Simple and Highly Convenient Two-Step Practical Procedure for the Synthesis of Optically Pure Methyl D-*erythro*-2,3-Dihydroxybutanoate

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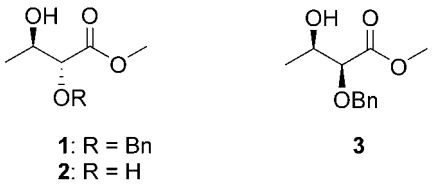
This paper is dedicated to the memory of the late and respected Professor S. Vancheesan.

Abstract: A synthesis of enantiopure methyl D-*erythro*-2,3-dihydroxybutanoate has been realized using two simple and consecutive reactions on D-erythronolactone as the starting material. The two reactions are lactone ring opening with hydrobromic acid in methanol and subsequent reductive debromination.

Keywords: C_4-chiral building block, dihydroxy esters, lactone, reductive dehalogenation

In connection with our ongoing efforts to chain extend highly functionalized alkyl halides particularly from the domain of carbohydrates with our newly developed Weinreb amide-based two-carbon homologating agent,[1] we needed multi-gram quantities of enantiopure **1** for a strategy aiming at the synthesis of differentially protected and acyclic forms of an important 2,3,6-trideoxyhexose sugar, amicetose.[2] To our complete surprise this substrate had not been synthesized in the literature earlier.[3] In contrast, the *threo*-configured compound **3** does appear in the literature three times.[4] Logically the target should be conveniently available from regioselective α-*O*-benzylation in the *erythro*-configured dihydroxybutanoate **2**. A quick survey of the literature brought about an even greater surprise by revealing the scarce availability of **2**, itself.[5] Just recently, Ley's group has reported an elegant procedure for the synthesis of enantiopure *anti*-2,3-dihydroxy esters through a highly diastereoselective lithium enolate aldol reaction of butane-2,3-diacetal-desymmetrized glycolic acid with aldehydes[6]. Our own needs, coupled with the fact that substrate **2** should be a very valuable chiral building block and chiral auxiliary for general use in synthetic organic chemistry, provided all the necessary impetus and a reason to devise a practical synthetic procedure for **2**.



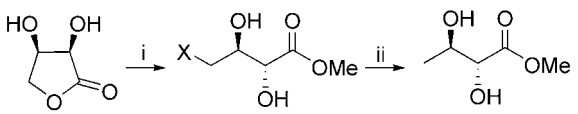
1: R = Bn
2: R = H

3

Figure 1.

We envisaged the synthesis of **2** through the halo derivative **4**, because of the convenience of the reductive dehalogenation and its possible obtainment from the readily accessible D-erythronolactone.[7] Although γ-butyrolactones have been opened with BBr_3[8] and Ph_3PBr_2[9] to afford 4-bromobutyric acid derivatives, D-erythronolactone has not been subjected to the same protocol. In fact the halo derivatives **4a** and **4b** are not reported in the literature.[10] Using a known procedure[11] for opening γ-lactones, D-erythronolactone **5** was converted to **4a** in 65% yield. Unfortunately reductive dechlorination failed to occur with Bu_3SnH in an attempt to achieve the desired transformation of **4a** to the target molecule **2** directly.

Presuming a probable interference from the free hydroxy groups, temporary isopropylidene protection of the two hydroxy functions in **4a** was made to arrive at **6a** and the latter was subjected to reduction. Even with **6a**, there was no trace of reductive dechlorination and the starting material was recovered quantitatively. Since it is an established fact that reductive deiodination is ex-



5 **4a**: X = Cl, **4b**: X = Br **2**

[i] dry HCl or HBr/methanol, 0 °C, and stirring at r.t, 48 h, 72%
[ii] Bu_3SnH/AIBN, benzene, reflux, 1.25 h, 83%; succeeds only with compound **4b**

Scheme 1.

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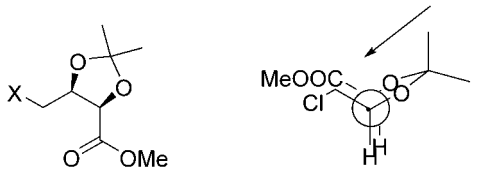

6

a: X = Cl
b: X = I
c: X = H

Figure 2.

tremely facile with Bu_3SnH, the Finkelstein reaction was attempted on **6a** for its conversion to the iodo derivative **6b**. To our surprise, the nucleophilic displacement of the chlorine in **6a** by iodide failed to occur even at 100 °C in DMF. Presumably the conformational rigidity imposed by the isopropylidene protection across the C2–C3 bond in **6a** is responsible for the failure of this displacement. The *syn* orientation of the $-CH_2Cl$ and COOMe groups, along the *gem*-dimethyl group in the dioxolane ring provides enormous steric hindrance to the approach of the iodide ion (Figure 2). The rigidity imposed by the isopropylidene protection precludes any chance of minimizing the steric hindrance through rotation along the C2–C3 bond.

