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Practical Synthesis of an L-Fructose-Derived Ketone Catalyst for Asymmetric Epoxidation of Olefins

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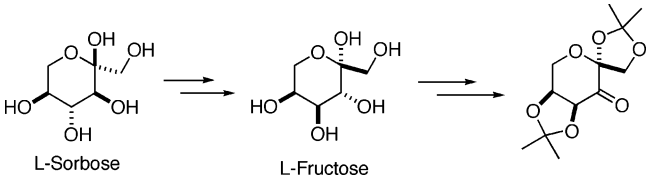
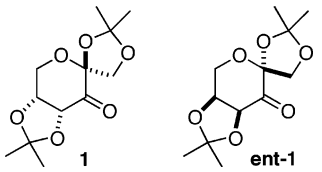


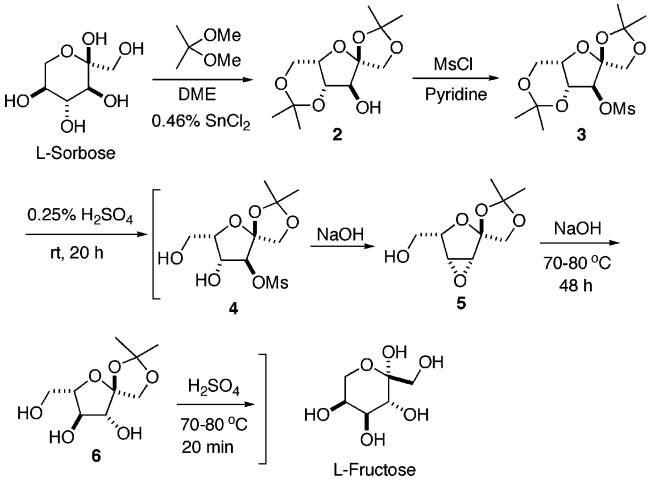
An L-fructose-derived ketone catalyst for asymmetric epoxidation of trans- and trisubstituted olefins was efficiently prepared from L-sorbose in five steps.

Dioxiranes generated in situ from chiral ketones have been shown to be effective for asymmetric epoxidation of olefins.[1] In our earlier studies, we have shown that fructose-derived ketone **1** (Scheme 1) displayed high enantioselectivity for a wide range of trans- and trisubstituted olefins.[2] Ketone **1** is readily prepared from very inexpensive D-fructose by ketalization and oxidation.[2,3] The enantiomer of ketone **1** (ketone **ent-1**) is synthesized in the same way from L-fructose,[2b] which can be prepared from readily available L-sorbose by ketalization, mesylation, and one-pot acid−base treatment based on the reported procedure (Scheme 2).[4] Ketone **ent-1** prepared in this way shows the same enantioselectivity for epoxidation as ketone **1**.[2b] However, one drawback associated with the synthesis of ketone **ent-1** is that the preparation of L-fructose from L-sorbose requires a relatively long time, and some steps are sensitive to reaction conditions.[4,5] This consequently hinders the usage of ketone **ent-1** for asymmetric epoxidation. Considering that ketone **ent-1** is potentially useful,[6] efforts have been made to further improve its synthesis. Herein we wish to report our detailed studies on this subject.

SCHEME 1



SCHEME 2. Original Synthesis of L-Fructose (ref 4)



The ketalization of L-sorbose appears to be very sensitive to reaction conditions such as the amount of $SnCl_2$, temperature, and reaction time (Schemes 2 and 3). Compound **2** is likely to be a kinetic product and is easy to isomerize. A prolonged reaction time leads to a mixture of isomers; thus, the reaction is usually stopped once the solution becomes clear.[4,2b,5] Under such reaction conditions, we found that the efficiency of the reaction is affected by the quality and the crystalline state of the L-sorbose. Presumably, the crystalline state of L-sorbose influences its solubility, thus affecting the reaction time. We found that it is beneficial to pulverize the L-sorbose and quench the reaction before the L-sorbose is completely consumed so that the reaction time is shortened and isomerization of compound **2** can be minimized (the remaining L-sorbose can be readily recovered by filtration and reused). The formed ketal **2** is used directly for mesylation to give mesylate **3** in ca. 40% yield over two steps after recrystallization (Scheme 3).

