inhibition was noncompetitive versus ATP (Figure 1B). No inhibition was observed in experiments in which the glucose concentration was very high (10 mM, ca. 50 × K_m) and the concentrations of ATP and inhibitor were varied from 24–240 μM and 0–276 μM, respectively.

Inhibition by acetylene **5** was determined under similar conditions; competition with glucose, [ATP] = 600 μM, [glucose] = 80–2000 μM, [**5**] = 0, 454, 908, and 1560 μM, competitive inhibition with K_{is} = 2.5 ± 0.3 mM; competition with ATP, [ATP] = 24–600 μM, [glucose] = 1000 μM, [**5**] = 0, 474, 948, and 1896 μM, noncompetitive inhibition with K_{ii} = 1.7 ± 0.2 mM.

During control experiments in the absence of hexokinase, it was shown that neither **4** at 552 μM nor **5** at 1544 μM, the highest concentrations used in the assays, is a substrate of the coupling enzyme G-6-PDH. Similarly, control experiments in the presence of 2.0 mM NADP, 40 mM glucose-6-phosphate, or 1.0 mM $Mg(OAc)_2$ in buffer with **4** at 552 μM or **5** at 1544 μM revealed no inhibition of the coupling enzyme.

Inhibition by Allenes 6R and 6S. The inhibitor concentrations were varied from 0.6–2.4 mM at [glucose] = 200 μM and [ATP] = 1.2 mM. At each inhibitor concentration, the observed rate of reaction was corrected for the background rate of inhibitor oxidation by G-6-PDH, measured in the absence of hexokinase. IC_{50} values of 1.7 (**6R**) and 10 mM (**6S**) were determined from plots of v_o/v_i versus [I].

Preincubation Studies with 4, 5, 6R, and 6S. Hexokinase was incubated at 25 °C with amide **4** (1380 mM), acetylene **5** (5.8 mM), allene **6R** (3.4 mM), or allene **6S** (2.85 mM), and aliquots were diluted 1:5 with the assay mixture after 0, 1, 2, and 3 h ([glucose] = 400 μM, [ATP] = 120 μM). The rate of loss of enzyme activity was compared to controls which contained hexokinase and buffer in the absence of inhibitor; the half-life of hexokinase under these conditions was about 1 h. Hexokinase was somewhat stabilized in the presence of the amide **4** ($t_{1/2}$ = 2 h); no slow-binding inhibitory behavior was observed for any of the compounds.

Inhibition by Thioester 7. The assay was conducted in the presence of 60 μM ATP (K_m) and 2.0 mM glucose (10 K_m) at inhibitor concentrations of 0–4.5 mM. An IC_{50} for **7** of 3.6 mM was determined from a plot of v_o/v_i vs [I]. In a similar experiment, an IC_{50} value of 12 mM was determined for the diphosphonate **38** present as a contaminant in the preparation of **7**. No increase in the inhibitory activity with time was observed on incubation of 11 mM **7** and 5 mM glucose in the presence of hexokinase over a 3-h period.

Acknowledgment. This work was supported by a cooperative grant from the National Institutes of Health and Bristol-Myers Company. We thank Jillian S. Imagire for excellent technical assistance.

Registry No. **4**·2Li, 136839-32-2; **5**·2Li, 136839-33-3; **6***R*·2Li, 136891-70-8; **6***S*·2Li, 136839-29-7; **7**·3Li, 136839-34-4; **12**, 108865-15-2; **13**, 111056-67-8; (*R*)-**14**, 136839-36-6; (*S*)-**14**, 136839-37-7; **15**, 136839-39-9; **16**, 136839-40-2; **17**, 136839-41-3; **18**, 136839-42-4; **19**, 136839-43-5; **20**, 136839-44-6; **21**, 136839-45-7; **22**, 136839-46-8; **23**, 136839-47-9; **24**, 136839-48-0; **25**, 136839-49-1; (*R*)-**26**, 136856-88-7; (*S*)-**26**, 136839-59-3; **27**, 136839-50-4; **28**, 136839-51-5; **29***R*, 136846-43-0; **29***S*, 136839-30-0; **31b***R*, 136839-53-7; **31b***S*, 136839-31-1; **32**, 136839-54-8; **33***R*, 136839-55-9; **33***S*, 136839-52-6; **34**, 97893-01-1; **35**, 136839-56-0; **37**, 136839-57-1; **38**, 136839-58-2; 3,5-*O*-(*S*)-benzylidene-6,8,9-trideoxy-1,2-*O*-isopropylidene-7-(4-nitrobenzoyl)-α-D-*glycero*-D-*gluco*-non-8-yno-1,4-furanose, 136839-35-5; *O*-ethyl *S*-methyl [[(ethoxyphosphinyl)methyl]thio]phosphonate, 136839-38-8; 5′-adenylic acid, 61-19-8; hexokinase, 9001-51-8.

Supplementary Material Available: IR and NMR data for all synthetic intermediates and kinetic plots for enzyme assays (11 pages). Ordering information is given on any current masthead page.

Stereoselective α-Glycosylation of Nitro Sugar Evernitrose: Synthesis of the Terminal AB Unit of Everninomicin Antibiotics

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The stereoselective α-glycosylation of branched-chain nitro sugar evernitrose (**17**, 2,3,6-trideoxy-3-*C*-methyl-4-*O*-methyl-3-nitro-α-L-*arabino*-hexopyranose) is described. 1-*O*-*p*-Nitrobenzoyl derivatives 18β and 18α were prepared as glycosyl donors starting from evernitrose **17** and its methyl glycoside **12**, respectively. Glycosylation of **18** and 4-*O*-benzoyl-2,6-dideoxy-D-*arabino*-hexopyranoside **15** in CH_2Cl_2 in the presence of TMS triflate promoter at −78 °C gave the α-linked disaccharide **19** exclusively. Alkaline treatment of the protected glycoside **19** led to disaccharide **20**. Curacin derivative **7** and 18α were coupled again by using TMS triflate in CH_2Cl_2 at −78 °C to give crystalline α-linked disaccharide **23** exclusively in 73% yield. Hydrogenolytic cleavage of the phenolic benzyl ether completed the synthesis of the terminal AB unit of everninomicins **8**. The structure and stereochemistry of everninonitrose methyl glycoside **8** have been tentatively deduced from the ^1H NMR spectrum and confirmed by single-crystal X-ray analysis. Reduction of **8** with Al/Hg in aqueous ethanol afforded everninosamine methyl glycoside **9**, the terminal AB unit of antibiotic 13-384 component 5 (**5**).

Introduction

The everninomicins[1,2] are produced by *Micromonospora carbonaceae* and belong to the novel class of orthosomycin oligosaccharide antibiotics.[3] They exhibit excellent in vitro and in vivo activities against Gram-positive bacteria and *Neisseria*, including strains resistant to, e.g., β-lactams, tetracyclines, and macrolides.[4] Studies of the structure-activity relationship in the everninomicin group indicated that the antibacterial activity is associated both with the C–D spiroortholactone linkage and the hydroxyl group in the phenolic ester residue.[1]

(1) Ganguly, A. K. In *Topics in Antibiotic Chemistry*; Sammes, P. G., Ed.; Ellis Horwood: Chichester, 1978; Vol. 2, Part B, p 49.
(2) (a) Waitz, J. A.; Patel, M. G.; Marquez, J. A.; Kalyanpur, M. G.; Horan, A. C. U.S. Pat. 4,597,968 (Cl. 424/118; A61K 35/74), 1 Jul 1986, US Appl. 623,266, 21 Jun 1984; *Chem. Abstr.* **1986**, *105*, 170628q. (b) Ganguly, A. K.; Pramanik, B.; Chan, T. M.; Sarre, O.; Liu, Y.-T.; Morton, J.; Girijavallabhan, V. *Heterocycles* **1989**, *28*, 83.
(3) Wright, D. E. *Tetrahedron* **1979**, *35*, 1207.
(4) Ganguly, A. K.; Sarre, O. Z.; Greeves, D.; Morton, J. *J. Am. Chem. Soc.* **1975**, *97*, 1982.

