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A simple and practical approach to enantiomerically pure (*S*)-3-hydroxy-γ-butyrolactone: synthesis of (*R*)-4-cyano-3-hydroxybutyric acid ethyl ester

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Abstract—The oxidation of α- or β-(1,4) linked disaccharides or oligosaccharides with cumene hydroperoxide in the presence of a base gave (*S*)-3,4-dihydroxybutyric acid, which was cyclized under acidic conditions to furnish (*S*)-3-hydroxy-γ-butyrolactone. This was subsequently converted into (*R*)-cyano-3-hydroxybutyric acid ethyl ester, an intermediate for statin based drugs and other related compounds.

1. Introduction

(*S*)-3-Hydroxy-γ-butyrolactone is an important synthetic intermediate for a variety of chiral compounds. It serves as key intermediate for the preparation of neuromediator (*R*)-GABOB, L-carnitine,[1] and HMG-CoA reductase inhibitor, CI-981.[2] (*S*)-3-Tetrahydrofuran derived from 3-hydroxy-γ-butyrolactone is an intermediate for an AIDS drug.[3] (*S*)-3-Hydroxy-γ-butyrolactone has been reported as a satiety agent as well as a potentiating agent to neuroleptic drugs.[4] Its utility as a synthetic intermediate for a variety of natural products is well documented.[5]

The synthesis of (*S*)-3-hydroxy-γ-butyrolactone has been accomplished by employing various synthetic strategies. A commonly used strategy for its synthesis and for its intermediate (*S*)-3-hydroxybutyric acid derivatives is from the enzymatic or catalytic β-keto ester reduction.[6] It has also been prepared from the selective reduction of L-malic acid ester.[7] There have been reports of its synthesis from carbohydrate sources as well, either using just a base or a combination of a base and an oxidant. The treatment of a carbohydrate containing glucose substituent in the 4-position, such as cellobiose, amylose, and cellulose with alkali, has been shown to produce a low yield of the desired material along with D,L-2,4-dihydroxybutyric acid, glycolic acid, isosaccharinic acid, ketones, diketones, glycolic acid, and a plethora of other degradation and condensation products.[8] Similarly, the alkaline oxidation of a carbohydrate containing a glucose substituent at the 4-position is known to give a dicarbonyl compound, which is then oxidized to furnish (*S*)-3,4-dihydroxybutyric acid.[9] The yield reported for the desired compound is very low due to the formation of a large number of by-products.

Defunctionalization of a carbohydrate has been attracting much attention as a useful synthetic tool for the enantioselective synthesis of a variety of compounds. The synthesis of a chiral compound with a desired number of stereogenic centers could be achieved by eliminating the unneeded stereogenic centers quickly from the carbohydrate precursors. Though a large number of small scale complex syntheses of (*S*)-3-hydroxy-γ-butyrolactone have been developed, the majority of these methods suffer from drawbacks such as multi-step synthesis, long reaction times, high temperature, enzymatic methods, and use of expensive metal catalysts for the reduction of the prochiral center, side reactions, low enantiomeric purity, and overall low yield of product. Therefore, there is genuine need for a simple and inexpensive method for the large-scale preparation of (*S*)-3-hydroxy-γ-butyrolactone and its derivatives.[10] We, herein, report the synthesis of the title compound

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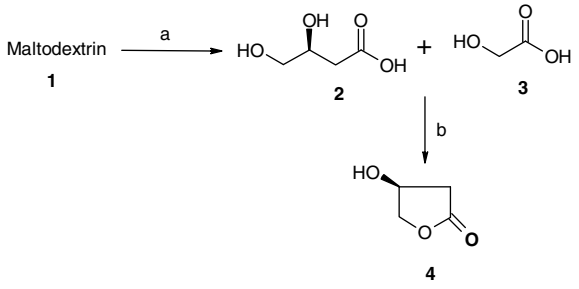
by employing the oxidation of a 1,4-linked D-hexose sugar under basic conditions.

