Synthesis of 1-*O*-R-5-Deoxy-β-D-ribofuranosides with $(CH_3)_2As$ and $(CH_3)_2As{=}O$ as Substituents at the 5-Position and a Methyl or 2′,3′-Dihydroxypropyl Group as the Aglycone in the 1-Position

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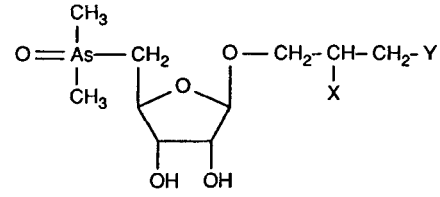
Six arsenic-containing β-D-ribofuranosides, including the naturally occurring (2′R)-dimethyl[1-*O*-(2′,3′-dihydroxypropyl)-5-deoxy-β-D-ribofuranos-5-yl]arsine oxide, were prepared in multi-step reactions from D-ribose and tetramethyldiarsine. The synthetic procedure uses the early substitution of the hydroxy group with bromine at C5, subsequent attachment of a chiral three-carbon aglycone at C1, and final delivery of arsenic at C5. The synthesis provides a viable route for the preparation of multigram quantities of the natural product.

Keywords: arsenic-containing ribofuranosides; arsenosugars; (2′R)-dimethyl[1-*O*-(2′,3′-dihydroxypropyl) - 5 - deoxy - β - D - ribofuranos - 5 - yl]arsine oxide

INTRODUCTION

Organoarsenic compounds are present in a variety of marine organisms. Marine algae accumulate substantial amounts of arsenic from seawater.[1,2] Examination of a variety of marine algal species revealed dimethyl(ribosyl)arsine oxides, **1**, to be the major arsenic compounds.[2]

The wide occurrence of dimethyl(ribosyl)arsine oxides in marine algae suggests that the formation of these types of compounds is a general response of marine algae to arsenate. The isolation and purification of these arsenosugars from algae is a tedious, time-consuming operation that produces only milligram quantities of the desired compounds. The availability of larger amounts of synthetic samples will facilitate the development of chromatographic methods for the identification and purification of these compounds, the study of their toxicity, the establishment of their chemical reactivity and the elucidation of their biotransformations.



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X, Y: OH, OH; OH, OSO_3H
OH, SO_3H; NH_2, OSO_3H
OH, $OP(OH)O_2CH_2CH(OH)CH_2OH$

The synthesis and properties of the arsenosugar (2′*R*)-dimethyl[1-*O*-(2′,3′-dihydroxypropyl)-5-deoxy-β-D-ribofuranos-5-yl]arsine oxide (**2**; X = Y = OH in formula **1**) from the commercially available 1-*O*-acetyl-2,3,5-tri(*O*-benzoyl)-β-D-ribofuranose have been reported.[3–5] We describe an alternative method for the preparation of compound **2** starting from D-ribose.

EXPERIMENTAL

Materials

Cacodylic acid (commercial herbicide, 515 g l^{-1}) was obtained from Vineland Chemical Co. Inc., Vineland, NJ, USA. D-Ribose (99%), *p*-

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toluenesulfonyl chloride (98%), palladium on activated carbon (10% Pd), 2,2-dimethyoxypropane (98%), hypophosphorous acid (50% wt solution in water), and trifluoroacetic acid (99%) were purchased from Aldrich Chemical Co. and used as received. Hydrogen peroxide (30% solution) and glacial acetic acid were obtained from Mallinckrodt Chemical Works. D-Mannitol, magnesium shavings, sodium bromide, sodium borohydride, potassium hydroxide, sodium hydroxide, sodium sulfate and hydrochloric acid were obtained from Fisher Scientific Co. *p*-Toluenesulfonic acid (98%), ammonium hydroxide, sulfuric acid and sodium hydrogencarbonate were all ACS reagents purchased from Matheson Coleman & Bell (Cincinnati, OH, USA). Benzyl chloride (J. T. Baker, Marieta, CA, USA) and lead tetra-acetate (Eastman Kodak Co.) were used as received. *N*,*N*-Dimethylformamide (Fisher Scientific), pyridine (Matheson Coleman & Bell) and xylene (Central Texas Chemical Co.) were distilled before use. All other solvents were ACS reagent-grade. Hydrogen was purchased from Airco Inc., Montvale, NJ, USA. Nitrogen (pre-purified) was obtained from Bob Smith Corp., Bryan, TX, USA. Sephadex LH-20-100 (25–100 μm) and Sephadex G-15 (25–100 μm) were supplied by Sigma Chemical Co. Merck-grade 60 silica gel (60 Å, 230–400 mesh) was purchased from Aldrich Chemical Co. Polygram silica gel/UV-254 (0.25 mm, without gypsum) was obtained from Macherey–Nagel & Co. Cellulose Eastman chromagram sheet (with fluorescent indicator) and silica gel Eastman chromagram sheet (100 μm thick, without fluorescent indicator) were products of Eastman Kodak Co.

Instrumentation and analyses

^{1}H and ^{13}C NMR spectra were obtained 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). Melting points (uncorrected) were determined on a Fisher–Johns melting point apparatus. Optical rotations were determined with a Jasco DIP-360 digital polarimeter with concentrations given in grams of substance in 100 ml of solvent. Mass spectra were recorded on a Hewlett–Packard 5995c quadrupole gas chromatograph–mass spectrometer at 70 eV electron energy. Elemental analyses were performed by Galbraith Laboratories Inc., Knoxville, TN, USA.

Syntheses

Methyl 2,3-O-isopropylidene-β-D-ribofuranoside (3)

Methyl 2,3-*O*-isopropylidene-β-D-ribofuranoside (**3**) was obtained as an oil following Lerner's procedure[6] from D-ribose in 79% yield. The compound was pure according to ^{1}H NMR.

Methyl 2,3-O-isopropylidene-5-O-p-tolylsulfonyl-β-D-ribofuranoside (4)

This compound was prepared from compound **3** according to Lerner's procedure.[6] The white crystals (81% yield) were pure according to ^{1}H NMR and melted at 83–84° (lit.[6,7] 83–84 °C, 85–86 °C).

