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Short Communication

Facial Synthesis of Versatile Chiral α,β-Unsaturated Esters from Isopropylidenated D-Pyranopentoses

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During last several decades an enormous amount of work has been devoted to developing chiral auxiliaries for asymmetric synthesis [Pellissier, 2006; Ager *et al.*, 1996]. Especially chiral α,β-unsaturated esters have been widely used in asymmetric Diels-Alder reactions [Lim and Koh, 2005; Koh, 2006], cycloaddition addition reaction [Baskaran *et al.*, 1997; Herdeis, *et al.*, 1999] and dihydroxylation reactions [Reetz, *et al.*, 1996]. Above mentioned asymmetric reactions need pure form of chiral *trans* or *cis*-α,β-unsaturated esters with chirality at γ-position in order to create new chiral centers with good diastereofacial selectivity, because it has been well known that the chirality at γ-position of α,β-unsaturated ester plays a critical role in asymmetric synthesis.[Stork and Kahn, 1983; Trost and Mignani, 1986].

As our programmed research for the asymmetric Diels-Alder reactions, a series of differently substituted α,β-unsaturated esters with γ-position chirality are demanded as chiral dienophiles. In this communication convenient synthesis of versatile chiral α,β-unsaturated esters from isopropylidenated D-pyranopentoses will be introduced.

D-Pyranopentoses (**3**, **9**, **14**) are six-membered ring lactols protected aldehydes by an intramolecular hemiacetal formation. In addition, each isopropylidenated D-pyranopentose has different stereochemical configuration at C-2, which eventually affords different stereochemical configuration at γ-position of resulting chiral α,β-unsaturated esters. Therefore these latent aldehydes (**3**, **9**, **14**) can be used for Wittig reaction with stabilized ylide.

Isopropylidenation of D-arabinose with 2,2-dimethoxypropane (**1**) gave exclusively 3,4-*O*-isopropylidene-D-*arabino*pyranose (**3**) [Kiso and Hasegawa, 1976] which was treated with triphenylphosphoranyledene acetate (**2**) in chloroform at room temperature.

Two chain elongated *trans*- enonate (**4**) and *cis*- enonate (**5**) were observed in ^{1}H-NMR (20 : 80, *trans* : *cis*) and were obtained as an inseparable mixture in 73% yield. The major *cis*-isomer **5** showed smaller coupling constant between H2 and H3 ($J_{2,3}$ 11.5 Hz) than that of *trans* isomer **4** ($J_{2,3}$ 15.7 Hz). After acetylation, flash chromatography separation afforded the pure acetylated *trans* isomer (**6**) and acetylated *cis* isomer (**7**). Enholm group protected 2-hydroxy group of compound **3** with with tert-butyldimethylsilyl chloride (TBDMSCl) and used it for similar Wittig reaction [Enholm and Trivellas, 1989]. TBDMS-protected compound also provided 13 : 87 ratio of *trans-cis* products in *cis* major. The fully protected lactol used by Enholm, however, needed four-step reactions to be prepared from simple carbohydrate, which is contradictory to our objective of decreasing reaction steps to obtain stereoisomerically pure unsaturated enonate in high yield. Recently Martin group [Harcken and Martin, 2001] reported improved *trans*-selectivity for Wittig reaction with enantiomer of compound **3**.

For a comparative study another lactol **9** was prepared from D-ribose. The same procedure for isopropylidenation of D-ribose with 2,2-dimethoxypropane (**1**) gave only 2,3-*O*-isopropylidene-D-ribofuranose instead of desired lactol **9**. Horton's isopropylidenation method with 2-methoxypropene (**8**) at low temperature (0°C), so called kinetic acetonation, afforded 3,4-*O*-isopropylidene-D-ribopyranose **9** as a major product [Gelas and Horton, 1975].

