# A Two-Step Preparation of a New $C_4$ Chiral Building Block Derivative of D-Erythronic Acid

M. C. B. V. de Souza, M. N. da Silva, V. F. Ferreira*

Universidade Federal Fluminense, Instituto de Química, CEG-GQO, Campus do Valonguinho, Niterói, CEP 24020-150, Rio de Janeiro, Brazil.

Fax 55-21-620-7749; e-mail cegvito@vm.uff.br

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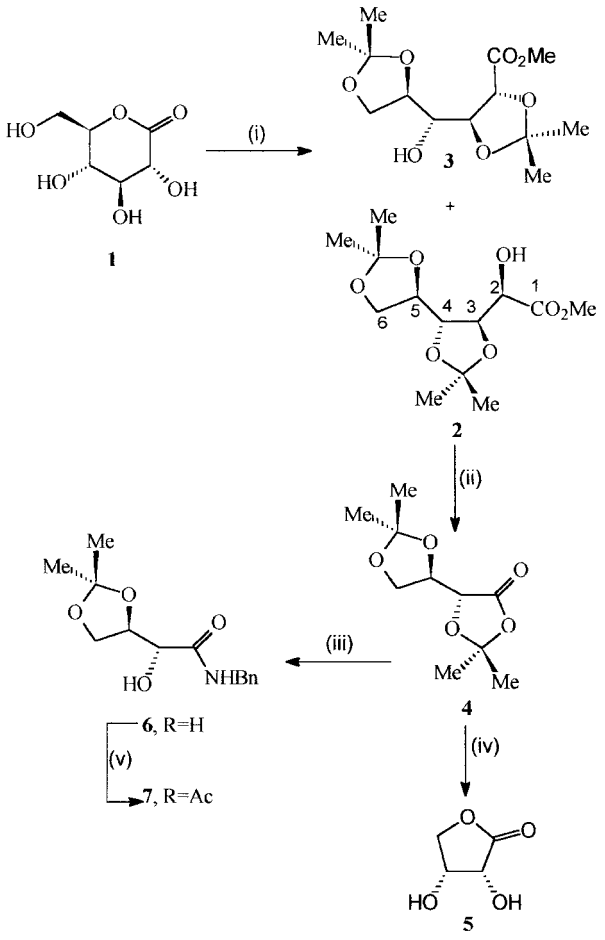
**Abstract:** 1,2;3,4-Di-*O*-isopropylidene-D-erythronic acid (2,2,2',2'-Tetramethyl-[R,R-(4,4'-bi-1,3-dioxolan)]-5-one) **4**, a new $C_4$ chiral building block derivative of D-erythronic acid was prepared in two steps from D-glucono-δ-lactone.

There has been continuous interest in new functionalised $C_4$ chiral building blocks. These compounds have been playing an important role in many syntheses of natural products.[1] However, only a few $C_4$ chiral building blocks are available, such as tartaric acid,[2] 3,4-*O*-isopropylidene-L-erythronate,[3a] L-threose,[3b-e] D-erythrose and, D-erythronolactone.[4] The latter compound and its 2,3-isopropylidene derivative are the most versatile four-carbon unity and have been prepared by degradative processes starting with L-rhamnose,[4a] D-ribose,[4b] D-ribonolactone,[4c] D-glucose,[4d,e] potassium D-glucuronate,[4f] isoascorbic acid,[4g,h] and D-arabinose.[4i]

In connection with a program aiming to study the oxidative degradation of carbohydrates, we developed a procedure for obtaining (-)-2,2,2',2'-tetramethyl-[R,R-(4,4'-bi-1,3-dioxolan)]-5-one (**4**), a new derivative of D-erythronic acid, in two steps from D-glucono-δ-lactone (**1**) as outlined in the Scheme. It is worth mentioning that the enantiomer of 4 (i.e., S,S) was prepared from potassium 3,4-*O*-isopropylidene-L-erythronate.[3a]

The 3,4 and 5,6-diol functionalities of D-glucono-δ-lactone (**1**) were selectively protected[5] producing the di-*O*-isopropylidene ester **2** along with its unreported isomer **3** in 68% and 18% yield respectively. Cleavage of C2-C3 bond of **2** was performed by oxidation[6] with $CrO_3$/pyridine/$Ac_2O$ (1:2:1) producing (-)-**4** in 75% yield. The latter compound was converted to D-erythronolactone **5** by acid hydrolysis of acetal groups showing the same absolute configuration ($[\alpha]^D_{20}$ -69.4, c 0.5, $H_2O$; lit.[4g] $[\alpha]^D_{20}$ -72, c 0.5, $H_2O$). In order to demonstrate the synthetic versatility of this compound it was reacted with benzylamine affording erythronamide **6** (75% yield).

