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EFFICIENT SYNTHESIS OF (R)-5-(2-HYDROXYETHYL)-2(5H)-FURANONE FROM (R)-MALIC ACID

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Abstract. The title compound has been synthesized in five steps, 48% overall yield, from (R)-malic acid.

Current endeavours in these laboratories require derivatives of the branched sugars D-erythro-2,3,5-trideoxy-3C-hydroxymethyl (and mercaptomethyl)-hexofuranose (**1**) as chiral building blocks for the synthesis of analogs of nucleosides (**2**).[2,3]

1a, X= OR
1b, X= SR

B= A, C, G, U

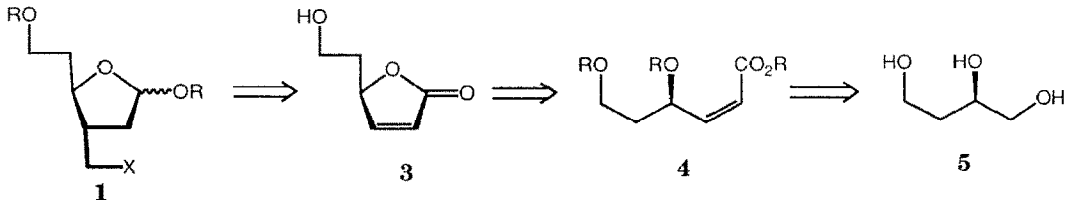
2

The branched-chain sugars[4] of type **1a** or **1b** could be synthesized through a Michael addition of an hydroxymethyl[5] or mercaptomethyl[6] synthetic equvalent to a derivative of the butenolide **3** (scheme 1). This compound has previously been synthesized in racemic form from trans-3-hexenedioic acid, and converted to the pheromone (±)-eldanolide[7]. The enantiomer of compound **3** has been prepared in a very low yield by Labelle and Guindon[8] as a side product in the studies of the mechanism of the iodoetherification reaction of 4,6-dihydroxy-2-hexenoic acid. While the work described here was in progress, Suemune el *al.*[9] reported the synthesis of **3** in 8 steps (6.5% overall yield) from 1,4-cyclohexadiene, using a lipase-mediated kinetic resolution as key step. Because this sequence is not entirely satisfactory for our purposes, we have developed a new route to compound **3.**

In this paper we report the synthesis of the title compound (**3**) in 5 steps and 48% overall yield from commercially avalaible (R)-malic acid. The synthesis of **3** also constitues a formal synthesis of natural (+)-eldanolide[7].

Our retrosynthetic plan is shown in *Scheme 1*.

Scheme 1



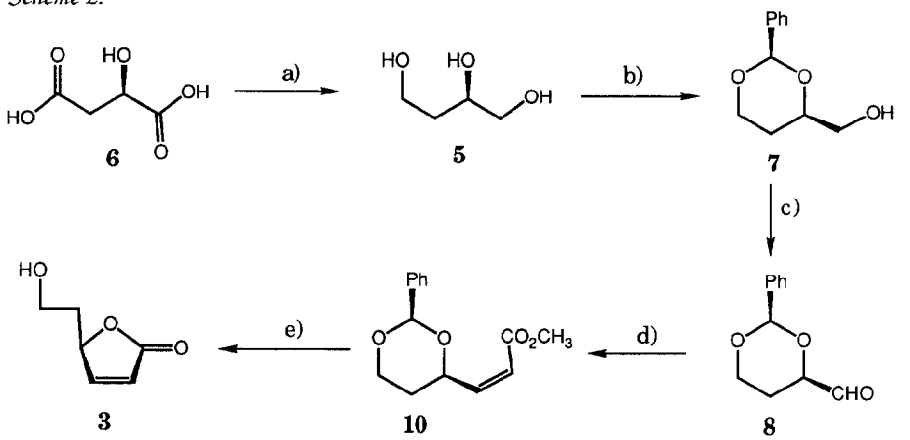
1 **3** **4** **5**

The sense of the chirality in compound **3** is the same as in (R)-1,2,4-butanetriol (**5**). To convert **5** to the butenolide **3**, it is necessary to protect selectively the hydroxy groups of C-2 and C-4 and to elongate the chain to a (Z)-α,β-unsaturated ester (compound **4**) These two goals could be achieved taking advantage of the known tendency of polyhydroxy-compounds to give 6-membered cyclic acetals when reacted with benzaldehyde under thermodinamically controlled conditions[10], and the Z-stereoselective Wittig reaction between α-alkoxy aldehydes and methoxycarbonylmethylenetriphenylphosphorane (**9**, *Scheme 2*) in methanol[11].

