87655-06-9; **15**, 16170-45-9; **18**, 81981-13-7; **18a**, 87639-21-2; **18b**, 81981-14-8; **19**, 87639-22-3; **19a**, 87639-23-4; **19b**, 87639-24-5; **20**, 81981-17-1; **20a**, 87639-25-6; **20b**, 81981-18-2; **21**, 87639-26-7; **22**, 87639-27-8; **22a**, 87639-28-9; (*E*)-**22b**, 87639-29-0; (*Z*)-**22b**, 87639-30-3; **22c**, 87639-31-4; **23**, 87639-32-5; **23a**, 87639-33-6; **23b**, 87655-08-1; **23c**, 87639-34-7; **24**, 63399-81-5; **24a**, 87639-35-8; **25**, 87639-36-9; (*E*)-**26**, 87639-37-0; (*Z*)-**26**, 87639-38-1; Bu_3SnH, 688-73-3; $(Bu_3Sn)_2O$, 56-35-9; PMHS, 9004-73-3; $Pd(PPh_3)_4$, 14221-01-3; $PhCH_2Br$, 100-39-0; 2-(propargylthio)benzothiazole, 42477-59-8; (1-propynyl)tributylstannane, 64099-82-7; allenyltrimethylstannane, 4104-88-5; trimethyltin chloride, 1066-45-1; propargyl bromide, 106-96-7; allene, 463-49-0; tributyltin chloride, 1461-22-9; cinnamaldehyde, 104-55-2; β-bromostyrene, 103-64-0; 1,5-diphenyl-1,4-pentadien-3-ol, 3185-53-3; sodium cyanide, 143-33-9; trimethylsilyl cyanide, 7677-24-9; 4-methylcinnamaldehyde, 1504-75-2; 4-methoxycinnamaldehyde, 1963-36-6; *p*-anisaldehyde, 123-11-5; 4-chlorocinnamaldehyde, 1075-77-0; 4-nitrocinnamaldehyde, 1734-79-8; acetylene, 74-86-2; 5-phenylpent-4-en-1-yn-3-ol, 14604-31-0; 6-phenylhex-5-en-2-yn-4-ol, 87639-39-2; trimethylsilyl chloride, 75-77-4; tetraallytin, 7393-43-3.

Synthesis of Daunosamine[1]

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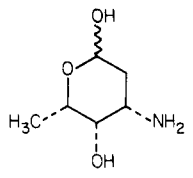
An efficient synthesis of daunosamine (1), the carbohydrate component of a group of biologically important anthracycline antibiotics, from readily available arabinose is reported.

Daunosamine (1, 3-amino-2,3,6-trideoxy-L-*lyxo*-hexose)[2]



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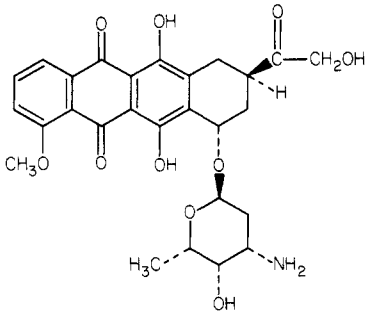

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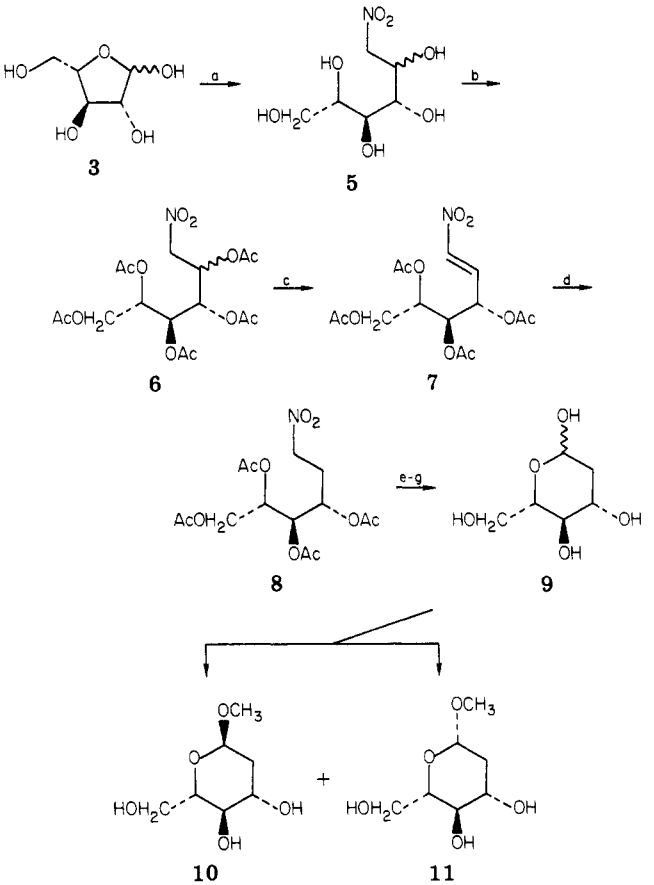
is the carbohydrate component of a group of anthracycline antibiotics which have attracted great attention because of their activity against a wide range of experimental and human tumors.[3] Adriamycin (**2**),[4] in particular, possesses impressive activity against a broad range of solid tumors, especially against soft tissues and bone sarcomas, and has established itself clinically as a potent agent in various chemotherapeutic combination regimens.

These results stimulated considerable research on the synthesis of these antibiotics and their analogues in many laboratories. Our efforts were directed towards the preparation of semisynthetic antibiotics from modified aglycones and daunosamine. Studies on the mode of action of these antibiotics and on structure–activity relationships clearly revealed the importance of the daunosamine portion toward activity.[5,6]

The need for large amounts of this amino sugar could be met only by synthesis. Previous to our work, two syntheses of L-daunosamine from L-rhamnose[7] and D-mannose,[8] respectively, had been reported. Since then three additional preparations of **1** from carbohydrate

Scheme I[a]



[a] (a) CH_3NO_2, CH_3ONa, CH_3OH; (b) $BF_3{\cdot}(C_2H_5)_2O$, $(CH_3CO)_2O$; (c) $NaHCO_3$, $C_6H_5CH_3$, Δ; (d) H_2/Pd-C, EtOAc; (e) $Ba(OH)_2{\cdot}8H_2O$; (f) H_2SO_4; (g) $BaCO_3$; (h) AG 50-X4(H^+), CH_3OH.

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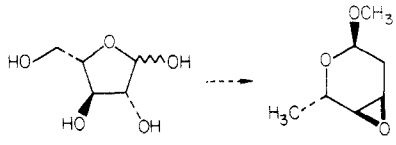
precursors[9-11] and two asymmetric syntheses[12,13] of 1 have been published.

Our plans called for a synthesis amenable to large-scale preparation, based on inexpensive materials, and encompassing an intermediate from which not only daunosamine but also related derivatives could be derived. A successful achievement of these goals is described in this and the accompanying paper.

A logical choice for the key intermediate was the known 3,4-anhydrohexopyranoside 4,[7] which we planned to synthesize from readily available L-arabinose (3). This sugar



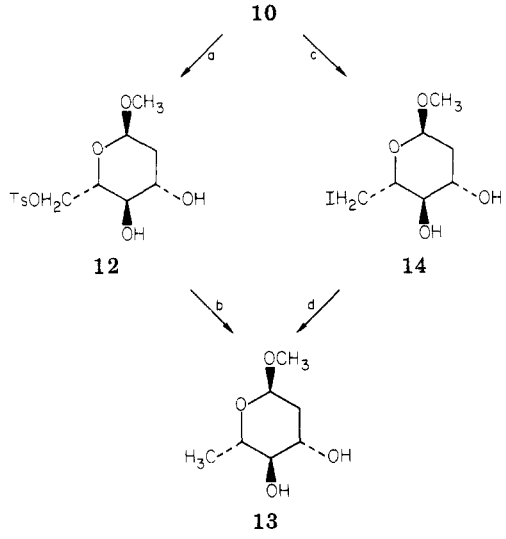
3 4

already contains two of the required chiral centers in the correct configuration, but it had to be transformed into a hexose homologue. This one-carbon enlargement was achieved by a sequence of reactions based on similar work by Sowden and Fischer (Scheme I).[14,15]

Although this sequence could be carried out without purification of intermediates with only a small loss in yield (35% overall), it was more practical, mainly in large-scale runs, to purify intermediates by crystallization. Condensation of L-arabinose (3) with nitromethane in the presence of sodium methoxide gave the crystalline mixture of epimers 5 in 70% yield. The optimal condensation time was found to be 24 h; longer reaction times improved the yield only marginally and gave rise to increasing amounts of dark decomposition products. Acetylation of mixture 5 in acetic anhydride in the presence of boron trifluoride etherate[15] gave in high yield the crystalline pentaacetates 6 which upon treatment with sodium bicarbonate in hot toluene yielded the nitroolefin 7[14] in nearly quantitative yield. The *E* geometry of the double bond was confirmed by NMR. Selective hydrogenation of the double bond under controlled conditions in ethyl acetate over palladium catalyst afforded the saturated nitro derivative 8. This compound was converted in high yield into 2-deoxy-L-*arabino*-hexose (9) by way of a modified Nef reaction[16] using barium hydroxide and sulfuric acid.

