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SYNTHETIC APPROACHES TO KASUGAMINE*†

STEPHEN HANESSIAN AND ROBERT MASSE
Department of Chemistry, University of Montreal, Montreal, Quebec (Canada)
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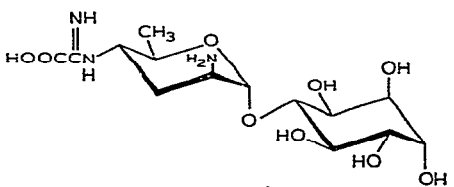
ABSTRACT

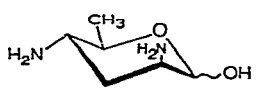
Reactions are described that lead to an immediate, chemical precursor of kasugamine, the amino-sugar component of the aminocyclitol antibiotic kasugamycin. The key reaction involved the introduction of a bromine atom by a stereoselective ring-opening of a benzylidene acetal.

INTRODUCTION

Kasugamine is the amino-sugar component of the aminocyclitol antibiotic kasugamycin[1]. It has a unique arrangement of amino and deoxy groups and, unlike other amino-sugars of the same class of antibiotics, it does not contain an oxygen



Kasugamycin



Kasugamine

function other than at the anomeric position and that involved in ring formation. The antibiotic, probably the simplest among the aminocyclitol type[2] structures, has been of continued interest because of a reported therapeutic effect on *Pseudomonas aeruginosa* infections in humans[3]. Its structure, established in 1966 by chemical means[4], has been confirmed by X-ray crystallographic data, and a total synthesis of the racemic antibiotic, starting from 3,4-dihydro-6-methyl-2*H*-pyran-2-one has been reported[6]. The synthesis of methyl kasugaminide has been reported by Nakajima and coworkers[7], starting from 3-deoxyhexose precursors, and by another group[8].

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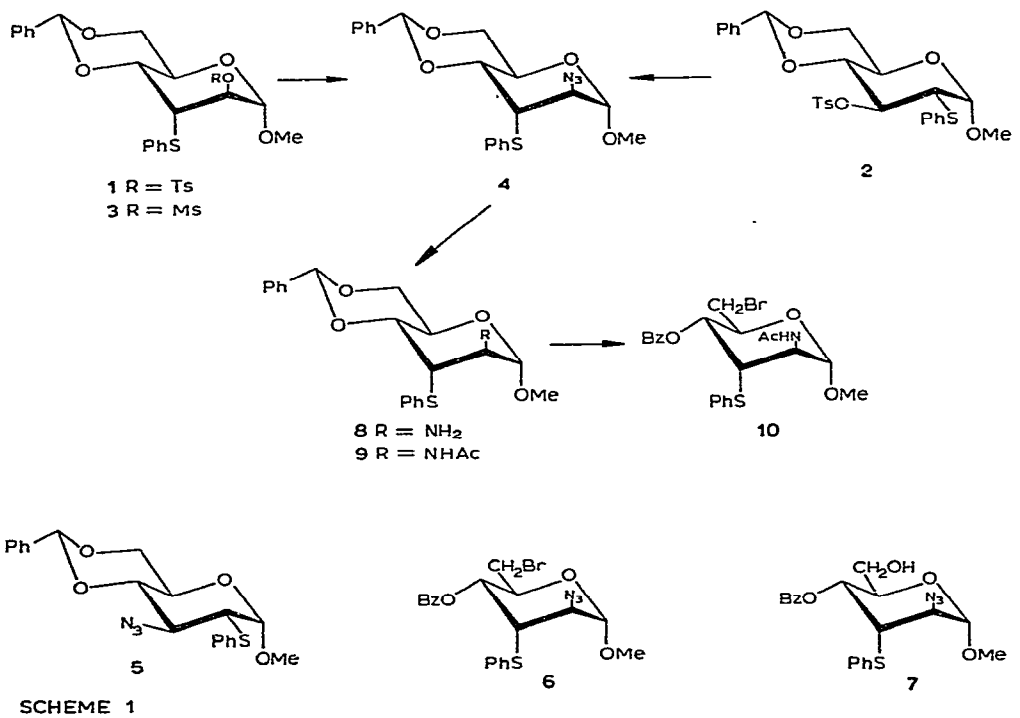
†Dedicated to Dr. Horace S. Isbell, in honour of his 75th birthday.

As part of a program concerning aminocyclitol antibiotics[9], we now report on various synthetic approaches to the kasugamine-type structure and to its immediate, chemical precursors. A consideration of the nature and stereochemical orientation of the amino groups in kasugamine made us aware of the necessity to develop synthetic approaches involving fewer steps and in high yields. Our approach is thus based on the stereocontrolled formation of functionalized intermediates that would also be of utility as precursors to other types of related amino-sugars.

