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Practical Synthesis of Shi's Diester Fructose Derivative for Catalytic Asymmetric Epoxidation of Alkenes

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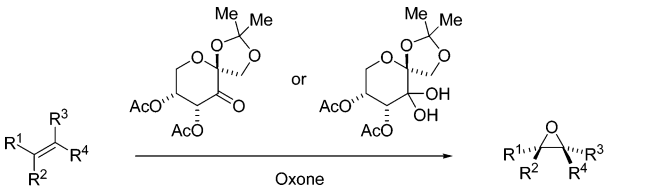
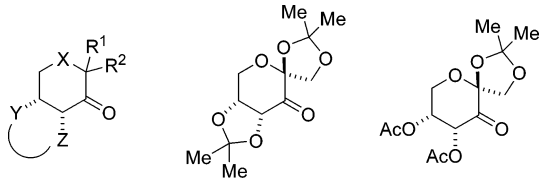
Received August 9, 2005



(49-75% yield; 81-96% ee)

A practical synthesis of Shi's diester **3** for catalytic asymmetric epoxidations has been developed. The catalyst has been prepared in multigram quantities from D-fructose in four steps with a 66% overall yield. Efficiency, cost, and selectivity aspects of the reagents involved for its preparation have been taken care of during its preparation. The workup procedures have been simplified to the bare minimum, rendering a very practical preparation method. The well-known high efficiency of this catalyst **3** in the epoxidation of α,β-unsaturated carbonyl compounds has also proved to be high in unfunctionalized alkenes.

Chiral dioxiranes (generated from potassium peroxomonosulfate and ketones) are practically unrivaled in their use as agents for the asymmetric epoxidation of specific kinds of alkenes (unfunctionalized *trans*-alkenes and trisubstituted olefins).[1] In the asymmetric catalytic version of this transformation, the chiral dioxirane is generated in situ from catalytic amounts of a chiral ketone which is regenerated upon epoxidation.[2] Following the first asymmetric epoxidation using a chiral ketone reported by Curci,[3] numerous chiral ketones have been studied by several research groups.[2] Outstanding work in this area has been published by Shi's group, which has led to the development of highly efficient epoxidation catalysts with the general structure **1**.[4,5] Fructose-derived ketone **2**, which is commercialy available, is the most well-known asymmetric catalyst from this series. High enantioselectivity has been obtained with its use in the epoxidation of a wide variety of trans-, cis-, and trisubstituted alkenes. The scope and the different factors that govern the transformation have been well studied, rendering this asymmetric transformation very valuable and of wide-ranging application.[4,5] Shi's diester fructose derivative **3** appears even more attractive than **2** as far as the alkene scope (it can be further used for α,β-unsaturated esters) and catalyst robustness (it is not so easily degraded in the reaction media by an undesired Baeyer–Villiger reaction) are concerned.[5j] We wish to report here the development of a most practical procedure for the synthesis of **3** that allows its preparation in multigram amounts without any intermediate purification and its application in the epoxidation of a number of unfunctionalized alkenes. In addition, the isolation and characterization of a carbonyl hydrate of **3** depicting the same catalytic activity and enantioselectivity in the epoxidation reaction is also reported.



1 **2** **3**

D-Fructose has been transformed into **4** following the procedure described by Kang and co-workers.[6] The reaction was performed in acetone, which acted as both reagent and solvent (50 mol of acetone per mol of D-fructose) at room temperature using sulfuric acid as the catalyst (ca. 30 mol %), and the product could be easily isolated in ca. 50% yield after recrystallization.[7] Compound **4** was converted to **2** by using the ruthenium-promoted oxidation of secondary alcohols developed by Morris and Kiely[8] and further improved by Mio et al. (Scheme 1).[9] This transformation, which uses catalytic amounts of a ruthenium precursor and sodium metaperiodate as the stoichiometric oxidant, renders compound **2** in almost quantitative yield.[9] The selective deketalization of **2** has been described by Shi and co-workers using

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(1) (a) Adam, W.; Curci, R.; Edwards, J. O. *Acc. Chem. Res.* **1989**, *22*, 205–211. (b) Murray, R. W. *Chem. Rev.* **1989**, *89*, 1187–1201. (c) Curci, R.; Dinoi, A.; Rubino, M. F. *Pure Appl. Chem.* **1995**, *67*, 811–822. (d) Adam, W.; Smerz, A. K. *Bull. Soc. Chim. Belg.* **1996**, *105*, 581–599. (e) Denmark, S. E.; Wu, Z. *Synlett* **1999**, 847–859. (f) Adam, W.; Saha-Möller, C. R.; Zhao, C.-G. *Org. React.* **2002**, *61*, 219–516.