2. Results and discussion

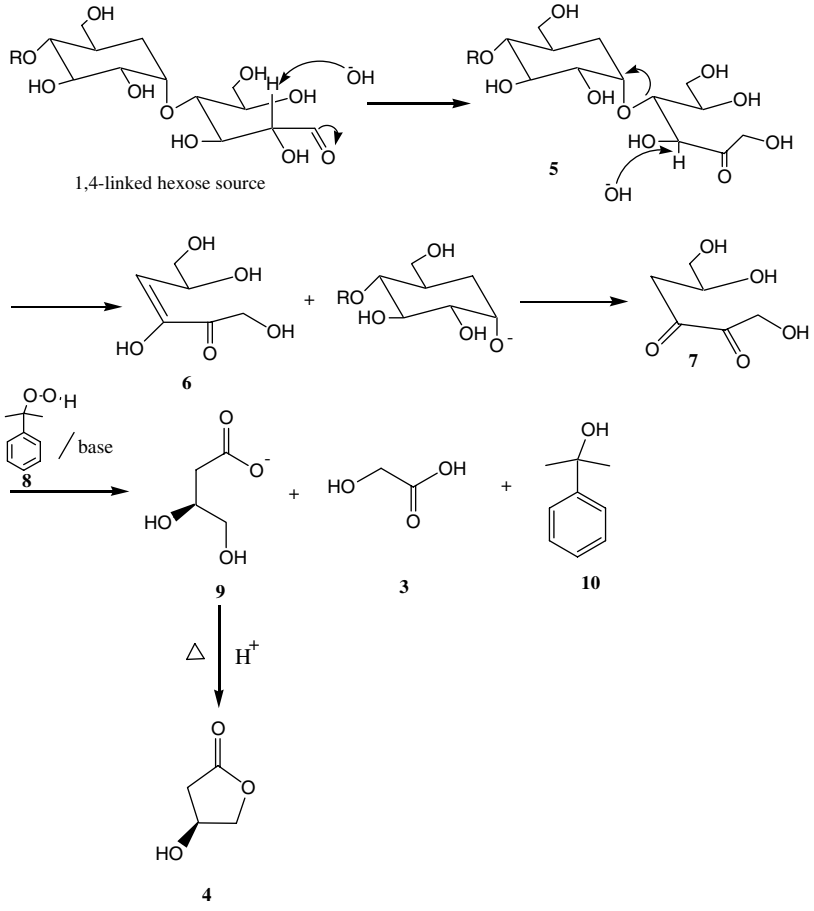
The synthesis of (*S*)-3-hydroxy-γ-butyrolactone started from the readily available carbohydrate source as depicted in Scheme 1. Thus, a 1,4-linked D-hexose sugar, such as maltose/maltodextrin/lactose, was treated with cumene hydroperoxide under basic conditions at 70 °C to give 3,4-dihydroxybutyric acid **2**, which was cyclized in the presence of an acid to afford the desired butyrolactone **4** in reasonably good yield.



Scheme 1. Reagents and conditions: (a) NaOH, 40 °C, 2 h, then 80% cumene hydroperoxide, 70 °C, 10 h; (b) concd H_2SO_4.

The advantages of the present method are that it is simple, practical, and economical. Initially, various D-hexose sugars were screened in order to obtain the best possible yield of the desired product. While the reaction of maltodextrin with 80% cumene hydroperoxide in the presence of sodium hydroxide gave 56% yield of the butyrolactone **4**, maltose under similar reaction conditions afforded a slightly lower yield (54%). However, other carbohydrate sources such as lactose gave only moderate yields of the desired product. Similarly, amongst the various oxidizing agents screened, cumene hydroperoxide proved to be an ideal reagent. The use of other oxidizing agents, such as hydrogen peroxide, *tert*-butyl hydroperoxide, and Oxone, gave only poor yields of product. Similarly, the use of solid bases such as K-L, K-Y, Cs-KL, Na-MCM in place of sodium hydroxide, afforded the desired lactone only in low yield.

The reaction mechanism for the formation of (*S*)-3-hydroxy-γ-butyrolactone from a 1,4-linked hexose source, such as maltodextrin, maltose, etc., is illustrated in Scheme 2. Thus, treatment of 1,4-linked hexose source with base leads to an isomerization to the 4-linked ketose **5**, which readily undergoes β-elimination to form



Scheme 2. Proposed mechanism for the formation of (*S*)-3-hydroxy-γ-butyrolactone from 1,4-linked hexose source with cumene hydroperoxide in the presence of base.

enone **6**. Subsequent tautomerization leads to the formation of diketone **7**, which is readily cleaved with cumene hydroperoxide **8** to give the salt of (*S*)-3,4-dihydroxybutyric acid **9** and glycolic acid **3**. Cumene alcohol **10** is also formed as by-product. Acidification and concentration gave the desired lactone **4**.