Methyl 5-bromo-5-deoxy-2,3-O-isopropylidene-β-D-ribofuranoside (5)

A 2-liter, single-necked, round-bottomed flask equipped with a reflux condenser and a magnetic stirring bar was charged with methyl 2,3 - *O* - isopropylidene-5-*O*-*p*-toluenesulfonyl-β-D-ribofuranoside (**4**) (70.0 g, 0.195 mol), sodium bromide (35.0 g, 0.340 mol) and *N*,*N*-dimethylformamide (700 ml). The mixture was stirred and refluxed for 1.5 h, cooled to room temperature, and concentrated to 120 ml at 50 °C on a rotary evaporator under an aspirator vacuum. Water (700 ml) was added to the concentrate. The aqueous solution was extracted with two 200-ml portions of diethyl ether and then with four 100-ml portions of diethyl ether. The diethyl ether was distilled from the combined extracts. The oily residue was distilled under vacuum to give 44.1 g (85%) of methyl 5-bromo-5-deoxy-2,3-*O*-isopropylidene-β-D-ribofurnoside (**5**) as a yellowish oil, b.p.$_{10}$ 101–103 °C. $[\alpha]_D^{26}$ −79.6° (*c* 9.4, chloroform); lit.[8,9] $[\alpha]_D^{25}$ −80° (*c*. 2.61, chloroform), $[\alpha]_D^{25}$ −79° (*c* 6.4, methanol). The compound was pure according to its ^{1}H and ^{13}C NMR spectra. ^{1}H NMR in $CDCl_3$: δ 5.01, s, $^3J_{1,2}$ ~0.0 Hz, β-H1. ^{13}C NMR in $CDCl_3$:δ 109.3, C1.

Tetramethyldiarsine

Tetramethyldiarsine was synthesized by reducing a solution of dimethylarsinic acid with hypophosphorous acid.[10] Tetramethyldiarsine was obtained as a colorless liquid in 60% yield, b.p. 160–162 °C. (**Caution**: Tetramethyldiarsine burns with a light blue flame upon exposure to air.) The

NMR spectrum in $CDCl_3$ consisted of a singlet at 1.00 ppm in the ^1H NMR and a singlet at 6.10 ppm in the ^{13}C NMR.

Dimethyl(1-*O*-methyl-5-deoxy-2,3-O-isopropylidene-β-D-ribofuranos-5-yl]arsine (6)

A dry, 100-ml, round-bottomed flask fitted with a nitrogen inlet, a reflux condenser and a magnetic stirrer was flushed with nitrogen and charged with methyl 5-bromo-5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranoside (**5**) (10.0 g, 37.4 mmol), tetramethyldiarsine (12.0 ml, 82.7 mmol), and xylene (12 ml). The solution was refluxed under nitrogen for nine days. Excess tetramethyldiarsine, dimethylbromoarsine, and solvent were removed at 60 °C under a vacuum of 10 Torr (oil pump) for 4 h. The residue was dissolved in diethyl ether (70 ml) and the solution was filtered. The filtrate was evaporated under an aspirator vacuum. The residue was dissolved in chloroform (100 ml) and the resulting solution washed with two 50 ml portions of water. The organic solution was concentrated on a rotary evaporator under an aspirator vacuum at 40 °C. The residue was distilled in a nitrogen atmosphere under reduced pressure ($b.p._{10}$ 102–103 °C) to give dimethyl(1-*O*-methyl-5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranos-5-yl]arsine (**6**) as an oil (8.9 g, 81%). The compound was pure according to ^1H and ^{13}C NMR spectroscopic analyses. ^1H NMR in $CDCl_3$: δ 4.95, s, $^3J_{1,2}$ ~0.0 Hz, β-H1. ^{13}C NMR in $CDCl_3$: δ 109.7, C1.

Dimethyl(1-O-methyl-5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranos-5-yl)arsine oxide (7)

Into a 200-ml, round-bottomed flask was placed dimethyl(1-*O*-methyl-5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranos-5-yl)arsine (**6**) (8.9 g, 30.5 mmol) dissolved in 60 ml of diethyl ether. The flask was fitted with a pressure-equalizing addition funnel containing 5.0 ml of 30% hydrogen peroxide (49 mmol). The hydrogen peroxide solution was added dropwise at room temperature to the reaction mixture, which was being stirred for an additional 2 h and then the mixture was extracted with two 50-ml portions of water. The water extracts were combined and washed with two 30-ml portions of diethyl ether. The ether washes were combined and extracted with two 20-ml portions of water. The two 20-ml extracts were combined, washed with two 20-ml portions of diethyl ether, and then combined with the previous water extract (100 ml). The combined aqueous extracts (~140 ml) were 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-2,3-*O*-isopropylidene-β-D-ribofuranos-5-yl]arsine oxide (**7**) as a very thick oil (8.5 g, 91%), which after prolonged drying over phosphorus pentoxide yielded very hygroscopic white crystals. Found: C, 40.06; H, 6.94. Calcd for $C_{11}H_{21}AsO_5 \cdot H_2O$: C, 40.50; H 7.11%. The compound was pure according to ^1H and ^{13}C NMR spectroscopic analyses. ^1H NMR in D_2O: δ 5.09, s, $^3J_{1,2}$ ~0.0 Hz, β-H1. ^{13}C NMR in D_2O: δ 109.9, C1.

