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A Convenient and Versatile Route for the Stereoselective Synthesis of Monosaccharides via Key Chiral Synthons Prepared from Achiral Sources

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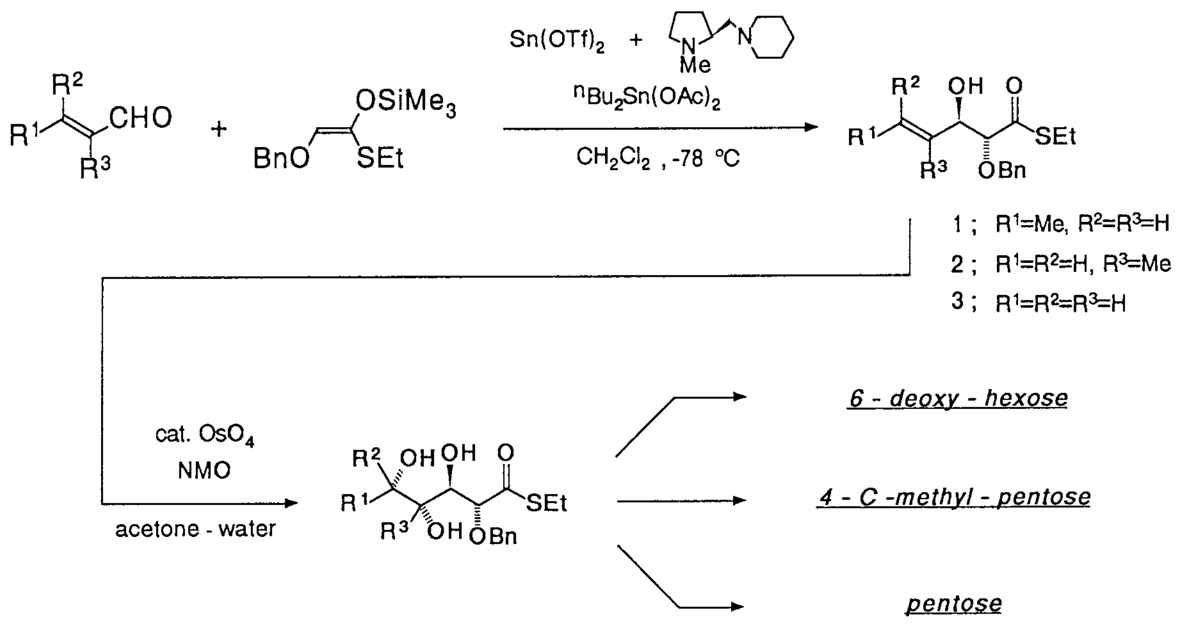
Three types of sugars, 6-deoxy-L-tallose, 4-C-methyl-D-ribose, and D-ribose were synthesized from both achiral starting materials, α,β-unsaturated aldehydes and silyl enol ethers of α-benzyloxy thioesters, by successive asymmetric aldol and vicinal dihydroxylation reactions.

Several glycosides containing sugars such as 6-deoxy-L-galactose,1) 6-deoxy-L-mannose,2) 6-deoxy-L-tallose,3) etc. have been known as one of the physiologically important substances because of their specific behaviors in biological system and also many kinds of branched sugars, such as L-streptose,4) L-vinelose,5) L-mycarose,6) etc. have been discovered in a variety of antibiotics. Since such carbohydrates scarcely exist in nature, the chemical synthesis of this class of compounds is one of the current interests in synthetic organic chemistry.

In the past decades, the chemical synthesis of monosaccharides made a great advancement based on stereoselective addition reactions of 2,3-O-isopropylidene-D-or L-glycelaldehyde7) or 4-O-benzyl-2,3-O-



Scheme 1.

