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## A NOVEL PENTOSE SYNTHESIS VIA PALLADIUM(II)-CATALYZED CYCLIZATION OF AN UNSTABLE HEMIACETAL

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**Abstract** – PdCl<sub>2</sub>(PhCN)<sub>2</sub> (5 mol%)-catalyzed cyclization of a hemiacetal derived from (*E,2S,3R*)-2,3-isopropylidenedioxy-6-(tetrahydro-2*H*-pyran-2-yl)-4-hexenal and methanol gave substituted furanoside in moderate yield, exclusively via 5-*exo*-mode cyclization, without the need for a reoxidant. New stereogenic centers at C1 and C4 on the tetrahydrofuran ring showed preferential 1*R* and 4*R* stereochemistry due to anomeric effect ( $n_o-\sigma^*_{c-o}$ ) and A<sup>1,2</sup> strain, respectively. This methodology was applied to stereocontrolled synthesis of pentoses: D-ribose and L-lyxose.

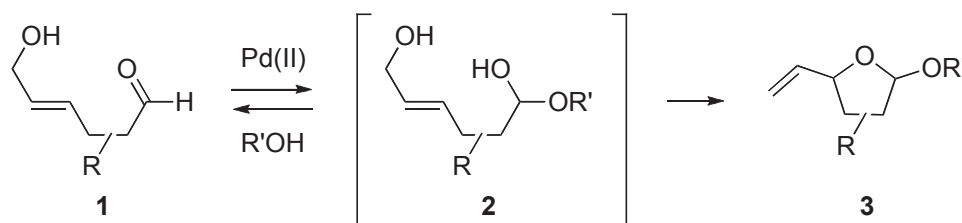
### INTRODUCTION

Substituted tetrahydrofuran moieties are often found in natural products, biologically active compounds and drugs such as antivirals.<sup>1</sup> Therefore, the stereocontrolled synthesis of substituted tetrahydrofuran derivatives has received considerable attention. Among reported methods, intramolecular cyclization of  $\pi$ -olefin-palladium complex is a powerful tool for the construction of heterocycles.<sup>2</sup> However, because the Pd(II) catalyst is reduced to Pd(0) at the end of the reaction, most of these methods require a reoxidant such as O<sub>2</sub>/CuCl<sub>2</sub> or 1,4-benzoquinone (BQ) to transform Pd(0) to Pd(II) and regenerate the catalyst. Recently, Kawai and co-workers have reported palladium(II)-catalyzed stereospecific synthesis of 2,6-substituted tetrahydropyrans from olefinic alcohol,<sup>3</sup> and we have reported stereoselective synthesis of 2,4,6-trisubstituted tetrahydropyrans from olefinic hemiacetal without a reoxidant.<sup>4</sup> To the best of our knowledge, however, there have been few reports on the construction of a tetrahydrofuran ring by palladium(II)-catalyzed cyclization without a reoxidant.<sup>5</sup> As a continuation of our work, we focus here on tetrahydrofuran. Herein, we present a novel strategy for stereocontrolled tetrahydrofuran ring construction

with palladium(II) catalyst via hemiacetal as a nucleophile and its application in syntheses of D-ribose and L-lyxose.<sup>6</sup>

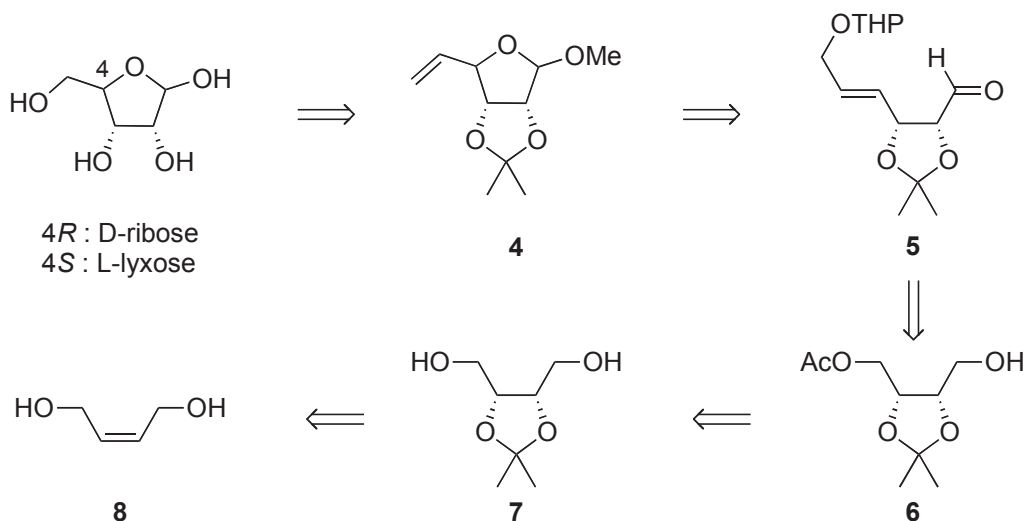
## RESULTS AND DISCUSSION

Our synthetic plan to attain a substituted tetrahydrofuran ring by palladium(II)-catalyzed cyclization is outlined in Scheme 1. The unstable hemiacetal **2** derived from aldehyde **1** and alcohol (R'OH) reacts as a nucleophile with the olefin moiety activated by palladium(II) catalyst to give the substituted furanoside **3**.



**Scheme 1.** Synthetic plan for furanoside **3** by Pd(II)-catalyzed cyclization via unstable hemiacetal **2**

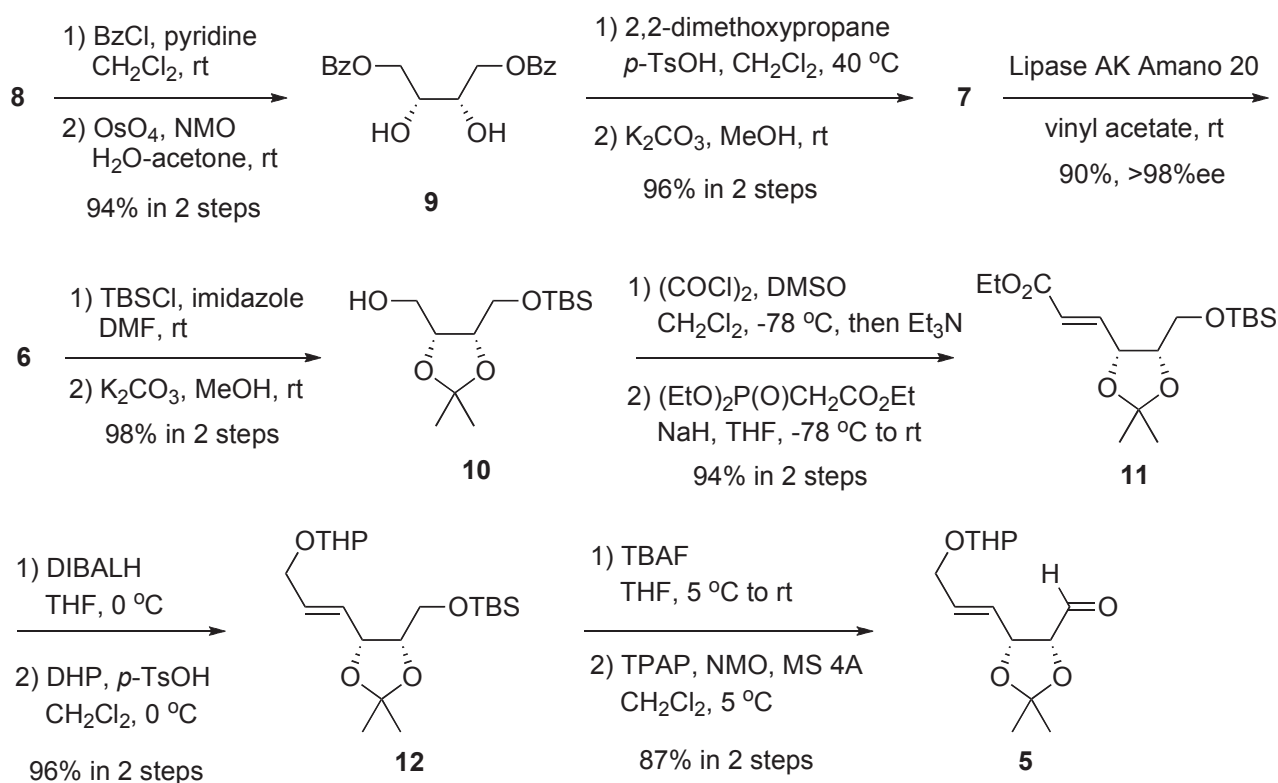
Our retrosynthetic analysis for D-ribose is illustrated in Scheme 2. We envisioned that the pentose would be obtained by transformation of 4-vinylfuranoside (**4**), and the tetrahydrofuran ring would be constructed by palladium(II)-catalyzed cyclization of the hemiacetal derived from aldehyde **5**. Aldehyde **5** would be readily prepared by side chain elongation of acetate **6**, followed by oxidation of the resulting alcohol. Optically active acetate **6** was to be synthesized by asymmetric acetylation of *meso*-diol **7** using lipase. Finally, *meso*-diol **7** would be readily available from the simple achiral *cis*-2-butene-1,4-diol (**8**).