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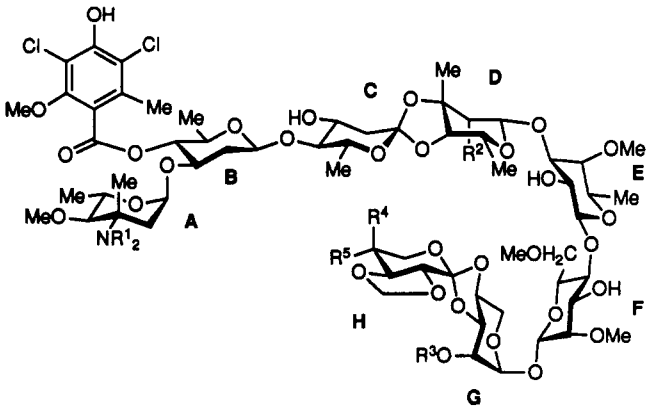
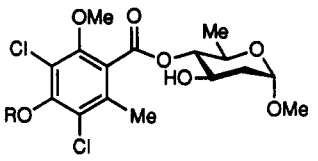
Recently, the ortholactone CD fragment has been synthesized using glycosyloxyselenation–deselenation methodology.[5] We have previously reported the synthesis of dichloroisoeverninic acid[6] and curacin (**6**),[7] the common terminal AB subunit of orthosomycin antibiotics curamycin, flambamycin, and avilamycin.[3]

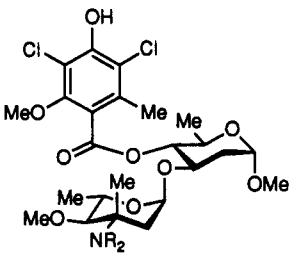


		R^1	R^2	R^3	R^4	R^5
1	everninomicin B	O	OH	Me	H	CH(OMe)Me
2	everninomicin C	O	H	Me	H	H
3	everninomicin D	O	H	Me	H	(*S*)-CH(OMe)Me
4	13-384-1	O	OH	H	X	H
5	13-384-5	H	OH	H	X	H

X = orsellinoyl



6, R = H, curacin
7, R = Bn



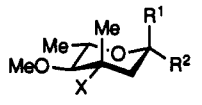
8, R = O, everninonitrose
9, R = H, everninosamine

Everninomicin B (**1**), C (**2**), D (**3**), and component 1 of antibiotic 13-384 (**4**) each contain a methyl-branched nitro sugar, evernitrose (residue A), which is linked glycosidically to the D-olivose residue B of these orthosomycins. A new approach to the synthesis of evernitrose developed by our group made this rare sugar easily available on a gram scale.[8] In the last years, considerable progress has been achieved in stereoselective syntheses of oligosaccharides in the field of 2,6-dideoxy sugars and even branched-chain sugars.[9] Although diverse glycoside antibiotics with promising antibacterial and antitumor activity that contain a methyl-branched nitro sugar have been discovered,[10] to the best of our knowledge, glycosylation of nitro sugars at all has been yet unknown.

We now present the stereoselective α-glycosylation of the branched-chain nitro sugar evernitrose using α- or β-1-*p*-nitrobenzoates and use of these glycosyl donors in the synthesis of everninonitrose **8**, the AB deoxy disaccharide unit of everninomicins. In addition, the reduction of everninonitrose to its amino analogue **9**, the terminal AB component of the related antibiotic 13-385-5 (**5**)[2] is described.

Results and Discussion

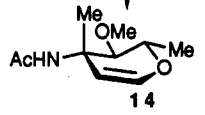
The iodoalkoxylation of glycals results in stereoselective formation of 2-deoxy-2-β-iodo-α-glycosides via trans-diaxial nucleophilic opening of a transient cyclic 1,2-iodonium species by the glycosyl acceptor.[11,12] The methyl glycosides **10**[8] and **12**[8] were subjected to acetolysis at −25 °C and afforded the α-1-acetate **11** and the 1-acetate **13** as 4:1 mixture of the α- and β-anomers, respectively.



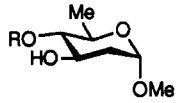
	X	R^1	R^2
10	NHAc	OMe	H
11	NHAc	OAc	H
12	NO_2	OMe	H
13	NO_2	H,OAc	

11

SiO_2, toluene
reflux, 60%



14



15, R = Bz
16, R = H

Treatment of the acetolysis product **11** in boiling toluene with silica gel caused elimination to yield the crystalline glycal **14**.[13] Reaction of the 4-*O*-benzoyl-protected olivoside **15**[14] and glycal **14** in acetonitrile in the presence of *N*-iodosuccinimide (NIS) for 5 days at room temperature failed to give any disaccharide. Moreover, no condensation was observed when iodonium di-*sym*-collidine perchlorate in dichloromethane was used or when the more nucleophilic[15] diol **16** was employed as the aglycon unit in the NIS procedure. In all cases, slow decomposition of the methyl-branched glycal occurred.

A novel glycosylation method, recently developed by Terashima et al., allows the condensation of anthracyclinones with 1-*O*-acyl and 1-*O*-*tert*-butyldimethylsilylated aminodeoxy sugar derivatives in the presence of

(5) (a) Beau, J.-M.; Jaurand, G.; Esnault, J.; Sinay, P. *Tetrahedron Lett.* **1987**, *28*, 1105. (b) Trumtel, M.; Tavecchia, P.; Veyrieres, A.; Sinay, P. *Carbohydr. Res.* **1990**, *202*, 257.

(6) (a) Dornhagen, J.; Scharf, H.-D. *Tetrahedron* **1985**, *41*, 173. (b) Dornhagen, J.; Scharf, H.-D. *Z. Naturforsch., Teil B* **1985**, *40*, 1541.

(7) Jütten, P.; Dornhagen, J.; Scharf, H.-D. *Tetrahedron* **1987**, *43*, 4133.

(8) Jütten, P.; Scharf, H.-D. *Carbohydr. Res.* **1991**, *212*, 93.

(9) For a recent review of glycosylation of 2-deoxy sugars, see: Thiem, J.; Klaffke, W. *Top. Curr. Chem.* **1990**, *154*, 285.

(10) (a) Hirayama, N.; Kasai, M.; Shirahata, K.; Ohashi, Y.; Sasada, Y. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 2112. (b) Hoeksema, H.; Mizsak, S. A.; Baczynskj, L.; Pschigoda, L. M. *J. Am. Chem. Soc.* **1982**, *104*, 5173. (c) Ishii, K.; Kondo, S.; Nishimura, Y.; Hamada, M.; Takeuchi, T.; Umezawa, H. *J. Antibiot.* **1983**, *36*, 451. (d) Mallams, A. K.; Puar, M. S.; Rossman, R. R.; McPhail, A. T.; Macfarlane, R. D.; Stephens, R. L. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1497. (e) Kawai, H.; Hayakawa, Y.; Nakagawa, M.; Furihara, K.; Seto, H.; Otake, N. *Tetrahedron Lett.* **1984**, *25*, 1941. (f) Kind, R.; Hütter, K.; Zeeck, A.; Schmidt-Bäse, K.; Egert, E. *J. Antibiot.* **1989**, *42*, 7.

(11) Thiem, J.; Karl, H.; Schwentner, J. *Synthesis* **1978**, 696.

