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SYNTHESIS OF METHYL 2-ACETAMIDO-2,3,6-TRIDEOXY-β-L-*lyxo*-HEXOPYRANOSIDE*

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ABSTRACT

The title glycoside, having the daunosamine structure but with amination at C-2 instead of C-3, was synthesized in nine steps from 2-acetamido-2-deoxy-D-glucose. The sequence also provided preparative access to methyl 2-acetamido-2,3-dideoxy-α-D-*ribo*-hexopyranoside and its 4,6-benzylidene acetal.

INTRODUCTION

In a quest for anthracycline antibiotics[2] of improved antitumor potential, and as part of a structure–activity evaluation of analogs of these antibiotics, we have synthesized stereochemical and structural variants of daunosamine[3], coupled them to suitable aglycons[4], and subjected the products to *in vivo* antitumor screening in mice [4–6]. A survey of much of this work has recently been published[7]. Thus far, our results and those of others[8] reveal a strong dependence on the stereochemistry and substitution pattern of the sugar.

As part of this program, we set out to prepare an analog in which the 2-deoxy and the 3-amino functionalities are interchanged. A rationale for preparing such a compound is based on the activities observed with the adriamycin and daunorubicin analogs having a 2-amino-2-deoxy-β-D-glucopyranosyl substituent at O-7; they show activities comparable to those of the parent drugs, although at higher dose levels[8,9]. Amination at C-2′ thus does not cause inactivation, suggesting that a 2′-amino analog differing (from daunorubicin or adriamycin) only in the position of the amino group might possess high efficacy and potency. In order to prepare such a compound, synthesis of the previously unknown sugar constituent was required. The present report describes the synthesis of this novel amino sugar (the title com-

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pound), together with a new route to its 6-hydroxylated 5-epimer (D-*ribo* configuration).

RESULTS AND DISCUSSION

Glycosidation of 2-acetamido-2-deoxy-D-glucose (**1**) with methanol gave[10] crystalline methyl 2-acetamido-2-deoxy-D-glucopyranoside (**2**) as a 17:3 α,β-mixture[11], benzylidenation of which[12] gave methyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-D-glucopyranoside (**3**) also as an anomeric mixture. Extensive recrystallization of **3** from methanol gave the pure α anomer, but with unacceptable losses; the α,β mixture was used directly in the next step. Treatment of **3** with trifluoromethanesulfonic (triflic) anhydride in pyridine at $-20°$, with gradual warming to $-5°$ during a 2-h period, gave the corresponding 3-triflates **4** as an anomeric mixture in high yield. This product was quite unstable until it had been isolated pure, and careful control of the preparative conditions was essential for assuring high yields. Recrystallization of **4** from methanol gave the pure α anomer, but only in low yield, because of decomposition on heating. The pure α anomer was stable during storage. The observed low-field (δ 5.01) signal for H-3 and the $J_{1,2}$ value (4.2 Hz) confirm the structural and anomeric assignment. There were no products arising from decomposition of **4**, although others[13] have observed 2,3-oxazolines resulting from attempts to displace sulfonate groups in 2-acetamido-2-deoxy-3-*O*-sulfonylglycosides.

The anomeric mixture of triflates (**4**) reacted with sodium benzenethioxide in *N*,*N*-dimethylformamide during 12 h at ~25° to give a mixture of methyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-3-*S*-phenyl-3-thio-α-D-allopyranoside (**5**) and its β anomer (**6**), from which **5** could be obtained in 20–30% yield by direct crystallization from methanol. Chromatography on silica gel was required in order to isolate **6**. Both anomers were obtained crystalline and analytically pure. Repetition of the benzenethioxide displacement-reaction with the pure α-triflate **4** gave the 3-phenylthio α-product **5** in >90% yield, demonstrating that the replacement was essentially quantitative. The analytical data for the products established that the triflate group had been replaced by phenylthio. Both products showed $J_{2,3}$ and $J_{3,4}$ values of 3 Hz, indicating that H-3 is equatorial, that the products had the *allo* configuration, and consequently that the products arose from direct SN2 displacement of the excellent C-3 leaving-group in **4** by the powerful PhS⁻ nucleophile, despite the presence of a very good, potential participating-group at C-2. Subsequent chemical conversions independently verified the replacement at C-3 by sulfur. The $J_{1,2}$ values of **5** and **6** were 3.0 and 9.0 Hz, respectively, indicating **5** to be the α, and **6** the β, anomer.

