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6-THIO- AND -SELENO-α-D-GLUCOSE ESTERS OF DIMETHYLARSINOUS ACID

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ABSTRACT

Syntheses of 1,2,3,4-tetra-*O*-acetyl-6-*S*-dimethylarsino-6-thio-α-D-glucopyranose (**4**), 6-*S*-dimethylarsino-6-thio-D-glucopyranose (**5**), 1,2,3,4-tetra-*O*-acetyl-6-*Se*-benzoyl-6-seleno-α-D-glucopyranose (**6**), 6,6′-diselenobis(1,2,3,4-tetra-*O*-acetyl-α-D-glucopyranose) (**7**), and 1,2,3,4-tetra-*O*-acetyl-6-*Se*-dimethylarsino-6-seleno-α-D-glucopyranose (**8**) are described. The n.m.r.-spectral properties of the compounds are given. The inertness of the α-anomeric species to nucleophilic attack is discussed in terms of the stereochemistry of the respective anomers.

INTRODUCTION

All previous reports in this series[1] have dealt with the preparation and properties of derivatives of β-D-glucopyranose. This paper describes the first successful syntheses of the α-anomeric derivatives. The use of thio- and selenopseudoureido derivatives as synthetic intermediates, previously used with great succes in the preparation of the β-anomeric derivatives, was not successful in the present investigation. Alternative intermediates were required and their preparation is described. An explanation of the failure of the α-D-glucopyranose to form the pseudoureido derivatives is offered.

DISCUSSION

In all of our previous studies[1], the preparation of thiopseudoureido and seleno- or *N,N*-dimethylselenopseudoureido derivatives from acetylated α-D-glucopyranosyl halides and acetylated 6-deoxy-6-halo-β-D-glucopyranose was found to proceed readily and in excellent yield. However, all attempts to prepare pseudoureido derivatives of α-D-glucopyranose by reactions between 1,2,3,4-tetra-*O*-acetyl-6-deoxy-6-iodo-α-D-glucopyranose[2] (**1**) and thiourea, or **1** and selenourea or *N,N*-substituted selenoureas in various organic solvents were unsuccessful.

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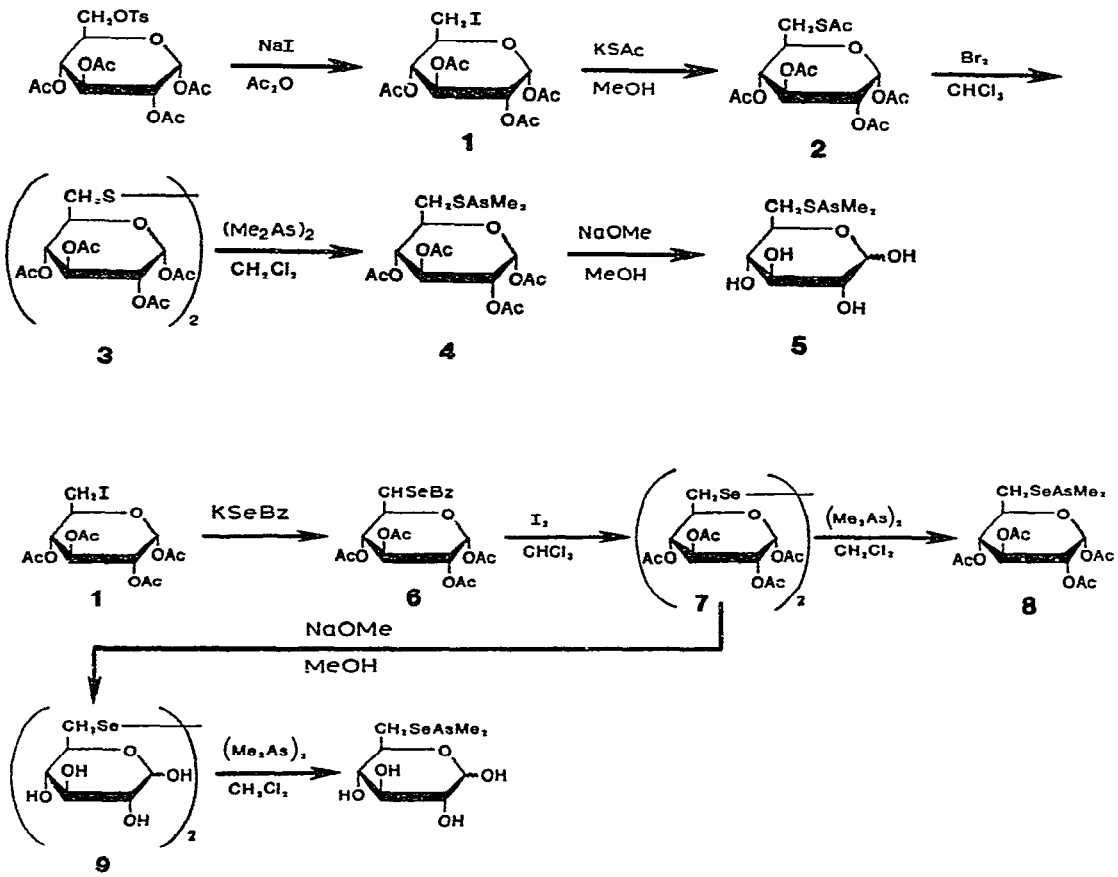
The preparation of alkyl- or aryl-thiols from alkyl- or aryl-xanthates in the presence of such bases as ethylenediamine or 2-aminoethanol has been described[3,4]. Attempts to prepare the disulfide **3** from 1,2,3,4-tetra-*O*-acetyl-6-*S*-ethoxy(thiocarbonyl)-6-thio-α-D-glucopyranose[5] or from 1,2,3,4-tetra-*O*-acetyl-6-*S*-methoxy-(thiocarbonyl)-6-thio-α-D-glucopyranose*, by basic or thermal cleavage of the xanthate ester groups to thiol under conditions that do not cause concurrent cleavage of the acetyl groups, were unsuccessful. The methods used were those that involve heating in pyridine or aniline, with subsequent oxidation.



