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Synthesis of Naturally Occurring Arsenic-Containing Carbohydrates

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We report the synthesis of (*S*)-2′-hydroxy-3′-sulfonylpropyl 5-deoxy-5-dimethylarsinoyl-β-D-riboside ammonium salt and (*S*)-2′-hydroxy-3′-sulfooxypropyl 5-deoxy-5-dimethylarsinoyl-β-D-riboside ammonium salt, two common naturally occurring arsenicals.

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Introduction

Arsenic-containing ribosides (arsenosugars) were first identified in the brown alga *Ecklonia radiata* almost 30 years ago,[1] and they were subsequently shown to be common constituents of algae and animals feeding on algae such as oysters and mussels.[2] Arsenosugars are considered key compounds in the cycling and transformation of arsenic in marine systems: they are biosynthesized as a result of arsenate being taken up by algae directly from seawater (because algae cannot distinguish arsenate from phosphate), and they might be the precursors to arsenobetaine, the predominant arsenical compound found in marine animals.[2]

Although 17 arsenosugars have been identified,[3] four compounds clearly dominate (Fig. 1). These compounds (dimethylarsinoyl, $Me_2As(O)-$, derivatives) have also recently been shown to have thio-analogues ($Me_2As(S)-$). The thio-analogues are trace constituents of algae[4] but can occur in significant quantities in molluscs, possibly as a result of metabolic changes that take place within the animal.[5–8]

Fundamental aspects such as the biosynthesis of arsenosugars and their possible biochemical roles in organisms have encouraged continuing studies over several years. Interest in the compounds intensified, however, as a result of human health issues related to the ingestion of arsenosugars contained in edible algae and molluscs. The major arsenical metabolite in the urine of humans eating algae or molluscs was shown[9,10] to be dimethylarsinate, the same arsenical produced from arsenate, a proven human carcinogen that can be a contaminant of drinking water as a result of natural geological processes.[11] These observations led to a more detailed study[12] of metabolic pathways using pure synthesized compound **1**, the arsenosugar most readily accessible by synthesis.[13–15] A subsequent related study, however, showed that the four major arsenosugars are likely to have different metabolic behaviour, and hence would need to be assessed independently.[16]

The human health concern regarding arsenic in foods has created a need for quantities of pure arsenosugars for toxicological assessment. We report a synthetic scheme able to deliver arsenosugars **1**, **2**, and **3**, together with their thio-analogues. A novel aspect of the scheme is the use of sulfur as a pseudo-protecting group for arsenic, thereby overcoming the otherwise recalcitrant behaviour of intermediates that contain the arsinoyl group during the synthesis. A preliminary account of this work has been reported.[17]

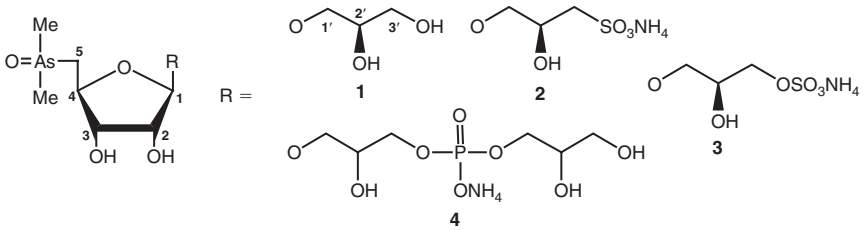

Fig. 1. Major arsenosugars present in algae.

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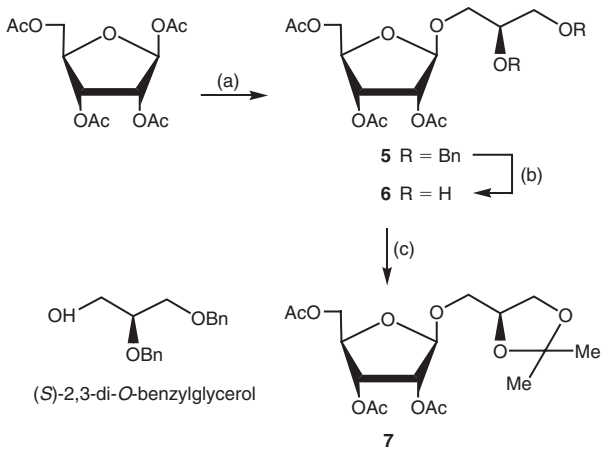
Results and Discussion

Our approach was to prepare the arsenosugar with the glycerol aglycone, compound **1**, followed by functionalization of the aglycone to provide compounds **2** and **3**. The glycoside **7** was obtained in a three step procedure from commercially available tetraacetyl ribose and (*S*)-2,3-di-*O*-benzylglycerol[18] essentially according to the method of McAdam et al.[13] We found that the reported glycosidation could be improved by using the catalyst $BF_3{\cdot}OEt_2$ and initiating the reaction at −25°C with subsequent warming of the reaction mixture to room temperature. The dibenzylated glycoside **5** was hydrogenated over Pd/C to give the diol **6**, which was converted into the acetonide **7** (Scheme 1).

Removal of acetyl groups gave the triol **8**, which was selectively chlorinated at the primary hydroxy group using Ph_3P and CCl_4 according to the method of Whistler and Anisuzzaman.[19] The product **9** was used directly in the arsenylation procedure since previous work had shown that free secondary hydroxy groups do not interfere with the arsenylation reaction.[20]

The arsenic group has been successfully introduced at C5 by nucleophilic substitution with sodium dimethylarsenide formed from dimethyliodoarsine and sodium.[13] We found, however, that the combined use of lithium and sodium to form the nucleophile gave more consistent and higher yields. Thus, generation of the nucleophile was initiated by reaction of dimethyliodoarsine with lithium to give tetramethyldiarsine ($(Me_2As)_2$),[21,22] which was cleaved in situ upon addition of finely cut sodium pieces. Reaction of the chloro compound **9** with sodium dimethylarsenide gave the trialkylarsine **10**; this compound, which is difficult to handle, was not isolated but directly converted into the arsine oxide **11** (Scheme 2). Removal of the acetal group in acidic medium gave compound **1**, and its subsequent treatment with H_2S provided its sulfur analogue **12** (Scheme 3). This compound had previously been prepared by a different route by Liu et al.[23]

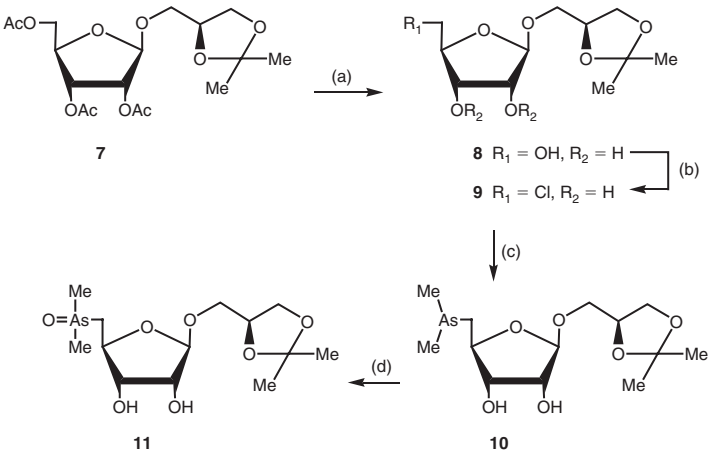


Scheme 1. (a) (*S*)-2,3-Di-*O*-benzylglycerol, $BF_3{\cdot}OEt_2$, MeCN, 85%. (b) Pd/C 5%, MeOH, 82%. (c) 2,2-Dimethoxypropane, *p*-TsOH, CH_2Cl_2, 85%.

