

An efficient synthesis of (S)-5-hydroxymethyl-2(5H)-furanone

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AN EFFICIENT SYNTHESIS OF (S)-5-HYDROXYMETHYL-2(5H)-FURANONE

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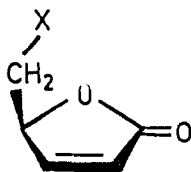
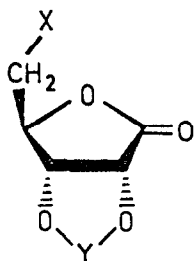
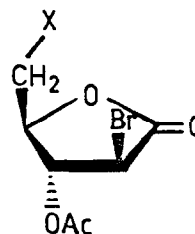
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Abstract: A three step synthesis of the title compound 1a from D-ribo-1,4-lactone in 48% yield is described. The concept centers on a novel NaHSO₃-induced trans-Br-OAc elimination of the readily prepared bromo-acetate mixture 3a,b to the corresponding butenolides 1e and 1f, the former of which, on hydrolysis and purification, yields pure 1a.

Title compound 1a and its derivatives 1b-d are valuable chiral starting materials for synthesizing natural products such as (+)-trans-burseran¹, (-)-isostegane¹, (+)-steganacin², (-)-verrucarinolactone³ and certain analogues of prostacyclin⁴ and chrysanthem acid⁴. Compounds 1a-c have been obtained⁵ from D-ribo-1,4-lactone and its 5-O-substituted derivatives by pyrolysis of the cyclic orthoformate esters 2a-c. Raney nickel desulfurization of 2d and 2e has given 1c⁶ and 1d⁴ respectively. The intermediacy of 1a during the hydrogenolysis of 2-bromo-2-deoxy-D-arabino-1,4-lactone to 4-(S)-hydroxymethyl-γ-butyrolactone has been demonstrated⁷. Non-carbohydrate-based routes have included a six-step synthesis of 1b,c from L-glutamic acid⁸ and of 1b via a route based on the asymmetric epoxidation of (Z)-4-benzyloxy-2-butenol⁹. A straightforward and operationally simple three-step synthesis of 1a from D-ribo-1,4-lactone is reported here.

Acetylated bromo-deoxyaldono-1,4-lactones, obtained by treating aldono-1,4-lactones with HBr in acetic acid (HBA), are useful carbohydrate intermediates¹⁰. Treatment of D-ribo-1,4-lactone (14.8 g, 0.10 mol) with HBA (65 mL of 33% soln)[2 h, room temp; dropwise addn of Ac₂O (65 mL); aq quenching, CH₂Cl₂ extraction and work-up after 2 more h]¹¹ gave an oily 6/1 mixture of 3a/3b (31.9 g): NMR (CDCl₃) δ 4.35 (d, CH₂OAc) / 3.72 (d, CH₂Br). This material in 2-PROH (300 mL) produced, on stirring with aq NaHSO₃ (41.6 g in 160 mL) [72 h, room temp; aq quenching, CH₂Cl₂ extraction, drying and solvent removal], a syrupy 6/1 mixture of 1e/1f (13.3 g): NMR (CDCl₃) δ 4.34 (d, CH₂OAc) / 3.72 (d, CH₂Br). Hydrolysis thereof [HCl 0.5M in MeOH, 100 mL; 18 h, 5°C; evaporation and chromatography (silica gel: CH₂Cl₂-EtOAc, 1:2)] then gave essentially pure, oily 1a (5.6 g; 48% overall): NMR (CDCl₃-CD₃OD, 3:1) δ 3.75 (dd, J = 12 and 4 Hz, 1H), 3.85 (dd, J = 12 and 4 Hz, 1H), 4.3 (s, 1H), 5.15 (tdd, J = 4, 2 and 1.5 Hz, 1H), 6.13 (dd, J = 5.5 and 2 Hz, 1H), 7.58 (dd, J = 5.5 and 1.5 Hz, 1H). Kugelrohr distillation provided material (bp 135°C/0.2 mm) solidifying at room temp: mp 39-41°C; [α]_D²⁰ -140° (c 3.18, H₂O)¹².

1 a-f2 a-e3 a,b

- 1 : a, X = OH; b, X = OCH₂Ph; c, X = OCPPh₃; d, X = OSi(t.Bu)Ph₂; e, X = OAc; f, X = Br.
2 : a, X = OH, Y = CHOEt; b, X = OCH₂Ph, Y = CHOEt; c, X = OCPPh₃, Y = CHOEt;
d, X = OCPPh₃, Y = C=S; e, X = OSi(t.Bu)Ph₂, Y = C=S.
3 : a, X = OAc; b, X = Br.

The NaHSO₃-induced elimination of 3a,b to butenolides 1e,f merits comment. Whereas NaHSO₃ has been mentioned only briefly as a method for bringing about a related trans-2-H-3-OAc elimination¹³, the trans-2-Br-3-OAc elimination described here appears to be unprecedented. Further aspects of the reaction, including its application to other bromo-aldonolactones, are currently under investigation and will be reported shortly.

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