A Concise Approach to the Synthesis of *L*- and *D*-Deoxyribose†

HU, Shou-Gang(胡守刚) **WU, Yi-Kang**(伍贻康) **WU, Yu-Lin***(吴毓林)

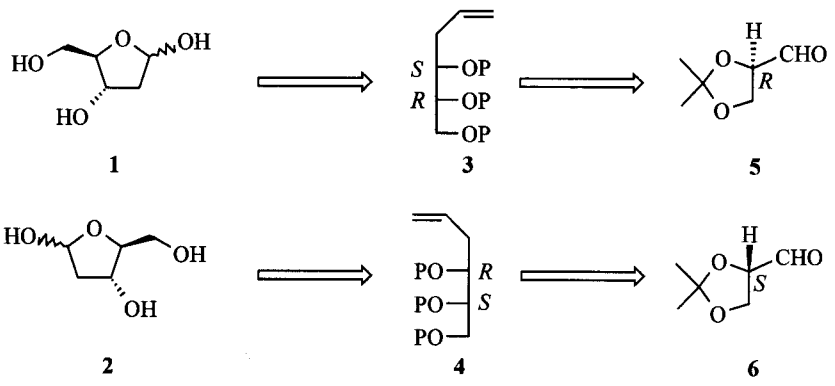
State Key Laboratory of Bioorganic and Natural Products Chemistry Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China

***D*-Deoxyribose, the basic structure unit of DNA, and its antipode *L*-deoxyribose were concisely synthesized from easily available *D*- and *L*-glyceralaldehydes using a known convenient diastereoselective propargylation as the key step.**

Keywords *L*-deoxyribose, *D*-deoxyribose, diastereoselective propargylation, *D*-glyceralaldehyde, *L*-glyceralaldehyde

2-Deoxy-*D*-ribose (**1**), the sugar part of DNA, is one of the most important starting material not only for the preparations of nucleosides, nucleotides, DNA and their analogs, but also for the syntheses of a number of other bio-active compounds.[1] Recently its antipode 2-deoxy-*L*-ribose (**2**) was also attracted widely attention, as it would be the central building block for the syntheses of modified nucleosides enantiomer, which may have great potential as useful antiviral agents.[2] Therefore the availability of both deoxyriboses has been a very interesting subject for the synthetic chemists. Especially a number of papers about the synthesis of 2-deoxy-*L*-ribose (**2**) have appeared in recent years.[3] Usually it was synthesized from other unnatural *L*-sugar or *D*-sugar through a quite long multi steps[3a-3j] and only in a few reports it was obtained using asymmetric synthesis approach as the key step.[3k] Last year while we were dealing with the syntheses of *L*-ribose and *L*-ribosides from *D*-galactose,[4] 2-deoxy-*L*-ribose (**2**) was also prepared from the same intermediate.[5] We also considered to develop an even more simple method for its synthesis through protected 2*S*,3*R*-trihydroxy-hex-5-en (**4**). Actually, Schmid *et al*.[6] has mentioned the synthesis of 2-deoxy-*D*-ribose (**1**) from protected 2*R*,3*S*-trihydroxy-hex-5-en (**3**), the antipode of compound **4**, in their report for a convenient route to 2-deoxy and 2,6-dideoxy carbohydrates (Scheme 1).

