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An efficient procedure for synthesis of fructose derivatives

Kui Yu [a,b], Xu Zhao [b], Wenjie Wu [a,*], Zhangyong Hong [b,*]

[a] College of Material Science and Chemical Engineering, Tianjin University of Science and Technology, Tianjin 300457, PR China
[b] State Key Laboratory of Medicinal Chemical Biology, College of Life Sciences, Nankai University, Tianjin 300071, PR China

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ABSTRACT

We developed a very simple procedure to prepare fructose derivatives or fructosides. This procedure waived the requirement of isomer separation, which is usually a very common and difficult problem in fructose derivative syntheses. In this procedure, the hydroxyl groups were differentiated to expedite the preparation of many kinds of other fructose derivatives and the alkoxy group in the fructosides could exchange easily with alcohols under the mild acidic condition, which offered a new method to synthesize other fructosides through alcohol exchanging. By using this procedure, we successfully synthesized fluorogenic fructose derivatives for high throughput enzyme screening. This methodology could expand the usage of the abundant fructose in organic synthesis.

Fructose is one of the most abundant natural products. Its derivatives have many important applications in biological or medical sciences. For examples, its analogs were tested as inhibitors for fructose transporter GLUT5;[1] 2,3:4,5-bis-*O*-(1-methylethylidene)-beta-D-fructopyranosesulfamate (Topiramate, brand name Topamax) is an anticonvulsant (antiepilepsy) drug approved by FDA;[2] fructose-1,6-diphosphate (FDP) is used as clinical drug in the prevention and treatment of acute hypophosphatemia and phosphate depletion, and also has substantial cytoprotective effects in a variety of ischemia-reperfusion injury scenarios;[3] fluorescent fructose derivatives were used as diagnostic reagents for breast cancer.[4] In addition, its unlimited source and three chiral hydroxyl groups make fructose very useful in organic synthesis.[5,6] For example, its diacetonide derivatives were used as catalyst for asymmetric epoxidation.[7] Among them, derivatives with 1- or 6-position modification are very common and useful.

Fructose exists as a mixture of two pyranoid, two furanoid, and one acyclic keto-form tautomers. Simple derivatizations of fructose, such as glycosidations, acylations, and alkylations, usually yield product mixtures of, at worst, all five tautomeric forms. Therefore, literature methods always required quite complex purification and low yield procedures to prepare derivatives.[5] Separation of the major component is cumbersome and highly detrimental to the yields obtainable. Considering the important applications of many derivatives of fructose, herein we report a new procedure for fructose derivative syntheses, in which the operation offered a single isomer product and waived complex isomer separation procedures.

We first test methods to efficiently differentiate the three hydroxyl groups in fructose, especially the two primary ones. Reaction of fructose with TsCl, TPSCl (2,4,6-triisopropylbenzene-sulfonyl chloride) or trityl chloride was very complex and showed low selectivity to these hydroxyl groups. Treatment of fructose with formic acid[8] afforded 6-formic fructose derivative but only in 25% yield. The reaction of fructose with 2,3-butadione, acetone, or benzaldehyde was also very complex.

Then we treated fructose with acidic MeOH and got methyl D-fructofuranoside **1** and **2** in 80% total yield with an isomer ratio of 1:1 (Scheme 1). But fructoside **1** and **2** were quite polar and showed little difference on TLC, and could only be separated by silica gel column with very careful operation. Then we treated α-methyl fructofuranoside **1** with acidic MeOH and 2,2-dimethoxypropane to afford α-methyl 1,3-*O*-isopropylidene-D-fructofuranoside **3** in 75% yield, in which 1,3-dihydorxyl group were selectively protected. However, to our surprise, when β-methyl D-fructofuranoside **2** was treated under the same acidic condition, the same product **3** was obtained in almost the same yield. In theory, because 1,3-dihydroxyl group in β-methyl fructofuranoside **2** exists as *trans*-form, they could not form cyclic acetonide. It means that the configuration of the methoxy group in **2** reversed under mild acidic conditions, and both glycoside **1** and **2** will offer the same product **3** under the same acidic conditions. Thus we tried to simplify the procedure and run in large scale in an one pot procedure, by skipping the separation procedure of the two polar isomers. Therefore, when the reaction mixture of the two fructofuranoside **1** and **2** obtained by the reaction of fructose with acidic MeOH was treated with 2,2-dimethoxypropane in the one pot procedure, product **3** was obtained directly in 70% yield.[9]

