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SYNTHESIS OF 2-DEOXY-L-RIBOSE VIA PALLADIUM(II)-CATALYZED CYCLIZATION

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Abstract – We present a total synthesis of 2-deoxy-L-ribose through intramolecular palladium(II)-catalyzed cyclization of aldehyde via an unstable hemiacetal intermediate as the key step.

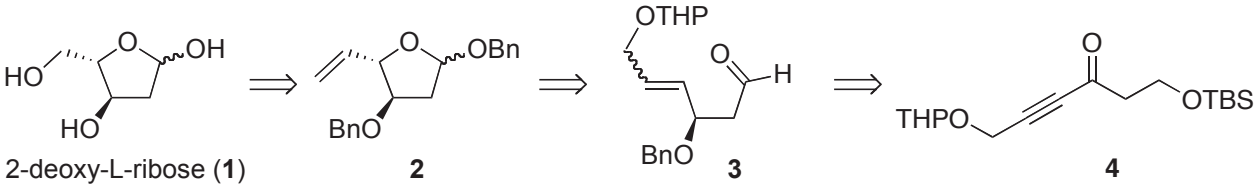
INTRODUCTION

Since the discovery that acquired immunodeficiency syndrome (AIDS) is due to infection with human immunodeficiency virus (HIV), nucleoside analogues have been key components of antiretroviral regimens to control HIV-1 infection. Various nucleoside analogues with modified sugar moieties, such as 3'-azido-3'-deoxythymidine (AZT),[1] have been developed as antiviral drugs. However, prolonged treatment with these agents leads to the emergence of a drug-resistance. On the other hand, the use of L-nucleosides and their analogues has increased due to their potent antiviral activity and generally low toxicity. Among them, L-thymidine (L-T),[2] L-(2'-fluoro-5-methylarabinofuranosyl)uracil (L-FMAU),[3] L-3'-thiacytidine (L-3-TC),[4] L-5-fluoro-3'-thiacytidine (L-FTC),[5] L-2',3'-dideoxycytidine (L-ddC),[6] and L-5-fluoro-2',3'-dideoxycytidine (L-FddC)[7] show potent antiviral activity with reduced toxicity compared to modified D-nucleosides. Consequently, L-nucleosides and L-carbohydrates, especially L-ribose and 2-deoxy-L-ribose are important synthetic targets.[8]

We recently reported new syntheses of D-ribose and 2-deoxy-D-ribose using palladium(II) catalyst.[9] We herein report a synthesis of 2-deoxy-L-ribose from the simple achiral material **5**.

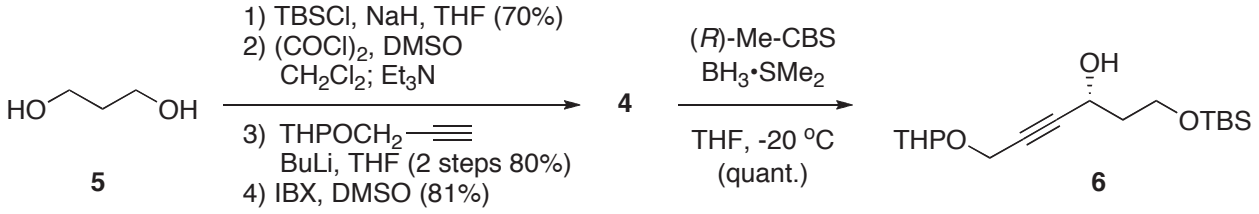
RESULTS AND DISCUSSION

Our retrosynthetic analysis (Scheme 1) proposes that 2-deoxy-L-ribose (**1**) can be derived from the 4-vinylfuranoside **2**. Compound **2** can be obtained by palladium(II)-catalyzed heterocyclization of benzyl alcohol with the aldehyde **3**, which is derived by CBS-mediated asymmetric reduction of the ynone **4**.



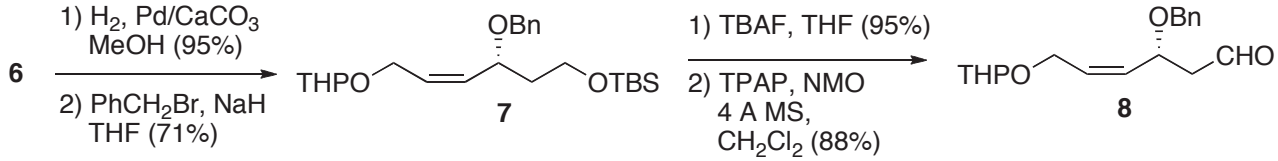
Scheme 1. Retrosynthetic analysis for 2-deoxy-L-ribose (**1**)

Synthesis of the chiral alcohol **6** is depicted in Scheme 2. Selective mono-silylation of propane-1,3-diol (**5**)[10] followed by Swern oxidation,[11] 1,2-addition with lithium 1-(2'-tetrahydropyranyloxy)-2-propynylide, and IBX oxidation led to the ynone **4** in 45% yield over 4 steps. Reduction of **4** according to the CBS protocol produced the alcohol **6** in a quantitative yield with 99% *ee*.[12]



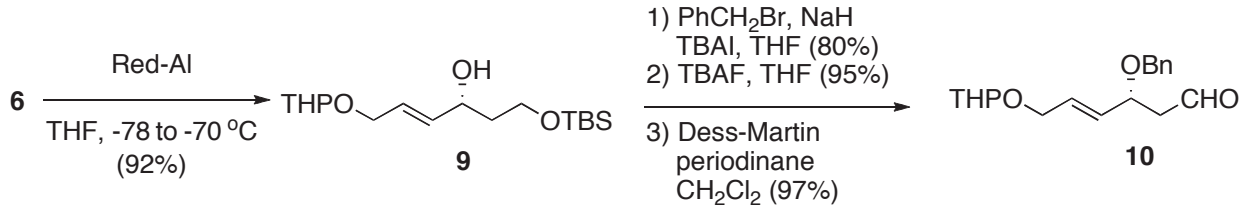
Scheme 2. Preparation of the Alcohol **6**

We next synthesized the (*Z*)-enal **8**. Stereoselective hydrogenation of the alkyne **6** with Lindlar catalyst followed by benzylation produced the (*Z*)-olefin **7** in 67% yield. After removal of the TBS group of **7** with Bu_4NF (TBAF) in THF, the resulting alcohol was treated with TPAP and NMO in CH_2Cl_2 to afford the aldehyde **8** in 84% yield over 2 steps.