However, a modification of the method of Horton *et al.*[6], which utilizes the oxidation of tetra-*O*-acetyl-1-*S*-acetyl-1-thio-β-D-glucopyranose with bromine to

*Prepared from 1,2,3,4-tetra-*O*-acetyl-6-deoxy-6-iodo-α-D-glucopyranose and potassium methylxanthate by refluxing in acetone for 30 min. The product was obtained only in the form of a syrup.

give bis(tetra-*O*-acetyl-β-D-glucopyranosyl) disulfide was successfully used to oxidize the α-6-thioacetate **2** (ref. 5) to disulfide **3** (ref. 7). The modification involves the use of one equivalent of bromine instead of an excess. Also, the preparation is limited to a small-scale (1.5 g of 6-thioacetate **2**) conversion. This method makes available the disulfide **3** in fewer steps and in an improved yield (73%) as compared to the method reported by Pacsu *et al.*[7]. They prepared the disulfide **3** in 52% yield by way of 1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranose 6-(sodium thiosulfate).

Compound **4** was prepared in quantitative yield by the homolytic addition of tetramethyldiarsine[8] to the disulfide **3**. The coupling constant and the chemical shift of the anomeric proton ($J_{1,2}$ 3.4 Hz, τ 3.7) are close to those of 1,2,3,4,6-penta-*O*-acetyl-α-D-glucopyranose ($J_{1,2}$ 3.3 Hz, τ 3.66)[9].

Deacetylation of **4** by sodium methoxide gave 6-*S*-dimethylarsino-6-thio-D-glucopyranose (**5**) as a 1:1 anomeric mixture. The coupling constants and chemical shifts (α anomer: $J_{1,2}$ 3.0 Hz, τ 4.2; β anomer: $J_{1,2}$ 8.0 Hz, τ 5.4) are close to those of α- and β-D-glucopyranoses (α anomer: $J_{1,2}$ 3.5 Hz, τ 4.68; β anomer: $J_{1,2}$ 7.5 Hz, τ 5.26)[10].