In the original procedure (Scheme 2), the one-pot transformation of mesylate **3** to L-fructose uses acetone as cosolvent and takes about 3 days. Our efforts were made to improve this process. After much experimentation, it was found that this transformation proceeded efficiently when the reaction was carried out in water without organic solvent. The selective deprotection of the 4,6-*O*-isopropylidene group of **3** can be easily achieved using 4.5% H_2SO_4 at room temperature for 3 h to give diol **4** cleanly.[7] After the solution became alkaline using

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(1) For reviews on chiral ketone-catalyzed asymmetric epoxidation, see: (a) Denmark, S. E.; Wu, Z. *Synlett* **1999**, 847. (b) Frohn, M.; Shi, Y. *Synthesis* **2000**, 1979. (c) Shi, Y. *Acc. Chem. Res.* **2004**, *37*, 488. (d) Yang, D. *Acc. Chem. Res.* **2004**, *37*, 497.

(2) (a) Tu, Y.; Wang, Z.-X.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806. (b) Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224. (c) Shu, L.; Shi, Y. *Tetrahedron* **2001**, *57*, 5213.

(3) Tu, Y.; Frohn, M.; Wang, Z.-X.; Shi, Y. *Org. Synth.* **2003**, *80*, 1.

(4) Chen, C.-C.; Whistler, R. L. *Carbohydr. Res.* **1988**, *175*, 265.

(5) For a stepwise synthesis of L-fructose from L-sorbose, see: Bach, T.; Hofer, F. *J. Org. Chem.* **2001**, *66*, 3427.

(6) For examples using ketone **ent-1**, see: (a) Morimoto, Y.; Iwai, T.; Kinoshita, *Tetrahedron Lett.* **2001**, *42*, 6307. (b) Morimoto, Y.; Takaishi, M.; Iwai, T.; Kinoshita, T.; Jacobs, H. *Tetrahedron Lett.* **2002**, *43*, 5849. (c) Altmann, K.-H.; Bold, G.; Caravatti, G.; Denni, D.; Flörsheimer, A.; Schmidt, A.; Rihs, G.; Wartmann, M. *Helv. Chim. Acta* **2002**, *85*, 4086. (d) Zhang, Q.; Lu, H.; Richard, C.; Curran, D. P. *J. Am. Chem. Soc.* **2004**, *126*, 36.

(7) While the reaction rate increased with the concentration of sulfuric acid, compound **4**'s stability decreased. Considering the stability of the compound and reaction time, 4.5% (w) H_2SO_4 (using 10 mL of 4.5% H_2SO_4 per gram of substrate) was found to work well. A prolonged reaction time could also lead to the decomposition of the compound.

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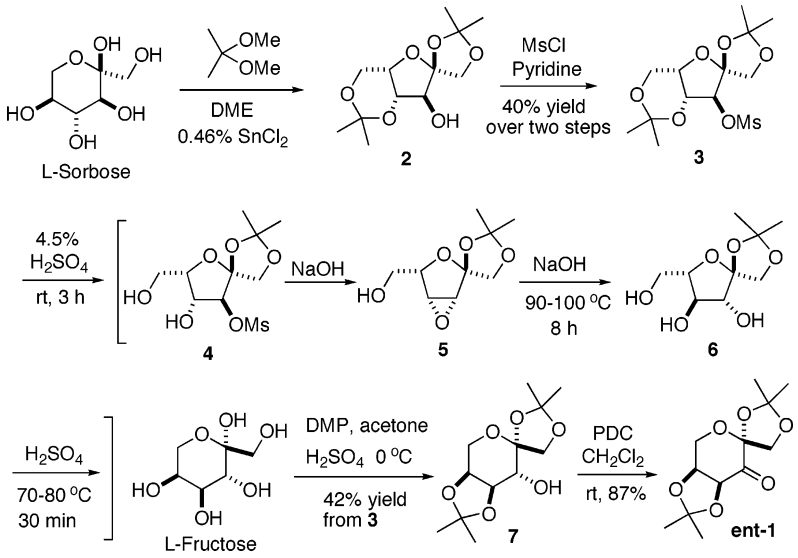
SCHEME 3. Improved Synthesis of L-Fructose-Derived Ketone Ent-1



9 M NaOH,[8] the conversion of compound **4** to triol **6** via epoxide **5** can be efficiently achieved at 90−100 °C in 8 h, which significantly shortens the reaction time. The 1,2-*O*-isopropylidene group of triol **6** was then easily removed as before to give a syrup[9] from which L-fructose was obtained by extraction with hot ethanol several times (Scheme 3). The crude L-fructose was directly ketalized with dimethoxypropane and H_2SO_4 in acetone to give alcohol **7** in 42% overall yield from mesylate **3** (Scheme 3). The oxidation of alcohol **7** with PDC gave ketone **ent-1** in 87% yield. The obtained ketone catalyst **ent-1** gives comparable results to **1** for asymmetric epoxidation.