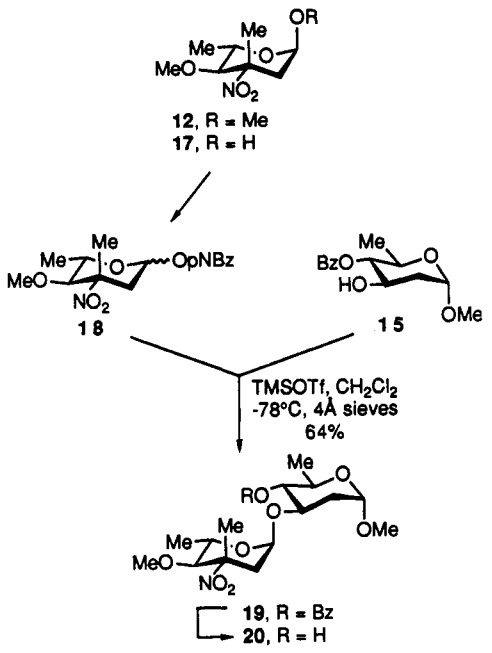
(12) (a) Lemieux, R. U.; Morgan, A. R. *Can. J. Chem.* **1965**, *43*, 2190. (b) Friesen, R. W.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 6656.

(13) Procedure adopted from: (a) Fuchs, E.-F.; Horton, D.; Weckerle, W.; Winter, B. *J. Antibiot.* **1979**, *32*, 223. (b) Horton, D.; Nickol, R. G.; Weckerle, W.; Winter-Mihaly, E. *Carbohydr. Res.* **1979**, *76*, 269.

(14) (a) Hanessian, S.; Plessas, N. R. *J. Org. Chem.* **1969**, *34*, 1045. (b) Stewart, A. O.; Williams, R. M. *Carbohydr. Res.* **1984**, *135*, 167.

(15) Thiem, J.; Gerken, M. *J. Org. Chem.* **1985**, *50*, 954.

Scheme I



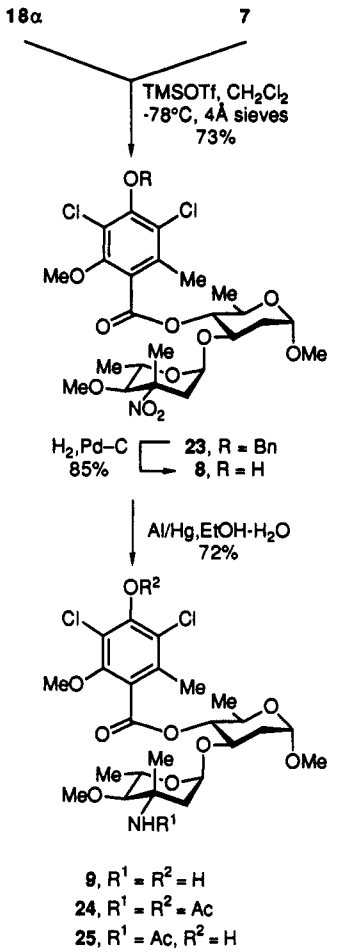
trimethylsilyl trifluoromethanesulfonate (TMSOTf).[16,17] This method provided only the α-anomer in high yield.

As a result of preliminary experiments the *p*-nitrobenzoate **18** was chosen as the most promising glycosyl donor. Evernitrose **17**[8] was acylated with *p*-nitrobenzoyl chloride in pyridine to give β-anomer **18**β almost exclusively in 90% yield. On the other hand, acidic hydrolysis of methyl glycoside **12**[8] and subsequent *p*-nitrobenzoylation led to a mixture of anomers (yield 80%) which gave pure **18**α upon recrystallization (Scheme I).

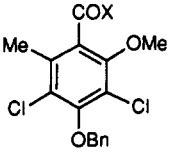
In the glycosylation reaction we used a modification of Terashima's procedure. The *p*-nitrobenzoate **18** was reacted with **15** using 4.2 equiv of TMS triflate promoter and powdered molecular sieves (4 Å) in dichloromethane at −78 °C. This low reaction temperature is of particular importance, since at higher temperatures rapid decomposition of **18** was observed. After completion of the reaction, excess of the promoter was neutralized with triethylamine at −78 °C in order to prevent cleavage of the acid labile deoxy sugar components. The α-linked 2′-deoxy disaccharide **19** was formed exclusively in 64% yield (Scheme I), though the α-glycoside bears a repulsive 1,3-syn-axial interaction between the 3′-methyl branch and the anomeric substituent.[18] The ^{1}H NMR spectrum of **19** exhibited H-1′ as a doublet of doublets with coupling constants $J_{1',2ax'}$ = 4.9, $J_{1',2eq'}$ = 1.3 Hz. The stereochemical outcome did not depend on the configuration at the anomeric center of the glycosyl donor. This result might be explained by the assumption of a common oxocarbenium ion intermediate. The remarkable selectivity for the attack from the α-side may be due to a combination of the anomeric effect and conformational demands of the cationic species.

Cleavage of the benzoate was accomplished with 0.5 M sodium hydroxide in aqueous dioxane or using the Zemplen method to give disaccharide **20** (Scheme I). We have previously reported the preparation of curacin **6** and its benzyl ether **7**.[7] These syntheses involved the acylation

Scheme II



of an olivose derivative with 4-*O*-benzyl-protected dichloroisoeverninoyl chloride **22**, which is easily accessible



from acid **21** with the reagent 1-chloro-*N*,*N*,2-trimethylpropenylamine.[19] An improved procedure for the preparation of acid chloride **22** is given in the Experimental Section. However, reaction of the anion of disaccharide **20** with acyl chloride **22** was not successful.

On the basis of these results a comparable glycosylation reaction using the curacin derivative **7**[7] as glycosyl acceptor could be expected. In fact, we obtained the everninonitrose derivative **23** stereospecifically in 73% yield (Scheme II). The H-4 triplet at δ 4.92 ($J_{3,4} = J_{4,5}$ = 9.4 Hz) in the ^{1}H NMR spectrum of **23** unambiguously proved that the nitro sugar was linked to position 3 of the olivose unit. Evidence for the α-glycosidic linkage can be obtained from the characteristic signals of H-1′, H-2ax′ and H-2eq′ displaying patterns with coupling constants $J_{1',2ax'}$ = 5.1, $J_{1',2eq'}$ = 1.7 Hz and $J_{2ax',2eq'}$ = 13.6 Hz.

Smooth hydrogenolytic cleavage of the phenolic benzyl ether in the presence of palladium on carbon completed the synthesis of everninonitrose methyl glycoside **8** (yield

(16) Kimura, Y.; Suzuki, M.; Matsumoto, T.; Abe, R.; Terashima, S. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 423.
(17) Kolar, C.; Dehmel, K.; Moldenhauer, H.; Gerken, M. *J. Carbohydr. Chem.* **1990**, *9*, 873.
(18) For glycosylation of branched-chain sugar eremosamine, see: Olsufyeva, E. N.; Backinowsky, L. V. *Tetrahedron Lett.* **1990**, *33*, 4805.
(19) Haveaux, B.; Dekkoker, A.; Rens, M.; Sidani, A. R.; Toye, J.; Ghosez, L. *Org. Synth.* **1979**, *59*, 26.

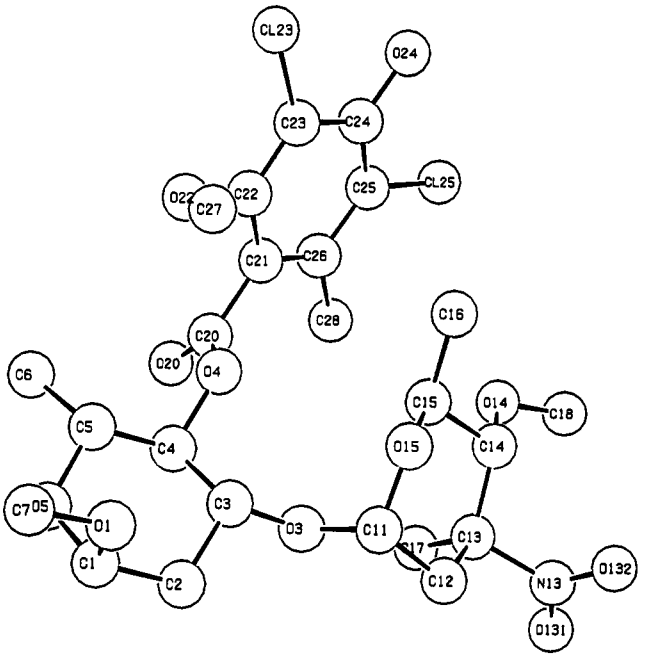


Figure 1. ORTEP plot of everninonitrose methyl glycoside 8.

