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SYNTHESIS OF METHYL 2,3,6-TRIDEOXY-3-(DIMETHYLAMINO)-β-L-*xylo*-HEXOPYRANOSIDE

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ABSTRACT

The title amino sugar was synthesized in six steps from methyl 4,6-*O*-benzylidene-2,3-dideoxy-3-trifluoroacetamido-α-D-*arabino*-hexopyranoside in a route based on Horton's synthesis of 3-amino-2,3,6-trideoxy sugars, but modified to avoid the problem of anhydro bridge formation. This modification was successful and all steps in the synthesis, except the final catalytic reduction, went cleanly in good to excellent yields.

INTRODUCTION

In recent years, *N,N*-dimethyl derivatives of 3-amino-2,3,6-trideoxyhexoses have been found to be constituents of a variety of antibiotics. Thus rhodosamine, which has the L-*lyxo* configuration, is found in anthracycline antitumor antibiotics, including the rhodomycins, pyrromycins, cinerubins, aclacinomycins, marcellomycin, and musettamycin[1]. The enantiomeric D-rhodosamine (megalosamine) occurs in the macrolide megalomicins[2] and the D-*arabino* configuration (angolosamine) is found in the macrolide angolamycin[3]. Considerable attention has been given to the synthesis of the corresponding primary amines, especially daunosamine (3-amino-2,3,6-trideoxy-L-*lyxo*-hexose)[4,5], which is part of the important anticancer drugs doxorubicin (adriamycin) and daunorubicin[6,7]. Less interest has been shown in the *N,N*-dimethyl derivatives, although D,L-megosamine was prepared from methyl *trans*-2,3,6-trideoxy-4,5-epoxy-DL-*threo*-hex-2-enoate[8]. Possibly this lack of interest is because of the close formal relationship of these primary and tertiary amines: one would only need to dimethylate the primary amines. Thus, rhodosamine might best be prepared by dimethylating daunosamine. Nevertheless, there might be certain examples in which the best route might not be through the primary amine. For example, in Horton's synthesis of 3-amino-2,3,6-trideoxy-L-*xylo*-hexopyranoside, it was found that attempted dehydrobromination of compound **1** gave the unexpected 3,6-anhydro product **2**[9]. This problem was avoided by carrying the potential 3-amino group through the synthesis as an azide until a late stage, although extra steps were required[9]. It occurred to us that the synthesis of

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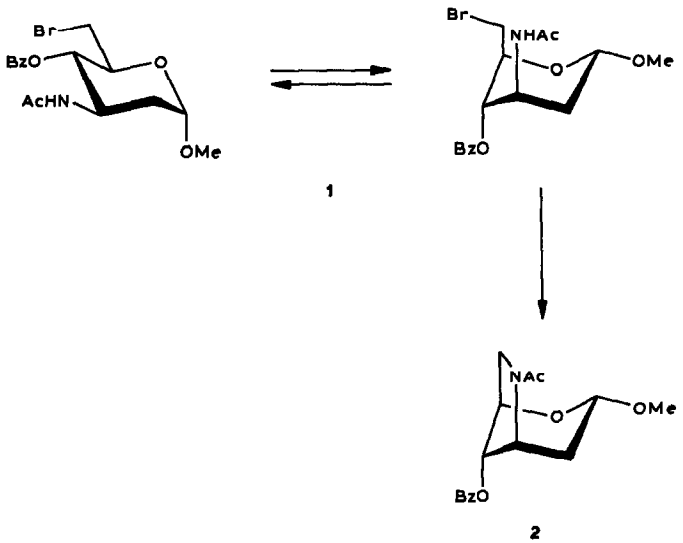
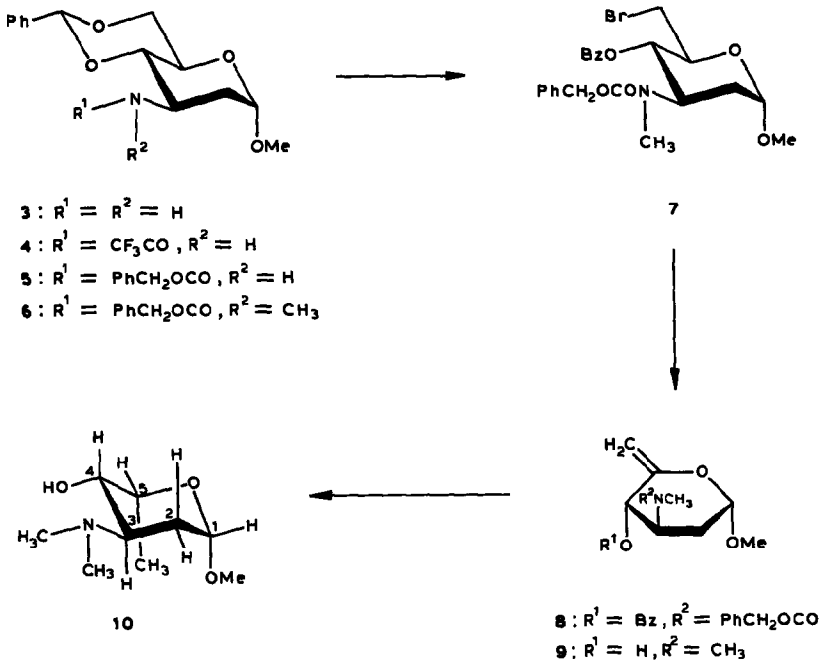