Without purification, oily 9 was dissolved in anhydrous methanol and treated with acidic ion exchange resin to afford in about 70% yield (from 8) an anomeric mixture of the methyl glycosides 10 and 11 in an approximate 8:2 ratio (see below). Slow crystallization from acetone gave the pure α-anomer 10 in large plates [mp 89–91 °C, $[\alpha]^{25}_D$ −132.63° (H_2O)]. The configurational assignment is based on comparison with the physical data reported[17] for the α-D-enantiomer [mp 91–92 °C, $[\alpha]^{25}_D$ +137.9° (H_2O)] and supported by NMR analysis. The anomeric mixture of 10 and 11 could be transformed completely into the crystalline α-anomer 10 by repeating the procedure of treating the

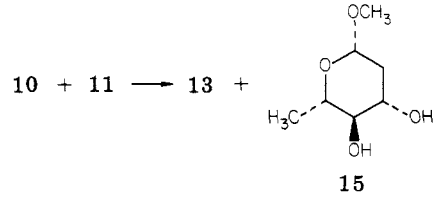
Scheme II[a]



[a] (a) TsCl, pyridine; (b) LAH, THF; (c) NIS, $P(C_6H_5)_3$, DMF; (d) Ra-Ni, CH_3OH.

mother liquors of the crystallization of 10, after evaporation to dryness, with acidic ion exchange resin in methanol and crystallizing the α-anomer. This compound has proven to be a useful intermediate not only for the preparation of daunosamine and related amino sugars but also for other important 2-deoxy sugars.

Reduction of 10 to the 2,6-dideoxypyranoside 13 was effected by two methods (Scheme II). Selective tosylation of the primary hydroxyl group of 10 with 1 equiv of tosyl chloride in pyridine gave in 75% yield the crystalline monotosylate 12, which was subsequently reduced with lithium aluminum hydride to liquid methyl 2,6-dideoxy-α-L-*arabino*-hexopyranoside (13). For the purpose of determining the composition of the anomeric mixture 9 obtained in the Nef reaction, the same reduction sequence was carried out with a mixture of anomers 10 and 11. The



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resulting anomers 13 and 15 were easily differentiated by inspection of their NMR spectra.[18] The features in the spectrum lending themselves for analysis are the signals for the methyl proton at C-6, for the methoxyl group, and for the anomeric proton.

The alternative pathway, 10 → 14 → 13, afforded 13 in high yield (65% overall) and also avoided the potentially dangerous lithium aluminum hydride reduction. Compound 10 was converted into the iodo derivative 14 with *N*-iodosuccimide and triphenylphosphine in dimethylformamide,[19] and the crude product was reduced to 13 with Raney nickel in boiling methanol.

The transformation of 13 to the desired key intermediate methyl 3,4-anhydro-2,6-dideoxy-α-L-*ribo*-hexopyranoside (4) (Scheme III) and subsequently to daunosamine followed in general the procedure first reported in a short

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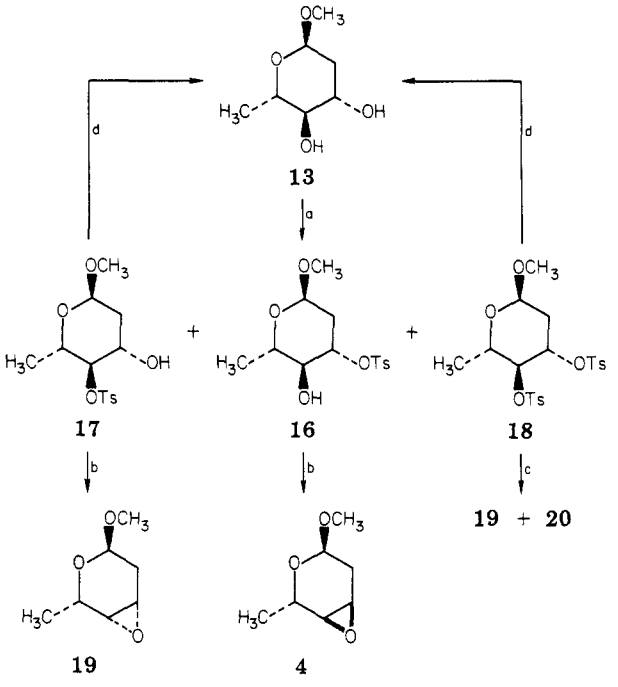
Scheme III[a]



[a] (a) TsCl, pyridine; (b) AG 1-X4(OH^-), CH_3OH; (c) $NaOCH_3$, CH_3OH; (d) Na/NH_3.

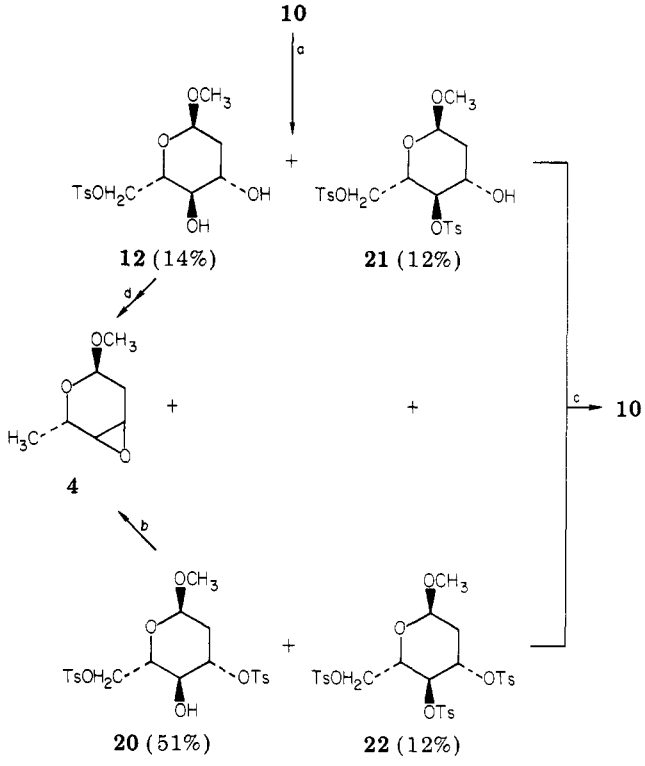
communication by Marsh and co-workers.[7] Tosylation of **13** with 1 equiv of tosyl chloride in pyridine gave a 4:1:1 mixture of **16–18** from which the desired 3-monotosylate **16** was isolated by chromatography in 55% yield. The byproducts **17** and **18** can be recycled by treatment with sodium in liquid ammonia.[20]

Treatment of the major tosylation product **16** with basic ion exchange resin in methanol[21] gave in excellent yield the 3,4-anhydro derivative **4**. Since we hoped that base treatment of the ditosylate **18** would afford additional **4**, compound **18** was reacted with sodium methoxide, only to give a mixture of the two isomeric epoxides **4** and **19** (vide TLC). The latter was prepared for comparison purposes from the 4-monotosylate **17** by treatment with basic ion exchange resin.

Since the formation of the undesired byproducts **17** and **18** could not be avoided during the tosylation of **13**, an alternative route to the 3,4-anhydro compound **4** was investigated (Scheme IV). Reaction of **10** with 2 equiv of tosyl chloride in pyridine gave a mixture of tosylates **12**, **20**, **21**, and **22** in the yields indicated. These compounds could easily be separated by HPLC on silica gel. Reduction of the major ditosylate **20** with sodium borohydride in 1,2-dimethoxyethane followed by addition of methanol to the reaction mixture gave the desired epoxide **4** in varying yields. Better and constant results (75% yield) were obtained when the intermediate in this reaction, the monotosylate **16**, was isolated and treated with basic ion exchange resin. The simplicity of this route and the fact that the major byproduct **12** can be converted to **4**, as shown before, makes the sequence outlined in Scheme IV the preferred one.

