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THE SYNTHESIS OF (R)-2',3'-DIHYDROXYPROPYL 5-DEOXY-5-DIMETHYLARSINOYL-β-D-RIBOSIDE, A NATURALLY-OCCURRING, ARSENIC-CONTAINING CARBOHYDRATE

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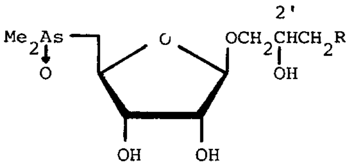
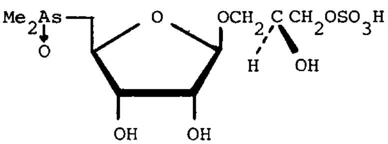
Abstract: The synthesis of (R)-2',3'-dihydroxypropyl 5-deoxy-5-dimethylarsinoyl-β-D-riboside is reported.

In 1977, a group led by Cannon reported the isolation of arsenobetaine ($Me_3As^+CH_2CO_2^-$) from the western rock lobster (Panulirus cygnus George),[1] and further investigations established the widespread occurrence of this arsenic compound in a variety of marine animals.[2] Subsequent to this pioneering discovery, Edmonds and Francesconi isolated two arsenic-containing carbohydrates from brown kelp (Ecklonia radiata), an important primary producer in the coastal ecosystem supporting the western rock lobster.[3] These compounds were assigned the structures (1) and (2),[4] and the configuration at C2' was inferred [(R) for (1); (S) for (2)] from an X-ray crystal structure on a related natural product, the sulfuric acid ester (3), itself isolated with (1) from the giant clam (Tridacna maxima).[5] It has been suggested that the source of (3) was symbiotic unicellular green algae living in the tissues of the giant clam,[5] and these observations imply that arsenic-containing carbohydrates may be widespread among marine algae (phytoplankton and macroalgae) and are likely to play a major role in the biotransformation of arsenic in marine systems.

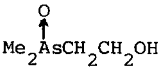


(1) R = OH

(2) R = SO_3H



(3)

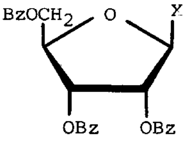


$$Me_2\overset{O}{\overset{\uparrow}{A}}sCH_2CH_2OH$$

(4)

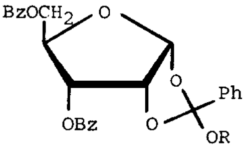
The biosynthetic origin of arsenobetaine and the β-D-ribosides (1) and (2) remained obscure, but a potential linkage between the two was beautifully demonstrated by anaerobic fermentation of *Ecklonia* to produce dimethylarsinoyl ethanol (4).[6] It seemed to us that a ready synthesis of (1) was required in order to provide amounts of material for biosynthetic and toxicological studies, and also to establish a route for the incorporation of a label (^{13}C) if deemed necessary.

The synthesis of (1) was naturally approached from a D-ribose unit, with the initial attachment of a chiral three-carbon aglycone at C1, and subsequent delivery of arsenic at C5. Thus, commercially available 1-O-acetyl-tri-O-benzoyl-β-D-ribofuranose (5) was converted (HCl/CH_2Cl_2) into the chloride (6) and thence the orthoester (7) in essentially quantitative yield by modifications of the literature procedures.[7,8] This orthoester was then treated with (S)-1,2-O-isopropylideneglycerol (8)/pyridinium p-toluenesulfonate in boiling toluene (the mixture was continuously distilled to remove the liberated methanol) to give, presumably, the orthoester (9), and this was rearranged in the presence of a catalytic amount of mercury (II) bromide to the β-D-riboside (10),[†] obtained as an oil {75%; $[\alpha]_D^{20}$ +35.9° ($CHCl_3$)}. The ^1H nmr (90 MHz) spectrum of (10) showed a singlet for H1 (δ 5.32), and the ^{13}C nmr (20.1 MHz)



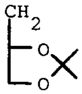
(5) X = OAc

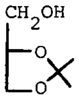
(6) X = Cl



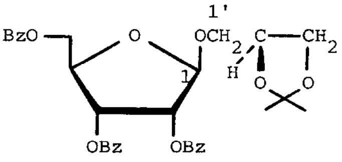
(7) R = Me

(9) R =

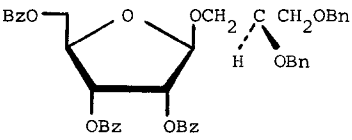




(8)



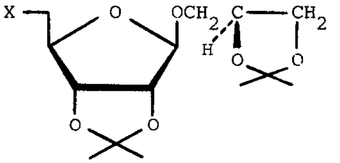
(10)



(10a)

spectrum (^{1}H broad-band decoupled) showed single resonances for C1,2 and C1'-3'. Alternatively, treatment of the acetate (5) with (S)-1,2-di-O-benzylglycerol[9]/tin (IV) chloride in dichloromethane[10] containing a little ethyldiisopropylamine gave an oil, presumably the β-D-riboside (11), which, after sequential treatment with H_2/Pd-C/EtOAc and then 2,2-dimethoxypropane/p-toluenesulfonic acid/CH_2Cl_2, gave a product identical in all respects to the glycoside (10) {$[\alpha]_D^{20}$ +36.1° ($CHCl_3$)}.