Benzylidene ring-opening in **5** by *N*-bromosuccinimide[14] gave 93% of crystalline methyl 2-acetamido-4-*O*-benzoyl-6-bromo-2,6-dideoxy-3-*S*-phenyl-3-thio-α-D-allopyranoside (**7**), characterized by spectral and elemental analyses (see Experimental section). The H-4 signal showed the expected, downfield shift (δ 3.93 for **5**,

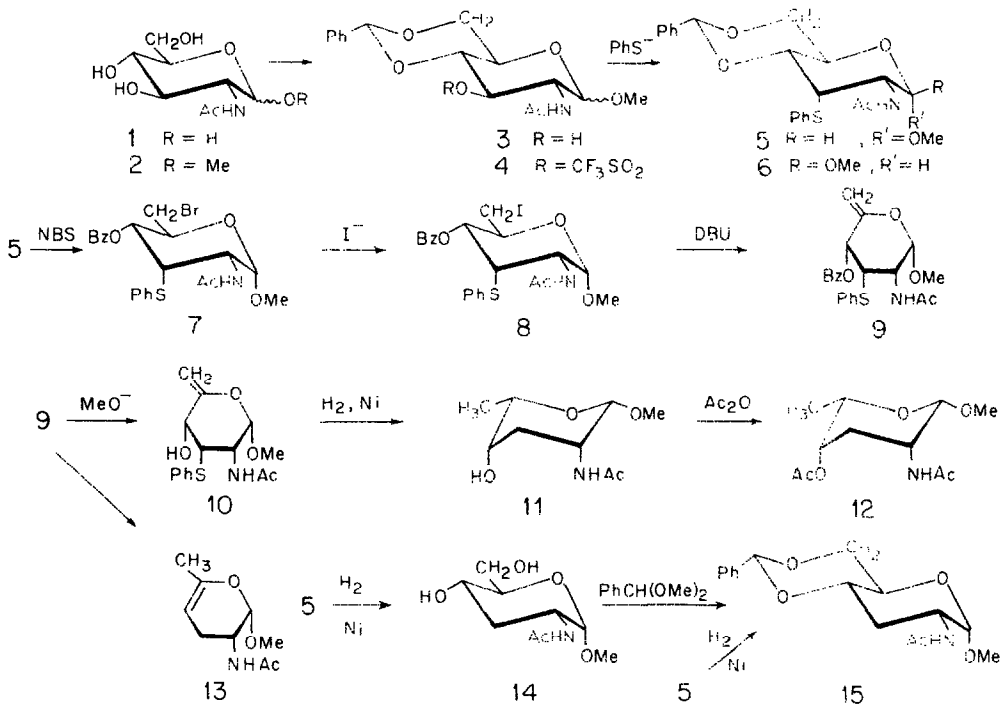
5.18 for **7**), and the $J_{4,5}$ value (10.0 Hz) indicated the $^4C_1$(D) conformation for **7**. The bromine atom in **7** was replaced by iodine; the t.l.c. mobility of the resultant 6-iodide (**8**) was almost identical with that of **7**, but their n.m.r. spectra were sufficiently different to establish completion of the reaction. The product was characterized by n.m.r.- and mass-spectral analyses.

Dehydrohalogenation of the iodide **8** was accomplished by the action of 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) in acetonitrile, and the resultant enol ether, methyl 2-acetamido-4-*O*-benzoyl-2,6-dideoxy-3-*S*-phenyl-3-thio-α-D-*ribo*-hex-5-enopyranoside (**9**), was obtained crystalline in 34% yield; side reactions, evident from t.l.c. examination, were responsible for the relatively low yield. The silver fluoride–pyridine elimination method[15], as frequently and effectively used in this laboratory[16] for dehydrobromination of 6-bromo-6-deoxyaldose derivatives, was found unsatisfactory for converting the bromide **7** into the alkene **9**; possibly, the sulfur atom present in **7** interferes with the reaction. The terminal, alkene functionality in **9** was readily evident from the n.m.r.-spectral lines for H-6,6′ (broad singlet at δ 4.49) and H-4 (doublet at δ 5.75, showing fine, allylic coupling). *O*-Debenzoylation of **9** by the method of Zemplén gave the crystalline 4-hydroxy analog **10** in 84% yield; an upfield shift of H-4 (to δ 4.65), together with i.r.- and mass-spectral data, helped to characterize compound **10**.

Hydrogenation of **10** in the presence of Raney nickel gave an ~12:1 mixture of methyl 2-acetamido-2,3,6-trideoxy-β-L-*lyxo*-hexopyranoside (**11**) and its α-D-*ribo* isomer, as indicated by the ^{1}H-n.m.r. spectrum of the mixture. Column chromatography on silica gel gave the pure L-*lyxo* isomer **11** crystalline in 27% yield. The ^{1}H-n.m.r. spectrum of **11** showed that both reduction of the 5,6-alkene and hydrogenolysis of the phenylthio group had occurred. The success of the conversion **10**→**11** is noteworthy, as hydrogenation of alkenes in the presence of Raney nickel is commonly supposed to be precluded when thio groups are present in the molecule.