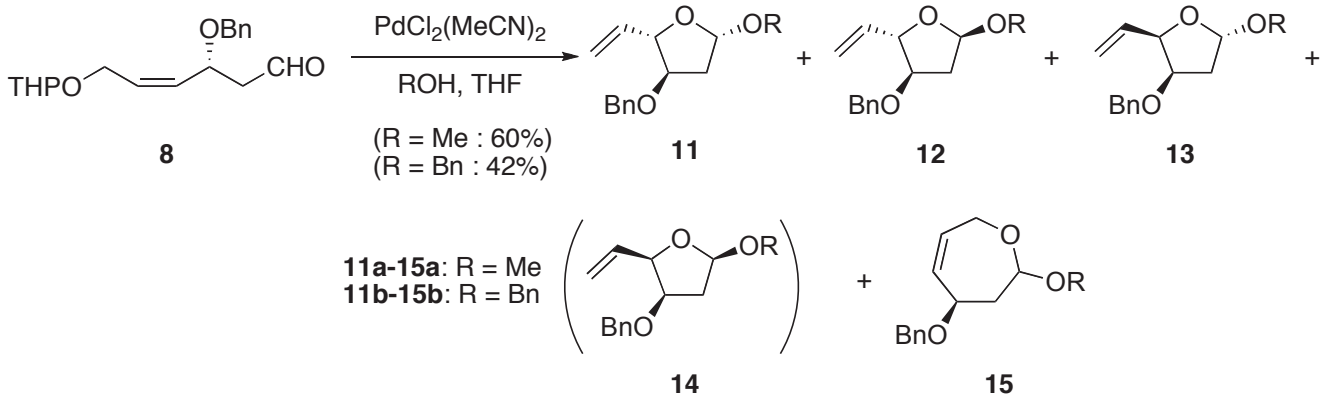
Scheme 3. Preparation of the (*Z*)-olefin **8**

We next synthesized the (*E*)-enal **10**. The alkyne **6** was treated with Red-Al® in THF at -78 °C to give the (*E*)-allylic alcohol **9** in 92% yield. Benzylation of **9** followed by removal of the TBS group with TBAF and Dess-Martin oxidation led to the (*E*)-enal **10** in 74% yield over 3 steps.



Scheme 4. Preparation of the (*E*)-olefin **10**

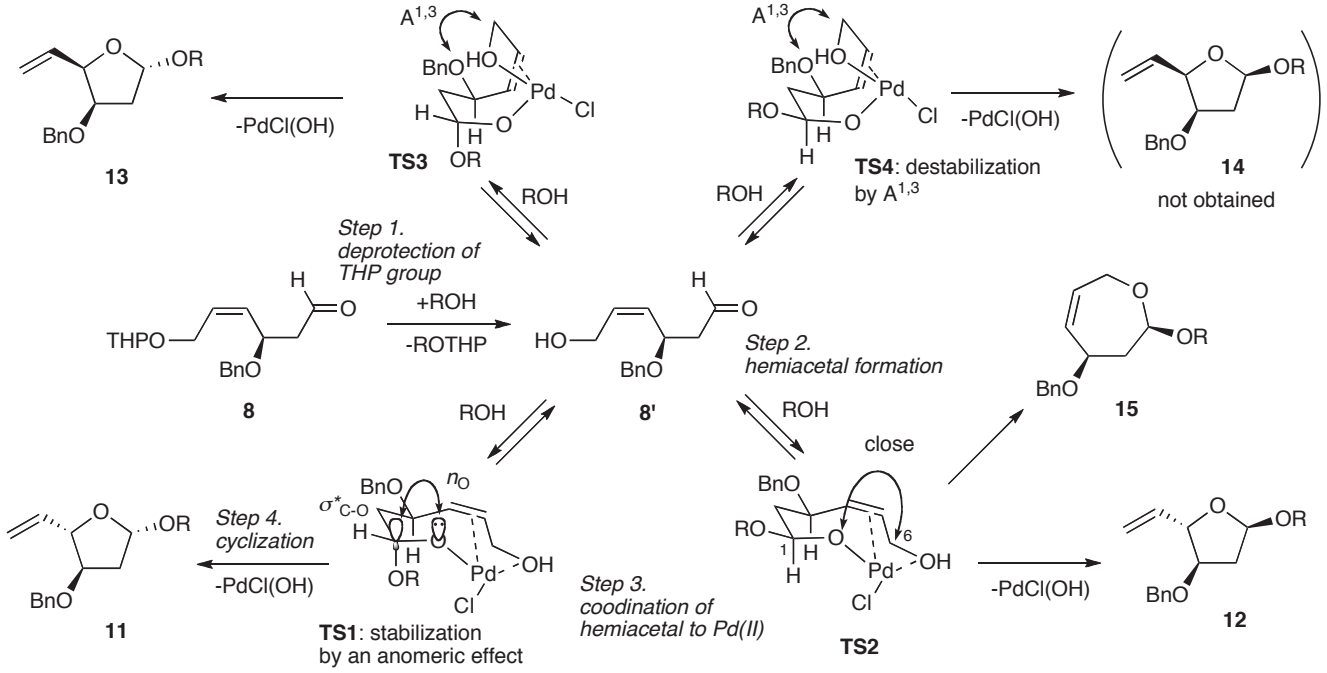
We examined cyclization of the aldehyde **8** with methanol or benzyl alcohol. Treatment of **8** with 5 mol% of $PdCl_2(MeCN)_2$ catalyst and 5 equiv. of MeOH in THF at room temperature furnished a mixture of cyclization products as a 1.5 : 1.0 : 0.2 : 0 : 3.6 mixture of **11a** : **12a** : **13a** : **14a** : **15a** in 60% isolated yield. It is noteworthy that Pd-catalyzed cyclization of the aldehyde **8** proceeded in the opposite regiochemical sense to give the seven-membered cyclic acetal **15a** as the major product (five-membered ring **11a**-**14a** : seven-membered ring **15a** = 0.75 : 1.0). In previous studies of the palladium(II)-catalyzed heterocyclization reactions, we have never obtained a seven-membered cyclization product.[9,13] When benzyl alcohol was used, the ratio of five-membered ring : seven-membered ring was increased to 2.1 : 1.0.