Lactol **9** has the opposite configuration at C-2 to lactol **3**, with retaining other configurations of stereocenters the same as lactol **3**. When lactol **9** was treated with ylide **2** at room temperature, two Wittig adducts **10** and **11** were obtained in high yield (91%). The major isomer **10** was the *trans*-isomer ($J_{2,3}$ 15.8 Hz) and was separable from the reaction mixture. The corresponding *cis*-isomer was obtained as butenolide and was characterized as acetylated form **13**. Coupling constant of butenolide **13** ($J_{2,3}$ 5.7 Hz) is relatively much smaller than that of comparable *cis* product **7** ($J_{2,3}$ 11.3 Hz). In addition, no methoxy signal of butenolide **13** is shown in ^{1}H-NMR, confirming **13** is ring closed butenolide. The *trans-cis* ratio of the reaction was

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Abbreviations: NMR, nuclear magnetic resonance; TBDMS, *tert*-butyldimethylsilyl; TLC, thin layer chromatography; IR, infra red; DMF, dimethylformamide

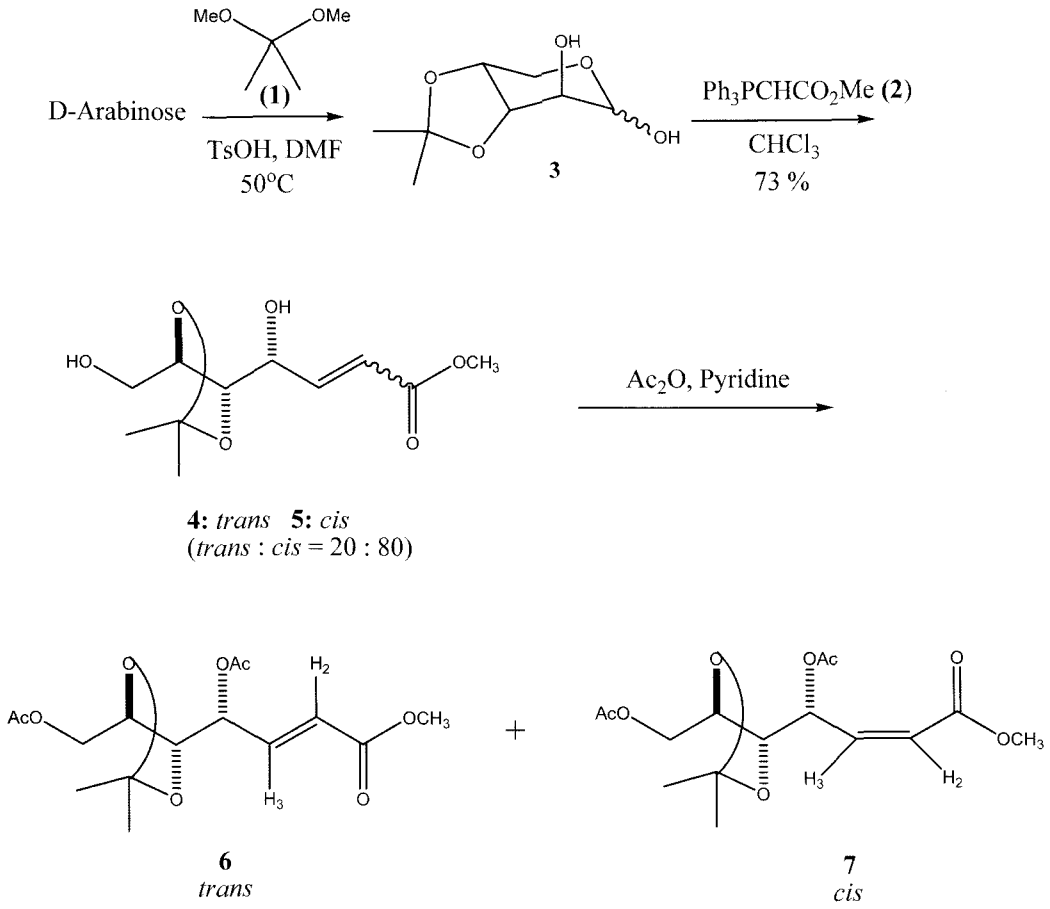

Fig. 1. Synthetic scheme for chiral α,β-unsaturated esters from D-arabinose.

92 : 8 in favor of the *trans* isomer. Interestingly, the opposite configuration C-2 of the 3,4-*O*-isopropylidene-D-pyranoses gave different *trans-cis* selectivity in Wittig reaction. Having inverted the *trans-cis* ratio between two pyranose lactols **3** and **9**, which have the opposite OH configuration at C-2, the 2-deoxy analogue **14** was prepared from 2-deoxy-D-*erythro*-pentose [Barbat *et al.*, 1983] and investigated.