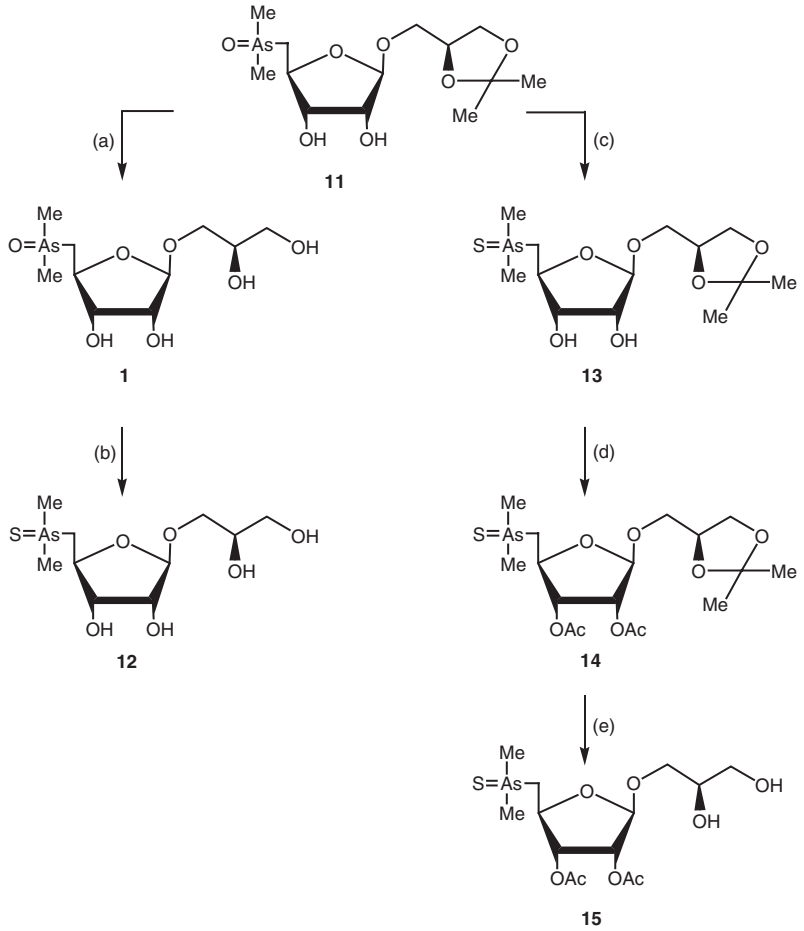
The strategy from this point was to acetylate the residual hydroxy groups of compound **11**, and then remove the isopropylidene group on the aglycone to give a diol suitable for introduction of the desired functional groups. Surprisingly, the arsine oxide **11** could not be acetylated – it remained steadfastly unreactive under standard acetylation conditions. Acetylation of the arsine **10**, however, gave the desired protected product. This result indicated that the polar dimethylarsinoyl group might be interfering with the reaction, and suggested to us that the arsine sulfide could be a more suitable substrate. Arsine sulfides are considerably less polar than their oxide analogues, they are easy to handle (in contrast to arsines), and they can readily be changed back to the oxide by treatment with H_2O_2.[5] Thus, sulfur might act as a pseudo-protecting group for the arsenic, allowing functionalization on the rest of the molecule, before being changed back to the arsine oxide in the final step. With this in mind, the oxide **11** was treated with H_2S to form the arsine sulfide **13**, which was readily acetylated to give **14**; removal of the isopropylidene group yielded the diol **15** (Scheme 3) which promised to serve as the key intermediate in the synthesis of the acidic derivatives **2** and **3**.

According to the method of Martinelli et al.[24] compound **15** was converted into the tosylate **16**, which was then simultaneously deprotected and sulfonated by treatment with Na_2SO_3 in water/MeOH (2/1, v/v) to yield the sulfonate **17** (Scheme 4). Regeneration of the arsine oxide moiety was achieved on treatment of the arsine sulfide with 30% H_2O_2 to give the product **2**.

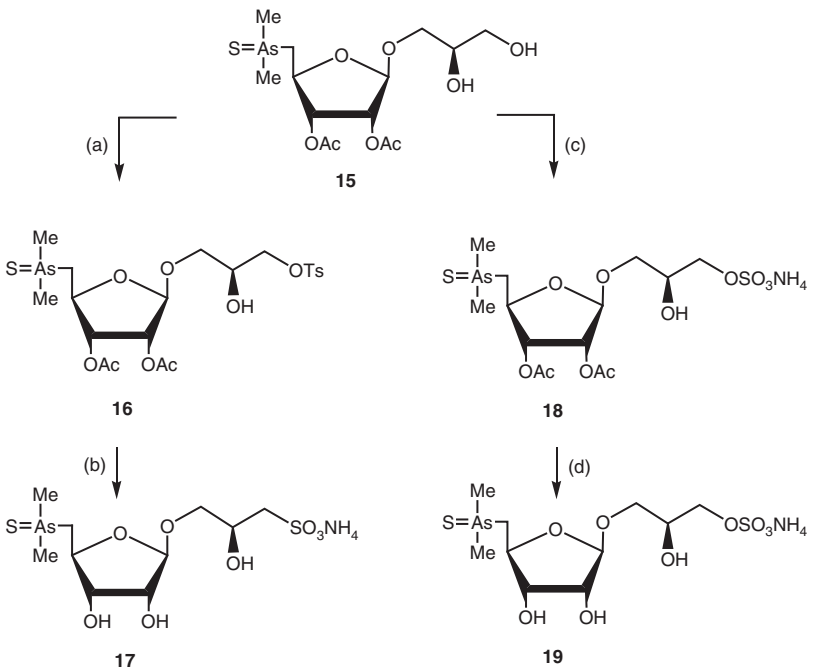
Treatment of the key intermediate **15** with sulfur trioxide triethylamine complex gave the sulfuric acid ester **18**, subsequent removal of acetyl groups (NaOMe) delivered compound **19** (Scheme 4). Regeneration of the arsine oxide as described for compound **2** gave the product **3**.