**Scheme 2.** Retrosynthesis of furanose

Our synthesis commenced with the benzylation of *cis*-2-butene-1,4-diol (**8**), followed by dihydroxylation with a catalytic amount of osmium tetroxide and *N*-methylmorpholine *N*-oxide at room

temperature to afford the diol **9** (Scheme 3). Protection of **9** in the presence of 2,2-dimethoxypropane as its acetonide followed by methanolysis of the resulting dibenzoate afforded the *meso*-diol **7** as a key intermediate. The *meso*-diol **7** was subjected to asymmetric acetylation with lipase AK Amano 20 in vinyl acetate to give almost optically pure acetate **6**.<sup>7</sup> The enantiopurity was confirmed by NMR analysis of both MPA esters of **6** and was determined to be >98% by <sup>1</sup>H NMR. Protection of the hydroxyl group of **6** in the presence of *tert*-butyldimethylsilyl chloride, followed by methanolysis of the resulting TBS ether gave the alcohol **10**. Swern oxidation of the alcohol **10** and Horner-Wadsworth-Emmons reaction of the resulting aldehyde afforded the  $\alpha,\beta$ -unsaturated ester **11**. Reduction of the ester **11** with DIBALH, followed by protection of the resulting alcohol in the presence of dihydropyran gave **12**. Finally, removal of the TBS group in **12** using tetra-*n*-butylammonium fluoride and oxidation of the resulting alcohol under Ley's condition in the presence of *N*-methylmorpholine *N*-oxide, MS 4A and a catalytic amount of tetra-*n*-propylammonium perruthenate afforded the aldehyde **5** in 62% yield over 13 steps from the simple achiral olefin **8**.

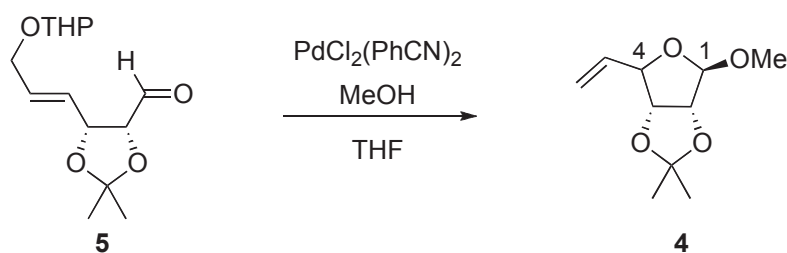


**Scheme 3.** Synthesis of aldehyde **5**

With the requisite aldehyde **5** in hand, we next focused on palladium(II)-catalyzed cyclization (Table 1). On the basis of our previous study, the cyclization was conducted in tetrahydrofuran and  $\text{PdCl}_2(\text{PhCN})_2$  was used as a Pd(II) catalyst.<sup>4</sup> When the aldehyde **5** was treated with 5 mol% of  $\text{PdCl}_2(\text{PhCN})_2$  and 5 equivalents of methanol in THF at room temperature, the cyclization proceeded smoothly and the

cycloadduct **4** was isolated as two diastereomers in 65% yield (entry 1). The stereochemistry of these diastereomers **4A** and **4B** was established by means of NOE experiments, and (1*R*,4*R*) and (1*R*,4*S*)-configurations were assigned, respectively, as shown in Figure 1. Then we investigated the effects of temperature, amounts of alcohol and Pd(II) catalyst, and additive. When the cyclization was run at 0 °C, the reaction was slower and the Pd(II) catalyst was deactivated and precipitated as palladium black before the substrate **5** was completely consumed. In contrast, when the reaction was conducted at 50 °C, the substrate **5** was consumed completely in 1 h. Under these conditions (entries 2 and 3), the cycloadduct **4** was obtained in lower yield. When the cyclization was performed in the presence of 20 equivalents of methanol, the yield of the cycloadduct **4** was not improved (entry 4). Meanwhile, when the reaction was conducted in the presence of 20 mol% of Pd(II) catalyst or 5 mol% of Pd(II) catalyst, 20 mol% of 1,4-benzoquinone (BQ) as reoxidant and 20 equivalents of methanol, the yield and selectivity were much lower (entries 5 and 6, respectively).

**Table 1.** Pd(II)-catalyzed cyclization of hemiacetal derived from **5**<sup>a</sup>



entry	Pd(II) (mol%)	MeOH (eq.)	additive (mol%)	temp. (°C)	time (h)	yield <sup>b</sup> (%)	ratio <sup>c</sup> 4 <i>R</i> :4 <i>S</i>
1	5	5	-	rt	2	65	3.0:1
2	5+5 <sup>d</sup>	5	-	0	4	57	2.4:1
3	5	5	-	50	1	53	3.5:1
4	5	20	-	rt	2	64	3.4:1
5	20	5	-	rt	2	50	1.5:1
6	5	20	BQ(20)	rt	2	44	1.1:1

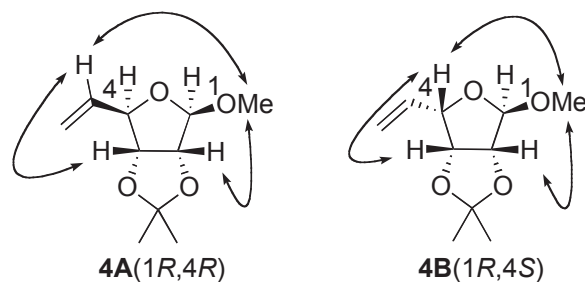
<sup>a</sup> All reactions were conducted in THF (0.02M) under an argon atmosphere.

<sup>b</sup> Isolated yields.

<sup>c</sup> The ratio was determined from 600 MHz <sup>1</sup>H NMR spectra.

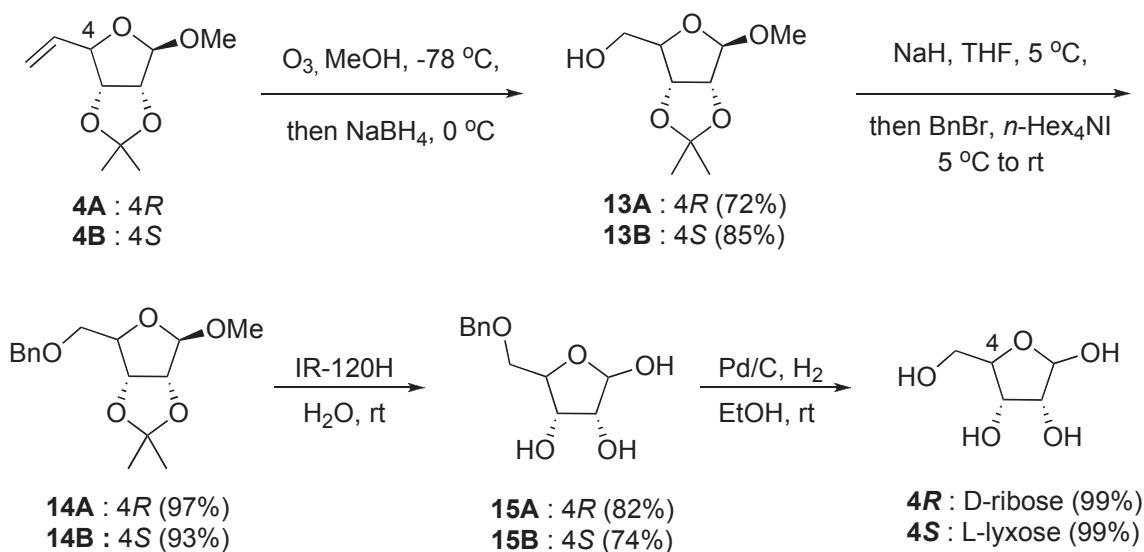
<sup>d</sup> 5 mol% of Pd(II) catalyst was added twice at 0 min and 2 h.

Although the selectivity of the cyclization was seemingly low under the conditions of entries 5 and 6, this result was not due to low selectivity of the cyclization, but reflected more rapid decomposition of the cycloadduct **4A** having (1*R*,4*R*)-configuration, as compared with **4B** having (1*R*,4*S*)-configuration.



