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An Improved Synthesis of (*R*)-2,3-Dihydroxypropyl 5-Deoxy-5-dimethylarsinyl-β-D-riboside, a Common Marine Arsenical

Robert V. Stick,[A,B] *Keith A. Stubbs*[A] *and D. Matthew G. Tilbrook*[A]

[A] Department of Chemistry, The University of Western Australia, 35 Stirling Highway, Crawley WA 6009, Australia.
[B] Author to whom correspondence should be addressed (e-mail: rvs@chem.uwa.edu.au).

An efficient synthesis of (*R*)-2,3-dihydroxypropyl 5-deoxy-5-dimethylarsinyl-β-D-riboside, a common marine arsenical, from D-ribose, (*S*)-2,3-dibenzyloxypropanol and iododimethylarsine is described.

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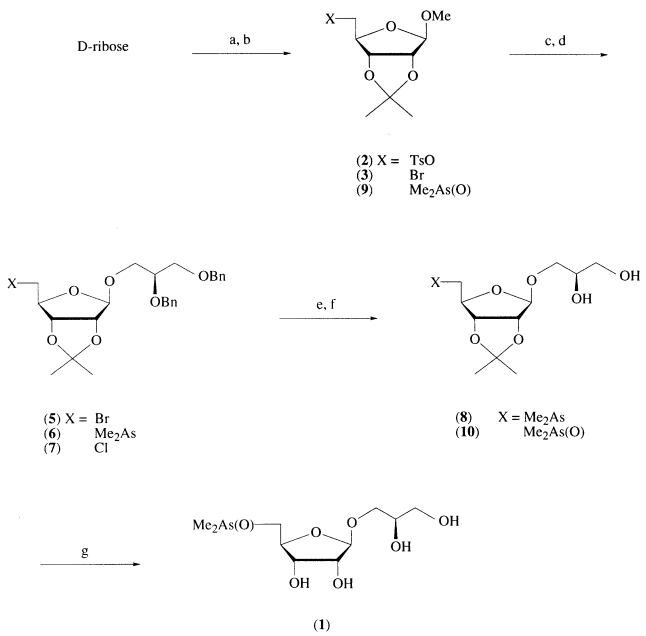
Arsenic is an element that is widely distributed in both the marine and terrestrial environments.[1] In the main, the natural arsenic-containing chemicals are benign in their action and pose little threat to mankind. However, recent anthropogenic activity has reversed this situation—for example, mining activity has resulted in huge stockpiles of the extremely toxic arsenic(III) oxide, and deep wells in arid areas have become contaminated with life-threatening levels of arsenic.

Some two decades ago, arsenobetaine ($Me_3As^+CH_2CO_2^-$) was identified as a major and widespread marine arsenical;[2] a little later, a range of glyceryl β-D-ribofuranosides, containing arsenic at C 5 of the D-ribose, were found to be widespread in the marine environment.[1] One of these compounds, (*R*)-2,3-dihydroxypropyl 5-deoxy-5-dimethylarsinyl-β-D-riboside (1), has proven to be a constant component of most marine flora studied to date. So common is compound (1) that it is now offered commercially and there have been calls for its supply in gram amounts.

In order to establish the structure of (1), particularly that of the stereochemistry of the glyceryl moiety, we set about its synthesis some years ago.[3] This successful piece of work was followed by a somewhat related route, described by Irgolic some years later.[4] Neither synthesis provides good quantities of compound (1). Here, we describe a hybrid synthesis starting with D-ribose that allows for the synthesis of gram amounts of (1) in a period of about three weeks.

D-Ribose was easily converted into the methyl β-D-ribofuranoside (2) (Scheme 1).[5] Although Irgolic describes the conversion of (2) into the bromide (3) with sodium bromide,[4] we found it much better to use tetrabutylammonium bromide [in dimethylformamide (DMF)]. The transacetalization of (3) with the alcohol (4) (Scheme2), as a neat melt according to Irgolic,[4] certainly produced the desired glyceryl β-D-ribofuranoside (5), but never in the quantitative yield quoted. We made many futile attempts to conduct this transformation in solution (toluene, xylene, DMF).



