A New Efficient Method for the Synthesis of *L*-Galactose†

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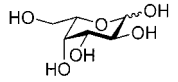
There is a growing need for the synthesis of non-natural *L*-sugars and naturally occurring rare *L*-sugars because of the medicinal potential of *L*-carbohydrates and related nucleosides due to their potent biological activity and lower toxicity compared to their *D*-counterparts.[1] *L*-Sugars are also used as the building block for the synthesis of *L*-oligonucleotides and enantio-DNA (DNA having *L*-sugar), which are valuable tools for studying protein-DNA interactions and are promising antisense agents.[2] Although certain *L*-sugars such as *L*-fucose, *L*-rhamnose, and *L*-arabinose are quite abundant in nature, *L*-galactose is a rare sugar and occurs as a minor component in agar-agar, chagual gum, red algae, flaxseed mucilage and a snail galactan.[3] There have been reports for the synthesis of *L*-galactose: (i) a synthesis by reduction of *L*-galactono-1,4-lactone,[4] (ii) a method based on the repeated asymmetric epoxidation starting from achiral 2-butene-1,4-diol.[5] (iii) a synthesis employing the Pummerer rearrangement starting from 6-*S*-phenyl-6-thio-*D*-galactose.[6] and (iv) an enzymatic synthesis by galactose oxidase-catalyzed oxidation of galactitol.[7] These methods have some limitations such as the lengthy synthesis, the carefully controlled reaction in certain steps, and/or the low yield of the product. Herein we report an efficient new method for the synthesis of *L*-galactose (**1**) starting from readily available inexpensive *L*-ascorbic acid (**2**).



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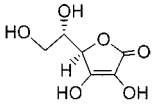

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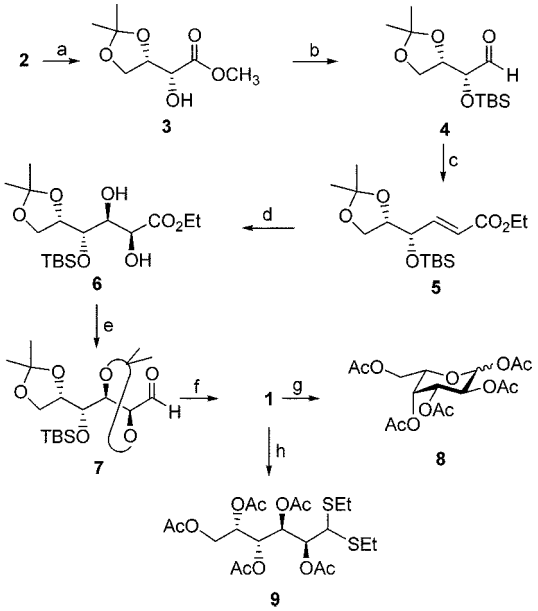
The synthesis commenced with transformation of *L*-ascorbic acid (**2**) into the methyl threonate **3** in 74% yield by the known procedure.[8] The hydroxyl group of the compound **3** was protected with *t*-butyldimethylsilyl (TBS) chloride (Scheme 1). The resulting TBS ether was subjected to reduction with DIBAL-H at 78 °C to give the aldelyde **4** in 87% yield. Wittig reaction of the aldehyde **4** with Ph_3P = $CHCO_2Et$ in the presence of a catalytic amount of benzoic acid provided the (E)-α,β-unsaturated ester **5** in 93% yield along with a small amount of (Z)-isomer (E/Z = 20 : 1). Dihydroxylation[9] of the compound **5** utilizing AD-mix-β in the presence of $MeSO_2NH_2$ in *t*-BuOH/H_2O afforded exclusively the diol **6** in 93% yield. Protection of the diol **6** with 2,2-dimethoxypropane followed by reduction of the resultant di-*O*-isopropylidene ester with DIBAL-H at 78 °C gave the protected *L*-galactose **7**.[10] Hydrolysis of the purified **7** with *c*-HCl in acetonitrile provided *L*-galactose (**1**), of which acetylation with acetic anhydride in the presence of a catalytic amount of DMAP in pyridine gave the *L*-galactose pentaacetate **8** in 80% yield in two steps. The crude aldelyde **7** could be used without purification for the subsequent hydrolysis and acetylation steps. ^1H and ^{13}C NMR spectra of the compound **8** were identical with those of *D*-galactose pentaacetate, which we prepared from *D*-galactose. For the purpose of further identification, *L*-galactose (**1**) was treated with EtSH in the presence of *c*-HCl to afford the acyclic *L*-galactose dithioacetal as white solid, of which acetylation with acetic anhydride gave the pentaacetyl-*L*-galactose dithioacetal **9** {$[\alpha]_D$ -10.7 (c 3.4, $CHCl_3$)}. ^1H and ^{13}C NMR spectra of the compound **9** was identical with those of its enantiomer, pentaacetyl-*D*-galactose dithioacetal {$[\alpha]_D$ +10.5 (c 3.4, $CHCl_3$) (lit[11]: $[\alpha]_D$ +9.8, $CHCl_3$) (lit[12]: $[\alpha]_D$ +11.31, c



Scheme 1. *Reagents and conditions*: (a) see reference 8, 74% in 3 steps; (b) (i) TBSCl, imidazole, DMF, rt, 12 h, 98%; (ii) DIBAL-H, CH_2Cl_2, -78 °C, 1 h, 87%; (c) Ph_3PCHCO_2Et, benzoic acid (cat.), CH_2Cl_2, rt, 4 h, 93%; (d) AD-mix-β, $MeSO_2NH_2$, *t*-BuOH-H_2O, rt, 30 min, then **5**, 0 °C, 12 h, 93%; (e) (i) 2,2-dimethoxypropane, TsOH (cat.), acetone, 4 h, 96%; (ii) DIBAL-H, CH_2Cl_2, -78 °C, 1 h, 89%; (f) *c*-HCl, CH_3CN-H_2O, rt, 1 h; (g) Ac_2O, DMAP (cat.), pyridine, 0 °C to rt, 5 h, 80% in 2 steps from **7**; (h) (i) EtSH, *c*-HCl, rt, 10 min; (ii) Ac_2O, DMAP (cat.), pyridine 0 °C to rt, 4 h, 91% in 3 steps from **7**.

[†]This paper is dedicated to the late Professor Sang Chul Shim.

2.2, $CHCl_3$)}, which we prepared from *D*-galactose. Thus, the conversion of *L*-ascorbic acid to the *L*-galactose penta-acetate **8** was accomplished in 37% overall yield.

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10. Compound **7**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.12 (s, 6H), 0.92 (s, 9H), 1.31 (s, 3H), 1.33 (s, 3H), 1.41 (s, 3H), 1.50 (s, 3H), 3.67-3.75 (m, 1H), 3.89-3.93 (m, 1H), 3.96-4.08 (m, 3H), 4.57 (dd, J = 6.5, 1.1 Hz, 1H), 9.81 (d, J = 1.1 Hz, 1H). ^{13}C NMR (63 MHz, $CDCl_3$) δ -4.11, -3.96, 18.44, 25.62, 26.07, 26.44, 26.48, 65.93, 73.37, 77.86, 78.31, 80.38, 109.12, 110.62, 201.46.
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