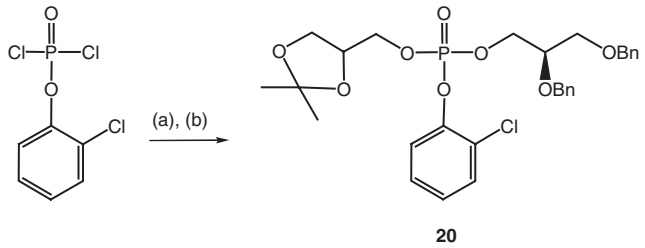
Scheme 2. (a) OH^- resin, MeOH, 82%. (b) Ph_3P, CCl_4, pyridine, 68%. (c) Li, Me_2AsNa, THF, Na, crude. (d) THF, H_2O_2, 66% for steps (c) and (d).



Scheme 3. (a) CF_3COOH/water, 85%. (b) H_2S, water, 93%. (c) H_2S, pyridine, 84%. (d) Ac_2O, pyridine, 77% based on compound **11**. (e) CF_3COOH/water, MeCN, 82%.



Scheme 4. (a) *p*-TsCl, Et_3N, Bu_2SnO, CH_2Cl_2, 72%. (b) Na_2SO_3, water/MeOH, NH_4^+ resin, 69%. (c) $Et_3N{:}SO_3$, pyridine, NH_4^+ resin, 58%. (d) NaOMe, MeOH, NH_4^+ resin, 80%.



Scheme 5. (a) (*S*)-2,3-Di-*O*-benzylglycerol, pyridine, CH_2Cl_2, 0°C to rt, crude. (b) (*R*,*S*)-2,3-*O*-Isopropylideneglycerol, 55% for steps (a) and (b).

We also attempted the synthesis of the phosphoric acid diester **4**. First, we prepared the model compound **20** by the phosphotriester approach (Scheme 5).[25,26] However, attempts to phosphorylate the diol **15** in an analogous fashion were unsuccessful. Further attempts will consider protecting the secondary hydroxy group of compound **15**, and include alternative phosphorylation reactions.[25]

The ^{1}H and ^{13}C NMR data and chromatographic behaviour for the synthetically prepared compounds **1**, **2**, and **3** are in good agreement with those reported for the natural products.[27,28] The described synthetic scheme provides the previously synthesized compound **1** in 17% overall yield in 7 steps and delivers two new synthetic products, sulfonic acid **2** and sulfuric acid ester **3**, each in 5% overall yield in 10 steps. The sulfur analogues **12**, **17**, and **19** are also obtained during this reaction sequence.

Experimental

All chemicals and solvents were purchased from Lactan/Roth (Graz, Austria), Sigma–Aldrich (Vienna, Austria), or Acros Chemicals (Geel, Belgium) and were used in the synthetic procedures without further purification. TLC was performed on silica gel 60 F_{254} (plastic sheets or glass plates), from Merck (Darmstadt, Germany). Compounds were visualized by UV_{254} detection or by dipping the TLC plates in a solution of vanillin (1.5 g)/H_2SO_4 (20 mL)/water (150 mL)/ethanol (125 mL) and subsequently heating the plate to 140°C. The procedure described by the term 'usual workup' contained the following steps: The organic layer, which contained the product, was washed successively with water, 5% H_2SO_4, saturated $NaHCO_3$, and water. The organic layer was then dried over $MgSO_4$ or Na_2SO_4. Similarly, the term 'workup' refers to this same series of steps except that the acidic washing step (5% H_2SO_4) was omitted. Column chromatography was performed on silica gel 60, 63–100 μm, from Merck (Darmstadt, Germany). Size exclusion chromatography was performed on Sephadex G-15 ($26 \times 600\,mm^2$, water as eluent) or Sephadex LH-20 ($26 \times 300\,mm^2$, MeOH as eluent) both supplied by Amersham Pharmacia Biotech AB (Uppsala, Sweden). Before the compounds were applied to Sephadex G-15, the column was pretreated with 0.1 M NH_4OH followed by equilibration with water. Anion exchange chromatography was performed on DEAE (diethylaminoethyl) Sephadex A-25 ($16 \times 300\,mm^2$), Amersham Biosciences AB (Uppsala, Sweden) using 0.05 M Tris (tris(hydroxymethyl)aminomethan) buffer, pH 8.0, as the eluent. Before compounds were applied, the column was washed with 0.5 M Tris buffer, pH 8.0, followed by equilibration with the eluent. Ion exchange resins were used after washing and cycling to constant titre with 5% (w/v) NaOH or NH_4OH (1 M) and 5% (w/v) HCl. Anion exchange resin refers to Dowex 1×8, from Fluka (Buchs, Switzerland). Cation exchange resin refers to Dowex 50WX8–200 supplied by Sigma–Aldrich (Steinheim, Germany). Melting points (uncorrected) were recorded on a Mettler FP62 melting point apparatus, from Mettler–Toledo (Giessen, Germany). Rotation values were measured on a Perkin–Elmer Polarimeter 341, from Perkin–Elmer (Ueberlingen, Germany) at ambient temperature (λ 589 nm). Elemental analyses were performed on a Carlo Erba/Fisons 1108 Elemental Analyzer, Fisons Instruments (Milan, Italy). ^{1}H and ^{13}C NMR spectra were recorded with Varian (400 MHz) or Bruker (360 and 500 MHz) instruments. Chemical shifts are given in ppm and are referenced to partially protonated solvent or internal standard: ^{1}H NMR: D_2O 4.83 ppm, $CDCl_3$ 7.24 ppm, TMS 0 ppm. ^{13}C NMR: $CDCl_3$ 77 ppm. Electrospray ionization mass spectra were recorded on an Agilent 1100 LC/MSD series single quadrupole mass spectrometer, Agilent Technologies (Waldbronn, Germany) with flow injection.

(R)-2′,3′-Dihydroxypropyl 2,3,5-Tri-O-acetyl-β-D-riboside **6**

(i) $BF_3{\cdot}OEt_2$ (7.4 g, 52 mmol) was added at −25°C to a mixture of 1,2,3,5-tetra-*O*-acetyl-β-D-ribose (15.0 g, 47 mmol) and (*S*)-2,3-di-*O*-benzylglycerol (14.0 g, 51 mmol) in acetonitrile (MeCN, 300 mL). The reaction mixture was allowed to warm to room temperature and then poured into a saturated $NaHCO_3$ solution under vigorous stirring. The product was extracted into dichloromethane (CH_2Cl_2) and after usual workup and removal of the organic layer, the residue was subjected to column chromatography (silica, cyclohexane/ethyl acetate (EtOAc), 4/1, v/v) to yield (*R*)-2′,3′-di-*O*-benzylpropyl 2,3,5-tri-*O*-acetyl-β-D-riboside **5** (21.2 g, 85%) as a pale yellow oil. δ_H (500 MHz, $CDCl_3$) 7.32 (10H, m, Ar), 5.31, 5.23 (2H, 2 × d, *J* 4.9, H2, 3), 5.00 (1H, s, H1), 4.65, 4.62 (2H, 2 × d, *J* 11.7, CH_2Ar), 4.53, 4.50 (2H, 2 × d, *J* 12.0, CH_2Ar), 4.28, 4.11 (3H, 2 × m, H4,5), 3.82 (1H, dd, *J* 10.4, 5.5, H1′), 3.72 (1H, m, H2′), 3.57 (3H, m, H1′,3′), 2.06, 2.02, 2.00 (9H, 3 × s, OAc). δ_C (125 MHz, $CDCl_3$) 170.2, 169.3, 169.2 (CO), 138.2–127.3 (Ar), 105.1 (C1), 78.3 (C4), 76.4 (C2′), 74.4, 73.1, 71.9, 71.3 (C2, C3, CH_2Ar), 69.4, 67.4 (C1′, C3′), 64.3 (C5), 20.4, 20.2, 20.1 (OAc). *m/z* (ESI) 569 $[M+K]^+$, 553 $[M+Na]^+$.

