Convenient Enantiopure Synthesis of (2*S*,3*R*)-2-*O*-Benzyl-3,4-*O*-isopropylidene-D-erythritol from D-(+)-Glucono-δ-lactone: A Potential C_4 Chiral Building Block

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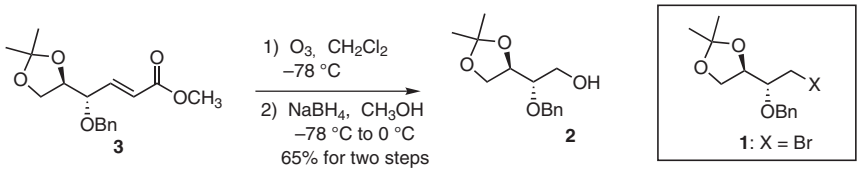
This paper is dedicated to Professor N. S. Narasimhan.

Abstract: A new convenient synthesis of (2*S*,3*R*)-2-*O*-benzyl-3,4-*O*-isopropylidene-D-erythritol has been achieved starting from extremely cheap and commercially available D-(+)-glucono-δ-lactone. It involves two carbon excisions using ozonolysis. The inbuilt stereochemistry ensures the enantiopurity of the target compound.

Key words: lactones, eliminations, ozonolysis, reduction



Scheme 1

In connection with our ongoing synthetic efforts towards 2-deoxy-C-aryl ribofuranosides, we needed a convenient and straight forward route to enantiomerically pure erythritol halo derivative **1**. Logically it should be possible to prepare **1** from the corresponding differentially protected enantiopure erythritol derivative **2**. A quick survey of the literature revealed a complete surprise. In sharp contrast to the abundantly available *threo* configured derivatives (obtained from tartaric acids), [1] the availability of the *erythro* configured analogue is extremely scarce.[2] Even from the corresponding appropriately protected enantiopure aldehyde, D-erythrose which could be converted to the erythritol derivative **2** there is little known. Two of the routes for the synthesis of this aldehyde rely on one carbon chain homologation of 2,3-*O*-isopropylideneglyceraldehyde. Dondoni uses 2-(trimethylsilylthiazole) as the formyl anion equivalent,[3] while Arroyo-Gomez employs (+)-(*R*)-methyl *p*-tolyl sulfoxide for the chain extension.[4] The latter depends on an effective Pummerer rearrangement[5] of the β-hydroxy sulfoxide to arrive at D-erythrose. Although both routes proceed with good to high stereoselectivity, they also involve tedious chromatographic techniques to separate the desired major diastereoisomer from the minor contaminant. The other routes available in the literature for this aldehyde are based on the carbon chain excision concept. Wang's method[6] involves a two-step, one carbon chain excision procedure on a pentose sugar derivative. The route is lengthy and a comparatively expensive sugar, D-(–)-arabinose, is required as the starting substrate for one carbon excision. The two other routes[7,8] use D-isoascorbic acid as the starting material in an oxidative carbon chain excision. One proceeds through a four carbon α-hydroxy ester intermediate and the other through D-erythronolactone. The former seems to be the most promising route, whereas the latter[8] demands a regioselective introduction of the benzyl ether protecting group onto the α-hydroxy group in D-erythronolactone in order to arrive at the erythritol derivative **2**. The dibutylstannylation/benzylation sequence has, however, only been carried out on a small scale and in moderate yields. In the light of this, the results presented herein are a significant improvement in the preparation of enantiopure erythritol derivative **2**.

The α,β-unsaturated ester **3** required as the starting material is conveniently obtained as depicted in Scheme 2 by the earlier approach of Chittenden.[9a] The 3,4 and 5,6-diol functionalities of D-(+)-glucono-δ-lactone **4** were selectively protected producing the di-*O*-isopropylidene α-hydroxy ester **5** in high yields.[9b] Initially a combination of Ph_3P/I_2/imidazole was used for direct deoxygenation[10] of the α-hydroxy group in **5** activated by a vicinal carbonyl group, we preferred to use a two-step method[9a] to arrive at methyl 2-deoxy-3,4:5,6-di-*O*-isopropylidene-D-(+)-gluconoate (**7**) in 77% overall yield. The steps involved are initial chlorination to provide the *manno*-configured chloro-derivative **6** as an intermediate and subsequent hydrogenolysis of the same to afford **7**. This was purely because of convenience and scalability. Treatment of **7** with sodi-

