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Synthesis of 1-*O*-(2′,3′-Dihydroxypropyl)5-deoxy-β-D-ribofuranosides with $(CH_3)_2As$, $(CH_3)_2As=S$ or $(CH_3)_3As^+$ Groups as Substituents at the 5-Position

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Eight arsenic-containing ribosides were prepared from dimethyl(1-*O*-methyl1-5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranos-5-yl)arsine and (2′*S*)-dimethyl[1-*O*-(2′,3′-isopropylidenedioxypropyl)-5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranos-5-yl]arsine. Reactions of the arsines with sulfur produced the compounds with a $(CH_3)_2As=S$ group as substituent in the 5-position. Treatment of these dimethyl(ribosyl)arsine sulfides with trifluoroacetic acid water removed the isopropylidene groups and gave the unprotected derivatives as thick oils in 80% yield. The arsines and methyl iodide gave the protected trimethyl(ribosyl)arsonium iodides. These arsonium iodides were reacted with trifluoroacetic acid/water. Anomeric mixtures of the deprotected compounds were isolated. Deprotection of the dimethyl(ribosyl)arsines proceeded without anomerization. Reaction of the dimethyl[1-*O*-(2′,3′-dihydroxypropyl)-5-deoxy-β-D-ribofuranos-5-yl]arsine with methyl iodide produced the pure β-anomer of the arsonium iodide. The yields in these reactions were approximately 80%.

Keywords: arsenic-containing ribofuranosides; arsenosugars; dimethyl(β-D-ribofuranos-5-yl]-arsine; dimethyl(β-D-ribofuranos-5-yl)arsine sulfides; trimethyl(β-D-ribofuranos-5-yl)arsonium iodides

INTRODUCTION

Arsenic is present in seawater at a concentration of a few micrograms per liter, chiefly as arsenate. Marine algae at the base of the food chain accumulate substantial amounts of arsenic from seawater.[1,2] Examination of a variety of marine algae[3–16] revealed dimethyl(ribosyl)arsine oxides (**1–6**) to be the major arsenic compounds in these organisms among 15 identified arsenosugars.[15] The six dimethyl(ribosyl)arsine oxides, **1–6**, differ only with respect to the side chain attached to the C1 position of the ribofuranosyl ring. The trimethyl(ribosyl)arsonium salt (**7**) was found in two species of algae.[7,14]

Current hypotheses claim that arsenate taken up by algae from seawater is reduced to arsenite, which is converted by *S*-adenosylmethionine in a multi-step reaction to dimethylarsinic acid. The product of the reaction of dimethylarsinic acid is then adenosylated by *S*-adenosylmethionine to give the dimethyl(adenosyl)arsine oxide (**6**).[2] Removal of the adenine group followed by reaction with available algal metabolites would afford the dimethyl(ribosyl)arsine oxides **1–5**. Some evidence suggests that these dimethyl(ribosyl)arsine oxides are transformed to arsenobetaine, the arsenic compound most frequently encountered in marine animals.[17]

In an earlier paper,[18] an alternative synthesis of the naturally occurring arsenosugar (2′*R*)-dimethyl[1-*O*-(2′,3′-dihydroxypropyl)-5-deoxy-β-D-ribofuranos-5-yl]arsine oxide (**2**) from D-ribose was described. Compound **2** was first reported by Stick and co-workers.[19,20] We now report the preparation of eight 1-*O*-(2′,3′-dihydroxypropyl)-5-deoxy-β-D-ribofuranosides with a $(CH_3)_2As$, $(CH_3)_2As=S$, or $(CH_3)_3As^+$ group as substituent at the 5-position from (2′*S*)-dimethyl[1-*O*-(2′,3′-isopropylidenedioxypropyl)-5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranos-5-yl]arsine (**11**), an intermediate in the previous synthesis.[18] Trimethylarsonium compounds have been identified as natural products[7,14] and the sulfides could be found in anoxic environments. Availability of

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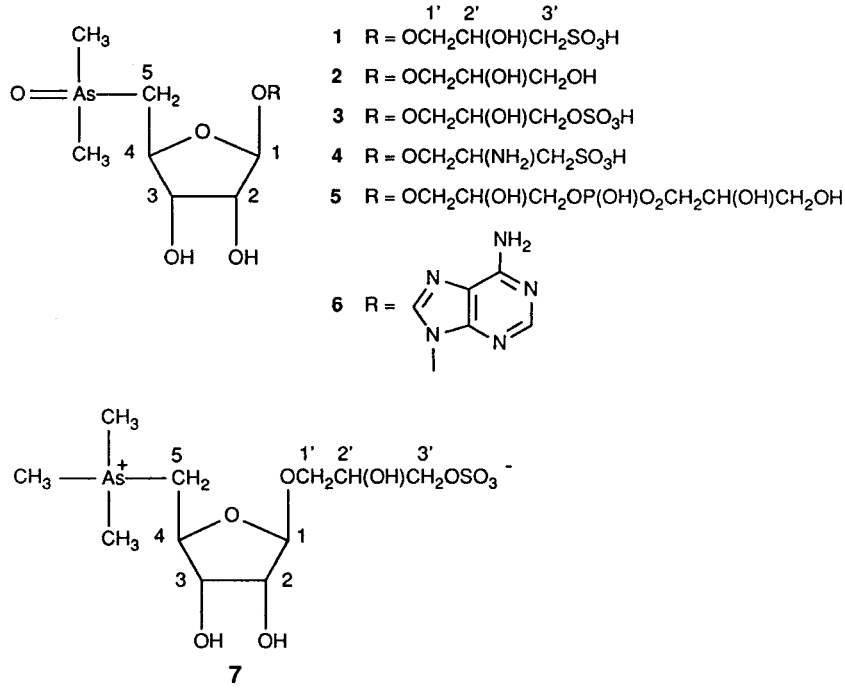


synthetic samples will facilitate chromatographic separation of these compounds, the evaluation of their toxicity and the study of their reactions.