Dimethyl(1-O-methyl-5-deoxy-β-D-ribofuranos-5-yl)arsine oxide (8)

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 oxide (**7**) (90 mg, 0.29 mmol) and water (0.4 ml). After all the material had been dissolved, trifluoroacetic acid (3.6 ml) was added and the solution was shaken for 20 s. The reaction mixture was immediately and quickly evaporated at 42 °C on a rotary evaporator under an oil pump vacuum (10 Torr). The evaporation was complete within 5 min. The residue was immediately dissolved in water (4 ml) and neutralized with sodium hydrogencarbonate. The neutralized solution was concentrated on a rotary evaporator under reduced pressure (15 Torr) at temperatures not higher than 35 °C. The concentrate was dissolved in methanol/water (1.5 ml, 1/1:v/v) and the solution was placed on 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 4.1-ml fractions. Each fraction was evaporated at 35 °C on a rotary evaporator under an aspirator vacuum. The fractions that left residues were dissolved in deuterium oxide. According to the NMR spectra of these solutions, the desired product was present in fractions 33–37. These fractions were combined and mixed with 15 ml of methanol. The resulting solution was concentrated at 35 °C on a rotary evaporator under a aspirator vacuum. The residue was dried in a vacuum oven (20 Torr) at 35 °C for 24 h to give dimethyl(1-*O*-methyl-5-deoxy-β-D-ribofuranos-5-yl)arsine oxide as a thick oil (43 mg, 55%) that was pure by ^1H and ^{13}C NMR spectroscopic analyses. ^1H NMR in D_2O: δ 4.90, d, $^3J_{1,2}$ 1.2 Hz, β-H1. ^{13}C NMR in D_2O: δ 108.5, C1. Found: C, 32.38; H, 6.65. Calcd for $C_8H_{17}AsO_5 \cdot 1.5H_2O$: C 32.55; H 6.83%.

(S)-2,3-Isopropylidenedioxypropan-1-ol
This compound was prepared according to the procedures of Rosenthal[11] and Eibl[12] from D-mannitol in 44% yield as a colorless oil. $[\alpha]_D^{26}$ + 13.8° (neat); lit.[9] $[\alpha]_D$ + 14.5° (neat). The compound was pure according to its ^{1}H NMR spectrum.

Transglycosylation of methyl-5-bromo-5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranoside (5) with (S)-2,3-isopropylidenedioxypropan-1-ol
A 50-ml, two-necked, round-bottomed flask equipped with a pressure-equalizing addition funnel and a total-reflux-partial-takeoff still head was charged with methyl 5-bromo-5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranoside (**5**) (3.0 g, 11.2 mmol), (*S*)-2,3-isopropylidenedioxypropan-1-ol (3.0 g, 22.7 mmol), concentrated hydrochloric acid (0.50 ml, 5.4 mmol) and acetone (10 ml). The reaction mixture was refluxed for 3 h. Then the solvent was slowly distilled off. After approximately 8 ml of solvent had distilled, fresh acetone (8 ml) was added through the addition funnel and the distillation was continued until another 8 ml of solvent had distilled. This procedure was repeated twice. The resulting reaction mixture was then poured into 50 ml of a saturated aqueous solution of sodium hydrogencarbonate. This solution was then extracted twice with chloroform (50 ml, 30 ml). The organic extracts were combined and concentrated at 50 °C on a rotary evaporator under an aspirator vacuum. The residue was dissolved in light petroleum ether (b.p. 35–60°C, 8 ml) and the solution was subjected to 'dry-column' flash chromatography (silica gel, Merck-grade 60, 60 Å, 230–400 mesh). The column consisted of a glass fritted funnel (diameter 70 mm, depth 55 mm) packed with silica gel (height 47 mm). The compound was eluted by successively adding 40-ml portions of light petroleum ether/ethyl acetate mixtures of increasing polarity. Elution began with 6.7% ethyl acetate in petroleum ether. The polar component, ethyl acetate, was then increased by 1.65% in each successive portion of the solvent mixture. The product was present in fractions 8–12. These fractions were combined and concentrated on a rotary evaporator under an aspirator vacuum to give an oil (2.9 g, 70%). This oil was a mixture of diastereomers of β-(2′*R*)- and β-(2′*S*)-2′,3′-isopropylidenedioxypropyl-5-bromo-5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranoside(**11a** and **11b**) according to ^{1}H and ^{13}C NMR spectroscopic analyses. ^{1}H NMR in $CDCl_3$: δ 5.15, s, $^3J_{1,2}$ ~0.0 Hz, β-H1. ^{13}C NMR in $CDCl_3$: δ 108.5, 108.4, C1; 86.7, 86.5, C2; 85.0, 84.9, C3; 82.5, C4; 32.4, C5; 68.6, C1′; 74.3, 74.1, C2′; 66.3, 66.2, C3′; 112.6, 26.3, 24.9, ribose isopropylidene; and 109.6, 26.7, 25.3, aglycone isopropylidene. Found: C, 45.98; H, 6.07; Br, 21.23. Calcd for $C_{14}H_{23}BrO_6$: C, 45.79; H, 6.31; Br 21.76%.

(S)-2,3-Bis(benzyloxy)propan-1-ol
This compound was prepared according to the procedures of Beving *et al.*[13] and Stick and co-workers[4] from D-mannitol in 40% yield as an oil. The product was pure by TLC (silica gel, ethyl acetate/light petroleum ether, 3:7; R_f 0.66) and ^{1}H and ^{13}C NMR spectroscopic analyses. $[\alpha]_D^{24}$ − 1.26° (neat).

(2′S)-2′,3′-Bis(benzyloxy)propyl-5-bromo-5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranoside (12)
A dry, 15-ml, single-necked, round-bottomed flask equipped with a magnetic stirring bar was charged with methyl 5-bromo-5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranoside (**5**) (3.0 g, 11.2 mmol), (*S*)-2,3-bis(benzyloxy)propan-1-ol (3.2 g, 11.6 mmol), and *p*-toluenesulfonic acid (0.25 g, 1.3 mmol). The stirred reaction mixture was heated at 80 °C under a vacuum of 30 Torr for 20 h. The resulting mixture was dissolved in chloroform (100 ml) and washed with saturated aqueous sodium hydrogencarbonate solution (60 ml). The chloroform solution was dried over anhydrous sodium sulfate and filtered. Evaporation of the filtrate on a rotary evaporator under an aspirator vacuum gave crude (2′*S*)-2′,3′-bis(benzyloxy)propyl-5-bromo-5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranoside (**12**) as an oil (5.6 g, 98%). This compound was used in the next experiment without further purification. The identity of the compound was confirmed by its ^{1}H and ^{13}C NMR spectra.