The stereochemistry at C-5 of product **11** could not be unambiguously determined, as the H-4 and H-5 resonances were coincident. A downfield shift of H-4 was observed, however, upon conversion of **11** into its 4-*O*-acetyl derivative **12**, allowing determination of $J_{4,5}$ (2.0 Hz), $J_{3e,4}$ (3.0 Hz), and $J_{3a,4}$ (4.0 Hz) on a first-order basis. The small values of the coupling constants observed are consistent only with the $^1C_4$ conformation as the preponderant chair-form for **12**. It was concluded that **12** and, therefore, **11** must have the L-*lyxo* configuration (and not the D-*ribo* configuration), because the latter compound would undoubtedly favor the $^4C_1$ conformation[3]; the $^1C_4$ conformation would be strongly destabilized by N-2–O-4 *syn*-diaxial interactions, by the bulk of an axial methyl group at C-5, and by an unfavorable, anomeric effect.

The high stereoselectivity achieved in the reduction of **10** is consistent with results of catalytic hydrogenations of other hex-5-enopyranosides[15–18]. Studies have shown that catalytic reduction of α-hex-5-enopyranosides gives, either exclu-



sively or mainly, the L enantiomers, whereas reduction of β-hex-5-enopyranosides gives mostly the D enantiomers.

It was not possible to reverse the order of the debenzoylation and Raney nickel-reduction reactions, because hydrogenation of **9** did not lead to the 4-*O*-benzoyl derivative of **11**, but afforded, instead, methyl 2-acetamido-2,3,4,6-tetradeoxy-α-D-*glycero*-hex-4-enopyranoside (**13**). The structure of **13** was deduced from ^{1}H-n.m.r.- and mass-spectral data. The n.m.r. spectrum indicated loss of the benzoyl and phenylthio groups, and the presence of only four ring-protons, plus the anomeric proton, together with an allylic methyl group (δ 1.75). Loss of the phenylthio group undoubtedly resulted from simple hydrogenolysis. Removal of the benzoyl group and rearrangement of the double bond, on the other hand, may be envisaged as proceeding through a six-membered, transition state, in which a single molecule of hydrogen simultaneously effects hydrogenolysis of benzoate and rearrangement of the double bond.

The 3-(phenylthio)-4,6-benzylidene acetal **5** reacted with freshly prepared Raney nickel to give, in 67% yield, the known methyl 2-acetamido-2,3-dideoxy-α-D-*ribo*-hexopyranoside[19-21] (**14**). This reaction further verified the structural assignment of **5**. If the Raney nickel used in this reaction was not fresh, hydrogenolysis of the 4,6-benzylidene acetal did not occur, and methyl 2-acetamido-4,6-*O*-benzylidene-2,3-dideoxy-α-D-*ribo*-hexopyranoside (**15**) was obtained. Compound **15** was characterized by comparison with published values. The structural

assignments of **14** and **15** were also supported by the observation that reaction of **14** with α,α-dimethoxytoluene gave **15**.

The preparation of **14** from **1** by the preceding procedure provides a practical route to this compound. As with the method of Haskell *et al.*[19], the essential feature is deoxygenation at C-3 by the three-step sequence of triflation, displacement by sodium benzenethioxide, and hydrogenolysis. The method just described requires fewer manipulations of the protecting groups, although the net yield reported by Haskell *et al.*[19] was higher. Both methods offer fewer steps and higher yields than that used by Brewer and Guthrie[20] and Kitahara *et al.*[21]. They prepared **14** from **15** (obtained, in turn, from methyl α-D-glucopyranoside) in eight steps by the method of Rosenthal and Catsoulacas[22].

Preparation of the target glycoside **11** by the route described here is simple and effective, despite two relatively low-yielding steps. The sequence demonstrates that a phenylthio substituent, introduced to effect eventual deoxygenation, does not interfere with the inversion at C-5 *via* the 5,6-alkene.

EXPERIMENTAL

General methods. — Evaporations were performed under diminished pressure at 40°. Melting points were determined with a Thomas–Hoover "Unimelt" apparatus and are uncorrected. Perkin–Elmer models 141 or 241 polarimeters were used for measurement of optical rotations. I.r. spectra were recorded with Perkin–Elmer model 457 or "Infracord" spectrophotometers. N.m.r. spectra were recorded by Herman Flynn at either 200 or 300 MHz with a Varian XL-200 or a Varian SC-300 spectrometer; the results are summarized in Table I. Mass spectra (electron impact, 70 e.V.) were obtained by C. R. Weisenberger with an AEI MS-9 spectrometer or by Jack Smith with an LKB 9000 spectrometer. Fragment assignments and notations are based on the work of Chizhov *et al.*[23]. Thin-layer chromatography (t.l.c.) was performed on silica gel GF_{254} (Analtech) plates; detection was by u.v. light or with ceric sulfate (1%)–sulfuric acid (10%) spray. Column chromatography was conducted with silica gel (E. Merck, No. 7734, 70–230 mesh). Solvent volumes are v/v; petroleum ether refers to fractions boiling at 30–65°; ether refers to diethyl ether. Microanalyses were performed by W. N. Rond or by Jane Wu and her associates.