EXPERIMENTAL

Materials

Trifluoroacetic acid (99%) and methyl iodide (Gold-label, 99.5%) were purchased from Aldrich Chemical Co. and used as received. Sulfur (precipitated powder) was obtained from Fisher Scientific Co. Sephadex LH-20-100 (25–100 μm) and Sephadex G-15 (25–100 μm) were supplied by Sigma Chemical Co. Dimethyl-(1-*O*-methyl-5-deoxy-2,3-*O*-iso-propylidene-*β*-D-ribofuranos-5-yl]arsine (**8**) and (2′*S*)-dimethyl-[1-*O*-(2′,3′-isopropylidenedioxypropyl)-5-deoxy-2,3-*O*-isopropylidene-*β*-D-ribofuranos-5-yl]arsine (**11**) were synthesized from D-ribose as described previously.[18]

Instrumentation and analyses

Melting points (uncorrected) were determined on a Fisher–Johns melting point apparatus. Optical rotations were measured with a Jasco DIP-360 digital polarimeter with concentrations expressed in grams of compound per 100 ml of solvent. ^{1}H and ^{13}C NMR spectra were recorded on a Varian XL-200 NMR spectrometer (200 MHz and 50.4 MHz, respectively). ^{1}H NMR spectra were also obtained on a Varian XL-400 NMR spectrometer (400 MHz). Mass-spectral measurements were performed on a Hewlett–Packard 5995c quadrupole gas chromatograph–mass spectrometer at 70 eV electron energy. Elemental analyses were carried out by Galbraith Laboratories Inc., Knoxville, TN, USA.

Syntheses

Dimethyl(1-*O*-methyl-5-deoxy-2,3-*O*-isopropylidene-*β*-D-ribofuranos-5-yl)arsine sulfide (9)

A 50-ml, round-bottomed flask equipped with a magnetic stirrer, a reflux condenser and a nitrogen inlet was charged with dimethyl(1-*O*-methyl-5-deoxy-2,3-*O*-isopropylidene-*β*-D-ribofuranos-5-yl)arsine (**8**) (0.470 g, 1.61 mmol), powdered sulfur (0.50 g, 16 mmol), and absolute ethanol (10 ml). The suspension was stirred and refluxed for 6 h. After cooling to room temperature, the suspension was filtered. The filtrate was evaporated to dryness at 40 °C on a rotary evaporator under an aspirator vacuum to give white crystals. The crystals were dissolved with slight warming in

8 ml of methanol, and the solution was filtered to remove undissolved sulfur. To remove the last traces of sulfur, the filtrate was evaporated to dryness again. The residue was dissolved in 2 ml of hot methanol and the hot solution was filtered. The filtrate was diluted with methanol to about 7 ml, and then this solution was allowed to evaporate at room temperature in contact with air. After two days, very large, colorless crystals were collected by filtration and washed with a small amount of cold methanol to give pure dimethyl-(1-*O*-methyl-5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranos-5-yl)arsine sulfide (**9**). The mother liquor was concentrated on a hot plate to about 1 ml and allowed to cool. The crystals thus formed were separated by filtration and washed with a small amount of cold methanol (total yield 0.40 g, 77%), m.p. 148–149.5 °C. $[\alpha]_D^{26}$ +1.6 (*c* 1, methanol). ^{1}H NMR in $CDCl_3$: δ 4.98, s, $^3J_{1,2}$ ~0.0 Hz, β-H1. ^{13}C NMR in $CDCl_3$: δ 110.6 C1. Found: C, 40.87; H, 6.65. Calcd for $C_{11}H_{21}AsO_4S$: C, 40.74; H, 6.53%. EI MS: *m/z* 324 (5.6%, M^+), 309 (18.9%, $[M-CH_3^+]$).

Dimethyl(1-O-methyl-5-deoxy-β-D-ribofuranos-5-yl)arsine sulfide (10)

Into a 50-ml, round-bottomed flask was placed dimethyl(1-*O*-methyl-5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranos-5-yl)arsine sulfide (**9**) (105 mg, 0.32 mmol) and a mixture of water/trifluoroacetic acid (4 ml, 1:9 v/v). The flask was shaken for about 20 s to dissolve the sulfide. The reaction mixture was allowed to stand for 5 min and was then immediately placed in a rotary evaporator and kept there at 42 °C under an oil pump vacuum (10 Torr) for 6 min to evaporate most of the solvent. Benzene (5 ml) was added to the concentrate. The solution was concentrated again at 42 °C/10 Torr to remove the remaining trifluoroacetic acid. The resulting syrup was immediately dissolved in 4 ml of water and neutralized (universal pH paper) with an aqueous 2 M ammonium hydroxide solution. The neutralized solution was concentrated at 40 °C on a rotary evaporator under reduced pressure (15 Torr). The concentrate was dissolved in methanol/water (1.5 ml, 1:1 v/v). The solution was transferred to a Sephadex LH-20-100 column (79 cm × 2 cm). Methanol/water (1:1 v/v) was passed through the column. The effluent was collected in 5-ml fractions. Each fraction was evaporated at 40 °C on a rotary evaporator under an aspirator vacuum. The fractions that left residues upon evaporation were dissolved in deuterium oxide and ^{1}H NMR spectra were taken, according to which the desired product was present in fractions 32–36. These fractions were combined and mixed with 15 ml of methanol. The resulting solution was concentrated at 40 °C on a rotary evaporator under an aspirator vacuum. The residue was dried in a vacuum oven (20 Torr) at 40 °C for 24 h to give dimethyl(1-*O*-methyl-5-deoxy-β-D-ribofuranos-5-yl)arsine sulfide (**10**) as a thick oil (71 mg, 80%) that was pure by ^{1}H and ^{13}C NMR spectroscopic analyses. ^{1}H NMR in D_2O: δ 4.90, $^3J_{1,2}$ 1.3 Hz, β-H1. ^{13}C NMR in D_2O: δ 108.3, C1.