Scheme 5. Pd(II)-catalyzed cyclization of the aldehyde **8**

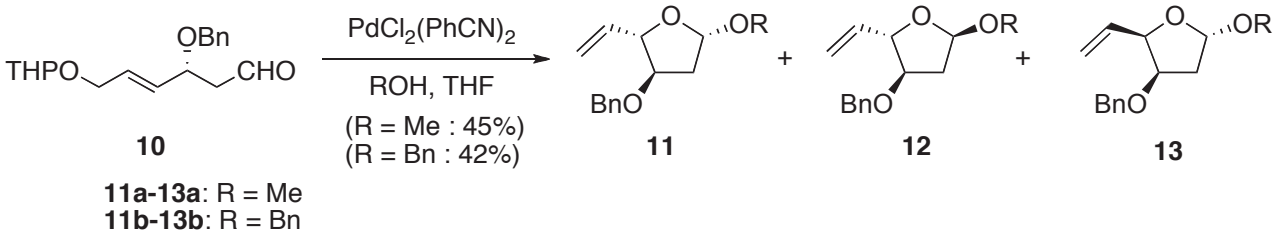
A plausible mechanism for the cyclization of the aldehyde **8** is shown in Scheme 6. First of all, deprotection of the tetrahydropyranyl group with ROH in the presence of the palladium(II) catalyst, which behaves as a Lewis acid, gives the allylic alcohol **8'** (Step 1). Then, the hemiacetal intermediate is formed by 1,2-addition of ROH to the aldehyde **8'** (Step 2). Pd π-complex is formed by coordination of $PdCl_2L_n$ with the allylic alcohol, and one of the π-faces of the olefin may be preferentially recognized with the assistance of the adjacent hydroxyl group of the hemiacetal (Step 3). The resulting complex may be present as an equilibrium mixture of four structures (**TS1** – **TS4**). Although the conformations of **TS1** and **TS3** are stabilized by the anomeric (n_O-$\sigma^*_{C\text{-}O}$), the conformations of **TS2** and **TS4** are not. Although conformations **TS3** and **TS4** are strongly destabilized by $A^{1,3}$ strain, the conformations **TS1** and **TS2** are

not. Because of these two factors, the overall mechanism can account for the observed predominant formation of **11** and **12**. In addition, the seven-membered cyclization of **TS2** easily proceeds to afford **15** because the distance between the alcohol of hemiacetal and C-6 position is very near.



Scheme 6. Plausible mechanism of Pd(II)-catalyzed cyclization

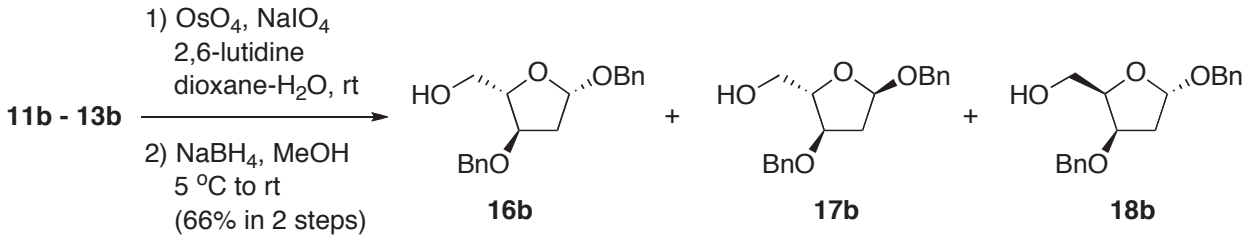
We next examined cyclization of the (*E*)-enal **10** with MeOH or benzyl alcohol. In this case, only the five-membered ring was formed, and no seven-membered ring product was obtained. When MeOH was used, a 14 : 7.5 : 1.0 mixture of **11a** : **12a** : **13a** was formed in 45% isolated yield. When benzyl alcohol was used, the furanoside mixture **11b**-**13b** was obtained in 42% yield, and the ratio of 4*S*-isomer : 4*R*-isomer (**11b**+**12b** : **13b**) was decreased to 8.5 : 1.0.



Scheme 7. Pd(II)-catalyzed cyclization of the aldehyde **10**

The mixture of the cyclized products **11b**-**13b** was converted to the primary alcohols **16b**-**18b** (Scheme 8). Double-bond oxidation of the mixture **11** with sodium periodate, a catalytic amount of osmium tetroxide,

and 2,6-lutidine in dioxane/H_2O followed by reduction with $NaBH_4$ in MeOH gave the primary alcohols **16b-18b**, which could be separated by silica gel column chromatography (**16b** : **17b** : **18b** = 4.6 : 3.6 : 1).



Scheme 8. Transformation of **11b** - **13b** to the primary alcohols **16b** - **18b**

The relative stereochemistry of **16b** - **18b** was established by NOE experiments (Figure 1).

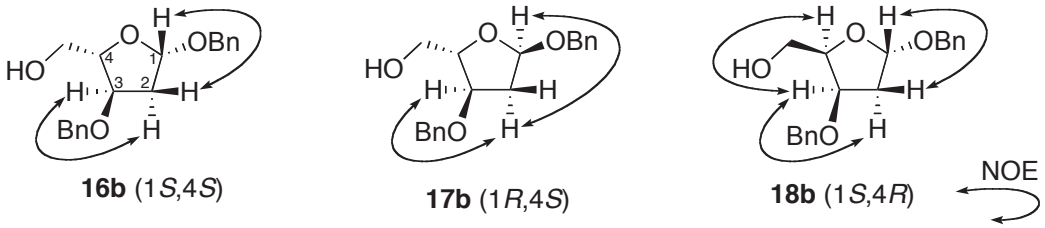
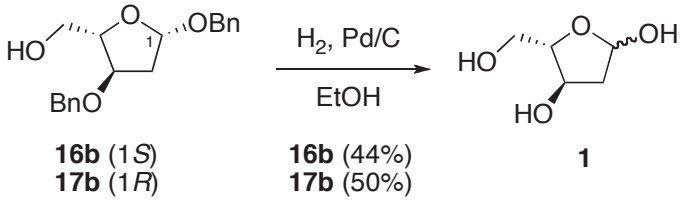


Figure 1. NOE correlations in the primary alcohols **16b** - **18b**

Finally, the benzyl groups in **16b** and **17b** were removed at atmospheric pressure of hydrogen in EtOH with palladium over charcoal (10%). After 2 days, 2-deoxy-L-ribose (**1**) was obtained in 44% and 50% yield, respectively. The product was easily purified by silica gel column chromatography. The product was identical in terms of spectral data to an authentic sample of 2-deoxy-L-ribose.



Scheme 9. Transformation of **16b** and **17b** to 2-deoxy-L-ribose (**1**)

In summary, we have developed a synthesis of 2-deoxy-L-ribose by using palladium(II)-catalyzed cyclization as a key reaction. The cyclization was proceeded under mild conditions, affording the substituted furanoside. The synthesis involved 13 steps and 2-deoxy-L-ribose was obtained in 3.4% overall yield from propane-1,3-diol.