**Figure 1.** NOE experiment of **4**

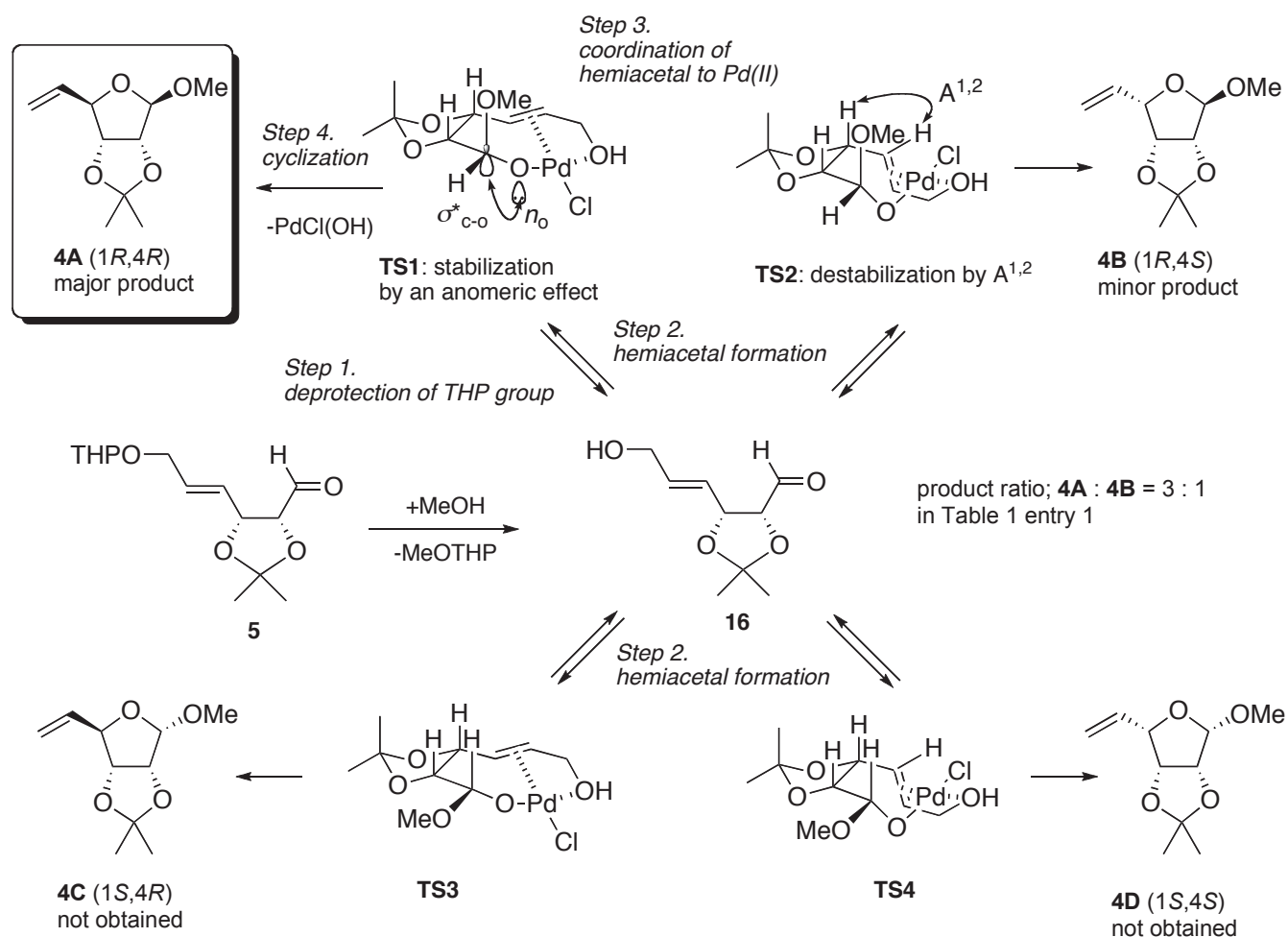
We then focused on the further transformation of **4A** and **4B** into D-ribose and L-lyxose, respectively (Scheme 4). Ozonolysis of the major cycloadduct **4A** followed by in situ reduction with sodium borohydride afforded the alcohol **13A** in 72% yield. Protection of the hydroxyl group of **13A** in the presence of benzyl bromide and a catalytic amount of tetra-*n*-hexylammonium iodide gave **14A** in 97% yield. Removal of the acetal groups of **14A** in the presence of IR-120H, a strong acid ion-exchange resin, in water afforded the triol **15A** in 82% yield.<sup>8</sup> Finally, deprotection of the benzyl group in **15A** by hydrogenolysis with Pd/C in ethanol furnished D-ribose in 99% yield. Similarly, **4B** was transformed into L-lyxose in 58% yield over 4 steps.



**Scheme 4.** Syntheses of D-ribose and L-lyxose

A plausible mechanism for the Pd(II)-catalyzed cyclization of hemiacetal derived from the aldehyde **5** is illustrated in Scheme 5. First of all, deprotection of the tetrahydropyranyl group with methanol in the presence of the palladium(II) catalyst, which behaves as a Lewis acid, gives the allylic alcohol **16** (Step 1). Then, the hemiacetal intermediate is formed by the reaction of aldehyde and methanol (Step 2). Pd  $\pi$ -complex is formed by coordination of PdCl<sub>2</sub>L<sub>n</sub> with the allylic alcohol, and one of the  $\pi$ -faces of the

olefin may be preferentially recognized with the assistance of the adjacent hydroxyl group of the hemiacetal (Step 3). This complex may be present in equilibrium with four complexes (**TS1**, **TS2**, **TS3** and **TS4**) owing to the formation of hemiacetal having other stereochemistry and coordination of PdCl<sub>2</sub>L<sub>n</sub> with the other π-face of the olefin. Although the conformations **TS1** and **TS2** are stabilized by anomeric effect ( $n_o-\sigma^*_{c-o}$ ), the conformations **TS3** and **TS4** are not. In addition to this, although the conformations **TS2** and **TS4** are destabilized by A<sup>1,2</sup> strain, the conformations **TS1** and **TS2** are not. Therefore, the cyclization of the hemiacetal derived from aldehyde **4** proceeds preferentially through the preferred conformation **TS1**. A *syn*-attack of the hydroxyl group in the hemiacetal on the electrophilic sp<sup>2</sup> carbon in **TS1** occurs intramolecularly from the same side of the Pd-complex in a 5-*exo*-trigonal fashion to give a σ-Pd complex, followed by *syn*-elimination of PdCl(OH)L<sub>n</sub> to afford furanoside **4A** having (1*R*,4*R*)-configuration. In the catalytic cycle, PdCl(OH)L<sub>n</sub> may catalyze the reaction by itself or regenerate PdCl<sub>2</sub>L<sub>n</sub> with chloride ion. For this reason, this Pd(II)-catalyzed cyclization proceeds very smoothly in the absence of any reoxidant.



**Scheme 5.** Plausible mechanism of Pd(II)-catalyzed cyclization

In conclusion, we have developed a novel method for tetrahydrofuran ring construction by means of PdCl<sub>2</sub>(PhCN)<sub>2</sub>-catalyzed cyclization of hemiacetal as a nucleophile, without the need for a reoxidant. This cyclization proceeds under mild conditions, affording the substituted furanoside, which was used for the synthesis of pentose. Further application of this methodology to the synthesis of other sugars and natural products is in progress.

## EXPERIMENTAL

**General Remarks:** All moisture sensitive reactions were carried out under an argon atmosphere. Anhydrous solvents were obtained as follows: tetrahydrofuran (THF) and dichloromethane were purchased from Kanto Chemical Co., Ltd.; *N,N*-dimethylformamide (DMF) and dimethyl sulfoxide (DMSO) was distilled from CaH<sub>2</sub>. Triethylamine was distilled from KOH. Column chromatography was performed with Silica gel 60N and Fuji BW-820. Analytical thin layer chromatography (TLC) was conducted on precoated TLC plates (silica gel 60F<sub>254</sub>, Merck) visualized under UV light and stained with either phosphomolybdic acid or *p*-anisaldehyde. Melting points were determined with Yanaco micro melting point apparatus and were uncorrected. IR spectra were measured with a JASCO Model FT/IR-6100 spectrometer. Mass spectra (MS) and high resolution mass spectra (HRMS) were recorded at a JEOL JMS-700 or JMS-T100TD spectrometer. Elemental analyses were performed on a Yanaco MT-5. Optical rotations ( $[\alpha]_D$ ) were determined with a JASCO P-1020 polarimeter. <sup>1</sup>H NMR spectra were recorded at 300 MHz with a JEOL JNM-ECX 300 spectrometer or 600 MHz with a JEOL JNM-ECP 600 using tetramethylsilane (TMS) as the internal standard (0.00 ppm). Chemical shifts were reported in ppm ( $\delta$ ) downfield from TMS. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, m = multiplet. <sup>13</sup>C NMR spectra were recorded at 75 MHz with a JEOL JNM-ECX 300 spectrometer with chemical shifts reported in ppm ( $\delta$ ).