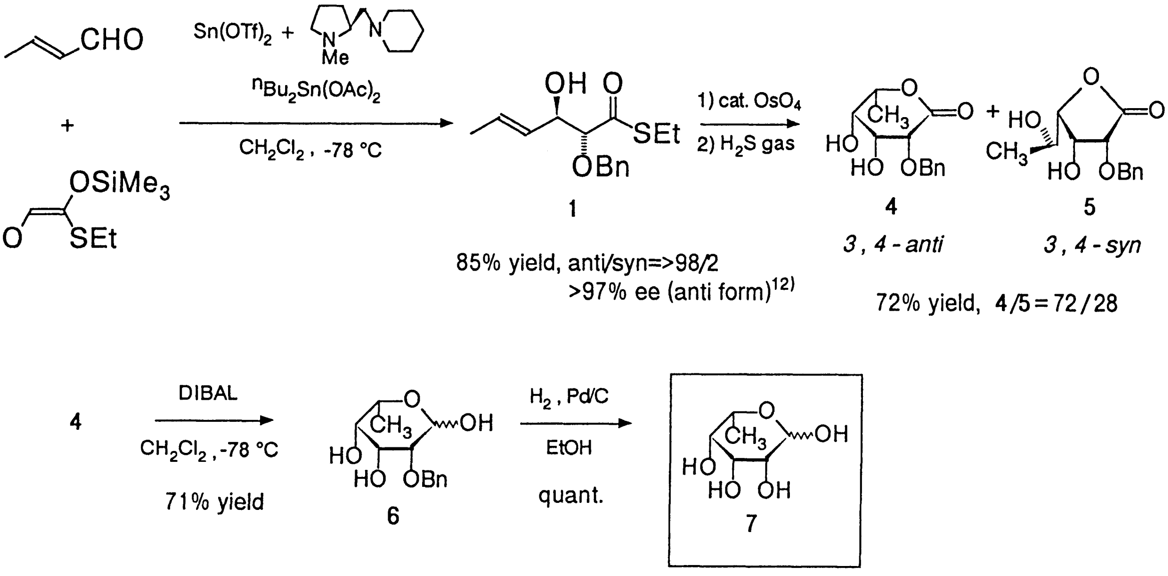
isopropylidene-L-threose[8)] with enolate components or allyl nucleophiles, therefore, many examples of the effective synthesis of sugars including natural and unnatural forms were demonstrated. In the above synthesis, one of the starting materials, glyceraldehyde or threose derivatives, is prepared from natural chiral pools, D or L-mannitol and L-tartalic acid, respectively.

We planned to prepare useful chiral synthons **1**, **2**, and **3**, as precursors for the synthesis of the above rare sugars from simple achiral compounds according to the synthetic strategy shown in Scheme 1.

The chiral induction was accomplished by the asymmetric aldol reaction between both achiral α,β-unsaturated aldehydes and silyl enol ethers of α-benzyloxy thioesters.[9)] The successive oxidation of the olefinic part of the resulted dihydroxy thioesters[10)] can demonstrate fundamental route for construction of various sugars. In this communication, we wish to describe a new stereoselective synthesis of 6-deoxy-L-tallose, 4-C-methyl-D-ribose and D-ribose, in order to illustrate the usefulness of this strategy.