(2′S)-Dimethyl(1-O-(2′,3′-isopropylidenedioxypropyl)-5-deoxy-2,3-O-isopropylidene-β-D-ribofuranos-5-yl)arsine sulfide (12)

A 50-ml, round-bottomed flask equipped with a magnetic stirrer, a reflux condenser and a nitrogen inlet was charged with (2′*S*)-dimethyl[1-*O*-(2′,3′-isopropylidenedioxypropyl)-5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranos-5-yl)arsine (**11**) (0.484 g, 1.23 mmol), sulfur (0.50 g, 16 mmol) and absolute ethanol (15 ml). The suspension was stirred and refluxed for 6 h. After cooling to room temperature, the suspension was filtered. The filtrate was evaporated on a rotary evaporator at 40 °C under an aspirator vacuum to give an oily residue which crystallized upon standing overnight. The crystals were dissolved with slight warming in 15 ml of methanol. The solution was filtered to remove the remaining sulfur. The filtrate was evaporated to dryness at 40 °C under an aspirator vacuum on a rotary evaporator to give white crystals, which were then dissolved in 8 ml of hot ethanol. The solution was allowed to cool slowly, and colorless long needles formed which were collected by filtration and washed with a small amount of cold ethanol to give pure (2′*S*)-dimethyl[1-*O*-(2′,3′-isopropylidenedioxypropyl)-5-deoxy-2,3-*O*-β-D-ribofuranos-5-yl)-arsine sulfide (**12**). The mother liquor was concentrated on a hotplate to about 3 ml and allowed to cool. The crystals thus formed were separated by filtration and washed with a small amount of cold ethanol. Total yield 0.43 g, 83%; m.p. 125–126.5 °C. $[\alpha]_D^{26}$ +0.9° (*c* 1.5, methanol). ^{1}H NMR in $CDCl_3$: δ 5.11, s, $^3J_{1,2}$ ~0.0 Hz, β-H1. ^{13}C NMR in $CDCl_3$: δ 109.4, C1. Found: C, 44.83; H, 6.99. Calcd for $C_{16}H_{29}AsO_6S$: C, 45.28; H, 6.89%. EI MS: *m/z* 409 (19.5%, $[M-CH_3]^+$), 392 (1.3%, $[M-S]^+$), 377 (58.0%, $[M-CH_3-S]^+$).

(2′R)-Dimethyl[1-O-(2′,3′-dihydroxypropyl)-5-deoxy-β-D-ribofuranos-5-yl]arsine sulfide (13)

Into a 50-ml, round-bottomed flask was placed

(2′*S*)-dimethyl[1-*O*-(2′,3′-isopropylidenedioxypropyl)-2,3-*O*-isopropylidene-5-deoxy-β-D-ribofuranos-5-yl]arsine sulfide (**12**) (150 mg, 0.353 mmol) and a mixture of water/trifluoroacetic acid (6 ml, 1:9 v/v). The procedure was exactly the same as for the preparation of arsine sulfide **10** except that 4.8 ml fractions were collected in the Sephadex LH-20-100 separation. According to the NMR spectra, the desired product was present in fractions 31–35. These fractions were combined and mixed with 15 ml of methanol. The resulting solution was concentrated at 30 °C on a rotary evaporator under an aspirator vacuum. The residue was dried in a vacuum oven (30 Torr) at 40 °C for 24 h to give (2′*R*)-dimethyl[1-*O*-(2′,3′-dihydroxypropyl)-5-deoxy-β-D-ribofuranos-5-yl]arsine sulfide (**13**) as a thick oil (118 mg, 97%) that was pure according to the ^{1}H and ^{13}C NMR spectra. $[\alpha]_D^{26}$ +9.6° (*c* 1.1, methanol). ^{1}H NMR in D_2O: δ 4.99, d, $^3J_{1,2}$ 1.0 Hz, β-H1. ^{13}C NMR in D_2O: δ 107.4, C1.

(2′S)-Trimethyl[1-O-(2′,3′-isopropylidenedioxypropyl)-5-deoxy-2,3-O-isopropylidene-β-D-ribofuranos-5-yl]arsonium iodide (14)

A 50-ml, round-bottomed flask equipped with a magnetic stirrer and a nitrogen inlet was charged with (2′*S*)-dimethyl-1-*O*-(2′,3′-isopropylidenedioxypropyl)-5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranos-5-yl]arsine (**11**) (0.34 g, 0.87 mmol), methyl iodide (1.0 ml, 16 mmol), and diethyl ether (12 ml). The reaction mixture was stirred at room temperature for two days under nitrogen. A white precipitate slowly formed. Diethyl ether (20 ml) was added to the reaction mixture to complete the precipitation of the arsonium salt. The precipitate was separated by filtration and washed with cold diethyl ether and then dissolved in a minimal amount of absolute ethanol. The compound was reprecipitated by addition of diethyl ether (40 ml) to the ethanolic solution. The precipitate was separated again by filtration and dried in a vacuum oven (30 Torr) at 35 °C for 24 h to give (2′*S*)-dimethyl[1-*O*-(2′,3′-isopropylidenedioxypropyl)-5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranos-5-yl]arsonium iodide (**14**) (0.33 g, 71%) as a white solid, m.p. 139–141 °C. $[\alpha]_D^{26}$ +15.1° (*c* 1.4, methanol). ^{1}H NMR in D_2O: δ 5.30, s, $^3J_{1,2}$ ~0.0 Hz, β-H1. ^{13}C NMR in D_2O: δ 111.6, C1. Found: C, 37.71; H, 6.08; As, 14.71. Calcd for $C_{17}H_{32}AsIO_6$: C, 38.22; H, 6.04; As 14.02%.

