SYNTHESIS AND ANTITUMOR ACTIVITY OF ANTHRACYCLINE DISACCHARIDE GLYCOSIDES CONTAINING DAUNOSAMINE

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Daunosamine, as its 4-*O*-acetyl-3-*N*-trifluoroacetyl glycosyl chloride derivative (**1b**), has been coupled α-L-glycosidically to the 3- and 4-mono-*O*-acetyl derivatives of L-rhamnal to afford disaccharide glycal derivatives, whose conversion into the corresponding 2-deoxyglycosides by sequential alkoxyiodination–tributylstannane reduction has been evaluated. The sequence successfully demonstrated with the methyl glycosides was successfully extended with daunomycinone as the aglycon, providing a preparative route to 7-*O*-[3-*O*-(3-amino-2,3,6-trideoxy-α-L-*lyxo*-hexopyranosyl)-2,6-dideoxy-α-L-*arabino*-hexopyranosyl]daunomycinone hydrochloride (**15**), an analogue of natural anthracycline antibiotics containing daunosamine and a 2,6-dideoxy-L-hexose.

Most of the natural anthracycline antibiotics with oligosaccharide side chains, as in the rhodomycin and cinerubin series, contain daunosamine as the sugar directly attached to the anthracyclinone and are of interest as antitumor agents[1]. Only in a few cases, daunosamine appears as the non reducing terminal sugar[2,3]. These compounds also showed high degree of antitumor activity. As part of our program to obtain new anthracycline antibiotics, we decided to synthesize derivatives having daunosamine as the terminal non reducing sugar, in order to compare their biological activity with the natural products, and to be able to make conclusions about the importance of the sequence of sugars in the oligosaccharide side chain.

Synthetic analogs of daunorubicin and doxorubicin have been extensively investigated in our laboratory[4,5]. Conventional Koenigs–Knorr coupling between daunomycinone or 14-protected adriamycinone and appropriate glycosyl halides is sometimes complicated by low yields and mixtures of anomers. An alternative two-step synthesis[6] offers significant advantage. The first step involves *trans*-alkoxyhalogenation of appropriate glycal precursors with *N*-iodosuccinimide (NIS) and daunomycinone (DNM). This glycosidation method has proved useful with sugar aglycons, as demonstrated by THIEM *et al.*[7~9], with DNM as shown in earlier work from our group[10], and more recently by DANISHEFSKY *et al.*[11]. The second step employs dehalogenation with tributylstannane (Bu_3SnH). This general sequence was used by UMEZAWA *et al.*[12] to obtain simple 2-deoxy-α-glycosides, and the steric course of dehalogenation of methyl 2-haloglycosides by Bu_3SnD has been studied in detail in our laboratory[13].

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Results and Discussion

Chemical Synthesis

4-*O*-Acetyl-1,5-anhydro-2,3,6-trideoxy-3-trifluoroacetamido-L-*lyxo*-hex-1-enitol (**1a**) (Scheme 1), a stable, activated daunosamine derivative[14] was converted into the glycosyl chloride derivative **1b**, which was immediately coupled with 3-*O*-acetyl-L-rhamnal (**2**, readily prepared[15] by selective acetylation of L-rhamnal) under conventional typical Koenigs–Knorr conditions to afford the α-L-(1→4)-linked disaccharide glycal derivative **3** in 40% yield. Treatment of this glycal with hydrogen chloride in benzene, followed by Koenigs–Knorr reaction with methanol afforded only the monosaccharide methyl β-L-glycoside **4**, obtained in low yield. No traces of disaccharide glycoside **7** were detected. Similar results were observed when the daunosamine derivative **1b** was coupled to 4-*O*-acetyl-L-rhamnal[15] (**8**) (Scheme 2) to afford the α-L-(1→3)-linked disaccharide glycal derivative **9**; again treatment with HCl and then with methanol gave only the monosaccharide glycoside **4**. These results indicate that the glycal disaccharides **3** and **9** undergo hydrolysis by dry HCl, affording the glycosyl chloride (**1b**) of daunosamine, which then reacts with methanol to give the glycoside **4**.

The failure of this conventional glycosidation sequence with the disaccharide glycals **3** and **9** prompted evaluation of the NIS-ROH glycosidation[7~9] and Bu_3SnH dehalogenation[12] as a route to the model methyl glycosides **7** and **12**.

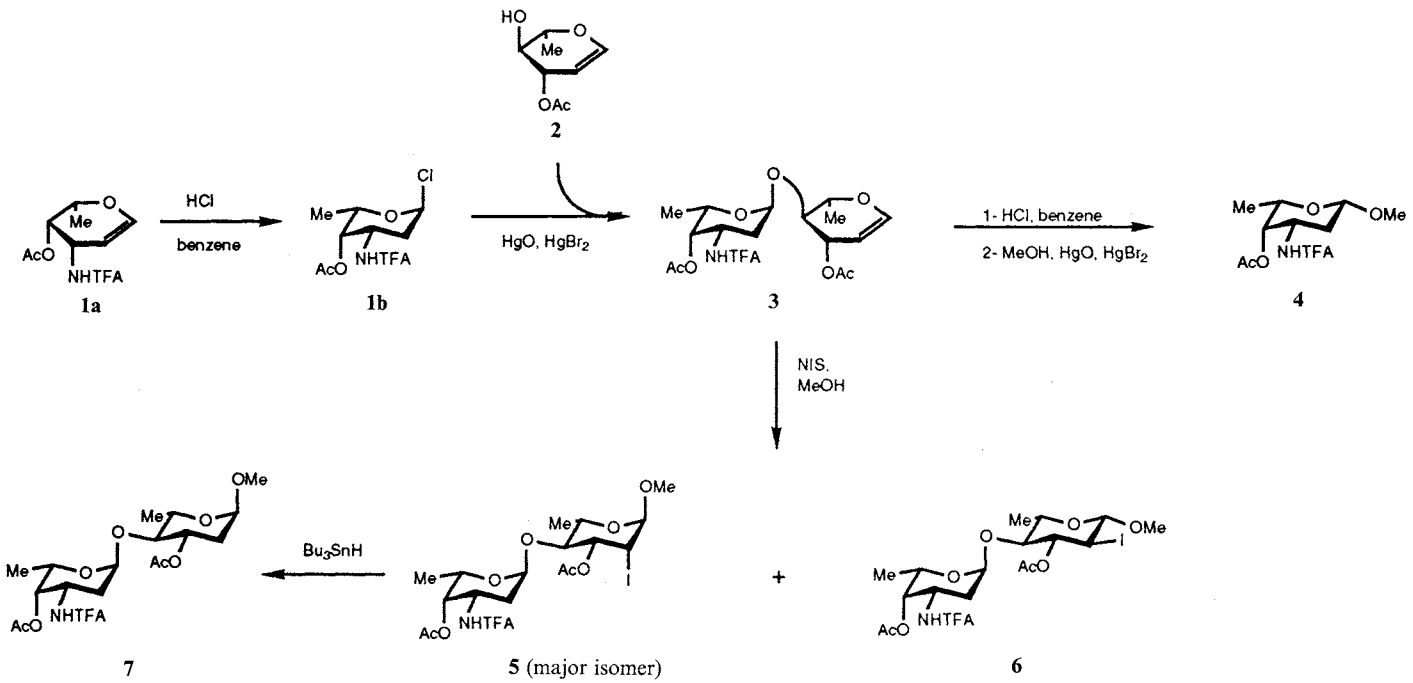
Treatment of the (1→4)-linked glycal **3** (Scheme 1) with NIS and methanol gave a 3.8:1 mixture of *trans* methyl 2-iodo disaccharides **5** and **6**. The *trans*-diaxial isomer **5** was expected to be the major product, based on our previous studies concerning the stereochemistry of NIS-MeOH addition to the double bond of glycals[16,17]. This mixture was resolved by column chromatography and the major 1,2-*trans*-diaxial product (**5**) was deiodinated with Bu_3SnH to afford the final methyl glycoside disaccharide **7**, crystalline in 73% yield.