The acetylated α-6-selenobenzoic ester **6** was prepared in quantitative yield by refluxing 1,2,3,4-tetra-*O*-acetyl-6-deoxy-6-iodo-α-D-glucopyranose[2] (**1**) and potassium selenobenzoate[11] in acetone. The white crystalline compound is stable in air. The coupling constant ($J_{1,2}$ 3.4 Hz) and chemical shift (τ 3.7) of the anomeric proton were taken as evidence of the α-anomeric configuration.

Oxidation of **6** by bromine to give **7** proceeded in very low yield (18%). The use of iodine, a milder oxidant, improved the yield to 77–81% at ice–water temperature and to 58% at room temperature. The coupling constant ($J_{1,2}$ 3.4 Hz) and chemical shift (τ 3.7) of the anomeric proton were also indicative of the α-anomeric configuration.

Compound **8** was prepared in quantitative yield by addition of tetramethyldiarsine[8] to the diselenide **7**. As in the case of the β anomer of **8**, the compound is stable in air but difficult to recrystallize from organic solvents without decomposition. The α-anomeric configuration of **8** is indicated by the coupling constant (3.4 Hz) and chemical shift (τ 3.7) of the anomeric proton.

Attempts to prepare 6-*Se*-dimethylarsino-6-seleno-α-D-glucopyranose by addition of tetramethyldiarsine[8] to 6,6′-diselenobis(D-glucopyranose) were unsuccessful.

Mass spectrometry of compounds **4** and **8** by the electron-impact method showed molecular-ion peaks, *m/e* 468 (11%) and 516 (3%) [relative to H_3CCO^+, *m/e* (100%)]; less-intense peaks, *m/e* 137 (7%) and *m/e* 185 (6.6%) were observed for $^+SAsMe_2$ and $^+SeAsMe_2$. Fragmentation of **8** also showed an unidentified peak at *m/e* 183 (3.7%) which presumably contains the As–Se moiety.

Four basic fragmentation-pathways have been reported for hexopyranose pentaacetates under electron impact[12]. The major pathway for compound **4** is that designated as *A* by Chizhov *et al.*[12a], with modification in the later stage of fragmentation. According to this pathway, the molecular ion (*m/e* 468), by loss of the 1-acetoxyl group and further loss of an additional acetoxyl group from the sugar ring, gives a

fragment having *m/e* 349. The loss of $AsMe_2$ from this last fragment yields a major fragment having *m/e* 245 (23%). Subsequent to this stage, the fragmentation pathway follows that reported for the hexopyranose pentaacetates[12a]. A major fragmentation-pathway for hexopyranose pentaacetates, referred to as *C* by Chizhov and co-workers[12a], as well as a minor pathway referred to as *D*, were both observed as minor pathways in the electron-impact fragmentation of **4**. However, pathway *B*[12a] was not observed.