85%, Scheme II), the common AB unit of everninomicins B, C, D, and related antibiotic 13-384 component 1. Structure and stereochemistry of 8 were assigned on the basis of ^{1}H NMR spectroscopic data and were consistent with those reported for the degradation product of everninomicin D.[1,20]

Single crystal X-ray analysis of everninonitrose methyl glycoside 8 confirmed the absolute stereochemistry. In the solid-state structure (Figure 1) both pyranose rings adopt the chair form, $^4C_1$ (D) for olivose and $^1C_4$ (L) for the evernitrose residue. As a consequence of the 1,3-diaxial interactions between the methyl branch and the α-glycoside moiety the evernitrose chair is somewhat flattened. The relative conformation of the sugars in the disaccharide is specified by three parameters. The bond angle associated with the glycosidic linkage (C3–O3–C11) is 112.4°, while the dihedral angles Φ (C3–O3–C11–H11) and Ψ (C11–O3–C3–H3) have values of approximately −44° and +23°, respectively. Steric crowding in the polysubstituted aromatic acid causes a twist of two substituents, the carboxy and the methoxy group, out of the ring plane.[21] Since the C20–C21 (C–COO) and C22–O22 (C–OMe) bonds are now chiral axes, four diastereomeric conformers are possible. However, the crystal of methyl everninonitroside 8 subjected to X-ray structure determination contained only the *MP* isomer.

In the antibiotic 13-384 component 5 (**5**) a methyl-branched aminodeoxy sugar is found instead of evernitrose. The terminal AB unit of this antibiotic (**9**), which we call *everninosamine*, was intended to be prepared by chemical reduction of everninonitrose methyl glycoside 8. The presence of the dichloroisoeverninic ester and the 2,6-dideoxy glycosides exclude reactions in strongly alkaline medium or under acidic conditions. The chlorine substituents were labile when 8 was hydrogenated under pressure. Mild reduction of the nitro group was best accomplished with amalgamated aluminium[22] in aqueous ethanol at ambient temperature to afford a 72% yield of everninosamine methyl glycoside (**9**, Scheme II). The ampholyte **9** was converted further into the *N,O*-diacetyl derivative **24**. The phenolic acetate could then be hydrolyzed selectively with ammonia to give acetamido compound **25**, which formed a well-crystallizing etherate.

Experimental Section

General Remarks. See ref 8.

3-Acetamido-1-*O*-acetyl-2,3,6-trideoxy-3-*C*-methyl-4-*O*-methyl-α-L-*arabino*-hexopyranose (11). To a cold (−25 °C) solution of glycoside **10** (2.44 g, 10.5 mmol)[8] in EtOAc (150 mL) were added acetic anhydride (90 mL), acetic acid (65 mL), and concd H_2SO_4 (0.9 mL). The mixture was kept at −25 °C for 24 h, after which time $CHCl_3$ (150 mL) and anhydrous NaOAc (20 g) were added, and the mixture was allowed to attain rt. The salts were filtered off, and the filtrate was concentrated to dryness. Toluene was added to and evaporated from the residue which was dissolved in $CHCl_3$. The solution was clarified by filtration and then concentrated to afford a solid which was recrystallized from EtOAc–hexane to give 1.74 g (63%) of **11**: mp 133–134 °C, $[\alpha]^{22}_D$ −86° (*c* 1.02, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.29 (d, 3 H, Me-5), 1.39 (s, 3 H, Me-3), 1.85 (dd, 1 H, H-2eq), 1.97 (s, 3 H, NAc), 2.07 (s, 3 H, OAc), 3.09 (dd, 1 H, H-2ax), 3.51 (s, 3 H, MeO-4), 3.79 (dq, 1 H, H-5), 3.92 (d, 1 H, H-4), 5.72 (br s, 1 H, NH), 6.10 (d, J = 4.0 Hz, 1 H, H-1), $J_{1,2ax}$ = 4.7 Hz, $J_{1,2eq}$ = 1.0 Hz, $J_{2ax,2eq}$ = 14.4 Hz, $J_{4,5}$ = 9.7 Hz, $J_{5,6}$ = 6.0 Hz; ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.45 (C-6), 21.30 and 21.34 (Me-3 and *Me*COO), 24.57 (*Me*CON), 37.47 (C-2), 55.80 (C-3), 61.32 (MeO-4), 68.21 and 81.80 (C-4, 5), 91.88 (C-1), 169.43 and 170.02 (Me*C*ON and Me*C*OO). Anal. Calcd for $C_{12}H_{21}NO_5$ (259.3): C, 55.59; H, 8.16; N, 5.40. Found: C, 55.85; H, 8.38; N, 5.42.

1-*O*-Acetyl-2,3,6-trideoxy-3-*C*-methyl-3-nitro-L-*arabino*-hexopyranose (13). A solution of methyl evernitroside **12** (1.20 g, 5.5 mmol)[8] in EtOAc (75 mL) was treated with acetic acid (30 mL), acetic anhydride (45 mL), and concd H_2SO_4 (0.45 mL) at −25 °C according to the procedure used to prepare **11**. Purification of the crude product by chromatography (EtOAc–cyclohexane (1:1)) afforded 1.06 g (78% yield) of syrupy **13** as a 4:1 mixture of α,β-anomers.

3-Acetamido-1,5-anhydro-2,3,6-trideoxy-3-*C*-methyl-4-*O*-methyl-L-*arabino*-hex-1-enitol (14). A slurry of silica gel (20 g) in toluene (200 mL) was heated to boiling under reflux in a flask equipped with a water separator. 1-Acetate **11** (2.28 g, 8.8 mmol) was added, and heating was continued for 4 h. The silica gel was filtered off and washed thoroughly with EtOAc (5 × 25 mL). The combined filtrates were concentrated, and the solid residue was recrystallized from EtOAc–hexane to give 1.06 g (60%) of **14**: mp 122–124 °C, $[\alpha]^{23}_D$ +94° (*c* 1.57, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31 (s, 3 H, Me-3), 1.37 (d, 3 H, Me-5), 1.97 (s, 3 H, NAc), 3.54 (s, 3 H, MeO-4), 3.88 (dq, 1 H, H-5), 4.04 (d, 1 H, H-4), 4.69 (d, 1 H, H-2), 5.81 (br s, 1 H, NH), 6.22 (d, 1 H, H-1), $J_{1,2}$ = 6.0 Hz, $J_{4,5}$ = 9.7 Hz, $J_{5,6}$ = 6.4 Hz; ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.15 (C-6), 24.21 and 24.29 (Me-3 and *Me*CON), 54.81 (C-3), 61.22 (MeO-4), 72.53 and 80.56 (C-4, 5), 107.02 (C-2), 142.25 (C-1), 169.39 (Me*C*ON). Anal. Calcd for $C_{10}H_{17}NO_3$ (199.2): C, 60.30; H, 8.60; N, 7.03. Found: C, 60.41; H, 8.61; N, 7.10.