### *cis*-1,4-Dibenzoyloxy-2-butene

To a solution of diol **8** (10.0 g, 114 mmol) and pyridine (26.9 g, 340 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (200 mL) was added benzoyl chloride (36.7 g, 261 mmol) at 0 °C under an argon atmosphere. The mixture was stirred at the same temperature for 10 min and warmed up to rt. After stirring at the same temperature for 6 h, the reaction was quenched with aqueous HCl and ice cooled water. The resulting mixture was extracted with AcOEt (x 3). The combined organic layers were washed with 5% HCl, water, saturated aqueous NaHCO<sub>3</sub> solution and brine, dried over MgSO<sub>4</sub>, and concentrated *in vacuo*. The resulting solid was recrystallized from *n*-hexane to afford the dibenzoate (33.6 g, > 99% yield) as colorless plates. mp 59.0-60.0 °C; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  8.07-8.04 (m, 4H), 7.56 (tt, *J* = 11.4, 7.4 Hz, 2H), 7.46-7.41 (m, 4H), 5.96 (ddd, *J* = 5.3, 4.0, 1.1 Hz, 2H), 5.01 (dd, *J* = 4.0, 1.1 Hz, 4H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  166.3(2C),

133.1(2C), 130.0(2C), 129.7(6C), 128.4(4C), 60.6(2C); IR (KBr,  $\text{cm}^{-1}$ ) 1714, 1267, 708; MS (EI)  $m/z$  175 (12), 149 (7), 105 (100), 77 (28); (DART)  $m/z$  297 ( $[\text{M}+\text{H}]^+$ ); HRMS-DART calcd. for  $\text{C}_{18}\text{H}_{17}\text{O}_4$  ( $[\text{M}+\text{H}]^+$ ) 297.1127, found 297.1155.; Anal. Calcd. for  $\text{C}_{18}\text{H}_{16}\text{O}_4$ : C, 72.96, H, 5.44; Found : C, 72.86, H, 5.53.

#### **(2*R*\*,3*S*\*)-1,4-Dibenzoyloxybutane-2,3-diol (9)**

To a solution of the dibenzoate (5.00 g, 16.9 mmol) and *N*-methylmorpholine *N*-oxide (50% in water, 4.55 mL, 21.9 mmol) in acetone (60 mL) and water (20 mL) was added  $\text{OsO}_4$  (0.05 mol/ L in *t*-BuOH, 1.01 mL, 0.051 mmol) at rt. The mixture was stirred at the same temperature for 18 h. The precipitate was filtered, and washed with a minimum quantity of acetone. To the filtrate was added saturated aqueous  $\text{Na}_2\text{S}_2\text{O}_3$  solution (50 mL) at rt and the quenched mixture was stirred until the organic phase was cleared. The resulting mixture was concentrated *in vacuo*. The precipitate was filtered, and washed with a minimum quantity of acetone and water. The filtrate was extracted with  $\text{Et}_2\text{O}$  until the white solid was dissolved. The combined organic layers were washed with 10% HCl (x 2), water, saturated aqueous  $\text{NaHCO}_3$  solution and brine, dried over  $\text{MgSO}_4$ , and concentrated *in vacuo* to afford the diol **9** as white solid (5.25 g, 95% yield), which was used for next step without further purification. An aliquot was crystallized from AcOEt to give an analytical pure sample. colorless needles; mp 153.0-154.0 °C;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.09-8.05 (m, 4H), 7.59 (tt,  $J = 7.4, 1.6$  Hz, 2H), 7.48-7.43 (m, 4H), 4.65-4.64 (m, 4H), 4.01-3.99 (m, 2H), 2.95 (d,  $J = 4.5$  Hz, 2H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  167.5(2C), 133.4(2C), 129.8(4C), 129.5(2C), 128.5(4C), 70.7(2C), 66.2(2C); IR (KBr,  $\text{cm}^{-1}$ ) 3473, 1693, 1285, 1129, 710; MS (EI)  $m/z$  269 (7), 227 (5), 195 (13), 177 (9), 165 (63), 123 (29), 105 (100), 75 (79); (DART)  $m/z$  331 ( $[\text{M}+\text{H}]^+$ ); HRMS-DART calcd. for  $\text{C}_{18}\text{H}_{19}\text{O}_6$  ( $[\text{M}+\text{H}]^+$ ) 331.1182, found 331.1185.; Anal. Calcd. for  $\text{C}_{18}\text{H}_{18}\text{O}_6$ : C, 65.45, H, 5.49; Found : C, 65.55, H, 5.57.

#### **(2*R*\*,3*S*\*)-1,4-Dibenzoyloxy-2,3-isopropylidenedioxybutane**

To a solution of the diol **9** (400 mg, 1.21 mmol) and *p*-toluenesulfonic acid (2.1 mg, 0.0121 mmol) in  $\text{CH}_2\text{Cl}_2$  (4 mL) was added 2,2-dimethoxypropane (1.48 mL, 12.1 mmol). The reaction mixture was stirred at 40 °C for 3 h. After stirring, the mixture was cooled with ice bath and the reaction was quenched with saturated aqueous  $\text{NaHCO}_3$  solution. The organic layer was separated and the aqueous phase was extracted with AcOEt (x 2). The combined organic layers were washed with brine, dried over  $\text{MgSO}_4$ , filtered, and concentrated *in vacuo* to afford the acetonide protected dibenzoate as white solid (440 mg, 98% yield). An aliquot was recrystallized from hexane to give an analytical pure sample. colorless needles; mp 107.0-108.0 °C;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.08-8.03 (m, 4H), 7.56 (tt,  $J = 7.4, 1.5$  Hz, 2H), 7.47-7.39 (m, 4H), 4.64-4.56 (m, 4H), 4.53-4.45 (m, 2H), 1.52 (s, 3H), 1.42 (s, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  166.2(2C), 133.2(2C), 129.8(4C), 129.7(2C), 128.4(4C), 109.5, 74.8(2C), 62.9(2C), 27.7,



25.4; IR (KBr,  $\text{cm}^{-1}$ ) 1714, 1270, 1116, 1082, 711; MS (EI)  $m/z$  356 (39), 355 (89), 235 (36), 178 (28), 177 (93), 126 (52), 105 (100), 77 (73); (DART)  $m/z$  371 ( $[\text{M}+\text{H}]^+$ ); HRMS-DART calcd. for  $\text{C}_{21}\text{H}_{23}\text{O}_6$  ( $[\text{M}+\text{H}]^+$ ) 371.1495, found 371.1497.; Anal. Calcd. for  $\text{C}_{21}\text{H}_{22}\text{O}_6$ : C, 68.10, H, 5.99; Found : C, 68.04, H, 6.14.

**(2R\*,3S\*)-2,3-Isopropylidenedioxybutane-1,4-diol (7)**

A mixture of the acetonide protected dibenzoate (89.7 g, 242 mmol) and  $\text{K}_2\text{CO}_3$  (1.67 g, 12.1 mmol) in MeOH (242 mL) was stirred at rt for 15 h. The reaction was quenched with 6N HCl. After stirring for 5 min, the mixture was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane-AcOEt = 4:1 to AcOEt, gradient) to afford the diol **7** (38.5 g, 98% yield) as a white solid. mp 35.5-37.0 °C;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  4.33-4.27 (m, 2H), 3.85-3.74 (m, 4H), 2.46 (t,  $J = 4.6$  Hz, 2H), 1.48 (s, 3H), 1.38 (s, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  108.4, 76.8(2C), 60.9(2C), 27.6, 25.1; IR (KBr,  $\text{cm}^{-1}$ ) 3401, 2988, 2938, 1382, 1218, 1049; MS (EI)  $m/z$  149 (100), 137 (12), 123 (16), 111 (27), 97 (38), 83 (59), 71 (82), 57 (86); (DART)  $m/z$  163 ( $[\text{M}+\text{H}]^+$ ); HRMS-DART calcd. for  $\text{C}_7\text{H}_{15}\text{O}_4$  ( $[\text{M}+\text{H}]^+$ ) 163.0970, found 163.0982.

**(2S,3R)-4-Acetoxy-2,3-isopropylidenedioxybutanol (6)**

A suspension of the diol **5** (406 mg, 2.50 mmol) and Lipase AK Amano 20 (56 mg) in vinyl acetate (0.51 mL, 5.51 mmol) was stirred at rt for 9.5 h under an argon atmosphere. The mixture was diluted with AcOEt and filtered through a pad of Celite<sup>®</sup>. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane-AcOEt = 3:2) to afford the acetate **6** (463 mg, 90% yield, >98% ee) as a colorless oil. The enantiopurity of **6** was confirmed by NMR analysis of both MPA esters.  $[\alpha]_D^{20}$  18.3 ( $c$  0.40,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  4.39 (td,  $J = 6.9, 4.9$  Hz, 1H), 4.33-4.27 (m, 2H), 4.14 (dd,  $J = 11.7, 7.2$  Hz, 1H), 3.80-3.66 (m, 2H), 2.10 (s, 3H), 1.87 (t,  $J = 6.2$  Hz, 1H), 1.50 (s, 3H), 1.39 (s, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  170.1, 109.0, 76.9, 74.6, 63.0, 60.9, 27.6, 25.1, 20.9; IR (neat,  $\text{cm}^{-1}$ ) 3476, 2988, 2938, 1742, 1373, 1240, 1167; MS (EI)  $m/z$  189 (58), 173 (12), 131 (46), 129 (63), 115 (100), 113 (14), 87 (19), 85 (8), 73 (11), 69 (46), 59 (85); (DART)  $m/z$  205 ( $[\text{M}+\text{H}]^+$ ); HRMS-DART calcd. for  $\text{C}_9\text{H}_{17}\text{O}_5$  ( $[\text{M}+\text{H}]^+$ ) 205.1076, found 205.1069.

