Pergamon

Tetrahedron Letters, Vol. 38, No. 33, pp. 5819-5820, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01330-0

Isolation and Synthesis of 1-Deoxy-1-dimethylarsinoylribitol-5-sulfate, a Natural Constituent of *Chondria crassicaulis* and Other Red Algae

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Abstract: 1-deoxy-1-dimethylarsinoylribitol-5-sulfate has been synthesised from ribitol and shown to be identical with a natural constituent of *Chondria crassicaulis* and other red algae, some of which contribute to the human diet in Japan. © 1997 Elsevier Science Ltd.

It is well established that marine organisms, both plants and animals, including those eaten by man, contain appreciable concentrations of arsenic (up to ~100 μg/g wet weight)[1]. Identification of the compounds of arsenic present in marine-derived foodstuffs is essential before the toxicological testing necessary to allay the fears of health authorities and consumers can be undertaken. A survey by hplc, using ICP-MS as an element-specific detector, of the arsenic compounds present in a large range of Japanese algae revealed, besides dimethylarsinoylribosides that had already been identified and for which chromatographic standards were to hand, an unknown compound that was widely distributed in red algae and was the major arsenic compound in some, including yuna (*Chondria crassicaulis* Harvey)[2]. This novel compound was isolated from a fresh sample of yuna (2.88kg, 0.5μg/g As) by methanol extraction, solvent partitioning and ion-exchange and gel-permeation chromatography. ^{1}H and ^{13}C nmr spectra[3] of the compound indicated that it might have structure **1**, although the stereochemistry (based on ribitol, **2**) was inferred from its likely biogenesis from 1-deoxy-1-dimethylarsinoylribosides that have been isolated[1] from, and are assumed[4] to be widely distributed in, marine algae. The structure **1** was confirmed by its synthesis from **2**.

The simple strategy of introducing the dimethylarsinoyl- moiety to a 1-halo-ribitol proved impossible because attempts to halogenate ribitol, **2** [using CBr_4, or CCl_4, triphenylphosphine (TPP) in pyridine or DMF] gave only, in high yield, the THF derivative **3**. 1-Chlorination was finally achieved by treatment of 1,2-4,5 di-*O*-isopropylidene ribitol, **4**, with CCl_4 and TPP in CH_2Cl_2. Presumably decay of the initially formed oxyphosphonium intermediate was sufficiently hindered for chlorination to proceed preferentially on a terminal carbon with rearrangement of the isopropylidene group from 1,2- to 2,3- through a cyclic phosphorus intermediate[5]. A similar rearrangement has been reported previously[6]. That no stereochemical inversion occurred at C3 during this reaction was demonstrated by deprotecting the 1-chloro- compound **5** (aqueous TFA) whereby the THF derivative **3** was produced as the only product. Dimethylarsenic was delivered to C1 by the procedure of Stick[7] which involved treatment of **5** with Me_2AsNa[8] and oxidation of the resulting arsine with H_2O_2. However, nmr spectra showed the presence of two products, **6** and **7** which yielded **8** and **9** upon treatment with aqueous TFA (**6** and **7** were not separated from each other). Separation of **8** from **9** was achieved on a GS 220 HQ gel permeation column (Asahipak, Tokyo) using 0.01M acetic acid as eluent.

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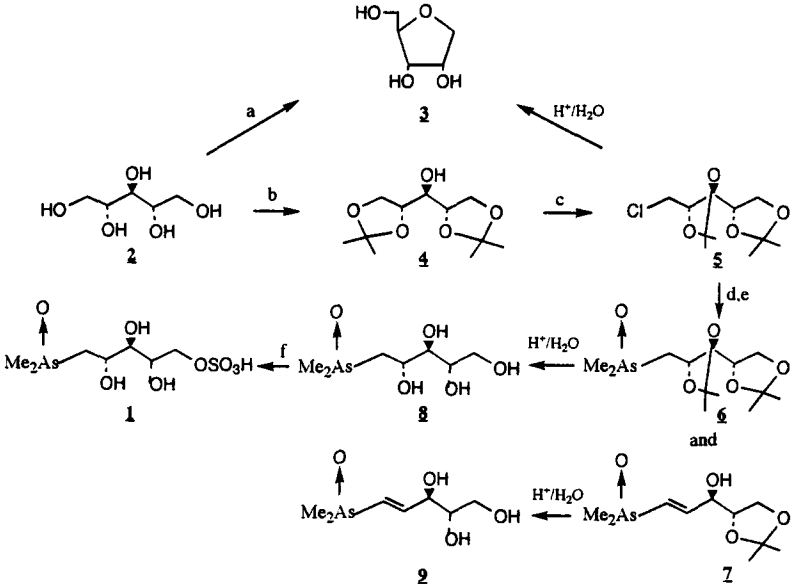
Sulfation of the primary hydroxyl group of **8** was accomplished with complete regioselectivity using SO_3-NEt_3 complex in DMF (0°C, 4h) to yield the target compound **1**.



a) CBr_4 or CCl_4, TPP, pyridine or DMF, rt, 90%; b) acetone, 2,2-dimethoxypropane, H^+; rt, 2h, 95% c) CCl_4, TPP, CH_2Cl_2, rt, 4h, 15%; d) Me_2AsI + Na→Me_2AsNa, THF; e) H_2O_2, THF, rt, equal yields (32%) of **6** and **7**; f) SO_3-NEt_3 complex (1.5 equiv), DMF, 0°,4h, 68%.

The small quantity of **1** obtained from the natural source precluded any possibility of obtaining configurational data. However, **1** is likely to have a configuration consistent with its probable biogenesis from 1-deoxy-1-dimethylarsinoyl-β-D-ribosides[1]. The synthesis described here yielded a racemic mixture which was in all other respects identical to the natural compound isolated from *Chondria crassicaulis*. All compounds in the Scheme were fully characterised by ^1H and ^{13}C nmr spectra and satisfactory CI mass spectra and/or combustion analyses were obtained for separated new compounds. The way is now open for the synthesis of sufficient quantities of **1** to allow a full assessment of its toxicological significance to be made.

Acknowledgments: We thank Drs RV Stick, R Franzen and T Sano for discussions and Mrs C Suzuki for nmr spectra.

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3. ^1H nmr (500 MHz, D_2O) δ1.83, 1.85, 2s, 6H, 2xMe; 2.46, dd, $J_{5,5}$ 14.0Hz, $J_{4,5}$ 10.4Hz, H1; 2.50, dd, $J_{5,5}$ 14.0Hz, $J_{4,5}$ 3.1Hz, H1; 3.77, dd, $J_{2,3}$ 8.0Hz, $J_{3,4}$ 4.3Hz, H3; 3.87, m, $J_{1,2}$ 5.8Hz, $J_{1,2}$ 2.7Hz, $J_{2,3}$ 8.0Hz, H4; 4.16, dd, $J_{1,1}$ 10.7Hz, $J_{1,2}$ 5.8Hz, H5; 4.25, dd, $J_{1,1}$ 10.7Hz, $J_{1,2}$ 2.7Hz, H5; 4.30, m, $J_{4,5}$ 10.4Hz, $J_{4,5}$ 3.1Hz, $J_{3,4}$ 4.3Hz, H2. ^{13}C nmr (130 MHz, D_2O) δ14.10, 14.96, 2xMe; 33.05, C1; 66.50, C2; 69.57, C5; 69.86, C4; 73.56, C3.
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(*Received in Japan* 20 *May* 1997; *revised* 20 *June* 1997; *accepted* 27 *June* 1997)