It was observed that the downstream process and work-up procedure played an important role in the isolation and purification of product **4**. In the case of cumene hydroperoxide as an oxidizing agent, the acidic work-up of reaction mixture showed the formation of a number of products by TLC. During column purification, the faster moving by-products were separated and analyzed by GC/GC–MS/spectral data. The compounds obtained were cumene alcohol **10**, phenol, α-methylstyrene **11**, and polymerized product. The major compound found was the dimer of α-methylstyrene and a polymeric product of high molecular mass as shown by GC. The cumene alcohol, which is one of the by-products of the reaction, led to α-methylstyrene and the polymeric product under acidic work-up as shown in Scheme 3. Therefore, in order to avoid the formation of by-products, the work-up procedure was modified. Cumene alcohol was first recovered by the extraction of the reaction mixture with diethyl ether, then the aqueous layer extract was subjected to the acidic work-up (for details, see Section 4.3).

Our next aim was to convert the hydroxy butyrolactone **4** into useful chiral intermediate such as the cyano ester **13** of pharmaceutical importance. It was envisaged that compound **13** could easily be derived from butyrolactone **4**. It should be mentioned that the utility of **13** as a chiral intermediate in the preparation of statin based drugs (cholesterol lowering drugs), such as mevacor, atorvastatin, lipitor, etc., and other related compounds has already been demonstrated.[2]

In order to achieve the synthesis of **13** (Scheme 4), butyrolactone **4** was first treated with 30–33% HBr in AcOH/EtOH to afford the corresponding bromo ester **12** in 85% yield. The subsequent treatment with sodium cyanide furnished the cyano compound **13** (by direct displacement of bromo with cyano) in about 50% yield. In our initial attempt for the preparation of cyano compound **13** via an epoxide, it was observed that the conversion of the bromo compound **12** to the epoxide was not a clean reaction but led to the formation of an unsaturated ester as a major side product, resulting in the facile elimination of hydroxyl group.

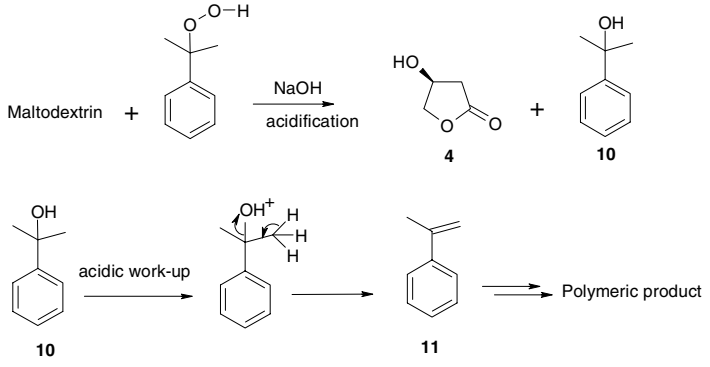
3. Conclusion

In conclusion, a method for preparing enantiomerically pure (*S*)-3-hydroxy-γ-butyrolactone by the oxidation of a (1,4)-linked disaccharide or oligosaccharide with cumene hydroperoxide has been developed. The process uses an inexpensive and readily available carbohydrate as the chiral pool material. The hydroxy butyrolactone has further been converted into (*R*)-cyano-3-hydroxybutyric acid ethyl ester, which is a useful intermediate for the statin based drugs and other related compounds.

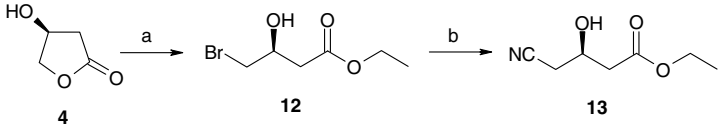
4. Experimental

4.1. General information

The solvents were purified and dried by the standard procedures prior to use; petroleum ether of boiling range 60–80 °C was used. Optical rotation was measured using sodium D line on a JASCO-P-1020-polarimeter. Infrared spectra were recorded on a Perkin Elmer FT-IR spectrometer. ^{1}H NMR spectra were recorded on a Bruker AC-200 spectrometer. The mass spectra were recorded



Scheme 3.



Scheme 4. Reagents and conditions: (a) 30–33% HBr in AcOH/EtOH, reflux, 8 h, 85%; (b) NaCN, DMF, rt, overnight, 50%.

either by GC–MS or with a Finnigan LC–MS mass spectrometer. Enantiomeric excess was measured using either chiral HPLC or by comparison of specific rotations.

