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Synthesis of two arsenic-containing cyclic ethers: model compounds for a novel group of naturally-occurring arsenolipids

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ABSTRACT

Two previously unknown arsenic-containing cyclic ethers have been synthesized, namely (((2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)methyl)dimethylarsine oxide and its C-1 epimer (((2*S*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)methyl)dimethylarsine oxide as its trifluoroacetate salt. The compounds serve as model compounds for a new group of unidentified arsenolipids observed in a unicellular alga and sediments.

The natural product chemistry of arsenic in the sea has continued to attract interest since the first reports of arsenobetaine in lobster[1] and of arsenosugars in algae.[2] Although these water-soluble organoarsenicals can be abundant in seafood, they are considered to present no toxicological risk to humans and interest in their presence in organisms has centred largely on describing their biosynthetic pathways. The focus in recent years has changed, however, following the identification of several types of lipid-soluble forms of arsenic, the so-called arsenolipids, which account for typically 10–30% of the total arsenic content in marine organisms.[3] The types of arsenolipids identified so far include, arsenic-containing derivatives of fatty acids, hydrocarbons and fatty alcohols,[4–7] and more recently arsenic-containing phosphatidylcholines[8] and ethanolamines.[8] In addition to raising fundamental questions of the possible biological role of arsenolipids, in membranes, for example, issues regarding their possible toxicity have been raised following the observation that some of the arsenolipids show cytotoxicity to human cells,[9,10] and they are able to cross the blood–brain barrier of the fruit fly.[11]

Our recent investigations on the natural occurrence of arsenolipids have revealed the presence of a novel compound class in a unicellular alga, *Dunaliella tertiolecta*, and in sediments. The properties and mass spectrometric data of these compounds suggested a cyclic ether as one of the most promising base structures with a long and variable hydrocarbon chain imparting lipophilicity to the molecules. To gain evidence for the proposed structure for the new arsenolipid, we synthesized two of the possible cyclic ether isomers and compared their chromatographic and mass spectrometric properties with those of the acid-hydrolysed natural product from *Dunaliella tertiolecta*. The cyclic ethers **1** and **2** (Fig. 1) can be formally considered as CH_2-extended arsenic-containing ribose derivatives,[12–19] lacking the anomeric centre.

This manuscript reports the synthesis of the two epimers **1** and **2** of the previously unknown arsenic-containing cyclic ether ((3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)methyl) dimethylarsine oxide.

The synthesis of the trifluoroacetate salt of cyclic ether **1** started from inexpensive and readily available D-(−)-ribose and was achieved in a straightforward 8-step synthesis in a combined yield of 4% (Scheme 1). The synthesis towards the central intermediate **5** has already been described in the literature[20,21] and was performed analogously. Starting from D-(−)-ribose, vicinal alcohol protection was achieved using acetone and sulfuric acid to give **3**. Primary alcohol protection at position C-5 using TBS-Cl yielded **4**. A Corey–Chaykovsky reaction[22,23] using trimethylsulfoxonium iodide and potassium *tert*-butoxide gave the central intermediate **5** in a yield of 59%.[20,21]

In order to transform the newly introduced primary alcohol into a suitable leaving group, an Appel reaction[24,25] using PPh_3 and CCl_4 was performed to give **6** in a yield of 66%. Introduction of Me_2(As) was achieved using Me_2AsI/Na[14,16,26] and the resulting arsine was then oxidized with H_2O_2 to the considerably more polar arsine oxide **7** in a combined yield of 40% (2 steps).[14,16] Silyl ether depro-

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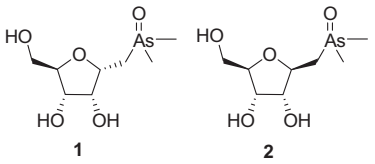