2,3,6-Trideoxy-3-*C*-methyl-4-*O*-methyl-3-nitro-1-*O*-(*p*-nitrobenzoyl)-β-L-*arabino*-hexopyranose (18β). *p*-Nitrobenzoyl chloride (0.99 g, 5.3 mmol) was added to a solution of L-evernitrose **17** (1.00 g, 4.8 mmol)[8] in pyridine (25 mL) at 0 °C and then stirred at rt overnight. The reaction mixture was concentrated in vacuo, and a solution of the residue in CH_2Cl_2 was washed with several portions of water, dried ($MgSO_4$), and concentrated to give **18β** as a glass after column chromatography (EtOAc–cyclohexane (1:1)): yield 1.56 g (90%); $[\alpha]^{20}_D$ −21° (*c* 1.25, $CHCl_3$). The NMR spectrum of this showed the presence of the β-anomer almost exclusively. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43 (d, 3 H, Me-5), 1.79 (s, 3 H, Me-3), 2.36 (dd, 1 H, H-2eq), 2.66 (dd, 1 H, H-2ax), 3.46 (s, 3 H, MeO-4), 3.67 (dq, 1 H, H-5), 3.87 (d, 1 H, H-4), 6.07 (dd, 1 H, H-1), 8.20–8.32 (m, 4 H, aryl-H), $J_{1,2ax}$

(20) Ganguly, A. K.; Sarre, O. Z.; Szmulewicz, S. *J. Chem. Soc., Chem. Commun.* **1971**, 746.

(21) Similar torsional phenomena were observed for the aromatic acid of calicheamicins: Nicolaou, K. C.; Ebata, T.; Stylianides, N. A.; Groneberg, R. D.; Carrol, P. J. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1097.

(22) Wislicenus, H.; Kaufmann, L. *Ber. Dtsch. Chem. Ges.* **1895**, *28*, 1323.

= 9.7 Hz, $J_{1,2eq}$ = 2.3 Hz, $J_{2ax,2eq}$ = 12.6 Hz, $J_{4,5}$ = 9.7 Hz, $J_{5,6}$ = 6.0 Hz; ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.94 (Me-3), 18.46 (C-6), 41.17 (C-2), 60.92 (MeO-4), 72.12, 83.95 (C-4, 5), 89.26 (C-3), 91.64 (C-1), 123.64 (C_m pNBz), 131.11 (C_o pNBz), 134.38 (CCOO pNBz), 150.97 (CNO_2 pNBz), 162.75 (COO). Anal. Calcd for $C_{15}H_{18}N_2O_8$ (354.3): C, 50.85; H, 5.12; N, 7.91. Found: C, 51.12; H, 5.20; N, 8.00.

2,3,6-Trideoxy-3-*C*-methyl-4-*O*-methyl-3-nitro-1-*O*-(*p*-nitrobenzoyl)-α,β-L-*arabino*-hexopyranose (18) and -α-L-*arabino*-hexopyranose (18α). A solution of methyl α-L-evernitroside **12** (8.2 g, 37.4 mmol)[8] in 0.05 M H_2SO_4 in 1:1 water–dioxane (500 mL) was heated at 90 °C for 28 h, neutralized with $BaCO_3$, filtered, and extracted with CH_2Cl_2. The extract was dried ($MgSO_4$) and concentrated to a syrup (7.5 g), a solution of which in pyridine (50 mL) at 0 °C was treated portionwise with *p*-nitrobenzoyl chloride (10.2 g, 54.9 mmol) and stirred at room temperature overnight. The reaction mixture was poured into water and extracted with CH_2Cl_2. The extracts were combined and washed successively with cold 10% aqueous H_2SO_4, water, saturated aqueous $NaHCO_3$, and water, dried ($MgSO_4$), and evaporated to dryness (10.6 g of **18**). Recrystallization from $CHCl_3$–diisopropyl ether afforded 4.8 g (36%) of **18α**. Concentration of the mother liquor left 5.8 g of a solid mixture of anomers (β–α ratio 6–10:1). Compound **18α** had mp 161–163 °C: $[\alpha]^{23}_D$ −110° (*c* 1.02, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40 (m, 3 H, Me-5), 1.92 (s, 3 H, Me-3), 2.41 (dd, 1 H, H-2eq), 2.76 (dd, 1 H, H-2ax), 3.48 (s, 3 H, MeO-4), 3.90 (m, 2 H, H-4, 5), 6.48 (dd, 1 H, H-1), 8.18–8.22, 8.31–8.35 (m, 4 H, aryl-H), $J_{1,2ax}$ = 4.7 Hz, $J_{1,2eq}$ = 1.3 Hz, $J_{2ax,2eq}$ = 14.4 Hz, ABX_3 system with virtual couplings for Me-5, H-4 and H-5; ^{1}H NMR (300 MHz, C_5D_5N) δ 1.35 (d, 3 H, Me-5), 3.96 (d, 1 H, H-4), 4.07 (dq, 1 H, H-5), $J_{4,5}$ = 9.5 Hz, $J_{5,6}$ = 6.0 Hz; ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.38, 18.58 (Me-3 and C-6), 39.81 (C-2), 61.04 (MeO-4), 69.07, 83.87 (C-4, 5), 89.17 (C-3), 91.83 (C-1), 123.83 (C_m pNBz), 130.81 (C_o pNBz), 134.86 (*C*COO pNBz), 150.94 (CNO_2 pNBz), 162.96 (COO). Anal. Calcd for $C_{15}H_{18}N_2O_8$ (354.3): C, 50.85; H, 5.12; N, 7.91. Found: C, 50.65; H, 5.28; N, 7.87.

Methyl 4-*O*-Benzoyl-3-*O*-(2,3,6-trideoxy-3-*C*-methyl-4-*O*-methyl-3-nitro-α-L-*arabino*-hexopyranosyl)-2,6-dideoxy-α-D-*arabino*-hexopyranoside (19). To a mixture of **18** (1.53 g, 4.3 mmol), glycoside **15** (1.15 g, 4.3 mmol), and molecular sieves (4 Å; 2 g) in CH_2Cl_2 (10 mL) at −78 °C was added TMS triflate (4.2 equiv) in CH_2Cl_2 (20 mL) during 45 min under argon. After the mixture was stirred for 2 h at −78 °C, NEt_3 (5 mL) was added and the mixture was filtered off. The filtrate was washed with water, dried ($MgSO_4$), and concentrated. Column chromatography of the residue (toluene–EtOAc (24:1)) gave 1.26 g (64%) of syrupy **19**: $[\alpha]^{24}_D$ −46° (*c* 1.17, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (d, 3 H, Me-5′), 1.23 (d, 3 H, Me-5), 1.53 (s, 3 H, Me-3′), 1.69 (ddd, 1 H, H-2ax), 2.01 (dd, 1 H, H-2eq′), 2.26 (ddd, 1 H, H-2eq), 2.38 (ddd, 1 H, H-2ax′), 3.19 (s, 3 H, MeO-1), 3.35 (s, 3 H, MeO-4′), 3.38 (dq, 1 H, H-5′), 3.53 (d, 1 H, H-4′), 3.92 (dq, 1 H, H-5), 4.19 (ddd, 1 H, H-3), 4.81 (dd, 1 H, H-1), 4.93 (dd, 1 H, H-1′), 5.00 (dd, 1 H, H-4), 7.41–7.48 (m, 2 H, H_m BzO-4), 7.53–7.61 (m, 1 H, H_p BzO-4), 8.02–8.06 (m, 2 H, H_o BzO-4), $J_{1,2ax}$ = 3.7 Hz, $J_{1,2eq}$ = 1.3 Hz, $J_{2ax,2eq}$ = 12.8 Hz, $J_{2ax,3}$ = 11.4 Hz, $J_{2eq,3}$ = 5.2 Hz, $J_{3,4}$ = 9.4 Hz, $J_{4,5}$ = 9.7 Hz, $J_{5,6}$ = 6.2 Hz, $J_{1',2ax'}$ = 4.9 Hz, $J_{1',2eq'}$ = 1.3 Hz, $J_{2ax',2eq'}$ = 13.4 Hz, $^4J_{2ax',Me-3'}$ = 0.7 Hz, $J_{4',5'}$ = 9.6 Hz, $J_{5',6'}$ = 6.0 Hz; ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.67, 17.87, 17.90 (Me-5,3′,5′), 34.61 (C-2), 41.11 (C-2′), 54.73 (MeO-1), 60.46 (MeO-4′), 65.88, 66.18, 70.67, 75.55, 84.37 (C-3,4,5,4′,5′), 90.17 (C-3′), 92.39, 98.08 (C-1,1′), 128.39 (C_m BzO-4), 129.66 (C_o BzO-4), 129.88 (CCOO BzO-4), 133.18 (C_p BzO-4), 165.69 (Ph*C*OO). Anal. Calcd for $C_{22}H_{31}NO_9$ (453.5): C, 58.27; H, 6.89; N, 3.09. Found: C, 58.28; H, 7.03; N, 3.32.