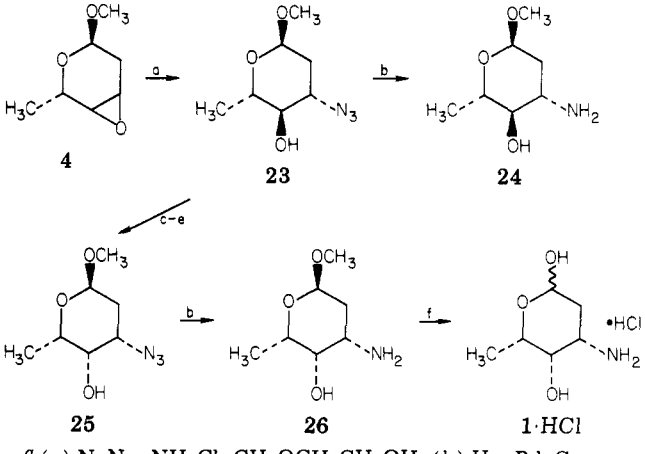
With the key intermediate **4** readily available, the synthesis of daunosamine (**1**) was completed following previously reported procedures[7] (Scheme V). Trans-diaxial opening of the epoxide ring with sodium azide in methoxyethanol–water in the presence of ammonium chloride

Scheme IV[a]



[a] (a) TsCl, pyridine; (b) $NaBH_4$-DME, CH_3OH; (c) Na/NH_3; (d) see Schemes II and III.

Scheme V[a]



[a] (a) NaN_3, NH_4Cl, $CH_3OCH_2CH_2OH$; (b) H_2, Pd-C, MeOH; (c) MsCl, pyridine; (d) C_6H_5COONa, DMF; (e) NaOH; (f) HCl.

at elevated temperatures[22] gave the azide **23**. The structural assignment was confirmed by catalytic hydrogenation of **23** to methyl α-L-acosaminide (**24**).[23] The required inversion at C-4 was carried out smoothly in a sequence of reactions[24] involving mesylation of **23**, displacement reaction of the mesylate with sodium benzoate, and subsequent mild alkaline hydrolysis of the benzoate, without purification of intermediates. Hydrogenation of the resulting azide **25** over palladium catalyst yielded methyl α-L-daunosaminide (**26**), identical in all respects with authentic material.[7] Finally, hydrolysis of the methyl gly-

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coside with dilute hydrochloric acid gave crystalline daunosamine hydrochloride (1·HCl), identical with material obtained by the procedure of Horton and Weckerle.[8] The practicality of this synthesis has been substantiated by the preparation of large amounts of daunosamine derivatives.

Experimental Section

General. Melting points were taken in capillaries with a Thomas-Hoover melting point apparatus and are uncorrected. Proton magnetic resonance spectra were recorded on a Varian XL-100 or T-60 spectrometer with Me_4Si as internal reference (δ 0). Infrared spectra were obtained on a Beckman IR-9 or IR-12 spectrometer. The mass spectra were taken with a CEC 21-110 mass spectrometer at 70 eV using a direct insertion probe. Optical rotations were measured on a Perkin-Elmer polarimeter, Model 141. Analytical high-pressure liquid chromatography was carried out on a μ-Porasil column (300 × 4 mm) employing a Waters Associates Liquid Chromatograph equipped with a Model R401 differential refractometer, a Model 6000A solvent delivery system, and a Model U6K Universal injector. Preparative high-pressure liquid chromatography was performed on two Silica Prep-Pak 500 cartridges using a Waters Associates Prep LC 500. Silica Gel Merck 60 (70–230 mesh) was used for column chromatography. TLC was carried out on Merck precoated TLC plates Silica Gel 60, F-254; spots were visualized by spraying the plates with a 10% solution of sulfuric acid in ethanol or with a solution of 1,3-naphthalenediol in 2% ethanolic sulfuric acid followed by heating the plates at 100 °C. Pyridine was distilled from BaO and dimethoxyethane was distilled from CaH_2. Tetrahydrofuran was passed through a column of neutral alumina (Woelm, activity I) and 2-methylethanol was dried over $MgSO_4$. Methanol and DMF were stored over Linde 3-Å molecular sieves. Ion exchange resins were purchased from Bio-Rad Laboratories.

Mixture of 1-Nitro-1-deoxy-L-glucitol and 1-Nitro-1-deoxy-L-mannitol (5). To a slurry of 100 g (0.66 mol) of L-arabinose in 200 mL of anhydrous methanol and 360 mL of nitromethane was added in one portion a solution of 50 g (0.93 mol) of sodium methoxide in 600 mL of anhydrous methanol. The suspension was mechanically shaken for 50 h. The solids were then removed by filtration under a nitrogen blanket and the filter cake was washed with 2 × 200 mL of cold methanol. The wet solids were suspended in 500 mL of cold methanol, the suspension was shaken for 15 min and then filtered. The filter cake was washed successively with 100 mL of cold methanol and 100 mL of ether. The material was dissolved in 300 mL of deionized water, placed on a column of 700 g of ion exchange resin [AG 50W-X4 (H^+)], and eluted with ca. 1500 mL of water. The progress of the elution was monitored by TLC (plates were not developed). The eluate was concentrated under reduced pressure until precipitation occurred (ca. 300 mL). To the mixture was added 500 mL of 2B ethanol and the volume was concentrated again to approximately 300 mL. This procedure was repeated twice more. The final concentrate was stored overnight at 4 °C. The crystalline material was collected by filtration, washed with cold 2B ethanol until the filtrate was nearly colorless and subsequently with ether, and dried under a blanket of nitrogen to afford 86.4 g (61%) of the mixture **5**. This material was used for subsequent reactions without further purification.

Mixture of 2,3,4,5,6-Penta-*O*-acetyl-1-deoxy-1-nitro-L-glucitol and 2,3,4,5,6-Penta-*O*-acetyl-1-deoxy-1-nitro-L-mannitol (6). To a stirred suspension of 50 g (0.237 mol) of mixture **5** in 400 mL of acetic anhydride was added 4 mL of boron trifluoride etherate. After 30 min of stirring at room temperature, an additional 2 mL of boron trifluoride etherate was added, and the completion of the acetylation was checked by TLC (chloroform–acetone, 9:1). The clear solution was then added during 1 h to 1 L of stirred crushed ice with the occasional addition of more ice to keep the mixture at 0 °C. The mixture (ca. 3.5 L) was kept at 4 °C overnight. The precipiate was collected by filtration, washed thoroughly with water, and air-dried to afford 88.8 g (89%) of the mixture of acetates **6**. This material was of sufficient purity for subsequent reactions.

3,4,5,6-Tetra-*O*-acetyl-1,2-dideoxy-1-nitro-L-*arabino*-hex-1-enitol (7). A suspension of 100 g (0.24 mol) of pentaacetates **6** and 100 g of sodium bicarbonate in 800 mL of toluene was heated with mechanical stirring in an atmosphere of nitrogen for 2.5 h at 86 °C. Completion of the reaction was assured by HPLC analysis [toluene–ethyl acetate (8:2), flow rate 1 mL/min, t = 2.0 and 2.2 min for **7** and **6**, respectively]. The hot mixture was filtered and the filter cake was washed with 800 mL of hot toluene. The filtrate after storing overnight at 4 °C produced, in two crops, 84.3 g (98%) of crystalline, colorless 3,4,5,6-tetra-*O*-acetyl-1,2-dideoxy-1-nitro-L-*arabino*-hex-1-enitol (**7**), mp 102–106 °C, suitable for the next step.

A sample was recrystallized from absolute ethanol to yield pure **7**: mp 114–115 °C; $[\alpha]^{25}_D$ −33.8° (*c* 5.10, $CHCl_3$) [lit.[14] mp 115–116 °C; $[\alpha]^{28}_D$ −31.8° (*c* 5.0, $CHCl_3$)]; IR ($CHCl_3$) 1753 (CH_3COO), 1667 (C=C trans), 1538 and 1365 cm^{-1} (NO_2); NMR ($CDCl_3$) δ 2.02, 2.04, and 2.12 (4 s, 12 H, 4 OAc), 4.13, 4.22 (*AB*X, 2 H, J_{gem} = 12.5, $J_{5,6}$ = 4 and 2.5 Hz, CH_2OAc), 5.18 (m, 1 H, CH-5), 5.39 (dd, 1 H, $J_{3,4}$ = 2.5 and $J_{4,5}$ = 8.5 Hz, CH-4), 5.81 (dd, 1 H, $J_{2,3}$ = 4 and $J_{3,4}$ = 2.5 Hz, CH-3), 6.99, 7.09 (*AB*X, 2 H, J_{trans} = 13.5 Hz, CH-1 and CH-2).