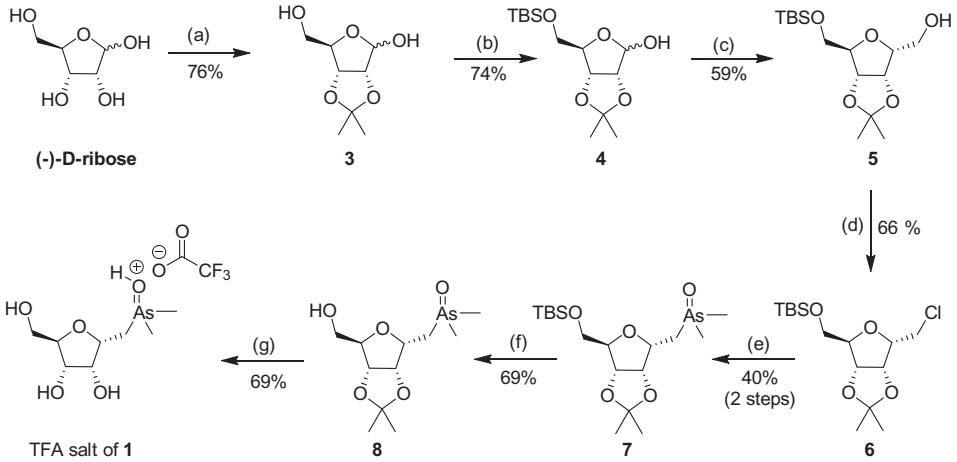
Figure 1. Epimers **1** and **2** as model compounds for a novel group of naturally-occurring arsenolipids.

tection was performed using TBAF to give **8** in a yield of 69%, and acetonide deprotection was achieved using TFA/H_2O (10+1 v/v) to afford **1** as its TFA salt in a yield of 69%.[14,16] When the TFA salt of **1** was applied to a cation-exchange column, which was washed with water then aqueous NH_3, we obtained **1** in its free form, which is clearly shown by a ca. 0.5 ppm upfield shift in ^{1}HNMR of the methyl groups attached to arsenic. The pK_a[27] value of **1-HCl** was measured to be ~3.5.

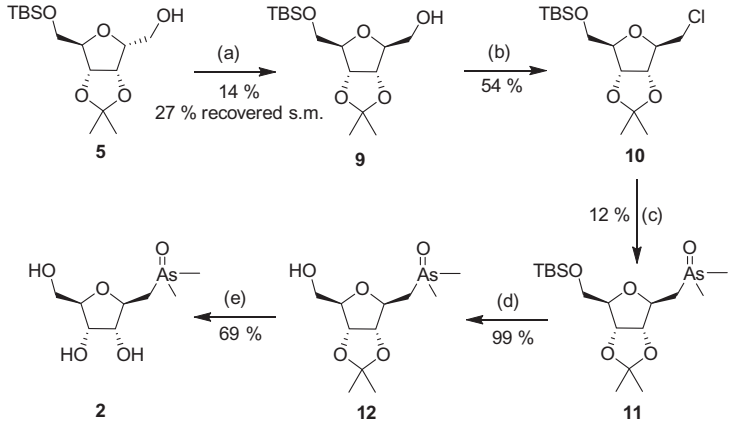
Cyclic ether **2** was synthesized in a similar manner (Scheme 2). Starting from the central intermediate **5**,[20,21] epimerization in position C-1 was achieved in a three-step procedure, as already described for this compound in the literature:[20] a Swern-oxidation[28–31] was followed by treatment with Et_3N and an ensuing reduction using $NaBH_4$ gave the known **9** in a yield of 14% (27% recovered starting material).[20] The low yield can be attributed to an incomplete epimerization (starting material was recovered) and to difficulties in product isolation.

The primary alcohol was then transformed into the corresponding chloride (again PPh_3/CCl_4) to give **10** in a satisfactory yield of 54%.[24,25] Introduction of $Me_2(AsO)$ using Me_2AsI/Na[14,16,26] gratifyingly gave **11** in a yield of 12% (2 steps), without any additional oxidation step needed (spontaneous oxidation: no H_2O_2 addition). Compound **11** was isolated as a colourless solid, whereas epimer **7** was isolated as yellow oil. Silyl ether deprotection using TBAF gave **12** in a yield of 99%. Acetonide deprotection using TFA/H_2O (10+1 v/v) afforded **2**, surprisingly, without the accompanying TFA salt formation as observed for **1**.[14,16] Interestingly, compound **2** turned out to be not basic as no protonation occurred even at pH = 0.85 (D_2O). Further investigations will be directed towards this exceptional observation.