Methyl 3-*O*-(2,3,6-Trideoxy-3-*C*-methyl-4-*O*-methyl-3-nitro-α-L-*arabino*-hexopyranosyl)-2,6-dideoxy-α-D-*arabino*-hexopyranoside (20). (a) A solution of **19** (1.00 g, 2.2 mmol) in 0.5 M NaOH in 1:1 water–dioxane (30 mL) was stirred for 6 d at rt, and extracted with CH_2Cl_2. The extract was dried ($MgSO_4$) and concentrated to a syrup, column chromatography (cyclohexane–EtOAc (10:1)) of which gave 0.48 g (62%) of **20**: mp 66–68 °C (petroleum ether), $[\alpha]^{23}_D$ +13 (*c* 1.03, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31 (d, 3 H, Me-5), 1.37 (d, 3 H, Me-5′), 1.67 (ddd, 1 H, H-2ax), 1.76 (s, 3 H, Me-3′), 2.09 (ddd, 1 H, H-2eq), 2.14 (dd, 1 H, H-2eq′), 2.51 (ddd, 1 H, H-2ax′), 3.08 (td, *J* = 8.9 and 2.2 Hz, 1 H, H-4), 3.31 (s, 3 H, MeO-1), 3.43 (s, 3 H, MeO-4′), 3.59 (dq, 1 H, H-5), 3.74 (ddd, 1 H, H-3), 3.77 (d, 1 H, H-4′), 3.80 (d, 1 H, HO-4), 3.88 (dq, 1 H, H-5′), 4.72 (dd, 1 H, H-1), 5.01 (dd, 1 H, H-1′), $J_{1,2ax}$ = 3.7 Hz, $J_{1,2eq}$ = 1.2 Hz, $J_{2ax,2eq}$ = 13.1 Hz, $J_{2ax,3}$ = 11.6 Hz, $J_{2eq,3}$ = 5.3 Hz, $J_{3,4}$ = 8.4 Hz, $J_{4,5}$ = 9.4 Hz, $J_{4,HO-4}$ = 2.1 Hz, $J_{5,6}$ = 6.3 Hz, $J_{1',2ax'}$ = 4.9 Hz, $J_{1',2eq'}$ = 1.8 Hz, $J_{2ax',2eq'}$ = 13.6 Hz, $^4J_{2ax',Me-3'}$ = 0.6 Hz, $J_{4',5'}$ = 9.5 Hz, $J_{5',6'}$ = 6.0 Hz; ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.93, 18.31, 18.50 (Me-5,3′,5′), 35.72 (C-2), 41.13 (C-2′), 54.50 (MeO-1), 60.88 (MeO-4′), 67.06, 67.32, 76.16, 79.28, 84.31 (C-3,4,5,4′,5′), 89.85 (C-3′), 96.25, 98.02 (C-1,1′). Anal. Calcd for $C_{15}H_{27}NO_8$ (349.4): C, 51.56; H, 7.79; N, 4.01. Found: C, 51.39; H, 7.87; N, 4.09.

(b) A solution of **19** (1.00 g, 2.2 mmol) in 0.1 N methanolic NaOMe (20 mL) was kept for 7 d at rt. The solution was treated with weakly acidic ion-exchange resin (such as Lewatit CNP 80). The resin was removed by filtration, and the filtrate was concentrated. The residue was purified by column chromatography (toluene–EtOAc (8:1)) to give 0.48 g (62%) of pure **20**.

4-(Benzyloxy)-3,5-dichloro-2-methoxy-6-methylbenzoyl Chloride (22). 1-Chloro-*N*,*N*,2-trimethylpropenylamine (3.67 g, 27.5 mmol)[19] was added under argon to an ice-cooled solution of **21** (8.53 g, 25.0 mmol)[6] in CH_2Cl_2 (100 mL), and the mixture was stirred for 4 h at rt. Solvent and *N*,*N*-dimethyl isobutyramide were evaporated in vacuo, and the residue was subjected to Kugelrohr distillation (190–200 °C (0.01 mbar)) to yield 7.45 g (79%) of **22** as a colorless oil which crystallized slowly: mp 28–30 °C; IR 1790, 1775 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.39 (s, 3 H, Me-6), 3.94 (s, 3 H, MeO-2), 5.03 (s, 2 H, PhCH_2O-4), 7.34–7.43 and 7.53–7.57 (m, 5 H, aryl-H BnO-4); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.16 (Me-6), 62.37 (MeO-2), 75.06 (PhCH_2O-4), 121.77, 126.29, 131.48, 131.63 (C-1,3,5,6), 128.45, 128.52, 128.58 (*C*H BnO-4), 135.85 (*C*CH_2 BnO-4), 151.10, 153.91 (C-2,4), 166.66 (COCl); mass spectrum, *m*/*e* 358/360/362/364 (97:100:34:4, M^+), 323/325/327 (100:63:13, M^+ − Cl), 232/234/236 (100:66:12, M^+ − Cl − C_7H_7), 189/191/193 (100:58:7), 111/113 (100:27), 91 (base peak, $C_7H_7^+$).

Methyl 4-*O*-(4-(Benzyloxy)-3,5-dichloro-2-methoxy-6-methylbenzoyl)-3-*O*-(2,3,6-trideoxy-3-*C*-methyl-4-*O*-methyl-3-nitro-α-L-*arabino*-hexopyranosyl)-2,6-dideoxy-α-D-*arabino*-hexopyranoside (23). To a solution of **7** (4.70 g, 9.7 mmol)[7] and glycosyl donor **18α** (3.80 g, 10.7 mmol) in CH_2Cl_2 (50 mL) was added powdered molecular sieves (4 Å; 6 g), and the solution was stirred for 30 min. The mixture was cooled to −78 °C, and a solution of TMS triflate in CH_2Cl_2 (50 mL; 50 g/250 mL) was introduced dropwise under an argon atmosphere during 60 min. After the mixture was stirred for 30 min, NEt_3 (15 mL) was added, and the mixture was filtered off. The filtrate was washed with water, dried ($MgSO_4$), and concentrated. The solid residue was recrystallized from ethanol to give 4.8 g (73%) of **23**: mp 133–135 °C, $[\alpha]^{24}_D$ −24° (*c* 1.02, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 (d, 3 H, Me-5′), 1.38 (d, 3 H, Me-5), 1.71 (s, 3 H, Me-3′), 1.78 (ddd, 1 H, H-2ax), 2.03 (dd, 1 H, H-2eq′), 2.19 (ddd, 1 H, H-2eq), 2.41 (s, 3 H, Me-6″), 2.42 (dd, 1 H, H-2ax′), 3.33 and 3.35 (2 s, 6 H, MeO-1,4′), 3.52 (dq, 1 H, H-5′), 3.64 (d, 1 H, H-4′), 3.85 (dq, 1 H, H-5), 3.91 (s, 3 H, MeO-2″), 4.16 (ddd, 1 H, H-3), 4.78 (dd, 1 H, H-1), 4.92 (t, 1 H, H-4), 4.95 (dd, 1 H, H-1′), 5.02 and 5.06 (AB, 2 H, PhCH_2O-4″), 7.35–7.44, 7.53–7.59 (m, 5 H, aryl-H), $J_{1,2ax}$ = 3.7 Hz, $J_{1,2eq}$ = 1.4 Hz, $J_{2ax,2eq}$ = 13.0 Hz, $J_{2ax,3}$ = 11.5 Hz, $J_{2eq,3}$ = 5.0 Hz, $J_{3,4}$ = $J_{4,5}$ = 9.4 Hz, $J_{5,6}$ = 6.4 Hz, $J_{1',2ax'}$ = 5.1 Hz, $J_{1',2eq'}$ = 1.7 Hz, $J_{2ax',2eq'}$ = 13.6 Hz, $J_{4',5'}$ = 9.5 Hz, $J_{5',6'}$ = 6.1 Hz; ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.61, 17.93, 18.27, 19.25 (Me-5,3′,5′,6″), 35.06 (C-2), 40.54 (C-2′), 54.80 (MeO-1), 60.72 (MeO-4′), 62.11 (MeO-2″), 66.15, 66.40, 70.84, 76.82 (C-3,4,5,5′), 74.93 (PhCH_2O-4″), 84.39 (C-4′), 90.08 (C-3′), 92.73, 97.91 (C-1,1′), 121.72, 126.27, 126.35 (C-1″,3″,5″), 128.52, 128.54, 128.56 (*CH*PhCH_2O-4″), 134.77, 135.96 (C-6″ and *CC*H_2PhCH_2O-4″), 153.28 (C-2″,4″), 165.68 (COO). Anal. Calcd for $C_{31}H_{39}Cl_2NO_{11}$ (672.6): C, 55.36; H, 5.84; N, 2.08. Found: C, 55.40; H, 5.84; N, 2.23.