This new procedure offers an inexpensive and convenient method to obtain **4** as a new derivative of D-erythronolactone. Since the preparation of the S,S enantiomer of 4 is known,[3a] the R,R enantiomer **4** may be of considerable interest in asymmetric synthesis.




*Reagents and conditions*: (i) $Me_2C(OMe)_2$, PTSA, $H_2SO_4$, MeOH, 80%, ref.[5]; (ii) 4eq [$CrO_3$, Pyridine, $Ac_2O$] (1:2:1), $CH_2Cl_2$, 75%, ref.[7]; (iii) $BnNH_2$, toluene, room temp., quantitative; (iv) MeOH, $H_2O$, 8 days, quantitative; (v) $Ac_2O$, pyridine, 24 h, room temp., quantitative

**Scheme**

## Experimental Section

High resolution fast atom bombardment mass spectra (HRFABMS) were recorded in a 3-NBA matrix in the positive ion mode on a VG ZAB-E mass spectrometer. Low resolution electron-impact mass spectra (12 eV) were measured on a Hewlett Packard 5985 instrument. NMR experiments were performed on Varian XL-300 instruments; signals are reported in parts per million (δ), referenced to the solvent used. All NMR pulse sequences were run using standard Varian software version 4.3. IR spectra were recorded on a Perkin-Elmer 1420 spectrophotometer as potassium bromide pellet. Freshly purified samples were used for measurement of physical constants and spectral data.

**3,4;5,6-Di-*O*-isopropylidene-D-gluconate methyl ester (2)[5] and 2,3;5,6-Di-*O*-isopropylidene-D-gluconate methyl ester (3)** - A solution of D-glucono-δ-lactone (**1**, 10 g, 56.2 mmoles), 2,2-dimethoxypropane (17 mL, 137.3 mmoles), p-toluenesulfonic acid (113 mg, 0.6 mmoles) in 6 mL of dry acetone was stirred for 48 h at room temperature under nitrogen. To this solution was added solid sodium carbonate (3g), stirred for an additional 2 h and the mixture filtered under vacuum. The solvent was removed under reduced pressure and the residue was chromatographed over silica gel using a gradient from hexane to ethyl acetate. Compound **2**[5] (11.5 g) was obtained in 68 % yield along with **3** (3 g) in 18% yield.

**3**, colorless oil; IR ($cm^1$) 3500 (OH), 1750 (C=O); $^1$H NMR (300 MHz, $CDCl_3$) δ (ppm) 4.57 (d, 1 H, J = 7.8 Hz, H-2), 4.42 (dd, 1-H, J = 7.8 and 1.8 Hz, H-3), 4.12-4.08 (m, H-6), 4.07 - 4.00 (m, H-5), 3.79 (s, 3-H, OMe), 3.66 (ddd, 1-H, J = 9.0, 8.4 and 1.8 Hz, H-4), 2.16 (d, 1-H, J = 9.0 Hz, OH), 1.49, 1.45, 1.41 and 1.35 (4s, 12-H, 4 Me); $^{13}$C NMR (75 MHz, $CDCl_3$) δ (ppm) 170.9 (C-1), 111.5 and 109.4 ($\underline{C}Me_2$), 77.7 (C-3), 76.0 (C-5), 74.9 (C-2), 70.5 (C-4), 66.9 (C-6), 52.3 (OMe), 26.7, 26.5, 25.6 and 25.2 (4-Me); FAB-HRMS $(M-15)^+$ = 275.1130 (calcd 275.1130).