Methyl 2-acetamido-2-deoxy-3-O-trifluoromethylsulfonyl-α,β-D-glucopyranoside (**4**). — Trifluoromethanesulfonic anhydride (10 mL, 18 g, 62 mmol) was added to a solution of methyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α,β-D-glucopyranoside (**3**; 10 g, 31 mmol) in pyridine (300 mL) at −20° under nitrogen. The mixture was allowed to warm during 1 h to −5°, and kept at that temperature for an additional 1.5 h. T.l.c. (9:1 toluene–methanol) showed essentially complete conversion of the anomeric alcohols into their corresponding, faster-moving triflates, the α and β anomers of both **3** and **4** being clearly differentiated in this solvent system. The mixture was poured into ice–water, and the resulting precipitate

TABLE I

^{1}H-N.M.R.-SPECTRAL DATA FOR COMPOUNDS **4–13**

Compound[a]	*Chemical shifts (δ)*[b] *(first-order couplings, Hz, in parentheses)*											
	H-1 ($J_{1,2}$)	*H-2* ($J_{2,3}$)	*H-3* ($J_{3,4}$)	*H-4* ($J_{4,5}$)	*H-5* ($J_{5,6}$)	*H-6* ($J_{6,6'}$)	*H-6'* ($J_{5,6'}$)	*Aryl*	*NH* ($J_{2,NH}$)	*PhCH*	*OMe*	*Ac*
4[c]	4.78d (4.0)	4.65dt (10.0)	5.01t (10.0)		← 3.8–4.0 and 4.3–4.4 → (2nd order)			7.3–7.6	3.82 (10)	5.61	3.44	2.07
5[c]	4.66d (3.0)	4.6–4.8[d]	3.88t (4.0)	3.93dd (9.0)	4.21m (5.0)	4.36dd (10.5)	3.80t (10.5)	7.2–7.6	6.55d (10)	5.62	3.46	2.08
6[c]	4.52d (9.0)	4.2–4.5[d] (4.0)	4.06t (4.0)	← 3.9–4.1m →		← 4.2–4.5[d] →	3.86t	7.2–7.6	6.15d (9.0)	5.65	3.55	1.97
7[c]	4.78d (4.0)	4.7–4.9[d] (4.0)	4.32t	5.18dd (10.0)	4.53m (2.5)	3.76dd (11.0)	3.5–3.7dd[d] (7.0)	6.8–7.8	6.44d (9.0)		3.55	2.11
8[c]	4.69d	4.6–4.8[d] (4.0)	4.21t (4.0)	5.01dd (10.0)	4.1–4.3[d] (2.0)	3.46dd (11.0)	3.24dd (8.0)	6.8–7.8	6.36d (9.0)		3.50	2.04
9[e]	4.77d (3.0)	4.8–5.0[d] (4.5)	4.10t (4.5)	5.7–5.8m		← 4.94 → (broad s)		6.8–8.0	6.43d (9.5)		3.52	2.08
10[e]	4.74d (2.0)	4.7–4.9[d] (5.0)	3.87t (5.0)	4.4–4.6m		← 4.86 and 4.95 → (d)		7.2–7.5	6.40d (9.0)		3.48	2.04
11[e]	4.44d (2.0)	4.2–4.3 (3.5)[f] (4.5)[g]	2.19dt[h] (3.5)[h]	1.88dt[i] (4.5)[i]	← 3.6–3.8 → (2nd order) (6.5)	1.36d			6.4–6.7		3.54	2.03
12[e]	4.46d (2.0)	4.2–4.4 (3.0)[f] (4.0)[g]	2.20dt[h] (3.0)[h]	1.90dt[i] (4.0)[i]	4.93sx (2.0)	3.80dq (6.5)	1.12d		6.12d (9.0)		3.52	2.11
13[e]	4.81d (3.0)	4.5–4.6	← 1.9–2.3[d] →		4.1–4.25m	1.75m			5.5–5.7		3.48	2.00

[a] In chloroform-*d*. [b] Signal multiplicities: d, doublet; dd, doublet of doublets; dq, doublet of quartets; dt, doublet of triplets; m, multiplet; s, singlet; sx, sextet; t, triplet. [c] At 300 MHz. [d] Signal partially overlapped. [e] At 200 MHz. [f] $J_{2,3e}$. [g] $J_{2,3a}$. [h] H-3*e* and $J_{3e,4}$ values. [i] H-3*a* and $J_{3a,4}$ values. $J_{3a,3e}$ = 15.0 Hz.

was collected by vacuum filtration, washed with water, air-dried for 2 h, and dried *in vacuo* over calcium sulfate for 18 h. This product (14 g) was used without further purification in the next step. An analytically pure sample of the α anomer (faster-moving in t.l.c.) of **4** was obtained by recrystallization of a portion of the crude product from methanol; m.p. 135° (dec.), $[\alpha]_D^{29}$ +20.2° (*c* 0.74, chloroform); ν_{max}^{KBr} 3300 (NH), 1670, and 1530 cm^{-1} (NHCO).

Anal. Calc. for $C_{17}H_{20}F_3NO_8S$ (455.36): C, 44.84; H, 4.43; N, 3.08; S, 7.04. Found: C, 45.05; H, 4.67; N, 3.03; S, 6.88.