2,3,6-trideoxy-(dimethylamino)-L-*xylo*-hexopyranoside (**10**), a new compound epimeric with both rhodosamine and angolosamine, might proceed directly in a Horton-type approach because the bulky substituents on the 3-amino group could prevent the molecule from assuming the conformation needed for forming a 3,6-anhydro bridge. We decided to use methyl and benzyloxycarbonyl substituents on the 3-amino group at this stage in the synthesis. The latter group can be reduced to methyl by lithium aluminum hydride. In this manner, a relatively short route to **10** might be obtained.

RESULTS AND DISCUSSION

Our starting compound was methyl 3-amino-4,6-*O*-benzylidene-2,3-dideoxy-α-D-*arabino*-hexopyranoside **3**, the "wrong" isomer obtained in the Horton synthesis of daunosamine[4]. Actually, we did not synthesize this compound from D-mannose, but we prepared it by hydrolyzing a sample of the *N*-trifluoroacetyl derivative **4** which was generously donated by Bristol–Myers Company. Treatment of **4** with sodium hydroxide followed by benzyl chloroformate gave the *N*-benzyloxycarbonyl derivative **5** in 98% yield. Introduction of the *N*-methyl group was accomplished in 91% yield by treating **5** with sodium hydride and methyl iodide in *N,N*-dimethylformamide. Treatment of the product **6** with *N*-bromosuccinimide then gave the 6-bromo derivative **7** in 75% yield. The critical step of dehydrobromination with silver fluoride in pyridine gave a single product **8** in 71% yield.

In order to complete the synthesis of **10**, it was necessary to reduce the benzyloxycarbonyl group to methyl, hydrolyze the 4-benzoate, and reduce the 5,6-methylene group to methyl. The first two transformations were effected readily in 88% yield (crude) by reduction with lithium aluminum hydride. Catalytic reduction



of the product **9** gave in 37% yield an oil that was shown by its n.m.r. spectrum to be a mixture of the desired compound **10** and ~30% of another compound. Purification by chromatography gave 16% of **10**. The other compound was not isolated and purified. However, analysis of the n.m.r. spectrum of the mixture suggested that the other compound in the C-5 epimer of **10**. Thus, the peaks for H-1, H-2, H-3, and the various methyl groups were the same for both compounds, except for small chemical-shift differences (Experimental). Analysis of the multiplets for hydrogens on C-4 and C-5 revealed that they each contained contributions from two different splitting-patterns. The differences in these patterns reflected the orientation of H-5 in each compound: Equatorial H-5 in **10** coupled with H-4 to give $J_{4,5}$ = 3.3 Hz, whereas axial H-5 in the other compound is coupled with H-4 to give $J_{4,5}$ = 9.9 Hz. Calculated patterns for these multiplets, based on a 7:3 mixture of the components, closely matched the observed patterns. Although a single product from a 5,6-ene was reported in the Horton synthesis of daunosamine[4], it is not improbable that **7**, which is epimeric at C-3 with the corresponding daunosamine intermediate, would give a mixture of 5-epimers.