RESULTS AND DISCUSSION

Since the introduction of a deoxy function at C-6 and an amino function at C-4 could be done[7] at later stages of the synthesis, the structural aspects to be considered first were the introduction of the remaining deoxy and amino functions. In a first approach (Scheme 1), the readily available methyl 4,6-*O*-benzylidene-3-*S*-phenyl-3-



SCHEME 1

thio-α-D-altropyranoside[10] was chosen as starting material, with the objective of introducing a potential, axial amino-group at C-2 *via* the ring opening of an episulfonium-ion intermediate. The resulting product could then be subjected to a ring opening of the benzylidene acetal with *N*-bromosuccinimide[11] (NBS), followed by reductive desulfuration and dehalogenation with Raney nickel, thus giving access to the 4-hydroxy analog of kasugamine. In pursuit of this initial objective, the crystalline

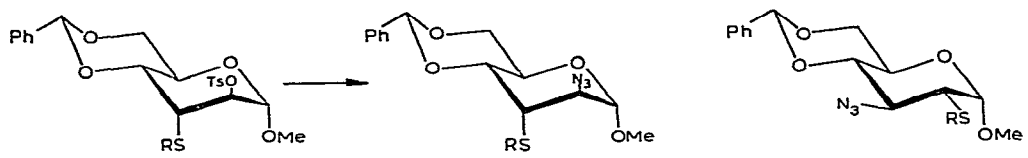
sulfonates **1** and **3** were prepared in high yield. Previously, we had shown that sulfonic esters of this type were prone to undergo a diaxial–diequatorial rearrangement[12], and care was exercised in handling these substances when in solution. In fact, when a solution of **1** in benzene was heated, the D-*gluco* isomer **2** was isolated in almost quantitative yield. The stereochemical assignment was made by analogy with similar transformations in this series and on the basis of n.m.r. spectroscopic data.

Treatment of **1** or **3** with sodium azide in methyl cellosolve gave the crystalline 2-azido derivative **4** in high yield. The same product was also obtained by similar treatment of **2**, but the yield was lower (52%). The introduction of the azide group can be explained on the basis of a regiospecific ring-opening of an intermediate *S*-phenylsulfonium ion, as called for in the original synthetic plan. The D-*altro* stereochemistry was assigned on the basis of n.m.r. spectroscopic data and precedents in the literature[13]. When a solution of **1** in methyl cellosolve was initially heated for 5 min and then treated with sodium azide in the usual manner, a small amount of a compound, isomeric with the major product **4**, was also formed, and it was assigned the D-*gluco* stereochemistry on the basis of spectroscopic data. A definitive, mechanistic interpretation for the divergent yields of **4** during its formation from **1** and **2** cannot be given. It could be speculated that the formation of the intermediate episulfonium ion[14] from **1** would be more favored, because of a favorable, stereoelectronic orientation of the nucleophilic sulfur atom with respect to the axial leaving-group, and a consequent relief of non-bonded 1,3-diaxial interactions.

Reduction of the azide function in **4** was effected with sodium borohydride in a mixture of *N*,*N*-dimethylformamide (DMF) and methanol, and a crystalline 2-amino derivative **8** was obtained in 91% yield. Acetylation then gave the corresponding 2-acetamido derivative **9**. The potential deoxy function at C-6 was introduced by separate treatment of **4** and **9** with NBS, and the corresponding 6-bromo derivatives **6** and **10** were obtained in yields of 50% and 53%, respectively. In the first reaction, a small amount of the benzoate **7** was also formed, resulting from a ring opening of the intermediate 4,6-benzoxonium ion by traces of moisture. Various attempts at effecting a simultaneous or a sequential reduction of the bromo, phenylthio, and azido groups let to mixtures due to a partial desulfuration of the phenylthio group. In a different approach aimed at introducing a potential deoxy function at C-3 in **10**, the latter compound was treated with methyl iodide, anticipating an intramolecular attack by the 2-acetamido group on a methylphenylsulfonium iodide intermediate, followed by the attack of iodide ion on the resulting oxazolinium ion. Again, various attempts in this direction were unsuccessful and led to the recovery of starting material.

The regiospecific introduction of such nucleophiles as azide ion and the carbanion derived from diethyl malonate[15], *via* 2,3-episulfonium ion intermediates, led us to explore the possibilities with other alkylthio derivatives. Controlled tosylation of methyl 4,6-*O*-benzylidene-3-*S*-ethyl-3-thio-α-D-altropyranoside and the corresponding 3-*S*-benzyl analog[16] gave the corresponding, crystalline sulphonates **11** and **12**, respectively. It should be mentioned that the participating ability of the alkylthio sulfur atom in these derivatives generally leads to mixtures of 2- and 3-chloro ana-

logs[17] as a result of the ready formation of 2,3-episulfonium ions from the initially formed sulphonates. Care had to be exercised in the manipulation of the crude, crystalline 3-alkylthio 2-sulphonates in order to avoid a diaxial–diequatorial rearrangement[12]. When the benzyl analog **12** was treated with sodium azide in methyl cellosolve, the major product was the expected, 2-azidoaltroside derivative **14**. A small amount (4.0%) of the D-*gluco* isomer was also formed. In the reaction of the 3-ethylthio derivative, an 18% yield of the crystalline 2-azidoaltroside **13** was obtained (Scheme 2).



