Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Supplementary information

A heterogeneous Pd-Bi/C catalyst in the synthesis of L-lyxose and L-ribose from naturally occurring D-sugars

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Contents

Experimental Section

Preparation and characterization of palladium-bismuth catalysts

Carbon-supported palladium-bismuth catalysts were prepared as follows. For Pd-Bi/C (Pd:Bi 5:1 atomic ratio), 1.0102 g of Pd/C (10 wt.%, Degussa), was suspended in H_2O (15 ml) at 50 ^oC and $Bi(NO_3)_3 \cdot 5H_2O$ (0.0921 g) was added. After stirring the mixture at 50 ^oC for 3 h, 37 % formaldehyde (0.2 ml) was added. The mixture was heated at 82 ^oC under N_2 for 12 h. The precipitate obtained after filtration was washed with water to obtain the desired catalyst. The same procedure was used to prepare Pd-Bi/C with atomic ratios of 1:1 to 8:1. Prior to use, the catalyst was reduced under H_2 flow for 2 h at 150 ^oC.

The nitrogen adsorption/desorption isotherms of the Pd-Bi/C samples were measured with a Micromeritics Tristar 3000. Before the measurement, the sample was degassed at 100 ^oC for 6 h to remove physisorbed water. The surface area was determined using the Brunauer–Emmett–Teller (BET) method. The pore size distribution was calculated from the desorption branch of the isotherm using the Barrett–Joyner–Halenda (BJH) equation. The total pore volume of the sample was taken from the volume of nitrogen adsorbed at the P/P^o of 0.99. The crystal structure and phase of the samples were determined with a Siemens D5005 powder x-ray diffractometer equipped with a Cu anode and variable primary and secondary beam slits. The diffractograms were measured from 2θ of 5^o to 120^o, using a step size of 0.02^o and a dwell time of 1s/step. The average crystallite size was calculated using the Scherrer equation. X-ray photoelectron spectroscopy (XPS) was used to determine the surface elemental composition. The measurements were made with a VG Escalab MkII using a Mg anode (1253.6 eV, 300 W). The binding energies are referenced to the carbon 1 s peak of CH at 284.6 eV. The peak areas were determined

after peak fitting and normalized with the manufacturer's atomic sensitivity factors for the different elements.

Identification of products

Melting points were determined with a Buchi 535 melting point apparatus and were uncorrected. Proton and ^{13}C NMR spectra were measured at 300 MHz with a Bruker Avance 300 NMR spectrometer using tetramethylsilane (TMS) as the internal standard. Chemical shifts were reported in ppm downfield from TMS. Mass spectrometry (MS) and high resolution-mass spectrometry electron ionization (HR-MS EI) were taken with a Finnigan MAT95XL-T and Micromass VG7035 double focusing mass spectrometer of high resolution, respectively. Optical rotations were measured by a Perkin Elmer 341 polarimeter in a 1 dm cell. Analytical and preparative thin layer chromatography (TLC) were conducted on precoated TLC plates (silica gel 60 F254, Merck).

General procedure for oxidation of D-ribose (1) to D-ribonate (2) over Pd-Bi/C catalyst

A 150 mL three-necked round-bottomed flask was charged with Pd-Bi/C catalyst (50 mg) and deionized water (50 mL). The suspension was heated to 50 °C and the catalyst was treated by bubbling in 0.5 L min^{-1} hydrogen for 25 min. After this, nitrogen was introduced to purge out any remaining hydrogen. A solution of D-ribose (Carbosynth, 1.05 g, 7 mmol) water (70 mL) adjusted to pH 9, was poured into the round-bottomed flask and oxygen (0.5 L min^{-1}) was bubbled into the reactor. The pH of the reaction was maintained at pH 9 by adding KOH (0.5 M) solution with the pH autotitrator (Mettler

Toledo DL-50). The progress of the catalytic reaction was removing aliquots at regular time intervals and analyzing by HPLC (Shimadzu SPD-10AV equipped with a UV-visible detector, 200 nm). A Jordi Gel DVB organic acid column (250 mm length x 10 mm diameter) was used with 0.05 M H_2SO_4 as the eluent (flow rate 1.5 ml min^{-1}). Under the operating conditions, the retention time for D-ribose and ribonic acid is 8.5 min and 7.6 min, respectively.