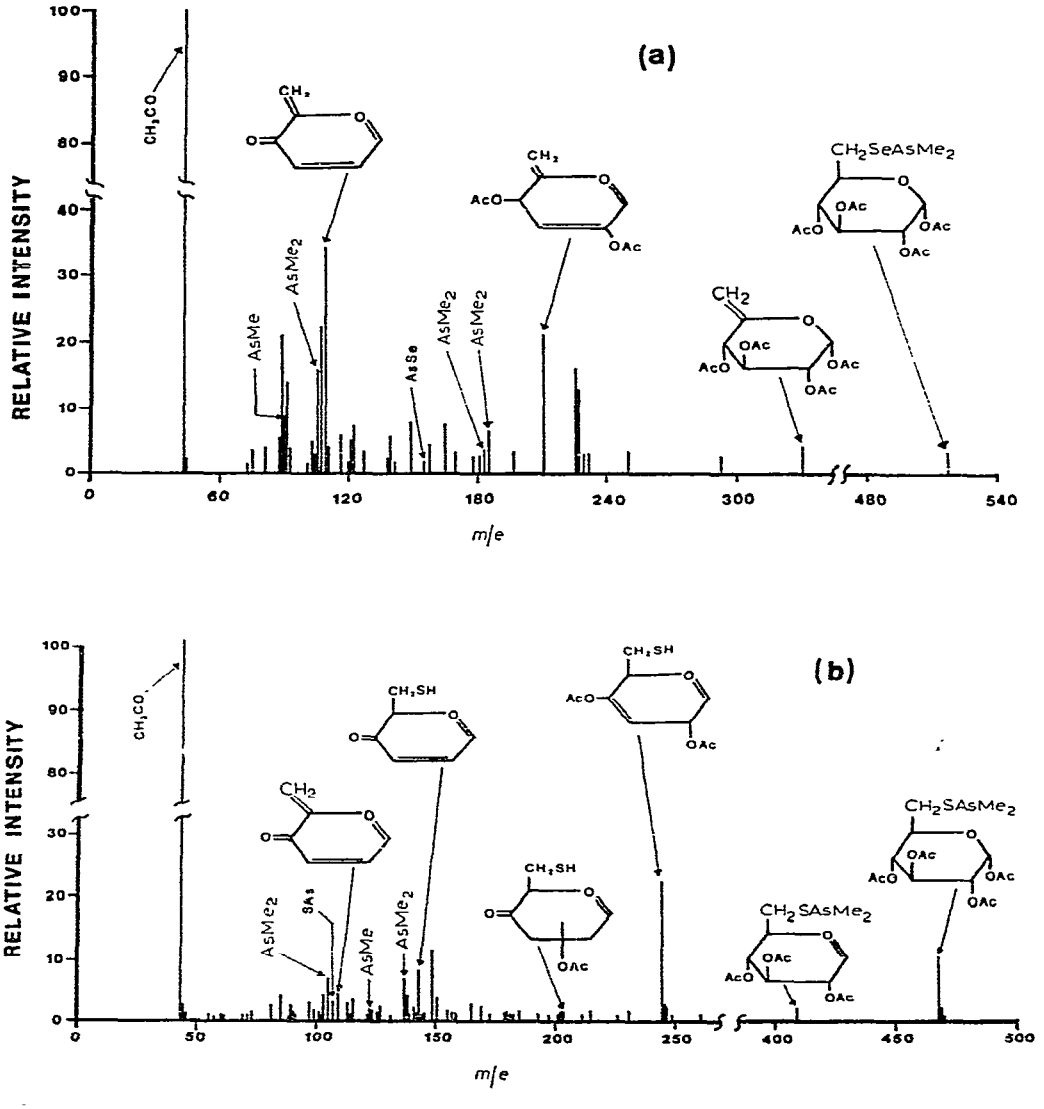
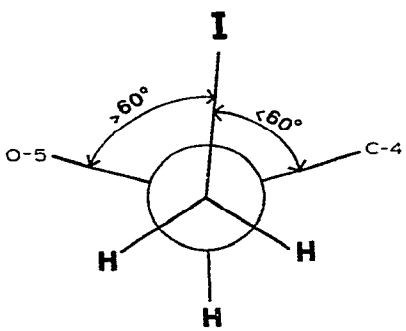


Fig. 1. The mass spectrum of (*a*) 1,2,3,4-tetra-*O*-acetyl-6-*Se*-dimethylarsino-6-seleno-α-D-glucopyranose (**8**) and (*b*) 1,2,3,4-tetra-*O*-acetyl-6-*S*-dimethylarsino-6-thio-α-D-glucopyranose (**4**).

The greater lability of the selenium–carbon bond causes compound **8** to suffer fragmentation primarily by loss of $SeAsMe_2$. This is followed by the previously mentioned pathway *A*[12a]. Similar observations were reported by Chizhov *et al.*[12c]. in their studies of the mass spectra of 6-deoxy-6-halogeno-α-D-glucopyranose tetraacetates. The lability of the iodine–carbon bond results in the loss of iodine as the first step in the fragmentation of this compound. This fragmentation represents the major pathway (*A*). Pathways *C* and *D* were observed as minor pathways for compound **8**, but pathway *B* was not observed. The mass-spectral patterns are shown in Fig. 1.