Methyl 4-*O*-(3,5-Dichloro-4-hydroxy-2-methoxy-6-methylbenzoyl)-3-*O*-(2,3,6-trideoxy-3-*C*-methyl-4-*O*-methyl-3-nitro-α-L-*arabino*-hexopyranosyl)-2,6-dideoxy-α-D-*arabino*-hexopyranoside (α-Methyl Glycoside of Evernonitrose) (8). A solution of **23** (4.8 g, 7.1 mmol) in methyl *tert*-butyl ether (150 mL) was hydrogenated for 1 h in the presence of 10% palladium on carbon (0.25 g). After filtration of the

catalyst, the filtrate was concentrated, and the solid residue was recrystallized from diisopropyl ether–hexane to give 3.55 g (85%) of 8: mp 110–112 °C, $[\alpha]^{23}_D$ –37° (*c* 1.22, $CHCl_3$); IR (KBr) 3350 (OH), 2840 (OCH_3), 1740 (C=O), 1540, 1350 (NO_2) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.85 (d, 3 H, Me-5′), 1.37 (d, 3 H, Me-5), 1.70 (s, 3 H, Me-3′), 1.78 (ddd, 1 H, H-2ax), 2.03 (dd, 1 H, H-2eq′), 2.20 (ddd, 1 H, H-2eq), 2.40 (s, 3 H, Me-6″), 2.43 (dd, 1 H, H-2ax′), 3.34 and 3.35 (2 s, 6 H, MeO-1,4′), 3.51 (dq, 1 H, H-5′), 3.63 (d, 1 H, H-4′), 3.85 (dq, 1 H, H-5), 3.92 (s, 3 H, MeO-2″), 4.16 (ddd, 1 H, H-3), 4.80 (dd, 1 H, H-1), 4.93 (t, J = 9.5 Hz, 1 H, H-4), 4.94 (dd, 1 H, H-1′), 6.4 (br, 1 H, HO-4″), $J_{1,2ax}$ = 3.7 Hz, $J_{1,2eq}$ = 1.4 Hz, $J_{2ax,2eq}$ = 13.0 Hz, $J_{2ax,3}$ = 11.4 Hz, $J_{2eq,3}$ = 5.0 Hz, $J_{3,4}$ = 9.4 Hz, $J_{4,5}$ = 9.6 Hz, $J_{5,6}$ = 6.4 Hz, $J_{1',2ax'}$ = 4.9 Hz, $J_{1',2eq'}$ = 1.7 Hz, $J_{2ax',2eq'}$ = 13.5 Hz, $J_{4',5'}$ = 9.6 Hz, $J_{5',6'}$ = 6.2 Hz; ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.61, 17.92, 18.21, 19.19 (Me-5,3′,5′,6″), 35.00 (C-2), 40.63 (C-2′), 54.82 (MeO-1), 60.70 (MeO-4′), 62.11 (MeO-2″), 66.12, 66.41, 70.75, 76.66 (C-3,4,5,5′), 84.37 (C-4′), 90.11 (C-3′), 92.67, 97.94 (C-1,1′), 113.27, 117.67, 121.98 (C-1″,3″,5″), 134.71 (C-6″), 150.26, 153.55 (C-2″,4″), 165.71 (COO). Anal. Calcd for $C_{24}H_{33}Cl_2NO_{11}$ (582.4): C, 49.50; H, 5.71; N, 2.40. Found: C, 49.59; H, 5.82; N, 2.56.

Crystal Structure Determination of 8. The compound crystallizes in monoclinic space group $P2_1$ (No. 4) with a = 9.205 (6) Å, b = 15.699 (9) Å, c = 10.317 (4) Å, and β = 107.10 (4)°. With Z = 2, a volume of 1424.86 Å^3, and M_r = 582.44 we obtained a calculated density of D_{calc} = 1.357 g cm^{-3}, while the total number of electrons in the cell amounts to $F(000)$ = 612. A total number of 7086 reflections ($\pm h \pm k + 1$) has been collected at room temperature on an ENRAF-NONIUS four-circle diffractometer employing graphite-monochromated Mo K_α radiation (λ = 0.71069 Å). The data have been corrected for Lorentz and polarization but not for absorption effects (μ = 2.90 cm^{-1} for Mo K_α). The structure has been solved by direct methods (GENSIN,[23] SIMPEL[24]) as implemented in the XTAL 2.6 program package.[25]

A total of 4829 observed reflections ($\sin\theta/\lambda_{max}$ = 0.6, $I > 2\sigma(I)$) and a total number of 343 parameters (calculated hydrogen positions) have been included in a full-matrix least-squares refinement process converging to R = 0.041 (R_w = 0.045), a residual electron density of 0.3 e Å^{-3}, and a final shift error smaller than 0.012.

Methyl 3-*O*-(3-Amino-2,3,6-trideoxy-3-*C*-methyl-4-*O*-methyl-α-L-*arabino*-hexopyranosyl)-4-*O*-(3,5-dichloro-4-hydroxy-2-methoxy-6-methylbenzoyl)-2,6-dideoxy-α-D-*arabino*-hexopyranoside (Methyl α-Glycoside of Everninosamine) (9). To a solution of 8 (1.05 g, 1.9 mmol) in 9:1 ethanol–water (100 mL) was added aluminium amalgam (freshly prepared from 10 g of aluminium turnings),[2] and the mixture was stirred at rt for 2 h. The gray reaction mixture was filtered off, the solid was washed with ethanol, and the combined filtrate and washes were treated with a fresh batch of aluminium amalgam (5 g) for 1 h. After filtration the solution was adjusted to pH 6.5 with 1 M phosphate buffer (pH 4.5) and concentrated (to a volume of approximately 50 mL). The concentrate was cooled in an ice bath, and the crystalline solid was collected, column chromatography ($CHCl_3$–methanol (9:1) of which gave 0.76 g (72%) of pure 9: $[\alpha]^{24}_D$ –34° (*c* 1.00, MeOH); IR (KBr) 3480, 3430, 3315 (OH and NH_2), 2940, 2840 (OCH_3), 1740, 1725 (C=O), 1605, 1550 cm^{-1}; mass spectrum m/e 520 (M^+ – OMe), 480/482/484 (100:68:19), 377, 376 (M^+ – $C_8H_{17}NO_3$), 345 (M^+ – OMe – $C_8H_{17}NO_3$), 233/235/237 (100:63:12, $C_9H_7Cl_2O_3^+$), 86 (base peak), 57, 58.

