Taming Carbohydrate Complexity: A Facile, High-Yield Route to Chiral 2,3-Dihydroxybutanoic Acids and 4-Hydroxytetrahydrofuran-2-ones with Very High Optical Purity from Pentose Sugars

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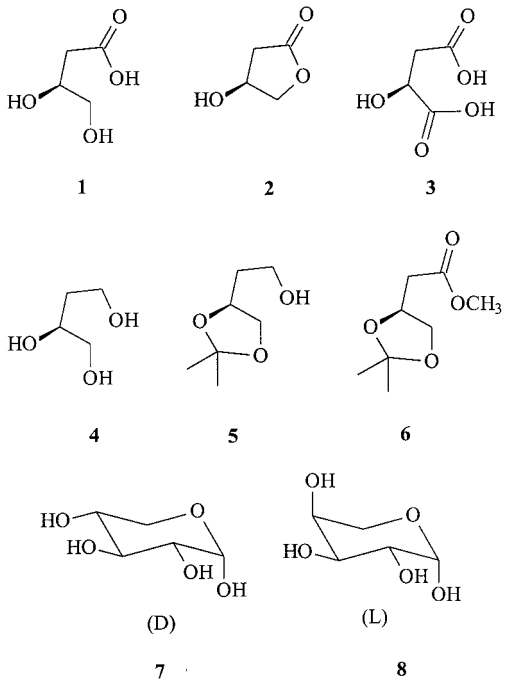
(*S*)-3,4-Dihydroxybutanoic acid and its γ-lactone ((*S*)-4-hydroxytetrahydrofuran-2-one) are important four-carbon synthons obtainable from some substituted D-hexose sugars and from L-malic acid. Until now there has been no easy route to the *R*-isomers because of the rarity both of suitably substituted L-hexose sugars and D-malic acid. Here we describe a method for preparing both enantiomeric forms of the free acids and their corresponding γ-lactones from pentose sugars.

The *S*-isomers of 3,4-dihydroxybutanoic acid (**1**, Chart 1) and the corresponding γ-lactone **2** have recently been used in the preparation of a chiral membrane probe,[1] pH-sensitive liposomes,[2] drug intermediates,[3−5] advanced two-dimensional supramolecular systems,[6] and azetidinones.[7] These same molecules or close derivatives from (*S*)-malic acid (hydroxybutanedioic acid) **3** have been used to prepare a variety of chiral substructures and pharmaceutical intermediates.[8−14] Compounds **1** and **2** were obtained by the selective oxidative cleavage of 4-linked hexopyranose sources such as lactose, starch, cellulose, cellobiose, maltose, and maltodextrins.[1] In the preparation of **1** and **2** by this method, the chiral centers are derived from the 5-position of a hexose that always has the D-configuration. The mechanism of the reaction involves the isomerization of the reducing aldose sugar to a ketose, which readily affords a 2,3-diketone by β-elimination of the 4-alkoxy function and tautomerization of the enol so formed. The diketone is cleaved by peroxide anion to yield the products.[15]

Chart 1



The preparation of **1** and **2** from malic acid often involves the reduction of the acid to the corresponding butanetriol (**4**) followed by conversion to (*S*)-4-hydroxymethyl-2,2-dimethyl-1,3-dioxolane (**5**). The lone alcohol function is often oxidized to the level of an acid or aldehyde. The triol **4** and derivatives are readily obtainable from **1** by a simple reduction (with half as many equivalents compared to the malic acid case). Treatment of **1** with 2,2-dimethoxypropane and methanol with a trace of acid easily affords the 4-carboxymethyl-1,3-dioxolane **6** without the expense of the reduction and oxidation steps required if malic acid were used. Compounds **1** and **2** therefore allow access to a wide spectrum of optically pure three- and four-carbon synthons with very well-established uses.

Because the abundant naturally occurring hexoses have the D-configuration, it has not been possible to use this chemistry to access the complimentary range of compounds that can be afforded by the (*R*)-lactone. Two of the pentose sugars, arabinose (**7**) and xylose (**8**), occur abundantly as both the D- and the L-forms. L-Arabinose is especially abundant and is a predominant component of the complex carbohydrates found in sugar beet pulp and some wood pulp residues. Substitution of the 3-position of L-arabinose with a good leaving group such as an acetal ring residue should make it susceptible to alkaline peroxide oxidation to yield the (*R*)-dihydroxybutyric acid (Scheme 1) through the formation of an α-dicarbonyl intermediate. This is assuming that conditions can be found in which the myriad of possible competing reactions such as oxidation of the aldehyde group or aldol condensations do not compete. Acetals afford a quick