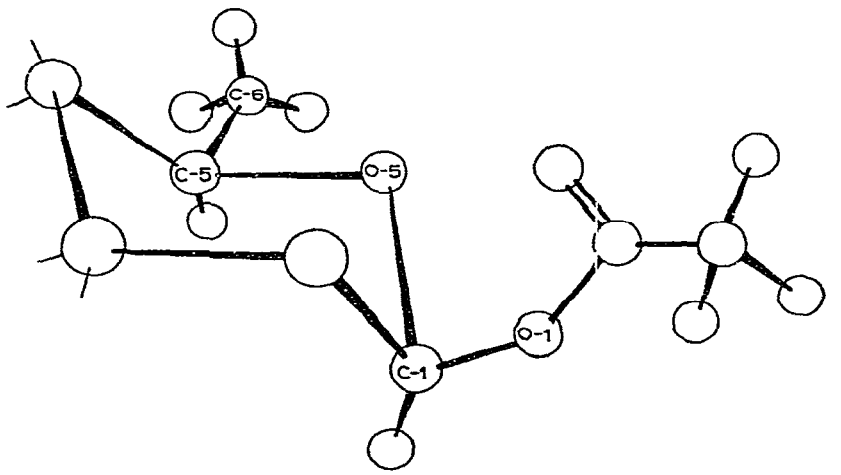
Relative reactivities of the anomeric species. — The difference in reactivity toward nucleophilic substitution at C-6 of α- and β-anomers of various sugars has been recognized for some time and was noted by Tipson in his review on sugar sulfonates[13]. Thus, in the displacement of sulfonate at C-6 by iodide, the β-anomers of several monosaccharide derivatives were found to give consistently greater equilibrium yields. The conclusion to be drawn is that the β-anomers are more reactive towards SN2 reactions than the α-anomers. In the present work, the 6-deoxy-6-iodo-α-glucopyranose derivatives were found to be unreactive toward nucleophilic displacement by thio- or seleno-ureas. The corresponding β-anomers have been found to undergo this reaction readily and with excellent yields[14]. One of the stable C-6–C-5 rotamers of 1,2,3,4-tetra-*O*-acetyl-6-deoxy-6-iodo-D-glucopyranose is that

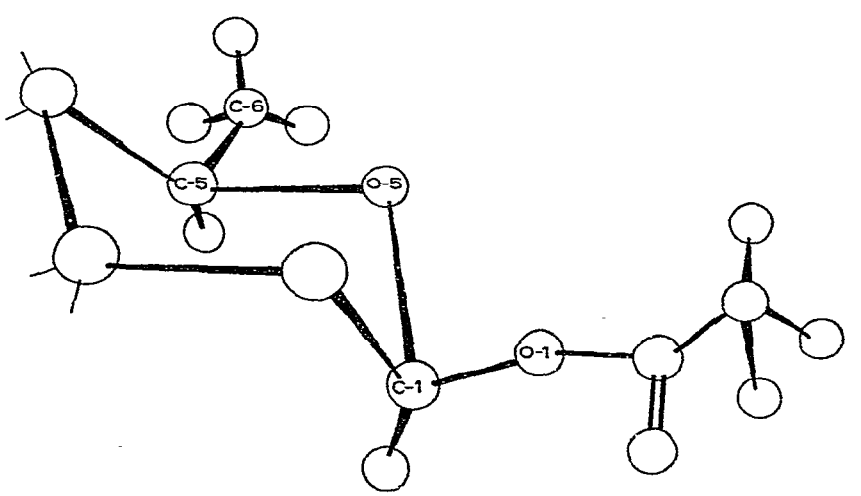


shown. Although this may not represent the most stable rotamer, it is the most stable one that is least resistant to backside, nucleophilic attack. Furthermore, this orientation would lead to a transition state that minimizes the interaction between the dipoles induced by the entering and leaving groups and the permanent ring-oxygen dipole, an important consideration in SN2 reactions of hexopyranose 6-sulfonates, as noted by Richardson[15]. At the time of nucleophilic substitution, therefore, the favored orientation is that shown in the scheme. As the only difference between the molecules under discussion is in the anomeric configuration, and because this difference affects the reactivities so remarkably, it seems logical to examine the

interaction between C-1 and/or its acetoxyl substituent and C-6 and/or its iodo substituent.