Similarly, treatment of the (1→3)-linked glycal **9** (Scheme 2) with NIS-MeOH afforded a mixture of 1,2-*trans* isomers **10** and **11**, here in 3.2:1 ratio. The major, *trans*-diaxial product **10** was likewise treated with Bu_3SnH to give the methyl glycoside disaccharide **12**, crystalline in 76% yield.

Structural Assignments for Disaccharide Methyl Glycosides Derivatives **5**, **6**, **7**, **10**, **11** and **12**

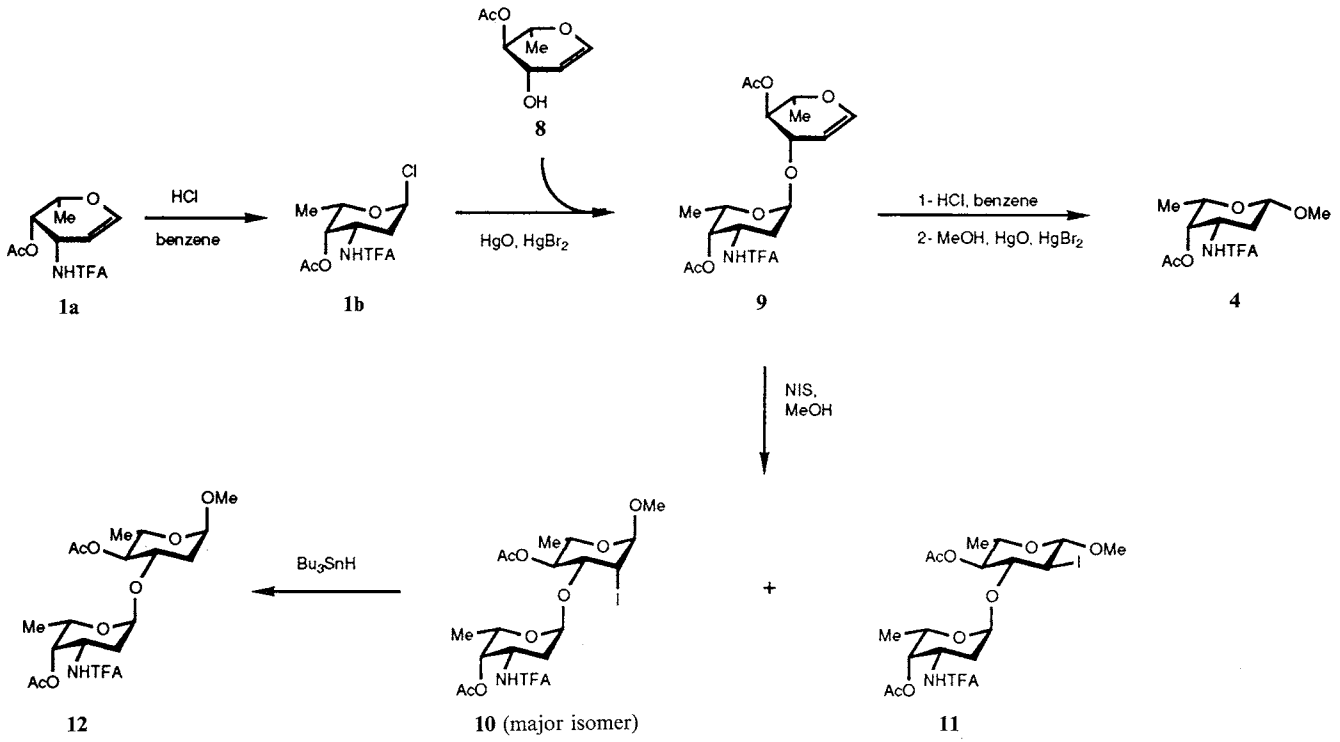
The products obtained by methoxyiodination of the double bond of **3** (products **5** and **6**) and **9** (products **10** and **11**), showed large $J_{3,4}$ (8.5~9.3 Hz) and $J_{4,5}$ (8.9~9.0 Hz) values, indicating the *trans*-diaxial disposition between H-3–H-4 and H-4–H-5 in the favored $^1C_4$ (L) conformation. The small values of $J_{2,3}$ (4.2 Hz) in compounds **5** and **10** indicate the L-*manno* configuration. Large values of $J_{2,3}$ (11.2~10.5 Hz) observed for compounds **6** and **11** signify the L-*gluco* configuration. The large values of $J_{1,2}$ (8.9~9.0 Hz) for compounds **6** and **11** likewise accord with their having the β-L-*gluco* configuration. Small (1.4~0 Hz) $J_{1,2}$ coupling constants, again support assignment of the α-L-*manno* configuration to compounds **5** and **10**. The structural assignment for compounds **5** and **10** was further consolidated from NMR data on their Bu_3SnH reduction-products, compounds **7** and **12**, respectively. Both of these 2-deoxyglycosides showed two small coupling constants between H-1 and the protons at C-2 ($J_{1,2\,eq}$ close to zero and $J_{1,2\,ax}$=3.7, 3.1 Hz for **7** and **12**, respectively), indicating that H-1 is equatorial. Compounds **7** and **12** also showed large $J_{3,4}$ (9.1~9.3 Hz) and $J_{4,5}$ (9.1~9.5 Hz) values, indicating the *trans*-diaxial disposition between H-3–H-4 and H-4–H-5 in the favored $^1C_4$ (L) conformation.

Scheme 1.



NIS: *N*-iodosuccinimide

Scheme 2.



NIS: *N*-iodosuccinimide

Glycosidation of 9 with Daunomycinone

Alkoxyiodination of disaccharide glycal **9** (Scheme 3) with NIS-DNM afforded the *trans*-diaxial addition product **13** as the only observed product, isolated crystalline in 50% yield. Deiodination by Bu_3SnH gave the 2-deoxyglycoside **14** in 55% yield. Deprotection of **14** by transesterification with NaOMe and then amide hydrolysis with aqueous NaOH, afforded, after crystallization from HCl-MeOH and ether, the target anthracycline disaccharide glycoside **15** in 32% yield as a crystalline product.

