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Decarboxylative Cascade Reactions of Dihydroxyfumaric Acid: A Preparative Approach to the Glyoxylate Scenario

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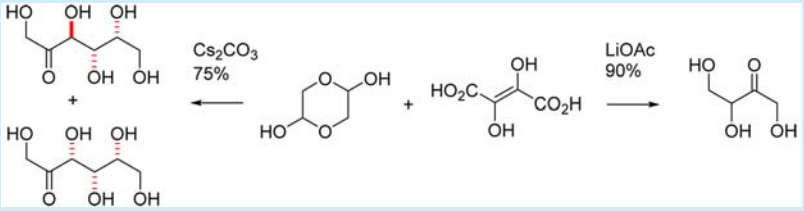
Supporting Information



ABSTRACT: An operationally simple protocol is reported to generate an α-hydroxyacyl anion by the decarboxylation of dihydroxyfumaric acid. To date, the "missing" utilization of the hydroxyacyl anion in highly chemo- and stereoselective cascade reactions enables short and direct construction of carbohydrates.

The α-hydroxyacetyl structure is widespread in natural products and bioactive molecules. It is present in many natural products, such as steroids and carbohydrates.[1] A synthon to this functionality is the α-hydroxyacyl anion. A synthetic equivalent to this α-hydroxyacyl anion is the "umpoled" hydroxyacetaldehyde.[2]

By the 1,2-addition of this umpoled hydroxyacetaldehyde to carbonyl compounds, direct access to α-hydroxyl carbonyl compounds is given. However, generation of a hydroxy acyl anion equivalent is far from a simple transformation.[3] Instead, it is still a challenge for an organic chemist. There are only a few reports that describe the construction of the α-hydroxyl carbonyl functionality in carbohydrates by metal-containing reagents.[4] These are multistep procedures, and they are mostly connected with an excess of metal-organic reagents and with extensive use of protective groups.[5] For organo-catalyzed retro-formose reactions that generate an acyl anion from unprotected carbohydrates as formaldehyde equivalents, see ref 6. For aldol-based approaches to pentoses and hexoses, see ref 7.

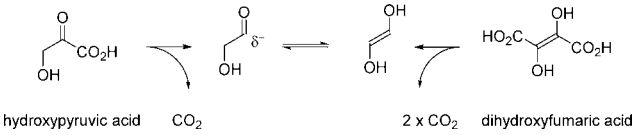
In contrast to these rare examples of the chemical synthesis, a hydroxyacyl anion can easily be generated by enzymatic decarboxylation of hydroxypyruvic acid. Formation of the hydroxyacyl anion is usually catalyzed by transketolases. By a subsequent 1,2-addition to a carbonyl compound, corresponding aldol products are observed with mostly high enantioselectivities.[8] By a combination of this enzymatic aldol reaction with a transamination process, optically pure 1,2-amino alcohols are accessible.[9] These methods, however, are limited to defined substrates.

Recently, direct and amine-catalyzed access to α-hydroxyacyl anions was elaborated utilizing hydroxypyruvic acid or its lithium salt. An approach to optically active carbohydrates is given when used with chiral aldehydes in this operationally simple decarboxylative reaction.[10]

At the same time, Krishnamurthy et al. reported analytical investigations of decarboxylative reactions of the dilithium salt of dihydroxyfumaric acid.[11] Their studies of the decarboxylative reaction of dihydroxyfumaric acid with small hydroxylated aldehydes support the Eschenmoser "glyoxylate scenario". This glyoxylate scenario proposes dihydroxyfumarate and glyoxylate as crucial constituents of primordial metabolisms.[12]

With two decarboxylative steps of dihydroxyfumaric acid, access to a hydroxyacyl anion, which can act as a nucleophile, is given. On the other hand, the same synthon, the α-hydroxy acylanion, can be obtained by decarboxylation of hydroxypyruvic acid (Scheme 1). Both decarboxylative pathways are important transformations in the metabolism of pentoses and are both catalyzed by transketolases.[13]

Scheme 1. Formation of a Hydroxyacyl Anion by Decarboxylation



However, no preparative exploitation of decarboxylation of dihydroxyfumaric acid in reactions with aldehydes has been reported so far. To explore the potential for such usage, in initial experiments, we tested reaction conditions that have been utilized in decarboxylative reactions of pyruvic acid.[10a] A reaction was not observed with catalytic or equimolar amounts of amines or amino acids. These results strongly contrast those that were obtained by decarboxylative aldol reactions of α- or β-keto acids.