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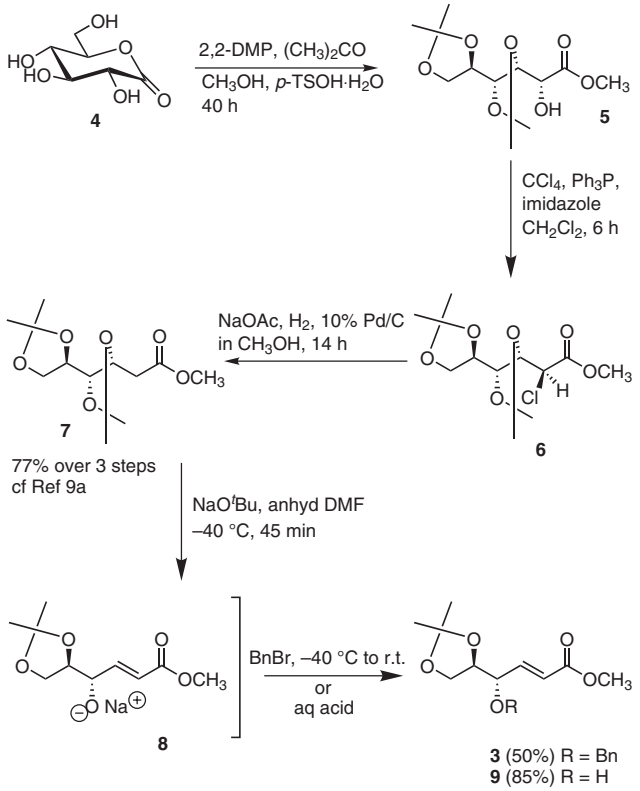
um *tert*-butoxide in anhydrous DMF at –40 °C results in a facile β-elimination and concomitant ring-opening of the internal isopropylidene ketal to furnish the sodium salt **8** in situ. Quenching the reaction with benzyl bromide afforded the α,β-unsaturated ester **3** in 50% yield. The formation of the *O*-benzyl derivative was evident from two doublets in the ^{1}H NMR spectrum of the product at 4.42 ppm and 4.64 ppm with a coupling constant of 11.7 Hz each. The ester functionality was confirmed from the IR (1724 cm^{-1}) and ^{13}C NMR (166.3 ppm) spectrum of the product. Unfortunately, the isolated yield of the product **3** could not be increased beyond 50%, despite stirring the sodium salt **8** with benzyl bromide at room temperature for a long period of time. However, quenching of salt **8** with acid resulted in excellent yields of the hydroxy derivative **9** (85%). Derivative **9** can be conveniently benzylated in good yield to furnish **3**. Finally, ozonolysis of the double bond in compound **3** at –78 °C followed by addition of sodium borohydride at the same temperature afforded the desired (2*S*,3*R*)-2-*O*-benzyl-3,4-*O*-isopropylidene-D-erythritol (**2**) in 65% isolated yield. The stereochemical integrity of the compound was evident from the specific rotation of the compound {$[\alpha]_D^{27}$ +21.7 (*c* 1, $CHCl_3$)], which was in conformity with the value reported in the literature[11] {$[\alpha]_D^{26}$ –22 (*c* 1, $CHCl_3$), enantiomer of **2**}.

The procedure presented herein offers an inexpensive and convenient method to obtain optically pure and differentially protected erythritol derivative **2**, a potential C_4 chiral building block. The route also has considerable flexibility; incorporation of other protecting groups on the C_2-OH could lead to a range of derivatives. Since multigram quantities of **7** can be routinely obtained by a well-established procedure from extremely cheap and commercially available D-(+)-gluconolactone (**4**), there seems to be no difficulty in applying the strategy based on the chain excision concept and described herein for the target molecule **2**. The complete enantiopurity is safeguarded and ensured by the inbuilt stereochemistry at C_4 and C_5 in **7** or consequently in **3**, which remains intact during the synthetic sequence. One-pot ozonolysis and subsequent sodium borohydride reduction of the α,β-unsaturated ester **3** has been carried out on a two millimole scale. Other procedures and protocols from the literature for C=C double bond cleavage would be worthy of further exploration and may result in the optimization of this route.



