-*lyxo*-hexopyranose) and L-acosamine (3-amino-2,3,6-trideoxy-L-*arabino*-hexopyranose), the amino sugar components of the anti-tumor, anthracycline glycoside antibiotics[2,3] daunomycin, adriamycin, and carminomycin, and of the vancomycin-type antibiotic actinoidin[4], respectively. Biological studies on semi-synthetic anthracycline glycoside antibiotic analogues have revealed that the second generation representatives, 4′-epidaunomycin and 4′-epiadriamycin, containing L-acosamine as

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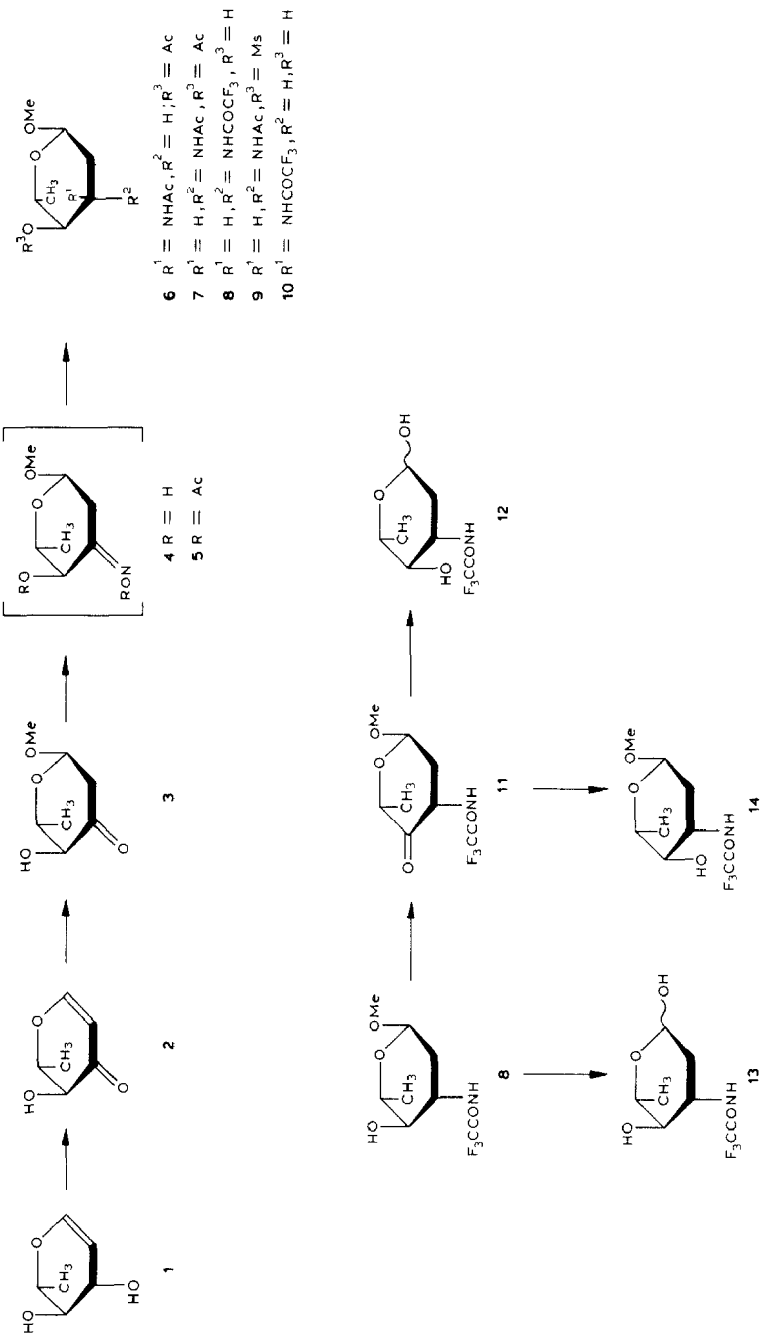
†Present address: Research Group of Antibiotics of the Hungarian Academy of Sciences, Debrecen, H-4010 Hungary.

‡On leave from Department of Agricultural Chemistry, Gifu University, Gifu, Japan.