Under the same Wittig reaction conditions, **14** gave a *trans-cis* mixture (**15**, **16** respectively, 83 : 17 by ^{1}H-NMR) in 90% yield. For easy separation, TBDMS silyation of hydroxy group afforded pure *trans*-isomer (**17**) and corresponding *cis*-isomer (**18**).

The readily available 3,4-*O*-isopropylidenated D-pyranopentoses (**3**, **9**, **14**) which have opposite or no stereocenter configuration at C-2 position can be used to give high yield (73-91%) of corresponding chiral α,β-unsaturated esters. It is also noteworthy the intramolecular Michael addition reactions were not observed after Wittig reaction between ylide **3** and 3,4-*O*-isopropylidenated D-pyranopentoses, which have been commonly observed with furanose derivatives [Popsavin, *et al.*, 2004]. Newly formed *trans*-, *cis*-isomers with different configuration at γ-position have considerable potential for investigation of various asymmetric synthesis as chiral building blocks.

Typical procedure for Wittig reaction with 3,4-*O*-isopropylidene-D-ribopyranose (**9**) is described as follow. To a solution of 3,4-*O*-isopropylidene-D-ribopyranose (**9**, 3.9 g, 20.5 mmol) in $CHCl_3$ (100 mL) was added 1.3 equiv. of methyl (triphenylphosphoranylidene) acetate (**2**, 8.92 g, 26.7 mmol) and the solution was stirred overnight at room temperature. T.l.c. of the mixture showed three spots (2 : 1 EtOAc-hexane, R_f 0.52-major product, R_f 0.42-minor product, and R_f 0.31-byproduct). The solvent was evaporated to give a syrup which was treated with 200 mL of ether to afford the precipitated byproduct Ph_3OP. The precipitate was filtered off and filtrate was evaporated. The residue was charged onto silica gel and flash chromatography (1 : 1 EtOAc-hexane) afforded the pure *trans* product, **10** (4.11 g, 81.2%) and mixture of *trans* product **10** and lactone **11**.

Trans-alkene **10** was a syrup; $[\alpha]_D$ –68.4 (*c* 1, $CHCl_3$); R_f 0.52 (2 : 1 EtOAc-hexane); ^{1}H-NMR (400 MHz, DMSO-d_6) δ 6.99 (dd, 1H, $J_{2,3}$ 15.8 Hz, $J_{3,4}$ 4.3 Hz, H-3), 6.04 (dd, 1H, $J_{2,4}$ 1.4 Hz, H-2), 5.50 (d, 1H, 4-OH), 4.86