(2′S)-2′,3′-Dihydroxypropyl-5-bromo-5-deoxy-2,3-O-isopropylidene-β-D-ribofuranoside (13)
A 250-ml, single-necked flask equipped with a gas-outlet side arm and a large magnetic stirring bar was charged with crude (2′*S*)-2′,3′-bis(benzyloxy)propyl-5-bromo-5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranoside (**12**) (5.6 g, 11.0 mmol), palladium on activated carbon (10% Pd, 400 mg, 0.376 mmol Pd) and methanol (70 ml). The flask was then connected to a hydrogen reservoir at 1 atm and the system was flushed with hydrogen three times by applying an aspira-

tor vacuum to the flask and then filling it with hydrogen. Then the gas outlet was closed and the reaction mixture was vigorously stirred. The hydrogenation reaction was complete within 25 min (total hydrogen consumption: 415 μm at 1 atm and 25 °C, 18.5 mmol). The reaction mixture was filtered. The filtrate was concentrated on a rotary evaporator under an aspirator vacuum to give crude (2′*S*)-2,3′-dihydroxypropyl-5-bromo-5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranoside (**13**) as an oil (3.8 g, 100%). This compound was not further purified. The identity of the compound was confirmed by ^{1}H and ^{13}C NMR spectroscopy.

(2′S)-2′,3′-Isopropylidenedioxypropyl-5-bromo-5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranoside (11a)

A dry, 200-ml, single-necked, round-bottomed flask equipped with a magnetic stirring bar was charged with crude (2′*S*)-2′,3′-dihydroxypropyl-5-bromo-5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranoside (**13**) (3.8 g, 11.6 mmol), 2,2-dimethoxypropane (8 ml, 65.1 mmol), dichloromethane (50 ml) and *p*-toluenesulfonic acid (0.25 g, 1.3 mmol). The reaction mixture was stirred at room temperature for 24 h. The solution was then transferred to a 250 ml separatory funnel and washed with a saturated aqueous solution of sodium hydrogencarbonate (50 ml). The organic layer was separated. The aqueous layer was extracted with chloroform (50 ml). The organic extracts were combined and concentrated at 50 °C on a rotary evaporator under an aspirator vacuum. The residue was dissolved in light petroleum ether (8 ml) and the solution was subjected to 'dry-column' flash chromatography (silica gel, Merck-grade 60, 60 Å, 230–400 mesh). The dry column consisted of a glass fritted funnel (diameter 70 mm, depth 55 mm) packed with silica gel (height 47 mm). The compound was eluted by adding successive 40-ml portions of light petroleum ether/ethyl acetate solvent mixture of increasing polarity. Elution was started with 6.7% ethyl acetate in light petroleum ether. Thereafter, the more polar component, ethyl acetate, was increased by 1.65% in each successive portion of the solvent mixture. The product was present in fractions 9–12. These fractions were combined and concentrated on a rotary evaporator under an aspirator vacuum to give (2′S)-2′,3′-isopropylidenedioxypropyl-5-bromo-5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranoside (**11a**) as an oil (2.1 g, 50%). $[\alpha]_D^{26}$ −68.5° (*c* 2, chloroform). This compound was a single diastereomer, β-(2′*S*)-2′,3′-isopropylidenedioxypropyl-5-bromo-5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranoside (**11a**) according to ^{1}H and ^{13}C NMR spectroscopic analyses. ^{1}H NMR in $CDCl_3$: δ 5.15, s, $^3J_{1,2}$ ~0.0 Hz, β-H1. ^{13}C NMR in $CDCl_3$: δ 108.5, C1; 86.8, C2; 85.1, C3; 82.5, C4; 32.4, C5; 68.6, C1′; 74.1, C2′; 66.4, C3′; 112.6, 26.3, 24.9, ribose isopropylidene; 109.6, 26.7, 25.3, aglycone isopropylidene. Found: C, 46.06; H, 6.05; Br, 21.17. Calcd for $C_{14}H_{23}BrO_6$: C 45.79; H 6.31; Br 21.76%. EI MS: *m/z* 351 (30.8%, $[M(^{79}Br)-CH_3]^+$), 353 (31.1%, $[M(^{81}Br)-CH_3]^+$).

(2′S)-Dimethyl[1-O-(2′,3′-isopropylidenedioxypropyl)-5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranos-5-yl]arsine (14)

A dry, 50-ml, round-bottomed flask fitted with a nitrogen inlet, a reflux condenser, and a magnetic stirring bar was flushed with nitrogen and charged with (2′*S*)-2′,3′-isopropylidenedioxypropyl-5-bromo-5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranoside (**11**) (2.6 g, 7.08 mmol), tetramethyldiarsine (3.5 ml, 24.1 mmol), and xylene (3.5 ml). The solution was refluxed under nitrogen for nine days. Dimethylbromoarsine, excess tetramethyldiarsine and solvent were removed by heating the reaction mixture under a vacuum of 10 Torr (oil pump) at 60 °C for 4 h. The residue was dissolved in diethyl ether (20 ml) and the solution was filtered. The filtrate was then evaporated under an aspirator vacuum. The residue was dissolved in light petroleum ether (3 ml) and the solution was applied to a silica gel flash chromatographic 'dry column'. The dry column consisted of a glass fritted funnel (diameter 40 mm, depth 50 mm) packed with silica gel (height 42 mm). The compound was eluted by adding successive 20-ml portions of light petroleum ether/ethyl acetate solvent mixture of increasing polarity. Elution was started with 7.5% ethyl acetate in light petroleum ether. Thereafter, the more polar component, ethyl acetate, was increased by 1.25% in each successive portion of the solvent mixture. The product was present in fractions 7–11. These fractions were combined and evaporated on a rotary evaporator under an aspirator vacuum at 40 °C to give (2′*S*)-dimethyl[1-*O*-(2′,3′-isopropylidenedioxypropyl)-5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranos-5-yl]arsine (**14**) as an oil (2.4 g, 86%), $[\alpha]_D^{26}$ −32.4° (*c* 1.1, chloroform). ^{1}H NMR in $CDCl_3$: δ 5.08, s, $^3J_{1,2}$ ~0.0 Hz, β-H1. ^{13}C NMR in $CDCl_3$: δ 108.8, C1. Found: C, 48.30;

H, 7.28; As, 19.50. Calcd. for $C_{16}H_{29}AsO_6$: C, 48.98; H, 7.45; As, 19.10%. EI MS: *m/z* 377 (64.5%, $[M-CH_3]^+$), 392 (1.7%, M^+).