3,4,5,6-Tetra-*O*-1,2-dideoxy-1-nitro-L-*arabino*-hexitol (8). A stirred solution of 10.0 g (27.6 mmol) of the olefin **7** in 600 mL of ethyl acetate was hydrogenated over 1 g of 10% palladium-on-carbon catalyst at room temperature and atmospheric pressure until a sharp decrease in the hydrogen uptake occurred. After removal of the catalyst by filtration through a bed of Celite filter aid, the filtrate was concentrated under reduced pressure to a clear colorless oil which crystallized upon standing. Recrystallization from 200 mL of ether yielded 7.8 g (78%) of white crystalline **8** sufficiently pure for the next step. For analytical purposes, crude **8** was purified by preparative HPLC with benzene–ethyl acetate (8:2) as the eluant at a flow rate of 250 mL/min. The eluate corresponding to the first peak was evaporated to dryness and the solid residue was recrystallized from benzene to afford analytically pure **8**: mp 91–92 °C; $[\alpha]^{25}_D$ −30.17° (*c* 2.5094, $CHCl_3$) [Lit.[14] mp 91–92 °C; $[\alpha]^{26}_D$ +29.4° (*c* 2.5, $CHCl_3$) for the D enantiomer]; IR ($CHCl_3$) 1750 (CH_3COO), 1560 and 1373 cm^{-1} (NO_2); NMR ($CDCl_3$) δ 2.05, 2.06, 2.07, and 2.15 (4 s, 12 H, 4 OAc), 2.23 (m, 2 H, CH_2-2), 4.13, 4.22 (*AB*X, 2 H, J_{gem} = 12.5, $J_{5,6vic}$ = 4 and 2.5 Hz, CH_2OAc), 4.38 (t, 2 H, J = 7.5 Hz, CH_2NO_2), 5.12, 5.24, 5.27 (3 m, 3 H, $J_{4,5vic}$ = 8.5 Hz, CH-3, 4, and 5).

Anal. Calcd for $C_{14}H_{21}NO_{10}$ (363.32): C, 46.28; H, 5.83; N, 3.86. Found: C, 46.42; H, 5.73; N, 3.79.

Methyl 2-Deoxy-α-L-*arabino*-hexopyranoside (10). A suspension of 56.5 g (0.16 mol) of **8** and 140 g (0.44 mol) of barium hydroxide octahydrate in 1.2 L of water was stirred at room temperature until solution was attained. Small amounts of insoluble material were removed by filtration through a bed of Celite filter aid. The resulting clear filtrate was added slowly from a dropping funnel into a stirred, ice-cold solution of 90 mL (1.63 mol) of concentrated sulfuric acid in 1.5 L of water at such a rate as to keep the temperature below 10 °C. The mixture was stirred at room temperature overnight and then 350 g of solid barium carbonate was added carefully in small portions to neutralize the reaction. Insoluble material was removed by filtration through Celite filter aid and the filtrate was concentrated to dryness under reduced pressure at 50 °C. To assure total dryness, azeotropically distilled toluene was added to and removed under reduced pressure from the residue several times. The clear viscous oil was dissolved in 1 L of anhydrous methanol, 15 mL of methanol-washed ion exchange resin (AG 50W-X4, H^+)[25] was added, and the mixture was stirred to room temperature under a blanket of nitrogen until glycosidation was complete (ca. 5 days, TLC analysis with chloroform–methanol–acetic acid, 95:25:2). The resin was removed by filtration and the clear filtrate was passed through a column of 200 g of basic alumina (Woelm W200). The column was washed thoroughly with methanol. The combined eluate was concentrated to dryness under reduced pressure to afford 23.9 g (86%) of a liquid mixture of methyl glycosides **10** and **11**; NMR ($CDCl_3$ + Me_2SO-d_6) singlets for OCH_3 at δ 3.18 (major **10**) and 3.38 (minor, **11**). The mixture was dissolved in 100 mL of acetone and the solution was kept at 4 °C for 7 days. The crystalline precipitate was collected by filtration and washed with acetone to afford 8.2 g of methyl 2-deoxy-α-L-*arabino*-hexopyranoside (**10**)

(25) O'Connor, S.; Lam, L. K. T.; Jones, N. D.; Chaney, M. O. *J. Org. Chem.* **1976**, *41*, 2087.

in large colorless plates: mp 89–91 °C; $[\alpha]^{25}_D$ −132.63° (*c* 0.9922, H_2O); [lit.[17] mp 91–92 °C; $[\alpha]^{22}_D$ +137.9° (H_2O) for the D enantiomer]; NMR (Me_2SO-d_6) δ 1.42, 1.85 (2 ddd, 2 H, J_{gem} = 12.5, $J_{1,2ax}$ = 3.5, $J_{1,2eq} \simeq 1$, $J_{2ax,3}$ = 11.5, $J_{2eq,3}$ = 5 Hz, CH_2-2), 2.99 (dt, 1 H, J_{CHOH} = 5 and $J_{3,4} = J_{4,5}$ = 9 Hz, CH-4), 3.18 (s, 3 H, OCH_3), 3.20–3.60 (m, 4 H, CH-3, CH-5, and CH_2-6), 4.30 (t, 1 H, *J* = 6 Hz, C_6-O*H*), 4.61, 4.71 (2 d, 2 H, J_{CHOH} = 5 Hz, 2 OH), 4.63 (d, 1 H, $J_{1,2ax}$ = 3.5 Hz, CH-1).

Anal. Calcd for $C_7H_{14}O_5$ (178.18): C, 47.18; H, 7.92. Found: C, 47.11, H, 8.02.

The mother liquor was evaporated to dryness, dissolved in anhydrous methanol, treated with anion exchange resin, and filtered through basic alumina. Crystallization of the concentrated eluate from acetone produced additional **10**. This procedure was repeated several times until the mixture of **10** and **11** was completely transformed into crystalline **10**.

Methyl 2-Deoxy-α-L-*arabino*-hexopyranoside 6-*p*-Toluenesulfonate (12). To a stirred, ice-cold solution of 1.4 g (7.9 mmol) of **10** in 10 mL of anhydrous pyridine was added slowly in an atmosphere of nitrogen a solution of 1.5 g (8 mmol) of freshly recrystallized[26] tosyl chloride. The resulting clear colorless solution was allowed to stand under refrigeration overnight. After removal of the solvent at 30 °C and reduced pressure, traces of pyridine were removed by three times adding toluene to and removing from the residue. The crude tosylate **12** was chromatographed on 200 g of silica gel with toluene–ethyl acetate (1:1) as the eluant. Fractions of approximately 10 mL were collected and the progress of the chromatography was monitored by TLC (toluene–ethyl acetate, 1:1). Fractions 100–250 were combined and removal of the solvent afforded 1.94 g (74%) of a clear colorless oil which crystallized upon standing to give pure **12**: mp 115–116 °C (after recrystallization from ether); $[\alpha]^{25}_D$ −92.38° (*c* 1.0165, CH_3OH); IR ($CHCl_3$) 3600 (OH), 1364, 1176 cm^{-1} (SO_2); NMR ($CDCl_3$) δ 1.64, 2.10 (2 ddd, 2 H, J_{gem} = 12.5, $J_{1,2ax}$ = 3.5, $J_{1,2eq} \simeq 1$, $J_{2ax,3}$ = 11.5, $J_{2eq,3}$ = 5 Hz, CH_2-2), 2.45 (s, 3 H, CH_3-C_6H_4), 2.82, 3.17 (br, 2 H, 2 OH), 3.27 (s, 3 H, OCH_3), 3.38 (t, 1 H, $J_{3,4} = J_{4,5}$ = 9 Hz, CH-4), 3.65, 3.90 (2 m, 2 H, CH-3 and CH-5), 4.23, 4.37 (*ABX*, 2 H, J_{gem} = 11, $J_{5,6vic}$ = 2 and 4 Hz, CH_2-6), 4.72 (d, 1 H, $J_{1,2ax}$ = 3.5 Hz, CH-1), 7.35, 7.81 (AA′BB′, 4 H, J_0 = 9 Hz, CH_3-C_6H_4).

Anal. Calcd for $C_{14}H_{20}O_7S$ (332.37): C, 50.59; H, 6.07. Found: C, 50.69; H, 6.04.

