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# Concise synthesis of enantiopure *erythro*-saccharinic acid lactone and potassium (2*R*,3*R*)-2,3,4-trihydroxy-2-methylbutanoate

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**Abstract**—A short and efficient approach was applied to the total synthesis of *erythro*-saccharinic acid lactone and the leaf-closing substance potassium (2*R*,3*R*)-2,3,4-trihydroxy-2-methylbutanoate from a 2-*C*-hydroxymethyl-D-erythrose derivative, using a combined strategy.


Potassium (2*R*,3*R*)-2,3,4-trihydroxy-2-methylbutanoate (**1**, Fig. 1), a leaf-closing substance of the leguminous tropical plant *Leucaena leucocephalam*, was recently isolated by Ueda et al.[1] In general, most of the plants belonging to the legume family keep their leaves closed during the night and open them in the morning.[2] This phenomenon, controlled by their internal biological clocks, is called nyctinasty.[3] Practically, this circadian rhythmic movement of the leaves is regulated by the interaction of leaf-opening and leaf-closing bioactive compounds. Since nyctinasty is very important for the survival of these legumes and the active factors usually differ from plant to plant, these compounds could be used as ecological friendly herbicides.[1,4] Specifically, *L. leucocephalam* poses a serious threat to the environment because it grows rapidly and inhibits the growth of surrounding plants by the secretion of allelochemicals.[5] This results in the disruption of the ecosystem and a selectively effective herbicide against it is desirable.


**Figure 1.** Structures of targeted natural products **1** and (−)-**2**.

On the other hand, 2-*C*-methyl-D-erythrono-1,4-lactone [or *erythro*-saccharinic acid lactone, (−)-**2**, Fig. 1] is the first aldonolactone isolated from plants which, not surprisingly, are members of the leguminosae family: *Astragalus lusitanicus* L.[6a] (a plant which shows a high degree of toxicity for cattle) and *Cicer arietinum* L.[6b] (a valuable source of protein and oil in semi-arid tropical regions). Later, the same compound was found in other plant extracts[6c] and identified as an oviposition stimulant of the butterfly *Papilio bianor* from *Orixa japonica*[6d] and as a metabolite of the 1-deoxy-D-xylulose biosynthetic pathway of plants.[6e] Obviously, lactone (−)-**2** is structurally related to butanoate **1** and, in fact, is probably the natural precursor of the latter. Enantiopure (−)-**2** is also a potential useful chiral building block in the synthesis of other natural products.[7]

Lactone (−)-**2** was previously synthesized using either chiral pool approaches[7,8] or via an asymmetric aldol reaction.[9] There was until lately only one precedent synthesis of **1** by Gogoi and Argade, but as the racemate.[10] During our on-going synthesis, the same group[11] reported the preparation of both **1** and (−)-**2** in optically pure form via an enzyme catalyzed reaction.

In continuation of our natural product synthesis, employing acetonides of D- and L-erythroses as starting materials,[12] we report here a new and very efficient approach for the synthesis of enantiopure **1** and (−)-**2**.

Since **1** could be prepared upon saponification of (−)-**2**, we envisaged a retrosynthetic strategy using lactone **3** as an advanced precursor (Scheme 1). This compound

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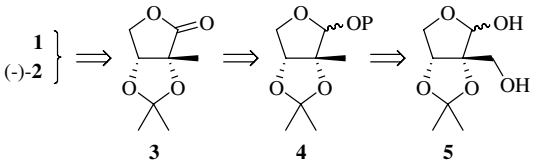
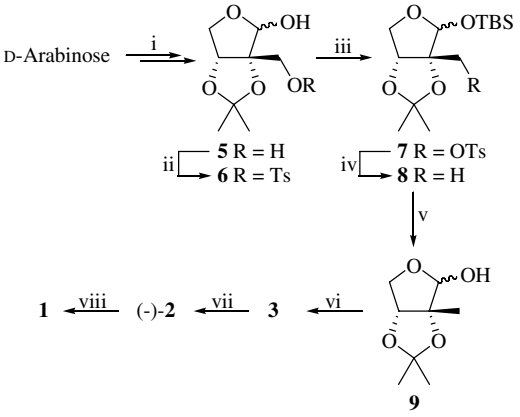



**Scheme 1.** Retrosynthetic analysis.

could derive from the protected lactol **4** (P = a suitable protecting group), which in turn could derive from D-erythrose derivative **5**. The latter is easily accessible from D-arabinose and has undoubtedly the correct stereochemistry at the quaternary carbon centre.