Having in hand epimers **1** and **2**, we next compared the chromatographic and mass spectroscopic properties of the synthesized model compounds with those of the acid-hydrolysed natural product from *Dunaliella tertiolecta* (see Supporting information for further details). The natural arsenical and the two model compounds were treated with 0.25 mol·L^{-1} HCl (50 °C, 12 h) and the hydroly-



Scheme 1. Synthesis of the TFA salt of **1**. Reagents and conditions: (a) 0.1 equiv H_2SO_4, acetone, rt, 18 h; (b) 1.2 equiv imidazole, 0.97 equiv TBS–Cl, DCM, rt, 16 h; (c) 1.5 equiv KO*t*Bu, 1.5 equiv trimethylsulfoxonium iodide, DMSO, 0 °C–>rt, 2.5 h; (d) 1.6 equiv PPh_3, 0.2 equiv imidazole, CCl_4, 95 °C, 16 h; (e) Na/Me_2AsI, THF, rt, 4 h then H_2O_2, THF, 45 min; (f) 1.1 equiv TBAF, THF, 0 °C–>rt, overnight; (g) TFA/H_2O 10+1 (v/v), 10 min. TBS: *tert*-butyl-dimethylsilyl.



Scheme 2. Synthesis of **2**. Reagents and conditions: (a) 4.2 equiv DMSO, 2.2 equiv $(COCl)_2$, DCM, 2.5 h, −78 °C, Et_3N; then: Et_3N, rt, 48 h, DCM/^{i}PrOH; then: $NaBH_4$, MeOH/Et_2O; (b) 1.5 equiv PPh_3, 0.2 equiv imidazole, CCl_4, 90 °C, 15 h; (c) Na/Me_2AsI, THF, rt, 15 h; (d) 1.1 equiv TBAF, THF, 0 °C–>rt, overnight; (e) TFA/H_2O 10+1 (v/v), 10 min. TBS: *tert*-butyl-dimethylsilyl.

Table 1
ESI-HRMS comparison between the natural unknown arsenical and the synthesized model compounds **1** and **2**. Samples were hydrolysed using 0.25 mol·L^{-1} HCl

m/z (calculated)	Composition	Relative intensity		
		Natural unkn.	Compound **1**	Compound **2**
55.0542	C_4H_7	2.1	5.7	3.6
73.0284	$C_3H_5O_2$	2.4	6.6	6.3
83.0491	C_5H_7O	17.0	8.5	6.9
85.0284	$C_4H_5O_2$	0.0	13.1	20.8
102.9523	C_2H_4As	2.0	3.3	0.0
104.9680	C_2H_6As	11.5	19.0	2.4
111.0441	$C_6H_7O_2$	100.0	1.9	0.7
122.9786	C_2H_8OAs	5.8	11.9	0.0
138.9735	$C_2H_8O_2As$	6.3	2.1	0.0
251.0276	$C_8H_{16}O_4As$	5.8	62.3	0.0
269.0364	$C_8H_{18}O_5As$	14.6	100.0	100.0

sates analyzed by cation-exchange HPLC/mass spectrometry. The two model compounds gave similar retention times (compound **1**: rt ~4.0 min, compound **2**: rt ~4.1 min), somewhat shorter than that for the hydrolysed natural arsenical (rt ~5.2 min). Mass spectrometric measurements revealed similar fragmentation patterns for the three compounds, but significant differences in signal intensities of the respective fragments (Table 1). On the basis of these data showing non-identity with the cyclic ether, we speculate that a (deoxy)-pyranose with the same molecular formula could be also considered as a possible base structure for the new lipid group.

The developed synthetic strategy gave access to the arsenic-containing cyclic ethers **1** and **2**, which were used as model compounds for a novel type of arsenolipid identified in *Dunaliella tertiolecta*. The obtained data provide important information for structure elucidation of this novel type of arsenolipid; further studies are currently underway in our laboratory.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.08.097.

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