* Corresponding authors. Tel./fax: +86 22 23498707.
E-mail addresses: wwjie@tust.edu.cn (W. Wu), hongzy@nankai.edu.cn (Z. Hong).

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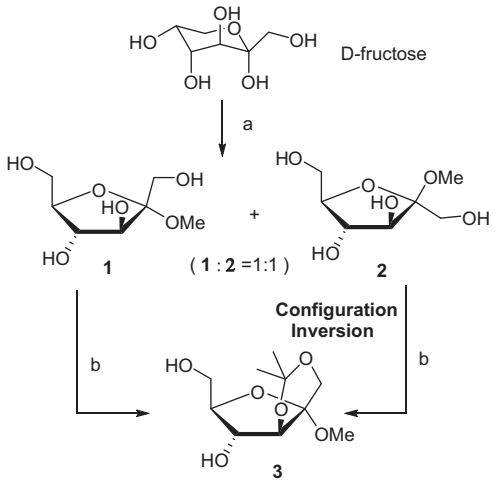
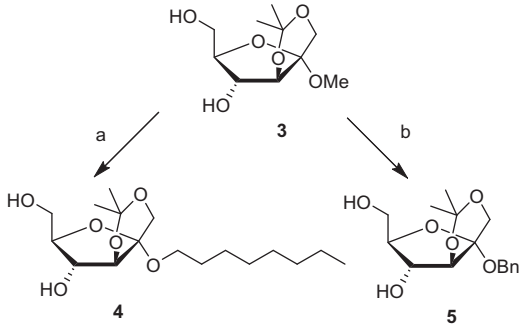


Scheme 1. 'One pot' synthesis of α-methyl 1,3-*O*-isopropylidene-fructofuranoside **3**. Reagents and conditions: (a) MeOH, cat. TsOH, rt, overnight; (b) Then added 2,2-dimethoxypropane, rt, 40 min, 70%.

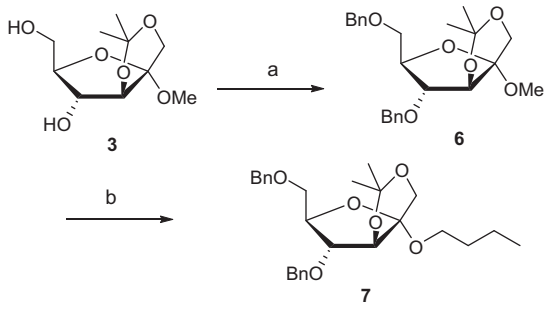


Scheme 2. Synthesis of 1,3-*O*-isopropylidene-α-D-fructofuranoside **4** and **5**. Reagents and conditions: (a) vinyl acetate/acetone/1-octanol = 1:1:1, 1% TsOH, rt, 30 min, 60%; (b) vinyl acetate/acetone/BnOH = 1:1:1, 1% TsOH, rt, 30 min, 70%.