1
2
3
4 R = H
5 R = Ac
6 R¹ = NHAc, R² = H, R³ = Ac
7 R¹ = H, R² = NHAc, R³ = Ac
8 R¹ = H, R² = NHCOCF₃, R³ = H
9 R¹ = H, R² = NHAc, R³ = Ms
10 R¹ = NHCOCF₃, R² = H, R³ = H
11
12
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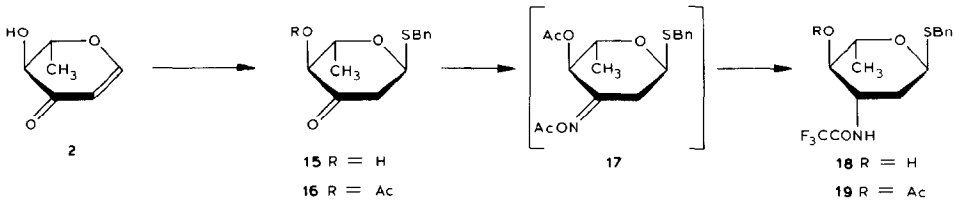

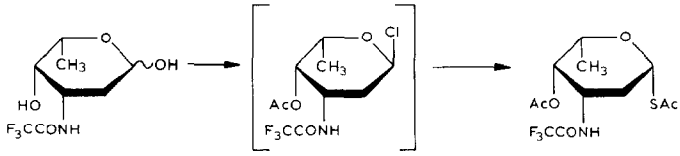

the amino sugar moiety possess an anti-cancer activity comparable to that of daunomycin and adriamycin, and are less toxic and cardiotoxic than the parent antibiotics[3].

The already published, carbohydrate-based syntheses of L-acosamine and L-daunosamine derivatives[5,6] proceed through multistep sequences and are tedious. As an extension of the simple method elaborated by the Bognár group[7] for the stereoselective production of L-ristosamine (3-amino-2,3,6-trideoxy-L-*ribo*-hexose) derivatives, we now describe a facile and efficient route to *N*-trifluoroacetyl-L-acosamine (**13**), *N*-trifluoroacetyl-L-daunosamine (**12**), and also to their hitherto unknown 1-thio analogs (**18** and **20**).

RESULTS AND DISCUSSION

A previous paper reported[7] that the catalytic hydrogenation of oxime **4**, derived from methyl 2,6-dideoxy-α-L-*erythro*-hexopyranoside-3-ulose (**3**), gave, after acetylation, a 39:7 mixture of methyl 3-acetamido-4-*O*-acetyl-2,3,6-trideoxy-α-L-*ribo*-hexopyranoside (**6**, methyl *N*-acetyl-4-*O*-acetyl-α-L-ristosaminide) and the C-3 epimeric L-*arabino* compound (**7**, methyl *N*-acetyl-4-*O*-acetyl-α-L-acosaminide). By this method the *ribo* (*i.e.*, ristosamine) isomer **6** could be obtained in about 20% overall yield from L-rhamnal (**1**). In 1982, the Brimacombe group[8] described an essentially similar route for the preparation of *N*-acetyl-L-ristosamine, involving the catalytic hydrogenation of the 4-*O*-methoxymethyl and 4-*O*-(2-methoxyethoxymethyl) ether derivatives of oxime **4** in the presence of Adams' catalyst.

In the present work, when the di-*O*-acetyl oxime **5** was treated with the borane–oxolane adduct, the reduction proceeded with even higher but opposite stereoselectivity, affording methyl 3-acetamido-4-*O*-acetyl-2,3,6-trideoxy-α-L-

arabino-hexopyranoside (**7**) in excellent yield after alkaline hydrolysis and acetylation, together with about 3% of the *ribo* isomer **6**, as shown by g.l.c. examination.

Similar reduction of **5**, followed by trifluoroacetylation and subsequent *O*-deacylation gave, as the exclusively isolable product, methyl 2,3,6-trideoxy-3-trifluoroacetamido-α-L-*arabino*-hexopyranoside (**8**, methyl *N*-trifluoroacetyl-α-L-acosaminide) in 67% yield (based on **3**). The structure of **8** was proved by comparison of the physical properties to those[9] of methyl *N*-trifluoroacetyl-α-L-acosaminide and also by its ^{1}H-n.m.r. spectrum. The large values of the $J_{3,4}$ and $J_{2a,3}$ coupling constants (9.5 and 11.5 Hz, respectively) clearly showed the *equatorial* orientation of the C-3 amino group in the favored $^1C_4$(L) conformation (see data in Table I).