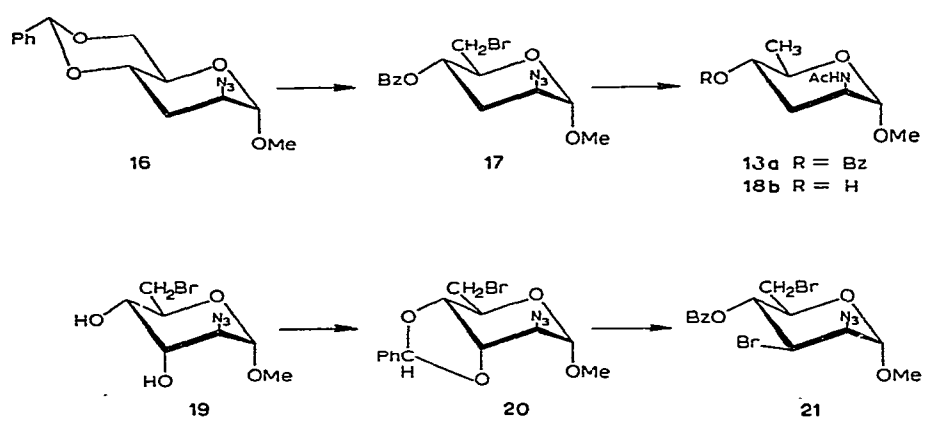
11 R = Et
12 R = CH_2Ph

13 R = Et
14 R = CH_2Ph

SCHEME 2

Clearly then, the phenylthio group appeared to be the most suitable, in terms of a regiospecific introduction of a potential amino function at C-2 in high yield. However, as pointed out earlier, difficulties encountered in its reductive removal posed a limitation on the approach in spite of the ready availability of all the intermediates.

In a modification of an existing approach to kasugamine[7], methyl 4,6-*O*-benzylidene-3-deoxy-α-D-*ribo*-hexopyranoside was tosylated[18], and the product was treated with sodium azide to give methyl 2-azido-4,6-*O*-benzylidene-2,3-dideoxy-α-D-*arabino*-hexopyranoside[7] (**16**) (Scheme 3). Although displacement reactions of 2-sulfonates in hexopyranosides are not common[19], the introduction of the axial azido



16 17 18a R = Bz
18b R = H

19 20 21

SCHEME 3

function occurred with relative ease, no doubt due to the absence of a C-3 substituent. Treatment of **16** with NBS in carbon tetrachloride effected smooth opening of the benzylidene ring and gave the corresponding 6-bromo derivative **17** in 80% yield. The latter compound was reduced and *N*-acetylated to give the 6-deoxy analog **18a** which in turn, was debenzoylated to the known methyl 2-acetamido-2,3,6-trideoxy-α-D-*arabino*-hexopyranoside[7] (**18b**). Although **18b** was obtained pure, it was non-crystalline; however, the spectroscopic and other physical characteristics were in accord with those of a sample synthesized independently according to the published procedure[7].

In a final approach, methyl 2-azido-4-*O*-benzoyl-6-bromo-2,6-dideoxy-α-D-altropyranoside[20], readily obtained from the appropriate benzylidene acetal, was debenzoylated to **19**. Treatment of **19** with benzaldehyde and zinc chloride afforded the 3,4-*O*-benzylidene derivative **20** as a syrup, which upon treatment with NBS gave crystalline methyl 2-azido-4-*O*-benzoyl-3,6-dibromo-2,3,6-trideoxy-α-D-mannopyranoside (**21**) in 82% yield. This versatile, polyfunctional derivative is obtained from readily available precursors by two benzylidene ring-opening reactions with NBS.

Sequential reduction, *N*-acetylation, and debenzoylation of **21** gave **18b** in high yield. The formation of **18b** indicates that the second bromine atom was introduced by a preferential attack at C-3. If it is assumed that the preponderant conformation in the ground state is **20**, or a skew form derived therefrom, then the attack of bromide ion[20] must take place *via* an equatorial or quasi-equatorial approach. It is of interest that a configurationally related compound, methyl 2,6-dichloro-2,6-dideoxy-3,4-*O*-isopropylidene-α-D-altropyranoside previously synthesized in this laboratory[21], was found to exist in a skew-boat conformation by X-ray crystallographic studies[22]. When the conformationally and configurationally related methyl 2-*O*-benzoyl-3,4-*O*-benzylidene-β-D-arabinopyranoside was treated with NBS, both of the expected bromo derivatives were formed as a result[23] of an attack at C-3 and C-4. It is difficult to assess the extent to which a neighboring-group participation of the 2-benzoate group and the formation of 2,3-benzoxonium ions[23] could influence the conformation of the intermediates, and hence the sites of bromination.