With the above background our hopes now hinged on the bromo derivative **4b**. Simple stirring of D-erythronolactone **5** with a saturated solution of HBr in methanol afforded the bromoester **4b** in an isolated yield of 72%. To our satisfaction clean reductive debromination occurred with Bu_3SnH/AIBN and furnished the desired target **2** in a high isolated yield of 83%. To our further delight, the use of toxic Bu_3SnH could further be completely avoided by the use of Zn/NH_4Cl in methanol at 65 °C for the same transformation of **4b** to **2**. The reaction is easily scaleable and the isolated yields are in the range 72–75%

In conclusion, the present study provides a ready and convenient access to enantiomerically pure and hitherto inaccessible methyl D-*erythro*-2,3-dihydroxybutanoate (**2**). This should open new vistas for its use as a potential C_4 chiral building block or auxiliary in other synthetic endeavours.

Experimental Section

Methyl D-*erythro*-4-Bromo-2,3-dihydroxybutanoate (4b)

To a stirred solution of D-erythronolactone **5** (2 g, 16.9 mmol) in methanol (10 mL) was bubbled dry HBr at 0 °C until saturation. The flask was completely closed and the solution then stirred at room temperature for 48 h. On completion of the reaction, methanol was evaporated and the residue was subjected to silica gel chromatography to furnish the pure product; yield 2.6 g (72%); R_f: 0.3 (hexane/ethyl acetate, 1:1); mp 84–87 °C; $[\alpha]_D$: −19.7 (*c* 1, MeOH); ^1H NMR ($CDCl_3$, 300 MHz): δ = 3.57 (d, *J* = 5.7 Hz, 2H), 3.80 (bs, 1H). 3.85 (s, 3H), 4.11 (m, 1H), 4.38 (d, *J* = 3.9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 34.1, 53.5, 72.6, 73.3, 173.0; IR (KBr): ν = 3361(b), 1942, 1717 cm^{-1}; HRMS (CI): *m/z* = 212.9787; calcd. for $C_5H_9BrO_4$ (MH^+): 212.9963.

Methyl (2*R*,3*R*)-2,3-Dihydroxybutanoate (2)

Method A (reductive debromination using tributyltin hydride): To a stirred solution of bromo compound **4b** (1.06 g, 5 mmol) in benzene (25 mL) was added Bu_3SnH (1.59 mL, 6 mmol) and a catalytic amount of AIBN. The mixture was refluxed for 1.5 h, after which the solvent was evaporated and the residue subjected to silica gel chromatography; yield: 0.56 g (83%).

Method B (reductive debromination using Zn/NH$_4$Cl): To a stirred solution of the bromo compound **4b** (2.12 g, 10 mmol) in methanol (30 mL) was added ammonium chloride (0.532 g, 10 mmol) and zinc dust (1.3 g, 20 mmol). After stirring the reaction mixture for 12 h at 65 °C and subsequent cooling to room temperature, the reaction mixture was filtered through a celite bed (4 inch). To ensure complete removal of the product occluded in the zinc and other inorganic residues on the celite bed, thorough washing with additional volumes of methanol (3 × 20 mL) was done. The original filtrate and the methanol washings were combined and evaporated to dryness on the rotary evaporator. The residue was redissolved in ethyl acetate (60 mL) and washed with saturated sodium bicarbonate solution, dried and concentrated. The residue subjected to silica gel chromatography; yield: 0.96 g (72%); R_f: 0.16 (hexane/ethyl acetate, 1:1); $[\alpha]_D$: −15.8 (*c* 1.1, MeOH) {Lit[6] $[\alpha]_D$: −16.0 (*c* 1.1, MeOH)}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.18 (d, *J* = 6 Hz, 3H), 3.46 (bs, 2H). 3.80 (s, 3H), 4.06–4.10 (m, 1H), 4.24 (d, *J* = 3.42 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 17.7, 53.0, 69.5, 74.9, 173.5; IR (KBr): ν = 3418 (b), 2935, 1736 cm^{-1}; HR-MS (ES): m/z = 135.0674; calcd. for $C_5H_{10}O_4$ $[M+H]^+$: 135.0658; HR-MS (CI): *m/z* = 135.0659; calcd. for $C_5H_{10}O_4$ $[M+H]^+$: 135.0658; anal. calcd. for $C_5H_{10}O_4$: C 44.77, H 7.51; found: C 44.50, H 7.45.

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