Removal of the benzoyl protecting groups (NaOMe/MeOH) from (10) then gave a triol which was not purified but converted (2,2-dimethoxypropane/HCl in dichloromethane) to the di-O-isopropylidene derivative (11),[†] also obtained as an oil {66%; $[\alpha]_D^{20}$ -77° ($CHCl_3$)}.



(11) X = OH

(12) X = Cl

(13) X = $AsMe_2$

(14) X = $\underset{\overset{\downarrow}{O}}{AsMe_2}$

The structure of (11) was confirmed from an analysis of the ^{13}C nmr spectrum, which showed two signals (δ 109.8 and 112.8) for quaternary carbon in 1,3-dioxolane rings.[11] Treatment of (11) with N-dichloromethylene-N,N-diethylammonium chloride ($Et_2\overset{+}{N}{=}CCl_2Cl^-$) in dichloromethane gave the chloride (12)[†] as an oil {86%; $[\alpha]_D^{20}$ -76° ($CHCl_3$)} which was converted into the trialkyarsine (13),[‡] an oil, upon exposure to Me_2AsNa[12] in THF (80%). The ^{1}H nmr spectrum of (13) showed two resonances for Me_2As (δ 0.98, 0.99) and a multiplet for H5, 5 (δ 1.70, AB part of ABX pattern). Oxidation of (13) (H_2O_2/THF) then gave the arsine oxide (14)[†] {83%; $[\alpha]_D^{20}$ -7.5° ($CHCl_3$)} which crystallized when very dry. The ^{1}H nmr spectrum again showed two resonances for $Me_2As \to O$ (δ 1.73, 1.76) and a similar downfield movement of H5, 5 (δ 2.35, m, AB part of ABX pattern). Treatment of (14) with CF_3COOH/H_2O (9:1) then gave the natural product (1)[†] as an oil {78%; $[\alpha]_D^{20}$ -2.6° (MeOH)}, identical in all respects (tlc, ^{1}H and ^{13}C nmr) with material isolated from Ecklonia and Tridacna.

[†] The purity of these compounds was established by combustion analysis.

[‡] Compound (13) could not be purified sufficiently to obtain a C, H analysis, but gave As, 18.8% ($C_{16}H_{29}AsO_6$ requires As, 19.1%).

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References

1. Edmonds, J.S., Francesconi, K.A., Cannon, J.R., Raston, C.L., Skelton, B.W., and White, A.H., Tetrahedron Lett., 1977, 1543.
2. Luten, J.B., Riekwel-Booy, G., v.d. Greef, J., and ten Noever de Brauw, M.C., Chemosphere, 1983, 12, 131.
3. Edmonds, J.S., and Francesconi, K.A., Nature, 1981, 289, 602.
4. Edmonds, J.S., and Francesconi, K.A., J. Chem. Soc. Perkin Trans I, 1983, 2375.
5. Edmonds, J.S., Francesconi, K.A., Healy, P.C., and White, A.H., J. Chem. Soc. Perkin Trans I, 1982, 2989.
6. Edmonds, J.S., Francesconi, K.A., and Hansen, J.A., Experientia, 1982, 38, 643.
7. Hanessian, S., and Banoub, J., Methods Carbohydr. Chem., 1980, 8, 237.
8. Yung, N., and Fox, J.J., Methods Carbohydr. Chem., 1963, 2, 108.
9. (S)-1,2-Di-O-benzylglycerol was prepared from 3,4-O-isopropylidene-D-mannitol (Wiggins, L.F., J. Chem. Soc., 1946, 13) by benzylation ($PhCH_2Br$/NaH-imidazole/DMF), selective hydrolysis (HOAc/H_2O, 7:3 at 100°), cleavage of the diol {$Pb(OAc)_4$/THF} and reduction ($NaBH_4$/aq. THF) of the resulting aldehyde (Eibl, H., and Westphal, O., Liebigs Ann. Chem., 1970, 738, 161).
10. Hanessian, S., and Banoub, J., Methods Carbohydr. Chem., 1980, 8, 243.
11. Buchanan, J.G., Chacón-Fuertes, M.E., Edgar, A.R., Moorhouse, S.J., Rawson, D.I., and Wightman, R.H., Tetrahedron Lett., 1980, 21, 1793.
12. Feltham, R.D., Kasenally, A., and Nyholm, R.S., J. Organometal. Chem., 1967, 7, 285.

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