EXPERIMENTAL

Melting points are uncorrected. N.m.r. spectra were obtained for solutions in chloroform-*d* at 60 or 100 MHz, with tetramethylsilane as internal standard (*s*, singlet; *d*, doublet, *q*, quartet; *m*, multiplet; *b*, broad). The i.r. spectra (Nujol) were recorded on a Beckman IR-8 instrument. Optical rotations were measured with a Perkin–Elmer Model 141 automatic spectropolarimeter. T.l.c. was performed on silica gel GF_{254} (Merck), and the spots were detected with sulfuric acid, ammonium molybdate[24], and by visualization under a u.v. lamp. Column chromatography was effected on short columns of silica gel GF_{254} with application of moderate suction. Conventional processing signifies the drying of organic solutions over anhydrous sodium sulfate, filtration, and evaporation under diminished pressure.

Methyl 4,6-O-benzylidene-3-S-phenyl-3-thio-2-O-p-tolylsulfonyl-α-D-altropyranoside (**1**). — A solution containing 17.32 g (46.3 mmoles) of methyl 4,6-*O*-benzylidene-3-*S*-phenyl-3-thio-α-D-altropyranoside[10] in 250 ml of pyridine was cooled to 0° and treated with 29.9 g (0.15 mmole) of toluene-*p*-sulfonyl chloride in portions and with stirring. After standing at room temperature for 60 h, the solution was poured into ice–water and, the precipitate was filtered off and redissolved in 300 ml of dichloromethane. The solution was washed successively with M hydrochloric acid, saturated, aqueous sodium hydrogen carbonate, and water, and processed as usual to give a crystalline residue. Recrystallization from benzene–pentane gave **1** (20.6 g, 84%), m.p. 146–147°; $[\alpha]_D^{25}$ +19° (*c* 2.15, chloroform). N.m.r. data: τ 5.30 (*s*, H-1); 5.10 (*m*, H-2); 6.08 (*m*, H-3); 4.33 (*s*, PhC*H*); 6.60 (*s*, OMe); 7.60 (*s*, C_6H_4Me).

Anal. Calc. for $C_{27}H_{28}O_7S_2$: S, 12.13. Found: S, 12.29.

Methyl 4,6-O-benzylidene-2-S-phenyl-2-thio-3-O-p-tolylsulfonyl-α-D-glucopyranoside (**2**). — A solution of **1** (1.90 g, 3.60 mmoles) in 20 ml of anhydrous benzene was heated under reflux for 50 h. The solvent was then evaporated, and the resulting solid was recrystallized from ethanol to give **2** (1.85 g, 97.4%), m.p. 128–129°, $[\alpha]_D^{25}$ −79.3° (*c* 2.05, chloroform). N.m.r. data: τ 5.10 (*d*, $J_{1,2}$ 3.2 Hz; H-1); 6.82 (*dd*, $J_{2,1}$ 3.2, $J_{2,3}$ 7.8 Hz; H-2); 4.63 (*s*, PhC*H*); 6.56 (*s*, OMe); 7.80 (*s*, C_6H_4Me).

Anal. Calc. for $C_{27}H_{28}O_7S_2$: S, 12.13. Found: 12.27.

Methyl 2-azido-4,6-O-benzylidene-2-deoxy-3-S-phenyl-3-thio-α-D-altropyranoside (**4**). — (*a*) From **3**. To a solution of **3** (0.15 g, 0.25 mmole) in 10 ml of methyl cellosolve was added sodium azide (57 mg, 0.88 mmole), and the suspension was heated under reflux for 45 min. The solvent was evaporated by codistillation with toluene, and the resulting residue was dissolved in 50 ml of dichloromethane. After washing with water, the organic phase was processed in the usual manner to give a colorless solid that was homogeneous by t.l.c. (benzene–ethyl acetate, 4:1). Recrystallization from ethanol–pentane gave **4** (80 mg, 81%), m.p. 95–96°, $[\alpha]_D^{25}$ +1.0° (*c* 3.75, chloroform). N.m.r. data: τ 5.30 (*s*, H-1); 4.35 (*s*, PhC*H*); 6.53 (*s*, OMe).

Anal. Calc. for $C_{20}H_{21}N_3O_4S$: C, 60.07; H, 5.25; N, 10.52, S, 8.02. Found: C, 59.99; H, 5.32; N, 9.91; S, 8.19.

(*b*) From **1**. By essentially the procedure described in (*a*), **1** (1.06 g, 2.0 mmoles) gave **4** (0.78 g, 98%) as a chromatographically homogeneous, crude product. After recrystallization from the same solvent mixture, the product had m.p. 95–96°.

(*c*) From **2**. By applying to **2** the experimental procedure described in (*a*), **4** was obtained in 62% yield.