This remarkably high stereoselectivity of the borane reduction can be explained by the hypothesis that the coordination of the borane–oxolane reagent either to N-3 or to O-4 takes place from the sterically less-hindered lower side[10] of the pyranoside ring of oxime **5**, followed by hydride transfer from the upper side of the ring. Thus, the C-3–N bond becomes *equatorial* and H-3 is *axial*. On the other hand, catalytic hydrogenation presumably proceeds through a molecular-adsorption mechanism providing, in most cases, a mixture of the diastereoisomeric, reduced products.

As the only example hitherto reported for the reduction of a C-3 oxime derivative of a 2,3-dideoxy sugar with borane, Rosenthal and Catsoulacos[11] obtained a 3:1 mixture of methyl 3-acetamido-4,6-*O*-benzylidene-2,3-dideoxy-α-D-*arabino*- and -*ribo*-hexopyranoside from the corresponding C-3 oxime acetate. In the 2-amino-2-deoxyhexose series, Lemieux *et al.*[12] found that the reduction of isopropyl 2-acetoxiimino-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranoside with borane is highly stereoselective and provides the corresponding 2-amino-2-deoxy-glucopyranoside and -mannopyranoside derivatives in a 19:1 ratio.

The conversion of methyl 2,6-dideoxy-α-L-*erythro*-hexopyranoside-3-ulose (**3**) into methyl *N*-trifluoroacetyl-α-L-acosaminide (**8**) could be performed in a one-pot operation affording product **8** with an overall yield of 41% based on L-rhamnal (**1**). Mild acid hydrolysis of **8** gave *N*-trifluoroacetyl-L-acosamine (**13**) in 81% yield.

The aforementioned, simple and efficient synthesis for L-acosamine derivatives prompted us to convert the *arabino*-glycoside **8** into L-daunosamine (L-*lyxo*) derivative **14** by the inversion of the configuration at C-4. Such reaction has been performed first by Marsh *et al.*[13] with compound **9**, and then by other workers[14,15], by means of the nucleophilic displacement of OMs-4 of suitably protected 4-*O*-methylsulfonyl derivatives of 3-amino-3-deoxy sugars with sodium acetate.

An analogous conversion was expected to proceed, as well, by the method worked out for the transformation[16] of methyl *N*-trifluoroacetyl-α-L-ristosaminide (**10**) into its C-4 epimeric *xylo*-isomer, involving oxidation of free OH-4 and subsequent reduction of the resulting C-4 ulose derivative.

Although oxidation of **8** with ruthenium tetraoxide gave the desired methyl 2,3,6-trideoxy-3-trifluoroacetamido-α-L-*threo*-hexopyranoside-4-ulose (**11**) in about 70% yield, the reaction was not complete even after 30 h with a large excess of the

TABLE I

^{1}H-N M R SPECTRAL DATA[a] OF **8, 11, 13, 14, 16, 18, 19,** AND **20**

Compound	*Chemical shifts (δ)*							
	H-1	*H-2e*	*H-2a*	*H-3*	*H-4*	*H-5*	*CH-5*	*Others*
8[b]	4.72	2.15	1.88	3.75	3.26	4.25	1.32	3.36, OMe; 7.65, N*H*
11	4.88	2.93	1.93	5.00		4.42	1.33	3.48, OMe; 7.19, N*H*
13[c]	5.46		2.25–1.90	4.45	3.40	4.15	1.50	6.60, O*H*-1; 5.40, O*H*-4; 9.45, N*H*
14	4.74	2.10	1.68	4.25	3.55	3.90	1.26	3.36, OMe; 6.70, N*H*
16	5.40	3.10	2.55		4.88	4.49	1.32	2.20, OAc; 3.70, PhCH_2
18	5.17		2.22–1.96[d]	4.28–4.00	3.18	4.28–4.00	1.28	6.34, N*H*; 3.72, PhCH_2
19	5.16	2.70	2.07	4.35	4.53	4.29	1.16	2.08, OAc; 3.73, PhCH_2; 6.63, N*H*
20[e]	5.28		2.00–1.88		5.02		1.18	2.17, OAc; 2.33; SAc; 6.60, N*H*
	Coupling constants[f]							
	$J_{1,2e}$	$J_{1,2a}$	$J_{2e,3}$	$J_{2a,3}$	$J_{2e,2a}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	*Others*
8[b]	~1	3.5	5.0	11.5	14.0	9.5	9.5	6.0	$J_{3,NH}$ 7.8
11	1.25	3.3	6.2	12.4	12.5			6.5	$J_{3,NH}$ 7.7
13[c]						9.7	9.7	6.0	$J_{3,NH}$ 8.8; $J_{1,OH}$ 3.5; $J_{4,OH}$ 6.4
14	~1	3.5	4.2	12.5	12.5	~1	~1	6.5	$J_{3,NH}$ 8
16		7.7			14.8		10.6	7.7	$J_{H,H}$ (PhCH_2S) 7.7
18	~1	4.2			14.0	9.9	9.9	6.5	$J_{3,NH}$ 8; $J_{H,H}$ (PhCH_2S) 7.6
19	1.6	5.6	4.0	9.6	14.0	10.0	10.0	6.4	$J_{3,NH}$ 8; $J_{H,H}$ (PhCH_2S) 7.6
20[e]	3.6	10.0				2.20	2.60	6.2	