Scheme 1. a) (i) MeOH, acetone, HCl (ii) *p*-toluenesulfonyl chloride, pyr; b) Bu_4NBr, DMF; c) (*S*)-2,3-dibenxyloxypropanol (4), camphorsulfonic acid; d) $(CH_3)_2AsI$, Na, THF; e) Na, THF, $NH_{3(l)}$; f) H_2O_2/H_2O THF; g) TFA/H_2O (9 : 1)

For the introduction of an arsenic atom at C 5 of (5) we balked at the use of the difficult to prepare, toxic and pyrophoric cacodyl ($Me_2AsAsMe_2$).[4] Instead, we relied on the use of our tried and tested iododimethylarsine–sodium couple,[3] and this produced the surprisingly stable (to air oxidation) arsine (6). A by-product in the formation of (6) was the original alcohol (4), probably the result of a Vasella-

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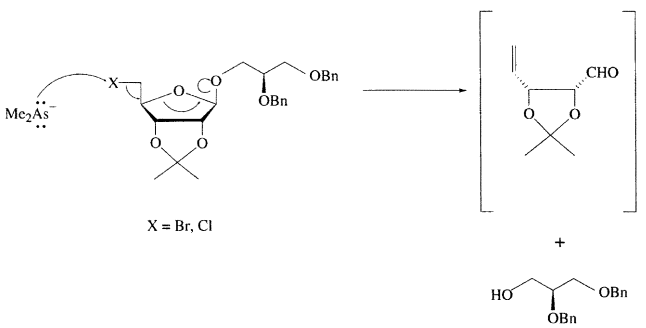

Scheme 2

type reductive elimination[6,7] of the bromide (5) (Scheme 2). The use of the chloride (7) did little to improve matters and we accepted the reasonable yield of the arsine (6).

Any attempt to remove the benzyl protecting groups from (6) by hydrogenolysis failed, probably owing to poisoning of the palladium catalyst by the arsine residue in the substrate. Nevertheless, treatment of (6) with sodium in liquid ammonia gave the diol (8).

An attractive conclusion now was to treat the diol (8) with iodine in methanol, thereby removing the isopropylidene group[8] and converting the arsine, after hydrolytic workup, into the arsine oxide.[9] Although the desired natural product (1) was formed, there was apparently some leakage to the methyl D-ribofuranoside (9). Therefore, the diol (8) was easily oxidized to the arsine oxide (10) and a subsequent and careful treatment with aqueous trifluoroacetic acid gave the natural product (1).[3]

Experimental

Experimental details have been given previously.[10]

*Methyl 2,3-*O*-Isopropylidene-5-*O*-p-toluenesulfonyl-β-*D*-riboside (2)*

The tosylate (2) was prepared following a two-step procedure as described by Lerner,[5] with the exception that the reaction was quenched with saturated $NaHCO_3$, not water as reported, to give (2) as colourless crystals (40%), $[\alpha]_D$ –49.6° (lit.[11] –50.0°), m.p. 81–82°C (EtOH: lit.[5] 83–84°C).

*Methyl 5-Bromo-5-deoxy-2,3-*O*-isopropylidene-β-*D*-riboside (3)*

A mixture of the tosylate (2) (8.7 g, 24 mmol) and tetrabutylammonium bromide (23 g, 72 mmol) in DMF was heated under reflux (24 h). Concentration of the mixture and usual workup (Et_2O) gave a pale yellow oil. Rapid suction-filtration chromatography (EtOAc/petrol, 17 : 83) yielded the bromide (3) as a colourless oil (5.6 g, 89%), $[\alpha]_D$ –79° (lit.[4] –79.6°). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.31, 1.48, 2 × s, CMe_2; 3.25–3.42, m, 2H, H 5; 3.32, s, OCH_3; 4.25–4.35, m, H 4; 4.53–4.58, m, H 3; 4.65–4.70, m, H 2; 4.99, s, H 1.

*Methyl 5-Chloro-5-deoxy-2,3-*O*-isopropylidene-β-*D*-riboside*

A mixture of the tosylate (2) (7.3 g, 20 mmol) and tetrabutylammonium chloride (16 g, 59 mmol) in DMF was heated at reflux (36 h). Concentration of the mixture and usual workup (Et_2O) gave a pale yellow oil. Rapid-suction filtration column chromatography (EtOAc/petrol, 17 : 83) yielded the title chloride as a pale yellow oil (3.1 g, 71%), $[\alpha]_D$ –92° (lit.[12] –93°). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.28, 1.43, 2 × s, CMe_2; 3.29, s, OCH_3; 3.38–3.59, m, 2H, H 5; 4.25–4.29, m, H 4; 4.55, d, $J_{2,3}$ 6.2 Hz, H 3; 4.64, d, H 2; 4.99, s, H 1.