The structure and conformation of **10** were confirmed by mass-spectral and n.m.r. evidence given in the Experimental section. In particular, the couplings of H-1 with the H-2 protons (t, $J_{1,2}$ = 3.3 Hz) showed that H-1 was equatorial, the coupling of H-3 with H-4 and the H-2 protons ($J_{3,2a} = J_{3,4}$ = 9.9 Hz) showed that H-3 and H-4 were axial, and the coupling of H-4 with H-5 showed that H-5 was equatorial. Structure **10** should be the favored conformation, based on the anomeric effect and steric considerations.

In summary, the synthesis outlined for **10** succeeded in overcoming the problem of anhydro bridge formation. Lack of stereoselectivity and low yield in the final step, catalytic reduction of 5,6-ene **9**, prevented a high overall yield of **10** (6.7% from **4**). Nevertheless this synthesis was useful. The method developed for preventing anhydro bridge formation might be valuable in the synthesis of certain other mono- and di-methylamino sugars.

EXPERIMENTAL

General methods. — Concentration of solutions was performed under diminished pressure on a rotary evaporator. Melting points were determined with a Mel-Temp apparatus and are uncorrected. A Perkin–Elmer Model 241MC polarimeter and 1-dm tubes were used for measurement of specific rotations. I.r. spectra were recorded with a Beckman IR-33 spectrophotometer with samples prepared as potassium bromide pellets, unless otherwise indicated. N.m.r. spectra were recorded on either a Varian EM-360L 60 MHz spectrometer or a Bruker WM 250 MHz spectrometer; chemical shifts refer to an internal standard of tetramethylsilane (δ = 0.00). T.l.c. was performed with Silica Gel G (E. Merck, Darmstadt, F.R.G.) and detection was achieved by u.v. light and with sulfuric acid. Mass spectra were recorded on a Varian-MAT 311 double-focusing high-resolution spectrometer operating at an ionizing potential of 70 eV and an accelerating potential of 8 kV; the source temperature (direct-inlet system) was 150°. Microanalyses were performed by the University of Arizona Analytical Center.

*Methyl 4,6-O-benzylidene-3-(benzyloxycarbonyl)amino-2,3-dideoxy-α-*D-arabino-*hexopyranoside* (**5**). — A solution of **4** (2.5 g, 6.9 mmol) in tetrahydrofuran (20 mL) was treated with M sodium hydroxide (20 mL) and the mixture was stirred for 24 h at 25°. It was cooled to 0°, treated with M sodium hydroxide (10 mL) and benzyl chloroformate (1.5 mL), and stirred for 2 h at 0° and then 8 h at 25°. The resulting mixture was evaporated and the residue was treated with cold water, whereupon the product solidified. It was washed with water, dried in air, and crystallization from chloroform–petroleum ether (65–110° fraction). This procedure gave 2.7 g (98%) of **5** as white flakes, m.p. 194–195°, $[\alpha]_{546}^{25}$ +42.7° (*c* 1.0 chloroform); ν_{max}^{KBr} 3300 (NH), 1690 (amide I), and 1540 cm^{-1} (amide II); n.m.r. ($CDCl_3$): δ 1.75 (1 H, m, H-2*a*), 2.30 (1 H, m, H-2*e*) 3.35 (3 H, s, OCH_3), 3.50–4.45 (5 H, m, sugar), 4.70 (1 H, t $J_{1,2}$ 2.3 Hz, H-1), 5.0 (2 H, s, PhCH_2), 5.48 (1 H, PhC*H*), and 7.30 (10 H, m, Ph).

Anal. Calc. for $C_{22}H_{25}NO_6$ (399.442): C, 66.15; H, 6.31; N, 3.51. Found: C, 66.18; H, 6.14; N, 3.40.