Tosylation of an anomeric mixture of **10** and **11** under conditions described above gave a mixture of tosylates (4 g) which were separated on 4 g of silica gel (ether–methanol, 98:2) to give 1.2 g of the α-anomer **12** and 127 mg of a clear colorless oil. Crystallization of this material from ether afforded pure methyl 2-deoxy-β-L-*arabino*-hexopyranoside 6-*p*-toluenesulfonate: mp 113–114 °C, $[\alpha]^{25}_D$ +22.75° (*c* 0.9936, CH_3OH); IR ($CHCl_3$) 3590 (OH), 1365 and 1178 cm^{-1} (SO_2); NMR ($CDCl_3$) δ 1.56, 2.19 (2 ddd, 2 H, J_{gem} = 12.5, $J_{1,2ax}$ = 10, $J_{1,2eq}$ = 2, $J_{2ax,3}$ = 11.5, $J_{2eq,3}$ = 5 Hz, CH_2-2), 2.44 (s, 3 H, CH_3-C_6H_4), 2.86, 3.23 (2 s, 2 H, 2 OH), 3.30–3.70 (m, 3 H, CH-4, 5, and 6), 3.41 (s, 3 H, OCH_3), 4.28 (dd, 1 H, $J_{1,2ax}$ = 10, $J_{1,2eq}$ = 2 Hz, CH-1), 4.31 (m, 2 H, CH_2-6), 7.34, 7.81 (AA′BB′, 4 H, J_0 = 8.5 Hz, CH_3-C_6H_4).

Anal. Calcd for $C_{14}H_{20}O_7S$ (332.37): C, 50.59; H, 6.07. Found: C, 50.34; H, 6.05.

Methyl 2,6-Dideoxy-α-L-*arabino*-hexopyranoside (13). A. To a stirred solution of 7.7 g (23.2 mmol) of **12** in 250 mL of anhydrous tetrahydrofuran was added under a blanket of nitrogen 2.6 g (68.5 mmol) of lithium aluminum hydride. After stirring the mixture at room temperature for 70 h excess hydride was destroyed by carefully adding 100 mL of ethyl acetate and subsequently 80 mL of water to the ice-cold, stirred mixture. The pH of the mixture was then adjusted to 6 by the addition of 5 N hydrochloric acid and the precipitate was removed by filtration through Celite filter aid. The filtrate was passed through a column of 200 mL of ion exchange resin (AG 501-X8). The column was washed with 200 mL of water and the combined eluate was evaporated to dryness under reduced pressure. The residue was taken up in dichloromethane and after drying over magnesium sulfate the organic solution was concentrated to a clear oil under reduced pressure. Distillation in a Büchi Kugelrohrofen apparatus at 92 °C (oven temperature) and at 0.05 mmHg afforded 2.22 g (59%) of **13**: $[\alpha]^{25}_D$ −142.21° (*c* 1.3607, $CHCl_3$) [lit.[18] bp 70–80 °C (0.01 mmHg); $[\alpha]^{25}_D$ −152.5° (*c* 0.7, acetone)]; IR ($CHCl_3$) 3590, 3400 (OH), 1235 cm^{-1} (OCH_3); NMR ($CDCl_3$) δ 1.27 (d, 3 H, *J* = 7 Hz, CH_3-6), 1.65, 2.11 (2 ddd, 2 H, J_{gem} = 12.5, $J_{1,2ax}$ = 3.5, $J_{1,2eq} \simeq 1$, $J_{2ax,3}$ = 11.5, $J_{2eq,3}$ = 5 Hz, CH_2-2), 3.05 (t, 1 H, $J_{3,4} = J_{4,5}$ = 9 Hz, CH-4), 3.31 (s, 3 H, OCH_3), 3.80 (s, 2 H, 2 OH), 3.60 (dq, 1 H, $J_{4,5}$ = 9, $J_{5,6}$ = 7 Hz, CH-5), 3.85 (m, 1 H, CH-3), 4.72 (d, 1 H, $J_{1,2ax}$ = 3.5 Hz, CH-1).

Anal. Calcd for $C_7H_{14}O_4$ (162.19): C, 51.84; H, 8.70. Found: C, 51.69; H, 8.68.

An anomeric mixture of tosylates was reduced as described above. Distillation of the crude product in a short-path distillation apparatus at 90 °C (oil bath temperature) and 0.07 mmHg afforded an 82:18 mixture of the α-anomer **13** and the β-anomer **15**, respectively, as a clear oil. In the NMR ($CDCl_3$) the following peaks were assigned to the minor anomer **15**: δ 1.33 (d, 3 H, *J* = 7 Hz, CH_3-6), 3.48 (s, 3 H, OCH_3), 4.28 (dd, 1 H, $J_{1,2ax}$ = 10, $J_{1,2eq}$ = 2 Hz, CH-1_{eq}).

B. To an ice-cold solution of 10 g (56 mmol) of **10** and 25 g (112 mmol) of *N*-iodosuccinimide in 200 mL of anhydrous dimethylformamide was added under a stream of nitrogen 30 g (114 mmol) of triphenylphosphine in portions of ca. 5 g each. Additions were made after the previous one was completely dissolved. After completed addition, the mixture was heated at 50 °C for 1 h and subsequently evaporated to dryness at 30 °C under reduced pressure to afford a dark, oily residue, consisting mainly of methyl 2,6-dideoxy-6-iodo-α-L-*arabino*-hexopyranoside (**14**). The crude material was taken up in 500 mL of methanol, 50 mL of methanol-washed Raney nickel was added, and the stirred mixture was heated at reflux temperature. The progress of the reaction was monitored by TLC analysis ($CHCl_3$–CH_3OH–HOAc, 95:25:2) in 1-h intervals, and additional portions (50 mL) of Raney nickel were added until all starting material was reduced. After removal of the catalyst by filtration through Celite filter aid, the filtrate was concentrated and chromatographed on 1 kg of silica gel (chloroform–methanol, 9:1) to give, after distillation in a Büchi Kugelrohrofen apparatus at 100–110 °C (0.05 mm), 5.6 g (62%) of pure liquid **13**.

Methyl 2,6-Dideoxy-α-L-*arabino*-hexopyranoside 3-*p*-Toluenesulfonate (16). When the procedure for the preparation of **12** was followed, 4.8 g (29.5 mmol) of **13** was tosylated with 5.7 g (30 mmol) of *p*-toluenesulfonyl chloride.[26] Chromatography on 750 g of silica gel (toluene–ethyl acetate, 7:3) yielded 2.2 g (16%) of liquid methyl 2,6-dideoxy-α-L-*arabino*-hexopyranoside 3,4-di-*p*-toluenesulfonate (**18**), NMR ($CDCl_3$) 1.23 (d, 3 H, *J* = 7 Hz, CH_3-6), 2.43 (s, 6 H, 2 CH_3-C_6H_4), 3.23 (s, 3 H, OCH_3), and 4.8 g (51%) of **16** as a clear viscous oil which crystallized on standing. A portion (900 mg) was dissolved in 200 mL of boiling pentane, 10 mL of ether was added, and the mixture was concentrated to 50 mL by boiling on the steam bath. The solution was kept at room temperature for 24 h and the crystalline precipitate was collected by filtration to give analytically pure **16**: mp 84–85 °C; $[\alpha]^{25}_D$ −108.78° (*c* 1.0075, $CHCl_3$); IR ($CHCl_3$) 3620, 3520 (OH), 1360, 1175 cm^{-1} (SO_2); NMR ($CDCl_3$) δ 1.30 (d, 3 H, *J* = 6 Hz, CH_3-6), 1.79 (ddd, 1 H, J_{gem} = 12.5, $J_{1,2ax}$ = 3.5, $J_{2ax,3}$ = 11.5 Hz, CH_2-2, axial H), 2.09 (m, 1 H, J_{gem} = 12.5, $J_{1,2eq} \simeq 1$ Hz, $J_{2eq,3}$ = 5.5 Hz, CH_2-2, equatorial H), 2.46 (s, 3 H, CH_3-C_6H_4), 2.55 (d, 1 H, *J* = 3.5 Hz, C_4-OH), 3.27 (s, 3 H, OCH_3), 3.28 (dt, 1 H, J_{CHOH} = 3.5, $J_{3,4} = J_{4,5}$ = 9 Hz, CH-4), 3.73 (dq, 1 H, $J_{4,5}$ = 9, $J_{5,6}$ = 6 Hz, CH-5), 4.66 (d, 1 H, $J_{1,2ax}$ = 3.5 Hz, CH-1), 4.74 (ddd, 1 H, $J_{2ax,3}$ = 11.5, $J_{2eq,3}$ = 5.5, $J_{3,4}$ = 9 Hz, CH-3), 7.36 7.83 (AA′BB′, 4 H, J_0 = 8.5 Hz, CH_3-C_6H_4).

Anal. Calcd for $C_{14}H_{20}O_6S$ (316.36): C, 53.15; H, 6.37. Found: C, 53.30; H, 6.58.