Treatment of (2′S)-trimethyl[1-O-(2′,3′-isopropylidenedioxypropyl)-5-deoxy-2,3-O-isopropylidene-β-D-ribofuranos-5-yl]arsonium iodide (14) with a mixture of trifluoroacetic acid and water

Into a 50-ml, round-bottomed flask was placed (2′*S*)-trimethyl[1-*O*-(2′,3′-isopropylidenedioxypropyl)-5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranos-5-yl]arsonium iodide (**14**) (206 mg, 0.376 mmol) and a mixture of water/trifluoroacetic acid (8 ml, 1:9 v/v). The flask was shaken for about 20 s, then the reaction mixture was immediately evaporated at 42 °C on a rotary evaporator under an oil pump vacuum (10 Torr) for 7 min. Ethanol (8 ml) was added to the concentrate. The solution was concentrated again to remove the remaining trifluoroacetic acid. The resulting syrup was dissolved in 6 ml of water and neutralized (universal pH paper) with an aqueous 2 M ammonium hydroxide solution. The neutralized solution was concentrated at 42 °C on a rotary evaporator under reduced pressure (15 Torr). The concentrate was dissolved in methanol/water (1.5 ml, 1:1 v/v) and the solution was transferred to a Sephadex LH-20-100 column (79 cm × 2 cm). Methanol/water (1:1 v/v) was then passed through the column. The effluent was collected in 4.7 ml fractions. Each fraction was evaporated at 42 °C on a rotary evaporator under an aspirator vacuum. Part of the residue left upon evaporation was dissolved in deuterium oxide and ^{1}H NMR spectra were taken, according to which the desired product was present in fractions 30–35. The residues from these fractions were combined and mixed with 20 ml of methanol. The resulting solution was concentrated at 42 °C on a rotary evaporator under an aspirator vacuum. The residue was dried in a vacuum oven (20 Torr) at 40 °C for 24 h to give an anomeric mixture of (2′*R*)-trimethyl[1-*O*-(2′,3′-dihydroxypropyl)-5-deoxy-β-D-ribofuranos-5-yl]arsonium iodide (**15a**) and (2′*R*)-trimethyl[1-*O*-(2′,3′-dihydroxypropyl)-5-deoxy-α-D-ribofuranos-5-yl]arsonium iodide (**15b**) as a thick oil (135 mg, 77%). The anomeric ratio, $\alpha/\beta = 1{:}1.2$, was determined by integrating the α and β H1 values in the ^{1}H NMR. ^{1}H NMR in D_2O: δ 5.01, d, $^3J_{1,2}$ 1.0 Hz, **15a** β-H1; δ 5.17, d, $^3J_{1,2}$ 4.4 Hz, **15b** α-H1. ^{13}C NMR in D_2O: δ 107.6, **15a** C1. δ 102.8, **15b** C1.

(2′R)-Dimethyl[1-O-(2′,3′-dihydroxypropyl)-5-deoxy-β-D-ribofuranos-5-yl]arsine (16)

Into a nitrogen-purged, 50-ml, round-bottomed

flask was placed (2′*S*)-dimethyl-[1-*O*-(2′,3′isopropylidenedioxypropyl)-5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranos-5-yl]arsine (**11**) (215 mg, 0.548 mmol) and a mixture of water/trifluoroacetic acid (8 ml, 1:9 v/v). The solution was stirred for 9 min and then the reaction mixture was immediately evaporated at 42 °C on a nitrogen-purged rotary evaporator under an oil pump vacuum (10 Torr) for 8 min. Benzene (8 ml) was added to the concentrate. The solution was concentrated again to remove the remaining trifluoroacetic acid. The resulting syrup was dissolved in 8 ml of water and neutralized (universal pH paper) with an aqueous 2 M ammonium hydroxide solution. The neutralized solution was concentrated at 42 °C on a nitrogen-purged rotary evaporator under reduced pressure (15 Torr). The concentrate was dissolved in methanol/water (2 ml, 1:1 v/v) and the solution was transferred to a Sephadex LH-20-100 column (79 cm × 2 cm). Methanol/water (1:1 v/v) was then passed through the column. The effluent was collected in 4.5-ml fractions. Each fraction was evaporated at 42 °C on a nitrogen-purged rotary evaporator under an aspirator vacuum. The fractions that left residues after evaporation were dissolved in deuterium oxide and ^{1}H NMR spectra were taken, according to which, the desired product was present in fractions 40–45. These fractions were combined and mixed with 20 ml of methanol. The resulting solution was concentrated at 42 °C on a nitrogen-purged rotary evaporator under an aspirator vacuum (15 Torr). The residue was dried in a vacuum oven (20 Torr) at 40 °C for 24 h to give (2′*R*)-dimethyl[1-*O*-(2′,3′-dihydroxypropyl)-5-deoxy-β-D-ribofuranos-5-yl]arsine (**16**) as a thick oil (125 mg, 73%). $[\alpha]_D^{26}$ −5.6° (*c* 1.1, methanol). The compound was pure according to ^{1}H NMR. ^{1}H NMR in D_2O: δ 4.96, s, $^3J_{1,2}$ ~0.0 Hz, β-H1.