In summary, we have described a practical synthesis of L-fructose-derived ketone catalyst **ent-1**. One key improvement in the current process was the use of water without organic solvent during the acid−base reaction sequence from mesylate **3** to L-fructose, which greatly reduces the reaction time required for the process. Multigram quantities of the ketone catalyst have been readily prepared. The described improvement should be helpful for those who may wish to use this ketone catalyst.

Experimental Section

Synthesis of Mesylate 3 from L-Sorbose. A solution of dry 1,2-dimethoxyethane (80 mL) containing $SnCl_2$ (2.0 g, 0.01 mol) was added to a suspension of L-sorbose (pulverized)[10] (400.0 g, 2.22 mol) in 2,2-dimethoxypropane (1200 mL) with vigorous stirring. The mixture was refluxed gently with stirring under N_2 at 70 °C (bath temperature) for 2.3 h (carefully monitored by GC[11] to avoid isomerization of compound **2** to other isomers). At this point, there is still a substantial amount of solid (L-sorbose) remaining in the reaction mixture. The reaction was quenched immediately with Et_3N (10 mL), filtered to remove the unreacted L-sorbose (78.0 g), and the solid was washed with EtOAc (100 mL). The filtrate was concentrated to give compound **2** as a syrup.

The above syrup was dissolved in pyridine (966 mL). After cooling with an ice bath, methanesulfonyl chloride (213.0 mL, 2.75 mol) was added dropwise via an additional funnel over 2 h. After stirring at 0 °C for an additional 3 h (monitored by TLC), the reaction mixture was poured into ice−water (6000 mL), stirred for 30 min, and filtered. The filter cake was washed with water several times and recrystallized from ethanol (ca. 670 mL) to give mesylate **3** as a white crystal (300.8 g, 40% yield over two steps based on L-sorbose) (50% yield over two steps based on the recovered starting material): mp 120−122 °C; $[\alpha]^{25}_D = -28.0$ (*c*, 1.06, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.88 (d, J = 1.8 Hz, 1H), 4.46 (dd, J = 3.3, 1.8 Hz, 1H), 4.25 (d, J = 9.9 Hz, 1H), 4.22 (m, 1H), 4.20 (d, J = 9.9 Hz, 1H), 4.01 (dd, J = 13.2, 3.0 Hz, 1H), 3.92 (dd, J = 13.2, 3.0 Hz, 1H), 3.16 (s, 3H), 1.55 (s, 3H), 1.47 (s, 3H), 1.42 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 111.5, 109.8, 98.2, 84.2, 73.3, 73.25, 72.1, 60.4, 38.9, 28.3, 26.0, 25.9, 20.1. Anal. Calcd for $C_{13}H_{22}O_8S$: C, 46.14; H, 6.55. Found: C, 46.00; H, 6.39.

Synthesis of Alcohol 7 from Mesylate 3. A suspension of mesylate **3** (pulverized) (100.0 g, 0.30 mol) in 4.5% (w) H_2SO_4 (1000 mL) was stirred at room temperature until all the starting material had been consumed as monitored by TLC (3 h).[7] After it was made alkaline with 9 M NaOH (200 mL, 1.80 mol), the reaction mixture was heated at 90−100 °C until the reaction was completed as monitored by TLC (8 h).[12] After being acidified to pH ∼1 with 9 M H_2SO_4 (∼50 mL), the reaction mixture was heated at 70−80 °C for 30 min,[9] neutralized (pH 7.0) with 9 M NaOH (∼44 mL), and concentrated to give a residue. The resulting residue was extracted by refluxing with ethanol (4 × 500 mL). The ethanol solution was concentrated to give L-fructose as a yellow syrup.

To a suspension of the above L-fructose syrup[13] in acetone (500 mL) was added 2,2-dimethoxypropane (109.0 mL, 0.89 mol). After cooling to 0 °C, concentrated H_2SO_4 (4.15 mL, 0.074 mol) was added dropwise under N_2. The resulting reaction mixture was stirred at 0 °C for 6 h (carefully monitored by GC[14]). After addition of concentrated NH_4OH (25 mL), the reaction mixture was concen-

(8) Although a higher concentration of base can accelerate the reaction, the reaction mixture becomes complex. Considering the reaction efficiency and stability of the product, using 9 M NaOH and refluxing for 8 h worked well.