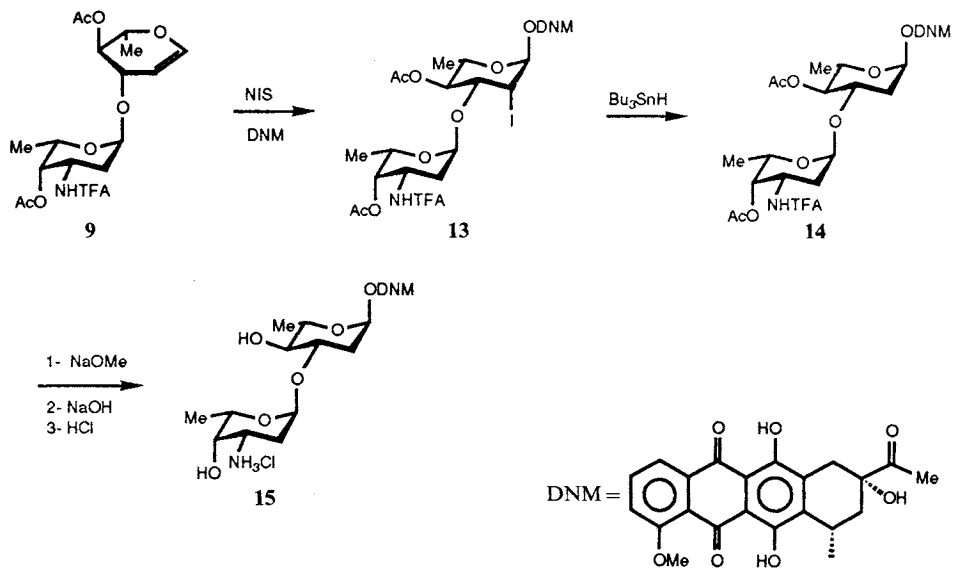
Structural Assignments for Compounds 13, 14 and 15

The alkoxyiodination product **13** derived from disaccharide glycal **9** showed large $J_{3',4'}$ (9.3 Hz) and $J_{4',5'}$ (9.3 Hz) couplings, indicating the *trans*-diaxial disposition of H-3′–H-4′ and H-4′–H-5′ in the favored $^1C_4$ (L) conformation. The small value of $J_{2,'3'}$ (4.0 Hz), indicates the L-*manno* configuration, and the small $J_{1',2'}$ (1.4 Hz) coupling constant indicates the α-L-anomeric configuration. The last assignment was confirmed by studies on the deiodination product **14**. Compound **14** showed two small coupling constants between H-1′ and the hydrogen atoms at C-2′ ($J_{1',2'eq} = \sim 0$ and $J_{1',2'ax} = 3.4$ Hz), indicating that H-1′ is equatorial. Compound **14** also showed large $J_{3',4'}$ (9.1 Hz) and $J_{4',5'}$ (9.4 Hz) values, further supporting the *trans*-diaxial disposition between H-3′–H-4′ and H-4′–H-5′ in the favored $^1C_4$ (L) conformation. The final deprotected product, compound **15**, shows the same coupling pattern as **14**: small coupling constants between H-1′ and C-2′ protons ($J_{1',2'eq} = \sim 0$ and $J_{1',2'ax} = 3.3$ Hz), confirming the equatorial disposition of H-1′. The large couplings between H-3′–H-4′ ($J_{3',4'} = 9.1$ Hz) and H-4′–H-5′ ($J_{4',5'} = 8.5$ Hz), confirm the *trans*-diaxial disposition of these hydrogens in the favored $^1C_4$ (L) conformation.

Biological Testing

The disaccharide glycoside **15** (NSC 6549947) was submitted to the National Cancer Institute for testing in the human cell line-based *in vitro* anticancer screen, and was tested on two separate occasions. The tests involved exposure to close to 60 cell lines. The compound showed no appreciable cell-line

Scheme 3.



NIS: *N*-iodosuccinimide
DNM: daunomycinone

selectivity, with total growth inhibition (-log[concentration]) against all lines of >4. The IC_{50} value against all lines was 4.01. The compound thus displayed only marginal activity.

Conclusions

This work demonstrates a potentially general and effective synthetic method for producing an oligosaccharide terminated at the reducing end by a glycal, and coupling this in a two-step sequence to a sensitive, highly functionalized alcohol, to produce the corresponding 2-deoxyglycoside of the alcohol and the oligosaccharide. The approach is shown to be particularly effective in synthesis of anthracycline glycosides.

Experimental

General Methods

Solvents were dried and redistilled just prior to use. Melting points were determined in open glass capillaries by using a Thomas-Hoover apparatus, and are uncorrected. Optical rotations were measured with a Perkin-Elmer Model 141 polarimeter, ^{1}H NMR spectra were recorded at 500 MHz with a Bruker AM-500 spectrometer by C. E. COTTRELL. The samples were dissolved in the indicated solvent and the chemical shifts (ppm) refer to an internal standard of tetramethylsilane ($\delta = 0.0$ ppm). All signal assignments for the disaccharide glycals and methyl glycosides were verified by ^{13}C-^{1}H correlation experiments. Evaporations were performed under vacuum. TLC was performed on precoated aluminum sheets (0.2 mm) and glass plates (0.25 mm) coated with Silica gel $60F_{254}$ (E. Merck, Darmstadt); components were detected by spraying the plates with 0.1 M ceric sulfate in 2 M sulfuric acid, with subsequent heating. Column chromatography was performed with Silica gel 60 (230~400 mesh, E. Merck, Darmstadt). High resolution FAB mass spectra were recorded in a Kratos MS-30 apparatus by Mr. C. R. WEISENBERGER. Elemental analysis were determined by Atlantic Microlab (Atlanta, GA).

4-*O*-(4-*O*-Acetyl-2,3,6-trideoxy-3-trifluoroacetamido-α-L-*lyxo*-hexopyranosyl)-3-*O*-acetyl-1,5-anhydro-2,6-dideoxy-L-*arabino*-hex-1-enitol (3)

4-*O*-Acetyl-1,5-anhydro-2,6-dideoxy-3-trifluoroacetamido-L-*lyxo*-hex-1-enitol[14] (**1a**) (1.0 g, 3.7 mmol) was dissolved in dry benzene (100 ml) and the solution evaporated to half its volume. HCl gas was then bubbled through the magnetically stirred solution for 10 minutes at 5°C. After 5 minutes at room temperature, the solvent was evaporated. The residue was redissolved in dry CH_2Cl_2, the solution evaporated, and the residue redissolved again, affording a solution of the glycosyl chloride **1b** in dry CH_2Cl_2.