(2′R)-Trimethyl[1-O-(2′,3′-dihydroxypropyl-5-deoxy-β-D-ribofuranos-5-yl]arsonium iodide (15a)

Into a nitrogen-purged, 50-ml, round-bottomed flask was placed (2′*S*)-dimethyl-[1-*O*-(2′,3′-isopropylidenedioxypropyl)-5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranos-5-yl]arsine (**11**) (105 mg, 0.268 mmol) and a mixture of water/trifluoroacetic acid (4 ml, 1:9 v/v). The solution was stirred for 9 min and then immediately evaporated at 42 °C on a nitrogen-purged rotary evaporator under an oil pump vacuum (10 Torr) for 6 min. Benzene (8 ml) was added to the concentrate. The solution was concentrated again to remove the remaining trifluoroacetic acid. The resulting syrup was dissolved in 6 ml of water and neutralized with an aqueous 2 M ammonium hydroxide solution. The neutralized solution was concentrated at 42 °C on a nitrogen-purged rotary evaporator under reduced pressure (15 Torr) to give crude (2′*R*)-dimethyl[1-*O*-(2′,3′-dihydroxypropyl)-5-deoxy-β-D-ribofuranos-5-yl]arsine (**16**) as a syrup. This crude product was dissolved in methanol (8 ml) and the solution was transferred to a nitrogen-purged, 50-ml round-bottomed flask equipped with a reflux condenser and a nitrogen-inlet side arm. Methyl iodide (0.4 ml, 6.4 mmol) was added to the solution and the reaction mixture was refluxed for 3 h under nitrogen. The reaction mixture was then concentrated at 42 °C on a rotary evaporator under reduced pressure (15 Torr). The concentrate was dissolved in methanol/water (1.5 ml, 1:1 v/v) and the solution was transferred to a Sephadex LH-20-100 column (79 cm × 2 cm). Methanol/water (1:1 v/v) was then passed through the column. The effluent was collected in 4.5-ml fractions. Each fraction was evaporated at 42 °C on a rotary evaporator under an aspirator vacuum. The fractions that left residues after evaporation were dissolved in deuterium oxide and ^{1}H NMR spectra were taken, according to which the desired product was present in fractions 31–36. These fractions were combined and mixed with 20 ml of methanol. The resulting solution was concentrated at 42 °C on a rotary evaporator under an aspirator vacuum. The residue was dried in a vacuum oven (20 Torr) at 40 °C for 24 h to give (2′*R*)-trimethyl[1-*O*-(2′,3′ - dihydroxypropyl) - 5 - deoxy - β - D - ribo - furanos-5-yl]arsonium iodide (**15a**) as a thick oil (99 mg, 81%). The compound was pure according to ^{1}H and ^{13}C NMR. ^{1}H NMR in D_2O: δ 5.01, d, $^3J_{1,2}$ 1.0 Hz, β-H1. ^{13}C NMR in D_2O: δ 107.6, C1.

Trimethyl(1-*O*-methyl-5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranos-5-yl)arsonium iodide (17)

A 50-ml, round-bottomed flask equipped with a magnetic stirrer and a nitrogen inlet side arm was charged with dimethyl(1-*O*-methyl-5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranos-5-yl]arsine (**8**) (0.50 g, 1.7 mmol), methyl iodide (1.0 ml, 16 mmol) and diethyl ether (15 ml). The reaction mixture was stirred at room temperature for 24 h under nitrogen. A white precipitate formed during the reaction. Diethyl ether (25 ml) was added to the reaction mixture to complete the precipitation of the arsonium salt. The precipitate was separated by filtration, washed with cold

diethyl ether, dissolved in a minimal amount of methanol and reprecipitated by addition of diethyl ether (70 ml). The precipitate was separated again by filtration and dried in a vacuum oven (30 Torr) at 35 °C for 24 h to give trimethyl-(1-*O*-methyl-5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranos-5-yl]arsonium iodide (**17**) (0.59 g, 79%) as a white solid, m.p. 179.5–181 °C. $[\alpha]_D^{26}$ +15.1° (*c* 1.4, methanol). ^{1}H NMR in D_2O: δ 5.16, s, $^3J_{1,2}$ ~0.0 Hz, β-H1. ^{13}C NMR in D_2O: δ 111.1, C1. Found: C, 33.08; H, 5.63. Calcd for $C_{12}H_{24}AsIO_4$: C, 33.20; H, 5.57%.