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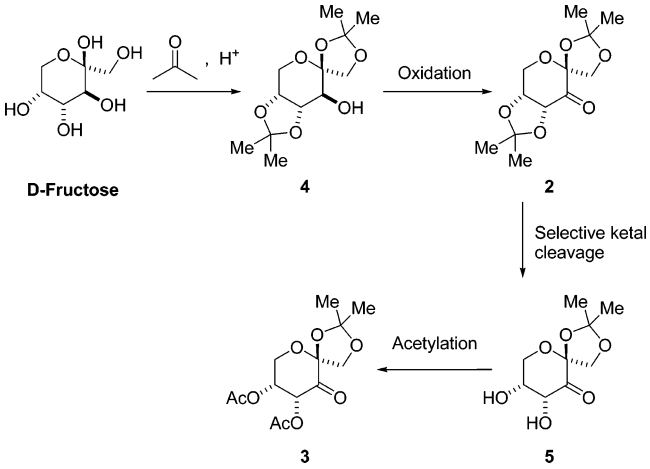
(3) (a) Curci, R.; Fiorentino, M.; Serio, M. R. *Chem. Commun.* **1984**, 155–156. (b) Curci, R.; D'Accolti, L.; Fiorentino, M.; Rosa, A. *Tetrahedron Lett.* **1995**, *36*, 5831–5834.

(4) (a) Tu, Y.; Wang, Z.-X.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806–9807. (b) Wang, Z.-X.; Shi, Y. *J. Org. Chem.* **1997**, *62*, 8622–8623. (c) Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224–11235. (d) Wang, Z.-X.; Tu, Y.; Frohn, M.; Shi, Y. *J. Org. Chem.* **1997**, *62*, 2328–2329. (e) Cao, G.-A.; Wang, Z.-X.; Tu, Y.; Shi, Y. *Tetrahedron Lett.* **1998**, *39*, 4425–4428. (f) Zhu, Y.; Tu, Y.; Yu, H.; Shi, Y. *Tetrahedron Lett.* **1998**, *39*, 7819–7822. (g) Frohn, M.; Dalkiewicz, M.; Tu, Y.; Wang, Z.-X.; Shi, Y. *J. Org. Chem.* **1998**, *63*, 2948–2953. (h) Frohn, M.; Wang, Z.-X.; Shi, Y. *J. Org. Chem.* **1998**, *63*, 6425–6426. (i) Wang, Z.-X.; Shi, Y. *J. Org. Chem.* **1998**, *63*, 3099–3104. (j) Tu, Y.; Wang, Z.-X.; Frohn, M.; He, M.; Yu, H.; Tang, Y.; Shi, Y. *J. Org. Chem.* **1998**, *63*, 8475–8485. (k) Wang, Z.-X.; Miller, S. M.; Anderson, O. P.; Shi, Y. *J. Org. Chem.* **1999**, *64*, 6443–6458. (l) Feng, X.; Shu, L.; Shi, Y. *J. Am. Chem. Soc.* **1999**, *121*, 11002–11003. (m) Zhu, Y.; Manske, K. J.; Shi, Y. *J. Am. Chem. Soc.* **1999**, *121*, 4080–4081. (n) Wang, Z.-X.; Cao, G.-A.; Shi, Y. *J. Org. Chem.* **1999**, *64*, 7646–7650. (o) Warren, J. D.; Shi, Y. *J. Org. Chem.* **1999**, *64*, 7675–7677. (p) Shu, L.; Shi, Y. *Tetrahedron Lett.* **1999**, *40*, 8721–8724.