Methyl 3-azido-4,6-O-benzylidene-3-deoxy-2-S-phenyl-2-thio-α-D-glucopyranoside (**5**) — A solution of the sulphonate **1** (18.0 g) in 200 ml of methyl cellosolve was heated at 85–90° for 5 min. Analysis of an aliquot by t.l.c. (benzene–ethyl acetate, 4:1) revealed **1**, the isomer **2**, and a polar compound at the origin of the t.l.c. plate. Sodium azide (18.0 g, 8 mmoles) was added, and the suspension was heated under reflux with stirring for 1 h. The solvent was evaporated, the residue was suspended in dichloromethane, and processing was continued in the usual manner to give a syrup. Crystallisation from ethanol–pentane gave **4** (4.5 g, 33%), m.p. 95–96°.

The mother liquors were evaporated to dryness, and the resulting syrup was taken up in ethanol–water to give **5** (0.2 g), m.p. 120–122°, $[\alpha]_D^{25}$ −49.6° (*c* 1.36, chloroform). N.m.r. data: τ 5.21 (*d*, $J_{1,2}$ 3.5 Hz, H-1); 6.93 (*dd*, $J_{2,1}$ 3.6, $J_{2,3}$ 10.5 Hz; H-2); 4.47 (*s*, PhC*H*); 6.60 (*s*, OMe).

Anal. Calc. for $C_{20}H_{21}N_3O_4S$: C, 60.07; H, 5.25; N, 10.52; S, 8.02. Found: C, 60.11; H, 5.32; N, 10.32; S, 8.17.

*Methyl 2-azido-4-*O*-benzoyl-6-bromo-2,6-dideoxy-3-*S*-phenyl-3-thio-α-*D*-altropyranoside* (**6**). — To a solution of **4** (2.07 g, 5.2 mmoles) and *N*-bromosuccinimide (1.15 g, 6.47 mmoles) in 75 ml of carbon tetrachloride were added 4.0 g of barium carbonate, and the suspension was heated under reflux with stirring for 2 h. The color of the solution changed progressively to yellow–orange and then to colorless at the end of the reaction. Filtration and evaporation gave a syrup that was dissolved in dichloromethane, and the solution was washed with water and processed as usual to give a colorless solid. Recrystallization from ethanol–pentane gave **6** (1.19 g, 53%), m.p. 92.5–94°, $[\alpha]_D^{25}$ −26.3° (*c* 5.0, chloroform). N.m.r. data: τ 5.22 (*d*, $J_{1,2}$ 2.6 Hz, H-1); 4.57 (*dd*, $J_{4,3}$ 4.0, $J_{4,5}$ 5.8 Hz; H-4); 6.46 (*s*, OMe).

Anal. Calc. for $C_{20}H_{20}BrN_3O_4S$: C, 50.22; H, 4.21; Br, 16.70; N, 8.77; S, 6.70. Found: C, 50.16; H, 4.26; Br, 16.98; N, 8.61; S, 6.84.

In another experiment, in which the carbon tetrachloride was not dried (alumina) prior to use and contained traces of water, the reaction gave two products. These were the expected bromide **6** (0.73 g, 34%; m.p. 93–94°), and 0.25 g of methyl 2-azido-4-*O*-benzoyl-2-deoxy-3-*S*-phenyl-3-thio-α-D-altropyranoside (**7**), isolated as a syrup; ν_{max} 1710 (ester) and 3460 cm^{-1} (hydroxyl). N.m.r. data: τ 5.32 (*d*, $J_{1,2}$ 2.5 Hz; H-1); 4.60 (*dd*, $J_{4,3}$ 3.0, $J_{4,5}$ 5.7 Hz; H-4); 6.61 (*s*, OMe).

*Methyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-3-*S*-phenyl-3-thio-α-*D*-altropyranoside* (**9**). — A solution of **4** (1.12 g, 2.81 mmoles) in a mixture of 4 ml of *N,N*-dimethylformamide and 25 ml of methanol was treated portionwise with 1.37 g (36.1 mmoles) of sodium borohydride at 0°. After being kept at room temperature for 15 h, the solution was evaporated to dryness by codistillation with 1-butanol, the residue was dissolved in 75 ml of dichloromethane, the solution was washed with water, and the organic phase was processed in the usual manner to give 0.948 g (91%) of methyl 2-amino-4,6-*O*-benzylidene-2-deoxy-3-*S*-phenyl-3-thio-α-D-altropyranoside (**8**), m.p. 147–148°, $[\alpha]_D^{25}$ −41.8° (*c* 2.0, chloroform). *Anal.* Calc. for $C_{20}H_{23}NO_4S$: C, 64.32; H, 6.21; N, 3.75; S, 8.59. Found: C, 64.11; H, 6.32; N, 3.66; S, 8.32.

A portion of **8** (0.623 g, 1.67 mmoles) was acetylated in pyridine (8 ml) in the usual way to give **9** (0.6 g, 88%), m.p. 194–195.5° (from ethanol–pentane), $[\alpha]_D^{25}$ +16.8° (*c* 2.20, chloroform). N.m.r. data: τ 5.27 (*s*, H-1); 6.47 (*s*, OMe); 4.18 (*s*, PhC*H*); 7.61 (*s*, NCOCH_3); 3.34 (*b*, N*H*).