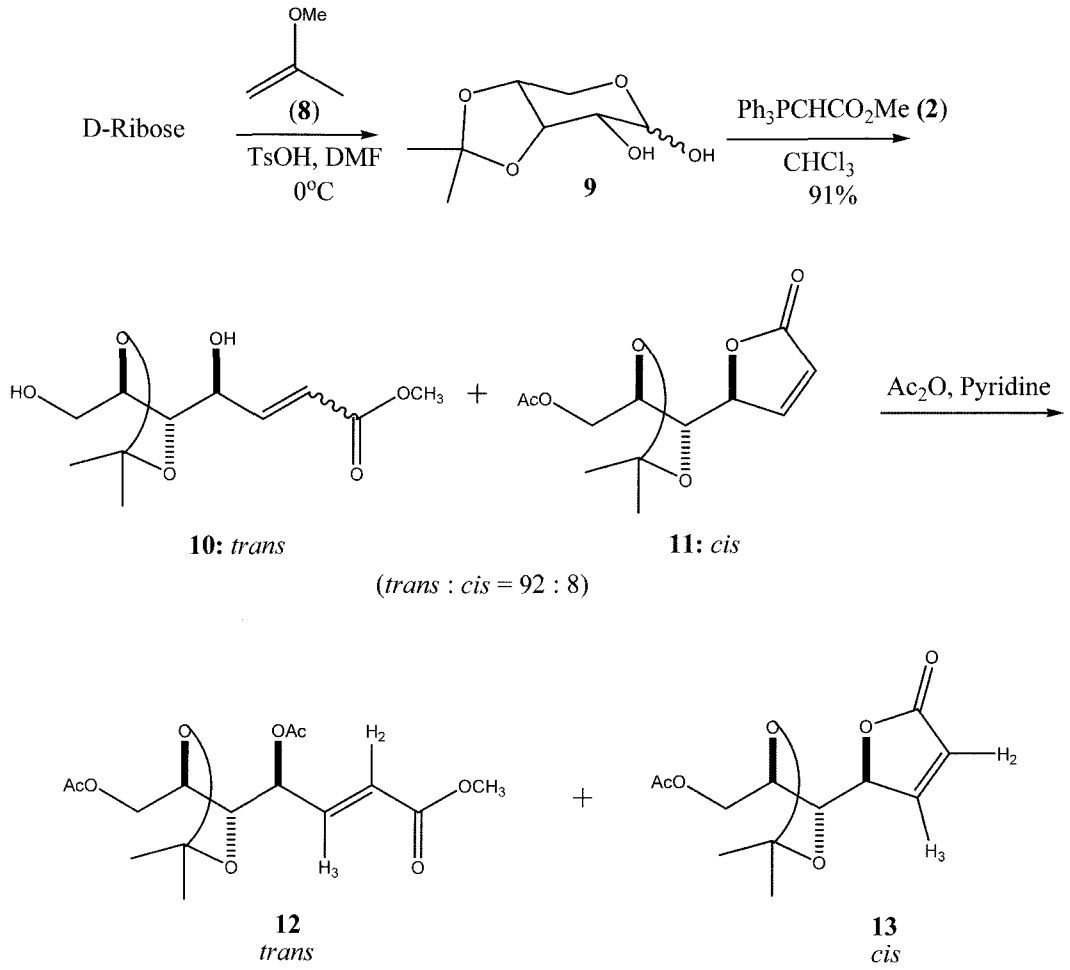

Fig. 2. Synthetic scheme for chiral α,β-unsaturated esters from D-ribose.

(t, 1H, 7-OH), 4.28 (m, 1H), 4.17 (m, 1H), 3.86 (dd, 1H, *J* 8.5 Hz, *J* 6.1 Hz), 3.72 (m, 1H), 3.53 (dd, 1H, *J* 6.9 Hz, *J* 11.7 Hz), 3.65 (s, 3H, OCH_3), 1.34 (s, 3H, CH_3), 1.24 (s, 3H, CH_3); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 167.0 (C-1), 147.5 (C-3), 120.9 (C-2), 108.7 (**C**ME_2), 79.2, 77.5, 68.8, 60.5, 51.6 (OCH_3), 27.6 (Me), 25.1 (Me); IR (neat) 3392, 2990, 2952, 1714 (C = O), 1660, 1440, 1384, 1384, 1275, 1220, 1042 cm^{-1}; MS: *m/z* (relative intensity) 247 (16.7, M+1), 231 (20.7), 189 (35.6), 131 (34.6), 129 (26.8), 97 (27.5), 59 (100).

The mixture of **10** and lactone **11** was acetylated with Ac_2O in pyridine as solvent. Routine work-up and flash chromatography (1 : 3 EtOAc-hexane) gave **12** (180 mg, 2.8%) and **13** (390 mg, 7%). The total yield was 91% and *trans-cis* ratio was 92 : 8.