Scheme 2[9a]

All the solvents and reagents were distilled before use. Melting points were determined in a capillary tube with a Toshniwal melting point apparatus and are uncorrected. NMR spectra were recorded on Bruker [300 MHz or 400 MHz (^{1}H NMR), 75 MHz or 100 MHz (^{13}C NMR)] NMR spectrometer or Jeol 400 MHz NMR spectrometer using TMS as a reference. IR spectra were recorded on Shimadzu IR 470 spectrometer. EI mass spectra and HRMS were accomplished at 70 eV using a Finnigan MAT 8230 spectrometer. Chemical ionization mass spectra and HRMS were accomplished at 10eV using a Q TOF MICRO spectrometer. Microanalyses were performed on a Perkin Elmer Instrument Series II, CHNS/O Analyzer 2400 analyzer or Heraeus analyzer. Optical rotations were measured with a Jasco, DIP-370-Digital polarimeter at room temperature. To monitor the formation of compounds **3**, **5**–**7**, and **9**, TLC were performed on pre-coated silica gel plates (Merck 5554), which were visualized by dipping them into a solution of cerium(IV) sulfate (1 g), ammonium molybdate (21 g), concd H_2SO_4 (31 mL), and H_2O (made up to 500 mL); the TLC plates were later heated to 100 °C. Silica-gel column chromatography was performed using silica gel (100–200 mesh) purchased from Acme (India).

Methyl 2-deoxy-3,4:5,6-di-*O*-isopropylidene-D-gluconoate (7)

To a solution of α-hydroxy ester **5**[9b] (10 g, 34.48 mmol) in CH_2Cl_2 (50 mL) at 0 °C, PPh_3 (20.95 g, 79.96 mmol) was added portionwise over 10 min. After the complete dissolution of PPh_3, imidazole (2.57 g, 37.79 mmol) followed by CCl_4 (19.2 mL, 206.88 mmol) were added. The temperature of the reaction mixture was gradually raised to r.t. (27–30 °C) and stirring was continued for 5 h. The reaction mixture was concentrated by removal of the solvent at reduced pressure and the residue was purified by silica-gel column chromatography (EtOAc–hexane, 9.5:0.5) to afford α-chloro ester **6** as a colorless oil (9.0 g, 85%).

To a solution of the α-chloro ester **6** (5 g, 16.23 mmol) in MeOH (30 mL) at r.t. (ca 27–30 °C), was added NaOAc (4.92 gm, 60 mmol) and Pd/C (10%, 0.400 g). The reaction mixture was subjected to hydrogenation at r.t. and a pressure of 50 psi. After 6 h MeOH was evaporated and EtOAc (50 mL) was added to the residue and the Pd/C removed by filtration. The EtOAc layer was washed with H_2O (2 × 15 mL) and dried over anhyd Na_2SO_4. The residue obtained after concentration was purified by a silica-gel column chromatography (EtOAc–hexane, 9:1), to afford pure 2-deoxy ester **7** as a low melting solid (3.62 g, 82%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.33, 1.37, 1.38, 1.39 (12 H, 4 s, 4 × CH_3), 2.58 (1 H, dd, *J* = 15.6, 8.8 Hz, O=CC*H*H), 2.84 (1 H, dd, *J* = 15.9, 3.2 Hz, O=CCH*H*), 3.59 (1 H, dd, *J* = 7.8, 8.3 Hz, COCHOCO], 3.72 (3 H, s, OCH_3), 3.95 (1 H, dd, *J* = 8.8, 4.9 Hz, CH*H*-

CHO), 4.04 (1 H, m, CH_2CHO), 4.14 (1 H, dd, J = 8.5, 6.1 Hz, C*H*HCHO), 4.34 (1 H, td, J = 8.3, 2.9 Hz, C*H*OCH$_2$C=O).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.1, 26.6, 26.9, 27.0 (4 × CH_3), 38.3 (CH_2C=O), 51.7 (OCH_3), 67.7 (CH_2), 76.64 (CO*C*OCO), 76.6 (CH_2CO), 80.3 (*C*OCH$_2$C=O), 109.5, 109.6 [*C*(CH$_3$)$_2$], 171.0 (C=O).

Methyl 4-*O*-Benzyl-5,6-*O*-isopropylidene-D-*erythro*-(*E*)-2-hexenoate (3)

To a solution of 2-deoxy ester **7**[9a] (0.548 g, 2 mmol), in anhyd DMF (3 mL) under a nitrogen atmosphere cooled to –78 °C, was added dropwise a solution of *t*-BuONa (0.230 g, 2.4 mmol) in anhyd DMF (3 mL). The mixture was stirred at the same temperature for 30 min, and later quenched with BnBr (0.354 mL, 3 mmol). The temperature of the reaction mixture was gradually raised to r.t. (27–30 °C) and allowed to stir at this temperature for 8 h. Then the reaction mixture was poured into a solution of sat. NH_4Cl (15 mL). The aq solution was extracted with Et_2O (4 × 10 mL), and the combined organic layers were washed with H_2O (10 mL), dried over anhyd Na_2SO_4, and evaporated to obtain a residue, which was purified by silica-gel column chromatography (EtOAc–hexane, 0.5:9.5) to afford pure **3** as a colorless oil (0.310 g, 50%).