(R)-*2,3-Dibenzyloxypropyl 5-Bromo-5-deoxy-2,3-*O*-isopropylidene-β-D-riboside (5)*

The β-D-riboside (5) was prepared following the procedure of Irgolic,[4] with the exceptions that camphorsulfonic acid was used in preference to *p*-toluenesulfonic acid, and the reaction was subjected to usual workup (EtOAc). Flash chromatography (EtOAc/petrol, 8 : 92) gave (5) as a colourless oil (43%), $[\alpha]_D$ –52.7° (lit.[4] –53.2°). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.37, 1.55, 2 × s, CMe_2; 3.22–3.97, m, 7H, H 5, aglycon; 4.37–4.43, m, H 4; 4.56–4.79, m, 6H, H 2,3,C**H**$_2$Ph; 5.15, s, H 1; 7.37, 10H, Ph.

(R)-*2,3-Dibenzyloxypropyl 5-Chloro-5-deoxy-2,3-*O*-isopropylidene-β-D-riboside (7)*

Camphorsulfonic acid (170 mg) was added to a mixture of methyl 5-chloro-5-deoxy-2,3-*O*-isopropylidene-β-D-riboside (190 mg, 0.85 mmol) and the dibenzylglycerol (4) (230 mg, 0.85 mmol), and the mixture was stirred at 80°C and 25 torr (20 h). Usual workup (EtOAc) and flash chromatography (EtOAc/petrol, 3 : 22) yielded the *chloride* (7) as a colourless oil (150 mg, 40%), $[\alpha]_D$ –55.3° (Found: C, 64.9; H, 6.7%. $C_{25}H_{31}ClO_6$ requires C, 64.9; H, 6.8%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.39, 1.53, 2 × s, CMe_2; 3.41–3.60, m, 5H, aglycon; 3.70–3.82, m, 2H, AB part of ABX pattern, H 5; 4.31–4.38, m, H 4; 4.56–4.75, m, 6H, H 2,3,C**H**$_2$Ph; 5.11, s, H 1; 7.27–7.42, 10H, Ph. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 24.9, 26.4, C**Me**$_2$; 44.2, C 5; 67.3, 69.7, 2C, aglycon CH_2; 72.3, 73.5, 2C, **C**H$_2$Ph; 76.7, aglycon CH; 82.2, 85.1, 86.7, C 2,3,4; 108.4, C 1; 112.6, **C**Me$_2$; 127.7, 127.8, 128.4, 138.1, 138.4, Ph.

(R)-*2,3-Dibenzyloxypropyl 5-Deoxy-5-dimethylarsino-2,3-*O*-isopropylidene-β-D-riboside (6)*

(i) Iododimethylarsine (370 mg, 1.6 mmol) was added to sodium (75 mg, 3.0 mmol) in dry THF (7 mL) with stirring under argon.[3] After the addition, the yellow mixture was stirred (30 min, 20°C) and then allowed to stand under argon (1 h). The supernatant liquid was added to the bromide (5) (200 mg, 0.4 mmol) and the mixture was stirred (1 h). The reaction was quenched (H_2O) and, after usual workup (EtOAc) and flash chromatography (EtOAc/petrol/triethylamine, 6 : 93 : 1), the *arsine* (6) was obtained as a colourless oil (87 mg, 41%), $[\alpha]_D$ –24.8° (Found: C, 61.0; H, 7.1%. $C_{27}H_{37}AsO_6$ requires C, 60.9; H, 7.0%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.98, 0.99, 2 × s, $AsMe_2$; 1.38, 1.47, 2 × s, CMe_2; 1.59–1.89, m, 2H, AB part of ABX pattern, H 5; 3.51–3.98, m, 5H, aglycon; 4.28–4.33, m, H 4; 4.51–4.78, m, 6H, H 2,3, C**H**$_2$Ph; 5.09, s, H 1; 7.33–7.39, m, 10H, Ph. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 9.17, 9.23, $AsMe_2$; 25.0, 26.5, C**Me**$_2$; 34.7, C 5; 67.2, 70.3, 2C, aglycon CH_2; 72.2, 73.4, 2C, **C**H$_2$Ph; 76.9, aglycon CH; 85.0, 85.7, 85.8, C 2,3,4; 108.8, C 1; 112.2, **C**Me$_2$; 127.6, 127.7, 128.3, 128.4, 138.2, 138.5, Ph.

(ii) Iododimethylarsine (250 mg, 1.1 mmol) and sodium (51 mg, 2.2 mmol) in dry THF (5 mL) were used, as described above, to react with the chloride (7) (125 mg, 0.3 mmol), and the mixture was stirred (3 h). The reaction was quenched (H_2O) and, after usual workup (EtOAc) and flash chromatography (EtOAc/petrol, 1 : 10), the arsine (6) was obtained as a colourless oil (70 mg, 49%). The ^{1}H NMR (300 MHz) spectrum for the compound was in good agreement with that obtained from the bromide (5).