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.; dimethylsulfoxide (DMSO) was distilled from CaH_2. 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 $60F_{254}$, Merck) visualized under UV light and stained with either phosphomolybdic acid or *p*-anisaldehyde. 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. Optical rotations ($[\alpha]_D$) were determined with a JASCO P-1020 polarimeter. ^{1}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 (δ) downfield from TMS. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, m = multiplet. ^{13}C NMR spectra were recorded at 75 MHz with a JEOL JNM-ECX 300 spectrometer with chemical shifts reported in ppm (δ).

6-(*tert*-Butyldimethylsilyloxy)-1-(tetrahydropyran-2-yloxy)-hex-2-yn-4-ol (*dl*-6). To a suspension of NaH (5.73 g, 131 mmol, 55% in dispersion oil) in THF (120 mL) was added propane-1,3-diol (10.00 g, 131.4 mmol) in THF (130 mL) at 0 °C under an Ar atmosphere and the mixture was stirred for 1 h. The mixture was cooled to 0 °C, then TBSCl (21.8 g, 144.6 mmol) was added at the same temperature. The resulting mixture was stirred at room temperature for 2 h. The reaction mixture was quenched with ice and the aqueous layer was extracted with AcOEt (x 3). The combined organic layers were washed with aqueous $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (eluent with Hex : AcOEt = 80 : 20) to afford 1-*tert*-butyldimethyl-silyloxypropan-3-ol (22.9 g, 92%) as a colorless oil.

To a stirred -78 °C solution of DMSO (25.6 mL, 361 mmol) in CH_2Cl_2 (580 mL) under an Ar atmosphere was added oxalyl chloride (15.7 mL, 181 mmol). The mixture was stirred for 15 min and a solution of 1-(*tert*-butyldimethylsilyloxy)propan-3-ol (22.9 g, 120 mmol) in CH_2Cl_2 (22 mL) was added dropwise. After stirring for 30 min at -78 °C, triethylamine (75.5 mL, 542 mmol) was added at -78 °C, and the resulting mixture was allowed to warm to room temperature. After 30 min, the reaction mixture was quenched with ice and 10 % aqueous HCl. The aqueous layer was extracted with CH_2Cl_2 (x 2). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$. The solvent was removed under reduced pressure to give the crude aldehyde, which was used in the next step without further purification.

A solution of propargyl THP ether (20.23 g, 107 mmol) in THF (170 mL) was cooled to -78 °C and

treated with *n*-BuLi (1.6 M in hexane solution, 74.0 mL, 118.15 mmol) under an Ar atmosphere. The mixture was stirred at the same temperature for 1 h. A solution of the crude aldehyde (20.23 g, 107.4 mmol) in THF (20 mL) was added to the mixture at -78 °C. After stirring for 1 h at the same temperature, the reaction mixture was quenched with saturated NH_4Cl and the aqueous layer was extracted with AcOEt (x 2). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (eluent with Hex : AcOEt = 9 : 1) to afford the alcohol ***dl*-6** (21.0 g, 2 steps 52%) as a yellow oil.

***dl*-6**: a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.81 (t, *J* = 3.1 Hz, 1H), 4.73-4.63 (m, 1H), 4.15 (dd, *J* = 15.8, 1.7 Hz, 1H), 3.90 (dt, *J* = 15.5, 3.1 Hz, 1H), 4.06-3.99 (m, 1H), 3.88-3.79 (m, 2H), 3.56-3.49 (m, 1H), 3.42 (dd, *J* = 6.2, 1.9 Hz, 1H), 2.06-1.95 (m, 1H), 1.92-1.82 (m, 1H), 1.80-1.46 (m, 6H), 0.90 (s, 9H), 0.09 (d, *J* = 2.4 Hz, 6H); IR (neat, cm^{-1}) 3421, 3029, 2950, 2240,1454, 1089, 836, 695.

6-(*tert*-Butyldimethylsilyloxy)-1-(tetrahydropyran-2-yloxy)hex-2-yn-4-one (4). To a solution of ***dl*-6** (0.84 g, 2.54 mmol) in DMSO (12.7 mL) was added IBX (2.14 g, 7.62 mmol) and the mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with AcOEt, and the mixture was quenched with saturated aqueous $NaHCO_3$ solution and saturated aqueous $Na_2S_2O_3$ solution at 0 °C. The aqueous layer was extracted with Et_2O (x 3). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (eluent with Hex : AcOEt = 93 : 7) to afford the ynone **4** (0.67 g, 81%) as a colorless oil.

4: a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.67 (t, *J* = 3.1 Hz, 1H), 4.42 (s, 1H), 3.97 (t, *J* = 6.5 Hz, 1H), 3.87-3.79 (m, 1H), 3.59-3.52 (m, 1H), 2.77 (t, *J* = 6.2 Hz, 1H), 1.87-1.48 (m, 6H), 0.88 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (75MHz, $CDCl_3$) δ: 185.80, 97.23, 88.31, 84.88, 62.08, 58.33, 53.88, 48.40, 30.16, 25.89, 25.32, 18.90, 18.31, -5.38; IR (neat, cm^{-1}): 2952, 2856, 2216, 1680, 1472, 1388, 1361, 1256, 1202, 1166, 1121, 1102, 1061, 1032, 1006, 966, 941, 902, 871, 836, 778; HRMS (EI): calcd. for $C_{17}H_{30}O_4Si$ 326.1913, found 326.1905.

(*R*)-6-(*tert*-Butyldimethylsilyloxy)-1-(tetrahydropyran-2-yloxy)-hex-2-yn-4-ol (6). To a solution of the ynone **4** (3.09 g, 11.6 mmol) in THF (116 mL) was added (*R*)-2-methyl-CBS-oxazaborolidine reagent (1 M solution in toluene, 1.16 mL, 1.16 mmol) and borane-methyl sulfide complex (BMS) (0.66 mL, 6.96 mmol) at 0 °C under an Ar atmosphere. The mixture was stirred at room temperature for 1 h. The reaction mixture was quenched with MeOH at 0 °C and saturated aqueous NH_4Cl solution. The aqueous layer was extracted with AcOEt (x 2). The combined organic layers were washed with aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (eluent with Hex : AcOEt = 9 : 1) to give the alcohol **6** (3.13 g, 98%) as a pale yellow oil.

6: a yellow oil; $[\alpha]^{20}_D$ 11.8 (*c* 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.81 (t, *J* = 3.1 Hz, 1H), 4.73-4.63 (m, 1H), 4.15 (dd, *J* = 15.8, 1.7 Hz, 1H), 3.90 (dt, *J* = 15.5, 3.1 Hz, 1H), 4.06-3.99 (m, 1H),

3.88-3.79 (m, 2H), 3.56-3.49 (m, 1H), 3.42 (dd, *J* = 6.2, 1.9 Hz, 1H), 2.06-1.95 (m, 1H), 1.92-1.82 (m, 1H), 1.80-1.46 (m, 6H), 0.90 (s, 9H), 0.09 (d, *J* = 2.4 Hz, 6H); IR (neat, cm^{-1}) 3421, 3029, 2950, 2240, 1454, 1089, 836, 695; HRMS (FAB): calcd. for $C_{17}H_{32}O_4Si$-Na $(M+Na)^+$ 351.1969, found 351.1958.