R_f 0.75 (hexane–EtOAc, 9:1); $[\alpha]_D^{25}$ +18.6 (*c* 1, $CHCl_3$).

IR (neat): 2976, 1724, 1657, 1449, 1372 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.33, 1.41 (6 H, 2 s, 2 × CH_3), 3.76 (3 H, s, OCH_3), 3.87–3.90 (1 H, m, CH*H*CO), 3.91–3.95 (1 H, m, CHOBn), 4.02–4.04 (1 H, m, C*H*HCO), 4.07– 4.11 (1 H, m, CHOBnC*H*O), 4.42 (1 H, d, J = 11.7 Hz, C*H*HC$_6$H$_5$), 4.64 (1 H, d, J = 11.7 Hz, CH*H*C$_6$H$_5$), 6.12 (1 H, d, J = 15.0 Hz, COC*H*=CH), 6.92 (1 H, dd, J = 15.0, 6.0 Hz, CH=C*H*), 7.26–7.35 (5 H, m, ArH)

^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.1, 26.6 (2 × CH_3), 51.7 (OCH_3), 66.7 (CH_2), 71.7 (*C*H$_2$C$_6$H$_5$), 76.64 (COBn), 78.8 (COBn*C*O), 109.8 [*C*(CH$_3$)$_2$], 123.6 (C=O*C*H=CH), 127.9, 128.5 and 137.4 (ArC), 145.0 (CH=*C*H), 166.3 (C=O).

2-*O*-Benzyl-3,4-*O*-isopropylidene-D-erythritol (2)

A solution of the ester **3** (306 mg, 1 mmol) in anhyd CH_2Cl_2 (5 mL) was cooled to –78 °C and flushed with N_2. Ozone gas was bubbled through the solution until a pale blue color remained. Stirring was continued for 10 min; a solution of Ph_3P (288 mg, 1.1 mmol) in CH_2Cl_2 (5 mL) was added at the same temperature. After 15 min, MeOH (2 mL), and $NaBH_4$ (43.2 mg, 1.2 mmol) were added at –78 °C. The temperature was raised to r.t. (27–30 °C) and stirring was continued at this temperature for 1 h. The organic solvents were evaporated, and H_2O (15 mL) was added. The pH of the aqueous layer was adjusted to pH 7 by dropwise addition of HOAc. The aqueous layer was extracted with EtOAc (3 × 10 mL), and the combined organic layers were dried over anhyd Na_2SO_4 and evaporated to obtain a residue, which was purified by silica-gel column chromatography (hexane–EtOAc, 8.5:1.5) to afford pure **2** as a colorless oil (0.163 g, 65%).

R_f 0.6 (hexane–EtOAc, 1:1); $[\alpha]_D^{27}$ +21.7 (*c* 1, $CHCl_3$) [Lit.[11] –22.0 (*c* 1, $CHCl_3$), *ent*-**2**].

IR (neat): 2936, 3456 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.35, 1.42 (6 H, 2 s, 2 × CH_3), 2.13 (1 H, br s, OH), 3.50–3.54 (1 H, m, CHOBn), 3.69–3.71 (1 H, m, C*H*HOH), 3.81–3.84 (1 H, m, CH*H*OH), 3.88 (1 H, dd, J = 8.3, 5.9 Hz, CH*H*CH), 4.08 (1 H, dd, J = 8.3, 6.8 Hz, C*H*HCH), 4.16–4.19 (1 H, m, CHO), 4.63 (1 H, d, J = 11.7 Hz, C*H*HC$_6$H$_5$), 4.67 (1 H, d, J = 11.7 Hz, CH*H*C$_6$H$_5$), 7.31–7.37 (5 H, m, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.1, 26.5 (2 × CH_3), 61.6 (CH_2O), 66.8 (CH_2OH), 72.6 (*C*H$_2$C$_6$H$_5$), 75.5 (CHO), 79.6 (CHOBn), 109.2 [*C*(CH$_3$)$_2$], 127.8, 128.3, 128.5, 137.8 (ArC).

HRMS: *m*/*z* calcd for $C_{14}H_{20}O_4$: 252.136159; found: 252.135781.

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