10.1021/jo051682h CCC: $30.25
Published on Web 10/28/2005

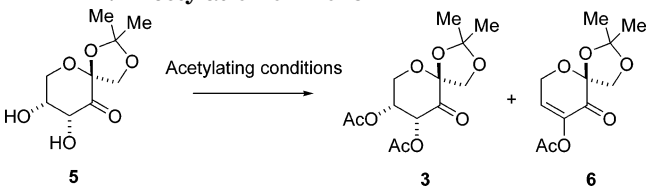
SCHEME 1



water and DDQ.[5j] Alternative deprotection methods[6,8] were studied for this transformation, and excellent results were obtained by allowing **2** to react at room temperature in a mixture of acetic acid and water (80:20 v/v). A simple elimination of this solvent mixture under vacuum afforded the deprotected compound **5** in high purity. The easy workup together with overcoming the toxicity and purification problems associated with DDQ renders this deprotection method very practical. Most interestingly, the crude mixture containing diol **5** could be directly acetylated to afford **3** without any further purification.

It is important to recall here that Ac_2O in the presence of DMAP has been reported by Shi as the reagent of choice for the diacetylation of **5**.[5j] However, we repeatedly observed that variable amounts of the elimination product **6** were formed together with the desired compound when DMAP was used as the catalyst in the acetylation step (Table 1). The structure of **6** was proved by X-ray analysis (see Supporting Information). Furthermore, we observed that the main factor,[10] which favored the formation of this byproduct, was the amount of catalyst (compare entries 1 and 2 in Table 1). Whereas the use of 2 mol % of the catalyst (entry 1) afforded a mixture of diacetate **3** and elimination product **6**, the use of 20 mol % of DMAP (entry 2) afforded exclusively the elimination product **6**. As a result of this problem, we decided to study milder and more selective acetylation conditions. The results are summarized in Table 1. The use of sodium acetate under microwave irradiation has been reported to be a useful catalyst for the acetylation of several carbohydrates.[11] Unfortunately, the use of this milder acetylation catalyst, even in a 1% molar amount, has turned out to be unselective, with the ratio of **3** to **6** being 63:37 (entry 3). On the contrary, $ZnCl_2$,[12] a very convenient and cheap Lewis acid, has given a high selectivity in the acetylation reaction under the same conditions in which AcONa was unselective (entry 4). The acetylation reaction can be carried out as well with very high selectivity in a very short period of time under thermal conditions (entry 5) or after 3 h at room temperature (entry 6).

TABLE 1. Acetylation of Diol 5



entry	acetylating agent	catalyst	reaction conditions	ratio **3**/**6**[a]
1	Ac_2O (3-fold molar excess)	DMAP (2 mol %)	DCM, rt, 16 h	64:36[b]
2	Ac_2O (3-fold molar excess)	DMAP (20 mol %)	DCM, rt, 16 h	1:99
3	Ac_2O (8.7-fold molar excess)	NaOAc (1 mol %)	Ac_2O; 50 °C, 5 min[c]	63:37
4	Ac_2O (8.7-fold molar excess)	$ZnCl_2$ (1 mol %)	Ac_2O; 50 °C, 5 min[c]	99:1
5	Ac_2O (8.7-fold molar excess)	$ZnCl_2$ (1 mol %)	Ac_2O; 50 °C, 15 min	99:1
6	Ac_2O (4-fold molar excess)	$ZnCl_2$ (2.5 mol %)	Ac_2O; rt, 3 h	99:1

[a] Measured by ^1H NMR after doing the same workup as described in ref 5j. [b] This value refers to the diacetylation of diol **5** as the raw material derived from **4**. A 75:25 ratio was observed when chromatographically pure starting material **5** was used. [c] The acetylation step was carried out under microwave irradiation.