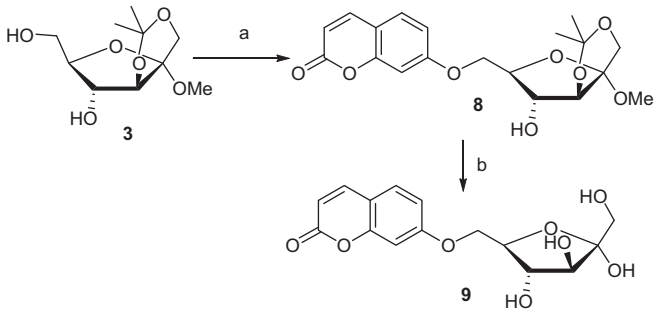
Usually the product from one pot will contaminate with a little bit of unknown byproduct from the NMR (about 5%) when silica gel chromatography separation was used for the purification, but it is easy to be removed in the follow up transformation. The 1-OH and 6-OH in compound **3** were differentiated and could be easily derivatized separately. This procedure will produce a single isomer product directly and waived any isomer separation, which is usually a very common and difficult problem in fructose derivative synthesis.

The configuration of the methoxy group in the β-methyl D-fructofuranoside **2** easily reversed under mild acidic condition. We proposed that the process may occur through a carbonion process, which resulted in the reversion of the configuration. Therefore, we thought that we may use this procedure to synthesize other fructosides by adding different alcohols under mild acidic condition. Under the reaction condition of vinyl acetate, acetone, PTSA, when 1-octanol or BnOH was added, 1,3-*O*-isopropylidene-α-D-fructofuranoside **4** and **5** were obtained in 60% and 70% yields, respectively (Scheme 2).[10] The 4,6-di-*O*-benzyl protected fructofuranoside **6** can also take the similar reaction by treatment with 2,2-dimethoxy propane/*n*-butyl alcohol and PTSA to afford α-butyl 4,6-di-*O*-benzyl-1,3-*O*-isopropylidene-D-fructofuranoside **7** in 80% yield (Scheme 3).[11] This procedure was quite simple to prepare fructosides.

The developed procedure is very simple and could be used to prepare many other kinds of fructose derivatives efficiently. 6-Coumarin D- and L-fructose (**9** and **12**) were used as fluorogenic



Scheme 3. Synthesis of α-butyl 4,6-di-*O*-benzyl-1,3-*O*-isopropylidene-D-fructofuranoside **7**. Reagents and conditions: (a) DMF, NaH, BnBr, 90%; (b) 2,2-dimethoxy propane/*n*-butyl alcohol = 1:1, cat. TsOH, rt, 30 min, 80%.



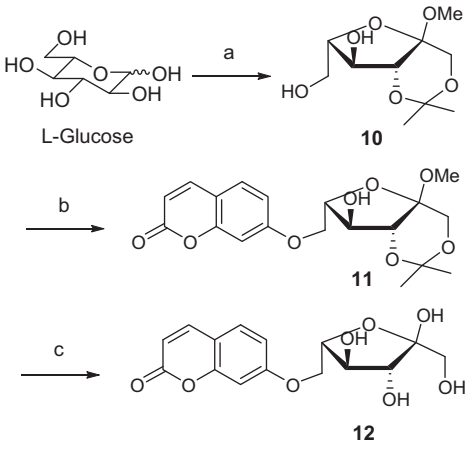
Scheme 4. Synthesis of D-fructose fluorogenic derivative **9** (6-coumarin-D-fructose). Reagents and conditions: (a) coumarin, PPh_3, DEAD, THF, 90%; (b) TFA/H_2O (19:1), rt, 70%.

markers[12] for high throughput screening of FDP and RhaD, which are two broadly used aldolases in organic synthesis.[13] The requirement of phosphoralated substrate seriously restricted the applications of aldolases,[14] and directed evolution is one possible way to solve this problem.[15,16] The published procedure only offered compound **9** in very low yield (7.8% overall yield) starting for D-fructose.[12] It was even more difficult to synthesize enough amount of **12** which required expensive unnatural L-fructose[17] as the starting material. Herein we used this procedure to efficiently synthesize these two fluorogenic fructose derivatives for directed enzyme evolution.