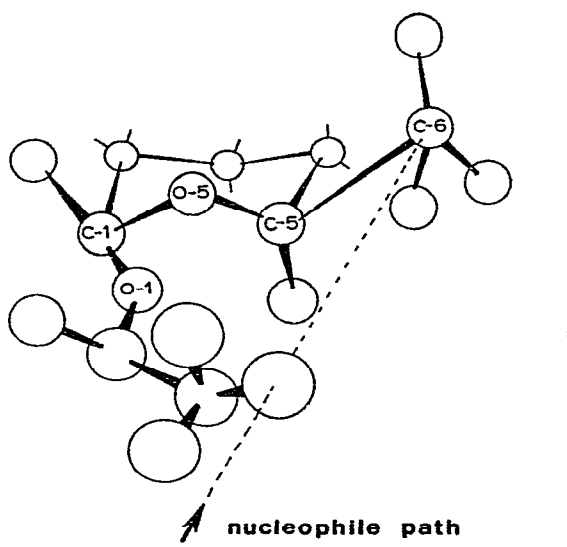
In 1,2,3,4-tetra-*O*-acetyl-6-deoxy-6-iodo-β-D-glucopyranose there are two C-1–acetoxyl rotamers that appear nearly equal in energy. In one rotamer, the carbonyl carbon–O-1 bond bisects the O-5–C-1–C-2 angle (E_2 conformation[16]), whereas in the other, the same bond bisects the O-5–C-1–H-1 angle (E_1 conformation[16]). The other staggered rotamer is less likely, because of unfavorable steric interaction with the 2-acetoxyl group. Similar conclusions have been reached about the conformational preference of an anomeric methoxyl group[17,18].





The spatial relationships between C-6 and C-1 for the pair of rotamers of the β anomer are shown in the preceding schemes. The orientation about the O-1–carbonyl (ester) bond is that noted by Gould[19]. In neither instance does there exist any apparent hindrance to nucleophilic attack at C-6. In fact, the closest approach by any orientation of the β-acetoxyl group to the line of nucleophilic attack is about 2 Å. However, the orientation that gives rise to this shortest distance is highly unstable.

When the α-anomer is subjected to the same conformational analysis, considerably different conclusions are reached. One rotamer at C-1 is much favored, namely that in which the carbonyl carbon–O-1 bond bisects the O-5–C-1–H-1 angle (*A1* conformation[16]). Similar conclusions have been reported concerning the most stable conformer of methyl glycosides[17,18]. This conformation, however, is not that of lowest energy because the carbonyl oxygen atom in the C-1 acetoxyl group and O-5 approach within 2.5 Å of one another, and this is considerably less than twice the van der Waals radius (2.8 Å). In order to relieve this repulsion, a twisting of the carbonyl oxygen atom away from O-5 is to be expected. This resulting, stable conformer for the α anomer brings the 1-acetoxyl methyl group directly into the path of a nucleophile attacking at C-6. Hence, the most stable C-1 acetoxyl conformer imposes considerable steric hindrance to an SN2 attack at C-6, as shown in the following diagram. Hughes and Speakman[20] have invoked a similar argument to



account for the lack of reactivity of the α anomer of 1,2,4,6-tetra-*O*-benzoyl-3-*O*-*p*-tolylsulfonyl-D-glucopyranoses toward nucleophilic substitution. The arguments presented are summarized by the premise that the energy of activation for the α

anomer is greater than the energy of activation of the β anomer. This relation should apply to both the forward and reverse reactions of the SN2 type at C-6.

In addition to the steric effects of the 1-acetoxyl group on the relative reactivities of the two anomers, there may also be a polar effect. In the β anomer the carbonyl carbon–oxygen dipole of the C-1 acetoxyl group interacts in a more favorable manner with the dipoles created by the entering and leaving groups at C-6 than does the same dipole in the α anomer. This polar effect may contribute to the stabilization of the transition state of the β anomer, relative to the α anomer.

EXPERIMENTAL

General methods. — Evaporations were conducted under diminished pressure in a rotary evaporator. Melting points were determined with a Thiele tube. N.m.r. spectra were measured at 60 MHz with a Varian T-60 or EM-360 spectrometer. Chemical shifts are given on the τ scale with tetramethylsilane ($\tau = 10.00$) as the internal standard for organic solution and the external standard for aqueous solutions. Microanalyses were determined by Galbraith Laboratories, Inc. Methods used for obtaining the mass spectra are described elsewhere[1].