At the same time, HgO (2.31 g, 10.7 mmol), $HgBr_2$ (1.48 g, 4.1 mmol) and powdered 4 Å molecular sieves (3.63 g) were mixed in dry CH_2Cl_2 (70 ml) and stirred magnetically for 1 hour at room temperature. To this mixture were succesively added a solution of 3-*O*-acetyl-L-rhamnal[15] (**2**, 1.32 g, 7.6 mmol) in dry CH_2Cl_2 (10 ml) and then the solution of glycosyl chloride **1b**. The mixture was magnetically stirred at room temperature with TLC monitoring (2:1 hexane-EtOAc). After 2 hours the mixture was filtered through Celite and the filtrate was successively washed with 30% aqueous KI, twice with water, and then dried (Na_2SO_4) and evaporated. The resultant syrup was resolved by column chromatography (5:1 hexane-EtOAc) to afford the disaccharide derivative **3** as a solid (640 mg, 39%). Compound **3** was crystallized from Et_2O-hexane; mp 144~146°C; $[\alpha]_D^{20}$ −80.0° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 6.40 (dd, 1H, $J_{1,2}=6.1$ and $J_{1,3}=1.0$ Hz, H-1), 6.23 (d, 1H, $J_{3',NH}=7.2$ Hz, N-H), 5.12~5.26 (m, 3H, H-3, H-1′ and H-4′), 4.75 (dd, 1H, $J_{2,3}=3.3$ Hz, H-2), 4.51 (1H, m, H-3′), 4.15 (q, 1H, $J_{5',6'}=6.5$ Hz, H-5′), 4.10 (m, 1H, $J_{5,6}=6.7$ Hz, H-5), 3.78 (dd, 1H, $J_{3,4}=5.4$ and $J_{4,5}=7.1$ Hz, H-4), 2.17 (s, 3H, CH_3CO), 2.06 (s, 3H, CH_3CO), 1.91~1.94 (m, 2H, H-2′ax and H-2′eq), 1.38 (d, 3H, CH_3), 1.13 (d, 3H, CH_3'); ^{13}C NMR ($CDCl_3$): δ 170.8 (CH_3CO), 170.4 (CH_3CO), 145.9 (C-1), 98.4 (C-2), 96.4 (C-1′), 75.7 (C-4), 73.2 (C-5), 70.2 (two overlapped signals C-3 and C-4′), 65.8 (C-5′), 45.1 (C-3′), 30.2 (C-2′), 21.1 (CH_3CO), 20.5 (CH_3CO), 17.5 (C-6), 17.1 (C-6′).

Anal Calcd for $C_{18}H_{24}F_3NO_8$: C 49.20, H 5.51, N 3.19.
Found: C 49.27, H 5.56, N 3.15.

4-*O*-Acetyl-3-*O*-(4-*O*-acetyl-2,3,6-trideoxy-3-trifluoroacetamido-α-L-*lyxo*-hexopyranosyl)-1,5-anhydro-2,6-dideoxy-L-*arabino*-hex-1-enitol (**9**)

The same procedure was used as for compound **3**, except that 4-*O*-acetyl-L-rhamnal[15] (**8**) was used instead of its 3-*O*-acetyl isomer **2**. A solid was obtained which was crystallized from Et_2O-hexane to afford pure **9** (820 mg, 50%); mp 184~185°C; $[\alpha]_D^{20}$ −73° (*c* 0.44, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 6.41 (dd, 1H, $J_{1,2}$=6.2 and $J_{1,3}$=1.3 Hz, H-1), 6.34 (br d, 1H, N-H), 5.16 (m, 1H, H-1'), 5.12 (m, 1H, H-4'), 4.97 (dd, 1H, $J_{3,4}$=4.6 and $J_{4,5}$=6.2 Hz, H-4), 4.76 (ddd, 1H, $J_{2,3}$=3.7 and $J_{2,4}$=0.6 Hz, H-2), 4.53 (m, 1H, $J_{2'ax,3'}$=11.0, $J_{2'eq,3'}$=5.5, $J_{3',4'}$=3.0 and $J_{3',NH}$=8.1 Hz, H-3'), 4.17 (q, 1H, $J_{5',6'}$=6.6 Hz, H-5'), 4.15 (q, 1H, $J_{5,6}$=6.7 Hz, H-5), 4.13 (m, 1H, H-3), 2.18 (s, 3H, CH_3CO), 2.06 (s, 3H, CH_3CO), 1.90 (m, 2H, H-2'ax and H-2'eq), 1.34 (d, 3H, CH_3), 1.13 (d, 3H, CH_3'); ^{13}C NMR ($CDCl_3$): δ 170.8 (CH_3CO), 169.7 (CH_3CO), 144.7 (C-1), 99.8 (C-2), 96.6 (C-1'), 72.9, 72.2, 70.9, 70.3 and 65.4 (C-3, C-4, C-5, C-4' and C-5'), 45.2 (C-3'), 30.2 (C-2'), 20.8 (CH_3CO), 20.4 (CH_3CO), 16.6 and 16.2 (C-6 and C-6').

Anal Calcd for $C_{18}H_{24}F_3NO_8$: C 49.20, H 5.51, N 3.19.
Found: C 49.46, H 5.54, N 3.13.

Attempted Conversion of Disaccharide Glycal Derivatives **3** and **9** into Methyl 2-Deoxyglycosides by Direct Halogenation–glycosidation

4-*O*-(4-*O*-Acetyl-2,3,6-trideoxy-3-trifluoroacetamido-α-L-*lyxo*-hexopyranosyl)-3-*O*-acetyl-1,5-anhydro-2,6-dideoxy-L-*arabino*-hex-1-enitol (**3**) (0.162 g, 0.37 mmol) was dissolved in dry benzene (10 ml) and the solution evaporated to half its volume. HCl gas was then bubbled through the magnetically stirred solution for 10 minutes at 5°C. After 5 minutes at room temperature, the solvent was evaporated. The residue was redissolved in dry CH_2Cl_2, the solution evaporated, and the residue redissolved again.

At the same time, HgO (0.23 g, 1.07 mmol), $HgBr_2$ (0.15 g, 0.41 mmol) and powdered 4 Å molecular sieves (0.36 g) were mixed in dry CH_2Cl_2 (7 ml) and stirred magnetically for 1 hour at room temperature. To this mixture were succesively added dry MeOH (30 μl, 0.76 mmol) and then the previously prepared solution. The mixture was magnetically stirred at room temperature with TLC monitoring (2:1 hexane-EtOAc). After 2 hours the mixture was filtered through Celite and the filtrate was successively washed with 30% aqueous KI, twice with water, and then dried (Na_2SO_4) and evaporated. The resultant syrup (~30 mg) showed by TLC, one major product. Purification by a small column chromatography (5:1 hexane-EtOAc) afforded pure **4** (20 mg, 0.07 mmol, 18%); mp 167~169°C, lit.[18] 170°C; $[\alpha]_D^{20}$ −20° (*c* 1.0, $CHCl_3$), lit.[18] −22°.

Comparable results were observed when 4-*O*-acetyl-3-*O*-(4-*O*-acetyl-2,3,6-trideoxy-3-trifluoroacetamido-α-L-*lyxo*-hexopyranosyl)-1,5-anhydro-2,6-dideoxy-L-*arabino*-hex-1-enitol (**9**) was used as the starting material.