For the *ee* determination, the alcohol **6** was converted into the corresponding benzoate derivative with benzoyl chloride (2equiv.) and pyridine (3 equiv.) in CH_2Cl_2 for 1 day. Aqueous workup, followed by short column chromatography on silica gel (euent with Hex : AcOEt = 97 : 3) afforded the crude benzoate. The crude benzoate was analyzed by chiral HPLC (Chiralcel OD-H, Hex : 2-propanol = 99.8 : 0.2, 1 mL/min), t_R = 12.2 min, t_S = 15.9 min.

(4*R*,*Z*)-4-Benzyloxy-6-(*tert*-butyldimethylsilyloxy)-1-(tetrahydropyran-2-yloxy)-hex-2-ene (7)

To a suspension of Lindlar catalyst (5 wt% of Pd, 119 mg) in MeOH (18 mL) was added a solution of the alkyne **6** (784 mg, 2.39 mmol) in MeOH (5 mL) at room temperature under an H_2 atmosphere. The suspension was stirred for 19 h at the same temperature. The reaction mixture was filtered through a celite pad and the pad was washed with ether. The filtrate was concentrated under reduced pressure to give the crude allylic alcohol, which was used in the next step without further purification.

To a suspension of NaH (113 mg, 2.59 mmol, 55% in dispersion oil) in THF (30 mL) was added a solution the crude allylic alcohol (780 mg, 2.36 mmol) in THF (10 mL) at 0 °C, then the mixture was stirred at room temperature for 1 h. To the suspension was added benzyl bromide (0.31 mL, 2.61 mmol) and tetra-*n*-butylammonium iodide (443 mg, 1.20 mmol) at room temperature, and the resulting mixture was stirred under reflux for 5 h. The reaction mixture was cooled with ice bath and diluted with Et_2O, then the mixture was quenched with saturated aqueous NH_4Cl solution. The aqueous layer was extracted with Et_2O (x 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude oil was purified by silica gel column chromatography (eluent with Hex : AcOEt = 95 : 5) to afford the benzyl ether **7** (713 mg, 71% yield) as a yellow oil.

7: a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.34-7.30 (m, 5H), 5.84-5.77 (m, 1H), 5.57-5.50 (m, 1H), 4.63-4.56 (m, 1H), 4.478 (dd, *J* = 4.2, 1.6 Hz, 0.5H), 4.40-4.33 (m, 2.5H), 4.189 (ddd, *J* = 12.8, 5.1, 1.8 Hz, 0.5H), 4.133 (ddd, *J* = 12.8, 7.7, 1.5 Hz, 0.5H), 3.978 (ddd, *J* = 12.5, 6.2, 1.5 Hz, 0.5H), 3.87-3.81 (m, 1H), 3.76-3.70 (m, 1H), 3.66-3.60 (m, 1H), 3.52-3.46 (1.5H), 2.01-1.78 (m, 2H), 1.76-1.68 (m, 1H), 1.68-1.48 (m, 5H), 0.876 (s, 4.5H), 0.874 (s, 4.5H), 0.05-0.02 (m, 6H); IR (neat, cm^{-1}): 2945, 2870, 1118, 742, 698; HRMS (FAB): calcd. for $C_{24}H_{40}O_4Si$-Na $(M+Na)^+$ 443.2595, found 443.2608.

(3*R*,*Z*)-3-(Benzyloxy)-6-(tetrahydropyran-2-yloxy)-hex-4-enal (8). To a solution of the TBS ether **7** (713 mg, 1.69 mmol) in THF (8.5 mL) was added tetra-*n*-butylammonium fluoride (1.0 M in THF, 1.86 mL, 1.86 mmol) at room temperature under an Ar atmosphere. The mixture was stirred at the same temperature for 19 h. The mixture was diluted with Et_2O, and washed with water. The aqueous layer was extracted with Et_2O (x 3). The combined organic layers were washed with brine, dried over $MgSO_4$,

filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (eluent with Hex : AcOEt = 86 : 14 to 60 : 40, gradient) to afford (3*R*,*E*)-3-(benzyloxy)-6-(tetrahydropyran-2-yloxy)hex-4-en-1-ol (490 mg, 95% yield) as a colorless oil.

To a solution of the allylic alcohol (490 mg, 1.60 mmol) in CH_2Cl_2 (4 mL) was added *N*-methylmorpholine *N*-oxide (281 mg, 2.4 mmol) and powdered MS 4A (800 mg) at room temperature under an Ar atmosphere. The suspension was stirred for 30 min, then TPAP (28 mg, 0.08 mmol) was added at the same temperature. The reaction mixture was stirred for 15 min, then diluted with CH_2Cl_2 and filtered through a pad of Celite®. The filtrate was washed with diluted HCl and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (eluent with Hex : AcOEt = 85 : 15) to afford the enal **8** (427 g, 88% yield) as a colorless oil.

8: a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.77-9.73 (m, 1H), 7.38-7.28 (m, 5H), 5.92-5.77 (m, 1H), 5.61-5.45 (m, 1H), 4.67-4.50 (m, 3H), 4.44-4.30 (m, 2H), 4.098 (ddd, *J* = 13.4, 7.6, 1.4 Hz, 1H), 4.031 (ddd, *J* = 13.1, 6.2, 1.4 Hz, 1H), 3.60-3.45 (m, 1H), 2.80-2.65 (m, 1H), 2.61-2.48 (m, 1H), 1.90-1.45 (m, 6H); IR (neat, cm^{-1}): 2942, 1724, 1454, 1027, 740, 699; HRMS (FAB): calcd. for $C_{18}H_{24}O_4$-Na $(M+Na)^+$ 327.1572, found 327.1565.

6-(*tert*-Butyldimethylsilyloxy)-1-(tetrahydropyran-2-yloxy)-hex-2-en-4-ol (9). To a solution of the alcohol **6** (1.30 g, 3.96 mmol) in THF (20 mL) was added Red-Al® (2.99 M solution in toluene, 4.0 mL, 11.9 mmol) at -78 °C under an Ar atmosphere, and the resulting mixture was allowed to warm into -35 °C. After stirring for 7 h, the mixture was diluted with AcOEt, and the reaction mixture was quenched with saturated aqueous NH_4Cl solution. The mixture was filtered througth a pad of Celite®, which was washed with AcOEt and H_2O. The filtrate was extracted with AcOEt (x 2). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude oil was purified by silica gel column chromatography (eluent with Hex : AcOEt = 88 : 12) to afford the (*E*)-allylic alcohol **9** (1.21 g, 92% yield) as a yellow oil.