1,2,3,4-Tetra-O-acetyl-6-S-dimethylarsino-6-thio-α-D-glucopyranose (**4**). — 6,6′-Dithiobis(1,2,3,4-tetra-*O*-acetyl-α-D-glucopyranose)[7] (**3**, 3 g) was dissolved with stirring in dichloromethane (60 ml) under a nitrogen atmosphere. Tetramethyldiarsine[8] (3 ml) was added dropwise to the solution. The solution was stirred overnight at room temperature, and then in the air for 1 h. The mixture was evaporated to dryness, and the residue was washed with water and dried to give a white solid (3.78 g, 97.9%). The product was recrystallized from methanol; m.p. 91–92°; n.m.r. (chloroform-*d*): τ 3.6 (1-proton doublet, H-1, $J_{1,2}$ 3.4 Hz), 4.3–5.2 (3-proton multiplets H-2,3,4), 5.6–6.2 (1-proton multiplet, H-5), 6.9–7.4 (2-proton multiplets, H-6,6′), 7.80, 7.92, 7.95 (3-, 6-, and 3-proton singlets, OAc), and 8.6 (6-proton singlet, Me_2).

Anal. Calc. for $C_{16}H_{25}AsO_9S$: C, 41.03; H, 5.38. Found: C, 41.48; H, 5.22.

6-S-Dimethylarsino-6-thio-D-glucopyranose (**5**). — To a suspension of compound **4** (1.2 g) in anhydrous methanol (15 ml) was added methanolic sodium methoxide [prepared from sodium (0.1 g) and methanol (20 ml)] dropwise until the solution became basic (pH ~8). The solution was stirred for 1 h at room temperature and then neutralized with Dowex 50W-X8 (H^+ form) resin. The mixture was filtered and the filtrate evaporated to dryness to yield a syrup (0.74 g, 96.1%). Addition of dichloromethane (20 ml) to the syrup yielded a white solid that was recovered by filtration. It was dried and found to have a poorly defined m.p.; n.m.r. (D_2O): τ 4.2 [1-proton doublet H-1 (α), $J_{1,2}$ 3.0 Hz], 5.4 [1-proton doublet, H-1 (β), $J_{1,2}$ 8.0 Hz], 5.6–7.0 (6-proton multiplets, H-2,3,4,5,6,6′), 8.0 (6-proton singlet, Me_2).

Anal. Calc. for $C_8H_{17}AsO_5S$: C, 32.01; H. 5.58. Found: C, 31.98; H, 5.67.

1,2,3,4-Tetra-O-acetyl-6-Se-benzoyl-6-seleno-α-D-glucopyranose (**6**). — 1,2,3,4-Tetra-*O*-acetyl-6-deoxy-6-iodo-α-D-glucopyranose[2] (**1**, 4.58 g) was dissolved with stirring in acetone (480 ml) under dry nitrogen. After 10 min, potassium seleno-

benzoate* (2.9 g) was added with stirring to give a greenish solution. The solution was boiled under reflux for 30 min and the precipitated selenium was removed by filtration. The greenish-yellow filtrate was evaporated to dryness, yielding a pink-yellow solid. To the solid was added chloroform (200 ml) and the white precipitate was removed by filtration. The filtrate was evaporated to dryness to give a flesh-colored solid (5.1 g, 99.0%). The product was recrystallized from methanol to give **6** as a white crystalline compound, m.p. 140–141°; n.m.r. (chloroform-*d*): τ 1.9–2.3, 2.3–3.0 (2-proton multiplets, 3-proton multiplets, aromatic protons), 3.7 (1-proton doublet, H-1, $J_{1,2}$ 3.4 Hz), 4.3–5.3 (3-proton multiplets, H-2,3,4), 5.5–6.1 (1-proton multiplet, H-5), 6.5–7.1 (2-proton multiplets, H-6,6'), 7.85, 7.92 (6-, and 6-proton singlets, OAc).

Anal. Calc. for $C_{21}H_{24}O_{10}Se$: C, 48.94; H, 4.69; Se, 15.33. Found: C, 48.99; H, 4.64; Se, 15.19.