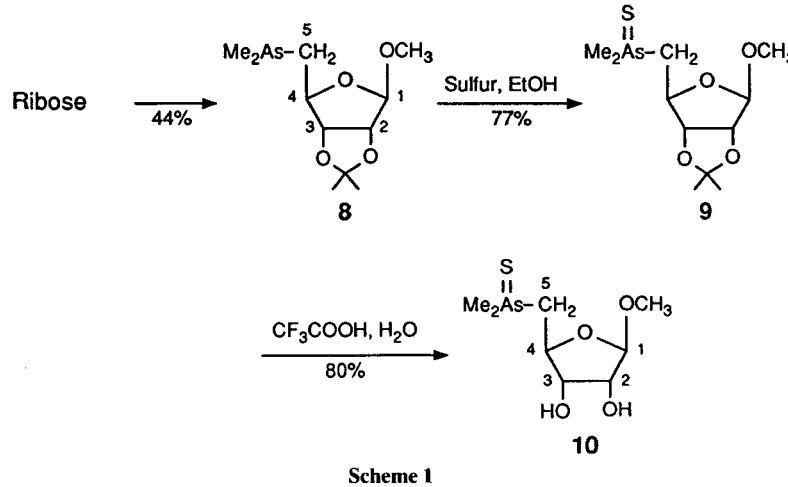
RESULTS AND DISCUSSION

The dimethyl(ribosyl)arsine sulfides and the trimethyl(ribosyl)arsonium iodides were prepared from appropriate dimethyl(ribosyl)arsines according to methods worked out for less complex tertiary arsines. The reactions of the arsines with excess sulfur[22] in refluxing ethanol yielded the arsine sulfides and, with excess methyl iodide in an organic solvent, the arsonium iodides.[23] The ribosylarsine sulfides and ribosylarsine iodides are solids with sharp melting points when the hydroxyls are protected by isopropylidene groups, but are thick oils as the unprotected compounds.

Dimethyl(5-deoxy-β-D-ribofuranos-5-yl)arsine sulfides

Marine waters and sediments usually contain sulfate at higher concentrations than freshwater systems. In anoxic marine environments sulfate can be reduced microbially to hydrogen sulfide. Subsequently, thiols can be produced by reaction of hydrogen sulfide with sedimentary organic matter.[24] Cullen and co-workers[25] demonstrated the conversion of $(CH_3)AsOOH$ and $CH_3AsO(OH)_2$ to methyl(alkylthio)arsines, $(CH_3)_nAsSR_{3-n}$ ($n = 1, 2$) in reactions with thiols and of $(CH_3)_2AsOOH$ to cacodyl sulfide, $[(CH_3)_2As]_2S$, in a reaction with hydrogen sulfide in anoxic, aqueous solutions of neutral pH. Trimethylarsine oxide gave trimethylarsine sulfide, trimethylarsine or both compounds, depending on the molar ratio of trimethylarsine oxide to H_2S or RSH.[25,26] Considering the high concentration of hydrogen sulfide and the presence of thiols in many anoxic marine sediments, the formation of dimethyl(ribosyl)arsine sulfides and dimethyl-(ribosyl)arsines from algal dimethyl(ribosyl)arsine oxides is likely whenever algae containing dimethyl(ribosyl)arsine oxide are deposited in sediments. The availability of synthetic samples of such arsenic-containing riboses will assist their detection and identification in marine systems and will facilitate the study of their biotransformation.

Dimethyl(1-*O*-methyl-5-deoxy-β-D-ribofuranos-5-yl]arsine sulfide (**10**) was prepared from the protected ribosylarsine **8** (Scheme 1). The ribosylarsine **8** was refluxed with a ten-fold molar excess of powdered sulfur in ethanol to give the protected ribosylarsine sulfide **9** as colorless crystals in 77% yield. Unlike the corresponding ribosylarsine oxide,[18] this compound is not hygroscopic and hence it is easier to handle and purify than similar arsine oxides. The isopropylidene protective group of the ribosylarsine sulfide **9** was removed by a brief treatment with trifluoroacetic



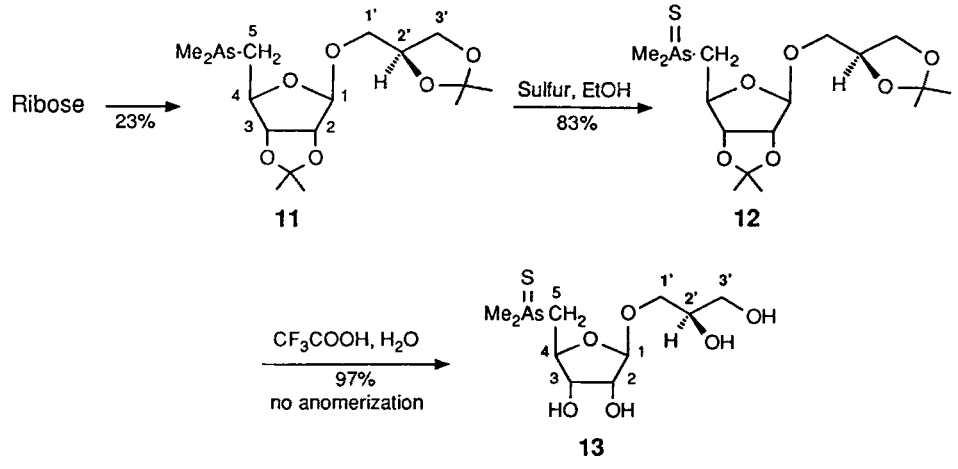
Scheme 1

acid/water. To remove the trifluoroacetic acid the solvent was immediately evaporated, the residue dissolved in benzene and the benzene evaporated again. The aqueous solution of the residue was neutralized with aqueous ammonia. The residue from the neutral aqueous solution was chromatographed on a Sephadex LH20 column with methanol/water (1:1 v/v) as mobile phase. The ribosylarsine sulfide **10** was obtained as a thick oil in 80% yield.