(2′S)-Dimethyl[1-O-(2′,3′-isopropylidenedioxypropyl)-5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranos-5-yl]arsine oxide (15)

Into a 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 (**14**) (1.5 g, 3.82 mmol) dissolved in 15 ml of tetrahydrofuran. The flask was fitted with a pressure-equalizing addition funnel containing 0.8 ml of 30% hydrogen peroxide (7.8 mmol). While the solution was stirred, the hydrogen peroxide solution was added dropwise at room temperature. The reaction mixture was stirred for an additional 2 h and then concentrated on a rotary evaporator under an aspirator vacuum. The residue was dissolved in 15 ml of water and washed with two 10-ml portions of diethyl ether. The ether washes were combined and extracted with 15 ml of water. This water extract was washed with two 10-ml portions of diethyl ether. The two aqueous solutions were combined and concentrated on a rotary evaporator under an aspirator vacuum below 45 °C. The concentrate was dried in a vacuum oven (20 Torr) at 40 °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]arsine oxide (**15**) as a syrup (1.4 g, 90%), $[\alpha]_D^{26}$ (*c* 9, methanol); lit.[4] $[\alpha]_D^{20}$ −7.7°. ^{1}H NMR in D_2O: δ 5.26, s, $^3J_{1,2}$ ~0.0 Hz, β-H1. ^{13}C NMR in D_2O: δ 109.3, C1. Found: C, 46.37; H, 7.47; As, 18.17. Calcd for $C_{16}H_{29}AsO_7$: C, 47.07; H, 7.16; As, 18.35%. EI MS: *m/z* 393 (85%, $[M-CH_3]^+$), 409 (8%, $[M+H]^+$.

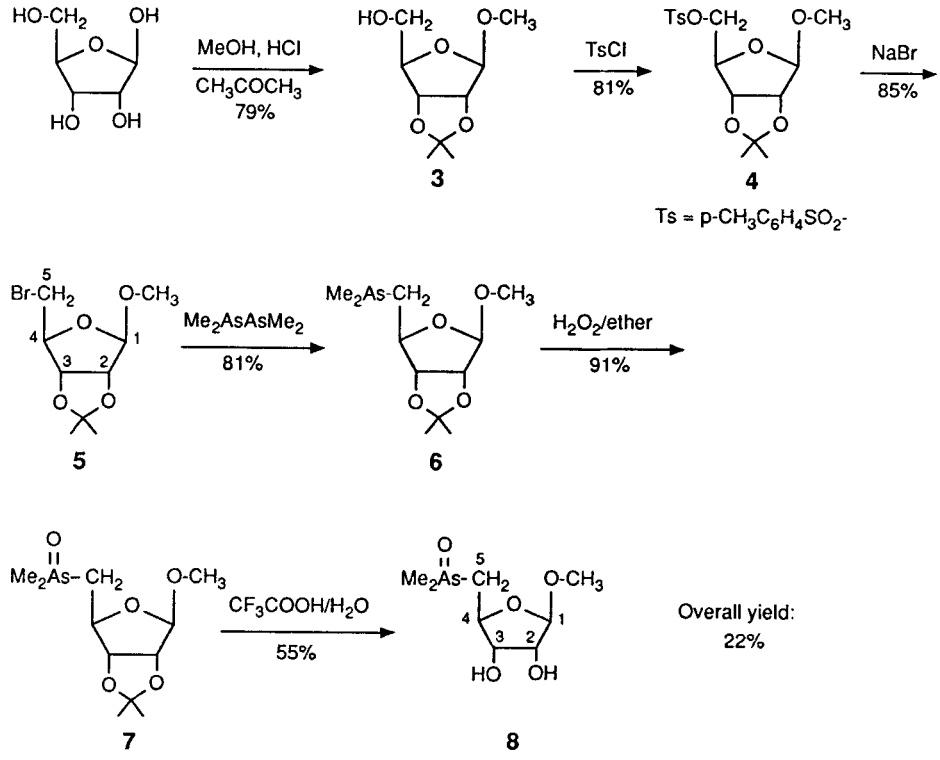
(2′R)-Dimethyl[1-O-(2′,3′-dihydroxypropyl)-5-deoxy-β-D-ribofuranos-5-yl]arsine oxide (2)

Into a 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 oxide (**15**) (0.33 g, 0.81 mmol) and a mixture of water/trifluoroacetic acid (8 ml, 1:9 v/v). The solution was stirred at room temperature for 10 min. The reaction mixture was then concentrated as quickly as possible on a rotary evaporator under reduced pressure (15 Torr) at temperatures not higher than 35 °C. Ethanol (5 ml) was added to the concentrate. The solution was then 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 on a rotary evaporator under reduced pressure (15 Torr) at temperatures not higher than 35 °C. 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 passed through the column. The effluent was collected in 5-ml fractions. Each fraction was evaporated under an aspirator vacuum at 35 °C. The fractions that left residues after evaporation were dissolved in deuterium oxide and ^{1}H NMR spectra were taken. According to the NMR spectra, the desired product was present in fractions 24–28. These fractions were combined and mixed with methanol (8 ml). The solution was evaporated under an aspirator vacuum. The residue was dissolved in methanol (15 ml) and evaporated again. The residue was dried in a vacuum oven (15 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 oxide (**2**) as a syrup (0.22 g, 83%). $[\alpha]_D^{26}$ −1.8° (*c* 3, methanol); lit.[4] $[\alpha]_D^{17}$ −2.6° (*c* 5.5 methanol). ^{1}H NMR in D_2O: δ 5.00, d, $^3J_{1,2}$ 1.2 Hz, β-H1. ^{13}C NMR in $CDCl_3$: δ 107.5, C1. Found: C, 33.64; H, 6.71; As, 21.84. Calcd for $C_{10}H_{21}AsO_7.1.5H_2O$: C, 33.81; H, 6.81; As, 21.09%, 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.