Anal. Calc. for $C_{22}H_{25}NO_5S$: C, 63.53; H, 6.06; N, 3.37; S, 7.72. Found: C, 63.35; H, 6.07; N, 3.28; S, 7.70.

*Methyl 2-acetamido-4-*O*-benzoyl-6-bromo-2,6-dideoxy-3-*S*-phenyl-3-thio-α-*D*-altropyranoside* (**10**). — To a solution of 0.276 g (0.66 mmole) of **9** and 0.167 (0.94 mmole) of *N*-bromosuccinimide in 15 ml of carbon tetrachloride, barium carbonate

(0.7 g) was added, and the suspension was stirred under reflux for 40 min. The suspension was filtered, the solvent was evaporated, and the residue was dissolved in chloroform and processed as usual. Recrystallisation of the resulting, colorless solid twice from a mixture of ethanol and petroleum ether gave **10** (0.163 g, 49.5%), m.p. 146–147°, $[\alpha]_D^{25}$ −5.0° (*c* 2.4, chloroform). N.m.r. data: τ 5.34 (*s*, H-1); 4.75 (*dd*, $J_{4,3}$ 4.0, $J_{4,5}$ 6.5 Hz, H-4); 6.53 (*s*, OMe); 7.97 (*s*, $NCOCH_3$); 3.83 (*dd*, N*H*).

Anal. Calc. for $C_{22}H_{24}BrNO_5S$: Br, 16.16; N, 2.83; S, 6.48. Found: Br, 16.75; N, 2.51; S, 6.38.

Attempted reduction and iodination of compounds **4**, **6**, *and* **10**. — (*a*) When solutions of **4** and **6** in ethanol were treated with Raney nickel (No. 28; W. R. Grace & Co., Pittsburg, Tenn.) at room temperature or at reflux temperature, mixtures of products were obtained in which the azido group was reduced to an amine but the phenylthio group was still present (detection with an acidic potassium permanganate spray on silica-gel plates).

(*b*) Compound **10** was treated with methyl iodide (room temperature and at reflux, up to 24 h) in the following solvents: methyl iodide, acetone, *N*,*N*-dimethylformamide (75–80°), *N*,*N*-dimethylformamide containing one equivalent of sodium iodide (70°). In each experiment, the starting material was recovered in high yield.

Methyl 4,6-O-benzylidene-3-S-ethyl-3-thio-2-O-p-tolylsulfonyl-α-D-altropyranoside (**11**). — A solution of methyl 4,6-*O*-benzylidene-3-*S*-ethyl-3-thio-α-D-altropyranoside (0.65 g, 1.99 mmoles) in 10 ml of anhydrous pyridine was cooled to 0° and treated protionwise with 2.5 g (13.1 mmoles) of tosyl chloride. After 3 days at 5°, the solution was poured into ice–water with stirring, and the colorless precipitate was filtered off, washed, and redissolved in dichloromethane. The solution was washed successively with M hydrochloric acid, aqueous sodium hydrogen carbonate, and water, and the organic phase was processed as usual, keeping the bath temperature below 30° during evaporation. The colorless solid was recrystallized from dichloromethane–ether to give **11** (0.7 g, 82%), m.p. 111.5–112.5°, $[\alpha]_D^{25}$ +78° (*c* 2.0, chloroform). N.m.r. data: τ 5.51 (*s*, H-1); 6.63 (*s*, OMe); 4.53 (*s*, PhC*H*); 7.59 (*s*, $C_6H_4CH_3$); 8.93 (*t*, CH_2CH_3).

Anal. Calc. for $C_{23}H_{28}O_7S_2$: S, 13.34. Found: 13.05.

Methyl 3-S-benzyl-4,6-O-benzylidene-3-thio-2-O-p-tolylsulfonyl-α-D-altropyranoside (**12**). — A solution of methyl 3-*S*-benzyl-4,6-*O*-benzylidene-3-thio-α-D-altropyranoside[16] (9.23 g, 23.8 mmoles) in 150 ml of anhydrous pyridine was cooled to 0° and treated portionwise with 20.0 g (105 mmoles) of tosyl chloride. Processing, as described for **11**, gave a colorless solid that was recrystallized from benzene–pentane to give **12** (10.0 g, 77.3%), m.p. 105–107°, $[\alpha]_D^{25}$ −27.4° (*c* 2.3, chloroform). N.m.r. data: τ 5.55 (*s*, H-1); 6.75 (*s*, OMe); 4.46 (*s*, PhC*H*); 7.60 (*s*, $C_6H_4CH_3$); 6.30 (*s*, SCH_2Ph).

Anal. Calc. for $C_{28}H_{30}O_7S_2$: S, 11.81. Found: S, 11.06.