(9) The reaction should be carefully monitored by TLC and quenched as soon as the reaction is finished. Heating the reaction mixture for a long time causes problems, possibly polymerization of the L-fructose.

(10) Large quantities of L-sorbose were purchased from MP Biomedicals, LLC (Aurora, OH).

(11) The GC retention time of the main peak is 3.32 min. Conditions: column, VA-5MS, Varian chromatography systems (VA-122553-20); oven, from 150 to 250 °C (20 °C/min); carrier, helium, head pressure 25 psi; detection: FID 250 °C.

(12) The disappearance and appearance of compounds **4**−**6** can be clearly detected by TLC. The R_f values of compounds **4**, **5**, and **6** are 0.57, 0.70, and 0.30, respectively, using EtOAc as a solvent.

(13) The obtained L-fructose was a sticky syrup. Freezing the syrup with dry ice led to a solid which was easier to manipulate.

trated to a solid which was then dissolved in CH_2Cl_2 (400 mL). The resulting solution was washed with water (2 × 200 mL), brine (200 mL), dried over Na_2SO_4, filtered, concentrated, and purified by silica gel chromatography (ethyl acetate: hexane, 1:5 to 1:3, v/v) to give alcohol **7** as a white solid (32.5 g, 42% yield from mesylate **3**): mp 115−116 °C; $[\alpha]^{25}_D = +142.4$ (*c*, 1.05, $CHCl_3$); IR (NaCl, film): 3458 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.21 (ddd, $J = 5.7$, 2.7, 0.6 Hz, 1H), 4.19 (d, $J = 9.0$ Hz, 1H), 4.14 (dd, $J = 6.9$, 5.7 Hz, 1H), 4.13 (dd, $J = 13.2$, 2.7 Hz, 1H), 4.02 (d, $J = 13.2$ Hz, 1H), 3.99 (d, $J = 9.0$ Hz, 1H), 3,67 (dd, $J = 8.1$, 6.9 Hz, 1H), 2.01(d, $J = 8.1$ Hz, 1H), 1.54 (s, 3H), 1.52 (s, 3H), 1.45 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 111.9, 109.4, 104.6, 76.8, 73.5, 72.3, 70.4, 60.8, 28.2, 26.6, 26.5, 26.2. Anal. Calcd for $C_{12}H_{20}O_6$: C, 55.37; H, 7.74. Found: C, 55.55; H, 7.60.

Synthesis of Ketone Ent-1. To a solution of alcohol **7** (10.4 g, 0.04 mol) in CH_2Cl_2 (100 mL) was added PDC (22.57 g, 0.06 mol), followed by freshly powdered 3 Å molecular sieves (37.6 g) and acetic acid (10 drops). After stirring at room temperature under N_2 overnight, the reaction mixture was filtered through a pad of silica gel and washed (ethyl ether:hexane, 1:1, v/v, 500 mL) until no product came out. The filtrate was concentrated and recrystallized from hot hexane (40−45 mL) to give ketone **ent-1** as a white crystal (9.0 g, 87%): mp 99−100 °C; $[\alpha]^{25}_D = +120.0$ (*c* 1.0, $CHCl_3$); IR (NaCl, film): 1743 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.73 (d, $J = 5.4$ Hz, 1H), 4.60 (d, $J = 9.6$ Hz, 1H), 4.55 (dd, $J = 5.4$, 2.4 Hz, 1H), 4.39 (dd, $J = 13.5$, 2.4 Hz, 1H), 4.12 (d, $J = 13.5$ Hz, 1H), 3.99 (d, $J = 9.6$ Hz, 1H), 1.55 (s, 3H), 1.46 (s, 3H), 1.40 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.9, 113.9, 110.7, 104.2, 78.1, 76.0, 70.1, 60.2, 27.4, 26.8, 26.3, 26.2. Anal. Calcd for $C_{12}H_{18}O_6$: C, 55.81; H, 7.02. Found: C, 56.09; H, 7.27.

(14) Alcohol **7** is the kinetic product of the reaction. Controlling the reaction time is important to minimize its isomerization to the thermodynamic product. The GC retention time of the main peak is 4.42 min. Conditions: column, VA-5MS, Varian chromatography systems (VA-122553-20); oven, 170 °C; carrier, helium, head pressure 25 psi; detection, FID 250 °C.

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Supporting Information Available: The NMR spectral data for compounds **3**, **7**, and **ent-1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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