4.2. Synthesis of (*S*)-3-hydroxy-γ-butyrolactone 4

In a two-necked 100 mL round bottom flask with a thermo well and reflux condenser was added maltodextrin (1.0 g, 2.77 mmol) dissolved in 0.16 M NaOH solution (0.32 g in 50 mL water, 7.93 mmol, 2.86 equiv). The reaction mixture was heated at 40 °C for 2 h. The color of the reaction mixture became yellowish to dark red. To this solution was added slowly 80% cumene hydroperoxide (0.7 mL, 3.66 mmol, 1.32 equiv). The reaction temperature was increased slowly to 70 °C and heated for another 10 h. The reaction mixture was cooled to 25 °C, and then to 0 °C temperature. The cooled reaction mixture was acidified with concd H_2SO_4 to pH 1. The acidified solution was concentrated to dryness at 55 °C, in order to remove glycolic acid and water. To the yellow colored syrup formed, was added 10 g of ice and then the mixture neutralized with solid sodium bicarbonate, extracted with ethyl acetate, and dried over sodium sulfate. The solvent was removed under reduced pressure. The residue obtained was purified by silica gel column chromatography using EtOAc/pet ether (4:6) as eluent to give **4** (0.16 g) as a colorless oil in 56% yield, $[\alpha]_D^{25} = -84.6$ (*c* 3.1, EtOH), lit.[11] $[\alpha]_D^{25} = -86.1$ (*c* 3.1, EtOH). The spectroscopic data (IR, ^{1}H NMR) are in accordance with those described in the literature.[11]

4.3. Modified work-up procedure for the recovery of cumene alcohol

4.3.1. Synthesis of (*S*)-3-hydroxy-γ-butyrolactone 4. In a 500 mL two-necked round-bottom flask, was placed maltodextrin (5 g) dissolved in 0.16 M NaOH solution (1.6 g in 250 mL water). The reaction mixture was heated at 40 °C for 2 h. To the reaction mixture was added 80% cumene hydroperoxide (3.5 mL, 1.32 equiv). After addition, the reaction temperature was increased to 70 °C and heated for 10 h. After the reaction was over, it was brought back to room temperature and the reaction mixture extracted with ether (2 × 50 mL). The organic layer was separated and the aqueous layer cooled to 0 °C. The pH of the solution was 8.16, and the aqueous layer acidified with concd H_2SO_4 (2.8 mL) to pH 1. The solution was concentrated to dryness at 60 °C and to the residue crushed ice was added and neutralized with sodium bicarbonate and then extracted with ethyl acetate (3 × 200 mL). The organic layer was washed with water and brine and dried over Na_2SO_4. The evaporation of the solvent and purification by silica gel column chromatography using pet ether/ethyl acetate (4:6) gave **4** (0.8 g) as a colorless oil in 56% yield.

4.3.2. Recovery of cumene alcohol. As mentioned in the modified work-up procedure, the reaction mixture was first extracted with diethyl ether (50 mL × 2). The organic layer was separated and concentrated. The residue obtained was purified by column chromatography. The yield (3.22 g) of the organic layer extract comprises of unreacted cumene hydroperoxide and cumune alcohol, which were fully characterized by NMR and GC–MS.

4.4. Synthesis of (*S*)-4-bromo-3-hydroxybutyric acid ethyl ester 12

To a cooled solution of hydroxy butyrolactone **4** (1.02 g, 10 mmol) was added with stirring 30–33% HBr (3 mL, 15 mmol) in glacial acetic acid. The reaction mixture was warmed to room temp and then heated to 60 °C under nitrogen for 5 h. Absolute ethanol was added to the reaction mixture and then left stirring at the same temp for 5 h. The solvent was evaporated and the residue taken in ethyl acetate, washed with 10% $NaHCO_3$, and then with water until the aq layer becomes neutral. The organic layer was dried over sodium sulfate and the solvent distilled. The residue was purified by silica gel column chromatography using ethyl acetate and pet ether (2:8) as eluent to give **12** (1.91 g) as a colorless oil in 85% yield. $[\alpha]_D^{25} = -10$ (*c* 1.2, EtOH), lit.[12] $[\alpha]_D^{20} = -11$ (*c* 1, EtOH).

The physical and spectroscopic data (IR, ^{1}H NMR) are in accordance with those described in the literature.[13]

4.5. Synthesis of (*R*)-4-cyano-3-hydroxybutyric acid ethyl ester 13

To a cooled solution of (*S*)-4-bromo-3-hydroxybutyric acid ethyl ester **12** (1.13 g, 5 mmol) dissolved in 5 mL of dry DMF was added with stirring NaCN (0.98 g, 20 mmol). The reaction mixture was stirred at room temperature overnight. DMF was evaporated under reduced pressure, the residue left was extracted with diethyl ether. The solvent was evaporated to afford **13** (0.43 g) as a light yellow liquid in 50% yield. $[\alpha]_D^{25} = -32.5$ (*c* 1, $CHCl_3$), lit.[2] $[\alpha]_D = -33.1$ (*c* 1.2, $CHCl_3$).

The physical and spectroscopic data (IR, ^{1}H NMR) are in accord with those described in the literature.[13]

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