The course of the triflation reaction was especially sensitive to the conditions employed. Under the conditions described here, complete conversion of **3** occurred within ~2.5 h, without significant formation of side products. However, if the reaction was not processed immediately, decomposition began to occur; even with immediate isolation, various degrees of decomposition were noticed. The isolation procedure that minimized decomposition involved pouring the mixture into ice–water, immediately collecting the precipitate, and washing it with a copious amount of water. The product, at this point, could be dried, and stored for several days without further decomposition.

Methyl 2-acetamido-4,6-O-benzylidene-2-deoxy-3-S-phenyl-3-thio-α- (**5**) *and -β-*D-*allopyranoside* (**6**). — Benzenethiol (21 mL, 24 g, 0.22 mmol) was added dropwise to a suspension of sodium hydride (50% in mineral oil; 7.4 g, 0.15 mol) in *N*,*N*-dimethylformamide (200 mL) at 0° under nitrogen. The mixture was stirred for 2 h at room temperature, and then cooled to 0°. A solution of the crude triflate **4** (14 g, 0.31 mol) in *N*,*N*-dimethylformamide (50 mL) was added in one portion to the cooled solution of sodium benzenethioxide, and the resulting solution was allowed to warm gradually to room temperature during 12 h. T.l.c. (9:1 toluene–methanol) showed conversion of the anomeric triflates into **5** plus **6**, which gave a single, faster-moving spot in t.l.c. in this solvent system. The mixture was diluted with toluene, successively washed with water, 5% aqueous sodium hydroxide, and water, dried (sodium sulfate), and evaporated. The residue was triturated with petroleum ether, to yield a light-yellow solid consisting of a mixture of the anomers **5** and **6**, as indicated by t.l.c. (resolution of **5** and **6** in t.l.c. was effected by using 100:1 chloroform–methanol as the eluant; the α anomer **5** was the faster-moving of the two products). Recrystallization of the mixture from methanol gave pure **5**; yield 2.6 g (20%); m.p. 183–184°, $[\alpha]_D^{27}$ −70.9° (*c* 0.8, chloroform); ν_{max}^{KBr} 3300 (NH), 1650, and 1550 cm^{-1} (NHCO); *m/z*: 415 ($M^{\cdot+}$), 356 ($M^{\cdot+}$ − NH_2Ac), and 266 (h_1).

Anal. Calc. for $C_{22}H_{25}NO_5S$ (415.50): C, 63.60; H, 6.04; N, 3.37; S, 7.72. Found: C, 63.74; H, 6.29; N, 3.40; S, 7.46.

A sample of pure **6** was obtained by evaporating the mother liquors, subjecting the residue to column chromatography (200:1→150:1→100:1 chloroform–methanol), and recrystallizing the chromatographed product from methanol; m.p. 224–225°, $[\alpha]_D^{27}$ −163°; *m/z*: 415 ($M^{\cdot+}$), 383 ($M^{\cdot+}$ − OCH_3), 356 ($M^{\cdot+}$ − NH_2Ac), and 325 (383 − NH_2Ac).

Anal. Calc. for $C_{22}H_{25}NO_5S$ (415.50): C, 63.60; H, 6.01; N, 3.37; S, 7.72. Found: C, 63.71; H, 6.15; N, 3.33; S, 7.74.

*Methyl 2-acetamido-4-O-benzoyl-6-bromo-2,6-dideoxy-3-S-phenyl-3-thio-α-*D*-allopyranoside* (**7**). — *N*-Bromosuccinimide (2.5 g, 14 mmol) and barium carbonate (2.5 g) were added to a solution of **5** (5.5 g, 13 mmol) in carbon tetrachloride (100 mL) and 1,1,2,2-tetrachloroethane (50 mL). The mixture was heated for 2 h at 80°, during which time the initially colorless solution became successively yellow, red, and faint yellow. T.l.c. (2:1 chloroform–acetone) showed complete conversion of **5** into a single, faster-migrating product. The cooled mixture was diluted with dichloromethane, and the barium salts were removed by vacuum filtration. The filtrate was washed with 5% aqueous sodium hydrogencarbonate, and evaporated. The residue was vacuum filtered through a pad of silica gel with 9:1 dichloromethane–ether. Evaporation of the filtrate gave **7** as a chromatographically pure, white solid; yield 6.1 g (93%). Recrystallization of a portion from methanol gave analytically pure **7**; m.p. 146–147°, $[\alpha]_D^{27}$ −47.0° (*c* 0.52, chloroform); ν_{max}^{KBr} 3400 (NH), 1750 (ester CO), 1670, and 1520 cm^{-1} (NHCO); *m/z*: 497 ($M^{\cdot+}$ + 4), 496 ($M^{\cdot+}$ + 3), 495 ($M^{\cdot+}$ + 2), 494 ($M^{\cdot+}$ + 1), 493 ($M^{\cdot+}$), 371 (B_1), 352 (A_2^2), 340 (A_2^1), 324 (C_2^2), 312 (C_2^1), 262 (B_3), 230 (A_3^1), and 204 (E_3^1).