The reaction conditions from entry 6 were chosen for the acetylation step as it appeared to us the most suitable option for large-scale preparations of the target catalyst. The whole synthetic sequence (oxidation of **4**, selective deprotection of **2**, and the final diacetylation of **5**) was performed, and analytically pure Shi's diester (compound **3**) could be isolated in 66% overall yield in the multigram scale (ca. 8 g) after a chromatographic filtration. Although the chromatographic purification could be carried out very straightforwardly, we tried to find alternative ways to override this method. An aqueous workup was essayed as well, and most interestingly, the carbonyl hydrate of compound **3** (the 1,1-diol **7**) rather than the parent carbonyl compound was isolated as a solid material in 41% overall yield. The structure of this newly isolated

(5) (a) Shu, L.; Shi, Y. *J. Org. Chem.* **2000**, *65*, 8807−8810. (b) Frohn, M.; Shi, Y. *Synthesis* **2000**, 1979−2000. (c) Tian, H.; She, X.; Xu, J.; Shi, Y. *Org. Lett.* **2001**, *3*, 1929−1931. (d) Zhu, Y.; Shu, L.; Tu, Y.; Shi, Y. *J. Org. Chem.* **2001**, *66*, 1818−1826. (e) Wang, Z.-X.; Miller, S. M.; Anderson, O. P.; Shi, Y. *J. Org. Chem.* **2001**, *66*, 521−530. (f) Tian, H.; She, X.; Shi, Y. *Org. Lett.* **2001**, *3*, 715−718. (g) Shu, L.; Shi, Y. *Tetrahedron* **2001**, *57*, 5213−5218. (h) Tian, H.; She, X.; Yu, H.; Shu, L.; Shi, Y. *J. Org. Chem.* **2002**, *67*, 2435−2446. (i) Feng, X.; Shu, L.; Shi, Y. *J. Org. Chem.* **2002**, *67*, 2831−2836. (j) Wu, X.-Y.; She, X.; Shi, Y. *J. Am. Chem. Soc.* **2002**, *124*, 8792−8793. (k) Shu, L.; Shen, Y.-M.; Burke, C.; Goeddel, D.; Shi, Y. *J. Org. Chem.* **2003**, *68*, 4963−4965. (l) Shu, L.; Wang, P.; Gan, Y.; Shi, Y. *Org. Lett.* **2003**, *5*, 293−296. (m) Wang, Z.-X.; Shu, L.; Frohn, M.; Tu, Y.; Shi, Y. *Org. Synth.* **2003**, *80*, 9−17. (n) Tu, Y.; Frohn, M.; Wang, Z.-X.; Shi, Y. *Org. Synth.* **2003**, *80*, 1−8. (o) Shu, L.; Shi, Y. *Tetrahedron Lett.* **2004**, *45*, 8115−8117. (p) Hickey, M.; Goeddel, D.; Crane, Z.; Shi, Y. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5794−5798. (q) Crane, Z.; Goeddel, D.; Gan, Y.; Shi, Y. *Tetrahedron* **2005**, *61*, 6409−6417. (r) Lorenz, J. C.; Frohn, M.; Zhou, X.; Zhang, J. R.; Tang, Y.; Burke, C.; Shi, Y. *J. Org. Chem.* **2005**, *70*, 2904−2911.

(6) Kang, J.; Lim, G. J.; Yoon, S. K.; Kim, M. Y. *J. Org. Chem.* **1995**, *60*, 564−577.

(7) Yields ranged in our hands from 46 to 53% in several operations.

(8) Morris, P. E., Jr.; Kiely, D. E. *J. Org. Chem.* **1987**, *52*, 1149−1152.

(9) Mio, S.; Kumagawa, Y.; Sugai, S. *Tetrahedron* **1991**, *47*, 2133−2144.

(10) We have observed that the workup procedure can affect as well the selectivity of the reaction. The treatment of **3** with basic compounds (either amines or dilute inorganic solutions such as 5% $NaHCO_3$) must be avoided as the ratio of elimination compound **6** increases very easily. Heating the acetylation crude mixture for long periods of time increases the ratio of elimination product, too.

(11) Limousin, C.; Cleophax, J.; Petit, A.; Loupy, A.; Lukacs, G. *J. Carbohydr. Chem.* **1997**, *16*, 327−342.

(12) $ZnCl_2$ was activated before using: it was heated at 240 °C in vacuo (3×10^{-3} mbar) for 6 h and used in the next few hours after activation.