**1,2;3,4-Di-*O*-isopropylidene-D-erythronic acid (4) -** Solid chromium trioxide (3.2 g, 32 mmoles) under nitrogen was added to a solution of dry pyridine (5.2 mL) in dry dichloromethane (100 mL). The mixture was stirred vigorously for 10 min and then a second solution of **2** (2 g, 6.9 mmoles) in dichoromethane (20 mL) was slowly added. The reaction mixture was stirred for 48 h and then filtered on a silica gel column and eluted with ethyl acetate. The filtrate was evaporated under reduced pressure affording a brown oil. Toluene (2 x 50 mL) was added to this oil and then evaporated under reduced pressure in order to remove trace of acetic acid. The resulting brown solid was chromatographed on a silica gel column and eluted with hexane/ethyl acetate (7:3) yielding **4** as white solid (1.12 g, 75 %). mp 70-71 $^{o}$C; $[\alpha]^{D}_{20}$ = -6.8 (c 0.66, $CHCl_3$); $[\alpha]^{D}_{20}$ lit.[3a] for enatiomer $[\alpha]^{D}_{20}$ = +7 (c 0.12 , $CHCl_3$); IR ($cm^{-1}$, KBr) 3500 (OH), 1750 (C=O); H¹ NMR (300 MHz, $CDCl_3$) δ (ppm) 4.52 (d, 1-H, J = 3.6 Hz, H-2), 4.41(dt, 1-H, J = 6.6 and 3.6 Hz, H-3), 4.08 (dd, 2-H, J = 6.6 and 0.6 Hz, H-4), 1.65, 1.57, 1.44 and 1.38 (4s, 12-H, 4Me); $^{13}$C (75 MHz, $CDCl_3$) δ (ppm) 169.9 (C-1), 111.1 and 110.4 ($\underline{C}Me_2$), 74.8 (C-2), 73.9 (C-3), 64.4 (C-4), 26.6, 26.1, 25.9 and 25.1 (4Me); HRFABMS $(M-15)^+$ 201.0775 (calcd = 201.0762).

**N-Benzyl-3,4-*O*-isopropylidene-D-erythronamide (6) -** A solution of **4** (500 mg, 2.31 mmoles), benzylamine (494 mg, 4.62 mmoles) in toluene (5 mL) was refluxed for 9 h. The solution was evaporated under reduced pressure forming a colorless oil which was dissolved in dichloromethane (10 mL), extracted with 10% HCl solution (2 x 5 mL), water (5 mL), and dried over anhydrous sodium sulfate. The solution was evaporated and the residue chromatographed on a silica gel column and eluted with hexane/ethyl acetate (7:3) yielding **6** as white solid (458 mg, 75 %). mp 67-68 $^{o}$C; $[\alpha]^{D}_{20}$ = -12 (c 0.66, $CHCl_3$); IR ($cm^{-1}$, KBr) 3440 and 3320 (OH and NH), 1650 (C=O); $^{1}$H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.38-7.26 (m, 5-H, Ph), 7.02 (bs, 1-H, NH), 4.58-4.45 (m, 2-H, $C\underline{H}_2Ph$), 4.12 (dd, 1-H, J = 6.9 and 3.0 Hz, H-2), 4.28 (q, 1H, J = 6.3 Hz, H-3), 4.10 (dd, 1-H, J = 8.7 and 6.3 Hz, H-4a), 3.99 (dd, 1-H, J = 8.7 and 6.3 Hz, H-4b), 3.42 (d, 1-H, J = 3.0 Hz, OH), 1.45 and 1.37 (2s, 6-H, 2-Me); $^{13}$C NMR (75 MHz, $CDCl_3$) δ (ppm) 170.9 (C-1), 137.6 (C-1'), 128.6, 127.4 and 127.3 (C-2', C-3', C-4'), 109.9 ($\underline{C}Me_2$), 75.9 (C-3), 70.6 (C-2), 66.0 (C-4), 43.2 ($\underline{C}H_2Ph$), 26.5 and 24.9 (2Me); HRFABMS $(M+1)^+$ 266.1392 (calcd = 266.1392).

D-**Erythronolactone** (**5**)- A solution of **4** (1.63 g, 7.6 mmoles) in methanol/ethyl acetate/water (1:1:1) was stirred at room temperature during 8 days and then evaporated under reduced pressure to yield **5** as white solid (896 mg, quantitative). mp 99-100 $^{o}$C (lit.[4g] 101-102 $^{o}$C); $[\alpha]^{D}_{20}$ -69.4 [c 0.5, $H_2O$; lit.[4g] $[\alpha]^{D}_{20}$ -72 (c 0.5, $H_2O$)]; IR ($cm^{-1}$, KBr) 3480 - 3200 (OH), 1770 (C=O); $^{1}$H NMR (300 MHz, $CDCl_3$) δ (ppm) 4.55 (d, 1-H, J = 4.5 Hz, H-2), 4.49-4.41 (m, H-3 and H-4); $^{13}$C NMR (75 MHz, $CDCl_3$) δ (ppm) 178.7 (C-1), 71.2 (C-2), 73.7 (C-4), 70.4 (C-3); LRFABMS m/z 119 $[(M+1)^+$, 28].

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