Methyl 2-azido-4,6-O-benzylidene-2-deoxy-3-S-ethyl-3-thio-α-D-altropyranoside (**13**). — A suspension of **11** (10.72 g, 22.3 mmoles) and sodium azide (5.0 g, 76.8 mmoles) in Methyl Cellosolve (200 ml) was heated under reflux with stirring for 1 h. The solvent was evaporated to dryness by codistillation with toluene, the residue was

suspensed in 300 ml of chloroform, and processing was continued in the usual manner. The crystalline product (7.06 g, 90%), m.p. 107.5–109°, contained two components (t.l.c.; benzene–ethyl acetate, 4:1) in a ratio of 1:1 (estimated by n.m.r. spectroscopy and by the intensities of spots in t.l.c.). Fractional crystallization from methanol gave **13** (1.45 g, 18%), m.p. 111–112°, $[\alpha]_D^{25}$ +21.9° (*c* 2.65, chloroform). N.m.r. data: τ 5.51 (*s*, H-1); 6.68 (*s*, OCH_3); 4.53 (*s*, Ph C*H*); 8.83 (*t*, CH_3CH_2); 7.33 (*q*, CH_2CH_3).

Anal. Calc. for $C_{16}H_{21}N_3O_4S$: C, 54.62; H, 5.97; N, 11.96; S, 9.12. Found: C, 54.55; H, 6.05; N, 11.96; S, 9.08.

Spectroscopic examination (n.m.r., i.r.) of the mother liquors indicated that the other component was the corresponding 3-azido-3-deoxy-D-*gluco* isomer, corresponding to **13**.

*Methyl 2-azido-3-*S*-benzyl-4,6-*O*-benzylidene-2-deoxy-3-thio-α-*D*-altropyranoside* (**14**) *and methyl 3-azido-2-*S*-benzyl-4,6-*O*-benzylidene-3-deoxy-2-thio-α-*D*-glucopyranoside* (**15**). — A suspension of **12** (7.24 g, 13.4 mmoles) and sodium azide (2.0 g, 30.8 mmoles) in Methyl Cellosolve (100 ml) was heated under reflux with stirring for 45 min. Filtration and evaporation gave a solid residue that was dissolved in 100 ml of chloroform, the solution was washed with water, and the organic phase was processed as usual to give a solid (6.40 g, 83.2%) that consisted of two compounds in the ratio of 4:1 (t.l.c.; benzene–ethyl acetate, 4:1). Fractional crystallization from methanol gave the D-*altro* isomer **14** as the first crop (2.54 g, 39.8%), m.p. 132.5–134°, $[\alpha]_D^{25}$ −106.3° (*c* 3.15, chloroform). N.m.r. data: τ 5.53 (*s*, H-1); 6.68 (*s*, OCH_3); 4.46 (*s*, PhC*H*); 6.20 (*s*, SCH_2Ph).

Anal. Calc. for $C_{21}H_{23}N_3O_4S$: C, 61.00; H, 5.61; N, 10.16; S, 7.75. Found: C, 61.11; H, 5.57; N, 10.10; S, 7.82.

The material recovered from the mother liquors was recrystallised to give the D-*gluco* isomer **15** (0.25 g, 45%), m.p. 150–152°, $[\alpha]_D^{25}$ −121.2° (*c* 2.50, chloroform). N.m.r. data: τ 5.57 (*d*, $J_{1,2}$ 3.5 Hz; H-1); 7.51 (*dd*, $J_{2,1}$ 3.5; $J_{2,3}$ 7.0 Hz; H-2); 6.73 (*s*, OCH_3); 4.54 (*s*, PhC*H*); 6.13 (*s*, SCH_2Ph).

Found: C, 61.85; H, 5.67; N, 10.10; S, 7.85.

The final mother-liquors contained a mixture of **14** and **15** that was not further separated.

*Methyl 2-azido-4-*O*-benzoyl-6-bromo-2,3,6-trideoxy-α-*D*-arabino-hexopyranoside* (**17**). — To a solution of 0.122 g (0.42 mmole) of methyl 2-azido-4,6-*O*-benzylidene-2,3-dideoxy-α-D-*arabino*-hexopyranoside[7] (**16**) and 86 mg (0.48 mmole) of *N*-bromosuccinimide in 10 ml of carbon tetrachloride was added barium carbonate (0.33 g), and the suspension was heated under reflux with stirring for 2 h. Filtration and evaporation gave a syrup that was dissolved in chloroform, and the solution was then processed as usual to afford **17** as a chromatographically homogeneous, colorless syrup (0.124 g, 80%), $[\alpha]_D^{25}$ +58.8° (*c* 3.40, chloroform); I.r. data 1720 (ester), 2100 cm^{-1} (azide). N.m.r. data: τ 5.37 (*s*, H-1); 7.74 (*m*, H-3,3'); 4.87 (*m*, $J_{4,3e}$ 5.5, $J_{4,3a}$ 9.5, $J_{4,5}$ 9.5 Hz; H-4); 6.53 (*s*, OCH_3).