(ii) The glycoside **5** (15.0 g, 28 mmol) was dissolved in methanol (MeOH, 200 mL) and hydrogenated over Pd/C (5%, 7.5 g) for 3 h. Filtration and evaporation gave an oil, which was subjected to column chromatography (silica, cyclohexane/EtOAc, 1/4, v/v), to deliver the diol **6** (8.1 g, 82% based on compound **5**). $[\alpha]_D$ −21.0° (c. 2.4 MeOH). (Found: C 47.9, H 6.3. $C_{14}H_{22}O_{10}$ requires C 48.0, H 6.3%.) δ_H (500 MHz, $CDCl_3$) 5.32 (1H, m, H3), 5.27 (1H, d, *J* 5.0, H2), 5.05 (1H, s, H1), 4.32 (2H, m, H4,5), 4.21 (1H, dd, *J* 12.8, 6.8, H5), 3.86 (1H, m, H2′), 3.74 (1H, dd, *J* 10.4, 6.5, H1′), 3.69 (1H, dd, *J* 11.4, 4.1, H3′), 3.63 (1H, dd, *J* 10.5, 4.0, H1′), 3.59 (1H, dd, *J* 11.4, 5.9, H3′), 2.12, 2.11, 2.07 (9H, 3 × s, OAc). δ_C (125 MHz, $CDCl_3$) 170.8, 169.8, 169.7 (CO), 105.6 (C1), 78.5 (C4), 74.6 (C2), 71.1 (C3), 70.6 (C2′), 70.1 (C1′), 64.2 (C5), 63.4 (C3′), 20.7, 20.5, 20.4 (OAc). *m/z* (ESI) 389 $[M+K]^+$, 373 $[M+Na]^+$.

(S)-2′,3′-O-Isopropylidenepropyl 2,3,5-Tri-O-acetyl-β-D-riboside **7**

The diol **6** (6.6 g, 19 mmol) in CH_2Cl_2 (120 mL) together with 2,2-dimethoxypropane (5.2 g, 50 mmol) and *p*-toluenesulfonic acid (*p*-TsOH) monohydrate (190 mg, 1.0 mmol) was stirred for 1 h. Workup and evaporation of the organic phase gave an oil, which was purified by column chromatography (silica,

cyclohexane/EtOAc, 4/1, v/v) to deliver the glycoside **7** (6.28 g, 85%) as a colourless oil. $[\alpha]_D$ −17.5° (c. 2.9 MeOH). (Found: C 52.1, H 6.7. $C_{17}H_{26}O_{10}$ requires C 52.3, H 6.7%.) δ_H (400 MHz, $CDCl_3$) 5.33 (1H, m, H3), 5.26 (1H, d, *J* 4.8, H2), 5.05 (1H, s, H1), 4.31 (2H, m, H4,5), 4.24 (1H, m, H2′), 4.15 (1H, m, H5), 4.05 (1H, dd, *J* 8.2, 6.7, H3′), 3.77 (2H, m, H1′,3′), 3.46 (1H, dd, *J* 10.2, 5.6, H1′), 2.11, 2.10, 2.06 (9H, 3 × s, OAc), 1.40, 1.36 (6H, 2 × s, CMe_2). δ_C (100 MHz, $CDCl_3$) 170.5, 169.6, 169.5 (CO), 109.4 (CMe_2), 105.4 (C1), 78.6 (C4), 74.6 (C2), 74.2 (C2′), 71.4 (C3), 68.4 (C1′), 66.5 (C3′), 64.5 (C5), 26.6, 25.3 (CMe_2), 20.7, 20.4, 20.3 (OAc). *m/z* (ESI) 429 $[M + K]^+$, 413 $[M + Na]^+$.

(S)-2′,3′-O-Isopropylidenepropyl β-D-Riboside ***8***

This material was prepared essentially according to the method of Stick and coworkers.[13] An anion exchange resin (10.0 g, Dowex 1, OH^-) was added to a solution of the glycoside **7** (5.0 g, 13 mmol) in MeOH (100 mL). The suspension was heated to 45°C and stirred for 1.5 h after which the reaction mixture was cooled and the resin filtered off. The solvent was evaporated and the residue subjected to column chromatography (silica, cyclohexane/EtOAc, 1/4, v/v) to yield the triol **8** (2.78 g, 82%) as a colourless oil. $[\alpha]_D$ −41.5° (c. 3.4 MeOH). (Found: C 48.4, H 7.6. $C_{11}H_{20}O_7 \cdot 0.5H_2O$ requires C 48.4, H 7.7%.) δ_H (500 MHz, D_2O) 5.07 (1H, s, H1), 4.46 (1H, m, H2′), 4.27 (1H, dd, *J* 7.0, 4.7, H3), 4.19 (1H, dd, *J* 8.4, 7.0, H3′), 4.12 (1H, d, *J* 4.7, H2), 4.07 (1H, m, H4), 3.82 (3H, m, H5,1′,3′), 3.68 (2H, m, H5, 1′), 1.50, 1.43 (6H, 2 × s, CMe_2). δ_C (125 MHz, D_2O) 109.8 (CMe_2), 106.5 (C1), 82.4 (C4), 74.0, 73.9 (C2,2′), 70.4 (C3), 67.5 (C1′), 64.9 (C3′), 62.4 (C5), 25.2, 23.8 (CMe_2). *m/z* (ESI) 303 $[M + K]^+$, 287 $[M + Na]^+$, 299 $[M + Cl]^-$.