*Methyl 4,6-O-benzylidene-3-N-benzyloxycarbonyl-2,3-dideoxy-3-methylamino-α-*D-arabino-*hexopyranoside* (**6**). — A solution of **5** (1.9 g, 4.8 mmol) in dry *N,N*-dimethylformamide (10 mL) under nitrogen was treated with sodium hydride (50% suspension in mineral oil, 0.24 g, 5.0 mmol). The mixture was stirred for 0.5 h at 25° and then treated with iodomethane (1 mL). After 20 h, the mixture was

evaporated and the residue was extracted with chloroform. This extract was washed with water, dried over sodium sulfate, and concentrated to low volume. Treatment of this concentrate with petroleum ether and cooling in an ice bath gave 1.8 g (91%) of **6** as white solid; m.p. 129–130°, $[\alpha]_{546}^{26}$ +75.8° (*c* 1.0, chloroform); ν_{max}^{KBr} 1680 cm^{-1} (amide C=O); n.m.r. ($CDCl_3$): δ 2.0 (2 H, m, H-2), 2.90 (3 H, s, NCH_3), 3.35 (3 H, s, OCH_3), 3.50–4.50 (5 H, m, sugar), 4.75 (1 H, m, H-1), 5.10 (2 H, s, PhCH_2), 5.45 (1 H, s, Ph*CH*), and 7.30 (10 H, m, Ph).

Anal. Calc. for $C_{23}H_{27}NO_6$ (413.469): C, 66.81; H, 6.58; N, 3.39. Found: C, 66.63; H, 6.80; N, 3.60.

*Methyl 4-O-benzoyl-3-N-benzyloxycarbonyl-6-bromo-2,3,6-trideoxy-3-methylamino-α-*D-arabino-*hexopyranoside* (**7**). — A solution of **6** (2.0 g, 4.1 mmol) in carbon tetrachloride (40 mL) was treated with *N*-bromosuccinimide (1.0 g, 5.6 mmol) and barium carbonate (3.0 g). The mixture was stirred at reflux temperature for 3 h, filtered, and the residual solid was washed with dichloromethane. The combined filtrate and wash was extracted with aqueous sodium hydrogensulfite and with dilute sodium hydrogencarbonate, dried over magnesium sulfate, and concentrated to a syrup. Purification of this product on a short column of silica gel with 9:1 benzene–acetone as solvent gave 1.80 g (75%) of **7** as a colorless syrup; $[\alpha]_{546}^{25}$ +64.3° (*c* 1.0, chloroform); ν_{max}^{neat} 1720 (ester), 1690 cm^{-1} (amide); n.m.r. ($CDCl_3$): δ 2.0 (2 H, m, H-2), 2.8 (3 H, s, NCH_3), 3.45 (3 H, s, OCH_3), 3.50 (2 H, m, H-6), 4.70 (1 H, t, $J_{1,2}$ 2.3 Hz, H-2, H-1), 5.20 (3 H, m, sugar), and 7.0–8.20 (10 H, m, Ph).

Anal. Calc. for $C_{23}H_{26}BrNO_6$ (492.365): C, 56.11; H, 5.32; Br, 16.23; N, 2.84. Found: C, 55.62; H, 5.16; 1 Br, 16.44; N, 3.11.

*Methyl 4-O-benzoyl-3-N-benzyloxycarbonyl-2,3,6-trideoxy-3-methylamino-α-*D-threo-*hex-5-enopyranoside* (**8**). — A mixture of **7** (2.0 g, 4.1 mmol), anhydrous silver fluoride (2.0 g), and dry pyridine (25 mL) was stirred for 18 h at 25°. It was then poured into diethyl ether (100 mL), stirred briefly, and filtered. Concentration of the ether solution gave a dark syrup from which toluene was evaporated to remove traces of pyridine. Purification of the residue on a column of silica gel with dichloromethane as solvent gave 1.19 g (71%) of **8** as a syrup; ν_{max}^{neat} 1725 (ester), 1710 (amide), 1660 cm^{-1} (C=C); n.m.r. ($CDCl_3$): δ 1.8–2.3 (2 H, m, H-2), 2.8 (3 H, s, NCH_3), 3.3 (3 H, s, OCH_3), 4.50–4.75 (3 H, m, H-1 and H-6 methylene), 5.0–5.2 (3 H, m, H-3 and PhCH_2), 5.70 (1 H, m, H-4), and 6.9–8.3 (10 H, m, Ph).