RESULTS AND DISCUSSION

Synthesis of dimethyl(1-O-methyl-5-deoxy-β-D-ribofuranos-5-yl)arsine oxide (8)

Dimethyl(1-*O*-methyl-5-deoxy-β-D-ribofuranos-5-yl)arsine oxide (**8**), a simple analog of naturally occurring arsenosugars, was chosen as the first synthetic target to define appropriate reaction conditions for the syntheses of more complex dimethyl(ribosyl)arsine oxides. Because the arsine oxide **8** is relatively easily obtained and can easily be monitored by ^{1}H NMR spectroscopy, it is also a good model compound for the naturally



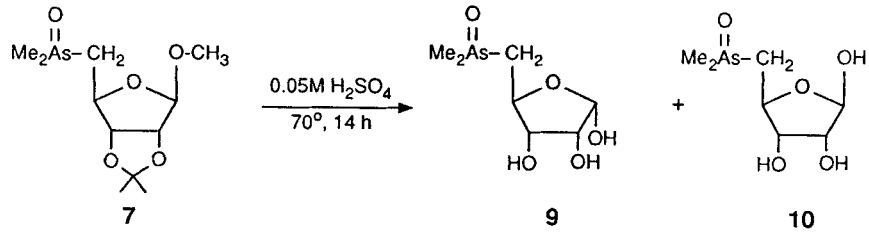
Scheme 1

occurring dimethyl(ribosyl)arsine oxides in the studies of their behavior in alkaline and acidic media. The synthesis of dimethyl(1-*O*-methyl-5-deoxy-β-D-ribofuranos-5-yl)arsine oxide (**8**) is outlined in Scheme 1.

The synthesis used D-ribose as a starting material. Thus, reaction of D-ribose with methanol and acetone in the presence of hydrochloric acid as catalyst produced in a one-step reaction methyl 2,3-*O*-isopropylidene-β-D-ribofuranoside (**3**) as an oil in 79% yield. The ^{1}H NMR spectrum of the isolated product proved that only the desired β-anomer was formed. Typical of the β-anomers of ribosides, the β-H1 resonance was a singlet showing little coupling to H2, $^3J_{1,2}$ ~0.0 Hz. The α-anomers consistently show larger α-H1–H2 couplings of 3.5–8 Hz.[4,5,14,15] Compound **3**, containing only one hydroxyl group, was easily converted to the corresponding tosylate **4** by treatment with *p*-toluenesulfonyl chloride in dry pyridine. Tosylate **4** was recrystallized from 95% ethanol and obtained as white crystals in 81% yield. It was then converted to methyl 5-bromo-5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranoside (**5**) by refluxing with sodium bromide in DMF for 1.5 h. The by-product of this reaction, sodium *p*-toluenesulfonate, was easily removed by washing with water. The bromide **5** was obtained as an oil in 85% yield by vacuum distillation.

In the initial attempt to convert bromide **5** into dimethyl(1-*O*-methyl-5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranos-5-yl)arsine (**6**), bromide **5** was treated with sodium dimethylarsinide in dry tetrahydrofuran. Dry-column flash chromatography of the product on silica gel gave the arsine **6** as an oil in ~48% yield. The ^{1}H NMR spectrum showed two resonances (δ 0.99 and 1.00 ppm) for the newly introduced diastereotopic methyl groups. The low yield of this method may stem from the decomposition of the ribose unit and the hydrolysis of protective groups under the rather harsh, basic conditions.

Alternatively, bromide **5** was refluxed with tetramethyldiarsine in xylene. The reaction proceeded slowly and took about nine days to achieve 95% conversion. At this point the reaction was terminated, because longer reaction times did not improve the yield. The readily volatile tetramethyldiarsine, dimethylbromoarsine and solvent were evaporated under vacuum. The residue was distilled under reduced pressure to give ribosylarsine **6** as an oil in 81% yield. The



[1]

product is relatively stable in air and oxidized only very slowly, but it must be kept under nitrogen for long-term storage.

The ribosylarsine **6** was then oxidized with hydrogen peroxide in diethyl ether to give dimethyl(1-*O*-methyl-5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranos-5-yl)arsine oxide (**7**) as a colorless syrup in 91% yield. This syrup crystallized after prolonged drying in a desiccator over phosphorus pentoxide. The resulting solid was very hygroscopic and difficult to handle.

Finally, treatment of ribosylarsine oxide **7** with trifluoroacetic acid/water (9:1 v/v) for 20 s, followed by immediate evaporation of the solvent and neutralization of the resulting syrup, selectively removed the isopropylidene protective group without cleaving the glycosidic bond and gave the desired product, dimethyl(1-*O*-methyl-5-deoxy-β-D-ribofuranos-5-yl)arsine oxide (**8**). This arsine oxide **8** was isolated as an oil in 55% yield by chromatography on a Sephadex LH-20 column with water/methanol (1:1 v/v) as the mobile phase. The overall yield from ribose was 22%.