[a]At 200 MHz for solutions in $CDCl_3$. [b]Recorded for a solution in (^{2}H)chloroform–($^2H_6$)acetone. [c]Recorded for a solution in di($^2H_3$)methyl sulfoxide. [d]Including the O*H*-4 signal. [e]Recorded at 90 MHz. [f]In Hz.

oxidant. Moreover, chromatographic separation of the product from unreacted **8** was necessary. However, by applying the chromium trioxide–dipyridyl system in the presence of acetic anhydride, reported to be a powerful oxidant for the fast oxidation of isolated hydroxyl groups of several carbohydrate derivatives[17], the oxidation was complete within 20–25 min and compound **11** could be readily isolated in 88% yield.

Reduction of **11** with lithium tri-*sec*-butylborohydride[18], a reagent that is reported[19] to favor the generation of *axial* hydroxyl groups from certain carbohydrate C-4 uloses, resulted in the desired methyl 2,3,6-trideoxy-3-trifluoroacetamido-α-L-*lyxo*-hexopyranoside (**14**, methyl *N*-trifluoroacetyl-α-L-daunosaminide) in 93% yield. Not even traces of the *arabino* glycoside **8** could be detected by t.l.c. examination. On the contrary, the reduction of uloside **11** with sodium borohydride has been claimed[9] to give the *arabino* glycoside **8** in 65% yield.

In one-pot operation, *N*-trifluoroacetyl-L-daunosamine (**12**) could be prepared from **11** in 78% yield by use of the aforementioned procedure and mild acid hydrolysis of the intermediary methyl glycoside **14**. The daunosamine derivative **12** was obtained in an overall yield of 28%, based on L-rhamnal.

Due to the electronegativity and magnetic anisotropy[20] of the carbonyl group at C-4, the chemical shifts of H-2*e*, -3, and -5 of **11** (see Table I) showed large downfield shifts (0.78, 1.25, and 0.17 p.p.m., respectively), as compared to the corresponding shifts of compound **8** or to that of **14** (0.83, 0.75, and 0.35 p.p.m., respectively).

These results and those described earlier[7,16] clearly demonstrate that 1,5-anhydro-2,6-dideoxy-L-*erythro*-hex-1-en-3-ulose (**2**) is an excellent "synthon" for the production of each of the 3-amino-2,3,6-trideoxyhexopyranoses of the L-series.

1-Thio-α-L-acosaminide derivatives, new representatives of the daunosamine-type sugars, were synthesized also from enone **2**. Michael-addition of phenylmethanethiol on **2** resulted in benzyl 2,6-dideoxy-1-thio-α-L-*erythro*-hexopyranoside-3-ulose (**15**) which was characterized in the form of the crystalline 4-acetate **16**. This is the first example of the preparation of a 2-deoxy-1-thioglycoside by a Michael-addition.