Anal. Calc. for $C_{23}H_{25}NO_6$ (411.453): C, 67.14; H, 6.12; N, 3.40. Found: C, 66.82; H, 6.11; N, 3.22.

*Methyl 2,3,6-trideoxy-3-dimethylamino-β-*L-xylo-*hexopyranoside* (**10**). — A solution of **8** (1.13 g, 2.75 mmol) in diethyl ether (50 mL) was treated with lithium aluminum hydride (0.6 g, 15.8 mmol) and the mixture was stirred at reflux for 4 h. Water was added dropwise to decompose the excess of hydride, then the mixture was diluted with water and filtered. The residue was washed thoroughly with methanol and the combined filtrate and wash was concentrated. The residue was extracted with tetrahydrofuran and this extract was filtered and evaporated. This

procedure gave 0.46 g (88% crude yield) of **9** as a yellowish oil; ν_{max}^{neat} showed no carbonyl absorption; n.m.r. ($CDCl_3$ + Me_2SO-d_6) showed $N(CH_3)_2$ at 2.25 p.p.m. and no phenyl or benzyl hydrogens. The product was used without further purification in the next step.

A mixture of **9** (0.5 g), methanol (20 mL), acetic acid (180 mg), and 10% palladium-on-charcoal (50 mg) was shaken with hydrogen in a Parr apparatus at 30 lb.in for 5 h. It was filtered and the filtrate was concentrated to give a yellow oil (185 mg, 37% crude yield) whose n.m.r. spectrum indicated a mixture containing ~70% of **10** and 30% of another compound. This mixture was separated by t.l.c. on a pre-coated silica gel plate (20 × 20 × 0.2 cm) with 1:4 (v/v) methanol–chloroform as solvent. The major band was scraped off and extracted with a methanol–dichloromethane mixture. Filtration and concentration of this extract gave 80 mg (16%) of **10** as a pale-yellow oil; $[\alpha]_{746}^{25}$ +48.1° (*c* 1.0, methanol); n.m.r. (250 MHz, $CDCl_3$): δ 1.37 (3 H, d, $J_{5,6}$ 7.0 Hz, 6 CH_3), 1.60–2.00 (2 H, m, H-2), 2.40 [6 H, s, $N(CH_3)_2$], 3.27 (1 H, dt, $J_{3,2a}$ 9.9, $J_{3,2e}$ 3.3, $J_{3,4}$ 9.9 Hz, H-3), 3.41 (3 H, s, OCH_3), 3.70 (1 H, dd, $J_{4,5}$ 3.3 Hz, H-4), 4.21 (1 H, dq, H-5), and 4.80 (t, $J_{1,2a} = J_{1,2e}$ = 3.3 Hz, H-1).

Anal. Calc. for $C_9H_{19}NO_3$: M^+ 189.13716. Found: 189.13649.

The second component of the mixture was not isolated and purified. It was identified as the C-5 epimer of **10** by subtracting the peaks for **10** from the n.m.r. spectrum of the mixture (250 MHz, $CDCl_3$): δ 1.32 (3 H, d, $J_{5,6}$ 7.0 Hz, 6 CH_3), 1.6–2.2 (2 H, m, H-2), 2.47 [6 H, s, $N(CH_3)_2$], 3.27 (1 H, dt, $J_{3,2a}$ 9.9 $J_{3,2e}$ 3.3 Hz, $J_{3,4}$ 9.9 Hz, H-3), 3.34 (3 H, s, OCH_3), 3.70 (1 H, dd, $J_{4,5}$ 9.9 Hz, H-4), 4.21 (1 H, dq, H-5), and 4.80 (t, $J_{1,2a} = J_{1,2e}$ 3.3 Hz, H-1).

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