9: a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.82 (dt, *J* = 15.8, 4.9 Hz, 1H), 6.39 (dd, *J* = 15.8, 4.5 Hz, 1H), 4.65 (t, *J* = 3.5 Hz, 1H), 4.43-4.35 (m, 1H), 4.28-4.21 (m, 1H), 4.00 (dd, *J* = 13.0, 5.3 Hz, 1H), 3.93-3.86 (m, 1H), 3.85-3.77 (m, 1H), 3.54-3.47 (m, 1H), 3.30 (d, *J* = 4.3 Hz, 1H), 1.88-1.68 (m, 2H), 1.65-1.51 (m, 6H), 0.90 (s, 9H), 0.08 (s, 6H); IR (neat, cm^{-1}): 3433, 2944, 2850, 1115, 980, 698; HRMS (FAB): calcd. for $C_{17}H_{34}O_4Si$-Na $(M+Na)^+$ 353.2124, found 353.2112.

(3*R*,*E*)-3-(Benzyloxy)-6-(tetrahydropyran-2-yloxy)-hex-4-en-1-ol. To a suspension of NaH (0.14 g, 3.22 mmol, 55% in dispersion oil) in THF (15 mL) was added a solution (*E*)-allylic alcohol **9** (0.76 g, 2.30 mmol) in THF (5 mL) at 0 °C, then the mixture was stirred at room temperature for 1 h. To the suspension was added benzyl bromide (0.41 mL, 3.45 mmol) and tetra-*n*-butylammonium iodide (0.22 g,

0.46 mmol) at 0 °C, then the mixture was stirred at room temperature for 10 min, and the resulting mixture was allowed to warm into 55 °C. After 10 h, the reaction mixture was cooled with ice bath and diluted with Et_2O, then the mixture was quenched with saturated aqueous NH_4Cl solution. The aqueous layer was extracted with Et_2O (x 2). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude oil was purified by silica gel column chromatography (eluent with Hex : AcOEt = 95 : 5) to afford (4*R*,*E*)-4-(benzyloxy)-6-(*tert*-butyl-dimethylsilyloxy)-1-(tetrahydropyran-2-yloxy)-2-hexene (0.83 g, 86% yield) as a yellow oil.

To a solution of the TBS ether (0.83 g, 1.97 mmol) in THF (10 mL) was added tetra-*n*-butylammonium fluoride (1.0 M in THF, 5.0 mL, 4.94 mmol) at 0 °C under an Ar atmosphere. The mixture was stirred at the same temperature for 10 min, warmed to room temperature. After stirring at the same temperature for 19.5 h, the mixture was diluted with Et_2O, and washed with water. The aqueous layer was extracted with Et_2O (x 2). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (eluent with Hex : AcOEt = 86 : 14 to 60 : 40, gradient) to afford (3*R*,*E*)-3-(benzyloxy)-6-(tetrahydropyran-2-yloxy)hex-4-en-1-ol (0.56 g, 93% yield) as a colorless oil.

primary alcohol: a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.39-7.26 (m, 5H), 5.83 (dt, *J* = 15.5, 5.3 Hz, 1H), 5.75-5.65 (m, 1H), 4.70-4.59 (m, 2H), 4.37 (d, *J* = 12.0 Hz, 1H), 4.33-4.24 (m, 1H), 4.12-4.00 (m, 2H), 3.93-3.83 (m, 1H), 3.83-3.68 (m, 2H), 3.57-3.48 (m,1H), 2.51-2.42 (m,1H), 1.98-1.48 (m, 8H); IR (neat, cm^{-1}): 3436, 2942, 2868, 1119, 1076, 1038; MS (EI) *m*/z: 177 (3), 113 (13), 107 (11), 91 (100), 85 (23), 55 (13); (DART) *m*/*z* 307 ; ($[M+H]^+$); HRMS-DART calcd. for $C_{18}H_{27}O_4$ ($[M+H]^+$) 307.19093, found 307.19094.

(3*R*,*E*)-3-(Benzyloxy)-6-(tetrahydropyran-2-yloxy)-hex-4-enal (10). To a solution of (3*R*,*E*)-3-(benzyloxy)-6-(tetrahydropyran-2-yloxy)hex-4-en-1-ol (510 mg, 1.67 mmol) in CH_2Cl_2 (16 mL) was added Dess-Martin periodinane (1.67 g, 3.34 mmol) at 0 °C. The mixture was warmed to room temperature and stirred for 1 h. After cooling, Dess-Martin periodinane (0.42 g, 0.84 mmol) was added to the mixture at 0 °C, then the resulting mixture was warmed up to room temperature and stirred for 1 h. The reaction was quenched with saturated aqueous $Na_2S_2O_3$ solution. To the quenched mixture was added saturated aqueous $NaHCO_3$ solution and the aqueous layer was extracted with CH_2Cl_2 (x 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (eluent with Hex : AcOEt = 85 : 15) to afford the enal **10** (470 mg, 93% yield) as a colorless oil.

10: a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.78-9.74 (m, 1H), 7.37-7.25 (m, 5H), 5.95-5.84 (m, 1H), 5.78-5.65 (m, 1H), 4.70-4.55 (m, 2H), 4.45-4.25 (m, 3H), 4.04 (ddd, *J* = 13.4, 5.5, 1.3 Hz, 1H), 3.94-3.82 (m, 1H), 3.60-3.46 (m, 1H), 2.76 (dddd, *J* = 16.5, 8.3, 2.8, 1.3 Hz, 1H), 2.63-2.52 (m, 1H),

1.92-1.48 (m, 6H); IR (neat, cm^{-1}): 2943, 2868, 1726, 1119, 1077, 1026, HRMS (FAB): calcd. for $C_{18}H_{24}O_4$-Na $(M+Na)^+$ 327.1572, found 327.1585.

(4*R*)-4-Benzyloxy-2-methoxy-2,3,4,7-trahydroxepine (15a). To a solution of (3*R*,*Z*)-3-(benzyloxy)-6-(tetrahydropyran-2-yloxy)hex-4-enal (**8**) (100 mg, 0.33 mmol) and MeOH (52.7 mg, 1.65 mmol) in THF (16 mL) was added $PdCl_2(MeCN)_2$ (4.3 mg, 0.016 mmol) at room temperature under an Ar atmosphere, then the mixture was stirred at the same temperature for 1.5 h. After stirring, the mixture was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (eluent with Hex : AcOEt = 98 : 2) to afford **15a** and **11a**-**13a** (77 mg, 60% yield) as a colorless oil.