*6,6'-Diselenobis(1,2,3,4-tetra-*O*-acetyl-α-*D*-glucopyranose)* (**7**). — Compound **6** (10.3 g) was dissolved with stirring in chloroform (150 ml) at ice-bath temperature. Iodine (5.08 g) dissolved in chloroform (250 ml) was added and the dark solution was stirred for 30 min. The black syrup was triturated with water (300 ml) and treated with sodium thiosulfate until the iodine color was discharged from the aqueous solution. The aqueous layer was decanted off and the dark-brown residue was recrystallized from 95% ethanol and decolorized with activated carbon to give **7** as a yellow solid (6.8 g, 81.3%).

After two recrystallizations from methanol, the product was obtained in the form of a yellow powder, m.p. 162–165°; n.m.r. (chloroform-*d*): τ 3.7 (1-proton doublet, H-1, $J_{1,2}$ 3.4 Hz), 4.2–5.2 (3-proton multiplets, H-2,3,4), 5.5-6.1 (1-proton multiplet, H-5), 6.6–7.1 (2-proton multiplet, H-6,6'), and 7.80, 7.90, 7.95 (3-, 6-, and 3-proton singlets, OAc).

Preparation of **7** *by oxidation with bromine.* — Compound **6** (0.95 g) was dissolved with stirring in chloroform (6 ml) at −10° and bromine (95 μl) in chloroform (13 ml) was added. The solution was maintained for 2 min at −10° and the solvent was evaporated off at room temperature to give a brown solid. The crude product was decolorized twice with activated charcoal in methanol and recrystallized from methanol to give a yellow powder (0.27 g, 17.8%), m.p. 157–160°.

Anal. Calc. for $C_{28}H_{38}O_{18}Se_2$: C, 40.79; H, 4.63; Se, 19.25. Found: C, 40.99; H, 4.67; Se, 19.03.

*1,2,3,4-Tetra-*O*-acetyl-6-*Se*-dimethylarsino-6-seleno-α-*D*-glucopyranose* (**8**). — To compound **7** (3 g), dissolved in dichloromethane (30 ml) with stirring under nitrogen, was added tetramethyldiarsine[8] (0.53 ml) dropwise. The solution was stirred overnight at room temperature, evaporated to dryness, washed with water, and dried to give pale-yellow solid (3.8 g, 99.5%), m.p. 83–86°; n.m.r. (chloroform-*d*):

*Potassium selenobenzoate was prepared by reduction of dibenzoyl diselenide[11] with a stoichiometric amount of potassium in 1,2-dimethoxyethane (distilled over sodium wire) overnight at room temperature under nitrogen. The gray precipitate containing potassium benzoate and black selenium was filtered off. The filtrate, after drying, gave a green solid (56–60% yield).

τ 3.7 (1-proton doublet, H-1, $J_{1,2}$ 3.4 Hz), 4.3–5.3 (3-proton multiplets, H-2,3,4), 5.7–6.3 (1-proton multiplet, H-5), 7.0–7.4 (2-proton multiplets, H-6,6'), 7.83, 7.97, 8.00 (3-, 6-, and 3-proton singlets, OAc), and 8.6 (6-proton singlet, Me_2). Attempts to recrystallize the product always resulted in some decomposition (deposition of elemental selenium).

Anal. Calc. for $C_{16}H_{25}AsO_9Se$: C, 37.29; H, 4.87; Se, 15.32. Found: C, 36.98; H, 5.03; Se, 15.25.

*Attemped preparation of 6-*Se*-dimethylarsino-6-seleno-*D*-glucopyranose.* — As with the β anomer, treatment of **8** with methanolic sodium methoxide was accompanied by loss of the -$AsMe_2$ moiety. Deacetylation of **7** (sodium methoxide) gave 6,6'-diselenobis(D-glucopyranose) (**9**) as a 2:3 mixture of the α and β anomers. Addition of tetramethyldiarsine to a suspension of **9** in dichloromethane gave a mixture of products, the major one being 6-*Se*-dimethylarsino-6-seleno-α,β-D-glucopyranose (n.m.r.). However, this compound was never isolated sufficiently pure for characterization.

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