Methyl 3-*O*-Acetyl-4-*O*-(4-*O*-acetyl-2,3,6-trideoxy-3-trifluoroacetamido-α-L-*lyxo*-hexopyranosyl)-2,6-dideoxy-2-iodo-α-L-manno- (**5**) and β-L-gluco- (**6**) pyranosides

To a solution of glycal derivative **3** (0.25 g, 0.57 mmol) and dry MeOH (0.1 ml, 2.5 mmol) in dry CH_3CN (3 ml), was added NIS (0.200 g, 0.89 mmol) and the reaction was monitored by TLC (2:1 hexane-EtOAc). After 2 hours the solution was diluted with CH_2Cl_2, washed with 10% aqueous $Na_2S_2O_3$, and finally with water, dried (Na_2SO_4), and evaporated to afford a syrup that was purified by column chromatography (5:1 hexane-EtOAc). Two pure fractions were isolated. The first one was an amorphous solid (181 mg, 53%) that characterized as the α-L-*manno* isomer **5**; $[\alpha]_D^{20}$ −76.3° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 6.29 (d, 1H, $J_{NH-3'}$=6.9 Hz, N-H), 5.24 (d, 1H, $J_{1',2'ax}$=3.6 Hz, H-1'), 5.10 (br s, 1H, H-4'), 4.96 (br s, 1H, H-1), 4.56 (dd, 1H, $J_{1,2}$=1.4 and $J_{2,3}$=4.2 Hz, H-2), 4.49 (dd, 1H, $J_{3,4}$=8.5 Hz, H-3), 4.48 (m, 1H, H-3'), 4.16 (q, 1H, $J_{5',6'}$=6.5 Hz, H-5'), 3.86 (m, 1H, $J_{5,6}$=6.2 Hz, H-5), 3.75 (t, 1H, $J_{4,5}$=8.9 Hz, H-4), 3.39 (s, 3H, OCH_3), 2.17 (s, 3H, CH_3CO), 2.10 (s, 3H, CH_3CO), 1.93 (td, 1H, $J_{2'ax,2'eq}$=12.5 and $J_{2'ax,3'}$=12.5 Hz, H-2'ax), 1.87 (dd, 1H, $J_{2'eq,3'}$=3.6 Hz, H-2'eq), 1.35 (d, 3H, CH_3), 1.13 (d, 3H, CH_3'); ^{13}C NMR ($CDCl_3$): δ 170.9 (CH_3CO), 168.4 (CH_3CO), 102.1 (C-1), 97.9 (C-1'), 79.0 (C-4). 72.4 (C-3), 70.1 (C-4'), 67.2 (C-5), 65.9 (C-5'), 55.1 (OCH_3), 45.1 (C-3'), 30.5 (C-2), 29.9 (C-2'), 20.9 (CH_3CO), 20.5 (CH_3CO), 18.1 (C-6), 16.7 (C-6').

Anal Calcd for $C_{19}H_{27}F_3INO_9$: C 38.20, H 4.56, I 21.24, N 2.34.
Found: C 38.27, H 4.57, I 21.16, N 2.30.

The second fraction was isolated as a solid (48 mg, 14%) which crystallized from EtOH and was characterized as the β-L-*gluco* isomer **6**; mp 200~202°C; $[\alpha]_D^{20}$ −89.6° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 6.19 (d, 1H, $J_{NH\text{-}3'}$=6.2 Hz, N-H), 5.28 (dd, 1H, $J_{3,4}$=9.0 Hz, H-3), 5.12 (br s, 1H, H-4'), 5.07 (d, 1H, $J_{1',2'ax}$=3.8 Hz, H-1'), 4.47 (d, 1H, $J_{1,2}$=8.9 Hz, H-1), 4.43 (dq, 1H, $J_{2'ax,3'}$=14.0 Hz, H-3'), 4.13 (q, 1H, $J_{5',6'}$=6.5 Hz, H-5'), 3.80 (dd, 1H, $J_{2,3}$=11.2 Hz, H-2), 3.55 (s, 3H, OCH_3), 3.53 (m, 1H, $J_{5,6}$=6.1 Hz, H-5), 3.44 (t, 1H, $J_{4,5}$=9.0 Hz, H-4), 2.16 (s, 3H, CH_3CO), 2.13 (s, 3H, CH_3CO), 1.89 (td, 1H, $J_{2'ax,2'eq}$=12.7 Hz, H-2'ax), 1.78 (dd, 1H, $J_{2'eq,3'}$=5.0 Hz, H-2'eq), 1.36 (d, 3H, CH_3), 1.10 (d, 3H, CH_3'); ^{13}C NMR ($CDCl_3$): δ 170.7 (CH_3CO), 169.4 (CH_3CO), 103.6 (C-1), 97.6 (C-1'), 80.8, 77.9, 70.9, 69.7 and 66.0 (C-3, C-4, C-5, C-4' and C-5'), 57.5 (OCH_3), 44.9 (C-3'), 29.8 and 29.7 (C-2 and C-2'), 21.2 (CH_3CO), 20.5 (CH_3CO), 18.0 and 16.7 (C-6 and C-6').

Anal Calcd for $C_{19}H_{27}F_3INO_9$: C 38.20, H 4.56, I 21.24, N 2.34.
Found: C 38.29, H 4.57, I 21.30, N 2.27.

Methyl 4-*O*-Acetyl-3-*O*-(4-*O*-acetyl-2,3,6-trideoxy-3-trifluoroacetamido-α-L-*lyxo*-hexopyranosyl)-2,6-dideoxy-2-iodo-α-L-manno- (**10**) and β-L-gluco- (**11**) pyranosides

The procedure just described was applied with the glycal derivative **9**. Column chromatographic purification (5 : 1 hexane - EtOAc) afforded two fractions. The first fraction was obtained as a solid (176 mg, 52%) that crystallized from EtOH and was characterized as the α-L-*manno* isomer **10**; mp 218~220°C; $[\alpha]_D^{20}$ −73.1° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 6.32 (d, 1H, $J_{NH\text{-}3'}$=6.4 Hz, N-H), 5.13 (br s, 1H, H-4'), 5.09 (d, 1H, $J_{1',2'ax}$=3.6 Hz, H-1'), 5.06 (t, 1H, $J_{4,5}$=9.5 Hz, H-4), 5.00 (s, 1H, H-1), 4.49 (m, 1H, H-3'), 4.35 (m, 2H, H-2 and H-5'), 3.84 (m, 1H, $J_{5,6}$=6.3 Hz, H-5), 3.42 (dd, 1H, $J_{2,3}$=4.2 and $J_{3,4}$=8.5 Hz, H-3), 3.37 (s, 3H, OCH_3), 2.17 (s, 3H, CH_3CO), 2.08 (s, 3H, CH_3CO), 1.93 (dd, 1H, $J_{2'eq,3'}$=5.1 and $J_{2'eq,2'ax}$=12.8 Hz, H-2'eq), 1.86 (td, 1H, $J_{2'ax,3'}$=12.5 Hz, H-2'ax), 1.22 (d, 3H, CH_3), 1.12 (d, 3H, CH_3'); ^{13}C NMR ($CDCl_3$): δ 171.1 (CH_3CO), 169.7 (CH_3CO), 102.5 (C-1), 98.8 (C-1'), 75.3 (C-3), 74.4 (C-4), 70.2 (C-4'), 67.2 (C-5), 66.9 (C-5'), 55.2 (OCH_3), 45.7 (C-3'), 33.4 (C-2), 30.2 (C-2'), 20.8 (CH_3CO), 20.6 (CH_3CO), 17.6 (C-6), 16.7 (C-6').