Indeed, hydroxymethyl erythrose **5**, available in multigram quantities from D-arabinose,[13] was initially derivatized to give tosylate **6** under mild conditions (Scheme 2). It is noteworthy that under these conditions the corresponding bis-tosylate was formed only in traces. Next, the hemiacetal hydroxy group of **6** was protected yielding a mixture of C-1 epimeric silyl ethers **7** (α and β anomers in a ratio of ca. 3:1). Although it was very easy to chromatographically separate these two isomers, there was practically no need to do so since both were equally useful for the on-going synthesis. Therefore, the mixture of **7** was subsequently reacted with $LiAlH_4$ in THF under reflux.[14] In this way, the 2-*C*-methyl-erythrose derivatives **8** were obtained in a very good combined yield. The removal of the silyl protecting group was performed under neutral conditions to afford lactols **9**, almost quantitatively. The latter were smoothly oxidized to give lactone **3**.[15] The completion of the synthesis was accomplished by a two-step procedure involving initially, removal of the acetonide group upon treatment with trifluoroacetic acid [to give (−)-**2**] and finally saponification on treatment with aqueous potassium hydroxide (to yield **1**). Both compounds were found to have identical physical and spectroscopic data




**Scheme 2.** Synthesis of (−)-**1** and **2**. Reagents and conditions: (i) Ref. 13; (ii) TsCl, pyridine, rt, 90%; (iii) TBSCl, imidazole, $CH_2Cl_2$, rt, 98%; (iv) $LiAlH_4$, THF, 60 °C, 96%; (v) TBAF, AcOH, THF, 0 °C to rt, 99%; (vi) $CrO_3$, pyridine, $Ac_2O$, $CH_2Cl_2$, rt, 89%; (vii) TFA, $H_2O$, 0 °C to rt, 95%; (viii) KOH, $H_2O$, 0 °C to rt, 99%.

with those reported in the literature.[16] {For (−)-**2**: $[\alpha]_D$ −60.2 (*c* 0.3, $H_2O$), lit.[7] $[\alpha]_D$ −61.2 (*c* 0.2, $H_2O$)}.[17]

Furthermore, there is another point of interest regarding the above described synthesis. The enantiomer of (−)-**2** is equally easy accessible in optically pure form using the same sequence of reactions but starting from L-arabinose.[18] This task was also investigated and (+)-**2** was obtained in a similar overall yield.[19] {For (+)-**2**: $[\alpha]_D$ +58.8 (*c* 0.5, $H_2O$), lit.[11] $[\alpha]_D$ +58.5 (*c* 0.5, $H_2O$)}.

In conclusion, the work described in this article presents a short and efficient synthetic approach towards the preparation of two natural products, (2*R*,3*R*)-2,3-dihydroxy-2-methyl-γ-butyrolactone [(−)-**2**] and potassium (2*R*,3*R*)-2,3,4-trihydroxy-2-methylbutanoate (**1**), making use of readily available, multigram quantities of D-arabinose derived chiron **5** and employing a combined retrosynthetic chiral pool route. The overall yields for both targets were approximately 70% in a six-step sequence involving relatively simple and inexpensive procedures.

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15. Compound **3** was found to have identical $^{1}H$ and $^{13}C$ NMR spectra with those reported in Ref. 7; $[\alpha]_D$ −82.0 (*c* 2.0, acetone).
16. For (−)-**2** see Ref. 7; for **1** see Refs. 1, 10 and 11.
17. It was practically impossible to obtain an optical rotation for **1** in $H_2O$ since this compound slowly decomposes at near neutral pH. See Refs. 1 and 10.
18. For the preparation of the enantiomer of **5** from L-arabinose see Ref. 12b.
19. $^{1}H$ and $^{13}C$ NMR spectra were identical with those of (−)-**2**.