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Synthetic routes for naturally-occurring arsenic-containing ribosides

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Abstract—The synthesis of (*R*)-2′,3′-dihydroxypropyl 5-deoxy-5-dimethylarsinoyl-β-D-riboside, (*S*)-2′-hydroxy-3′-sulfonylpropyl 5-deoxy-5-dimethylarsinoyl-β-D-riboside and (*S*)-2′-hydroxy-3′-sulfooxypropyl 5-deoxy-5-dimethylarsinoyl-β-D-riboside, common naturally-occurring arsenicals in algae and molluscs, is reported.

The observation that marine algae can contain exceedingly high concentrations of arsenic was first reported[1] at a pharmaceutical conference by Jones in the 1920s. Because algal products are widely used in the pharmaceutical industry, Jones attempted to allay possible fears in regard to their arsenic content, and indeed, he postulated that many of the beneficial effects of these products might be ascribed to their, at that time, unknown arsenic compounds. The structures of these compounds were subsequently found[2] to be a novel group of arsenic-containing ribosides, termed oxo-arsenosugars, and on-going work has shown[3] that these arsenicals are in all marine algae and most marine animals, particularly those feeding directly on algae such as molluscs. Although 17 oxo-arsenosugars have been identified so far, most of this 'arsenosugar-arsenic' is associated with just four compounds (Fig. 1).

The engaging structures of oxo-arsenosugars, together with their pivotal role in the cycling of arsenic in the sea and human health issues related to their presence in seafoods, have generated moderate interest in their biosynthesis, environmental fate and toxicology. Recently, this interest has increased because of two factors. First, the discovery that thio analogues[4–7] of oxo-arsenosugars are also natural constituents of marine organisms and the suggestion that these thio-arsenosugars may be integral to arsenic transformations; and second, the realisation that arsenosugars are extensively metabolised in sheep[8] and humans[9,10] to a multitude of arsenic metabolites including several thio-arsenicals of currently unknown toxicity. Investigations into the biosynthesis, metabolism and toxicity of arsenosugars are dependent on the availability of reasonable quantities of pure compound. To date, only compound **1** and its sulfur

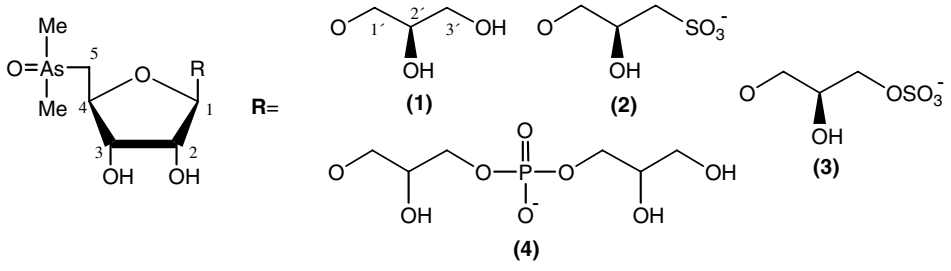

Figure 1. Major arsenosugars present in marine biota.

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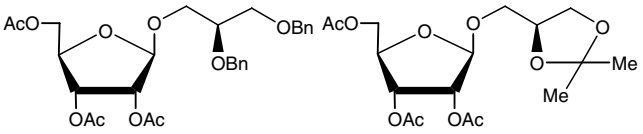
analogue of the four arsenosugars commonly found in marine organisms have been synthesised,[11–14] whereas the two predominant arsenosugars, compounds **2** and **3**, have so far proved difficult to synthesise and studies, for example, by McSheehy et al.,[15] with these compounds have, by necessity, been performed with small analytical quantities of natural product isolated from algal sources in the original studies over 20 years ago.[2,16]

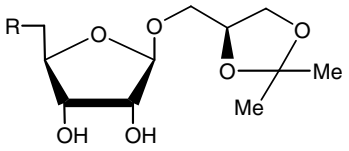
We report here the synthesis of the two major oxo-arsenosugars found in seafood, namely (*S*)-2′-hydroxy-3′-sulfonylpropyl 5-deoxy-5-dimethylarsinoyl-β-D-riboside (compound **2**) and (*S*)-2′-hydroxy-3′-sulfooxypropyl 5-deoxy-5-dimethylarsinoyl-β-D-riboside (compound **3**) as the ammonium salts, together with their thio-analogues, **14** and **16**. The key to the synthetic procedure was the novel use of sulfur which served as a pseudo-protecting group for the arsenic atom, while the required functional groups were introduced to the aglycone portion of the molecules. The synthesis conveniently provides these four compounds together with the previously synthesised compound **1**, thereby allowing comprehensive studies of their environmental and toxicological significance.