**(2R,3S)-4-(tert-Butyldimethylsilyl)oxy-2,3-isopropylidenedioxybutyl acetate**

To a solution of the acetate **6** (1.02 g, 4.99 mmol) in *N,N*-dimethylformamide (5 mL) were added imidazole (815 mg, 12.0 mmol) and *t*-butyldimethylsilyl chloride (902 mg, 5.99 mmol) at 0 °C under an argon atmosphere. The reaction mixture was stirred at rt for 1.5 h. The reaction mixture was diluted with  $\text{Et}_2\text{O}$ , and washed with water. The aqueous layer was extracted with diethyl ether (x 1). The combined organic layers were washed with brine, dried over  $\text{MgSO}_4$ , filtered, and concentrated *in vacuo*. The crude

was purified by silica gel column chromatography (hexane-AcOEt = 9:1) to afford the TBS ether (1.58 g, 99% yield) as a colorless oil.  $[\alpha]_D^{20}$  32.7 (*c* 0.95, CHCl<sub>3</sub>); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 4.47 (dd, *J* = 11.6, 3.1 Hz, 1H), 4.38 (ddd, *J* = 8.2, 6.3, 2.9 Hz, 1H), 4.20 (dd, *J* = 6.3, 6.2 Hz, 1H), 4.10 (dd, *J* = 11.6, 8.2 Hz, 1H), 3.67 (d, *J* = 6.2 Hz, 2H), 2.10 (s, 3H), 1.46 (s, 3H), 1.37 (s, 3H), 0.90 (s, 9H), 0.074 (s, 3H), 0.071 (s, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 170.9, 109.0, 76.8, 75.4, 63.6, 61.5, 27.8, 25.8(3C), 25.3, 21.0, 18.2, -5.5(2C); IR (neat, cm<sup>-1</sup>) 2987, 2955, 2932, 2858, 1746, 1372, 1250, 1091, 838, 778; MS (EI) *m/z* 303 (64), 245 (15), 243 (14), 203 (92), 143 (100), 117 (96), 115 (67), 75 (85), 73 (77); (DART) *m/z* 319 ([M+H]<sup>+</sup>); HRMS-DART calcd. for C<sub>15</sub>H<sub>31</sub>O<sub>5</sub>Si ([M+H]<sup>+</sup>) 319.1941, found 319.1939.

**(2R, 3S)-4-(tert-Butyldimethylsilyloxy)-2,3-isopropylidenedioxybutanol (10)**

To a suspension of the TBS ether (37.6 g, 118 mmol) and K<sub>2</sub>CO<sub>3</sub> (1.63 g, 11.8 mmol) in MeOH (190 mL) was stirred at rt for 3 h. The reaction was quenched with water and the solvent was concentrated *in vacuo*. The residue was diluted with AcOEt and water. The organic layer was separated and the aqueous phase was extracted with AcOEt (x 2). The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane-AcOEt = 4:1) to afford the alcohol **10** (32.3 g, 99% yield) as a colorless oil.  $[\alpha]_D^{20}$  3.9 (*c* 0.85, CHCl<sub>3</sub>); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 4.35 (dt, *J* = 6.8, 5.8 Hz, 1H), 4.23 (ddd, *J* = 8.9, 5.9, 4.1 Hz, 1H), 3.87-3.72 (m, 3H), 3.68 (dd, *J* = 10.7, 4.1 Hz, 1H), 3.01 (dd, *J* = 8.3, 5.8 Hz, 1H), 1.42 (s, 3H), 1.36 (s, 3H), 0.90 (s, 9H), 0.109 (s, 3H), 0.108 (s, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 108.4, 77.4, 76.9, 61.6, 60.8, 27.8, 25.8(3C), 25.2, 18.2, -5.52, -5.58; IR (neat, cm<sup>-1</sup>) 3490, 2986, 2954, 2931, 2885, 2858, 1254, 1218, 1085, 1057, 837, 778; MS (EI) *m/z* 261 (16), 161 (71), 131 (96), 117 (89), 75 (100), 73 (78), 59 (51); (DART) *m/z* 277 ([M+H]<sup>+</sup>); HRMS-DART calcd. for C<sub>13</sub>H<sub>29</sub>O<sub>4</sub>Si ([M+H]<sup>+</sup>) 277.1835, found 277.1830.

**Ethy (E,4R,5S)-6-(tert-Butyldimethylsilyloxy)-4,5-isopropylidenedioxy-2-hexenoate (11)**

To a solution of dimethyl sulfoxide (10.0 mL, 141 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (200 mL) was added oxalyl chloride (6.1 mL, 70.5 mmol) at -78 °C under an argon atmosphere. After stirring for 20 min, to the reaction mixture was added a solution of the alcohol **10** (13.0 g, 47.0 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL). The suspension was stirred at the same temperature for 30 min. To the mixture was added Et<sub>3</sub>N (29.5 mL, 212 mmol) at -78 °C, the suspension was warmed to rt and stirred at the same temperature for 30 min. The reaction mixture was poured into ice cooled water and 10% HCl, and the aqueous phase was extracted with CHCl<sub>3</sub> (x 1). The combined organic layers were washed with saturated aqueous NaHCO<sub>3</sub> solution and brine, filtered, and concentrated *in vacuo* to afford aldehyde (12.9 g) as a yellow color oil, which was immediately used for the next reaction without further purification. To a suspension of sodium hydride (60% in oil, 2.63 g, 65.8 mmol) in THF (250 mL) was added triethyl phosphonoacetate (14.1 mL, 70.5 mmol) at 0 °C under an argon atmosphere. The mixture was stirred at the same temperature for 30 min. To

the mixture was added a solution of aldehyde (12.9 g, 47 mmol) in THF (30 mL) at  $-78^{\circ}\text{C}$ , the mixture was stirred at the same temperature for 10 min and warmed to rt. After stirring at the same temperature for 10 min, the reaction mixture was diluted with AcOEt and poured into saturated aqueous  $\text{NH}_4\text{Cl}$  solution. The aqueous phase was extracted with AcOEt (x 2). The combined organic layers were washed with brine, dried over  $\text{MgSO}_4$ , and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane-AcOEt = 20:1) to afford the  $\alpha,\beta$ -unsaturated ester **11** (15.2 g, 94% yield in 2 steps) as a colorless oil.  $[\alpha]_{\text{D}}^{20}$  7.8 (*c* 0.74,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  6.99 (dd, *J* = 15.8, 5.2 Hz, 1H), 6.12 (dd, *J* = 15.8, 1.5 Hz, 1H), 4.81 (ddd, *J* = 6.9, 5.2, 1.5 Hz, 1H), 4.29 (ddd, *J* = 8.0, 6.9, 4.6 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.63 (dd, *J* = 10.1, 4.6 Hz, 1H), 3.53 (dd, *J* = 10.1, 8.0 Hz, 1H), 1.49 (s, 3H), 1.38 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H), 0.88 (s, 9H), 0.042 (s, 3H), 0.036 (s, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  166.0, 143.1, 122.3, 109.2, 78.3, 76.6, 61.8, 60.4, 27.6, 25.8(3C), 25.2, 18.2, 14.3, -5.6(2C); IR (neat,  $\text{cm}^{-1}$ ) 2985, 2955, 2931, 2886, 2858, 1724, 1257, 1162, 1097, 839, 778; MS (EI) *m/z* 344 ( $\text{M}^+$ , 7), 343 (28), 127 (100), 117 (86), 89 (54), 75 (68), 73 (72); (DART) *m/z* 345 ( $[\text{M}+\text{H}]^+$ ); HRMS-DART calcd. for  $\text{C}_{17}\text{H}_{33}\text{O}_5\text{Si}$  ( $[\text{M}+\text{H}]^+$ ) 345.2097, found 345.2105.