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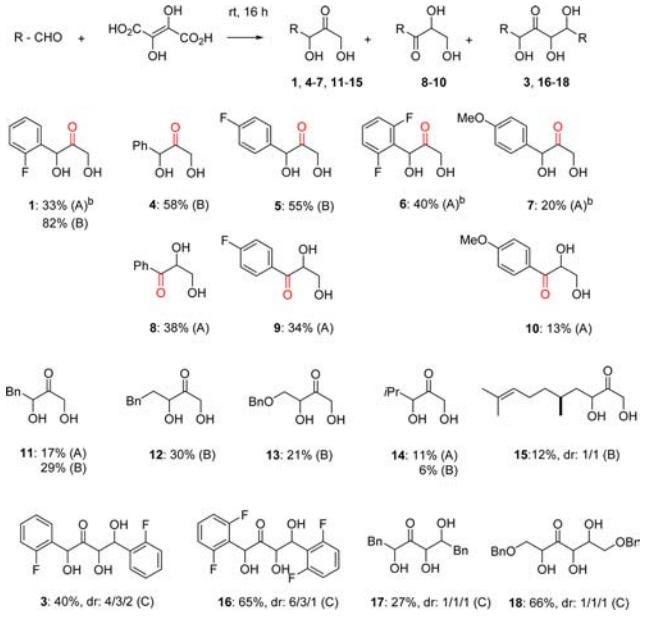
Similar to reactions with lithium hydroxypyruvate, we reacted isolated dilithium salt of dihydroxyfumaric acid and 2-fluorobenzaldehyde as substrates.[14] This reaction was carried out at room temperature in water/dioxane (3/2). Under these conditions, a decarboxylative aldol reaction was observed. A mixture of monosubstituted products **1**, corresponding tautomerized propiophenone **2**, and disubstituted dihydroxyacetone **3** was detected in an overall yield of 50% after 16 h.[15] The same results with regard to the yields and ratios of products **1**−**3** were obtained by the operationally simple in situ formation of the lithium salt of dihydroxyfumaric acid. To this end, further optimization was carried out by application of this in situ protocol. In a first series, we tested several different carbonates in reactions of dihydroxyfumaric acid with 2-fluorobenzaldehyde, which produced similar yields. Moreover, an extremely high regioselectivity was observed when cesium carbonate was used in these reactions. In contrast to reactions with the dilithium salt of dihydroxyfumaric acid, the substituted dihydroxyacetone **1** was detected as the only product (33%). Further optimization revealed a strong increase of yields when lithium salts of organic acids were used instead of the corresponding carbonates. Substituted dihydroxyacetone **1** was observed as the only product in reactions with 2-fluorobenzaldehyde. This product was obtained with good to high yields with lithium salts of tartaric acid (80%), citric acid (64%), lactic acid (55%), or malic acid (69%). Using 3 equiv of lithium acetate, substituted dihydroxyacetone **1** was isolated as the only product with 82% yield (method B, Scheme 2).[15] In these reactions, the great enhancement of yields, compared to that with deployment of basic salts of dihydroxyfumaric acid, is consistent with observations made in the decarboxylation of dihydroxyfumaric acid under different pH media.[16] The competing decarboxylative self-aldol reaction of dihydroxyfumaric acid can be suppressed when this decarboxylative aldol reaction is carried out under slightly acidic conditions (pH ∼3−4).

Scheme 2. Decarboxylative Aldol Reactions of Dihydroxyfumaric Acid with Aromatic Aldehydes[a]



[a]Method A: 1.5 equiv of Cs_2CO_3, 1.2 equiv of dihydroxyfumaric acid, 50 mol % of brucine, H_2O/dioxane, 1.0 equiv of aldehyde. Method B: 3.0 equiv of LiOAc, 1.5 equiv of dihydroxyfumaric acid, H_2O/dioxane, 1.0 equiv of aldehyde. Method C: 1.5 equiv of Cs_2CO_3, 1.0 equiv of dihydroxyfumaric acid, 50 mol % of brucine, H_2O/dioxane, 3.0 equiv of aldehyde. [b]Method A without brucine. Isolated yields; dr determined by ^1H NMR.