The synthesis involves direct introduction of (*S*)-1,2-di-*O*-benzylglycerol to a fully protected acetyl β-D-ribose, delivery of the arsenic group at C5, 'protection' of arsenic by forming an arsine sulfide, derivatisation steps at the aglycone, and re-generation of the desired oxo-arsenic moiety. Thus the commercially available 1,2,3,5-tetra-*O*-acetyl-β-D-ribose was treated with (*S*)-1, 2-di-*O*-benzylglycerol and BF_3OEt_2 in CH_3CN to give glycoside **5** (85%). We recommend this glycosidation as a simpler alternative to that previously reported.[11–14] Hydrogenolysis (Pd/C 5%, MeOH) of **5** and treatment of the formed diol with 2, 2-dimethoxypropane/*p*-toluenesulfonic acid in CH_2Cl_2[11] gave glycoside **6** (68% based on **5**).



(5) **(6)**

Removal of the ester groups by stirring compound **6** in MeOH with OH^- resin gave triol **7** (82%), which was converted into chloride **8** (68%) by the use of Ph_3P and CCl_4 in pyridine.[17] Although the arsenic group has been successfully introduced by nucleophilic substitution at C5 with sodium dimethyliodoarsine (Me_2As-Na),[11,18,19] we found that the combined use of lithium and sodium to form the nucleophile gave more consistent and higher yields. The so-obtained trialkylarsine **9** was not isolated but directly converted into arsine oxide **10** (H_2O_2, NMR: Tables 1 and 2) in 66% yield. Treatment of **10** with aqueous CF_3COOH gave compound **1** in 80% yield (NMR: Tables 1 and 2).



(7) R= OH

(8) R= Cl

(9) R= Me_2As

(10) R= $Me_2As(O)$

Table 1. ^1H NMR [400 MHz (compounds **10**, **12**, **1**) and 360 MHz (**2**, **3**)] spectral data of selected compounds

^1H NMR	H-1 (δ)	H-2 (δ)	H-3 (δ)	H-4 (δ)	H-5 (δ)	H-1′ (δ)	H-2′ (δ)	H-3′ (δ)	$AsMe_2$ (δ)	CMe_2 (δ)	COMe (δ)
10 ($CDCl_3$)	4.93 s	4.05 m	4.05 m	4.34 m	2.59 dd *J* 13.2, 5.2 2.27 dd *J* 13.2, 8.8	3.70 m 3.42 dd *J* 10.0, 5.6	4.22 m	4.05 m 3.70 m	1.77, 1.75 2s	1.40, 1.35 2s	
12 ($CDCl_3$)	5.02 s	5.26 m	5.26 m	4.62 m	2.46 dd *J* 13.2, 11.2 2.36 dd *J* 13.2, 2.0	3.74 dd *J* 10.0, 6.4 3.53 dd *J* 10.0, 4.0.	3.89 m	3.68 dd *J* 11.2, 3.6 3.57 dd *J* 11.2, 6.4	1.89, 1.85 2s		2.12, 2.07 2s
1 (D_2O)	5.06 s	4.17 d *J* 4.0	4.29 m	4.29 m	2.69 dd *J* 13.8, 3.0 2.54 dd *J* 13.8, 10.3	3.79 dd *J* 10.6, 6.2 3.64 m	3.94 m	3.64 m	1.92, 1.89 2s		
2 (D_2O)	5.06 s	4.17 d *J* 3.0	4.29 m	4.29 m	2.76 dd *J* 13.8, 2.7 2.63 dd *J* 13.8, 10.1	3.83 dd *J* 10.6, 5.6 3.67 dd *J* 10.6, 3.4	4.29 m	3.18 dd *J* 14.4, 5.4 3.06 dd *J* 14.4, 6.7	1.99, 1.96 2s		
3 (D_2O)	5.05 s	4.17 d *J* 3.4	4.29 m	4.29 m	2.75 dd *J* 13.9, 2.9 2.60 dd *J* 13.9, 10.1	3.85 dd *J* 10.6, 4.4 3.64 dd *J* 10.6, 3.2	4.09 m	4.09 m	1.98, 1.94 2s		

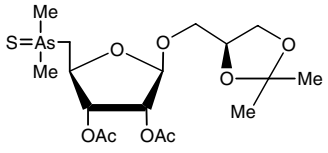
Chemical shifts (δ) are given in ppm relative to internal standard (TMS, 0 ppm) or partially protonated solvent (HDO, 4.83 ppm).