15a: a colorless oil; $[\alpha]^{20}_D$ -15.3 (*c* 0.50, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.36-7.32 (m, 5H), 5.95-5.87 (m, 1H), 5.672 (ddt, *J* = 11.4, 4.9, 2.4 Hz, 1H), 4.788 (dd, *J* = 9.3, 4.8 Hz, 1H), 4.54 (m, 1H), 4.36-4.26 (m, 1H), 3.92-3.81 (m, 1H), 3.365 (s, 3H), 2.358 (ddt, *J* = 13.8, 4.8, 2.1 Hz, 1H), 2.181 (ddd, *J* = 13.8, 11.7, 9.3 Hz, 1H), IR (neat, cm^{-1}) 2931, 1496, 1454, 1372, 1176, 1070, 1011, 945, 846, 736, 698. HRMS (FAB): calcd. for $C_{14}H_{18}O_3$-Na $(M+Na)^+$ 257.1153, found 257.1145.

11a-13a (diastereomer mixture): a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.36-7.27 (m, 5H), 6.08 (ddd, *J* = 17.2, 10.3, 7.3 Hz, 0.12H), 5.90 (ddd, *J* = 17.2, 10.3, 7.0 Hz, 0.53H), 5.82 (ddd, *J* = 17.2, 10.3, 6.6 Hz, 0.35H), 5.41 (dt, *J* = 17.2, 1.8 Hz, 0.12H), 5.36 (dt, *J* = 17.2, 1.5 Hz, 0.35H), 5.34 (dt, *J* = 17.2, 1.5 Hz, 0.53H), 5.32 (br d, *J* = 11.0 Hz, 0.12H), 5.19 (br d, 11.0 Hz, 0.35H), 5.17 (br d, *J* = 10.3 Hz, 0.53H), 5.17-5.15 (m, 0.12H), 5.11 (dd, *J* = 5.1, 2.2 Hz, 0.53H), 5.06 (dd, *J* = 5.5, 1.5 Hz, 0.35H), 4.59-4.45 (m, 3H), 4.20-4.17 (m, 0.12H) 4.09 (td, *J* = 6.2, 4.4 Hz, 0.53H), 3.81 (ddd, *J* = 8.4, 4.8, 3.7 Hz, 0.35H), 3.41 (s, 1.05H), 3.37 (s, 1.95H), 2.29 (ddd, *J* = 13.9, 8.1, 5.9 Hz, 0.35H), 2.29-2.25 (m, 0.12H), 2.21 (ddd, *J* = 13.2, 6.6, 2.2 Hz, 0.53H), 2.13 (dt, *J* = 13.2, 5.7 Hz, 0.53H), 2.15-2.09 (m, 0.12H), 2.01 (ddd, *J* = 13.9, 3.7, 1.5 Hz, 0.35H); IR (neat, cm^{-1}) 2930, 1498, 1175, 1068, 1000, 915.

(3*R*)-3,5-Bis(benzyloxy)-2-vinyltetrahydrofuran (11b-13b). To a solution of **10** (303 mg, 1.0 mmol) and BnOH (330 mg, 3.0 mmol) in THF (50 mL) was added $PdCl_2(MeCN)_2$ (13 mg, 0.05 mmol) at room temperature under an Ar atmosphere, then the mixture was stirred at the same temperature for 1.5 h. After stirring, the mixture was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (eluent with Hex : AcOEt = 98 : 2) to afford (3*R*)-3,5-bis(benzyloxy)-2-vinyl-tetrahydrofuran (**11b-13b**) (144 mg, 47% yield) as a colorless oil.

11b-13b (diastereomer mixture): a colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.38-7.24 (m, 10H), 6.10 (ddd, *J* = 17.6, 10.3, 7.2 Hz, 0.1H), 5.94 (ddd, *J* = 17.2, 10.3, 7.0 Hz, 0.52H), 5.85 (ddd, *J* = 16.9, 10.4, 6.7 Hz, 0.38H), 5.38 (ddt, *J* = 17.2, 4.0, 1.3 Hz, 0.9H), 5.44-5.30 (m, 0.3H), 5.32 (dd, *J* = 5.1, 2.2 Hz, 0.52H), 5.24 (dd, *J* = 5.7, 1.8 Hz, 0.38H), 5.21 (dt, *J* = 10.3, 1.3 Hz, 0.38H), 5.19 (dt, *J* = 10.3, 1.3 Hz, 0.52H), 4.77 (d, *J* = 11.7 Hz, 0.1H), 4.59-4.47 (m, 4H), 4.17-4.10 (m, 0.62H), 3.84 (ddd, *J* = 8.1, 5.7, 4.0 Hz, 0.38H), 2.36-2.2 7 (m, 1H), 2.24-2.20 (m, 0.1H), 2.18-2.13 (m, 0.52H); 2.10 (ddd, *J* = 15.9, 4.0, 1.8

Hz, 0.38H); MS (EI) *m*/*z* 254 (3), 182 (4), 163 (5), 159 (2), 108 (9), 107 (7), 91 (100), 79 (12), 77 (8), 65 (10), 51 (4): (DART) *m*/*z*: 311 ([M+H]$^+$); HRMS-DART: calcd. for $C_{20}H_{23}O_3$ ([M+H]$^+$) 311.16472, found 311.16753.

((3*R*)-3,5-Bis(benzyloxy)tetrahydrofuran-2-yl)methanol (16b-18b). To a solution of **11b-13b** (diastereomer mixture; 184 mg, 0.59 mmol) in 1,4-dioxane (5.6 mL) and H_2O (2 mL) was added 2,6-lutidine (128 mg, 1.94 mmol), $NaIO_4$ (256 mg, 1.18 mmol) and OsO_4 (0.05 mol/L in *tert*-BuOH, 0.3 mL, 0.012 mmol), then the mixture was stirred at room temperature for 16 h. The mixture was diluted with AcOEt and H_2O, the aqueous layer was extracted with AcOEt (x 2). The combined organic layers were washed with saturated aqueous $Na_2S_2O_3$ solution and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was diluted with MeOH (5 mL), to this solution was added $NaBH_4$ (45 mg, 1.18 mmol) at room temperature. After stirring at the same temperature for 1 h, the mixture was quenched with saturated aqueous NH_4Cl solution and concentrated *in vacuo*. The residue was diluted with AcOEt and H_2O, then the organic layer was separated and the aqueous layer was extracted with AcOEt (x3). The combined organic layers were washed with 1N HCl and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (eluent with Hex : AcOEt = 90 : 10 to 80 : 20, gradient) to afford ((3*R*)-3,5-bis(benzyloxy)tetrahydrofuran-2-yl)methanol (**16b-18b**) (123 mg, 66% yield). Three diastereomers were separated in this step.