With the optimized conditions in hand, we tested several aromatic aldehydes in these decarboxylative aldol reactions. The electronic nature of the aldehydes dictates the yields obtained. In reactions with electron-rich aldehydes (anisaldehyde), the expected substituted dihydroxyacetone **7** was detected in low yields (20%), whereas in reactions of 2-fluorobenzaldehyde, aldol adduct **1** was isolated in high yields (82%, Scheme 2). A clear and selective access to the regioisomeric dihydroxypropiophenones **8**−**10** was achieved by an amine-catalyzed ene-diol tautomerization of the initially formed substituted dihydroxyacetones. When used with catalytic amounts of brucine, a one-pot procedure for the formation of **8**−**10** was elaborated (method A, Scheme 2). Interestingly, this tautomerization was not observed even when used with isolated hydroxyacetone **1** or **6** under these conditions.

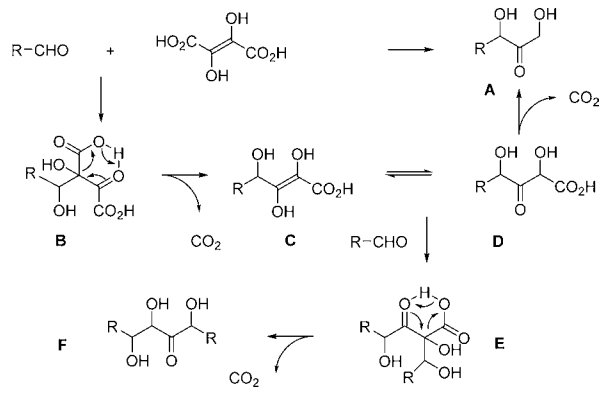
To explore the scope and limitations of this protocol, we tested several different enolizable aldehydes as substrates in these reactions. In general, the corresponding substituted dihydroxyacetones **11**−**15** were obtained with yields lower than those observed in reactions with aromatic aldehydes. Substituted dihydroxyacetone **15**—aldol adduct of dihydroxyfumaric acid and (*S*)-citronellal—was isolated as a 1/1 diastereomeric mixture. Tautomerization to the corresponding dihydroxypropanones, as observed by deployment of aromatic aldehydes, was not detected in this series.

When used with excess corresponding aldehydes, disubstituted dihydroxyacetones **3** and **16**−**18** were obtained. These compounds were isolated as diastereomeric mixtures of three stereogenic carbon atoms, which were installed during this decarboxylative cascade reaction (method C).

The following reaction mechanism is proposed: attack of the aldehyde on the ene-diol structure of dihydroxyfumaric acid yields intermediate **B**. Subsequent decarboxylation resulted in formation of intermediate **C**. Ene-diol **C** sets the stage for a following tautomerization to *β*-keto acid **D**. Following this path, formation of product **A** is observed. On the other hand, a second attack of the aldehyde is possible. *β*-Keto acid **E** is the intermediate for a second decarboxylation. This resulted in the formation of disubstituted hydroxyacetone **F** (Scheme 3).

The following example of these reactions sheds more light on the reaction mechanism: hydroxyacetaldehyde was also used as a substrate in these transformations (drawn as a dimeric structure

Scheme 3. Proposed Mechanism of the Decarboxylative Aldol Reaction of Dihydroxyfumaric Acid



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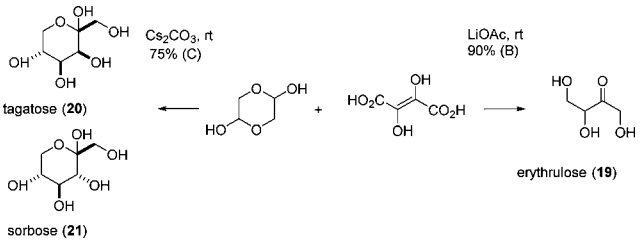
in Schemes 4 and 5). High regio- and chemoselectivities were observed in these experiments. Erythrulose **19** was obtained as the only product in nearly quantitative yields by deployment of lithium acetate (90%). In contrast, when used with cesium carbonate, tagatose **20** and sorbose **21** were identified in a ratio of nearly 1/1 (75% yield). Also, the same high yields and stereoselectivities were obtained by direct aldol reactions of **19** with hydroxyacetaldehyde under the same conditions.