On treatment with hydroxylamine followed by acetylation, compound **15** was converted into the *O*-acetyloxime **17** which was reduced with borane under conditions similar to those described for the preparation of **8**. After trifluoroacetylation and *O*-deacylation, a yield of 60% (based on **2**) of crystalline benzyl 2,3,6-trideoxy-3-trifluoroacetamido-1-thio-α-L-*arabino*-hexopyranoside (**18**, benzyl *N*-trifluoroacetyl-1-thio-α-L-acosaminide) was obtained. The large (10 Hz) $J_{2a,3}$ and $J_{3,4}$ coupling constants (see Table I) assigned in the ^{1}H-n.m.r. spectra (obtained with spin-decoupling experiments) of **18** and its 4-acetate **19** unequivocally showed the *axial* orientation of the H-3 proton and, thus, the *arabino* configuration of both compounds. The C-3 epimeric *ribo* isomer, presumably formed in traces during the reduction, could not be isolated.

4-*O*-Acetyl-1-*S*-acetyl-*N*-trifluoroacetyl-β-1-thio-L-daunosamine (**20**) was

synthesized as follows. Treatment of **12** with acetyl chloride for 22 h gave the corresponding glycosyl chloride, which was treated, without isolation, with potassium thioacetate. The large value of the $J_{1,2a}$ coupling constant (10 Hz) in the ^{1}H-n.m.r. spectrum of the product **20** clearly showed the β configuration of the 1-thioacetyl group.

EXPERIMENTAL

General methods. — Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. Optical rotations were measured with Rudolph Autopol III, Perkin Elmer 241, and Union PM-201 automatic polarimeters. ^{1}H-N.m.r. spectra were recorded with Nicolet NTCFT 1180 (200 MHz), Bruker WP 200 SY (200 MHz), and Hitachi R-22 (90 MHz) instruments. G.l.c. was performed with a Hewlett–Packard HP 5380 A instrument, equipped with a column of 3% ECNSS-M, at 150° (5°/min). T.l.c. was performed on Kieselgel G (Merck) with (*A*) 17:3 benzene–methanol and (*B*) 100:1 chloroform–methanol. For column chromatography, Silica gel 60 (Merck) was used with the eluent system (*B*). Evaporations were carried out under diminished pressure at 35–40°.

*Methyl 3-acetamido-4-*O*-acetyl-2,3,6-trideoxy-*α*-*L*-*arabino*-hexopyranoside (methyl* N*-acetyl-4-*O*-acetyl-*α*-*L*-acosaminide)* (**7**). — Compound **7** was prepared according to the procedure described for **8** starting from 320 mg (2 mmol) of **3**. G.l.c. investigation of the crude acetylation mixture of the syrupy product, obtained after reduction and alkaline hydrolysis, indicated the presence of **7** (89.6%, R_T 4.11 min), its *ribo* epimer (3.2%, R_T 2.60 min), and three minor components. The R_T values of authentic samples of **7** and **6** were 4.14 and 2.60 min, respectively. The reaction mixture was worked-up in the usual manner (due to its slight solubility in water, some product was lost on the extraction process), to obtain, after crystallization from ether–petroleum ether, pure **7** (280 mg, 57% based on **3**), m.p. 161–162°, $[\alpha]_D^{21}$ −188.2° (*c* 1.05, methanol); lit.[21] m.p. 163–164°, $[\alpha]_D^{22}$ −191° (*c* 0.52, methanol).

Anal. Calc. for $C_{11}H_{19}NO_5$ (245.27): C, 53.87; H, 7.81; N, 5.71. Found: C, 54.10; H, 7.77; N, 5.67.

*Methyl 2,3,6-trideoxy-3-trifluoroacetamido-*α*-*L*-*arabino*-hexopyranoside (methyl* N*-trifluoroacetyl-*α*-*L*-acosaminide)* (**8**). — To a solution of **3** (containing ~6% of the β anomer)[7] (2.5 g, 15.6 mmol) in abs. methanol (10 mL) was added a solution of hydroxylamine in abs. methanol (60 mL), prepared from hydroxylamine hydrochloride (7.5 g, 0.108 mol) and KOH (6.23 g, 0.111 mmol). After storage at room temperature for 4 h, the solvent was evaporated and the syrupy residue was acetylated with acetic anhydride (15 mL) in dry pyridine (20 mL) for 16 h. Work-up in the usual manner gave the crude oxime diacetate **5**, [ν_{max}^{film} 1655 (C=N), 1750 cm^{-1} (ester C=O)], which was dissolved in dry oxolane (30 mL). M Borane–oxolane complex in oxolane (70 mL, 70 mmol, Aldrich Chem. Co.) was dropwise added over a period of 30 min at 0 to −5°. Stirring was continued at 0° for additional 30