The next 600 mL of eluate yielded 1.3 g (14%) of **17**. Crystallization from ether gave pure methyl 2,6-dideoxy-α-L-*arabino*-hexopyranoside 4-*p*-toluenesulfonate (**17**): mp 127–128 °C; $[\alpha]^{25}_D$ −109.94° (*c* 0.9887, $CHCl_3$), IR ($CHCl_3$) 3430 (OH), 1360, 1175 cm^{-1} (SO_2); NMR ($CDCl_3$) δ 1.14 (d, 3 H, *J* = 6 Hz, CH_3-6), 1.69 (ddd, 1 H, J_{gem} = 13, $J_{1,2ax}$ = 3.5, $J_{2ax,3}$ = 11.5, CH_2-2, axial H), 2.22 (m, 1 H, J_{gem} = 13, $J_{1,2eq} \simeq 1$, $J_{2eq,3}$ = 5.5 Hz, CH_2-2, equatorial H), 2.44 (s, 3, CH_3-C_6H_4), 2.86 (d, 1 H, *J* = 4 Hz, C_3-OH), 3.26 (s, 3 H, OCH_3), 3.72 (dq, 1 H, $J_{4,5}$ = 9, $J_{5,6}$ = 6 Hz, CH-5), 4.10 (m, 2 H, CH-3 and CH-4), 4.68 (d, 1 H, $J_{1,2ax}$ = 3.5 Hz, CH-1),

(26) Fieser, L. F.; Fieser, M. "Reagents for Organic Synthesis"; Wiley: New York, 1967; Vol. I, p 1179.

7.36, 7.83 (AA'BB', 4 H, J_0 = 8.5 Hz, CH_3-C_6H_4).

Anal. Calcd for $C_{14}H_{20}O_6S$ (316.36): C, 53.15; H, 6.37. Found: C, 52.95; H, 6.19.

Methyl 3,4-Anhydro-2,6-dideoxy-α-L-*ribo*-hexopyranoside (4). A. To a solution of 4.8 g (15 mmol) of **16** in 250 mL of anhydrous methanol was added 20 mL of freshly prepared, methanol-washed ion exchange resin[21] (AG1-X4, OH^-). The suspension was stirred at ambient temperature under a blanket of nitrogen for 2 h. The resin was removed by filtration through Celite Filter Aid and the filtrate was evaporated to dryness under reduced pressure to afford 1.9 g (87%) of **4** as a clear liquid of sufficient purity to be used for subsequent reactions. For analysis, a sample was purified by bulb-to-bulb distillation in a Büchi Kugelrohrofen apparatus: bp 50–60 °C (oven temperature) at 0.05 mm; $[\alpha]^{25}_D$ −126.01° (*c* 1.0317, $CHCl_3$); IR ($CHCl_3$) 3010, 1240 cm^{-1} (epoxide); NMR ($CDCl_3$) δ 1.46 (d, 3 H, *J* = 7 Hz, CH_3-6), 2.09, 2.11 (2 d, 2 H, J_{vic} = 3.5 and 4 Hz, CH_2-2); 2.98 (d, 1 H, $J_{3,4}$ = 4.5 Hz, CH-4), 3.24 (m, 1 H, CH-3), 3.31 (s, 3 H, OCH_3), 4.12 (q, 1 H, *J* = 7 Hz, CH-5), 4.60 (dd, 1 H, J_{vic} = 3.5 and 4 Hz, CH-1); mass spectrum, *m/e* (relative intensity) 143 (1), 113 (59), 100 (25), 88 (30), 85 (28), 84 (31), 83 (15), 71 (50), 55 (42), 45 (50), 41 (100); TLC (toluene–ethyl acetate, 1:1) R_f 0.24.

Anal. Calcd for $C_7H_{12}O_3$ (144.17): C, 58.32; H, 8.39. Found: C, 58.42; H, 8.42.

B. To a stirred solution of 7 g (14.4 mmol) of methyl 2-deoxy-α-L-*arabino*-hexopyranoside 3,6-di-*p*-toluenesulfonate (**20**) in 150 mL of anhydrous 1,2-dimethoxyethan was added 2.5 g (66 mmol) of sodium borohydride. The suspension was heated in an argon atmosphere at 90–95 °C for 2 days; the reaction was monitored by TLC (toluene–ethyl acetate, 1:1). After removal of the solids by filtration through a bed of Celite filter aid, the filtrate was concentrated to 20 mL under reduced pressure at 30 °C. The residue was diluted with 100 mL of methylene chloride and the organic phase was washed with 100 mL of brine. The brine solution was backwashed with methylene chloride and the combined organic solution, after drying over Na_2SO_4, was evaporated under reduced pressure to yield 4.1 g (90%) of crude methyl 2,6-dideoxy-α-L-*arabino*-hexopyranoside 3-*p*-toluenesulfonate (**16**). This material was combined with 2.7 g of **16** obtained similarly from 6 g of **20** and dissolved in 100 mL of anhydrous methanol. To the solution was added 25 mL of methanol-washed ion exchange resin (AG1-X4, OH^-) and the mixture was stirred in an argon atmosphere overnight. Removal of the resin by filtration and evaporation of the filtrate to dryness under reduced pressure at 30 °C afforded 3.3 g (86%) of **4** of sufficient purity for further reactions.

Methyl 3,4-Anhydro-2,6-dideoxy-α-L-*lyxo*-hexopyranoside (19). Base treatment of the 4-tosylate **17** under conditions described above for **16** gave liquid **19**: NMR ($CDCl_3$ δ 1.34 (d, 3 H, *J* = 7 Hz, CH_3-6), 3.33 (s, 3 H, OCH_3). TLC (toluene–ethyl acetate, 1:1) R_f 0.31.

Tosylation of Methyl 2-Deoxy-α-L-*arabino*-hexopyranoside (10). When the procedure described for **12** was followed, 10 g (56.2 mmol) of **10** was tosylated with 22 g (115 mmol) of *p*-toluenesulfonyl chloride.[26] The crude reaction products were dissolved in 100 mL of toluene and separated by preparative HPLC at a flow rate of 250 mL/min. The separation was monitored by using a differential refractometer. Elution with ca. 3500 mL of a solvent mixture of toluene–ethyl acetate (9:1) afforded 4.4 g (12%) of methyl 2-deoxy-α-L-*arabino*-hexopyranoside 3,4,6-tri-*p*-toluenesulfonate (**22**) and subsequently 13.8 g (50.5%) of methyl 2-deoxy-α-L-*arabino*-hexopyranoside 3,6-di-*p*-toluenesulfonate (**20**). Both compounds were obtained as clear colorless oils which crystallized on standing. Analytical specimens were prepared by recrystallization from ether.

Compound **22**: mp 105–106 °C; $[\alpha]^{25}_D$ −90.19° (*c* 1.0622, $CHCl_3$); IR ($CHCl_3$) 1367, 1190 and 1178 cm^{-1} (SO_2); NMR ($CDCl_3$) δ 1.73 (ddd, 1 H, J_{gem} = 13, $J_{1,2ax}$ = 3.5, $J_{2ax,3}$ = 10.5 Hz, CH_2-2, axial H), 2.16 (ddd, 1 H, J_{gem} = 13, $J_{1,2eq}$ = 1.5, $J_{2eq,3}$ = 5 Hz, CH_2-2, equatorial H), 2.42 (s, 9 H, 3CH_3-C_6H_4), 3.21 (s, 3 H, OCH_3), 3.84 (ddd, 1 H, $J_{4,5}$ = 9, $J_{5,6}$ = 2 and 6.5 Hz, CH-5), 4.02, 4.34 (2 dd, 2 H, J_{gem} = 10.5, $J_{5,6}$ = 6.5 and 2 Hz, CH_2-6), 4.47 (t, 1 H, $J_{3,4}$ = $J_{4,5}$ = 9 Hz, CH-4), 4.61 (dd, 1 H, $J_{1,2ax}$ = 3.5, $J_{1,2eq}$ 1.5 Hz, CH-1), 4.76 (ddd, 1 H, $J_{2ax,3}$ = 10.5, $J_{2eq,3}$ = 5, $J_{3,4}$ = 9 Hz, CH-3), 7.26, 7.65; 7.32, 7.74, 7.32, 7.77 (3 AA'BB', 12 H, J_0 = 8.5 Hz, 3CH_3-C_6H_4).

Anal. Calcd for $C_{28}H_{32}O_{11}S_3$ (640.73): C, 52.49; H, 5.03. Found: C, 52.33; H, 5.04.