For acetylated *trans*-enonate **12**; $[\alpha]_D$ −11.4 (*c* 1, $CHCl_3$); R_f 0.47 (1 : 2 EtOAc-hexane); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.90 (dd, 1H, $J_{2,3}$ 15.8 Hz, $J_{3,4}$ 5.2 Hz, H-3), 5.94 (d, 1H, $J_{2,4}$ 1.5 Hz, H-2), 5.39 (m, 1H), 4.28-4.39 (m, 2H), 4.19 (dd, 1H, *J*7.8 Hz, *J*5.7 Hz), 3.99 (dd, 1H, *J* 6.7 Hz, *J* 13.8 Hz), 3.71 (s, 3H, OCH_3), 2.08 (s, 3H, $COCH_3$), 2.04 (s, 3H, $COCH_3$), 1.44 (s, 3H, CH_3), 1.32 (s, 3H, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.4 (**C**OMe), 169.0 (**C**OMe), 165.9 (C-1), 142.5 (C-3), 122.9 (C-2), 109.9 (**C**ME_2), 76.8, 75.0, 70.2, 61.9, 51.8 (OCH_3), 27.5 (Me), 25.1 (Me), 20.6 (double intensity, $COCH_3$); IR (neat) 2990, 2954, 1732 (C = O), 1666, 1438, 1374, 1312, 1218, 1174, 1086, 1044, 984 cm^{-1}; MS: *m/z* (relative intensity) 331 (22.9, M+1), 315 (90.7), 273 (89.7), 271 (25.7), 241 (23.4), 213 (52.9), 199 (19.1), 171 (30.5), 153 (55.0), 139 (41.7), 115 (100). *Anal.* Calc. for $C_{15}H_{22}O_8$ (330.33): C, 54.54; H, 6.71. Found: C, 54.34; H, 6.82.

For acetylated lactone **13**; $[\alpha]_D$ −74.4 (*c* 1, $CHCl_3$); R_f 0.40 (1 : 2 EtOAc-hexane); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.63 (dd, 1H, $J_{2,3}$ 5.7 Hz, $J_{3,4}$ 1.6 Hz, H-3), 6.18 (dd, 1H, $J_{2,4}$ 1.9 Hz, H-2), 4.93 (m, 1H), 4.57 (dd, 1H, *J* 3.8 Hz, *J* 5.8 Hz), 4.46 (m, 1H), 4.23 (dd, 1H, *J* 6.9 Hz, *J* 11.8 Hz), 3.84 (m, 1H), 2.08 (s, 3H, $COCH_3$), 1.46 (s, 3H, CH_3), 1.34 (s, 3H, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.4 (COMe), 170.2 (C-1), 155.6 (C-3), 122.2 (C-2), 109.9 (**C**ME_2), 79.7, 77.5, 75.3, 61.9, 27.5 (Me), 25.0 (Me), 20.8 (CO**C**H_3); IR (neat) 3100, 2988, 1780 (C = O),