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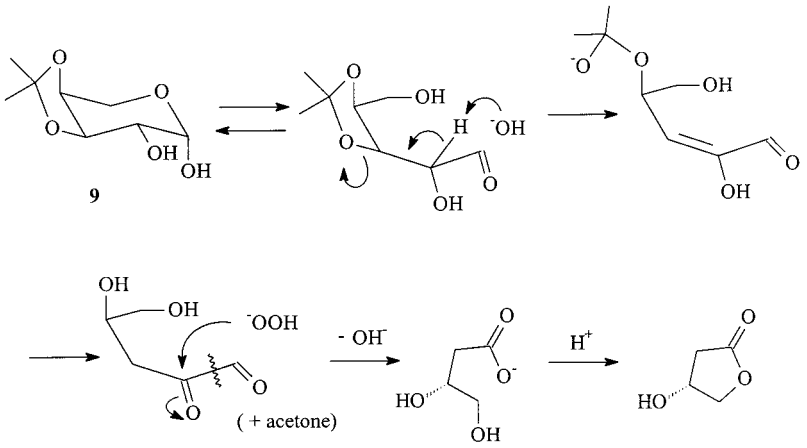
Scheme 1



straightforward way of selectively functionalizating hydroxyl groups, even in complicated molecular systems with several hydroxyl groups. The 3,4-*O*-isopropylidene acetal **9** can be prepared simply and in very high yield (>90%) from L-arabinose.[16] The oxidation of pentose acetals (or indeed any sugar acetals) to yield these products has never been described. Oxidation of **9** with hydrogen peroxide and sodium hydroxide under the conditions described before[1] readily yielded (*R*)-3,4-dihydroxybutanoic acid in >85% yield and 99.5% ee. Oxidation of the acetal of the D-sugar gave the corresponding (*S*)-lactone in the same yield and optical purity. The 3,5-*O*-isopropylidene acetals of xylose[16] also gave good conversion to the corresponding enantiomeric acids. The oxidation could be extended to the less attractive 2,3-acetal of D-ribose,[16] which also gave (*S*)-3,4-dihydroxybutanoic acid, but in much lower yield. 3-*O*-Galactosyl D-arabinose is also commercially available and is a good 3-linked pentose source to which this oxidation can be applied to yield (*S*)-3,4-dihydroxybutanoic acid.

Despite their availability and chiral richness, carbohydrates are still grossly underutilized as raw materials for fine chemistry. The oxidation of carbohydrates to yield (*S*)-3,4-dihydroxybutanoic acid and derivatives[1,15,17] is an important step forward in renewable resource chemistry. Here we provide for an expansion of renewable raw material resources and a broader stereochemistry palette which should considerably further our advancement toward a carbohydrate-based chiral chemistry. This method is superior in yield and far more simple than the other carbohydrate route that utilizes D- and L-ascorbic acid in a complex seven-step process that involves mesylation, halogenation, and a hydrogenation step.[18]

Experimental Section

Typical Procedures for Oxidation. 3,4-*O*-Isopropylidene-L-arabinose (30 g) was treated with 2700 mL of 0.36% sodium hydroxide and 27 g of 30% hydrogen peroxide. The mixture was heated at 65 °C for 10 h, neutralized, extracted with 1 volume of ethyl acetate, concentrated to a syrup, acidified to pH 1 with 6 M sulfuric acid, and concentrated at 40 °C until no more solvent was removed. The syrup was extracted with 1.5 L of ethyl acetate. The ethyl acetate layer was concentrated to yield 15.5 g (96%) of (*R*)-3-hydroxy-γ-butyrolactone. The product was >90% pure by gas chromatography and could be purified by silica chromatography using 9:1 chloroform:methanol. Chiral GC analysis on a cyclodextrin phase (Supelco Betadex) showed >99.8% of the *R*-isomer: ^{1}H NMR (300 MHz, D-chloroform) δ 2.28 (1H, dd, J = 18.0 + 0.2 Hz), 2.73 (1H, dd, J = 18.0 + 5.8 Hz), 4.13 (1H, dd, J = 9.8 + 0.2 Hz), 4.31 (1H, dd, J = 9.8 + 4.5 Hz, 4.48, (1H, m); ^{13}C NMR (75 MHz) 177.1, 76.8, 67.8, 37.7, $[\alpha]_D$ +87.4 (c = 3.1, ethanol), lit.[19] $[\alpha]_D$ +86°.

In an alternative procedure, the oxidation was carried out on 60 g of 3,4-*O*-isopropylidenearabinose, and the volumes of the liquid were considerably reduced, but the desired concentration of hydrogen peroxide and sodium hydroxide maintained by pumping in the solutions. The acetal was dissolved in 800 mL of water. Sodium hydroxide (40 g) dissolved in 300 mL of water and hydrogen peroxide (60 g) dissolved in 300 mL of water, were added to the heated solution (56 °C) over a 6 h period. Heating was continued for a further 3 h after the addition was completed. The product was isolated as the lactone as described above. The yield and purity were similar.

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