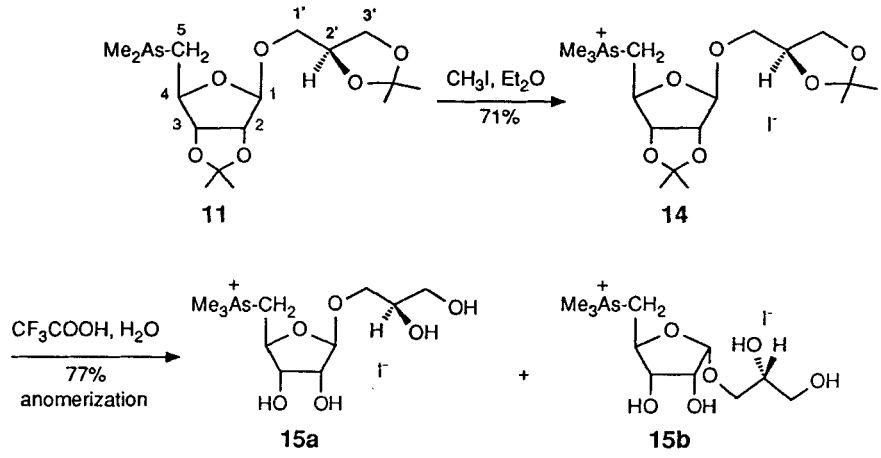
(2′*R*)-Dimethyl[1-*O*-(2′,3′-dihydroxypropyl)-5-deoxy-β-D-ribofuranos-5-yl]arsine sulfide **13** was synthesized in a similar manner using ribosylarsine **11** as a starting material (Scheme 2). The ribosylarsine **11** already has the desired three-carbon aglycone moiety with the required *S* configuration at C2′. Refluxing ribosylarsine **11** with an excess of sulfur in ethanol gave ribosylarsine sulfide **12** as colorless crystals in 83% yield. As expected, this compound, crystallizing in long needles, is also not hygroscopic. The ribosylarsine sulfide **12** was then treated with a mixture of trifluoroacetic acid and water for approximately 10 min to remove its isopropylidene protective groups. The reaction mixture was neutralized and separated on a Sephadex LH-20 column to give the ribosylarsine sulfide **13** as a syrup in 97% yield. The hydrolytic removal of the isopropylidene groups from sulfide **12** does not invert the configuration at C2′ of the glycerol group and does not cause anomerization. The ^{1}H and ^{13}C NMR spectra showed the presence of a single diastereomer. The β-H1 resonance was a doublet at δ 4.99 with a small coupling to H2 ($^{3}J_{1,2} = 1.0$ Hz) characteristic of β anomers.[18,20,21] In the ^{13}C NMR spectrum the β-C1 carbon appeared at δ 107.4 and there was no resonance characteristic of α anomers between δ 101 and δ 103.[18,21] It should be noted that the change in the designation of the configuration at C2′ from (*S*) in the protected compounds to (*R*) in the unprotected compounds is caused by the differing priorities assigned to the O–isopropylidene and O–H groups.

Trimethyl(5-deoxy-β-D-ribofuranos-5-yl)arsonium iodides

A trimethyl(ribosyl)arsonium salt was isolated from two species of algae and identified as 1′-[5-trimethylarsonio-5-deoxy-β-D-1-ribofuranosyl]-2′-hydroxy-3′-propyl sulfate **7**.[7,14] Instead of the dimethylarsinoyl group present in the algal ribosylarsine oxides **1–5**, compound **7** bears a trimethylarsonium group and may be a metabolic precursor of arsenobetaine, the ubiquitous organic arsenic compound in marine animals. In the initial attempt to prepare (2′*R*)-trimethyl[1-*O*-(2′,3′-dihydroxypropyl)-5-deoxy-β-D-ribofuranos-5-yl]arsonium iodide **15a**, the protected ribosylarsine **11** was treated with methyl iodide in diethyl ether to give the ribosylarsonium iodide **14** in 71% yield (Scheme 3). Compound **14** is not soluble in diethyl ether and was precipitated during the reaction as a white solid. This compound also was not hygroscopic. The ribosylarsonium iodide **14** was then treated with a mixture of trifluoroacetic acid and water for 20 s to remove its isopropylidene protective groups. The reaction mixture was neutralized and separated on a Sephadex LH-20 column. The product was an anomeric mixture of β-D-(1-*O*-glycerylribosyl)-



Scheme 2



Scheme 3

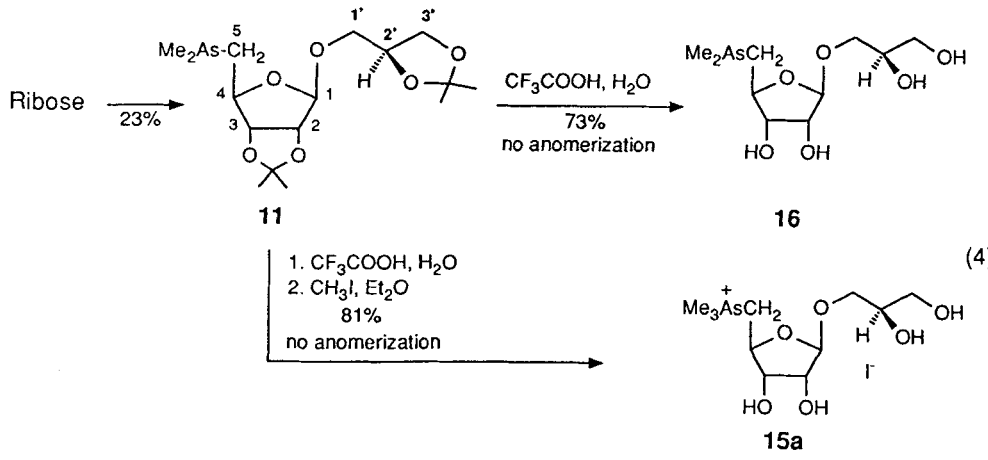
arsonium iodide **15a** and α-D-(1-*O*-glycerylribosyl)arsonium iodide **15b** in 77% yield. Anomerization occurred under acidic conditions during deprotection (**14**→**15**). The β-H1 resonance for **15a** was a doublet at δ 5.01 with a small coupling to H2 ($^3J_{1,2}$ 1.0 Hz). The α-H1 resonance for **15b** was a doublet at δ 5.17, with a larger vicinal coupling to H2 ($^3J_{1,2}$ = 4.4 Hz). The ^{13}C chemical shifts for β-C1 and α-C1 for **15a** and **15b** were δ 107.6 and δ 102.8, respectively. These ^1H and ^{13}C NMR values are typical of those previously observed for α and β anomers of ribosides.[18,20,21] The anomeric mixture contained **15b** and **15a** in a ratio (α/β) of 1:1.2. Attempts to isolate the β anomer **15a** from the mixture failed.