The 3,6-ditosylate **20** crystallized as the monohydrate: mp 104–114 °C; $[\alpha]^{25}_D$ −74.40° (*c* 1.0134, $CHCl_3$); IR ($CHCl_3$) 3605, 3520 (OH, H_2O), 1360, 1175 cm^{-1} (SO_2); NMR ($CDCl_3$) δ 1.72 (ddd, 1 H, J_{gem} = 13, $J_{1,2ax}$ = 3.5, $J_{2ax,3}$ = 10.5 Hz, CH_2-2, axial H), 2.04 (ddd, 1 H, J_{gem} = 13, $J_{1,2eq}$ = 1.5, $J_{2eq,3}$ = 5 Hz, CH_2-2, equatorial H), 2.43 (s, 6 H, 2 CH_3-C_6H_4), 2.91 (d, 1 H, *J* = 4 Hz, C_4-OH), 3.22 (s, 3 H, OCH_3), 3.55, 3.70 (2 m, 2 H, CH-4, CH-5), 4.27 (m, 2 H, CH_2-6), 4.67 (d, 1 H, $J_{1,2ax}$ = 3.5 Hz, CH-1), 4.75 (m, 1 H, CH-3), 7.33, 7.78 (2 AA'BB', 8 H, 2 CH_3-C_6H_4).

Anal. Calcd for $C_{21}H_{26}O_9S_2$·H_2O (504.57): C, 49.99; H, 5.59; S, 12.71; H_2O, 3.56. Found: C, 49.91; H, 5.63; S, 12.98; H_2O, 3.54.

The chromatography was continued with 2000 mL of toluene–ethyl acetate (1:1) to afford 3.2 g (12%) of **21** as a clear colorless oil which crystallized on standing. A sample was recrystallized from ethyl acetate–ether to give analytically pure methyl 2-deoxy-α-L-*arabino*-hexopyranoside 4,6-di-*p*-toluenesulfonate (**21**): mp 125–127 °C; $[\alpha]^{15}_D$ −94.85° (*c* 0.9309, $CHCl_3$); IR ($CHCl_3$) 3520 (OH), 1368, 1190, 1178 cm^{-1} (SO_2); NMR ($CDCl_3$) δ 1.62 (ddd, 1 H, J_{gem} = 13, $J_{1,2ax}$ = 3.5, $J_{2ax,3}$ = 10.5 Hz, CH_2-2, axial H), 2.16 (ddd, 1 H, J_{gem} = 13.5, $J_{1,2eq} \simeq 1$, $J_{2eq,3}$ = 5 Hz, CH-2, equatorial H), 2.44, 2.46 (2 s, 6 H, 2 CH_3-C_6H_4), 2.94 (d, 1 H, *J* = 3 Hz, C_3-OH), 3.21 (s, 3 H, OCH_3), 3.69 (ddd, 1 H, $J_{4,5}$ = 9, $J_{5,6}$ = 2 and 6.5 Hz, CH-5), 3.98, 4.34 (2 dd, 2 H, J_{gem} = 10.5, $J_{5,6}$ = 6.5 and 2 Hz, CH_2-6), 4.05 (m, 1 H, CH-3), 4.30 (t, 1 H, $J_{3,4}$ = $J_{4,5}$ = 9 Hz, CH-4), 4.65 (d, 1 H, $J_{1,2ax}$ = 3.5 Hz, CH-1), 7.31, 7.75, 7.34, 7.78 (2 AA'BB', 8 H, J_0 = 8.5 Hz, 2 $CH_3C_6H_4$).

Anal. Calcd for $C_{21}H_{26}O_9S_2$ (486.55): C, 51.84; H, 5.39; S, 13.18. Found: C, 51.79; H, 5.46; S, 13.37.

Finally, 1500 mL of ethyl acetate eluted 2.6 g (14%) of methyl 2-deoxy-α-L-*arabino*-hexopyranoside 6-*p*-toluenesulfonate (**12**): mp 114–116 °C; identical with material obtained previously.

Detosylation of Methyl 2-Deoxy-α-L-*arabino*-hexopyranoside 3,4,6-Tris(*p*-toluenesulfonate) (22). To a solution of 13.7 g of sodium in 500 mL of liquid ammonia was added over a period of 45 min a solution of 12 g of **22** in 80 mL of anhydrous tetrahydrofuran. The mixture was stirred and the reaction was then quenched by adding sodium ammonium chloride. After evaporation of the ammonia, the residue was treated with 2-methoxyethanol and the mixture was centrifuged. The clear supernatant was concentrated to dryness, the residue was treated with acetone, and the slurry was centrifuged. The concentrated supernatant was chromatographed on 500 g of silica gel ($CHCl_3$-CH_3OH, 9:1) to afford 1.4 g (42%) of methyl 2-deoxy-α-L-*arabino*-hexopyranoside (**10**), identical in all respects with an authentic sample.

Methyl 2,3,6-Trideoxy-3-azido-α-L-*arabino*-hexopyranoside (23). To a solution of 1.9 g (13.2 mmol) of **4** in 40 mL of 2-methoxyethanol was added 0.0025 mL of water, 1.2 g (22.4 mmol) of ammonium chloride, and 2.6 g (40 mmol) of sodium azide. The stirred mixture was heated at 100 °C in a nitrogen atmosphere for 2 h, the reaction progress being monitored by TLC (toluene–ethyl acetate, 1:1). After the reaction mixture was cooled to room temperature, the solvent was removed at 40 °C (0.1 mm). The residue was extracted three times with acetone. The combined extracts were evaporated to dryness under reduced pressure; chromatography of the liquid residue (3 g) on 300 g of silica gel (toluene–ethyl acetate, 8:2) afforded 2.0 g (81%) of **23** as a clear liquid, suitable for subsequent reactions. Further purification by distillation in a short-path distillation apparatus yielded analytically pure **23**: bp 60–65 °C (bath temperature), 0.05 mm; $[\alpha]^{25}_D$ −120.03° (*c* 1.2697, $CHCl_3$) [lit.[23] $[\alpha]^{25.5}_D$ −131.8° (*c* 0.5, $CHCl_3$)]; IR ($CHCl_3$) 3625, 3600 (OH), 2105 (N_3), 1127 cm^{-1} (OCH_3); NMR ($CDCl_3$) δ 1.29 (d, 3 H, *J* = 7 Hz, CH_3-6), 1.70 (ddd, 1 H, J_{gem} = 13, $J_{1,2ax}$ = 3.5, $J_{2ax,3}$ = 12 Hz, CH_2-2, axial H), 2.16 (ddd, 1 H, J_{gem} = 13, $J_{1,2eq} \simeq 1$, $J_{2eq,3}$ = 5 Hz, CH_2-2, equatorial H), 2.26 (d, 1 H, *J* = 3 Hz, C_4-OH), 3.11 (dt, 1 H, $J_{3,4}$ = $J_{4,5}$ = 9.5, $J_{4,OH}$ = 3 Hz, CH-4), 3.32 (s, 3 H, OCH_3), 3.68 (dq, 1 H, $J_{4,5}$ = 9.5, $J_{5,6}$ = 7 Hz, CH-5), 3.75 (m, 1 H, CH-3), 4.72 (d, 1 H, $J_{1,2ax}$ = 3.5 Hz, CH-1).

Anal. Calcd for $C_7H_{13}N_3O_3$ (187.19): C, 44.91; H, 7.00; N, 22.45. Found: C, 44.67; H, 7.08; N, 22.80.

Methyl 3-Amino-2,3,6-trideoxy-α-L-*arabino*-hexopyranoside (Methyl Acosaminide, 24). A mixture of 200 mg of **23** and 100 mg of 10% palladium-on-carbon catalyst in 50 mL

of methanol was hydrogenated at room temperature in a Parr apparatus at 3 atm for 15 h. The catalyst was removed by filtration and the solvent was evaporated under reduced pressure. Sublimation of the residue at 60 °C (0.5 mm) afforded crystalline **24**: mp 130–131 °C; $[\alpha]^{25}_D$ −144.96° (*c* 0.502, CH_3OH) [lit.[23] mp 132–133 °C, $[\alpha]^{26}_D$ −145.1° (*c* 0.61, CH_3OH)]; IR (KBr) 3335, 3290 cm^{-1} (NH_2); NMR ($CDCl_3$) δ 1.28 (d, J = 7 Hz, CH_3-6), 1.50, 1.98 (2 ddd, 2 H, J_{gem} = 13, $J_{1,2ax}$ = 3.5, $J_{1,2eq} \simeq 1$, $J_{2ax,3}$ = 11.5, $J_{2eq,3}$ = 4.5 Hz, CH_2-2), 1.94 (s, 3 H, OH and NH_2), 2.84 (t, 1 H, $J_{3,4}$ = $J_{4,5}$ = 9 Hz, CH-4), 2.97 (m, 1 H, CH-3), 3.32 (s, 3 H, OCH_3), 3.61 (dq, 1 H, $J_{4,5}$ = 9, $J_{5,6}$ = 7 Hz, CH-5), 4.67 (d, 1 H, $J_{1,2ax}$ = 3.5 Hz, CH-1).