(S)-2′,3′-O-Isopropylidenepropyl 5-Chloro-5-deoxy-β-D-riboside ***9***

The triol **8** (2.0 g, 7.6 mmol) was dissolved in pyridine (40 mL) and Ph_3P (6.0 g, 23 mmol) together with CCl_4 (11.6 g, 76 mmol) were added. The colourless solution turned brown; it was stirred at 45°C for 1.5 h by which time TLC analysis (silica, petroleum/acetone, 7/3, v/v) indicated the reaction to be complete. The solution was then diluted with MeOH, stirred for 5 min after which the solvent was evaporated to give a semicrystalline mass. The residue was suspended under vigorous stirring in slightly basic water (pH 8.0, NH_4OH), whereupon the product dissolved in water. The suspension was filtered and the filtrate extracted several times with CH_2Cl_2. The organic layers were combined and concentrated to give an oil, which was subjected to column chromatography (silica, cyclohexane/EtOAc, 1/4, v/v) to deliver the chloride **9** (1.46 g, 68%) as a pale yellow oil. $[\alpha]_D$ −40.0° (c. 2.5 MeOH). (Found: C 47.2, H 6.9. $C_{11}H_{19}O_6Cl$ requires C 46.8, H 6.7%.) δ_H (500 MHz, $CDCl_3$) 4.99 (1H, s, H1), 4.33 (1H, m, H3), 4.27 (1H, m, H2′), 4.14 (1H, m, H4), 4.09 (1H, d, *J* 4.8, H2), 4.05 (1H, dd, *J* 8.4, 6.6, H3′), 3.76 (2H, m, H1′,3′), 3.69 (2H, m, H5), 3.47 (1H, dd, *J* 10.5, 4.7, H1′), 1.42, 1.36 (6H, 2 × s, CMe_2). δ_C (125 MHz, $CDCl_3$) 109.6 (CMe_2), 107.2 (C1), 82.7 (C4), 75.1 (C2), 74.2 (C2′), 73.1 (C3), 68.2 (C1′), 66.2 (C3′), 45.5 (C5), 26.5, 25.3 (CMe_2). *m/z* (ESI) 305 $[M + Na]^+$, 317 $[M + Cl]^-$.

(S)-2′,3′-O-Isopropylidenepropyl 5-Deoxy-5-dimethylarsinoyl-β-D-riboside ***11***

Elemental lithium (120 mg, 17 mmol) was added to the chloride **9** (1.2 g, 4.3 mmol) and dimethyliodoarsine (2.0 g, 8.6 mmol) in dry tetrahydrofuran (THF, 15 mL) under an argon atmosphere. The suspension was stirred overnight whereupon all the lithium was dissolved. Sodium (396 mg, 17 mmol), cut into small pieces, was then added and the reaction mixture was stirred for 3 h. MeOH was added to the reaction mixture, which was then diluted with EtOAc and washed with water. The organic layer, containing the trialkylarsine **10**, was filtered through a plug of silica and the filtrate evaporated to dryness. The residue was taken up in THF (30 mL), cooled to 0°C, and treated with 30% H_2O_2 (3 mL). After stirring for 15 min, the solvent was removed and the residue subjected to column chromatography (silica, EtOAc/MeOH, 2/1, v/v) to give the arsine oxide **11** (1.03 g, 66%) as a brown oil. $[\alpha]_D$ −2.5° (c. 2.3 MeOH). (Found: C 40.5, H 6.7. $C_{13}H_{25}O_7As \cdot H_2O$ requires C 40.4, H 7.0%.) δ_H (500 MHz, $CDCl_3$) 4.93 (1H, s, H1), 4.34 (1H, m, H4), 4.22 (1H, m, H2′), 4.05 (3H, m, H2,3,3′), 3.70 (2H, m, H1′,3′), 3.42 (1H, dd, *J* 10.0, 5.6, H1′), 2.59 (1H, dd, *J* 13.2, 5.2, H5), 2.27 (1H, dd, *J* 13.2, 8.8, H5), 1.77, 1.75 (6H, 2 × s, $AsMe_2$), 1.40, 1.35 (6H, 2 × s, CMe_2). δ_C (125 MHz, $CDCl_3$) 109.4 (CMe_2), 108.0 (C1), 77.1 (C4), 76.2 (C3), 75.0 (C2), 74.3 (C2′), 68.7 (C1′), 66.6 (C3′), 37.1 (C5), 26.7, 25.2 (CMe_2), 16.1, 15.3 ($AsMe_2$). *m/z* (ESI) 407 $[M + K]^+$, 391 $[M + Na]^+$, 369 $[M + H]^+$.

(R)-2′,3′-Dihydroxypropyl 5-Deoxy-5-dimethylarsinoyl-β-D-riboside ***1***

This material was prepared essentially according to the method of Stick and coworkers.[13] The diol **11** (441 mg, 1.2 mmol) was dissolved in a mixture of CF_3COOH/water (3 mL, 9/1, v/v) and stirred for 10 min. The solution was concentrated and co-evaporated several times with NH_4OH (1 M). The residue thus obtained was dissolved in water and passed through a column of anion exchange resin (Dowex 1, OH^-) to give the tetrol **1** (335 mg, 85%) as a brown oil. δ_H (400 MHz, D_2O) 5.06 (1H, s, H1), 4.29 (2H, m, H3,4), 4.17 (1H, d, *J* 4.0, H2), 3.94 (1H, m, H2′), 3.79 (1H, dd, *J* 10.6, 6.2, H1′), 3.64 (3H, m, H1′,3′), 2.69 (1H, dd, *J* 13.8, 3.0, H5), 2.54 (1H, dd, *J* 13.8, 10.3, H5), 1.92, 1.89 (6H, 2 × s, $AsMe_2$). δ_C (90 MHz, D_2O) 109.4 (C1), 78.9 (C4), 77.7 (C3), 76.2 (C2), 72.0 (C2′), 70.7 (C1′), 64.2 (C3′), 37.8 (C5), 16.3, 15.9 ($AsMe_2$). *m/z* (ESI) 351 $[M + Na]^+$, 329 $[M + H]^+$.

(R)-2′,3′-Dihydroxypropyl 5-Deoxy-5-dimethylarsinothioyl-β-D-riboside ***12***

This material was prepared by an alternative procedure as described in the literature.[23] The tetrol **1** (50 mg, 0.15 mmol) was dissolved in water and H_2S was passed through the solution for 1 min. After stirring for 15 min, the solvent was evaporated and the residue passed through Sephadex G-15/water to give the arsine sulfide **12** (48 mg, 93%) as a brown oil. δ_H (500 MHz, D_2O) 5.04 (1H, s, H1), 4.39 (1H, m, H4), 4.31 (1H, dd, *J* 6.8, 4.6, H3), 4.17 (1H, d, *J* 4.6, H2), 3.93 (1H, m, H2′), 3.79 (1H, dd, *J* 10.6, 6.1, H1′), 3.67 (1H, dd, *J* 11.6, 4.9, H3′), 3.62 (1H, dd, *J* 10.6, 4.1, H1′), 3.61 (1H, dd, *J* 11.6, 6.5, H3′), 2.59 (2H, m, H5), 1.98, 1.96 (6H, 2 × s, $AsMe_2$). δ_C (125 MHz, D_2O) 107.1 (C1), 77.6 (C4), 75.3 (C3), 74.0 (C2), 70.0 (C2′), 68.7 (C1′), 62.2 (C3′), 37.4 (C5), 17.6, 17.5 ($AsMe_2$). *m/z* (ESI) 367 $[M + Na]^+$, 345 $[M + H]^+$.