Scheme 1



* E-mail: ylwu@pub.sioc.ac.cn

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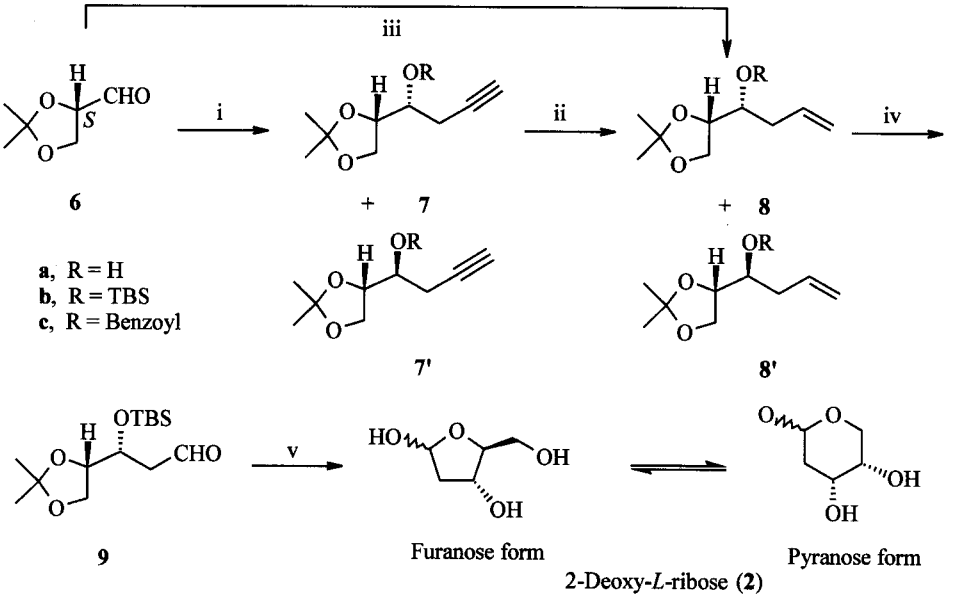
The most convenient way to the compounds **3** and **4** is the diastereoselective allylation or propargylation followed by partial hydrogenation of 2,3-*O*-isopropylidene glyceraldehyde **5** and **6** respectively. There have been a number of reports about the allylation of *D*-glyceraldehydes acetonide **5**, but only a few for *L*-glyceraldehydes acetonide **6**. Allylation of compound **5** with allylmagnesium chloride gave a 2:1 mixture of the diastereomers.[7] Somewhat better selectivity (6.5:1) has been achieved by indium metal and allyl bromide.[6] Chattopadhyay[8] reported that the Zn-mediated allylation of 2,3-*O*-cyclohexylidene-*D*-glyceraldehyde might give a very high diastereoselectivity (96.4:3.6). Recently Sharma *et al.*[9] also reported the same Zn-mediated allylation for compound **5**, but the selectivity was not mentioned. On the other hand, a high diastereoselectivity may be obtained, when compound **5** was treated with stoichiometric allyltitanium chiral complex[10] or the Brown chiral allylborane.[11] We have also developed a high diastereoselective propargylation of α-alkoxy aldehyde[12] without using any additional chiral auxiliary reagent and thus reaction products were used for the syntheses of leukotrienes.[13] Therefore, we try to apply this method for the syntheses of *L*-deoxyribose and also *D*-deoxyribose after optimization of the reaction condition and then partial hydrogenation of the propargylation product. On the other way we try to directly prepare the desired homoallyl alcohol under this reaction condition (Scheme 2).

2,3-*O*-Isopropylidene-*L*-glyceraldehyde (**6**) was treated with propargyl bromide and zinc dust in a solvent mixture of DMF and ether to give the homopropargyl alcohol **7a** + **7'a** in 70% yield. HPLC of its benzoate **7c** + **7'c** showed that their ratio was about 8.3:1. The crude homopropargyl alcohol without further purification was protected as TBS ether and purified by chromatography to give **7b** in 71% yield. ^{1}H NMR spectra of thus obtained **7b** showed that no diastereoisomer was detected. Partial hydrogenation of **7b** in the presence of Lindlar catalyst afforded the homoallyl alcohol **8b**. Compound **8a** could be obtained directly by allylation of **6** with allyl bromide and zinc dust in a solvent mixture of DMF and ether, but the erythro/threo (*anti*/*syn*) selectivity was only 2.6:1. The usual ozonation of **8b** gave aldehyde **9**, which was then treated with the solution of HCl in aqueous THF to remove both protecting groups TBS and acetonide. Thus obtained 2-deoxy-*L*-ribose (**2**) was an equilibrium mixture of pyranose and furanose form in a ratio of (4—5):1.