**(*E,4R,5S*)-6-(*tert*-Butyldimethylsilyl)oxy-4,5-isopropylidenedioxy-2-hexenol**

To a solution of the ester **11** (1.10 g, 3.20 mmol) in THF (16 mL) was added DIBALH (0.98 M in *n*-hexane, 6.6 mL, 6.4 mmol) at  $0^{\circ}\text{C}$  under an argon atmosphere. The mixture was stirred at the same temperature for 1.5 h. The reaction was quenched sequentially with methanol, ice cooled water and 10% HCl. The aqueous phase was extracted with AcOEt (x 3), the combined organic layers were washed with saturated aqueous  $\text{NaHCO}_3$  solution and brine, dried over  $\text{MgSO}_4$ , filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane-AcOEt = 3:1) to afford the alcohol (0.98 g, 99% yield) as a colorless oil.  $[\alpha]_{\text{D}}^{20}$  8.1 (*c* 0.72,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  5.97 (dt, *J* = 15.5, 5.2 Hz, 1H), 5.80 (dd, *J* = 15.5, 7.3 Hz, 1H), 4.67 (dd, *J* = 7.3, 6.3 Hz, 1H), 4.22-4.16 (m, 3H), 3.61 (d, *J* = 6.3 Hz, 2H), 1.47 (s, 3H), 1.37 (s, 3H), 1.31 (t, *J* = 6.2 Hz, 1H), 0.88 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  133.0, 126.7, 108.6, 78.5, 77.9, 63.0, 62.2, 27.9, 25.9(3C), 25.4, 18.3, -5.4(2C); IR (neat,  $\text{cm}^{-1}$ ) 3424, 2954, 2930, 2857, 1253, 1100, 838, 777; MS (EI) *m/z* 302 ( $\text{M}^+$ , 3), 301(10), 201(13), 187(31), 169(26), 157(19), 117(62), 89(36), 75(100), 73(56), 59(29); (DART) *m/z* 303 ( $[\text{M}+\text{H}]^+$ ); HRMS-DART calcd. for  $\text{C}_{15}\text{H}_{31}\text{O}_4\text{Si}$  ( $[\text{M}+\text{H}]^+$ ) 303.1992, found 303.1994.

**(*E,4R,5S*)-6-(*tert*-Butyldimethylsilyl)oxy-4,5-isopropylidenedioxy-1-(tetrahydropyran-2-yl)oxy-2-hexene (**12**)**

To a solution of the alcohol (8.30 g, 27.4 mmol) in  $\text{CH}_2\text{Cl}_2$  (125 mL) were added *p*-toluenesulfonic acid (240 mg, 1.37 mmol) and 2*H*-dihydropyran (3.8 mL, 41.2 mmol) at  $0^{\circ}\text{C}$  under an argon atmosphere. After stirring at the same temperature for 1 h, the reaction mixture was diluted with  $\text{CHCl}_3$  and the

reaction was quenched with saturated aqueous NaHCO<sub>3</sub> solution. The aqueous phase was extracted with CHCl<sub>3</sub> (x 2), and the combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane-AcOEt = 20:1) to afford the THP ether **12** (10.3 g, 97% yield as diastereomer mixtures) as a colorless oil. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 5.90 (dt, *J* = 15.9, 5.1 Hz, 1H), 5.79 (dd, *J* = 15.9, 6.2 Hz, 1H), 4.68-4.65 (m, 2H), 4.29-4.23 (m, 1H), 4.18 (dd, *J* = 12.5, 6.2 Hz, 1H), 3.99 (dt, *J* = 12.5, 5.4 Hz, 1H), 3.89-3.82 (m, 1H), 3.61 (d, *J* = 5.4 Hz, 2H), 3.54-3.47 (m, 1H), 1.81 - 1.67 (m, 6H), 1.47 (s, 3H), 1.37 (s, 3H), 0.88 (s, 9H), 0.054 (s, 3H), 0.049 (s, 3H); IR (neat, cm<sup>-1</sup>) 2936, 2857, 1119, 1097, 1079, 1026, 837, 777.

#### **(*E,2S,3R*)-2,3-Isopropylidenedioxy-6-(tetrahydro-2*H*-pyran-2-yl)oxy-4-hexenol**

To a solution of the THP ether **12** (21.0 g, 54.3 mmol) in THF (200 mL) was added tetra-*n*-butylammonium fluoride (1.0 M in THF, 81.5 mL, 81.5 mmol) at 5 °C under an argon atmosphere. The reaction mixture was stirred at the same temperature for 10 min, and then warmed to rt. After stirring at the same temperature for 2 h, the mixture was diluted with Et<sub>2</sub>O, and washed with water. The aqueous phase was extracted with Et<sub>2</sub>O (x 5). The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane-AcOEt = 7:3 to 1:1, gradient) to afford the alcohol (14.1 g, 95% yield) as a colorless oil. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 6.01-5.92 (m, 1H), 5.83-5.74 (m, 1H), 4.70 (t, *J* = 6.9 Hz, 1H), 4.63 (d, *J* = 2.1 Hz, 1H), 4.23 (dt, *J* = 13.0, 6.0 Hz, 2H), 4.05 (dt, *J* = 13.4, 6.5 Hz, 1H), 3.89-3.82 (m, 1H), 3.60-3.57 (m, 2H), 3.54-3.47 (m, 1H), 2.05-1.53 (m, 7H), 1.51 (s, 3H), 1.39 (s, 3H); IR (neat, cm<sup>-1</sup>) 3419, 2943, 2873, 1714, 1372, 1218, 1123, 1074, 1035, 975, 756; MS (DART) *m/z* 273 ([M+H]<sup>+</sup>); HRMS-DART calcd. for C<sub>14</sub>H<sub>25</sub>O<sub>5</sub> ([M+H]<sup>+</sup>) 273.1702, found 273.1702.

#### **(*E,2S,3R*)-2,3-Isopropylidenedioxy-6-(tetrahydro-2*H*-pyran-2-yl)-4-hexenal (**5**)**

To a suspension of the alcohol (1.05 g, 3.86 mmol) and MS 4A (2.00 g) in CH<sub>2</sub>Cl<sub>2</sub> (50 mL) was added *N*-methylmorpholine *N*-oxide (905 mg, 7.71 mmol), then the mixture was stirred for 1 h at rt. To the mixture was added tetra-*n*-propylammonium perruthenate (67 mg, 1.93 mmol) at 5 °C, and the mixture was stirred at the same temperature for 40 min. The mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub>, filtered through a pad of Celite<sup>®</sup> and the pad was washed with CH<sub>2</sub>Cl<sub>2</sub>. The filtrate was washed with saturated aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> solution, 1N HCl and brine, dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane-AcOEt = 1:1) to afford the aldehyde **5** (960 mg, 92% yield) as a yellow oil. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 9.57 (d, *J* = 3.1 Hz, 1H), 6.01 (dt, *J* = 15.3, 5.2 Hz, 1H), 5.67 (dddd, *J* = 15.3, 7.4, 2.9, 1.5 Hz, 1H), 4.89 (t, *J* = 7.2 Hz, 1H), 4.62-4.59 (m, 1H), 4.41 (dd, *J* = 7.4, 2.9 Hz, 1H), 4.30-3.78 (m, 3H), 3.55-3.45 (m, 1H), 1.88-1.35 (m, 6H), 1.63 (s, 3H), 1.44 (s, 3H); IR (neat, cm<sup>-1</sup>) 2984, 2940, 2871, 1736, 1382, 1218, 1119, 1068, 1025, 973, 870; MS (DART) *m/z* 271

([M+H]<sup>+</sup>); HRMS-DART calcd. for C<sub>14</sub>H<sub>23</sub>O<sub>5</sub> ([M+H]<sup>+</sup>) 271.1546, found 273.1545.