Anal. Calc. for $C_{22}H_{24}BrNO_5S$ (494.40): C, 53.54; H, 4.89; N, 2.83; S, 6.48. Found: C, 53.31; H, 4.99; N, 2.67; S, 6.41.

*Methyl 2-acetamido-4-O-benzoyl-2,6-dideoxy-6-iodo-3-S-phenyl-3-thio-α-*D*-allopyranoside* (**8**). — A mixture of **7** (2.5 g, 5.1 mmol) and sodium iodide (3.8 g, 2.6 mmol) in *N*,*N*-dimethylformamide (25 mL) was heated for 3 days at 90°. T.l.c. (9:1 toluene–methanol, 2:1 chloroform–acetone, or 1:1 ethyl acetate–hexane) misleadingly did not give any indication that a reaction had occurred. The cooled solution was evaporated, the residue was triturated with dichloromethane, undissolved salts were removed by vacuum filtration, and the filtrate was evaporated to a brown syrup that was subjected to column chromatography (1:1 ethyl acetate–hexane). Fractions containing pure material were combined, and evaporated, to give a white solid; yield 1.8 g (67%); *m/z*: 542 ($M^{\cdot+}$), 420 (M^+ − $PhCO_2N$), 400 (A_2^2), 388 (A_2^1), 372 (C_2^2), 310 (420 − PhSH), 280 (H_1^3), and 260 ($M^{\cdot+}$ − OCH_3 − PhSH − CH_2I).

*Methyl 2-acetamido-4-O-benzoyl-2,3-dideoxy-3-S-phenyl-3-thio-α-*D*-erythro-hex-5-enopyranoside* (**9**). — Diazabicyclo[5.4.0]undec-5-ene (DBU; 0.92 mL, 0.92 g, 6.0 mmol) was added to a solution of **8** (1.6 g, 3.0 mmol) in acetonitrile (50 mL), and the solution was kept for 3 days at room temperature. T.l.c. (2:1 ethyl acetate–hexane) showed the formation of **9** (slower-moving), together with a small amount of material that co-migrated with the starting iodide and some nonmigrating material. The reaction was continued for two additional days. T.l.c. showed no perceptible change in composition of the mixture. The solvent was evaporated, and the residue vacuum-filtered through a pad of silica gel (ether) to remove base-line material and color. Evaporation of the eluate, followed by crystallization of the residue

from methanol, gave **9** as white needles; yield 0.42 g (34%); m.p. 166–167°, $[\alpha]_D^{27}$ −96° (*c* 0.5, chloroform); $\nu_{max}^{CHCl_3}$ 3500 (NH), 1740 (ester CO), 1670 (amide I, C=C), and 1520 cm^{-1} (amide II); *m/z*: 413 ($M^{\cdot+}$), 304 ($M^{\cdot+}$ − SPh), 292 ($M^{\cdot+}$ − $PhCO_2^{\cdot}$), 259 ($M^{\cdot+}$ − $PhCO_2H$ − CH_3OH), and 182 (292 − PhSH).

Anal. Calc. for $C_{22}H_{23}NO_5S$ (413.49): C, 63.90; H, 5.61; N, 3.38; S, 7.75. Found: C, 63.45; H, 5.58; N, 3.38; S, 7.72.

*Methyl 2-acetamido-2,6-dideoxy-3-S-phenyl-3-thio-α-*D-erythro-*hex-5-enopyranoside* (**10**). — A catalytic amount of sodium methoxide was added to a solution of **9** (0.50 g, 1.2 mmol) in abs. methanol (25 mL), and the mixture was kept for 18 h at room temperature. T.l.c. (2:1 ethyl acetate–hexane) showed disappearance of starting material and formation of a single, slower-moving product. The solvent was evaporated, the residue was dissolved in dichloromethane, and the resulting solution was washed with water, dried (sodium sulfate), and evaporated. The residue was triturated generously with petroleum ether and sparingly with ether, to give **10** as fine, white needles; yield 0.31 g (84%); m.p. 147–148°, $[\alpha]_D^{27}$ +13° (*c* 1.0, chloroform); $\nu_{max}^{CHCl_3}$ 3450 (OH, NH), 1670 (amide I, C=C), and 1510 cm^{-1} (amide II); *m/z*: 309 ($M^{\cdot+}$), 277 ($M^{\cdot+}$ − CH_3OH), and 259 (277 − H_2O).