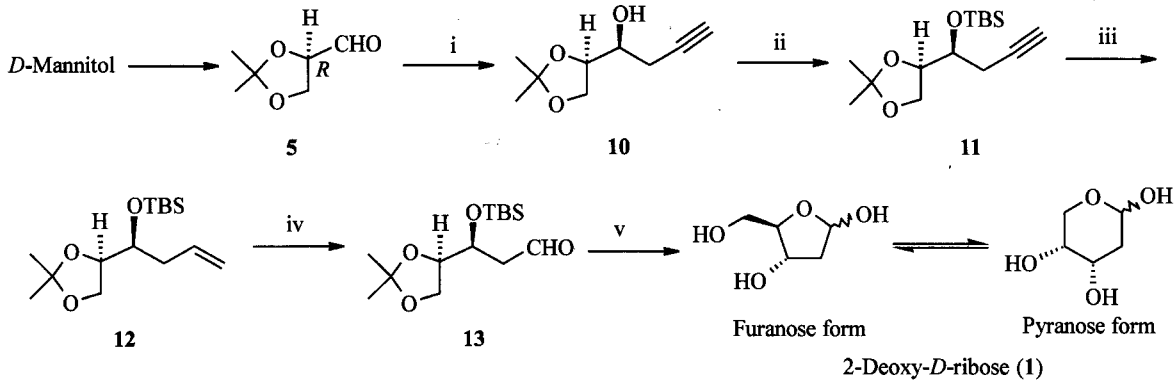
Along with the same protocol 2-deoxy-*D*-ribose (**1**) was also synthesized from the mannitol derived 2,3-*O*-isopropylidene-*D*-glyceraldehyde (**5**), and the physical data of synthesized sample were in accordance with those reported (Scheme 3).

Scheme 2



Reagents and conditions: i: Zn dust, propargyl bromide, DMF-ether; ii: H_2/Lindlar; iii: Zn dust, allyl bromide, DMF-ether; iv: O_3, CH_2Cl_2-MeOH, Me_2S; v: HCl, aqueous THF.

Scheme 3



Reagents and conditions: i: Zn dust, propargyl bromide, DMF-ether; ii: TBDMSCl, DMF; iii: H_2/Lindlar; iv: O_3, CH_2Cl_2-MeOH, Me_2S; v: HCl, aqueous THF.

In summary, *D*- and *L*-deoxyriboses are conveniently synthesized from corresponding glyceraldehyde acetonide through the diastereoselective propargylation.

Experimental

General mothods

IR spectra were recorded on Bio-Rad FTS-185 spectrometers. ^{1}H NMR spectra were obtained in $CDCl_3$ or CD_3OD on a Mereury-300 or Gemini-2000 spectrometer with TMS as the internal standard. Mass spectra were taken on an HP5973N or HP5989A instrument. HRMS (EI) spectra were obtained on an APEXIII 7.0 Tesla FTMS mass spectrometer. Optical rotations were measured on a Perkin-Elmer 241 MC polarimeter. Elemental analyses were carried out at the Microanalytic Laboratory of Shanghai Institute of Organic Chemistry. Flash column chromatography was performed on a silica gel H column (10—40 μm) with petrol ether-ethyl acetate or ethyl acetate-ethanol system as eluant.