Methyl 3-*O*-(3-Acetamido-2,3,6-trideoxy-3-*C*-methyl-4-*O*-methyl-α-L-*arabino*-hexopyranosyl)-4-*O*-(3,5-dichloro-4-hydroxy-2-methoxy-6-methylbenzoyl)-2,6-dideoxy-α-D-*arabino*-hexopyranoside (25). To a slurry of 9 (0.60 g, 1.1 mmol) in CH_2Cl_2 (15 mL) was added NEt_3 (3 mL). The resulting clear solution was treated with acetic anhydride (1 mL) under cooling in an ice bath and then stirred for 1 h. The mixture was concentrated, and the product was extracted with CH_2Cl_2. The solution was washed with saturated aqueous $NaHCO_3$ and water and dried ($MgSO_4$). Evaporation of solvent left 24 (0.64 g) as a foam, a part of which (0.57 g) was dissolved in MeOH (20 mL) and stirred in the presence of 25% aqueous NH_3 (5 mL) for 1 h. The solution was adjusted to pH 6.5 using 1 M aqueous KH_2PO_4. The solid was filtered off and dried to give 0.50 g (85%) of 25, recrystallization of which from EtOAc–ether afforded a well-crystallizing etherate.

Data for 24: $[\alpha]^{24}_D$ –30 (*c* 1.04, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.82 (d, 3 H, Me-5′), 1.31 (s, 3 H, Me-3′), 1.36 (d, 3 H, Me-5), 1.72 (br d, 1 H, H-2eq′), 1.78 (ddd, 1 H, H-2ax), 1.91 (s, 3 H, NAc), 2.19 (ddd, 1 H, H-2eq), 2.40, 2.41 (2 s, 6 H, OAc and Me-6″), 3.33 (s, 3 H, MeO-1), 3.40 (s, 3 H, MeO-4′), 3.50 (dq, 1 H, H-5′), 3.65 (d, 1 H, H-4′), 3.84 (dq, 1 H, H-5), 3.92 (s, 3 H, MeO-2″), 4.15 (ddd, 1 H, H-3), 4.78 (d, J = 2.7 Hz, 1 H, H-1), 4.86 (d, J = 4.7 Hz, 1 H, H-1′), 4.91 (t, 1 H, H-4), 5.31 (br s, 1 H, NH), $J_{1,2ax}$ = 3.7 Hz, $J_{1,2eq}$ = 1.1 Hz, $J_{2ax,2eq}$ = 13.1 Hz, $J_{2ax,3}$ = 11.4 Hz, $J_{2eq,3}$ = 5.0 Hz, $J_{3,4}$ = $J_{4,5}$ = 9.4 Hz, $J_{5,6}$ = 6.4 Hz, $J_{1',2ax'}$ = 4.8 Hz, $J_{1',2eq'} \leq$ 1.7 Hz, $J_{2ax',2eq'}$ = 13.6 Hz, $J_{4',5'}$ = 9.7 Hz, $J_{5',6'}$ = 6.0 Hz; ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.70, 17.93, 18.22, 20.40, 22.20 (Me-5,3′,5′,6″ and *Me*COO), 24.69 (*Me*CON), 35.18, 38.72 (C-2,2′), 54.78 (MeO-1), 56.25 (C-3′), 61.13, 62.24 (MeO-4′,2″), 66.01, 66.47, 70.42, 77.25, 82.53 (C-3,4,5,4′,5′), 94.06, 98.03 (C-1,1′), 120.85, 125.22, 127.99 (C-1″,3″,5″), 134.90 (C-6″), 146.05, 153.07 (C-2″,4″), 165.35, 166.79 (Ar*C*OO and Me*C*OO), 169.66 (MeCON).

Data for 25: mp 114–117 °C, $[\alpha]^{25}_D$ –34.2 (*c* 1.13, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.79 (d, 3 H, Me-5′), 1.31 (s, 3 H, Me-3′), 1.36 (d, 3 H, Me-5), 1.72 (br d, J = 14.1 Hz, 1 H, H-2eq′), 1.75 (ddd, 1 H, H-2ax), 1.93 (s, 3 H, NAc), 2.20 (ddd, 1 H, H-2eq), 2.39 (s, 3 H, Me-6″), 2.88 (dd, 1 H, H-2ax′), 3.33 (s, 3 H, MeO-1), 3.40 (s, 3 H, MeO-4′), 3.49 (dq, 1 H, H-5′), 3.68 (d, 1 H, H-4′), 3.84 (dq, 1 H, H-5), 3.91 (s, 3 H, MeO-2″), 4.14 (ddd, 1 H, H-3), 4.78 (d, J = 2.7 Hz, 1 H, H-1), 4.85 (d, J = 4.4 Hz, 1 H, H-1′), 4.92 (t, 1 H, H-4), 5.35 (br s, 1 H, NH), $J_{1,2ax}$ = 3.7 Hz, $J_{1,2eq}$ = 1.5 Hz, $J_{2ax,2eq}$ = 13.1 Hz, $J_{2ax,3}$ = 11.4 Hz, $J_{2eq,3}$ = 5.3 Hz, $J_{3,4}$ = $J_{4,5}$ = 9.4 Hz, $J_{5,6}$ = 6.4 Hz, $J_{1',2ax'}$ = 4.7 Hz, $J_{1',2eq'}$ < 2 Hz, $J_{2ax',2eq'}$ = 14.1 Hz, $J_{4',5'}$ = 9.7 Hz, $J_{5',6'}$ = 6.0 Hz; ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.69, 17.98, 18.21, 22.20 (Me-5,3′,5′,6″), 24.62 (*Me*CON), 35.09, 38.68 (C-2,2′), 54.77 (MeO-1), 56.34 (C-3′), 61.11, 62.08 (MeO-4′,2″), 65.92, 66.47, 70.25, 76.91, 82.36 (C-3,4,5,4′,5′), 93.95, 98.05 (C-1,1′), 113.40, 117.92, 121.81 (C-1″,3″,5″), 134.88 (C-6″), 150.50, 153.53 (C-2″,4″), 165.86 (Ar*C*OO), 169.92 (MeCON).

Data for 25·Et_2O: mp 122–124 °C, $[\alpha]^{23}_D$ –30.6 (*c* 0.94, $CHCl_3$); IR (KBr) ≈3700–3400 (OH), 3320 (NH), 2840 (OCH_3), 1740 (C=O ester), 1655 (C=O amide). Anal. Calcd for $C_{28}H_{37}Cl_2NO_8 \cdot Et_2O$: C, 53.89; H, 7.09; N, 2.09. Found: C, 53.92; H, 7.06; N, 2.25.

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Supplementary Material Available: Tables of fractional coordinates, thermal parameters, bond lengths, bond angles, and torsional angles from the X-ray crystallographic analysis of 8 (15 pages). Ordering information is given on any current masthead page.

(23) Hall, S. R. In *GENSIN XTAL 2.6 User's Manual*; Hall, S. R., Stewart, J. M., Eds.; Universities of Western Australia and Maryland, 1989.

(24) Schenk, H.; Hall, S. R. In *SIMPEL XTAL 2.6 User's Manual*; Hall, S. R.; Stewart, J. M., Eds.; Universities of Western Australia and Maryland, 1989.

(25) *XTAL 2.6 User's Manual*; Hall, S. R., Stewart, J. M., Eds.; Universities of Western Australia and Maryland, 1989.