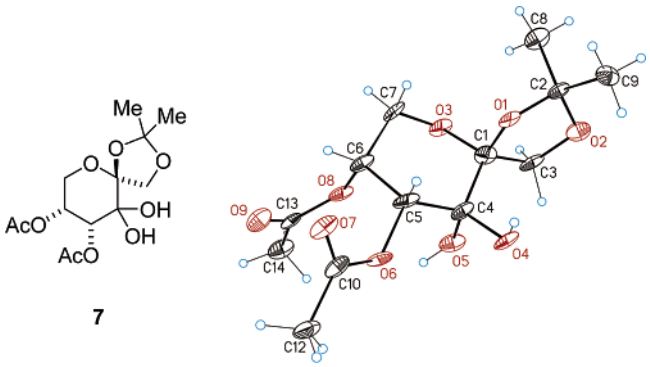


FIGURE 1. Ortep plot (ellipsoids drawn a 50% probability level) of the molecular structure of **7**.

material could be unambiguously proven by single-crystal X-ray structure analysis. The Ortep plot of the structure obtained using small crystal needles grown in 1,1,1-trichloroethane is shown in Figure 1.

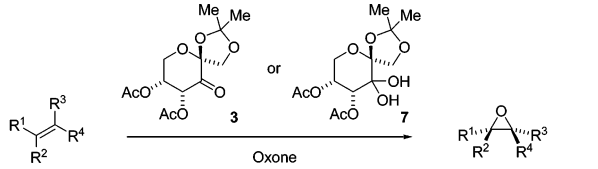
The preparation method for **3** described in this Note constitutes a good and more practical alternative to its described synthesis, as it is characterized by simple procedures, mild reaction conditions, easy workup procedures, and high reaction yields and selectivities. Furthermore, the possibility to isolate **7** just by changing the final workup procedure adds more value to this preparation method.

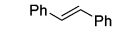
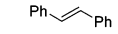
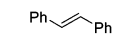
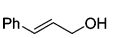
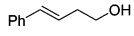
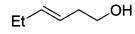
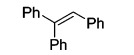
The epoxidation of different alkenes using diacetate **3** could be carried out straightforwardly. The epoxidations were performed in an aqueous−organic media (pH = 6 buffer[13] −CH_3CN−dimethoxyethane) in which the substrate, ketone **3**, and a phase transfer catalyst were first dissolved.[4h] The reactions were carried out normally with an 8−10% molar amount of catalyst at 0 °C as this temperature offered a good balance between conversion and selectivity at that catalyst loading. A solution of oxone in the pH 6 buffer and an aqueous solution of K_2CO_3 (generally 2.4 equiv) were simultaneously added to the substrate containing solution within 2 h with the help of two syringe pumps. The pH value increased from 6 to ca. 9 throughout the 2 h addition period. After the addition was complete, the reaction mixture was further stirred for 16 h without meaningful changes in the pH value. The epoxidation results have been summarized in Table 2.

Diacetate **3** (see Table 2) is very effective as epoxidation catalyst toward a variety of *trans*-aryl-substituted olefins (entries 1, 2, 4, 5, and 7 in Table 2). *E*-Stilbene could be epoxidized with good yield and enantioselectivity (53% yield, 90% ee) using 10 mol % of catalyst at 0 °C. The epoxidation product **9a** could be enantiomerically enriched up to >99% ee by recrystallization in hexane (entry 1). The enantioselectivity of the epoxidation can be increased up to 94% ee using 30 mol % catalyst (normal catalyst ratio for the standard Shi's catalyst **2**; entry 2) at the same temperature. A number of disubstituted *E*-allylic and homoallylic alcohols (entries 4−6) were epoxidized with the procedure described in this work too. The final epoxy alcohols were obtained in good to high enantioselectivities (81−96% ee), and it should be mentioned that 30 mol % amount of catalyst **3** was required to achieve 83% ee for epoxy alcohol **9d**. Trisubstituted olefins such as triphenylethylene could be epoxidized with high selectivity using diester **3** and the epoxidation procedure described in this work (entry 7).

(13) The pH = 6 buffer consisted of 6.8 g of KH_2PO_4 and 5.7 mL of 1 M KOH/L.