Anal Calcd for $C_{19}H_{27}F_3INO_9$: C 38.20, H 4.56, I 21.24, N 2.34.
Found: C 38.28, H 4.58, I 21.18, N 2.30.

The second fraction was isolated as a solid (54 mg, 16%) which crystallized from EtOH and was characterized as the β-L-*gluco* isomer **11**; mp 215~217°C; $[\alpha]_D^{20}$ −148° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 6.20 (d, 1H, $J_{NH\text{-}3'}$=7.2 Hz, N-H), 5.17 (m, 2H, H-1' and H-4'), 4.78 (t, 1H, $J_{4,5}$=9.0 Hz, H-4), 4.74 (q, 1H, $J_{5',6'}$=6.5 Hz, H-5'), 4.55 (m, 1H, H-3'), 4.48 (d, 1H, $J_{1,2}$=9.0 Hz, H-1), 3.95 (dd, 1H, $J_{3,4}$=8.7 Hz, H-3), 3.81 (dd, 1H, $J_{2,3}$=10.5 Hz, H-2), 3.54 (s, 3H, OCH_3), 3.48 (m, 1H, $J_{5,6}$=6.2 Hz, H-5), 2.16 (s, 3H, CH_3CO), 2.08 (s, 3H, CH_3CO), 1.89 (td, 1H, $J_{2'ax,2'eq}$=12.5 and $J_{2'ax,3'}$=13.5 Hz, H-2'ax), 1.81 (dd, 1H, $J_{2'eq,3'}$=4.8 Hz, H-2'eq), 1.20 (d, 3H, CH_3), 1.12 (d, 3H, CH_3'); ^{13}C NMR ($CDCl_3$): δ 170.9 (CH_3CO), 169.4 (CH_3CO), 104.1 (C-1), 97.2 (C-1'), 81.2 (C-3), 77.2 (C-4), 70.4 (C-4'), 70.0 (C-5), 66.6 (C-5'), 57.3 (OCH_3), 45.1 (C-3'), 31.5 (C-2), 30.3 (C-2'), 20.9 (CH_3CO), 20.6 (CH_3CO), 17.2 (C-6), 16.6 (C-6').

Anal Calcd for $C_{19}H_{27}F_3INO_9$: C 38.20, H 4.56, I 21.24, N 2.34.
Found: C 38.25, H 4.61, I 21.31, N 2.33.

Methyl 3-*O*-Acetyl-4-*O*-(4-*O*-acetyl-2,3,6-trideoxy-3-trifluoroacetamido-α-L-*lyxo*-hexopyranosyl)-2,6-dideoxy-α-L-*arabino*-hexopyranoside (**7**)

To a solution of the α-L-*manno* derivative **5** (100 mg, 0.17 mmol) in dry benzene (1 ml) was added Bu_3SnH (50 μl, 0.2 mmol) and a few mg of azobis (isobutyronitrile) (AIBN) in an inert atmosphere and the mixture was heated at 60°C. The reaction was complete after 2 hours (TLC). The mixture was diluted with CH_3CN and washed three times with hexane[19]. The solution was evaporated to a syrup that crystallized from EtOH - hexane to afford pure **7** (58 mg, 73%); mp 115~117°C; $[\alpha]_D^{20}$ −172° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 6.23 (d, 1H, $J_{NH\text{-}3'}$=7.1 Hz, N-H), 5.25 (d, 1H, $J_{1',2'ax}$=3.7 Hz, H-1'), 5.18 (dq, 1H, $J_{3,4}$=9.1 Hz, H-3), 5.12 (br s, 1H, H-4'), 4.70 (d, 1H, $J_{1,2ax}$=3.7 Hz, H-1), 4.48 (m, 1H, H-3'), 4.17 (q, 1H, $J_{5',6'}$=6.6 Hz, H-5'), 3.77 (m, 1H, $J_{5,6}$=6.2 Hz, H-5), 3.41 (t, 1H, $J_{4,5}$=9.1 Hz, H-4), 3.33 (s, 3H, OCH_3), 2.24 (dd, 1H, $J_{2eq,3}$=5.0 and $J_{2eq,2ax}$=12.8 Hz, H-2eq), 2.17 (s, 3H, CH_3CO), 2.03 (s, 3H, CH_3CO), 1.91 (td, 1H, $J_{2'ax,2'eq}$=12.4 and $J_{2'ax,3'}$=12.5 Hz, H-2'ax), 1.86 (dd, 1H, $J_{2'eq,3'}$=5.1 Hz, H-2'eq), 1.66 (td, 1H,

$J_{2ax,3}$=11.3 Hz, H-2ax), 1.30 (d, 3H, CH_3), 1.12 (d, 3H, CH_3'); ^{13}C NMR ($CDCl_3$): δ 170.9 (CH_3CO), 169.8 (CH_3CO), 97.7 (C-1), 97.5 (C-1'), 80.5 (C-4), 72.6 (C-3), 70.2 (C-4'), 66.1 (C-5), 65.8 (C-5'), 54.7 (OCH_3), 45.2 (C-3'), 32.6 (C-2), 30.2 (C-2'), 21.2 (CH_3CO), 20.6 (CH_3CO), 18.4 (C-6), 16.8 (C-6').

Anal Calcd for $C_{19}H_{28}F_3NO_9$: C 48.41, H 5.99, N 2.97.
Found: C 48.48, H 5.99, N 2.92.

Methyl 4-*O*-Acetyl-3-*O*-(4-*O*-acetyl-2,3,6-trideoxy-3-trifluoroacetamido-α-L-*lyxo*-hexopyranosyl)-2,6-dideoxy-α-L-*arabino*-hexopyranoside (**12**)

The conditions just described were applied to with the α-L-*manno* derivative **10**. Similar processing gave a solid that crystallized from EtOH to afford pure **12** (60 mg, 76%); mp 248~250°C; $[\alpha]_D^{20}$ −175.3° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 6.18 (d, 1H, $J_{NH\text{-}3'}$=7.0 Hz, N-H), 5.04 (br s, 1H, H-4'), 5.09 (br s, 1H, H-1'), 4.74 (d, 1H, $J_{1,2ax}$=3.1 Hz, H-1), 4.70 (t, 1H, $J_{3,4}$=9.3 Hz, H-4), 4.48 (m, 1H, H-3'), 4.10 (q, 1H, $J_{5',6'}$=6.5 Hz, H-5'), 4.02 (dq, 1H, $J_{2ax,3}$=11.5 and $J_{2eq,3}$=5.3 Hz, H-3), 3.74 (m, 1H, $J_{4,5}$=9.5 Hz, H-5), 3.32 (s, 3H, OCH_3), 2.16 (s and m, 4H, CH_3CO and H-2eq), 2.07 (s, 3H, CH_3CO), 1.90~1.77 (m, 3H, H-2ax, H-2'eq and H-2'ax), 1.16 (d, 3H, CH_3), 1.10 (d, 3H, CH_3'); ^{13}C NMR ($CDCl_3$): δ 170.9 (CH_3CO), 169.7 (CH_3CO), 98.1 (C-1), 97.8 (C-1'), 76.8 (C-4), 73.9 (C-3), 70.2 (C-4'), 65.7 (C-5), 65.3 (C-5'), 54.7 (OCH_3), 45.2 (C-3'), 36.9 (C-2), 30.2 (C-2'), 20.8 (CH_3CO), 20.6 (CH_3CO), 17.6 (C-6), 16.7 (C-6').