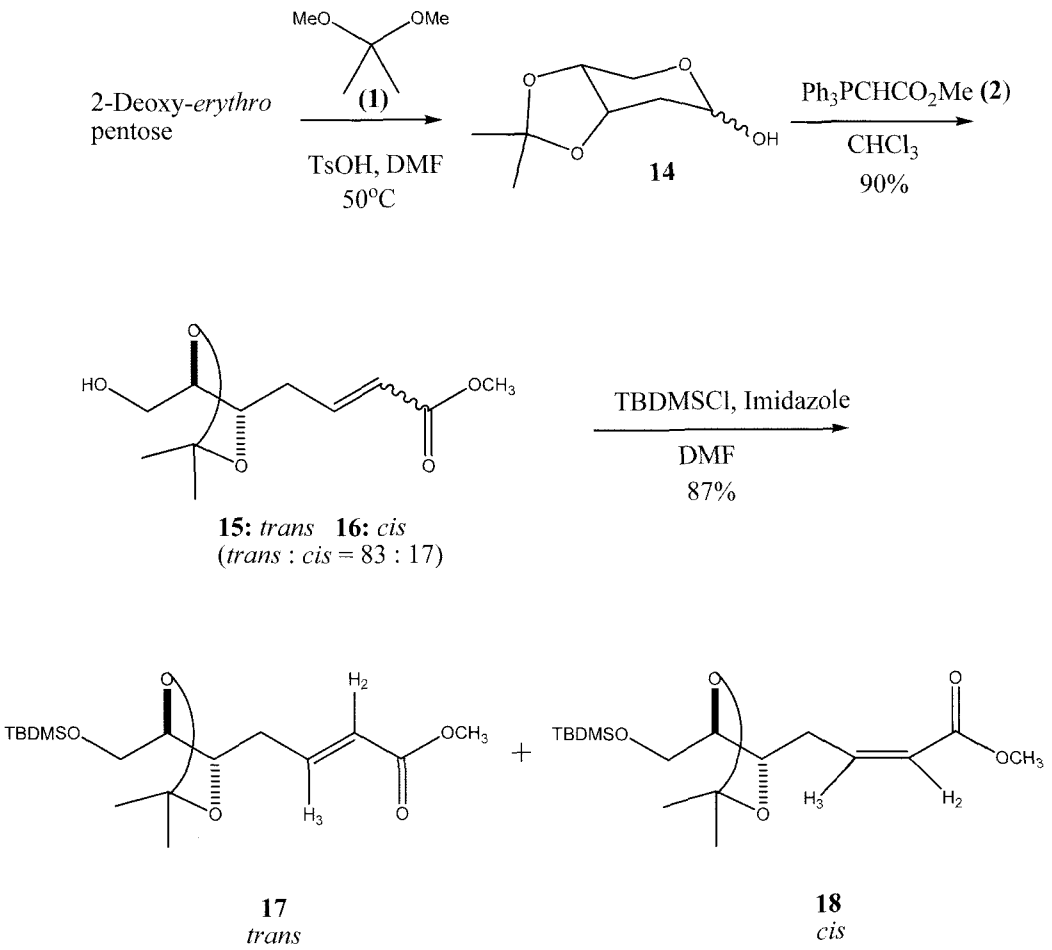

Fig. 3. Synthetic scheme for chiral α,β-unsaturated esters from 2-deoxy-D-erythropentose.

1748, 1238, 1164, 1088, 1040, 987 cm^{-1}; MS: *m/z* (relative intensity) 257 (30.4, M+1), 241 (36.0), 199 (100), 139 (23.2), 115 (47.7).

The preceding procedure was performed starting with 3,4-*O*-isopropylidene-D-arabinopyranose (**3**). After separation of byproduct Ph_3OP, an inseparable mixture of *trans* isomer **4** and *cis* isomer **5** was obtained in 73% yield (^{1}H-NMR *trans* : *cis* = 20 : 80). The mixture was acetylated and chromatography afforded pure acetylated *trans*-enonate **6** and *cis*-enonate **7**.

For acetylated *trans* isomer **6**; $[\alpha]_D$ –7.4 (*c* 1, $CHCl_3$); R_f 0.64 (1 : 1 EtOAc-hexane); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.90 (dd, 1H, $J_{2,3}$ 15.8 Hz, $J_{3,4}$ 5.6 Hz, H-3), 5.91 (dd, 1H, $J_{2,4}$ 1.3 Hz, H-2), 5.51 (m, 1H), 4.04-4.36 (m, 4H), 3.72 (s, 3H, OCH_3), 2.11 (s, 3H, $COCH_3$), 2.09 (s, 3H, $COCH_3$), 1.49 (s, 3H, CH_3), 1.34 (s, 3H, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.3 (**C**OMe), 169.3 (**C**OMe), 165.8 (C-1), 141.7 (C-3), 123.6 (C-2), 109.6 (**C**Me_2), 76.7, 74.8, 70.1, 62.3, 51.7 (OCH_3), 26.9 (Me), 25.2 (Me), 20.8 ($COCH_3$), 20.6 ($COCH_3$); IR (neat) 2997, 2958, 1719 (C = O), 1662, 1445, 1381, 1317, 1225, 1175, 1042 cm^{-1}; MS: *m/z* (relative intensity) 331 (26.8, M+1), 315 (94.3), 273 (90.8), 241 (26.2), 213 (58.1), 199 (23.9), 171 (32.5), 153 (61.2), 139 (43.3), 115 (100).