min, and then at room temperature for 2 h. The colorless solution was cooled to 0° and dry methanol (25 mL) added to decompose the excess of the reducing agent. After evaporation, the residue was dissolved in methanol (40 mL). Water (10 mL), and Amberlite IRA-410 C.P. (OH^-) ion-exchange resin (methanol wet, 35 g) were added and the mixture was stirred under reflux for 4 h. After the suspension had been cooled, the resin was removed by filtration and the filtrate evaporated and dried in the presence of P_2O_5. The dry, semi-crystalline residue was taken up in abs. ether (60 mL) and trifluoroacetic anhydride (12 mL) was added. After 3 h at room temperature, the clear solution was concentrated, and the residual solvent co-evaporated with hexane (3 × 10 mL). The residue was stored overnight in the presence of KOH. Methanol (30 mL) was added and the mixture kept at room temperature for 16 h. T.l.c. indicated the presence of **8**, R_F (*A*) 0.44, and only traces of the C-3 epimeric *ribo* compound **10**, R_F (*A*) 0.52, could be detected. The semicrystalline residue obtained after evaporation was purified by column chromatography (*B*) to give pure **8** (2.7 g, 67% based on **3**), m.p. 196–197° (subl.) $[\alpha]_D^{21}$ −110.8° (*c* 0.8, methanol); lit.[9] m.p. 195–197°, $[\alpha]_D$ −110° (*c* 0.2, methanol).

Anal. Calc. for $C_9H_{14}F_3NO_4$ (257.21): C, 42.02; H, 5.48; N, 5.45. Found: C, 42.06; H, 5.42; N, 5.40.

*Methyl 2,3,6-trideoxy-3-trifluoroacetamido-α-*L-threo-*hexopyranoside-4-ulose* (**11**). — To a solution of CrO_3–dipyridyl complex [in dry dichloromethane (30 mL), prepared from CrO_3 (800 mg, 8 mmol) and pyridine (1.30 mL, 16 mmol)] were simultaneously added compound **8** (514 mg, 2 mmol) and acetic anhydride (0.75 mL, 8 mmol), and the mixture was stirred at room temperature for 20 min when t.l.c. (*B*) showed that all of the starting **8** had disappeared. The mixture was poured onto the top of a column (30 × 2.5 cm) packed with Silicagel 60 and ethyl acetate, and eluted quickly with ethyl acetate in one fraction to remove the chromium salts. The eluate was evaporated, and the residual solvent co-evaporated with toluene (3 × 15 mL) to give colorless crystalline **11** (449 mg, 88%), m.p. 76–78° (lit.[9] m.p. 77–80°), $[\alpha]_D^{21}$ −101° (*c* 0.6, methanol); ν_{max}^{film} 1740 (ketone C=O), 1700 (amide I), and 1550 cm^{-1} (amide II).

Anal. Calc. for $C_9H_{12}F_3NO_4$ (255.19): C, 42.35; H, 4.74; N, 5.49. Found: C, 42.40; H, 4.72; N, 5.42.

*2,3,6-Trideoxy-3-trifluoroacetamido-*L-lyxo-*hexopyranose* (**12**, *N-trifluoroacetyl-*L-*daunosamine*). — A solution of **11** (880 mg, 3.44 mmol) in abs. oxolane (12 mL) was dropwise added to M lithium tri-*sec*-butylborohydride in oxolane (15 mL, 15 mmol) (Aldrich) at −50 to −60° with stirring. Stirring was continued for 3 h at −50°, and then water (12 mL) was cautiously added at −10°. The pH of the mixture was adjusted to 4 with 2M HCl and the mixture was extracted with dichloromethane (3 × 8 mL), the combined organic layer was evaporated, and the residue was treated with 20% (v/v) acetic acid (15 mL) at 100° for 1 h. T.l.c. examination of the hydrolyzate using authentic samples of **13** and **12** (*A*, 3 developments) showed the presence of the *lyxo* isomer **12** and traces of the *N*-deacylated by-product L-daunosamine. After evaporation and co-evaporation with benzene, a

solution of the residue in ethyl acetate (40 mL) was washed with water (3 × 8 mL), and the organic layer was dried (Na_2SO_4) and evaporated to give homogeneous, crystalline **12** (656 mg, 78.2%), m.p. 146–148°, $[\alpha]_D^{21}$ −144 → −135° (after 20 h, equil.; *c* 0.8, 1,4-dioxane); lit.[15] m.p. 149–150°, $[\alpha]_D^{20}$ −136° (equil.; *c* 1, 1,4-dioxane).