TABLE 2. Epoxidation Examples Using Diacetate 3 or Its Hydrate 7



Entry	Alkene	Reaction conditions	Yield	Ee (conf.)	Ee enrichment[a]
1		10 mol% **3**, 0ºC, 2[b]+16[c]h	53%[d]	90%[d], (*R,R*)-**9a**	Hexane, 46%, >99% ee
2		30 mol% **3**, 0ºC, 2[b]+16[c]h	75%	94%, (*R,R*)-**9a**	--
3		10 mol% **7**, 0ºC, 2[b]+16[c]h	49%	89%, (*R,R*)-**9a**	--
4		10 mol% **3**, 0ºC, 2[b]+16[c]h	68%	96%, (*R,R*)-**9b**	--
5		8 mol% **3**, 0ºC, 2[b]+16[c]h	67%	81%[e], (*R*)-**9c**	--
6		30 mol% **3**, 0ºC, 2[b]+16[c]h	[f]	83%[e], (*R,R*)-**9d**	--
7		8 mol% **3**, 0ºC, 2[b]+16[c]h	58%	87%, (*R*)-**9e**	Hexane, 45%, 90% ee

[a] The epoxide was recrystallized after chromatography to improve its ee. The solvent, overall yield, and ee are shown. [b] Oxone and base addition times. [c] Reaction time. [d] Mean value of four experiments. [e] In this case 7.2 equiv of K_2CO_3 were added. The pH value increased from 6 to 10. [f] Not determined (epoxy alcohol **9d** distilled together with the solvents during the workup).

It should be pointed out that hydrate **7** was as efficient as Shi's catalyst **3** in the epoxidation of *E*-stilbene (compare entries 1 and 3): stilbene oxide **9a** could be isolated in the same yield and with the same optical purity within experimental error. Although Shi has reported that other epoxidation catalysts related to **3** exist largely as hydrates,[5f] the involvement of these hydrate forms in the catalytic cycle has not even been considered. The fact that hydrate **7** as well as ketone **3** are catalytically active together with the equilibration of ketone **3** to hydrate **7** in hydroorganic media[14] poses them as plausible intermediates in the epoxidation cycle.

In summary, we have developed a practical synthesis of Shi's diacetate **3**. The key step in its preparation has been the optimization of acetylation conditions, which can render diacetate **3** in a highly chemoselective way. This goal has been achieved using $ZnCl_2$ as the Lewis acid for this transformation. Multigram amounts of catalyst have been routinely prepared in our group in a reproducible way with the described method. The use of Shi's diester **3** has been extended to a number of unfunctionalized alkenes, too. An efficient epoxidation procedure for this kind of alkene involving **3** and oxone in a hydroorganic medium at pH = 6−9 has been described. The catalyst has been shown to be more robust for these substrates than the ketone **2**, as high enantioselectivities are already obtained with only 10% molar amount of catalyst. Work is in progress to further extend the application of **3** and **7** to new substrates and to study the relevance of **7** in the catalytic cycle.

Experimental Section

Optimized Conditions for the Preparation of 4,5-Di-*O*-acetyl-1,2-*O*-isopropylidene-D-erythro-hexos-2,3-diulo-2,6-pyranose, 3. (a) Oxidation. Compound **4** (10.0 g, 38.42 mmol), Et_3BzNCl (442 mg, 1.92 mmol), $NaIO_4$ (12.4 g, 57.24 mmol), and K_2CO_3 (826 mg, 5.92 mmol) were vigorously stirred in a mixture of 33 mL of $CHCl_3$ and 33 mL of H_2O. $RuCl_3$ monohydrate (303 mg, 1.34 mmol) were added, and the reaction mixture was heated at 70 °C. 2-Propanol (11 mL) was added after 2 h, and the suspension was further stirred for 5 h. The reaction mixture was filtered through a Celite pad, and this material was washed with CH_2Cl_2 (2 × 35 mL). This solution was mixed with the filtrate, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were washed with saturated Na_2SO_3 (130 mL), brine (100 mL), and water (100 mL). The solid, which was obtained after drying and evaporating the solvents, was not purified further. ^{1}H NMR data were in agreement with the described ones.[9] (b) Selective deketalization. AcOH (80 mL) and water (20 mL) were added at once to the oxidation raw material from the previous step (8.77 g, 38.42 mmol referred to starting material **4**). The resulting solution was stirred for 12 h at room temperature. The solvents were removed in vacuo at room temperature, and the residue was dissolved in CH_2Cl_2 (50 mL). The solid, which was obtained after drying (an. $NaSO_4$) and evaporating the CH_2Cl_2, was not purified further. ^{1}H NMR and ^{13}C NMR data were in agreement with the described ones.[5j,15] (c) Acetylation. $ZnCl_2$ (132 mg, 0.96 mmol) was added to a suspension of diol **5** arising from part b (8.56 g, 38.42 mmol referred to starting material **4**) in Ac_2O (19.4 mL, 153.95 mmol), and the mixture was stirred under N_2 at room temperature for 3 h. The reaction mixture was diluted with AcOEt (20 mL), and the solution was passed through a neutral silica gel pad (15 g). SiO_2 was washed with AcOEt (100 mL), the combined organic solutions were gathered, AcOEt was removed in vacuo, and the resulting oil was chromatographed (75 g neutral SiO_2) using hexane/EtOAc (from 1:0 to 7:3) mixtures as the eluent. The oil, which was obtained after drying and evaporating the solvents, was used as the catalyst for the epoxidation of alkenes without any further purification (7.71 g, 66% overall yield). Physical and spectroscopic data were in agreement with the described ones.[5j] $[\alpha]^D_{25}$ −104 (*c* 0.95, $CHCl_3$) [lit.[5j] $[\alpha]^D_{25}$ −103 (*c* 0.98, $CHCl_3$)]; Anal. Calcd for $C_{13}H_{18}O_8$: C, 51.65; H, 6.00. Found C, 51.36; H, 6.10.