*Methyl 2-acetamido-2,3,6-trideoxy-β-*L-lyxo-*hexopyranoside* (**11**). — Raney nickel (W. R. Grace, No. 28; 5 mL) was added to a solution of **10** (0.25 g, 0.81 mmol) in abs. ethanol (25 mL). The mixture was stirred in a stoppered flask for 18 h. T.l.c. (9:1 chloroform–methanol) then showed formation of two closely migrating, slower-moving products, the faster of the two being **11**, and the other, its 5-epimer. T.l.c. also showed the presence of a third, even slower-moving, product. The mixture was stirred for 18 h under a stream of hydrogen. T.l.c. still showed the presence of **11** and its 5-epimer, but the third product had disappeared. The mixture was filtered, and the catalyst was washed with ethanol. The combined filtrate and washings were evaporated, and the residue was subjected to column chromatography (50:1 and 25:1 chloroform–methanol). Fractions containing only **11** were combined and evaporated. The product was obtained as a white solid; yield 45 mg (27%); m.p. 107–110°, $[\alpha]_D^{27}$ +31° (*c* 0.78, chloroform); $\nu_{max}^{CHCl_3}$ 3450 (OH, NH), 1670, and 1530 cm^{-1} (NHCO); *m/z*: 185 ($M^{\cdot+}$ − H_2O) and 171 ($M^{\cdot+}$ − CH_3OH).

Other fractions from the column contained additional **11** in admixture with its 5-epimer.

Anal. Calc. for $C_9H_{17}NO_4$ (203.24): C, 53.19; H, 8.43; N, 6.89. Found: C, 52.74; H, 8.30; N, 6.54.

*Methyl 2-acetamido-4-*O*-acetyl-2,3,6-trideoxy-β-*L-lyxo-*hexopyranoside* (**12**). — Acetic anhydride (0.5 mL) was added to a solution of **11** (20 mg, 98 μmol) in pyridine (5 mL), and the mixture was kept for 18 h at room temperature. T.l.c. (25:1 chloroform–methanol) then showed complete conversion of **11** into a single, faster-moving product. The excess of acetic anhydride was decomposed by the addition of water. The resulting solution was evaporated, and remaining traces of water and acetic acid were removed by co-evaporation of toluene from the residue,

which was then dried *in vacuo* over phosphorus pentaoxide, to give chromatographically pure **12** as a clear syrup; yield 22 mg (92%); *m/z*: 214 ($M^+ - OCH_3$) and 186 ($M^+ - CH_3CO_2^+$).

Methyl 2-acetamido-2,3,4,6-tetradeoxy-α-D-glycero-*hex-4-enopyranoside* (**13**). — Raney nickel (W. R. Grace, No. 28; 2 mL) was added to a solution of **9** (0.20 g, 0.48 mmol) in abs. ethanol (25 mL), and the mixture was stirred in a stoppered flask for 6 h. T.l.c. (2:1 ethyl acetate–hexane) then indicated complete disappearance of starting material, and the formation of a single, slower-moving product. The mixture was filtered, the catalyst washed with ethanol, the filtrate evaporated, and the residue dissolved in methanol to which silica gel had been added. The methanol was evaporated, and the impregnated silica gel was applied to a column of silica gel that was eluted with 2:1 ethyl acetate–hexane. Evaporation of fractions containing only **13** gave a white, amorphous solid, yield 50 mg (56%); *m/z*: 185 (M^+), 153 ($M^+ - CH_3OH$), 126 ($M^+ - NH_2Ac$), and 95 (126 – $\cdot OCH_3$).

Methyl 2-acetamido-2,3-dideoxy-α-D-ribo-*hexopyranoside* (**14**). — Raney nickel (15 mL, freshly prepared as described for desulfurization reactions[24]) was added to a suspension of compound **5** (2.0 g, 4.8 mmol) in methanol (50 mL), and the mixture was shaken for 3 h at room temperature. T.l.c. (9:1 benzene–methanol) showed complete disappearance of **5**, and formation of a single, slower-moving product. The mixture was filtered, and the nickel was washed with a large volume of methanol. Evaporation of the combined filtrate and washings gave **14** as a white, crystalline solid; yield 0.70 g (67%); m.p. 208–211°. Recrystallization from ethanol gave analytically pure **4**; m.p. 214–215° (lit.[19] m.p. 211–212°, lit.[20] m.p. 208–210°).

Anal. Calc. for $C_9H_{17}NO_5$ (219.24): C, 49.31; H, 7.82; N, 6.39. Found: C, 49.12; H, 7.64; N, 6.25.

Methyl 2-acetamido-4,6-O-benzylidene-2,3-dideoxy-α-D-ribo-*hexopyranoside* (**15**). — A solution of **14** (0.25 g, 1.1 mmol), α,α-dimethoxytoluene (0.40 g, 2.6 mmol), and *p*-toluenesulfonic acid monohydrate (0.02 g) in dry *N,N*-dimethylformamide (10 mL), in a 25-mL, round-bottomed flask equipped with an air-cooled condenser attached to a water aspirator, was stirred for 3 h at 75°. T.l.c. (9:1 benzene–methanol) then showed complete conversion of starting material into a single faster-moving product. The mixture was poured, with mechanical stirring, into a 10% aqueous solution of sodium hydrogensulfite (50 mL). After being stirred for 1 h, the initially gummy precipitate settled as a finely divided, amorphous solid. The product was collected by vacuum filtration, washed with water, and dried *in vacuo* over phosphorus pentaoxide; yield 0.27 g (77%). Recrystallization from oxolane–petroleum ether gave analytically pure **15**; m.p. 232° (dec.), $[\alpha]_D^{28}$ +51.1° (*c* 0.86, chloroform); lit.[20] m.p. 245° (subl.), $[\alpha]_D$ +55.5° (*c* 0.95); lit.[21] m.p. 224° (subl.), $[\alpha]_D$ +53.7° (*c* 1.0).