Table 2. ^{13}C NMR [100 MHz (compounds **10**, **12**, **1**) and 90 MHz (**2**, **3**)] spectral data of selected compounds

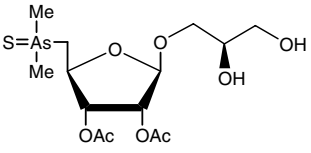
^{13}C NMR	C-1 (δ)	C-2 (δ)	C-3 (δ)	C-4 (δ)	C-5 (δ)	C-1′ (δ)	C-2′ (δ)	C-3′ (δ)	$AsMe_2$ (δ)	CMe_2 (δ)	CMe_2	CO (δ)	COMe (δ)
10 ($CDCl_3$)	108.0	75.0	76.2	77.1	37.1	68.7	74.3	66.6	16.1, 15.3	109.4	26.7, 25.2		
12 ($CDCl_3$)	105.4	75.0, 74.4		76.1	38.8	69.3	70.4	63.1	19.3			170.3, 170.1	20.5
1 (D_2O)	109.4	76.2	77.7	78.9	37.8	70.7	72.0	64.2	16.3, 15.9				
2 (D_2O)	108.2	74.9	76.4	77.3	36.7	71.3	67.0	54.4	15.1, 14.8				
3 (D_2O)	108.3	77.5, 76.7, 75.2			36.9	69.2, 68.9, 68.6			15.3, 15.1				

Chemical shifts (δ) are given in ppm relative to $CDCl_3$ (77 ppm). For spectra in D_2O, C1 carbon was set to reported chemical shift.[16]

We had intended to protect the residual free hydroxyl groups of the riboside moiety of **10** and then remove the isopropylidene group on the aglycone to give a diol suitable for the introduction of the desired functional groups. However, problems were immediately encountered when acetylation was attempted on arsenical **10**, stemming from the unexpected reactivity and polar nature of the arsinoyl moiety and the resulting difficulty in finding reaction conditions compatible with reactants and substrate. The arsine derivative **9**, although suitably less polar, proved very difficult to handle and was not further considered. In our quest for a more pliable intermediate, we converted oxide **10** (pyridine, H_2S) to sulfide which readily acetylated (Ac_2O) to give the fully protected arsine sulfide **11** (77% based on **10**). Cleavage of the acetal group (CF_3COOH/H_2O) delivered diol **12** (82%, NMR: Tables 1 and 2), which in stark contrast to its oxide analogue, proved very amenable to the formation of the desired sulfonate and sulfuric acid ester derivatives.

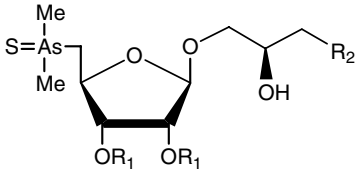


(11)



(12)

Reaction of **12** with Bu_2SnO, *p*-TsCl, and Et_3N in CH_2Cl_2[20] gave monotosylate **13** (72%), which was simultaneously deprotected and sulfonated by treatment with Na_2SO_3 in water/MeOH 2+1 v/v to yield sulfonate **14**.[21] Several attempted monotosylation reactions performed on the arsine oxide analogue of **12** failed, further indicating the currently unexplained, strongly negative influence of the dimethylarsinoyl group. Oxidation of crude **14** (H_2O_2) and purification by ion exchange chromatography (Sephadex DEAE/0.05 M Tris buffer, pH = 8.0), size exclusion chromatography (Sephadex G-15/water; Sephadex LH-20/MeOH) and passage through cation exchange resin in the ammonium form gave compound **2** as an oil (60%, based on monotosylate **13**).



(13) R_1= Ac; R_2= OTs

(14) R_1= H; R_2= SO_3^-

(15) R_1= Ac; R_2= OSO_3^-

(16) R_1= H; R_2= OSO_3^-

Reaction of **12** with $Et_3N{:}SO_3$[22] in pyridine (overnight) led to the protected sulfuric acid ester **15** (58%), which after deacylation (NaOMe) gave the crude arsine sulfide, compound **16**. Oxidation (H_2O_2) and purification as described for compound **2** gave the desired compound **3** as an oil (62%, based on compound **15**).

The ^1H and ^{13}C NMR data (Tables 1, and 2) and chromatographic behaviour for the synthetically prepared compounds **1**, **2** and **3** are in good agreement with the natural products isolated from the brown alga *Ecklonia radiata*.[16] The described synthetic scheme provides the previously synthesised compound **1** in 17% overall yield in 7 steps and delivers two new synthetic products, sulfonate **2** and sulfuric acid ester **3**, each in 5% overall yield in 10 steps, together with their thio-analogues.

Acknowledgements

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