Optimization of the Acetylation Conditions (Experiments Described in Table 1). A quantity of 510 mg of raw material **5** obtained as indicated in part b above (2.29 mmol referred to starting material **4**) and the catalyst were dissolved in the corresponding Ac_2O amount, and the mixture was stirred under N_2 at the given temperature for the given time in each case. The experiments under microwave irradiation were carried out in a CEM discover microwave reactor (temperature is automatically controlled by a noncontact infrared sensor that monitors and controls the temperature conditions of the reaction vessel). The reaction mixture was filtered through a short silica gel pad (5.0 g neutral SiO_2) eluting with a mixture of hexane/AcOEt, 1:1 v/v. The ratio between **3** and **6** was measured by integration of appropriated signals in the ^{1}H NMR spectra of the mixture after the chromatographic purification.

(5*S*)-9-Acetoyloxy-2,2-dimethyl-1,3,6-trioxaspiro[4.5]dec-8-en-10-one, 6. DMAP (940 mg, 7.68 mmol) and Ac_2O (14.5 mL, 115.49 mmol) were added to a solution of **5** (8.87 g, 38.42 mmol referred to starting material **4**, prepared as described in part b of the recipe for the preparation of **3**) under N_2 in 200 mL of CH_2Cl_2 at room temperature. The reaction mixture was filtered through a short SiO_2 gel column. The filtrate was concentrated, and the residue was chromatographed using hexane/AcOEt (from 1:0 to 3:2) mixtures as the eluent to give **6** as an oil (4.26 g, 17.59 mmol, 46% yield). This oil was recrystallized in hexane to get a white solid (3.37 g, 13.91 mmol, 36% overall yield). $[\alpha]^D_{25}$ −129 (*c* 0.90, $CHCl_3$); mp 63.7−64.4 °C; IR (ATR) 1764, 1702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.68 (dd, J = 4.3, 1.9 Hz, 1H), 4.79 (dd, J = 18.6, 1.8 Hz, 1H), 4.59 (d, J = 9.2 Hz, 1H), 4.42 (dd, J = 18.6, 4.3 Hz), 3.98 (d, J = 9.2 Hz, 1H), 2.20 (s, 3H), 1.52 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.1, 168.0, 140.9, 133.5, 113.7, 102.9, 70.8, 59.9, 26.5, 25.6, 20.2; HRMS calcd for $C_{11}H_4O_6$ 265.0688, Found 265.0685. Anal. Calcd for $C_{11}H_4O_6$: C, 54.54; H, 5.83. Found C, 54.20; H, 6.07.