Anal Calcd for $C_{19}H_{28}F_3NO_9$: C 48.41, H 5.99, N 2.97.
Found: C 48.49, H 5.99, N 2.95.

7-*O*-[4-*O*-Acetyl-3-*O*-(4-*O*-acetyl-2,3,6-trideoxy-3-trifluoroacetamido-α-L-*lyxo*-hexopyranosyl)-2,6-dideoxy-2-iodo-α-L-mannopyranosyl]-daunomycinone (**13**)

To a solution of glycal derivative **9** (0.50 g, 1.14 mmol) and daunomycinone (0.44 g, 1.10 mmol) in dry CH_3CN (8.7 ml) and dry THF (3.6 ml), was added NIS (0.37 g, 1.64 mmol) and the mixture was stirred magnetically at room temperature with TLC monitoring (3:1 toluene-acetone). Some daunomycinone still remained unreacted after 12 hours, and more **9** (0.25 g, 0.57 mmol) and NIS (0.19 g, 0.82 mmol) were added. After a further 2 hours the reaction was complete and the solution was diluted with CH_2Cl_2 (50 ml). The resulting solution was washed with a 10% aqueous $Na_2S_2O_3$ (2×30 ml) and water (2×30 ml), dried (Na_2SO_4), and evaporated to afford a red solid which was purified by column chromatography (50 g of silica gel, 8:1 toluene-acetone). The chromatographically major pure fraction was isolated as a red solid which crystallized from acetone-hexane to yield pure **13** (53 mg, 50%); mp 170~172°C; $[\alpha]_D^{20}$ +24.0° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 14.01 and 13.27 (s, 2H, OH-6 and OH-11), 8.03 (dd, 1H, $J_{1,2}$=7.8 and $J_{1,3}$=0.8 Hz, H-1), 7.80 (t, 1H, $J_{2,3}$=8.4 Hz, H-2), 7.40 (dd, 1H, H-3), 6.37 (d, 1H, $J_{NH\text{-}3''}$=6.8 Hz, N-H), 5.75 (d, 1H, H-1'), 5.24 (m, 1H, H-7), 5.10 (t, 1H, $J_{3',4'}$=9.3 and $J_{4',5'}$=9.3 Hz, H-4'), 5.07 (br s, 1H, H-4''), 5.00 (d, 1H, H-1''), 4.46 (m, 1H, H-3''), 4.43 (dd, 1H, $J_{1',2'}$=1.4 and $J_{2',3'}$=4.0 Hz, H-2'), 4.36 (q, 1H, $J_{5'',6''}$=6.6 Hz, H-5''), 4.15 (s, 1H, OH-9), 4.09 (s, 3H, OCH_3), 4.06 (m, 1H, $J_{4',5'}$=9.6 and $J_{5',6'}$=6.3 Hz, H-5'), 3.23 (dd, 1H, $J_{8eq,10eq}$=1.8 Hz, H-10eq), 3.22 (dd, 1H, $J_{3',4'}$=8.8 Hz, H-3'), 2.94 (d, 1H, $J_{10ax,10eq}$=18.7 Hz, H-10ax), 2.42 (s, 3H, H_3-14), 2.34 (br d, 1H, $J_{8ax,8eq}$=15.0 Hz, H-8eq), 2.16 (dd, 1H, $J_{7,8ax}$=4.4 Hz, H-8ax), 2.12 (s, 3H, CH_3CO), 2.09 (s, 3H, CH_3CO), 1.90 (dd, 1H, $J_{2''eq,3''}$=4.6 and $J_{2''eq,2''ax}$=12.5 Hz, H-2''eq), 1.81 (m, 1H, $J_{1'',2''ax}$=3.7 and $J_{2''ax,3''}$=12.8 Hz, H-2''ax), 1.27 (d, 3H, CH_3'), 1.04 (d, 3H, CH_3''); ^{13}C NMR (acetone-d_6): δ 211.67 (C-13), 187.27 and 186.93 (C-5 and C-12), 170.83 (CH_3CO), 170.13 (CH_3CO), 161.87 (C-4), 156.97 and 156.47 (C-6 and C-11), 136.56, 135.53 and 134.85 (C-2, C-6a, C-10a and C-12a), 120.92, 119.95 and 119.71 (C-1, C-4a and C-3), 111.72 and 111.68 (C-5a and C-11a), 105.57 and 99.48 (C-1' and C-1''), 76.49, 75.13, 74.07, 72.03, 69.84, 68.66 and 67.07 (C-3', C-4', C-4'', C-5'', C-5', C-7 and C-9), 56.79 (OCH_3), 45.92 (C-3''), 36.33 and 35.73 (C-8 and C-10), 32.86 (C-2''), 24.27 (C-14), 20.58 (CH_3CO), 20.33 (CH_3CO), 17.62 and 16.76 (C-6' and C-6'').

Anal Calcd for $C_{39}H_{41}F_3INO_{16}\cdot H_2O$: C 47.72, H 4.41, I 12.93, N 1.43.
Found: C 47.76, H 4.49, I 12.90, N 1.37.

7-*O*-[4-*O*-Acetyl-3-*O*-(4-*O*-acetyl-2,3,6-trideoxy-3-trifluoroacetamido-α-L-*lyxo*-hexopyranosyl)-2,6-dideoxy-α-L-*arabino*-hexopyranosyl]-daunomycinone (**14**)