In both the above preparations of the arsine (6), the presence of the alcohol (4) in the crude reaction mixture was obvious (TLC).

(R)-*2,3-Dihydroxypropyl 5-Deoxy-5-dimethylarsino-2,3-*O*-isopropylidene-β-D-riboside (8)*

Sodium (115 mg, 5.0 mmol) was added to a solution of the arsine (6) (370 mg, 0.70 mmol) in THF and liquid ammonia (11 mL, 3 : 8) at –78°C. The mixture was left (1 h) and then quenched with solid NH_4Cl. The ammonia was left to evaporate and, after the usual workup (CH_2Cl_2) and flash chromatography (EtOAc/petrol, 1 : 1), the *diol* (8) was obtained as a yellow oil (172 mg, 71%), $[\alpha]_D$ –20.1° (Found: C, 44.2; H, 7.2%. $C_{13}H_{25}AsO_6$ requires C, 44.1; H, 7.0%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.98, 0.99, 2 × s, $AsMe_2$; 1.38, 1.47, 2 × s, CMe_2; 1.55–1.89, m, 2H, AB part of an ABX pattern, H 5; 3.03, 2H, OH; 3.50–3.91,

m, 5H, aglycon; 4.23–4.26, m, H 4; 4.55–4.69, m, H 2,3; 5.06, s, H 1. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 9.63, 9.77, $AsMe_2$; 25.5, 27.0, C**Me**$_2$; 35.1, C 5; 64.3, 70.9, 2C, aglycon CH_2; 71.2, aglycon CH; 85.5, 86.1, 86.3, C 2,3,4; 110.0, C 1; 113.0, **C**Me_2.

(R)-*2,3-Dihydroxypropyl 5-Deoxy-5-dimethylarsinyl-2,3*-O-*isopropylidene*-β-D-*riboside (10)*

A solution of the arsine (8) (57 mg, 0.16 mmol) in THF (3 mL) was treated with 30% hydrogen peroxide (0.06 mL, 0.5 mmol) and the solution stirred (30 min). Evaporation and flash chromatography of the residue (MeOH/$CHCl_3$, 2 : 3) yielded the arsine oxide (10) as a colourless oil (49 mg, 82%), $[\alpha]_D$ –0.18° (lit.[13] –0.2°). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26, 1.43, 2 × s, CMe_2; 1.66, 1.78, 2 × s, $AsMe_2$; 2.21, dd, $J_{5,5}$ 14.1, $J_{4,5}$ 3.9 Hz, H 5; 2.82, dd, $J_{4,5}$ 12.9 Hz, H 5; 3.39–3.49, m, aglycon CH_2; 3.58, 3.91, AB part of ABX pattern, aglycon CH_2; 3.74–3.76, m, aglycon CH; 4.40–4.72, m, H 2,3,4; 5.06, s, H 1. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 15.03, 15.07, $AsMe_2$; 24.8, 26.3, C**Me**$_2$; 38.0, C 5; 64.3, 69.3, 2C, aglycon CH_2; 71.0, aglycon CH; 82.0, 85.0, 85.2, C 2,3,4; 108.9, C 1; 112.7, **C**Me_2.

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

The arsine oxide (10) (50 mg) was dissolved in trifluoroacetic acid/H_2O (9 : 1, 1 mL) and the solution stirred (10 min). Rapid concentration of the solution under vacuum at room temperature, followed by evaporation after the addition of water (2 mL) and pyridine (2 mL), gave a colorless syrup. Passage through a column of resin (Amberlite IRA 400, OH^-) gave the arsenical (1) (33 mg, 80%) as a syrup, $[\alpha]_D$ –2.5° (MeOH; lit.[3] –2.6°). ^{1}H NMR (300 MHz, D_2O) δ 1.68, 1.70, $AsMe_2$; 2.32, dd, $J_{5,5}$ 13.9, $J_{4,5}$ 9.6 Hz, H 5; 2.48, dd, $J_{4,5}$ 2.9 Hz, H 5; 3.39–3.49, m, aglycon CH_2; 3.44, 3.58, AB part of ABX pattern, aglycon CH_2; 3.72–3.76, m, aglycon CH; 3.97, d, $J_{2,3}$ 3.8 Hz, H 2; 4.08–4.14, m, H 3,4; 4.85, s, H 1. ^{13}C NMR (75.5 MHz, D_2O) δ 16.4, 16.8, $AsMe_2$; 38.4, C 5; 64.7, 71.2, 2C, aglycon CH_2; 72.6, aglycon CH; 76.5, 78.1, 79.2, C 2,3,4; 109.7, C 1.

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