Synthesis of **7b**

To a solution of **7a**[13] (2.88 g, 16.9 mmol) in DMF (6 mL) was added imidazole (3.00 g, 44.4 mmol), followed by TBDMSCl (3.19 g, 20.9 mmol), and the reaction mixture was kept at room temperature for 24 h. The reaction mixture was diluted with 40 mL of ether and washed with water and brine. The organic layer was dried over anhydrous $NaSO_4$. Removal of solvent and then flash chromatography (petroleum ether/ethyl acetate, 40:1) gave the product **7b** (3.36 g, 71%) as a clear liquid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.10 (s, 3H), 0.13 (s, 3H), 0.84 (s, 9H), 1.27 (s, 3H), 1.35 (s, 3H), 1.94 (dd, J = 2.3, 5.5 Hz, 1H), 2.37—2.41 (m, 2H), 3.62—3.78 (m, 2H), 3.82—3.94 (m, 1H), 3.98—4.08 (m, 1H); IR (film) ν: 3315, 2988, 2932, 1462 cm^{-1}; EIMS m/z (%): 269 ($M^+ - CH_3$, 13.27), 227 ($M^+ - C_4H_9$, 6.54), 209 (13.88), 183 (25.04), 169 (96), 73 (100); HRMS m/z calcd for $C_{14}H_{25}O_3Si$ ($M^+ - CH_3$) 269.1567, found 269.1570.

Synthesis of **8b**

To a solution of **7b** (650 mg, 2.3 mmol) in anhydrous methanol (35 mL) was added Lindlar catalyst (160 mg) and quinoline (100 μL). The mixture was stirred under a H_2 atmosphere at room temperature for 1 h. The reaction mixture was worked up by filtering and concentrating *in vacuo*. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 40:1) to give **8b** (655 mg, 100%) as a clear liquid. $[\alpha]_D^{20}$ −28.3 (*c* 1.1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.15 (s, 6H), 0.84 (s, 9H), 1.32 (s, 3H), 1.38 (s, 3H), 2.23—2.31 (m, 2H), 3.70—3.82 (m, 2H), 3.90—4.02 (m, 2H), 5.06—5.13 (m, 2H), 5.85 (dd, J = 10.2, 17.0 Hz, 1H); IR (film) ν: 3080, 2988, 1473 cm^{-1}; EIMS m/z (%): 271 ($M^+ - CH_3$, 4.62), 245 (3.03), 227 (3.99), 185

(34.76), 171 (50.6), 73 (100); HRMS *m/z* calcd for $C_{14}H_{27}O_3Si$ ($M^+ - CH_3$) 271.1724, found 271.1730.

Synthesis of **9**

Through a solution of **8b** (256 mg, 0.88 mmol) in a solvent mixture of anhydrous methanol and CH_2Cl_2 (5:1, 60 mL) at −78 ℃ was passed a stream of ozone, until a persistent blue color appeared. The solution was flushed with N_2 until no more ozone was detected and then to this mixture was slowly added dimethyl sulfide (2.2 mL, 30 mmol) at −78 ℃. The solution was then stirred at −20 ℃ for 1 h, then at ice bath temperature for 1 h and finally at room temperature for another 1 h. The mixture was concentrated and the residue was purified by flash chromatography (petroleum ether/ethyl acetate, 15:1) to give **9** (213 mg, 83%) as a clear and colorless liquid. $[\alpha]_D^{20}$ − 6.9 (*c* 0.7, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.08 (s, 3H), 0.10 (s, 3H), 0.85 (s, 9H), 1.32 (s, 3H), 1.39 (s, 3H), 2.64 (m, 2H), 3.78—3.85 (m, 1H), 4.00—4.12 (m, 3H), 9.82 (s, 1H); IR (film) ν: 2988, 2860, 1728 cm^{-1}; EIMS *m/z* (%): 273 ($M^+ - CH_3$, 8.37), 231 ($M^+ - C_4H_9$, 8.29), 187 (49.65), 173 (100); HRMS *m/z* calcd for $C_{13}H_{25}O_4Si$ ($M^+ - CH_3$) 273.1517, found 273.1529.