(S)-2′,3′-O-Isopropylidenepropyl 5-Deoxy-5-dimethylarsinothioyl-β-D-riboside ***13***

Hydrogen sulfide was passed through a solution of the arsine oxide **11** (40 mg, 0.11 mmol) in pyridine for 30 s. After stirring

the mixture for 10 min, the solvent was evaporated and the residue subjected to column chromatography (silica, EtOAc) to give the arsine sulfide **13** (35 mg, 84%) as a brown oil. $[\alpha]_D$ +5.7° (c. 1.6 MeOH). (Found: C 40.3, H 6.6. $C_{13}H_{25}O_6AsS$ requires C 40.6, H 6.5%.) δ_H (400 MHz, $CDCl_3$) 4.97 (1H, s, H1), 4.29 (2H, m, H3,4), 4.24 (1H, m, H2′), 4.11 (1H, d, *J* 3.8, H2), 4.05 (1H, dd, *J* 8.4, 6.6, H3′), 3.70 (2H, m, H1′,3′), 3.45 (1H, dd, *J* 10.8, 5.3, H1′), 2.44 (2H, m, H5), 1.88, 1.86 (6H, 2 × s, $AsMe_2$), 1.41, 1.36 (6H, 2 × s, CMe_2). δ_C (100 MHz, $CDCl_3$) 109.5 (CMe_2), 107.5 (C1), 78.3 (C4), 75.4, 75.1 (C2,3), 74.3 (C2′), 68.7 (C1′), 66.5 (C3′), 38.9 (C5), 26.7, 25.2 (CMe_2), 19.4, 18.6 ($AsMe_2$). *m/z* (ESI) 423 $[M + K]^+$, 407 $[M + Na]^+$.

(S)-2′,3′-O-Isopropylidenepropyl 5-Deoxy-5-dimethylarsinothioyl-2,3-di-O-acetyl-β-D-riboside **14**

The arsine oxide **11** (1.0 g, 2.7 mmol) was dissolved in pyridine (10 mL) and H_2S was passed through the solution for 1 min. After stirring for 15 min, TLC analysis (silica, EtOAc/MeOH, 4/1, v/v) indicated the conversion to the sulfur analogue **13** to be complete. Acetic anhydride (5 mL) was added and stirring was continued for 2 h. The reaction mixture was poured into aqueous $NaHCO_3$ solution under vigorous stirring. Extraction with CH_2Cl_2, workup, and evaporation of the organic layer gave a syrup, which was subjected to column chromatography (silica, EtOAc) to give the fully protected arsine sulfide **14** (970 mg, 77%) initially as an oil, which slowly crystallized. Recrystallization was performed from a mixture of hexane/ether/MeOH to give white needles. Mp (hexane/ether/MeOH) 96°C (dec.). $[\alpha]_D$ −7.1° (c. 1.9 MeOH). (Found: C 43.5, H 6.2. $C_{17}H_{29}O_8AsS$ requires C 43.6, H 6.2%.) δ_H (500 MHz, $CDCl_3$) 5.19 (2H, m, H2,3), 4.97 (1H, s, H1), 4.59 (1H, m, H4), 4.17 (1H, m, H2′), 3.99 (1H, dd, *J* 8.2, 6.6, H3′), 3.64 (2H, m, H1′,3′), 3.42 (1H, dd, *J* 10.0, 5.6, H1′), 2.30 (2H, m, H5), 2.05, 2.00 (6H, 2 × s, OAc), 1.83, 1.76 (6H, 2 × s, $AsMe_2$), 1.33, 1.29 (6H, 2 × s, CMe_2). δ_C (125 MHz, $CDCl_3$) 169.9, 169.7 (CO), 109.6 (CMe_2), 105.5 (C1), 76.1 (C4), 74.7, 74.3 (C2,3), 74.1 (C2′), 69.0 (C1′), 66.4 (C3′), 39.0 (C5), 26.7, 25.3 (CMe_2), 20.5, 20.4 (OAc), 19.5, 19.4 ($AsMe_2$). *m/z* (ESI) 507 $[M + K]^+$, 491 $[M + Na]^+$, 469 $[M + H]^+$.

(R)-2′,3′-Dihydroxypropyl 5-Deoxy-5-dimethylarsinothioyl-2,3-di-O-acetyl-β-D-riboside **15**

The fully protected arsine sulfide **14** (900 mg, 1.9 mmol) was dissolved in MeCN (25 mL) and a mixture of CF_3COOH/H_2O (8/2, v/v, 1 mL) was added. The solution was stirred for 15 min, after which it was neutralized (NH_4OH). The solvent was removed under reduced pressure and the obtained residue subjected to column chromatography (silica, EtOAc/MeOH, 4/1, v/v) to give the diol **15** (676 mg, 82%) as a yellow oil. $[\alpha]_D$ −10.2° (c. 1.8 MeOH). (Found: C 38.9, H 5.6. $C_{14}H_{25}O_8AsS$ requires C 39.3, H 5.8%.) δ_H (500 MHz, $CDCl_3$) 5.26 (2H, m, H2,3), 5.02 (1H, s, H1), 4.62 (1H, m, H4), 3.89 (1H, m, H2′), 3.74 (1H, dd, *J* 10.0, 6.4, H1′), 3.68 (1H, dd, *J* 11.2, 3.6, H3′), 3.57 (1H, dd, *J* 11.2, 6.4, H3′), 3.53 (1H, dd, *J* 10.0, 4.0, H1′), 2.50 (1H, dd, *J* 13.2, 11.2, H5), 2.36 (1H, dd, *J* 13.2, 2.0, H5), 2.12, 2.07 (6H, 2 × s, OAc), 1.89, 1.85 (6H, 2 × s, $AsMe_2$). δ_C (125 MHz, $CDCl_3$) 170.3, 170.1 (CO), 105.4 (C1), 76.1 (C4), 75.0, 74.4 (C2,3), 70.4 (C2′), 69.3 (C1′), 63.1 (C3′), 38.8 (C5), 20.5 (OAc), 19.3 ($AsMe_2$). *m/z* (ESI) 467 $[M + K]^+$, 451 $[M + Na]^+$, 429 $[M + H]^+$.

(S)-2′-Hydroxy-3′-O-tosylpropyl 5-Deoxy-5-dimethylarsinothioyl-2,3-di-O-acetyl-β-D-riboside **16**