4,5-Di-*O*-acetyl-3-hydroxy-1,2-*O*-isopropylidene-D-fructopyranose, 7. Oxidation, selective deketalization, and acetylation were carried out as described for **3** starting from compound **4** (10.0 g, 38.42 mmol). Ice (20.0 g) was added to the reaction mixture once the acetylation was complete (3 h stirring at room temperature). The precipitate was filtered off the solution, washed with ice−water (2 × 15 mL), and lyophilized to give **7** as a white solid (5.14 g, 41% overall yield). $[\alpha]^D_{25}$ −116 (*c* 0.98, $CHCl_3$); mp 91.1−93.7 °C; IR (ATR) 3467, 1735 cm^{-1}; ^{1}H NMR (500 MHz, D_2O) δ 5.34 (dd, J = 4.1, 1.8 Hz, 1H), 5.17 (d, J = 4.1 Hz, 1H), 4.39 (d, J = 9.5 Hz, 1H), 4.24 (dd, J = 13.6, 1.8 Hz), 4.06 (d, J = 9.5 Hz, 1H), 3.85 (dd, J = 13.6, 1.8 Hz, 1H), 2.16 (s, 3H), 2.13 (s, 3H), 1.55 (s, 3H), 1.47 (s, 3H); ^{13}C NMR (125 MHz, D_2O) δ 173.5, 172.7, 113.9, 106.7, 91.2, 70.3, 69.7, 68.7, 61.4, 26.0, 24.9, 20.3, 20.1; HRMS calcd for $C_{13}H_{20}O_9Na$ 343.1005, Found 343.1008. Anal. Calcd for $C_{13}H_{20}O_9$: C, 49.00; H, 6.51. Found C, 48.75; H, 6.29.

General Procedure for the Epoxidation of Alkenes. Alkene (2.22 mmol) and the required amount of catalyst **3** or **7** (8−30 molar %) were dissolved in acetonitrile/dimethoxymethane (44 mL, 1:2 v/v). A pH = 6 buffer solution (8 mL) and tetrabutylammonium hydrogen sulfate (35 mg, 0.10 mmol) were slowly added with stirring, and the mixture was cooled to the desired temperature. The flask was equipped with two syringe pumps; one of them was filled with a solution of oxone (2.23 g, 3.62 mmol) in the pH = 6 buffer (14 mL), and the other one with a solution of K_2CO_3 (744 mg, 5.33 mmol) in water (14 mL). The two solutions were added dropwise over a 2 h period (syringe pump). The solution was stirred at the desired temperature for the corresponding reaction time. The crude was quenched by addition of water (40 mL) and pentane (10 mL). The reaction mixture was extracted with an organic solvent (**9a** and **9e**: hexane, 4 × 40 mL; **9b**−**d**: 4 × 40 mL DCM). The combined organic extracts were washed with brine (50 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel.

The ee's were determined by chiral chromatography, and the configuration of the epoxides were established by comparison with either reported retention times or optical rotations (**9a**: chiralpak AD,[16] (*R*,*R*)-**9a** Rt 5.6 min, (*S*,*S*)-**9a** Rt 8.6 min; **9b**: chiralcel OD,[4i] (*S*,*S*)-**9b** Rt 19.3 min, (*R*,*R*)-**9b** Rt 21.9 min; **9c**: chiralcel OD,[4i] (*S*,*S*)-**9c** Rt 7.6 min, (*R*,*R*)-**9c** Rt 9.1 min; **9d**: Alphadex, (*S*,*S*)-**9d** Rt 26.9 min, (*R*,*R*)-**9d** Rt 27.4 min, (+)-(*R*,*R*)-**9d**;[4i] **9e**: chiralpak OD,[4c] (*S*)-**9e** Rt 10.6 min, (*R*)-**9e** Rt 17.4 min, (−)-(*R*)-**9e**.[17]

Acknowledgment. A.V.-F. thanks the ICIQ and "Ramón Areces" Foundations for financial support. N.N. and P.M. thank the "Programa Torres Quevedo".

Supporting Information Available: ^{1}H and ^{13}C NMR spectra for **2**−**7** and CIF data for **6** and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO051682H

(14) ESI mass spectra of compounds **3** indicated that an equilibration between the two species was taking place in hydroorganic solution, as the peak corresponding to the hydrate **7** could be observed in a pure sample of **3**. On the other hand, no peak corresponding to ketone **3** was observed in a sample of **7**.

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