Anal. Calc. for $C_{16}H_{21}NO_5$ (307.34): C, 62.53; H, 6.89; N, 4.56. Found: C, 62.55; H, 6.86; N, 4.42.

REFERENCES

1 Preliminary reports: T. F. GALLAGHER AND D. HORTON, *Abstr. Pap. N.E. Regional Meet. Am. Chem. Soc., 12th*, June 27–30, 1982, Abstr. 151; T. F. GALLAGHER, M. S. Thesis, The Ohio State University, 1982.
2 F. ARCAMONE, *Doxorubicin, Anticancer Antiobiotics*, Academic Press, New York, 1981; D. D. VON HOFF, M. ROZENWEIG, AND M. SLAREK, *Adv. Pharmacol. Chemother.*, 15 (1978) 1–50.
3 T.-M. CHEUNG, D. HORTON, AND W. WECKERLE, *Carbohydr. Res.*, 74 (1979) 93–103, and previous papers cited therein.
4 E.-F FUCHS, D. HORTON, W. WECKERLE, AND E. WINTER-MIHALY, *J. Med. Chem.*, 22 (1979) 406–411.
5 D. HORTON, W. PRIEBE, AND W. R. TURNER, *Carbohydr. Res* , 94 (1981) 11–25.
6 E.-F. FUCHS, D. HORTON, W. WECKERLE, AND B. WINTER, *J. Antibiot.*, 32 (1979) 223–238.
7 D. HORTON AND W. PRIEBE, in H. EL KHADEM (Ed.), *Anthracycline Antibiotics*, Academic Press, 1982, pp. 197–224.
8 D. W. HENRY, *Cancer Treat. Rep.*, 6315 (1979) 845–854.
9 M ISRAEL AND R. J. MURRAY, *J. Med. Chem.*, 25 (1982) 24–28.
10 A. B. FOSTER, D. HORTON, N. SALIM, M. STACEY, AND J. M. WEBBER, *J. Chem. Soc.*, (1960) 2587–2596.
11 R. A. GALEMMO, JR , AND D. HORTON, *Carbohydr. Res.*, in press.
12 A. NEUBERGER, *J. Chem. Soc.*, (1941) 50–51.
13 W. MEYER ZU RECKENDORF AND H. J. LENZEN, *Tetrahedron Lett.*, (1979) 3657–3658.
14 S. HANESSIAN, *Carbohydr. Res.*, 2 (1966) 86–88.
15 B. HELFERICH AND E. HIMMEN, *Ber.*, 61 (1928) 1825–1835; M. J. BLAIR, *Methods Carbohydr. Chem.*, 2 (1963) 415–418.
16 T.-M. CHEUNG, D HORTON, AND W. WECKERLE, *Carbohydr Res.*, 58 (1977) 139–151; D. HORTON, T.-M CHEUNG, AND W. WECKERLE, *Methods Carbohydr. Chem.*, 8 (1980) 201–205; compare, L. E. S. BARATA, A. J. MARSAIOLI, L. VALENTE, A. OLESKER, G. LUKACS, AND T. T. THANG, *Carbohydr. Res.*, 90 (1981) 326–328.
17 D. HORTON AND W. WECKERLE, *Carbohydr. Res.*, 44 (1975) 227–240.
18 I. PELYVÁS, F. SZTARICSKAI, L. SZILÁGYI, R. BOGNAR, AND J. TAMAS, *Carbohydr. Res.*, 76 (1979) 79–84.
19 T. H. HASKELL, P. W K. WOO, AND D. R. WATSON, *J. Org. Chem.*, 42 (1977) 1302–1305.
20 C. L. BREWER AND R. D. GUTHRIE, *J. Chem Soc., Perkin Trans. 1*, (1974) 657–660.
21 K. KITAHARA, S. TAKASHI, H. SHIBATA, N. KURIHARA, AND M. NAKAJIMA, *Agric. Biol. Chem.*, 33 (1969) 748–754.
22 A. ROSENTHAL AND P. CATSOULACOS, *Can. J. Chem.*, 47 (1969) 2747–2750.
23 N K. KOCHETKOV AND O. S. CHIZOV, *Adv. Carbohydr. Chem.*, 21 (1966) 39–93; O. S. CHIZHOV, L S. GOLOVKINA, AND N. S. WULFSON, *Carbohydr. Res.*, 6 (1968) 138–142
24 L F. FIESER AND M. FIESER, *Reagents for Organic Synthesis*, Vol 1, Wiley, New York, 1967, p. 729.