The diol **15** (200 mg, 0.47 mmol) in CH_2Cl_2 (4 mL) together with *p*-tosyl chloride (96 mg, 0.5 mmol), Et_3N (51 mg, 0.5 mmol), and Bu_2SnO (5 mg, 0.02 mmol) was stirred at 35°C for 1.5 h. The reaction mixture was then diluted (CH_2Cl_2) and filtered. After usual workup of the filtrate, the organic layer was evaporated and the residue was subjected to column chromatography (silica, EtOAc) to give the tosylate **16** (200 mg, 72%) as a yellow oil. $[\alpha]_D$ −1.8° (c. 1.4 MeOH). (Found: C 42.5, H 5.5. $C_{21}H_{31}O_{10}AsS_2 \cdot 0.5H_2O$ requires C 42.6, H 5.4%.) δ_H (500 MHz, $CDCl_3$) 7.78, 7.38 (4H, 2d, *J* 8.2, Ar), 5.25 (2H, m, H2,3), 5.00 (1H, s, H1), 4.72 (1H, m, H4), 4.10 (1H, dd, *J* 9.8, 6.4, H3′), 3.98 (1H, m, H2′), 3.91 (1H, dd, *J* 9.8, 5.4, H3′), 3.84 (1H, dd, *J* 10.0, 4.4, H1′), 3.52 (1H, dd, *J* 10.0, 3.8, H1′), 2.50 (1H, dd, *J* 13.2, 11.2, H5), 2.46 (3H, s, ArMe), 2.30 (1H, dd, *J* 13.2, 2.0, H5), 2.11, 2.07 (6H, 2 × s, OAc), 1.92, 1.84 (6H, 2 × s, $AsMe_2$). δ_C (125 MHz, $CDCl_3$) 169.9, 169.7 (CO), 145.3–127.9 (Ar), 105.3 (C1), 76.1 (C4), 74.7, 74.3 (C2,3), 69.2 (C3′), 67.6 (C1′,2′), 38.3 (C5), 21.6 (ArMe), 20.5 (OAc), 19.7, 19.2 ($AsMe_2$). *m/z* (ESI) 605 $[M + Na]^+$, 583 $[M + H]^+$, 567 $[M - Me]^+$.

(S)-2′-Hydroxy-3′-sulfonylpropyl 5-Deoxy-5-dimethylarsinoyl-β-D-riboside, Ammonium Salt **2**

(i) The tosylate **16** (240 mg, 0.41 mmol) was dissolved in a mixture of MeOH/water (1/1, v/v, 2 mL) and heated to 40°C. Na_2SO_3 (104 mg, 0.83 mmol) in water (1 mL) was added and the solution was stirred for 6 h at 40°C. The solution was then concentrated and the residue subjected to anion exchange chromatography (DEAE Sephadex/0.05 M Tris buffer, pH 8.0, 16 × 300 mm^2, elution volume 360 mL) followed by size exclusion chromatography (Sephadex G-15/water, 26 × 600 mm^2, elution volume 160 mL) to yield the sulfonic acid as the Tris salt. This procedure was repeated twice. Conversion into the ammonium salt was performed by passage through cation exchange resin (Dowex 50, NH_4^+). Subsequent size exclusion chromatography (Sephadex G-15/water) delivered (*S*)-2′-hydroxy-3′-sulfonylpropyl 5-deoxy-5-dimethylarsinothioyl-β-D-riboside, ammonium salt **17** (120 mg, 69%). δ_H (500 MHz, D_2O) 5.07 (1H, s, H1), 4.41 (1H, m, H4), 4.33 (2H, m, H3,2′), 4.20 (1H, d, *J* 4.4, H2), 3.86 (1H, dd, *J* 10.6, 5.6, H1′), 3.69 (1H, dd, *J* 10.6, 3.6, H1′), 3.21 (1H, dd, *J* 14.4, 5.0, H3′), 3.10 (1H, dd, *J* 14.4, 6.9, H3′), 2.64 (1H, dd, *J* 13.5, 10.2, H5), 2.58 (1H, dd, *J* 13.5, 3.2, H5), 2.00, 1.97 (6H, 2 × s, $AsMe_2$). δ_C (125 MHz, D_2O) 107.2 (C1), 77.6 (C4), 75.4 (C3), 74.1 (C2), 70.5 (C1′), 66.2 (C2′), 53.6 (C3′), 37.4 (C5), 17.7, 17.5 ($AsMe_2$). *m/z* (ESI) 407 $[M - NH_4]^-$.

(ii) Compound **17** (65 mg, 0.15 mmol) was dissolved in water (5 mL) and treated with 30% H_2O_2 (0.1 mL) at 0°C. The solution was stirred for 10 min after which the solvent was evaporated and the residue subjected to anion chromatography (DEAE Sephadex/0.05 M Tris buffer, pH 8.0, 16 × 300 mm^2, elution volume 250 mL) followed by desalting on Sephadex G-15/water (26 × 600 mm^2, elution volume 160 mL). The sulfonic acid was obtained as the Tris salt and passage through a column of cation exchange resin (Dowex 50, NH_4^+) delivered the sulfonic acid **2** as the ammonium salt which was further purified by size exclusion chromatography (Sephadex G-15/water) to deliver the sulfonic acid, ammonium salt **2** (53 mg, 87%) as a colourless oil. $[\alpha]_D$ +2.5° (c. 1.4 MeOH). (Found: C 28.5, H 6.2, N 3.0. $C_{10}H_{24}O_9AsNS \cdot 0.5H_2O$ requires C 28.7, H 6.0, N 3.3%.) δ_H

(360 MHz, D_2O) 5.06 (1H, s, H1), 4.29 (3H, m, H3,4,2′), 4.17 (1H, d, *J* 3.0, H2), 3.83 (1H, dd, *J* 10.6, 5.6, H1′), 3.67 (1H, dd, *J* 10.6, 3.4, H1′), 3.18 (1H, dd, *J* 14.4, 5.4, H3′), 3.06 (1H, dd, *J* 14.4, 6.7, H3′), 2.76 (1H, dd, *J* 13.8, 2.7, H5), 2.63 (1H, dd, *J* 13.8, 10.1, H5), 1.99, 1.96 (6H, 2 × s, $AsMe_2$). δ_C (90 MHz, D_2O) 108.2 (C1), 77.3 (C4), 76.4 (C3), 74.9 (C2), 71.3 (C1′), 67.0 (C2′), 54.4 (C3′), 36.7 (C5), 15.1, 14.8 ($AsMe_2$). *m/z* (ESI) 391 $[M - NH_4]^-$.

(S)-2′-Hydroxy-3′-sulfooxypropyl 5-Deoxy-5-dimethylarsinothioyl-2,3-di-O-acetyl-β-D-riboside ***18***

A solution of the diol **15** (200 mg, 0.47 mmol) in pyridine (4 mL) and $Et_3N{:}SO_3$ (136 mg, 0.75 mmol) was stirred for 24 h at room temperature. The pyridine was then concentrated and the residue subjected to column chromatography (silica, MeOH/EtOAc, 1/2, v/v) to give the crude sulfuric acid ester. The compound was dissolved in water and passed through a column of cation exchange resin (Dowex 50, NH_4^+) to give the sulfuric acid ester as the ammonium salt. Passage through Sephadex LH-20/MeOH delivered the sulfuric acid ester, ammonium salt **18** (142 mg, 58%) as a yellow oil. $[\alpha]_D$ −11.0° (c. 1.4 MeOH). (Found: C 30.9, H 5.3, N 2.6. $C_{14}H_{28}O_{11}AsNS_2{\cdot}H_2O$ requires C 30.9, H 5.5, N 2.6%.) δ_H (500 MHz, D_2O) 5.50 (2H, m, H2,3), 5.32 (1H, s, H1), 4.80 (2H, m, H4,2′), 4.37 (1H, dd, *J* 10.7, 5.5, H3′), 4.33 (1H, dd, *J* 10.7, 4.6, H3′), 4.08 (1H, dd, *J* 11.0, 5.5, H1′), 3.95 (1H, dd, *J* 11.0, 3.7, H1′), 2.87 (1H, dd, *J* 13.4, 11.0, H5), 2.60 (1H, dd, *J* 13.4, 2.7, H5), 2.28, 2.21 (6H, 2 × s, OAc), 2.09, 2.00 (6H, 2 × s, $AsMe_2$). δ_C (125 MHz, D_2O) 172.8, 172.7 (CO), 104.9 (C1), 76.3 (C4), 75.6 (C3), 75.0 (C2′), 74.7 (C2), 66.1, 66.0 (C1′,3′), 36.7 (C5), 20.5 (OAc), 18.2, 17.7 ($AsMe_2$). *m/z* (ESI) 507 $[M - NH_4]^-$.