An alternative route not troubled by anomerization was sought. Anomerization of the arsonium iodide **14** had occurred during deprotection under acidic conditions. The observation that deprotection of the similarly constituted dimethyl(ribosyl)arsine sulfide (Scheme 2) under the same conditions, but with no iodide in the reaction mixture, did not cause anomerization led to the hypothesis of the involvement of iodide in the α–β conversion. To avoid the presence of iodide during deprotection, the protected tertiary arsine **11** was stirred with a mixture of trifluoroacetic acid and water to remove the isopropylidene groups. The reaction mixture was then neutralized and separated on a Sephadex LH-20 column to give the unprotected β-D-ribosylarsine **16** in 73% yield (Scheme 4). This reaction proceeded without anomerization. No trace of the α-D-ribosylarsine in the product was detected by NMR spectroscopy. In the ^1H NMR spectrum, only a singlet with a small vicinal coupling for the β-H1 was observed at δ 4.96 ($^1J_{1,2}$ ~0.0 Hz).

The unprotected ribosylarsine **16** is much more easily oxidized by air than the corresponding ribosylarsine **11** and, therefore, must always be handled under nitrogen. To minimize the oxidation, the β-D-ribosylarsine **16** need not be purified. The crude product was immediately dissolved in methanol and refluxed with excess methyl iodide under nitrogen. The reaction mixture was then concentrated and purified on a Sephadex LH-20 column to give (2′*R*)-trimethyl[1-*O*-2′,3′-dihydroxypropyl)-5-deoxy-β-D-ribofuranos-5-yl]arsonium iodide **15a** in 81% yield from ribosylarsine **11**. The NMR evidence strongly supports the fact that **15a** is the β anomer. The β-H1 resonance was a doublet at δ 5.01 ($^3J_{1,2}$ 1.0 Hz). In the ^{13}C NMR spectrum the β-C1 carbon appeared at δ 107.5. There was no resonance characteristic of α anomers between δ 101 and δ 103.

Overall yields

The starting materials for the preparation of the dimethyl(ribosyl)arsine sulfides and the trimethyl(ribosyl)arsonium iodides were synthesized previously from D-ribose.[18] Dimethyl(1-*O*-methyl-2,3-isopropylidene-5-deoxy-β-D-furanos-5-yl)-arsine **8** was obtained from ribose in a four-step reaction in an overall yield of 44%. The reaction with sulfur proceeds with a 77% yield and the deprotection with a 80% yield (Scheme 1). Thus, the dimethyl(1-methyl-5-deoxy-β-D-ribofuranos-5-yl)arsine sulfide **10** can be prepared in a six-step reaction from D-ribose in a yield of 27%. (2′*S*)-



Scheme 4

Dimethyl[1-*O*-(2′,3′-isopropylidenedioxypropyl)-5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranos-5-yl]arsine **11**, the common starting material for the (2′*R*)-arsine sulfide **13** and the (2′*R*)-arsonium iodide **15a**, was prepared in a seven-step reaction from D-ribose in 23% yield.[18] The two-step conversions of this starting material to the arsine sulfide or arsonium iodide occur in 80% yield. Thus, the overall yield from ribose of these nine-step reactions was 18%. The new arsenic-containing ribosides were obtained in amounts of 300–600 mg for the C1-methoxy-substituted derivatives and in amounts of approximately 100 mg for derivatives with the 2′,3′-dihydroxy-1′-propoxy group. Larger-scale reactions were not attempted, but should not pose undue difficulties. The described procedures provide sufficient amounts of these arsenic-containing riboses for the development of chromatographic methods for their identification, the study of their toxicity and the elucidation of their metabolic fate.

(2′*R*)-Trimethyl[1-*O*-(2′,3′-dihydroxypropyl)-5-deoxy-β-D-ribofuranos-5-yl]arsonium iodide was also prepared by Francesconi and co-workers from the synthetic dimethyl(ribosyl)arsine oxide **2** by reduction of the arsine oxide with 2,3-dimercaptopropanol to the arsine, followed by the reaction of the arsine with methyl iodide in methanol. This small-scale reaction (9.5 mg starting material) produced the arsonium salt as the formate in 71% yield.[21] A similar reaction sequence with 83 mg of synthetic starting material gave the trimethyl(1-*O*-methyl-5-deoxyribofuranos-5-yl)arsonium iodide in 93% yield.[24] The protected compound, trimethyl(1-*O*-methyl-5-deoxy-2,3-isopropylidene-β-D-ribofuranos-5-yl)arsonium iodide, was prepared from the corresponding arsine (0.50 g) and methyl iodide in 79% yield. The deprotection was not attempted. Three other trimethyl(ribosyl)arsonium salts were prepared by Francesconi *et al.*[21] from milligram quantities of dimethyl(ribosyl)arsine oxides isolated from algae.

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