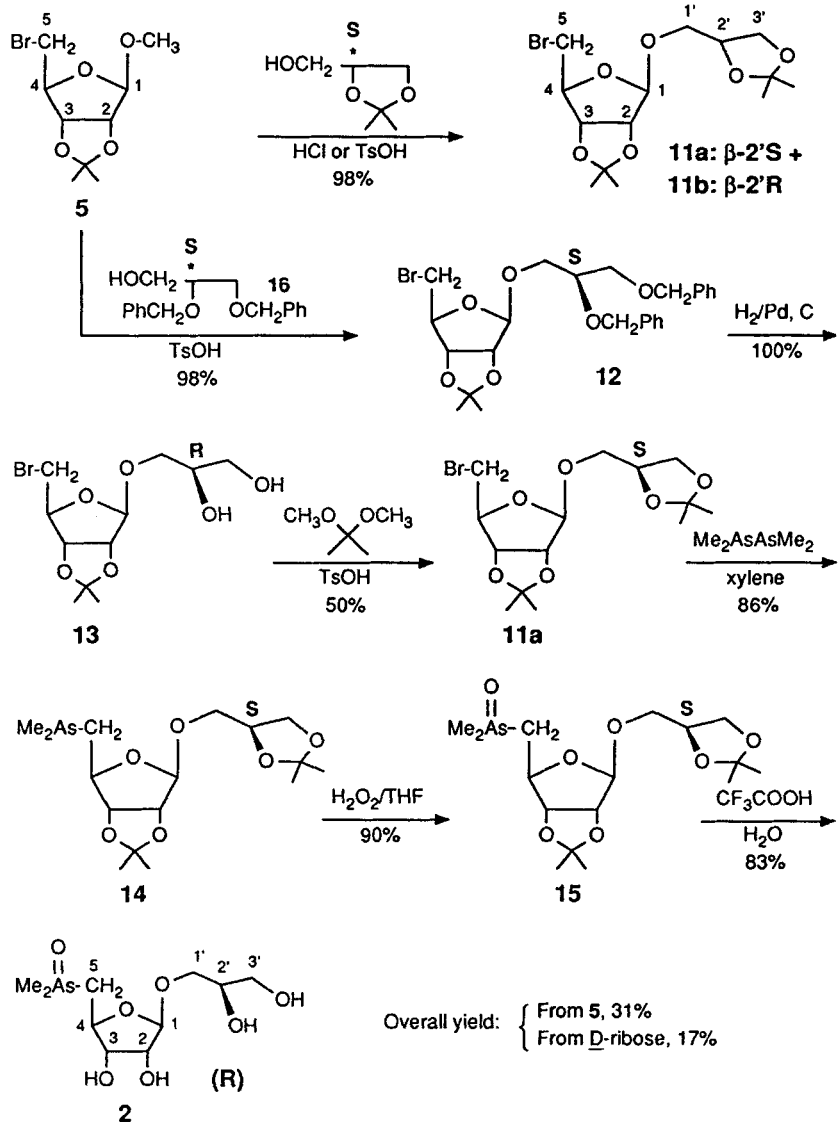
When hydrolysis of the arsine oxide **7** was carried out under more drastic, acidic conditions, the glycosidic bond was also cleaved. Thus, treatment of the arsine oxide **7** with aqueous 0.05 M sulfuric acid at 70 °C for 14 h gave α (**9**) and β (**10**) anomers of dimethyl(5-deoxy-D-ribofuranos-5-yl)arsine oxide in a 0.4:1.0 ratio (Eqn [1]). The α-H1 resonance for **9** was a doublet at δ 5.40 ($^3J_{1,2}$ = 4.2 Hz), while the β-H1 resonance for **10** was a doublet at δ 5.23 ($^3J_{1,2}$ = 1.5 Hz).

Synthesis of (2′R)-dimethyl[1-*O*-(2′,3′-dihydroxypropyl)-5-deoxy-β-D-ribofuranos-5-yl]arsine oxide (2)

The naturally occurring ribosylarsine oxide **2** was successfully synthesized by the introduction of the chiral three-carbon aglycone at C1 of the D-ribose unit followed by the attachment of the dimethylarsinoyl group at C5 (Scheme 2). In the initial attempts to transglycosylate the methyl glycoside **5**, (*S*)-2,3-isopropylidenedioxypropan-1-ol[11,12] was used as the three-carbon aglycone. The acetone solution of the two reagents in the presence of catalytic amounts of hydrochloric acid was refluxed, the solvent was distilled off during the reaction to remove the methanol liberated, and fresh acetone was added to the solution to compensate for solvent loss. Glycosides **11a** and **11b** were isolated in 70% yield after purification by flash chromatography on a dry column of silica gel. The glycosides so formed were a mixture β-2′*S* and β-2′*R* diastereomers, as evidenced by the very small coupling (almost zero) between β-H1 and H2 ($J_{1,2}$~0.0 Hz) in the ^{1}H NMR spectrum. In the α configuration α-H1 is a doublet ($^3J_{1,2}$ 3.5–8.0 Hz).[4,5,14,15] The most convincing evidence that the product was a mixture of β diastereomers comes from the ^{13}C NMR spectrum. Many of the carbon atoms (C1, C2, C3, C2′, C3′) each produced two very closely spaced resonances, strongly indicating that the product was a mixture of 2′*R* and 2′*S* diastereomers. Most importantly, there were two resonances typical of β anomers at δ 108.5 and 108.4 and no resonances between δ 101 and 103 typical of α anomers.

In another trial, the transglycosylation of methyl glycoside **5** with (*S*)-2,3-isopropylidenedioxypropan-1-ol was carried out without solvent with *p*-toluenesulfonic acid as the catalyst. The reaction mixture was heated at 80 °C and the released methanol was removed with a vacuum pump (50 Torr) to drive the reaction to completion. Again, the diastereomeric β-glycosides **11a** and **11b** were obtained in 68% yield. Very likely, either hydrochloric acid or *p*-toluenesulfonic acid had caused stereochemical change in the protected (*S*)-propanetriol prior to transglycosylation. The alcohol is known to racemize easily under acidic conditions.[16]

An alcohol which is stereochemically stable towards racemization under acidic conditions was needed for the transglycosylation of the methyl glycoside **5**. (*S*)-2,3-bis(benzyloxy)propan-1-ol (**16**)[3,11] was chosen for this purpose. The glycoside **5** was stirred with this alcohol in the presence of *p*-toluenesulfonic acid under vacuum (30 Torr) at



Scheme 2

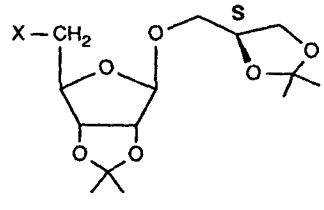
80 °C for 20 h to give glycoside **12**. The protective benzyl groups of glycoside **12** were removed by hydrogenation over 10% palladium on charcoal to give glyceryl glycoside **13**. The crude material was treated with 2,2-dimethyoxypropane and *p*-toluenesulfonic acid in dichloromethane to give glycoside **11a**, which was purified by flash chromatography on silica gel to provide the product as an oil in 50% yield from methyl glycoside **5**. The ^{1}H NMR spectrum of this material was simpler than the spectrum of the previously obtained mixture of β-2′*S* and β-2′*R* diastereomers. The β-H1 resonance was a singlet at δ 5.15 ($^3J_{1,2}$ ~0.0 Hz). In the ^{13}C NMR spectrum the β-C1 carbon appeared at δ 108.5. Only a single resonance was observed for each carbon and there was no resonance characteristic of α anomers between δ 101 and 103. This spectroscopic evidence strongly indicates that the product is the β-2′*S* diastereomer, **11a**.