(S)-2′-Hydroxy-3′-sulfooxypropyl 5-Deoxy-5-dimethylarsinoyl-β-D-riboside, Ammonium Salt ***3***

(i) The partially protected arsine sulfide **18** (165 mg, 0.31 mmol) was dissolved in MeOH (5 mL) and NaOMe in MeOH (1 M, 0.7 mL) was added. After complete deacetylation (10 min) the solution was adjusted to pH 8.0 (CH_3COOH). The solvent was evaporated and the residue subjected to anion exchange chromatography (DEAE Sephadex/0.05 M Tris buffer, pH 8.0, 16 × 300 mm^2, elution volume 500 mL) followed by size exclusion chromatography (Sephadex G-15/water, 26 × 600 mm^2, elution volume 190 mL). This procedure was repeated twice. The obtained Tris salt was passed through a column of cation exchange resin (Dowex 50, NH_4^+) to give the sulfuric acid ester as the ammonium salt. Subsequent size exclusion chromatography (Sephadex G-15/water) delivered (*S*)-2′-hydroxy-3′-sulfooxypropyl 5-deoxy-5-dimethylarsinothioyl-β-D-riboside, ammonium salt **19** (110 mg, 80%) as a colourless oil. δ_H (500 MHz, D_2O) 5.06 (1H, s, H1), 4.43 (1H, m, H4), 4.35 (1H, dd, *J* 7.0, 4.5, H3), 4.20 (1H, d, *J* 4.5, H2), 4.15 (3H, m, H2′,3′), 3.88 (1H, dd, *J* 10.6, 4.4, H1′), 3.66 (1H, dd, *J* 10.6, 3.2, H1′), 2.64 (1H, dd, *J* 13.5, 10.3, H5), 2.58 (1H, dd, *J* 13.5, 3.2, H5), 2.02, 1.99 (6H, 2 × s, $AsMe_2$). δ_C (125 MHz, D_2O) 107.1 (C1), 77.6 (C4), 75.4 (C3), 74.1 (C2), 68.2, 67.8, 67.6 (C1′,2′,3′), 37.2 (C5), 17.8, 17.5 ($AsMe_2$). *m/z* (ESI) 423 $[M - NH_4]^-$.

(ii) Compound **19** (65 mg, 0.15 mmol) was dissolved in water (5 mL) and stirred with 30% H_2O_2 (0.1 mL) at 0°C for 10 min. The solvent was evaporated and the residue subjected to anion exchange chromatography (DEAE Sephadex/0.05 M Tris buffer, pH 8.0, 16 × 300 mm^2, elution volume 300 mL) followed by size exclusion chromatography (Sephadex G-15/water, 26 × 600 mm^2, elution volume 190 mL) to give the sulfuric acid ester as the Tris salt. Passage through a column of cation exchange resin (Dowex 50, NH_4^+) followed by size exclusion chromatography delivered the sulfuric acid ester, ammonium salt **3** (55 mg, 85%) as a colourless oil, which slowly solidified. $[\alpha]_D$ +1.0° (c. 1.4 MeOH). (Found: C 27.9, H 5.8, N 3.1. $C_{10}H_{24}O_{10}AsNS$ requires C 28.2, H 5.6, N 3.3%.) δ_H (360 MHz, D_2O) 5.05 (1H, s, H1), 4.29 (2H, m, H3,4), 4.17 (1H, d, *J* 3.4, H2), 4.09 (3H, m, H2′,3′), 3.85 (1H, dd, *J* 10.6, 4.4, H1′), 3.64 (1H, dd, *J* 10.6, 3.2, H1′), 2.75 (1H, dd, *J* 13.9, 2.9, H5), 2.60 (1H, dd, *J* 13.9, 10.1, H5), 1.98, 1.94 (6H, 2 × s, $AsMe_2$). δ_C (90 MHz, D_2O) 108.3 (C1), 77.5, 76.7, 75.2 (C2,3,4), 69.2, 68.9, 68.6 (C1′,2′,3′), 36.9 (C5), 15.3, 15.1 ($AsMe_2$). *m/z* (ESI) 407 $[M - NH_4]^-$.

(R,S)-2,3-O-Isopropylidenepropyl-(R)-5,6-di-O-benzylpropyl-2-chlorophenyl Phosphate ***20***

The alcohol (*S*)-2,3-di-*O*-benzylglycerol (110 mg, 0.4 mmol) in CH_2Cl_2 (0.5 mL) was slowly added to an ice-cold solution that contained 2-chlorophenyl phosphorodichloridate (100 mg, 0.41 mmol) and pyridine (160 mg, 2.0 mmol) in CH_2Cl_2 (1.5 mL) under an argon atmosphere. After complete addition of the alcohol, the reaction mixture was stirred for 1 h at 0°C, and then allowed to warm to room temperature and stirred for an additional hour. TLC analysis (silica, cyclohexane/EtOAc, 2/1, v/v) indicated the formation of a less polar product. The alcohol (*R*,*S*)-2,3-*O*-isopropylideneglycerol (70 mg, 0.53 mmol) in CH_2Cl_2 (0.5 mL) was added to the solution that contained the presumed diester and the reaction mixture was stirred for 2 h. After workup, the organic layer was evaporated and the residue subjected to column chromatography (silica, cyclohexane/EtOAc, 2/1, v/v) to give **20** (128 mg, 55%) as a colourless oil. δ_H (360 MHz, $CDCl_3$) 7.32, 7.14 (14H, 2 × m, Ar), 4.63, 4.51 (4H, 2 × s, $2CH_2Ar$), 4.41–3.58 (10H, 6 × m, H1–6), 1.37, 1.32 (6H, 2 × s, CMe_2). δ_C (90 MHz, $CDCl_3$) 146.6–121.5 (Ar), 109.9 (CMe_2), 76.4, 73.8, 73.5, 72.3, 68.9, 68.3, 66.1 (C1–6, CH_2Ar), 26.7, 25.3 (CMe_2). δ_P (145.8 MHz, $CDCl_3$) −11.6. *m/z* (ESI) 599 $[M + Na]^+$, 577 $[M + H]^+$.

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