Anal. Calc. for $C_8H_{12}F_3NO_4$ (243.18): C, 39.51; H, 4.97; N, 5.76. Found: C, 39.58; H, 5.00; N, 5.69.

*2,3,6-Trideoxy-3-trifluoroacetamido-*L-arabino-*hexose (***13,** *N-trifluoroacetyl-*L-*acosamine).* — A solution of **8** (150 mg) in 20% (v/v) acetic acid (15 mL) was kept for 3 h at 100°. It was evaporated to dryness, and the crystalline residue dried (KOH) and recrystallized from methanol–dichloromethane to give **13** (115 mg, 81%), m.p. 204–206° (dec.), $[\alpha]_D^{21}$ −54 → −33° (equil. after 24 h; *c* 0.5, 1,4-dioxane); lit.[9] m.p. 202° (dec.), $[\alpha]_D$ −51 → −33.4° (after 2 h; *c* 0.5, 1,4-dioxane).

Anal. Calc. for $C_8H_{12}F_3NO_4$ (243.18): C, 39.51; H, 4.97; N, 5.76%. Found: C, 39.56; H, 5.07; N, 5.70%.

*Methyl 2,3,6-trideoxy-3-trifluoroacetamido-α-*L-lyxo-*hexopyranoside (***14,** *methyl* N-*trifluoroacetyl-α-*L-*daunosaminide).* — A solution of **11** (255 mg, 1 mmol) in abs. oxolane (6 mL) was dropwise added to M lithium tri-*sec*-butylborohydride in oxolane (4 mL, 4 mmol) at −50 to −60° with stirring. Stirring was continued for 3 h at −50°, and then water (9 mL) was cautiously added at −10° and the pH of the mixture adjusted to 7 with HCl. T.l.c. examination of the mixture (*B*, 3 developments) showed the exclusive presence of **14** and no traces of **8** could be detected. The mixture was extracted with dichloromethane (3 × 6 mL), and the combined organic layer dried (Na_2SO_4) and evaporated to give homogeneous, crystalline **14** (239 mg, 93%), m.p. 110–111°, $[\alpha]_D^{21}$ −196° (*c* 1.2, methanol) [lit.[9] m.p. 108–109°, $[\alpha]_D$ −195° (*c* 0.5, methanol)]; ν_{max}^{film} 3440, 3320 (OH, NH), 1705, 1690, 1550, and 1180 cm^{-1} (amide).

Anal. Calc. for $C_9H_{14}F_3NO_4$: C, 42.02; H, 5.48; N, 5.45. Found: C, 42.09; H, 5.42; N, 5.38.

*Benzyl 4-*O*-acetyl-2,6-dideoxy-1-thio-α-*L-erythro-*hexopyranosid-3-ulose* (**16**). — Compound **2** (128 mg, 1 mmol) was treated with phenylmethanethiol (124 mg, 1 mmol) as described for the preparation of **18**. The mixture was evaporated to dryness, co-evaporated several times with toluene, and the residue acetylated with acetic anhydride (0.2 mL) in pyridine (0.5 mL). The syrupy product obtained after conventional processing crystallized on storage at −4° for several weeks. Recrystallization from a small amount of methanol gave **16** (250 mg, 85%), m.p. 98–99°, $[\alpha]_D^{21}$ −437° (*c* 0.77, methanol).

Anal. Calc. for $C_{15}H_{18}O_4S$ (294.36): C, 61.20; H, 6.16; S, 10.89. Found: C, 61.23; H, 6.20; S, 11.04.