*Methyl 2-azido-3,4-*O*-benzylidene-6-bromo-2,6-dideoxy-α-*D*-altropyranoside* (**20**). — A solution of methyl 2-azido-4-*O*-benzoyl-6-bromo-2,6-dideoxy-α-D-altropyrano-

side[20] (1.20 g, 3.19 mmoles) in 60 ml of methanol was debenzoylated with a catalytic amount of sodium methylate. After neutralization with Dowex-50 (H^+) resin, the solution was filtered and processed as usual to give methyl 2-azido-6-bromo-2,6-dideoxy-α-D-altropyranoside (**19**) as a syrup (0.75 g, 85%), $[\alpha]_D^{25}$ +70.4° (*c* 3.60, chloroform).

A solution of **19** (2.27 g, 8.07 mmoles) in 5 ml of benzaldehyde and 10 ml of *p*-dioxane containing 1.5 g zinc chloride was stirred at room temperature for 24 h. The solution was poured into ice–water with vigorous stirring and extracted with chloroform, and the extract was processed as usual to give a syrup. Purification by chromatography on silica gel (hexane and hexane–ether) gave **20** as a syrup (2.20 g, 74%), $[\alpha]_D^{25}$ +3.5° (*c* 2.60, chloroform). N.m.r. data: τ 5.51 (*s*, H-1); 6.50 (*s*, OCH_3); 4.29 (*s*, PhC*H*).

Methyl 2-azido-4-O-benzoyl-3,6-dibromo-2,3,6-trideoxy-α-D-mannopyranoside (**21**). — To a solution of **20** (1.117 g, 3.01 mmoles) and *N*-bromosuccinimide (0.567 g, 3.18 mmoles) in 80 ml of carbon tetrachloride was added barium carbonate (3.0 g), and the suspension was heated under reflux with stirring for 40 min. After filtration and evaporation, the solid residue was dissolved in chloroform, and the solution was washed with water and processed in the usual manner to give a crystalline product. Recrystallization from ethanol gave **21** (1.10 g, 82%), m.p. 128–129°, $[\alpha]_D^{25}$ +41.2° (*c* 3.15, chloroform). N.m.r. data; τ 5.18 (*s*, H-1); 5.37 (*q*, H-3, $J_{3,2}$ 3.3, $J_{3,4}$ 10.0 Hz; H-3); 4.58 (*t*, H-4, $J_{4,3} = J_{4,5} = 10$ Hz; H-4); 6.52 (*s*, OMe). I.r. data: 1720 (ester) and 2110 cm^{-1} (azide).

Anal. Calc. for $C_{14}H_{15}Br_2N_3O_4$: C, 45.55; H, 4.09; Br, 21.64; N, 11.38. Found: C, 45.44; H, 4.12; Br, 21.61; N, 11.23.

Methyl 2-acetamido-2,3,6-trideoxy-α-D-arabino-hexopyranoside (**18b**). — (*a*) A suspension of **17** (0.518 g, 1.38 mmoles) in 60 ml of methanol containing 0.52 g of 5% palladium-on-charcoal and 0.5 g of barium carbonate was hydrogenated for 12 h. The suspension was filtered, the filtrate was treated with 2.0 ml of acetic anhydride, and after 1 h the solution was treated with a small piece of ice and then with aqueous sodium hydrogen carbonate. After evaporation of the solution to a small volume (~10 ml), the product was extracted with dichloromethane, and the solution was processed to give methyl 2-acetamido-4-O-benzoyl-2,3,6-trideoxy-α-D-arabino-hexopyranoside (**18a**) as a chromatographically homogeneous foam (0.36 g, 83%).

A portion (0.191 g, 0.62 mmole) of **18a** in 15 ml of anhydrous methanol was treated with a catalytic amount of sodium methylate. After standing for 10 h at room temperature, the solution was neutralized with Dowex-50(H^+) resin and filtered, and the filtrate was evaporated to dryness. The resulting syrup, which was essentially homogeneous by t.l.c. (benzene–ethyl acetate, 2.5:1), failed to crystallize and was purified by chromatography over silica gel to give **18b** as a colorless syrup (0.12 g, 95%), $[\alpha]^{25}$ +59.8° (*c* 1.10, ethanol); lit.[7] $[\alpha]_D^{25}$ +64° (*c* 1.0 ethanol).

(*b*) A suspension of **20** (1.49 g, 3.31 mmoles) in 100 ml of methanol containing 2.5 g of 5% palladium-on-charcoal and 2.0 g of barium carbonate was hydrogenated for 48 h. The suspension was filtered, the filtrate was treated with acetic anhydride,

and the solution was processed as in (*a*) to give 0.64 g (72%) of **21** as a chromatographically homogeneous foam (benzene–ethyl acetate–methanol, 3:1:0.1). Debenzoylation of **21** as in (*a*) gave **18b** as a chromatographically homogeneous, colorless syrup (0.4 g, 96%), $[\alpha]_D^{25}$ +60.1° (*c* 1.25, ethanol).

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