((2*S*,3*R*,5*S*)-3,5-Bis(benzyloxy)tetrahydrofuran-2-yl)methanol (16b): colorless oil ; $[\alpha]^{20}_D$ 64.3 (c 1.10, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.38-7.26 (m, 10H), 5.36 (dd, *J* = 5.9, 2.1 Hz, 1H), 4.76 (d, *J* = 11.7 Hz, 1H), 4.53 (d, *J* = 11.7 Hz, 1H), 4.49 (s, 2H), 4.35-4.26 (m, 2H), 3.76 (dd, *J* = 12.0, 2.7 Hz, 1H), 3.64 (ddd, *J* = 12.0, 8.5, 3.9 Hz, 1H), 2.54 (dd, *J* = 8.5, 3.4 Hz, 1H), 2.43 (ddd, *J* = 14.1, 6.9, 2.0 Hz, 1H), 2.23 (dt, *J* = 14.1, 5.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 137.7, 137.1, 128.53 (2C), 128.46 (2C), 128.0 (2C), 127.9, 127.8, 127.7 (2C), 104.0, 85.7, 79.0, 71.7, 70.0, 64.1, 40.2; IR (neat, cm^{-1}): 3447, 2925, 2872, 1455, 1361, 1104, 1043, 1026, 698, 607; MS (EI) *m*/*z* 254(1), 207 (7), 181 (4), 163 (2), 146 (2), 108 (32), 107 (25), 91 (100), 79 (41), 77 (26), 65 (12), 51 (12); (DART) *m*/*z* 315 ([M+H]$^+$); HRMS-DART calcd. for $C_{19}H_{23}O_4$ ([M+H]$^+$) 315.1596, found 315.1607.

((2*S*,3*R*,5*R*)-3,5-Bis(benzyloxy)tetrahydrofuran-2-yl)methanol (17b): colorless oil; $[\alpha]^{20}_D$ 34.3 (*c* 0.30, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.27 (m, 10H), 5.39 (dd, *J* = 5.2, 1.9 Hz, 1H), 4.73 (d, *J* = 11.9 Hz, 1H), 4.59 (d, *J* = 11.7 Hz, 1H), 4.51-4.41 (m, 1H), 4.49 (d, *J* = 11.9 Hz, 1H), 4.42 (d, *J* = 11.7 Hz, 1H), 4.20 (dt, *J* = 5.8, 4.3 Hz, 1H), 4.00-3.85 (m, 2H), 2.29 (ddd, *J* = 13.4, 6.7, 1.9 Hz, 1H), 2.19 (ddd, *J* = 13.4, 5.2, 5.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.9, 137.4, 128.6(2C), 128.4(2C), 128.00, 127.97(3C), 127.7, 127.6, 102.2, 79.4, 79.0, 71.8, 69.3, 61.8, 39.6; IR (neat, cm^{-1}) 3444, 2921, 2873, 1061, 1026, 737, 698; MS (EI) *m*/*z* 254(2), 207(3), 206(3), 182(3), 181(4),163(4), 149(3), 146(2), 108(34), 107(31), 91(100), 79(39), 77(29), 57(14); (DART) *m*/*z* 315 ([M+H]$^+$); HRMS-DART calcd. for $C_{19}H_{23}O_4$

([M+H]$^+$) 315.1596, found 315.1607.

((2*R*,3*R*,5*S*)-3,5-Bis(benzyloxy)tetrahydrofuran-2-yl)methanol (18b): colorless oil; $[\alpha]^{20}_D$ -160.4 (*c* 1.10, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.25 (m, 10H), 5.24 (dd, *J* = 5.3, 1.5 Hz, 1H), 4.81 (d, *J* = 12.4 Hz, 1H), 4.60 (d, *J* = 12.0 Hz, 1H), 4.54 (d, *J* = 12.4 Hz, 1H), 4.49 (d, *J* = 12.0 Hz, 1H), 4.20 (dd, *J* = 8.1, 4.0 Hz, 1H), 4.08-4.00 (m, 1H), 3.82 (dd, *J* = 11.9, 2.9 Hz, 1H), 3.61 (dd, *J* = 11.9, 2.9 Hz, 1H), 2.26 (ddd, *J* = 13.4, 8.3, 5.4 Hz, 1H), 2.12 (ddd, *J* = 14.1, 3.4, 1.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.0(2C), 128.4(2C), 128.3(2C), 127.8(2C), 127.7(2C), 127.5(2C), 102.7, 82.9, 78.1, 71.7, 68.9, 62.6, 39.1; IR (neat, cm^{-1}) 3445, 2920, 2872, 1454, 1360, 1207, 1113, 1043, 1027, 737, 698; MS (EI) *m/z* 207(11), 206(2), 10(21), 107(19), 91(100), 79(26), 77(18), 65(11), 51(10); (DART) *m/z* 315 ([M+H]$^+$); HRMS-DART calcd. for $C_{19}H_{23}O_4$ ([M+H]$^+$) 315.1596, found 315.1610.

2-Deoxy-L-ribose (1). To a solution of **16b** (42.3 mg, 0.135 mmol) in EtOH (2.5 mL) was added Pd/C (31.2 mg) at room temperature, then the reaction vessel was evacuated and back-filled with H_2 (x 5). After stirring for 6 days at room temperature, the mixture was filtered over a pad of Celite®, which was washed with MeOH. The filtrate was concentrated *in vacuo*. The crude material was purified by silica gel column chromatography (eluent with MeOH : $CHCl_3$ = 1 : 3) to afford 2-deoxy-L-ribose (**1**) (8.0 mg, 44 % yield) as a colorless amorphous solid.

2-Deoxy-L-ribose (**1**): colorless amorphous solid; $[\alpha]^{15}_D$ +59 (*c* 0.40, H_2O); [lit.,[14] $[\alpha]_D^{15}$ +60 (*c* 1.06, H_2O)]; ^{1}H NMR (300 MHz, CD_3OD) δ difficult to assign the spectra; ^{13}C NMR (75 MHz, CD_3OD) the equilibrium mixture of pyranose and furanose form and those epimer at C1; δ: 99.5, 99.4, 95.2, 93.1, 87.9, 86.7, 72.8, 72.5, 69.4, 69.2, 68.3, 66.6, 66.2, 64.5, 64.3, 63.2, 43.5, 43.1, 37.3, 36.6.

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