*Benzyl 2,3,6-trideoxy-3-trifluoroacetamido-1-thio-α-*L-arabino-*hexopyranoside (***18,** *benzyl* N-*trifluoroacetyl-1-thio-α-*L-*acosaminide).* — A mixture of **2** (640 mg, 5 mmol), phenylmethanethiol (0.621 g, 5 mmol), and a 0.6-mL aliquot of pyridine (5 mL) containing triethylamine (3 drops) was kept for 2 h at room

temperature. T.l.c. (*A*) indicated that all starting **2** had disappeared. Hydroxylamine hydrochloride (350 mg, 5.1 mmol) and abs. methanol (2.5 mL) were added and the mixture was shaken until all of the reagent dissolved. The formation of the oxime was complete within 4 h, the mixture was evaporated, and the residue treated with acetic anhydride (3 mL) in pyridine (3 mL). After the usual processing, an homogeneous, syrupy diacetyl oxime **17** was obtained which proved to be almost exclusively the α anomer; ^{1}H-n.m.r. (90 MHz, $CDCl_3$): δ 7.35 (5 H, arom.), 5.20 (dd, 1 H, $J_{1,2a}$ 4 Hz, H-1), 4.40 (m, 1 H, $J_{4,5}$ 9 Hz, H-5), 3.70 (s, 2 H, S-CH_2), 3.25 (m, 1 H, $J_{1,2e}$ 1.5 Hz, H-2*e*), 2.67 (m, 1 H, H-2*a*), 2.09, and 2.06 (2 s, 6 H, 2 OAc), and 1.20 (d, 3 H, CH_3-5).

A solution of crude **17** in abs. oxolane (10 mL) was treated with M borane–oxolane complex in oxolane (50 mL, 50 mmol) as described for the preparation of **8**. The alkaline hydrolysis was performed in a mixture of 10% aqueous NaOH (50 mL), 1,4-dioxane (10 mL), and methanol (15 mL) for 5 h at 100°. After being cooled, the mixture was extracted with oxolane (3 × 20 mL), and the combined organic extracts were dried (Na_2SO_4), evaporated, and dried (P_2O_5). The dry residue was treated with trifluoroacetic anhydride (5 mL) in dry ether (25 mL) for 4.5 h at room temperature. After evaporation and co-evaporation of the residual solvent with hexane, the crystalline residue was dissolved in methanol (25 mL), and the solution kept at room temperature for 16 h and concentrated. The crystalline residue was twice recrystallized from ether–petroleum ether to give pure **18** (1.05 g, 60% based on **2**), m.p. 154–155°, $[\alpha]_D^{21}$ −272° (*c* 0.85, methanol).

Anal. Calc. for $C_{15}H_{18}F_3NO_3S$ (349.36): C, 51.56; H, 5.19; N, 4.00; S, 9.18. Found: C, 51.62; H, 5.24; N, 4.05; S, 9.26.

*Benzyl 4-O-acetyl-2,3,6-trideoxy-3-trifluoroacetamido-1-thio-α-*L-arabino*-hexopyranoside* (**19**). — Acetylation of **18** (200 mg) in pyridine (3 mL) with acetic anhydride (1 mL) gave crystalline **19**, m.p. 165–166°, $[\alpha]_D^{21}$ −290° (*c* 0.8, methanol).

Anal. Calc. for $C_{17}H_{20}F_3NO_4$ (391.40): C, 52.16; H, 5.15; N, 3.58; S, 8.19. Found: C, 52.26; H, 5.17; N, 3.52; S, 8.25.

*4-O-Acetyl-1-*S*-acetyl-*N*-trifluoroacetyl-1-thio-β-*L*-daunosamine* (**20**). — To a suspension of *N*-trifluoroacetyl-L-daunosamine (**12**) (243 mg) in dry dichloroethane (1.0 mL) was added acetyl chloride (1.0 mL), and the mixture was stirred for 22 h at room temperature and evaporated *in vacuo* <20°. The crude halide was dissolved in dry acetone (4.0 mL) and potassium thioacetate (120 mg) was added. The mixture was stirred for 1 h at room temperature and evaporated, the residue extracted with chloroform, and the organic layer washed with 2M HCl, M Na_2CO_3, and water, dried (Na_2SO_4), and evaporated to give a crystalline product. Recrystallization from ether afforded **20** (245 mg, 71%) as needles, m.p. 184–185°, $[\alpha]_D^{25}$ ±0° (*c* 0.1, chloroform).

Anal. Calc. for $C_{12}H_{16}F_3NO_5S$: C, 41.98; H, 4.70; N, 4.08. Found: C, 41.86; H, 4.65; N, 4.13.

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