**(3R,4R)-3,4-Isopropylidenedioxy-5-methoxy-2-vinyltetrahydrofuran (4)**

To a solution of the aldehyde **5** (200 mg, 0.740 mmol) and MeOH (119 mg, 3.70 mmol) in THF (37 mL) was added PdCl<sub>2</sub>(PhCN)<sub>2</sub> (14 mg, 0.037 mmol) at rt under an argon atmosphere, then the mixture was stirred at the same temperature for 2 h. The reaction mixture was filtered through a pad of Florisil<sup>®</sup>, the pad was washed with AcOEt, and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane-AcOEt = 10:1) to afford the olefin **4** (104 mg, 70% yield) as a colorless oil. (2R,3R,4R,5R)-**4A**; colorless oil; [α]<sub>D</sub><sup>20</sup> -52.6 (*c* 0.84, CHCl<sub>3</sub>); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 5.88 (ddd, *J* = 17.9, 10.0, 8.0 Hz, 1H), 5.27 (ddd, *J* = 17.9, 1.3, 1.2 Hz, 1H), 5.16 (ddd, *J* = 10.0, 1.3, 1.2 Hz, 1H), 4.99 (s, 1H), 4.631 (d, *J* = 8.0 Hz, 1H), 4.626 (s, 2H), 3.35 (s, 3H), 1.50 (s, 3H), 1.32 (s, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 137.6, 117.3, 112.3, 109.3, 88.4, 85.5, 84.6, 54.6, 26.5, 25.0; IR (neat, cm<sup>-1</sup>) 2988, 2938, 2833, 1373, 1210, 1105, 1057, 1031, 868; MS (EI) *m/z* 280 (7), 279 (16), 243 (7), 225 (5), 205 (10), 185 (18), 169 (26), 167 (29), 165 (24), 149 (100), 111 (31); (DART) *m/z* 201 ([M+H]<sup>+</sup>); HRMS-DART calcd. for C<sub>10</sub>H<sub>17</sub>O<sub>4</sub> ([M+H]<sup>+</sup>) 201.1127, found 201.1129. (2S,3R,4R,5R)-**4B**; colorless oil; [α]<sub>D</sub><sup>20</sup> -24.6 (*c* 0.83, CHCl<sub>3</sub>); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 6.00 (ddd, *J* = 17.5, 10.3, 7.3 Hz, 1H), 5.45-5.38 (m, 1H), 5.37-5.32 (m, 1H), 4.92 (s, 1H), 4.68 (dd, *J* = 5.8, 3.7 Hz, 1H), 4.58 (d, *J* = 5.8 Hz, 1H), 4.39 (dd, *J* = 7.3, 3.7 Hz, 1H), 3.35 (s, 3H), 1.47 (s, 3H), 1.32 (s, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 132.3, 119.1, 112.6, 107.2, 85.3, 81.5, 81.1, 54.7, 26.1, 24.9; IR (neat, cm<sup>-1</sup>) 2989, 2937, 1373, 1211, 1104, 1021, 758; MS (EI) *m/z* : 279 (21), 243 (3), 239 (2), 205 (3), 185 (27), 167 (29), 149 (100), 125 (13), 111 (14); (DART) *m/z* 201 ([M+H]<sup>+</sup>); HRMS-DART calcd. for C<sub>10</sub>H<sub>17</sub>O<sub>4</sub> ([M+H]<sup>+</sup>) 201.1127, found 201.1123.

**((2R,3R,4R,5R)-(3,4-Isopropylidenedioxy-5-methoxy-2-tetrahydrofuranyl)methanol (13A)**

A gas of O<sub>3</sub> was bubbled into a solution of the olefin **4A** (300 mg, 1.50 mmol) in MeOH (10 mL) at -78 °C for 30 min, then O<sub>2</sub> was bubbled into the reaction mixture until the blue color solution was cleared. To the reaction mixture was added NaBH<sub>4</sub> (85 mg, 2.25 mmol) at 0 °C and the mixture was stirred at rt for 22 h. The mixture was concentrated *in vacuo*, the residue was diluted with AcOEt and quenched with 1N HCl. The aqueous phase was extracted with AcOEt. The combined organic layers were washed with saturated aqueous NaHCO<sub>3</sub> solution and brine, dried over MgSO<sub>4</sub>, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane- AcOEt = 3:1) to afford the alcohol **13A** (220 mg, 72% yield) as a colorless oil. [α]<sub>D</sub><sup>20</sup> -72.2 (*c* 1.02, CHCl<sub>3</sub>); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 4.98 (s, 1H), 4.84 (d, *J* = 5.8 Hz, 1H), 4.59 (d, *J* = 5.8 Hz, 1H), 4.44 (dd, *J* = 3.1, 2.7 Hz, 1H), 3.70 (ddd, *J* = 14.3, 2.7, 2.7 Hz, 1H), 3.61 (ddd, *J* = 14.3, 10.3, 3.1 Hz, 1H), 3.44 (s, 3H), 3.23 (dd, *J* = 10.3, 2.7 Hz, 1H), 1.49 (s, 3H), 1.32 (s, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 112.1, 109.9, 88.3, 85.8, 81.4, 63.9, 55.5, 26.3, 24.6; IR

(neat,  $\text{cm}^{-1}$ ) 3447, 2988, 2941, 1383, 1374, 1211, 1093, 1044, 871; MS (EI)  $m/z$  259 (2), 203 (2), 201 (4), 189 (91), 173 (100), 157 (55), 129 (29), 115 (36), 113 (82); (DART)  $m/z$  205 ( $[\text{M}+\text{H}]^+$ ); HRMS-DART calcd. for  $\text{C}_9\text{H}_{17}\text{O}_5$  ( $[\text{M}+\text{H}]^+$ ) 205.1076, found 205.1080.

**((2*S*,3*R*,4*R*,5*R*)-(3,4-Isopropylidenedioxy-5-methoxy-2-tetrahydrofuranyl))methanol (13B)**

A gas of  $\text{O}_3$  was bubbled into a solution of the olefin **4B** (150 mg, 0.75 mmol) in MeOH (8 mL) at  $-78^\circ\text{C}$  for 30 min, then  $\text{O}_2$  was bubbled into a reaction mixture until the blue color solution was cleared. To the reaction mixture was added  $\text{NaBH}_4$  (43 mg, 1.12 mmol) at  $0^\circ\text{C}$  and the mixture was warmed to rt. After stirring at the same temperature for 21 h, the mixture was concentrated *in vacuo*. The residue was diluted with AcOEt and 1N HCl. The aqueous phase was extracted with AcOEt (x 3). The combined organic layers were washed with saturated aqueous  $\text{NaHCO}_3$  solution and brine, dried over  $\text{MgSO}_4$  and concentrated *in vacuo*. The crude oil was purified by silica gel column chromatography (hexane-AcOEt = 4:1 to 2:1, gradient) to afford the alcohol **13B** (153 mg, < 85% yield) as an inseparable mixture which was colorless oil.  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  112.7, 107.0, 85.2, 80.4, 79.2, 61.1, 54.7, 25.9, 24.5.

**(2*R*,3*R*,4*R*,5*R*)-2-Benzylloxymethyl-3,4-isopropylidenedioxy-5-methoxytetrahydrofuran (14A)**

To a solution of the alcohol **13A** (1.00 g, 4.90 mmol) in THF (50 mL) was added NaH (235 mg, 5.39 mmol) at  $5^\circ\text{C}$ , then the mixture was stirred at rt for 1 h. To a suspension were added a solution of benzyl bromide (1.17 g, 6.86 mmol) and tetra-*n*-hexylammonium iodide (236 mg, 0.49 mmol) at  $5^\circ\text{C}$ , then the mixture was stirred at rt for 4.5 h. The reaction mixture was cooled with ice bath and the reaction was quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  solution. The aqueous phase was extracted with AcOEt (x 2). The combined organic layers were washed with brine, dried over  $\text{MgSO}_4$ , filtered and concentrated *in vacuo*. The crude oil was purified by silica gel column chromatography (hexane-AcOEt = 15:1) to afford the benzyl ether **14A** (1.40 g, 97% yield) as a yellow oil.  $[\alpha]_D^{20}$   $-52.2$  ( $c$  1.94,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.36-7.28 (m, 5H), 4.96 (s, 1H), 4.68 (dd,  $J = 5.8, 1.0$  Hz, 1H), 4.57 (d,  $J = 5.8$  Hz, 1H), 4.56 (s, 2H), 4.38 (ddd,  $J = 8.8, 7.8, 1.0$  Hz, 1H), 3.53 (dd,  $J = 8.8, 6.5$  Hz, 1H), 3.46 (dd,  $J = 7.8, 1.0$  Hz, 1H), 3.29 (s, 3H), 1.49 (s, 3H), 1.32 (s, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  138.0, 128.4(3C), 127.7(2C), 112.4, 109.3, 85.19, 85.18, 82.2, 73.3, 71.1, 54.8, 26.5, 25.0; IR (neat,  $\text{cm}^{-1}$ ) 2988, 2938, 2862, 1455, 1382, 1373, 1211, 1109, 1062, 871, 739, 699; MS (EI)  $m/z$  279 (26), 248 (31), 247 (100), 173 (36), 157 (26), 115 (30), 113 (33), 107 (42); (DART)  $m/z$  295 ( $[\text{M}+\text{H}]^+$ ); HRMS-DART calcd. for  $\text{C}_{16}\text{H}_{23}\text{O}_5$  ( $[\text{M}+\text{H}]^+$ ) 295.1546, found 295.1548.