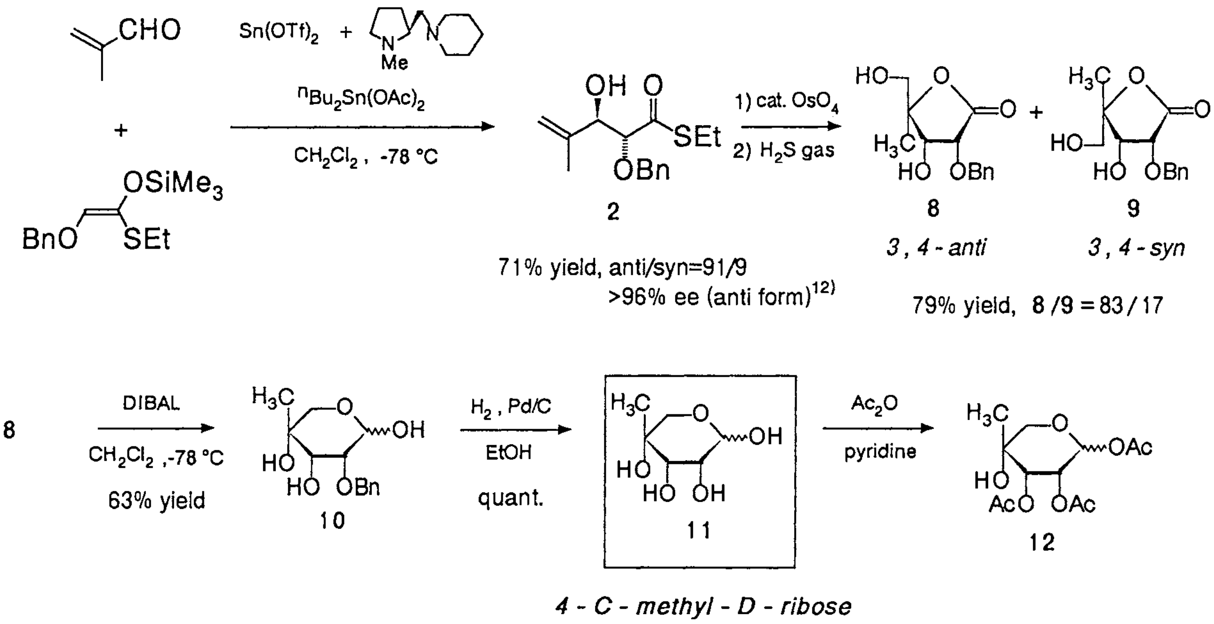
In the first place, the asymmetric aldol reaction between crotonaldehyde and silyl enol ethers of α-benzyloxy thioester was carried out in dichloromethane at -78 °C in the presence of a chiral promoter consisted of chiral diamine coordinated tin(II) triflate and dibutyltindiacetate. The corresponding aldol-type adduct **1** was obtained in 85% yield with >97% optical purity.[12)] Next, osmium oxidation of the chiral synthon **1** was performed in acetone-water (8/1) at room temperature in the presence of a catalytic amount of osmium tetraoxide (OsO_4) and a stoichiometric amount of N-methylmorpholineoxide (NMO) to result in the formation of the corresponding lactones **4** and **5** in 72% yield (**4** / **5** = 72/28). Then main lactone **4** was isolated and reduced with diisobutylaluminum hydride (DIBAL) in dichloromethane at -78 °C (71% yield), followed by deprotection of the benzyl group under Pd/C in ethanol. Thus, the desired 6-deoxy-L-tallose **7** was isolated in quantitative yield.[13)]

According to the same procedure, 4-C-methyl-D-ribose (**11**)[14)] and D-ribose (**16**)[15)] were synthesized starting from methacrolein and acrolein, respectively, as shown in the following schemes.