For acetylated *cis* isomer **7**; $[\alpha]_D$ –25.7 (*c* 0.85, $CHCl_3$); R_f 0.72 (1 : 1 EtOAc-hexane); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.22 (m, 1H, H-4), 6.13 (dd, 1H, $J_{2,3}$ 11.3 Hz, $J_{3,4}$ 7.5 Hz, H-3), 5.89 (dd, 1H, $J_{2,4}$ 1.1 Hz, H-2), 4.42-4.45 (m, 2H, H-5,6), 4.11-4.26 (m, 2H), 3.71 (s, 3H, OCH_3), 2.06 (double intensity, s, 6H, $2COCH_3$), 1.52 (s, 3H, CH_3), 1.33 (s, 3H, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.5 (**C**OMe), 169.8 (**C**OMe), 165.8 (C-1), 146.2 (C-3), 120.6 (C-2), 109.5 (**C**Me_2), 78.2, 74.8, 69.3, 62.7, 51.5 (OCH_3), 26.7 (Me), 25.2 (Me), 20.9 ($COCH_3$), 20.6 ($COCH_3$); IR (neat) 3045, 2971, 1780 (C = O), 1748, 1238, 1164, 1040, 987 cm^{-1}; *Anal.* Calc. for $C_{15}H_{22}O_8$ (330.33): C, 54.54; H, 6.71. Found: C, 54.65; H, 6.87.

The preceding procedure was performed starting with 2-deoxy-3,4-*O*-isopropylidene-D-erythropyranose (1.68 g, 9.7 mmol). ^{1}H-NMR revealed the Wittig mixture was 80 : 20 ratio of *trans-cis* adduct. Flash chromatography (1 : 1 EtOAc-hexane) gave inseparable mixture of **15** and **16** as a syrup (2.01 g, 90.4%). For separation of two isomers, the hydroxy group at C-7 was protected with t-

butyldimethylsilyl group in the following manner. The syrup (1.41 g, 6.1 mmol) was dissolved in 25 mL of DMF and t-butyldimethylsilyl chloride (TBDMSCl, 1.01 g, 6.72 mmol) and imidazol (448 mg, 6.72 mmol) were added to the solution, which was stirred overnight at room temperature. The solvent was evaporated to give a solid that was treated with 100 mL of dichloromethane. Undissolved solid was filtered and filtrate was evaporated to give syrup, which was passed through a chromatography column (1 : 10 EtOAc-hexane). The fast-moving spot gave *cis* product **18** (294 mg, 16%) and slowing-moving spot gave the trans product **17** (1.32 g, 71%). Total yield was 87% and *trans-cis* ratio was 83 : 17.

For *trans* isomer **17**; $[\alpha]_D$ –14.2 (*c* 0.55, $CHCl_3$); R_f 0.71 (1 : 3 EtOAc-hexane); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.01 (dt, 1H, $J_{2,3}$ 15.6 Hz, $J_{3,4}$ 7.0 Hz, H-3), 5.89 (dt, 1H, $J_{2,4}$ 1.3 Hz, H-2), 4.22 (m, 1H, *J* 6.2 Hz), 4.10 (dd, 1H, *J* 6.1 Hz), 3.70 (s, 3H, OCH_3), 3.63 (dd, 2H, *J* 10.1 Hz, *J* 6.0 Hz), 2.40-2.58 (m, 2H), 1.39 (s, 3H, CH_3), 1.31 (s, 3H, CH_3), 0.86 (s, 9H, Si-tBu), 0.04 (s, 6H, $SiMe_2$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 166.6 (C-1), 145.7 (C-3), 122.8 (C-2), 108.3 (**C**ME_2), 77.4, 75.9, 61.6, 50.9 (OCH_3), 32.4, 27.9 (Me), 25.3 (Me), 25.7 (SiC**Me**$_3$), 18.1 (Si**C**Me_3), -5.5 (Si**Me**$_2$); IR (neat) 2954, 2932, 2886, 2858, 1728 (C = O), 1660, 1472, 1436, 1380, 1370, 1256, 1218, 1168, 1110, 838 cm^{-1}.