These two objectives were accomplished. The overall synthetic sequence is indicated in *Scheme 2*. Reduction of (R)-malic acid (**6**) with borane-dimethyl sulfide complex afforded (R)-1,2,4-butanetriol in 97% yield after chromatography.[12] The triol (6.3 g, 60 mmol) was refluxed with a slight excess of benzaldehyde and a catalytic amount of p-toluenesulfonic acid in toluene solution under a Soxhlet extractor charged with 4 Å molecular sieves[13] to give a 87% yield of the six membered ring acetal (**7**)[14], along with a trace amount of its epimer (the trans-dioxane) and a small amount of the regioisomeric dioxolanes (as a *ca.* 1:1 mixture of cis- and trans-diastereoisomers, overall yield of dioxolanes: 10%).

Compound **7**, after chromatographic purification, was summited to the conditions of the Swern oxidation[15] to give the aldehyde **8**, which was dissolved in dry methanol and reacted with the phosphorane **9** to afford a readily separable mixture of **10** and its E-stereoisomer in a 92:8 ratio in 62% overall yield from **7**. Compound **10** was treated with acetic acid/water at room temperature to give the target molecule **3** in quantitative yield

Scheme 2.



a) $BH_3.SMe_2$, $B(OMe_3)$, THF, 0° to rt., 97%, b) PhCHO (1.15 eq.), TsOH (0.015 eq.), toluene, 4 Å molec. sieves, reflux, 87%; c) $(COCl_2)$, DMSO, CH_2Cl_2, -60°; Et_3N, -60° to rt; d) $PH_3P{=}CHCO_2CH_3$ (**9**) (1.5 eq.), CH_3OH, -70° to rt, 57% (2 steps); e) $AcOH/H_2O$ (4:1, v/v), rt, 99%.

The synthesis reported above can be scaled up (starting from 30 g of (R)-malic acid) without loss in yield, and it provides multigram amounts of the butenolide **3**, which can be a useful chiral building block for the synthesis of branched-chain sugars as well as in the synthesis of biologically active natural products such as the cytotoxic alkaloid (+)-retronecine[16], and pheromones[17] related to (+)-eldanolide. Work along these lines is in progress.[18,19]

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18.- All the compounds reported in this paper show satisfactory spectroscopic data. Some selected analytical data are: **7** (thick oil): $[\alpha]_D$= -9.4 ($CHCl_3$, c=1.2); ^{1}H-NMR ($CDCl_3$): δ= 7.53-7.33 (m, 5H), 5.56 (s, 1H), 4.31 (ddd, 1.3, 5.2, 11.4, 1H), 4.09-3.92 (m, 2H), 3.72-3.65 (m, 2H), 2.10 (broad s, exchange with D_2O, 1H), 2.04-1.83 (m, 1H), 1.51-1.41 (m, 1H) ppm.; ^{13}C-NMR ($CDCl_3$): δ= 138.4 (s), 128.9 (d), 128.4 (2C, d), 126.1 (2C, d), 101.3 (d), 77.6 (d), 66.6 (t), 65.6 (t), 26.8 (t) ppm. **8** (thick oil): ^{1}H-NMR ($CDCl_3$): δ= 9.73 (s, 1H), 7.57-7.36 (m, 5H), 5.61 (s, 1H), 4.40-4.32 (m, 2H), 4.01 (dt, 2.9, 11.7, 1H), 2.06-1.76 (m, 2H) ppm.; IR ($CHCl_3$): υ= 1705 cm-1; MS: m/z= 193 (10), 192 (M^+, 65), 191 (76), 163 (20), 122 (73), 105 (100). **10**: m p.= 68-70° ; $[\alpha]_D$= -63.2 ($CHCl_3$, c=1.2); ^{1}H-NMR ($CDCl_3$): δ= 7.53-7.47 (m, 2H), 7.40-7.32 (m, 3H), 6.37 (dd, 7.1, 11.7, 1H), 5.84 (dd, 1 4, 11.7, 1H), 5 62 (s, 1H), 5.53 (m, 1H), 4.30 (m, 1H), 4.11 (dt, 3.3, 11.4, 1H), 3.75 (s, 3H), 1.95-1.76 (m, 2H). **3** (oil): $[\alpha]_D$= - 48.2 ($CHCl_3$, c=2.2) (lit.[9]: -46.4); ^{1}H-NMR ($CDCl_3$): δ= 7.57 (dd, 1.5, 5.7, 1H), 6.12 (dd, 2.0, 5.7, 1H), 5.28-5.24 (m, 1H), 3.91-3.69 (m, 2H), 2.10-2.02 (m, 1H), 1.90-1.82 (m, and broad s, 2H) ppm.; ^{13}C-NMR ($CDCl_3$): δ= 173.7 (s), 157.7 (d), 120.8 (d), 81.4 (d), 58.3 (t), 36.0 (t) ppm.; IR ($CHCl_3$): υ= 3480, 1755, 1600, 1165, 1105, 1065, 1050, 815 cm-1; MS: m/z= 129 (24), 128 (M^+, 24), 110 (68), 99 (67), 97 (61), 82 (100).

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