**(2*S*,3*R*,4*R*,5*R*)-2-Benzylloxymethyl-3,4-isopropylidenedioxy-5-methoxytetrahydrofuran (14B)**

To a solution of the alcohol **13B** (180 mg, 0.88 mmol) in THF (8.8 mL) was added NaH (64 mg, 1.59 mmol) at rt, then the mixture was stirred at the same temperature for 30 min. To a suspension were added

a THF solution of benzyl bromide (316 mg, 1.85 mmol) and tetra-*n*-hexylammonium iodide (42 mg, 0.09 mmol) at rt, then the mixture was stirred at the same temperature for 23 h. The reaction was quenched with saturated NH<sub>4</sub>Cl solution, then the aqueous phase was extracted with AcOEt (x 2). The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The crude oil was purified by silica gel column chromatography (hexane-AcOEt = 10:1) to afford the benzyl ether **14B** (242 mg, 93% yield) as a yellow oil.  $[\alpha]_D^{20}$  - 31.9 (*c* 0.72, CHCl<sub>3</sub>); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.38-7.26 (m, 5H), 4.92 (s, 1H), 4.72 (dd, *J* = 5.8, 3.8 Hz, 1H), 4.67 (d, *J* = 12.0 Hz, 1H), 4.55 (d, *J* = 12.0 Hz, 1H), 4.55 (d, *J* = 5.8 Hz, 1H), 4.17 (ddd, *J* = 7.1, 4.2, 3.8 Hz, 1H), 3.83 (dd, *J* = 10.3, 4.2 Hz, 1H), 3.70 (dd, *J* = 10.5, 7.1 Hz, 1H), 3.34 (s, 3H), 1.43 (s, 3H), 1.30 (s, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 138.2, 128.4(2C), 127.8(2C), 127.6, 112.6, 107.3, 84.9, 80.0, 79.0, 73.5, 68.3, 54.7, 26.1, 24.9; IR (neat, cm<sup>-1</sup>): 2989, 2936, 1455, 1373, 1210, 1102, 874, 739, 698; MS (EI) *m/z* 279 (10), 178 (18), 145 (9), 107 (20), 92 (23), 91 (100), 87 (22), 77 (15), 55 (15); (DART) *m/z* 295 ([M+H]<sup>+</sup>); HRMS-DART calcd. for C<sub>16</sub>H<sub>23</sub>O<sub>5</sub> ([M+H]<sup>+</sup>) 295.1546, found 295.1544.

#### 5-*O*-Benzyl-D-ribose (**15A**)

To a suspension of the benzyl ether **14A** (260 mg, 0.88 mmol) in water (8.8 mL) was added Amberlite IR-120H (2.00 g) at rt, then the mixture was stirred at rt for 28 h. The mixture was saturated with NaCl and AcOEt was added to the mixture. After vigorously stirring for 5 min, the mixture was filtered and the aqueous phase was extracted with AcOEt (x 3). The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The crude oil was purified by silica gel column chromatography (hexane-AcOEt = 1:10) to afford the triol **15A** (173 mg, 82% yield) as a white solid.  $[\alpha]_D^{20}$  38.2 (*c* 0.86, CHCl<sub>3</sub>); <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ 7.38-7.23 (m, 5H), 5.23 (d, *J* = 3.6 Hz, 0.3H), 5.12 (s, 0.7H), 4.58 (s, 1.4H), 4.54 (s, 0.6H), 4.14-4.07 (m, 1H), 4.03-3.93 (m, 1.4H), 3.81 (dd, *J* = 4.8, 1.0 Hz, 0.6H), 3.69 (dd, *J* = 10.5, 3.6 Hz, 0.6H), 3.63-3.52 (m, 1.4H); <sup>13</sup>C NMR (75 MHz, CD<sub>3</sub>OD) δ major epimer : 139.6, 129.4(2C), 128.9(2C), 128.8, 103.3, 82.8, 77.0, 74.4, 73.3, 72.8; minor epimer : 139.6, 129.4(2C), 128.69, 128.66(2C), 98.0, 83.4, 74.4, 72.43, 72.38, 71.6; IR (KBr, cm<sup>-1</sup>) 3421, 3309, 2937, 2867, 1456, 1246, 1128, 1091, 1051, 1010, 948, 933, 844, 743, 698; MS (EI) *m/z* 222 (6), 149 (5), 131 (7), 107 (41), 92 (47), 91 (100), 73 (19), 65 (25); (DART) *m/z* 241 ([M+H]<sup>+</sup>); HRMS-DART calcd. for C<sub>12</sub>H<sub>17</sub>O<sub>5</sub> ([M+H]<sup>+</sup>) 241.1076, found 241.1167.

#### 5-*O*-Benzyl-L-lyxose (**15B**)

To a suspension of the benzyl ether **14B** (200 mg, 0.68 mmol) in water (5.1 mL) and 1,4-dioxane (5.1 mL) was added Amberlite IR-120H (2.00 g) at rt, then the mixture was stirred at rt for 106 h. The reaction mixture was filtered, the residue was washed with 1,4-dioxane and the filtrate was concentrated *in vacuo*. The crude oil was purified by silica gel column chromatography (hexane-AcOEt = 1:9) to afford the triol

**15B** (121 mg, 74 % yield) as a colorless oil.  $[\alpha]_{\text{D}}^{20}$  -36.9 (*c* 0.53,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  7.28-7.12 (m, 5H), 5.08 (d, *J* = 3.2 Hz, 0.65H), 5.01 (d, *J* = 4.7 Hz, 0.35H), 4.48-4.43 (m, 2H), 4.25-4.16 (m, 1.65H), 3.90 (t, *J* = 4.8 Hz, 0.35H), 3.81 (dd, *J* = 4.3, 3.2 Hz, 0.65H), 3.72 (dd, *J* = 10.0, 4.7 Hz, 0.35H), 3.64 (dd, *J* = 10.7, 4.3 Hz, 0.65H), 3.63-3.47 (m, 0.7H), 3.53 (dd, *J* = 10.7, 6.2 Hz, 0.65H)  $^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  major epimer : 139.6, 129.4(2C), 129.0(2C), 128.7, 103.0, 80.0, 78.6, 74.4, 72.6, 70.5; minor epimer : 139.5, 128.94(2C), 128.91, 128.87, 128.7, 97.6, 80.5, 74.3, 73.5, 72.1, 71.4; IR (neat,  $\text{cm}^{-1}$ ): 3388, 2926, 2870, 2514, 1076, 1027, 742, 699; MS (EI) *m/z*: 178 (3), 149 (4), 108 (9), 107 (23), 92 (13), 91 (100), 79 (10), 77 (11), 65 (10); (DART) *m/z* 241 ( $[\text{M}+\text{H}]^+$ ); HRMS-DART calcd. for  $\text{C}_{12}\text{H}_{17}\text{O}_5$  ( $[\text{M}+\text{H}]^+$ ) 241.1076, found 241.1079.

### D-Ribose

To a solution of the triol **15A** (50 mg, 0.21 mmol) in EtOH (2.1 mL) was added Pd/C (5 mg), then the reaction vessel was evacuated and back-filled with  $\text{H}_2$  (x 5). After stirring at rt for 51 h, the mixture was filtered through a pad of Celite<sup>®</sup> and the pad was washed with MeOH. The filtrate was concentrated *in vacuo*. The crude material was purified by silica gel column chromatography (MeOH) to afford D-ribose (31 mg, >99 % yield) as a colorless amorphous solid.  $[\alpha]_{\text{D}}^{20}$  -23.5 (*c* 1.50, MeOH);  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  4.91 (d, *J* = 4.8 Hz, 0.8H), 4.76 (d, *J* = 2.1 Hz, 0.2H), 3.91 (dd, *J* = 3.1, 2.7 Hz, 0.8H), 3.88-3.52 (m, 2.4H), 3.83 (dd, *J* = 8.4, 2.7 Hz, 0.8H), 3.49 (d, *J* = 3.1 Hz, 0.2H), 3.46-3.43 (m, 0.8H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  major epimer : 96.0, 73.3, 70.2, 69.2, 64.6; minor epimer : 95.3, 72.1, 71.3, 69.0, 64.6; MS (EI) *m/z*: 149 (1), 119 (5), 101 (5), 86 (18), 73 (100), 71 (21), 61 (19), 60 (58), 57 (15).

### L-Lyxose

To a suspension of the triol **15B** (36 mg, 0.15 mmol) in EtOH (2.5 mL) was added Pd/C (5 mg), then the reaction vessel was evacuated and back-filled with  $\text{H}_2$  (x 5). After stirring for 19.5 h at rt, the mixture was filtered over a pad of Celite<sup>®</sup> and the pad was washed with EtOH. The filtrate was concentrated *in vacuo*. The crude material was purified by silica gel column chromatography (MeOH) to afford L-lyxose (23 mg, >99 % yield) as a colorless amorphous solid.  $[\alpha]_{\text{D}}^{20}$  8.6 (*c* 1.13, MeOH);  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  4.83 (d, *J* = 3.4 Hz, 0.8H), 4.71 (br s, 0.2H), 3.88 (dd, *J* = 11.9, 3.6 Hz, 0.2H), 3.72-3.47(m, 5.6H), 3.14 (dd, *J* = 11.7, 6.9 Hz, 0.2H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  major epimer : 96.0, 72.5, 72.2, 69.2, 64.3; minor epimer : 96.0, 74.4, 70.1, 69.3, 64.1; MS (EI) *m/z*: 149 (1), 119 (6), 101 (6), 91 (7), 86 (8), 73 (100), 71 (21), 61 (28), 60 (63), 57 (16).

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