Synthesis of 2-*deoxy-L-ribose* (**2**)

A mixture of compound **9** (289 mg, 1 mmol) in an 1 mol/L HCl solution (50% aqueous THF, 4 mL) was stirred at room temperature for 12 h. It was then neutralized by saturated aqueous $NaHCO_3$ and concentrated *in vacuo*. The residue was purified by flash chromatography (CH_2Cl_2/MeOH, 10:1) to give **2** (134 mg, 100%) as a syrup. $[\alpha]_D^{20}$ + 56 (*c* 0.5, H_2O) [Lit.[3i] $[\alpha]_D^{20}$ + 52 (*c* 1.0, H_2O)]; ^{1}H NMR (CD_3OD, 300 MHz) δ: 1.58—2.26 (m, 2H), 3.40—4.26 (m, 4H), 4.63 (dd, *J* = 3.1, 7.6 Hz, H-1, α-P), 5.10 (t, *J* = 3.6 Hz, H-1, β-P), 5.42 (dd, *J* = 2.5, 5.4 Hz, H-1, α-F), 5.50 (t, *J* = 4.1 Hz, H-1, β-F).

Synthesis of **11**

Transformation of **10**[13] (1.13 g, 6.6 mmol) according to the same preparation procedure for **7b** gave **11** (1.37 g, 73%) as a clear liquid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.11 (s, 3H), 0.14 (s, 3H), 0.85 (s, 9H), 1.30 (s, 3H), 1.36 (s, 3H), 1.97 (dd, *J* = 2.17, 5.22 Hz, 1H), 2.42—2.48 (m, 2H), 3.72—3.80 (m, 1H), 3.80—3.87 (m, 1H), 3.96—4.04 (m, 1H), 4.10—4.18 (m, 1H).

Synthesis of **12**

Transformation of **11** (3.0 g, 10.6 mmol) according to the same preparation procedure for **8b** gave **12**[14] (2.75 g, 91.3%) as a clear liquid. $[\alpha]_D^{20}$ + 30.4 (*c* 0.89, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.06 (s, 3H), 0.08 (s, 3H), 0.90 (s, 9H), 1.35 (s, 3H), 1.41 (s, 3H), 2.27—2.33 (m, 2H), 3.70—3.85 (m, 2H), 3.90—4.02 (m, 2H), 5.02—5.12 (m, 2H), 5.79—5.87 (m, 1H); IR (film) ν: 3080, 2987, 1463, 1473 cm^{-1}; EIMS *m/z* (%): 271 ($M - CH_3$, 13.65), 245 (12.48), 229 (10.22), 185 (40.13), 171 (83.54), 73 (100).

Synthesis of **13**

Transformation of **12** (1.17 g, 4 mmol) according to the same preparation procedure for **9** gave **13**[14] (998 mg, 78%) as a clear, colorless liquid. $[\alpha]_D^{20}$ + 8.8 (*c* 0.85, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.09 (s, 3H), 0.12 (s, 3H), 0.90 (s, 9H), 1.35 (s, 3H), 1.40 (s, 3H), 2.66 (dd, *J* = 5.4, 2.4 Hz, 1H), 2.69 (dd, *J* = 5.4, 2.4 Hz, 1H), 3.80—3.87 (m, 1H), 4.07—4.14 (m, 3H), 9.80 (t, *J* = 2.6 Hz, 1H); IR (film) ν: 2989, 2739, 1729, 1473 cm^{-1}; EIMS *m/z* (%): 289 (M + 1, 11.06), 247 (31.49), 229 (11.85), 189 (43.46), 75 (100).

Synthesis of 2-*deoxy-D-ribose* (**1**)

Transformation of **13** (466 mg, 1.62 mmol) according to the same preparation procedure for **2** gave **1** (214 mg, 100%) as a syrup. $[\alpha]_D^{20}$ − 49 (*c* 1.0, H_2O), [lit.[15] $[\alpha]_D$ − 52 (*c* 1.05, H_2O)]; ^{1}H NMR (CD_3OD, 300 MHz) δ: 1.62—2.22 (m, 2H), 3.40—4.20 (m, 4H), 4.65 (dd, *J* = 3.7, 7.9 Hz, H-1, α-P), 5.14 (dd, *J* = 3.1, 4.2 Hz, H-1, β-P), 5.41 (dd, *J* = 2.45, 5.5 Hz, H-1, α-F), 5.49 (t, *J* = 4.3 Hz, H-1, β-F).

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