For *cis* isomer **18**; $[\alpha]_D$ +5.4 (*c* 0.55, $CHCl_3$); R_f 0.80 (1 : 3 EtOAc-hexane); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.36 (dt, 1H, $J_{2,3}$ 11.5 Hz, $J_{3,4}$ 7.1 Hz, H-3), 5.86 (dt, 1H, $J_{2,4}$ 1.8 Hz, H-2), 4.24 (ddd, 1H, *J* 9.0 Hz, 5.9 Hz, 4.2 Hz), 4.14 (m, 1H), 3.68 (dd, 2H, *J* 12.1 Hz, 6.1Hz,), 3.69 (s, 3H, OCH_3), 3.01 (m, 1H), 2.89 (m, 1H), 1.41 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 0.88 (s, 9H, Si-tBu), 0.07 (s, 6H, $SiMe_2$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 166.4 (C-1), 146.4 (C-3), 120.4 (C-2), 108.0 (**C**ME_2), 77.8, 76.7, 61.7, 50.9 (OCH_3), 29.4, 27.9 (Me), 25.4 (Me), 25.8 (SiC**Me**$_3$), 18.1 (Si**C**Me_3), -5.5 (Si**Me**$_2$); IR (neat) 2950, 2928, 2884, 1724 (C = O), 1648, 1438, 1378, 1250, 1214, 1190, 1172 cm^{-1}.

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References

Ager DJ, Prakash I, and Schaad DR (1996) 1,2-Amino alcohols and their heterocyclic derivatives as chiral auxiliaries in asymmetric synthesis. *Chem Rev* **96**, 835-876.

Barbat J, Gelas J, and Horton H (1983) Acetonation of L-fucose, L-rhamnose, and 2-deoxy-D-erythro-pentose under kinetically controlled conditions. *Carbohydr Res* **116**, 312-316.

Baskaran S, Baskaran C, Nadkarni PJ, Trivedi GK, and Chandrasekhar J (1997) Studies on cycloaddition reactions of 2,2-dimethyl-3,4-dihydro-2H-pyrrole N-oxide and N-(benzylidene)methylamine N-oxide with α,β-unsaturated lactones and esters. *Tetrahedron* **53**, 7057-7076.

Enholm EJ and Trivellas A (1989) Samarium(II) iodide mediated transformation of carbohydrates to carbocycles. *J Am Chem Soc* **111**, 6463-6465.

Harcken C and Martin SF (2001) Improved *E*-selectivity in the Wittig reaction of stabilized ylides with a-alkoxyaldehydes and sugar lactols. *Org Lett* **3**, 3591-3593.

Gelas J and Horton D (1975) Acetonation of D-ribose and D-arabinose with alkyl isopropenyl ethers. *Carbohydr Res* **45**, 181-195.

Herdeis C and Schiffer T (1999) Synthesis of nonracemic 2,3,6-trisubstituted piperidine derivatives from sugar lactones via tandem Wittig [2+3] cycloaddition reaction. A novel entry to *Prosopis* and *Cassia* alkaloids. *Tetrahedron* **55**, 1043-1056.

Kiso M and Hasegawa A (1976) Acetonation of some pentoses with 2,2-dimethoxypropane-N,N-dimethylformamide-p-toluenesulfonic acid. *Carbohydr Res* **52**, 95-101.

Koh D (2006) Stereoselective asymmetric Diels-Alder reaction of chiral lactone derived from D-glucose with cyclopentadiene. *Agr Chem Biotechnol* **49**, 62-64.

Lim Y and Koh D (2005) Facial synthesis of versatile chiral norbornenes as leukotriene D4 antagonists from D-glucose. *Agr Chem Biotechnol* **48**, 97-100.

Pellissier H (2006) Asymmetric domino reactions. Part A: Reactions based on the use of chiral auxiliaries. *Tetrahedron* **62**, 1619-1665.

Popsavin V, Grabez S, Popsavin M, Krstic I, Kojic V, Bogdanovic G, and Divjakovic V (2004) Wittig reaction with partially protected sugar lactol derivatives. Preparation of highly cytotoxic goniofufurone analogues. *Tetrahedron Lett* **45**, 9409-9413.

Reetz MT, Strack TJ, Mutulis F, and Goddard R (1996) Asymmetric dihydroxylation of chiral γ-amino α,β-unsaturated esters: Turning the mismatched into the matched case via protective group tuning. *Tetrahedron Lett* **37**, 9293-9296.

Stork G and Kahn M (1983) A highly stereoselective osmium tetroxide-catalyzed hydroxylation of γ-hydroxy α,β-usaturated esters. *Tetrahedron Lett* **24**, 3951-3954.

Trost BM and Mignani SM (1986) A stereospecific palladium mediated [3+2] cycloaddition. *Tetrahedron Lett* **27**, 4137-4140.