Coumarin was coupled with α-methyl 1,3-*O*-isopropylidene-D-fructofuranoside **3** at the 6-position through Mitsunobu reaction (PPh_3, DEAD) to afford α-methyl 6-coumarin-1,3-*O*-isopropylidene-D-fructofuranoside **8** in 90% yield (Scheme 4). The free 4-OH has no any influence to this process. Then **8** was deprotected with TFA at room temperature to afford the desired 6-coumarin-D-fructose **9** in 70% yield which has the same NMR spectrum with the published data.[12] The total yield for **9** was improved to 44% when calculated from fructose.

We then tried to use the above route to synthesize the L-form product. As unnatural L-fructose was expensive, we started the synthesis from cheap L-glucose. L-glucose was isomerized with $NaAlO_2$ as base to give a mixture of glucose, mannose, and fructose, in which fructose was the major component (70% from NMR) (Scheme 5). Without separation, the mixture was used directly for the following methyl glycosidation and acetonide protection. Product α-methyl 1,3-*O*-isopropylidene-L-fructofuranoside **10** was obtained in 40% yield in three steps. Then according to the similar procedure for compound **9**, Mitsunobu reaction and TFA deprotection, the desired 6-coumarin-L-fructose **12**[12] was obtained in five steps with a total yield of 27% in a multigram scale.

In conclusion, we developed a very simple procedure to prepare fructose derivatives or fructosides. This procedure waived the



Scheme 5. Synthesis of L-fructose fluorogenic derivative **12** (6-coumarin-L-fructose). Reagents and conditions: (a) (I) aquous $NaAlO_2$, rt, 2 days, (II) MeOH, cat. TsOH, rt, overnight, (III) 2,2-dimethoxy propane, rt, 40 min, 40% overall yield for three steps; (b) coumarin, PPh_3, DEAD, THF, 85%; (c) TFA/H_2O (19:1), rt, 80%.

requirement of isomer separation, which is usually a very common and difficult problem in fructose derivative syntheses. In this procedure, the hydroxyl groups were differentiated to expedite the preparation of many kinds of other fructose derivatives and the alkoxy group in the fructosides could exchange easily with alcohols under the mild acidic condition, which offered a new method to synthesize other fructosides through alcohol exchanging. By using this procedure, we successfully synthesized fluorogenic fructose derivatives for high throughput enzyme screening. This methodology could expand the usage of the abundant fructose in organic synthesis.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.03.045.