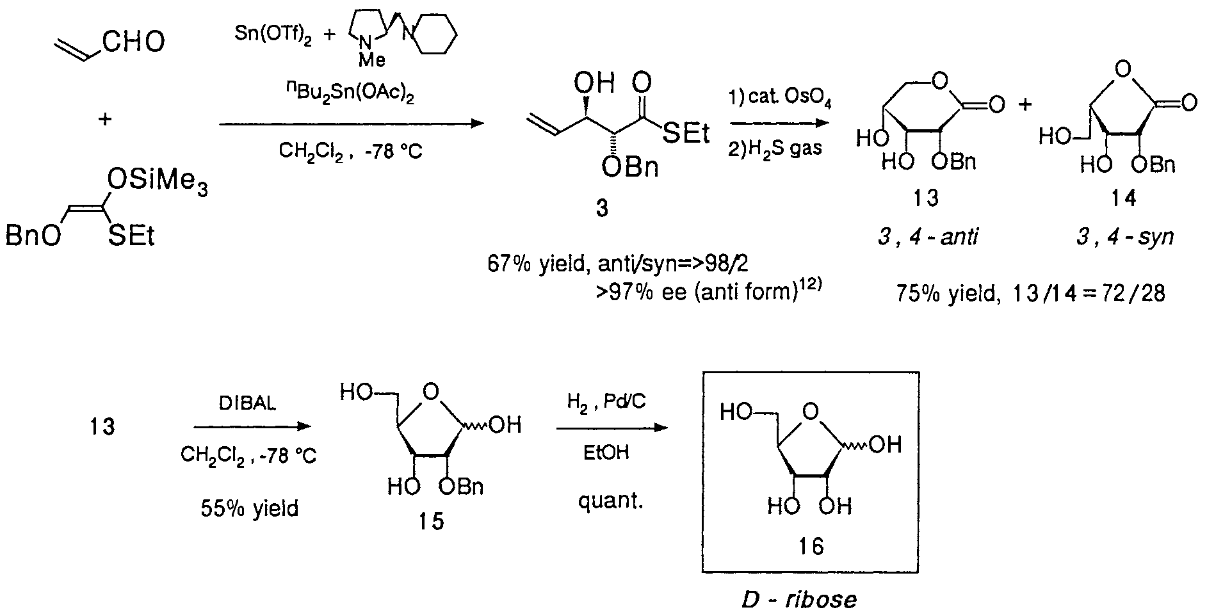


6 - deoxy - L - tallose

Scheme 2. Synthesis of 6 -deoxy - L - tallose.



Scheme 3. Synthesis of 4-C-methyl-D-ribose.



Scheme 4. Synthesis of D-ribose.

One of the most characteristic points of this route is that the main skeltons of sugars are constructed via the asymmetric carbon-carbon bond forming reaction between simple achiral molecules, α,β-unsaturated aldehydes and silyl enol ether of α-benzyloxy thioester, without using chiral pools from natural sources.[16]

It is noted that the present route can be expected to provide a useful tool for the synthesis of a wide variety of natural and unnatural sugars.

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11) $[\alpha]_D^{28}$ -21.4 ° (c 0.85 , H_2O) (lit.[17] $[\alpha]_D^{21}$ -18.9 ° (H_2O))

12) No Michael adduct was detected. The optical purity was determined by HPLC (see ref. 9).

13) Precise experimental conditions are as follows ; to a solution of tin (II) triflate and (S)-1-methyl-2-[(piperidin-1-yl)methyl]pyrrolidine in dichloromethane was added dibutyltindiacetate at room temperature. The mixture was stirred for 30 min and then cooled to -78 °C. Dichloromethane solution of silyl enol ether of S-ethyl 2-benzyloxyethanethioate and crotonaldehyde were successively added. The reaction mixture was further stirred for 20 h, and quenched with aqueous sodium hydrogenbicarbonate. After usual work up, the aldol adduct **1** was obtained in 85% yield (anti/syn=>98/2, anti form: >97% ee). Next, to a solution of this chiral synthon in acetone and water, NMO (120 mol%) and OsO_4 (5 mol%) was added at room temperature. The mixture was stirred for 6 h and then diluted with chloroform and quenched with H_2S gas. After filtlation, the crude product was purified by thin layer chromatography on silica gel, to afford the corresponding lactones **4** and **5** in 72% yield (**4** / **5** = 72/28). Then to the lacton **4** in dichloromethane, was added DIBAL in dichloromethane at -78 °C. The mixture was stirred for 1 h and then quenched with phosphate buffer (pH=7), and purified by thin layer chromatography on silica gel to give **6** in 71% yield. Finally, debenzylation of **6** was carried out in ethanol under hydrogen atmosphere utilizing 10% Pd/C as a catalyst to give 6-deoxy-L-tallose **7** in quantitative yield.

14) ^{1}H-NMR (CD_3OD) δ 1.17 (s, 3H), 3.25-3.78 (m, 4H), 4.67-5.10 (m, 5H); IR (neat) 3250 cm^{-1} ; $[\alpha]_D^{27}$ -30.8 ° (c 1.52, CH_3OH); **12**: ^{1}H-NMR ($CDCl_3$) δ 1.21 (d, 3H, J=3.2 Hz), 2.02-2.31 (m, 9H), 2.91-3.18 (m, 1H), 3.38-4.17 (m, 2H), 4.96-5.47 (m, 2H), 5.83-6.16 (m, 1H); IR (neat) 3490, 1750 cm^{-1} ; $[\alpha]_D^{28}$ -15.1 ° (c 1.57, $CHCl_3$).

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