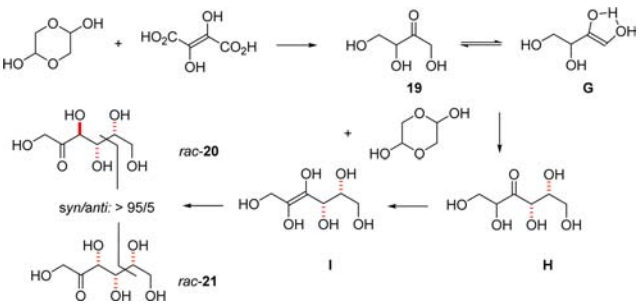
Scheme 4. Decarboxylative Aldol Reaction with Hydroxyacetaldehyde[a]



[a]Tagatose **20** and sorbose **21** were isolated and analyzed as their tetraacetates.[14]

A subsequent decarboxylative aldol/aldol/Ekenstein rearrangement cascade mechanism can be assumed for the formation of tagatose **20** and sorbose **21**. Decarboxylative aldol addition of hydroxyacetaldehyde and dihydroxyfumaric acid in the presence of lithium acetate yields **19**. A second aldol addition of hydroxyacetaldehyde with the intermediately formed **19** takes place only in the presence of cesium carbonate. This second aldol step proceeds with an extremely high degree of stereoselectivity. Only *syn*-configured product **H** was formed during this C−C bond formation. A requirement for this configurative outcome is the intermediately formed (*Z*)-enol **G**. A subsequent Ekenstein rearrangement takes place via the ene-diol **I**.[17] As a consequence, the corresponding **20** and **21** were formed with a high degree of diastereoselectivity (dr >95/5, Scheme 5). An epimerization of tagatose or sorbose was not observed under these reaction conditions.

Scheme 5. Cascade Mechanism for the Formation of Tagatose

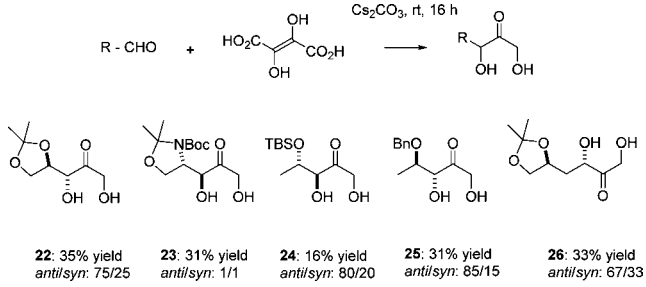


Several results of this investigation support these considerations. Erythrulose **19** was isolated with 90% yield when used with lithium acetate (method B, Scheme 4). In contrast, when used with benzyloxyacetaldehyde, a strong decrease of yields is observed under the same reaction conditions. The intramolecular activation of the carbonyl group of hydroxyacetaldehyde by hydrogen bonds does not occur when used with protected hydroxyacetaldehydes (e.g., benzyloxyacetaldehyde). As a result, aldol adduct **13** of benzyloxyacetaldehyde is observed with only 21% yield (Scheme 2). Similar trends for the outstanding reactivity of hydroxyacetaldehyde compared to that of the protected hydroxyacetaldehyde were reported for enzymatic aldol reactions.[18]

Furthermore, in contrast to the selective formation of tagatose **20** and sorbose **21** (Scheme 4), an unselective mixture of three diastereoisomers was detected in the decarboxylative reaction of benzyloxyacetaldehyde with dihydroxyfumaric acid under the same conditions (**18**, dr 1/1/1, Scheme 2). An Ekenstein rearrangement was not observed with benzyloxyacetaldehyde in these reactions. Subsequent cyclization to the corresponding hemiketal failed to occur.

Finally, we tested chiral oxygen-containing aldehydes in these decarboxylative aldol reactions. The corresponding substituted dihydroxyacetones **22**−**26** were isolated with good *anti*-diastereoselectivities (Scheme 6). By deploying such chiral

Scheme 6. Decarboxylative Aldol Reactions with Chiral Oxygen-Containing Enolizable Aldehydes[a]



[a]Method A: 2.25 equiv of Cs_2CO_3, 1.5 equiv of dihydroxyfumaric acid, H_2O/dioxane, 1.0 equiv of aldehyde; dr determined by ^1H NMR.

oxygen-containing aldehydes, an operationally simple access to enantiopure ketohexoses or ketopentoses is given. Racemization during the aldol reaction was not observed under these mild reaction conditions.

In summary, an operationally simple protocol was elaborated to generate the hydroxyacyl anion. Utilizing dihydroxyfumaric acid in decarboxylative aldol additions, we determined an easy access to this "umpoled" equivalent. This direct decarboxylative aldol reaction provides shortcuts for existing multistep routes to a keto-triol moiety in natural products, as this is true for different carbohydrates or for the synthesis of schweinfurthinol.[19] When used with chiral aldehydes, optically pure substituted dihydroxyacetones are obtained.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01287.

Experimental details (PDF)

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Notes

The authors declare no competing financial interest.

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