To a solution of **13** (0.200 g, 0.21 mmol) in dry benzene (6 ml), were added Bu_3SnH (0.2 ml, 0.8 mmol) and a few mg of AIBN in an inert atmosphere and the mixture was stirred magnetically at 45°C with TLC

monitoring (6:1 $CHCl_3$-acetone). After 48 hours the reaction was terminated by evaporation, and the remaining syrup was redissolved in CH_3CN and washed with hexane[19]. The acetonitrile solution was evaporated to afford a red solid which was purified by column chromatography (20 g silica gel, 15:1 $CHCl_3$-acetone). One pure fraction was isolated as a red solid, which crystallized from acetone-hexane to yield pure **14** (90 mg, 55%); mp 264~266°C; $[\alpha]_D^{20}$ +55.3° (*c* 0.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 14.01 and 13.29 (s, 2H, OH-6 and OH-11), 8.04 (d, 1H, $J_{1,2}$=7.8 Hz, H-1), 7.78 (t, 1H, H-2), 7.39 (d, 1H, $J_{2,3}$=8.2 Hz, H-3), 6.19 (d, 1H, $J_{NH\text{-}3''}$=7.4 Hz, N-H), 5.52 (d, 1H, $J_{1',2'ax}$=3.4 Hz, H-1'), 5.29 (br s, 1H, H-7), 5.04 (br s, 1H, H-4''), 4.99 (br s, 1H, H-1''), 4.74 (t, 1H, $J_{3',4'}$=9.1 and $J_{4',5'}$=9.4 Hz, H-4'), 4.52 (s, 1H, OH-9), 4.44 (m, 1H, H-3''), 4.08 (s, 3H, OCH_3), 4.04 (q, 1H, $J_{5'',6''}$=6.5 Hz, H-5''), 3.97 (m, 1H, $J_{5',6'}$=6.2 Hz, H-5'), 3.84 (m, 1H, $J_{3',2'ax}$=11.3 and $J_{3',2'eq}$=5.1 Hz, H-3'), 3.25 (d, 1H, H-10eq), 2.98 (d, 1H, $J_{10ax,10eq}$=18.9 Hz, H-10ax), 2.42 (s, 3H, H_3-14), 2.40~1.80 (m, 6H, H-8eq, H-8ax, H-2'eq, H-2'ax, H-2''eq and H-2''ax), 2.12 (s, 3H, CH_3CO), 2.09 (s, 3H, CH_3CO), 1.22 (d, 3H, CH_3'), 1.00 (d, 3H, CH_3''); ^{13}C NMR (Me_2SO-d_6): δ 211.13 (C-13), 186.10 (C-5 and C-12), 169.76 (CH_3CO), 169.18 (CH_3CO), 160.55 (C-4), 156.18 and 154.61 (C-6 and C-11), 135.53, 134.77, 134.54 and 134.42 (C-2, C-6a, C-10a and C-12a), 120.00, 118.94 and 118.85 (C-1, C-4a and C-3), 110.45 and 110.39 (C-5a and C-11a), 99.85 and 97.57 (C-1' and C-1''), 75.95, 75.09, 73.47, 70.33, 68.57, 65.53 and 64.24 (C-3', C-4', C-4'', C-5'', C-5', C-7 and C-9), 56.21 (OCH_3), 36.71 and 35.93 (C-8 and C-10), 31.59 and 28.74 (C-2' and C-2''), 23.80 (C-14), 20.42 (CH_3CO), 20.18 (CH_3CO), 16.99 and 16.16 (C-6' and C-6'').

Anal Calcd for $C_{39}H_{42}F_3NO_{16}$: C 55.91, H 5.05, N 1.67.
Found: C 55.78, H 5.08, N 1.65.

7-*O*-[3-*O*-(3-Amino-2,3,6-trideoxy-α-L-*lyxo*-hexopyranosyl)-2,6-dideoxy-α-L-*arabino*-hexopyranosyl]-daunomycinone Hydrochloride (**15**)

To a solution of **14** (0.175 g, 0.21 mmol) in dry MeOH (12 ml), was added 0.5 M methanolic NaOMe (1 ml). The solution turned from red to purple. The reaction was monitored by TLC (3:1 toluene-acetone) and after 4 hours the reaction was terminated by adding Dry Ice whereupon the color changed from purple back to red. The solution was diluted with CH_2Cl_2 washed with water, dried (Na_2SO_4), and evaporated to afford a red solid that was used in the next step without any further purification. The crude solid was suspended in 15 ml of 0.1 N aqueous NaOH. The color of the solution changed to purple. The reaction was monitored by TLC (3:1 toluene-acetone) until no more starting material could be detected (20 minutes). The reaction was stopped by adding 5% HCl until the solution became red (1.5 ml). The solution was then diluted with water (20 ml) and washed with CH_2Cl_2 (3×40 ml) and then extracted with 1-butanol until the aqueous solution became colorless. The 1-butanol solution was evaporated and the solid remaining was crystallized from 0.1 M HCl in MeOH and ether to give pure **15** (45 mg, 32%); mp 160~162°C (with decomposition); $[\alpha]_D^{20}$ +368° (*c* 0.05, MeOH); ^{1}H NMR (CD_3OD): δ 7.93 (d, 1H, $J_{1,2}$=6.8 Hz, H-1), 7.82 (dd, 1H, H-2), 7.54 (d, 1H, $J_{2,3}$=8.1 Hz, H-3), 5.38 (d, 1H, $J_{1',2'ax}$=3.3 Hz, H-1'), 5.16 (br s, 1H, H-1''), 5.10 (br s, 1H, H-7), 4.02 (s, 3H, OCH_3), 3.96 (m, 1H, $J_{4',5'}$=8.5 and $J_{5',6'}$=6.2 Hz, H-5'), 3.92 (q, 1H, $J_{5'',6''}$=6.7 Hz, H-5''), 3.78 (m, 1H, $J_{3',2'ax}$=11.7 and $J_{3',2'eq}$=5.1 Hz, H-3'), 3.56 (m, 2H, H-3'' and H-4''), 3.09 (t, 1H, $J_{3',4'}$=9.1 Hz, H-4'), 3.04 (d, 1H, H-10eq), 2.99 (d, 1H, $J_{10ax,10eq}$=18.0 Hz, H-10ax), 2.35 (s, 3H, H_3-14), 2.32 (d, 1H, $J_{8eq,8ax}$=13.0 Hz, H-8eq), 2.22 (dd, 1H, $J_{8ax,7}$=4.7 Hz, H-8ax), 2.16 (dd, 1H, $J_{2'eq,2'ax}$=14.0 Hz, H-2'eq), 1.90 (m, 2H, H-2''eq and H-2''ax), 1.72 (m, 1H, H-2'ax), 1.30 (d, 3H, CH_3'), 1.06 (d, 3H, CH_3''); ^{13}C NMR (CD_3OD): δ 213.58 (C-13), 187.87 and 187.54 (C-5 and C-12), 162.36 (C-4), 157.36 and 156.14 (C-6 and C-11), 137.14, 136.20, 135.80 and 135.73 (C-2, C-6a, C-10a and C-12a), 121.39, 120.48 and 120.20 (C-1, C-4a and C-3), 112.32 and 112.08 (C-5a and C-11a), 102.20 and 99.02 (C-1' and C-1''), 77.90, 77.56, 76.96, 71.63, 70.31, 67.83 and 67.27 (C-3', C-4', C-4'', C-5'', C-5', C-7 and C-9), 57.09 (OCH_3), 38.24 and 36.97 (C-8 and C-10), 33.49 and 29.42 (C-2' and C-2''), 24.60 (C-14), 18.10 and 16.89 (C-6' and C-6'').

Anal Calcd for $C_{33}H_{39}NO_{13}$: 657.2517, high resolution FAB mass spectra: 657.2500.

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