The glycoside **11a**, which has a bromomethyl group at C5 and all other functional groups properly protected, was ready for the introduction of the $(CH_3)_2As$ group at C5. Thus, glycoside **11a** was refluxed with tetramethyldiarsine in xylene under nitrogen for nine days. The reaction mixture was evaporated under vacuum and the residue was chromatographed on silica gel with ethyl

acetate/petroleum ether to give dimethyl(ribosyl)-arsine **14** as an oil in 86% yield. The product was sufficiently stable to be handled in air for short periods, but prolonged exposure to the air resulted in its oxidation.

The dimethyl(ribosyl)arsine **14** was oxidized with hydrogen peroxide in tetrahydrofuran to give dimethyl(ribosyl)arsine oxide **15** as a colorless syrup in 90% yield. This syrup hardened after prolonged drying to give a glass-like solid, which was very hygroscopic and difficult to handle. Finally, the arsine oxide **15** was treated with a mixture of trifluoroacetic acid and water (9:1 v/v) for 10 min to remove selectively its isopropylidene protective groups without cleaving the glycosidic bond. The reaction mixture was then neutralized and separated on a Sephadex LH-20 column with water/methanol (1:1 v/v) to give the arsine oxide **2** as a syrup in 83% yield. The overall yield from the methyl 5-bromo-2,3-isopropylidene-5-deoxy-β-D-ribofuranoside was 31% and from D-ribose, 17%. Dimethyl(ribosyl)arsine oxide **2** had characteristic β-H1 and β-C1 resonances at δ 5.00 ($^3J_{1,2}$ = 1.2 Hz) and δ 107.5 in the ^{1}H and ^{13}C spectra. The optical rotation for **2** of −1.8° was very close to the value of −2.6° reported by Stick and co-workers.[4]

The two methods that are available for the preparation of (2′*R*)-dimethyl-[1-*O*-(2′,3′-dihydroxypropyl)-5-deoxy-β-D-ribofuranos-5-yl]arsine oxide, one of the dimethyl(ribosyl)arsine oxides isolated from marine algae, both give overall yields of approximately 20%. The method of Stick and co-workers[4] uses the commercially available, but rather expensive, 1-*O*-acetyl-2,3,5-tri(*O*-benzoyl-β-D-ribofuranose, whereas the method reported in this paper starts with inexpensive D-ribose. The protected 5-haloriboses (**11a**, Scheme 2; **16**, X = Cl or Br) were obtained in reaction sequences that differed in the type of initial protecting groups, the sequence in which the isopropylidene protecting groups were introduced, and the reagent for the introduction of the halogen atom [$(Et_2N{=}CCl_2)^+Cl^-$ with **17**, X = OH;[4] NaBr with tosylate **4** (Scheme 1) followed by exchange of the C1 methyl (Scheme 2) to give **17** (X = Br)]. Stick's four-step sequence[4] has an overall yield of 46%, the six-step sequence from ribose, 28%. In these reaction sequences the introduction of the isopropylidene group to the ribose ring (66%)[4] and the glycerol aglycone (50%) are the low-yield steps. The substitution of the dimethylarsino group for halogen leading to **17** (X = Me_2As) was accomplished with sodium dimethylarsinide[4] or tetramethyldiarsine with approximately equal yields (81%, 86%). The reaction with tetramethyldiarsine avoids the use of metallic sodium needed for the generation of the sodium dimethylarsinide but requires a long (nine days) reaction time. The subsequent steps are the same in the two reaction schemes. All reactions but the last (deprotection of **17**, X = Me_2AsO, with CF_3COOH) were carried out with gram quantities in the range from 1.5 to 100 g. The deprotection step was performed with 220 or 330 mg. The size of the LH-20 column needed for purification of the final product limits the scale of reaction with trifluoroacetic acid. Prolonged contact between the product and trifluoroacetic acid, unavoidable with large-scale reactions because of the time required to evaporate the reaction mixture, might also lower the yield through cleavage of the aglycone. Both methods can be used to prepare multi-gram quantities of compound **2**.



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REFERENCES

1. W. R. Cullen and K. J. Reimer, *Chem. Rev.* **89**, 713 (1989).
2. K. A. Francesconi and J. S. Edmonds, Arsenic in the sea. In: *Oceanography and Marine Biology, an Annual Review*, Ansell, A. D., Gibson, P. N. and Barnes, M. (eds), UCL Press, London, 1993, Vol. **31**, p. 111, and references cited therein.
3. D. P. McAdam and R. V. Stick, *Tetrahedron Lett.* 251 (1986).
4. D. P. McAdam, A. M. A. Perera and R. V. Stick, *Aust. J. Chem.* **40**, 1901 (1987).

5. K. A. Francesconi, J. S. Edmonds and R. V. Stick, *Appl. Organomet. Chem.* **8**, 517 (1994).
6. L. M. Lerner, *Carbohydr. Res.* **53**, 177 (1977).
7. P. A. Levene and E. T. Stiller, *J. Biol. Chem.* **106**, 421 (1934).
8. S. Hanessian, M. M. Ponpipom and P. Lavallee, *Carbohydr. Res.* **24**, 45 (1972).
9. K. A. Francesconi, J. S. Edmonds, R. V. Stick, B. W. Skelton and A. H. White, *J. Chem. Soc., Perkin Trans. 1* 2707 (1991).
10. G. Petit, *Ann. Chim.* **16**, 5 (1941).
11. A. F. Rosenthal, *Methods Enzymol.* **35**, 429 (1975).
12. H. Eibl, *Chem. Phys. Lipids* **28**, 1 (1981).
13. H. F. G. Beving, H. B. Born and P. J. Garegg, *Acta Chem. Scand.* **21**, 208 (1967).
14. T. D. Inch, *Ann. Rev. NMR Spectrosc.* **2**, 35 (1969).
15. A. S. Serianni and R. Barker, *J. Org. Chem.* **49**, 3292 (1984).
16. J. J. Baldwin, A. W. Raab, K. Mensler, B. H. Arison and D. E. McClure, *J. Org. Chem.* **43**, 4876 (1987).