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*Typical 'one pot' procedure for **3**:* To anhydrous MeOH (10 ml) in flask was added TsOH (9 mg). The solution was stirred at rt for 5 min. Then fructose (1.8 g) was added, and the mixture was stirred overnight. To the reaction mixture was added 2,2-dimethoxy propane (10 ml). The mixture was stirred at rt for 40 min before terminated with anhydrous $NaHCO_3$ to neutralize the solution. The mixture was filtered and evaporated, then purified through silica gel column to afford product **3** (1.6 g, 70% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.19–3.87 (m, 5H), 3.82 (qd, J = 11.8, 4.3 Hz, 2H), 3.32 (s, 3H), 1.48 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 101.28, 98.79, 87.68, 79.62, 77.66, 62.79, 61.80, 48.75, 27.86, 19.27.
10. *Typical procedure for alcohol exchange experiment:* To compound **3** (500 mg) in flask was added (0.5 ml) vinyl acetate, (0.5 ml) acetone, and (0.5 ml) 1-octanol with a ratio of 1:1:1, then added 5 mg (1%) TsOH. The mixture was sittred at rt for 30 min and terminated with anhydrous $NaHCO_3$ by stirring until neutralization. The mixtrue was filtered, concentrated, and purified with silica gel column to afford a-octyl 1,3-*O*-isopropylidene-α-D-fructofuranoside **4** (380 mg, 70% yield). α-Benzyl 1,3-*O*-isopropylidene-α-D-fructofuranoside **5** was synthesized by the same procedure but exchanging 1-octanol to BnOH. For compound **4**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.24–3.90 (m, 5H), 3.90–3.75 (m, 2H), 3.69 (dt, J = 8.9, 6.9 Hz, 1H), 3.40 (dt, J = 9.0, 6.5 Hz, 1H), 1.65–1.16 (m, 18H), 0.89 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 101.70, 99.36, 89.01, 79.71, 78.41, 63.58, 62.86, 62.07, 32.47, 30.72, 29.98, 29.87, 28.81, 26.84, 23.32,19.67, 14.78. For compound **5**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.23 (m, 5H), 4.75 (d, J = 11.2 Hz, 1H), 4.49 (d, J = 11.2 Hz, 1H), 4.19 (dd, J = 2.5, 1.3 Hz, 1H), 4.14 (s, 1H), 4.03 (q, J = 12.1 Hz, 3H), 3.84 (dd, J = 7.2, 4.3 Hz, 2H), 1.50 (s,3H), 1.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.55, 129.15 (2C), 128.47, 128.37 (2C), 101.75, 98.80, 88.12, 79.51, 77.69, 63.74, 62.85, 62.39, 27.99, 19.22.
11. Compound **3** (1.8 g) was dissolved in DMF (about 18 ml). Then sodium hydride (0.9 g) and BnBr (3.95 g) were added to the solution, respectively. The mixture was stirred at rt until compound **3** disappeared while checking by TLC (PE/EA = 5/1). The mixture was diluted with EA, washed with deionized water and brine, dried with Na_2SO_4, and concentrated. Silica gel purification afforded oil 4,6-di-*O*-benzyl protected fructofuranoside **6** (2.0 g, 90% yield). To a solution of 2,2-dimethoxy propane (1.0 ml) and *n*-butyl alcohol (1.0 ml) with a ratio of 1:1 was added TsOH (10 mg). The mixture was stirred at rt for 30 min and concentrated with evaporator to remove methanol and excess 2,2-dimethoxy propane. Then to the residue were added *n*-butyl alcohol (1.0 ml) and compound **6** (100 mg) and the mixture was stirred at rt for 30 min before terminated with andydrous $NaHCO_3$. The mixture was filtered and evaporated, then purified through silica gel column to afford α-butyl 4,6-di-*O*-benzyl-1,3-*O*-isopropylidene-D-fructofuranoside **7** (90 mg, 80% yield). For compound **6**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (m, 10H), 4.72–4.40 (m, 4H), 4.24–4.15 (m, 1H), 4.08 (d, J = 1.1 Hz, 1H), 3.91 (d, J = 12.1 Hz, 1H), 3.80–3.72 (m, 2H), 3.62 (qd, J = 10.6, 5.4 Hz, 2H), 3.30 (s, 3H), 1.40 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.13, 138.03, 128.39 (4C), 127.99 (4C), 127.64 (2C), 103.40, 99.37, 85.43, 81.77, 79.88, 73.38, 72.28, 70.38, 62.11, 48.52, 26.61, 21.30. For compound **7**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49–7.14 (m, 10H), 4.65–4.41 (m, 4H), 4.21 (dd, J = 11.0, 5.0 Hz, 1H), 4.11 (d, J = 1.0 Hz, 1H), 3.90 (d, J = 12.1 Hz, 1H), 3.84–3.72 (m, 2H), 3.71–3.52 (m, 3H), 3.43 (dt, J = 9.2, 6.2 Hz, 1H), 1.62–1.24 (m, 4H), 1.42 (s, 3H), 1.33 (s, 3H), 0.91 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.22, 137.93, 128.31 (4C), 127.62 (4C), 127.54 (2C), 102.83, 99.13, 85.60, 81.57, 79.59, 73.31, 72.00, 70.46, 62.71, 60.65, 32.14, 26.81, 21.10, 19.35, 13.90.
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