Anal. Calcd for $C_7H_{15}NO_3$ (161.21): C, 52.16; H, 9.38; N, 8.69. Found: C, 52.24; H, 9.60; N, 8.81.

Methyl 3-Azido-2,3,6-trideoxy-α-L-*lyxo*-hexopyranoside (25). To a stirred solution of 277 mg (1.48 mmol) of **23** in 6 mL of anhydrous pyridine was added at 0 °C 0.55 mL (71 mmol) of methanesulfonyl chloride. The reaction mixture was allowed to stir at 0 °C for 6 h and subsequently poured onto 15 mL of crushed ice. The mixture was stirred until all the ice had melted and then extracted three times with 20 mL of ethyl acetate. The combined extract was washed successively with 1 N HCl, saturated $NaHCO_3$, and brine. The organic phase was dried over $MgSO_4$ and evaporated to dryness under reduced pressure to afford 330 mg of crystalline methyl 3-azido-2,3,6-trideoxy-α-L-*arabino*-hexopyranoside 4-methanesulfonate. A solution of this material and 540 mg of sodium benzoate in 25 mL of anhydrous dimethylformamide was heated at 135 °C under a blanket of nitrogen for 28 h. The solvent was removed at 45 °C (0.1 mm) and the residue was extracted six times with chloroform. The combined extract was concentrated and the residue was chromatographed on 33 g of silica gel (benzene–ethyl acetate, 9:1) to give 170 mg of methyl 3-azido-2,3,6-trideoxy-α-L-*lyxo*-hexopyranoside 4-benzoate. The benzoate was dissolved in 10 mL of a 0.1 N sodium hydroxide solution in methanol–water (4:1) and the solution was stirred at room temperature under a stream of nitrogen for 6.5 h. After removal of the solvent under reduced pressure, the residue was extracted four times with acetone. The combined organic solution was filtered; concentration of the filtrate under reduced pressure gave 127 mg (46%) of liquid **25** after distillation in a short-path distillation apparatus: bp 55–60 °C (bath temperature), 0.05 mm; $[\alpha]^{25}_D$ −145.29° (*c* 0.9099, $CHCl_3$); IR ($CHCl_3$) 3580 (OH) 2105 cm^{-1} (N_3); NMR ($CDCl_3$) δ 1.27 (d, 3 H, J = 7 Hz, CH_3-6), 1.80–2.20 (m, 3 H, CH_2-2 and OH), 3.33 (s, 3 H, OCH_3), 3.60–3.80 (m, 2 H, CH-3 and CH-4), 3.87 (q, 1 H, J = 7 Hz, CH-5), 4.80 (d, 1 H, J = 3.5 Hz, CH-1); mass spectrum, m/e (relative intensity) 187 (1), 156 (17), 145 (2), 129 (20), 113 (6), 150 (9), 86 (40), 72 (31), 69 (46), 58 (100), 45 (60), 43 (45).

Anal. Calcd for $C_7H_{13}N_3O_3$ (187.2): C, 44.91; H, 7.00; N, 22.45. Found: C, 44.84; H, 7.18; N, 22.67.

Methyl 3-Amino-2,3,6-trideoxy-α-L-*lyxo*-hexopyranoside (Methyl Daunosaminide, 26). To a solution of 185 mg (1 mmol) of **25** in 5 mL of methanol was added 300 mg of platinum oxide. The mixture was hydrogenated at room temperature and atmospheric pressure until the hydrogen uptake ceased. The catalyst was removed by filtration through Celite filter aid and the filtrate was evaporated to dryness under reduced pressure. Sublimation of the white solid residue at 50–60 °C (0.05 mg) afforded 146 mg (92%) of **26**. Recrystallization from ether gave analytically pure **26**: mp 110–112 °C; $[\alpha]^{25}_D$ −161.01° (*c* 1.0024, H_2O), $[\alpha]^{25}_D$ −173.79° (*c* 0.8274, $CHCl_3$) [lit.[7] mp 109–110 °C, $[\alpha]^{25}_D$ −210 ($CHCl_3$)]; IR ($CHCl_3$) 3580 (OH), 1122, 1050, 978 cm^{-1} (OCH_3); NMR ($CDCl_3$) δ 1.27 (d, 3 H, J = 7 Hz, CH_3-6), 1.68 (m, 5 H, CH_2-2, NH_2 and OH), 3.23, 3.38 (2 m, 2 H, CH-4 and CH-3), 3.32 (s, 3 H, OCH_3), 3.84 (q, 1 H, $J_{5,6}$ = 7 Hz, CH-5), 4.71 (t, 1 H, J_{vic} = 2.5 Hz, CH-1); mass spectrum, m/e (relative intensity) 143 (4), 104 (17), 86 (47), 72 (60), 59 (100), 44 (95).

Anal. Calcd for $C_7H_{15}NO_3$ (161.20): C, 52.16; H, 9.38; N, 8.69. Found: C, 52.15; H, 9.43; N, 8.60.

3-Amino-2,3,6-trideoxy-L-*lyxo*-hexose Hydrochloride (Daunosamine Hydrochloride, 1·HCl). A solution of 7 mg of **26** in 1 mL of 0.5 N hydrochloric acid was kept at room temperature for 18 h and subsequently heated at 80 °C for 2.5 h. Removal of the solvent under reduced pressure yielded 6 mg (75%) of daunosamine hydrochloride. Recrystallization from acetone afforded analytically pure **1**·HCl: mp 173 °C; $[\alpha]^{25}_D$ −59.94° (*c* 1.0510, H_2O) [lit.[8] 168–170 °C; $[\alpha]^{25}_D$ −65.4° (*c* 1.3, H_2O)]; IR (KBr) 3360 (OH), 2920, 2005 cm^{-1} (N^+H_3); NMR (Me_2SO-d_6) δ 1.08 (d, 3 H, J = 7 Hz, CH_3-6), 1.70 (m, 2 H, CH_2-2), 3.50, 3.56 (m, 2 H, CH-3 and CH-4), 3.96 (q, 1 H, J = 7 Hz, CH-5), 5.14 (br s, 1 H, CH-1), 5.27, 6.27 (b, 2 H, 2 OH), 8.08 (b, 3 H, N^+H_3); mass spectrum, m/e (relative intensity) 148 (1), 103 (2), 90 (45), 72 (90), 59 (60), 44 (100).

Anal. Calcd for $C_6H_{13}NO_3$·HCl (183.64): C, 39.24; H, 7.68; N, 7.63. Found: C, 39.09; H, 7.74; N, 7.40.

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Registry No. 1·HCl, 19196-51-1; **4**, 87858-16-0; *gluco*-**5**, 69257-51-8; *manno*-**5**, 6027-42-5; *gluco*-**6**, 87859-93-6; *manno*-**6**, 87858-13-7; **7**, 87858-14-8; **8**, 87858-15-9; **10**, 87782-50-1; **11**, 87782-51-2; **12**, 87782-52-3; **13**, 19131-10-3; **14**, 87782-54-5; **15**, 19131-11-4; **16**, 18981-61-8; **17**, 67758-44-5; **18**, 67758-43-4; **19**, 85439-70-9; **20**, 87782-55-6; **21**, 87782-57-8; **22**, 87782-56-7; **23**, 54623-22-2; **23** 4-methanesulfonate, 18981-62-9; **24**, 54623-23-3; **25**, 18981-64-1; **25** 4-benzoate, 19129-68-1; **26**, 18977-92-9; L-arabinose, 5328-37-0; nitromethane, 75-52-5; methyl 2-deoxy-β-L-*arabino*-hexopyranoside 6-*p*-toluenesulfonate, 87782-53-4.

Asymmetric Synthesis of Daunosamine[1]

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An asymmetric approach to L-daunosamine (**1**) from cyclopentadiene is described. Chiral centers and functional groups of the well-established intermediate in the synthesis of **1**, methyl 3,4-anhydro-2,6-dideoxy-α-L-*ribo*-hexopyranoside (**2**),[2,3] were derived from the asymmetrically formed 2(*S*)-methyl-3-cyclopenten-1(*S*)-ol (**3**)[4] by stereospecific epoxidation of **3** → **6** and Baeyer–Villiger ring enlargement of **7** → **8** and stereoselective reduction–glycosidation of **8** → **9** → **2**.

In the preceding paper,[2] we have outlined the objectives in the synthesis of the amino sugar L-daunosamine (**1**). Our strategy was to elaborate a practical preparation of methyl 3,4-anhydro-2,6-dideoxy-α-L-*ribo*-hexopyranoside

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