General procedure for one-pot transformation of D-ribonate (2) to 2,3-*O*-isopropylidene-D-ribonolactone (3)

The crude potassium-D-ribonate (2.01 g, obtained from oxidation of 1.5 g D-ribose) was dissolved in acetone (40 mL) and *conc.* HCl (37 %, 2 mL) was added dropwise to the solution. After stirring for 3 h at room temperature, $CuSO_4$ (4 g) was added and the resulting mixture was refluxed for 1.5 h. The mixture was cooled to room temperature and $NaHCO_3$ was added to neutralize the excess HCl. The mixture was filtered and the precipitate was washed with hot acetone (10 mL). The filtrate and washing were rotary evaporated to give the crude product in the form of a white solid. The crude product was dissolved in ethyl acetate (20 mL) and washed with deionized water (2 x 10 mL). Finally, the organic phase was rotary evaporated to dryness to afford 1.28 g of white crystalline solid **3** (68 % overall yield from D-ribose, mp 133 – 135 °C) [1]. Very pure material can be obtained by one to two additional recrystallization from hot ethyl acetate to yield solid **3** with melting point >140 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.38 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 3.79-3.83 (dd, 1H, C-5H), 3.97-4.01 (dd, 1H, C-5H), 4.60-4.64 (m, 1H, C-4H), 4.76-4.78 (d, 1H, C-3H),

4.80-4.84 (m, 1H, C-2H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 175.2, 113.1, 82.9, 78.3, 75.6, 61.8, 26.7, 25.4. $[\alpha]_D^{20}$ = -68.5° (c=1.00, $CHCl_3$), IR (KBr): 3455, 1762 cm^{-1}.

Reported [1]: mp 134-137°C; $[\alpha]^{24}_D$= −66.7^o (c=1.03, $CHCl_3$); IR (KBr): 3469, 1767 cm^{-1}.

[1] D. W. John, P. K. Vivekanand, E. M. Philip and B. T. Leroy, *Org. Synth.*, 2005, **82**, 75.

General procedure for epimerization of 2,3-*O*-isopropylidene-D-ribonolactone (3) to 2,3-*O*-isopropylidene-L-lyxonolactone (4)

Methanesulfonyl chloride (0.7 mL, 9 mmol) was added dropwise with stirring to an ice-cooled solution of 2,3-*O*-isopropylidene-D-ribonolactone (1.5 g, 8.0 mmol) in pyridine (5 mL) and the mixture was kept for 2 h at 0 °C. The reaction was quenched with water (5 mL) and CH_2C1_2 (15 mL) was added. The organic layer was separated and the aqueous layer was extracted with CH_2C1_2 (2 x 5 mL). The organic layers were combined and concentrated to obtain the semisolid mesylate. To this crude mesylate was added a solution of KOH (1.3 g, 23.2 mmol, 2.9 equiv) in water (10 mL), keeping the temperature at 25 °C. After stirring for 6 h at this temperature, the pH was adjusted to 2.5-3.0 by adding 1 M HCl. The acidic solution was concentrated *in vacuo* to afford a solid mass. The solid mass was triturated with acetone (15 mL) and heated to reflux for 15 min. The acetone was decanted and the procedure was repeated. The combined acetone was dried over Na_2SO_4, and filtered. The clear filtrate was concentrated *in vacuo* below 35 °C to afford 1.2 g (80 % yield) of product **4**.

Mp 93-94 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ1.39 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 3.92-4.06 (m, 2H, C-5H and C-5'H), 4.58-4.62 (m, 1H, C-4H), 4.84-4.90 (m, 2H, C-3H

and C-2H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 173.3, 114.6, 79.0, 76.2, 76.1, 60.9, 26.7, 25.8. $[\alpha]_D^{20}$= -85^o (c = 1.0, acetone); IR (KBr): 3425, 1781 cm^{-1}.

Compare: mp 98-99 ^{o}C [2], mp 92-93 ^{o}C [3]; $[a]_D^{25}$ = -89^o (c=1.0,acetone) [2], $[a]_D^{20}$ = -85.6^o (c =1.0, acetone) [3]; ^{1}H NMR (300 MHz, $CDCl_3$): δ1.36 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 2.72 (brs, 1H, OH), 3.9-4.01 (m, 2H, C-5H and C-5'H), 4.60-4.64 (m, 1H, C-4H), 4.83-4.89 (m, 2H, C-3H and C-2H) [2]; R (KBr):3423, 1778 cm^{-1}[2].

[2] H. Batra, R. M. Moriarty, R. P. V. Sharma, G. Stanciuc, J. P. Staszewski, S. M. Tuladhar and D. A. Walsh, *Org. Process Res. Dev.,* 2006, **10**, 484.

[3] M. Godskesen, I. Lundt, R. Madsen and B. Winchester, *Bioorg. Med. Chem*., 1996, **4**, 1857.

General procedure for reduction of 2,3-*O*-isopropylidene-L-lyxonolactone (4) to 2,3-*O*-isopropylidene-L-lyxose (5)

2,3-*O*-isopropylidene-L-lyxonolactone (0.5 g, 2.66 mmol) was dissolved in methanol (15 mL). The resulting solution was cooled to -20 °C and $NaBH_4$ (0.22 g, 5.4 mmol) was slowly added over 1 h. After stirring for 4 h, the solution was adjusted to pH 5-6 with 1 M HCl solution. Concentration *in vacuo* afforded a white solid. The white solid was suspended in CH_2Cl_2 (20 mL) and the suspension was heated to boiling. The hot suspension was filtered and the solids were rinsed with hot CH_2Cl_2 (10 mL). Purification by column chromatography on silica gel (hexane/ethyl acetone 3:2) followed by concentration *in vacuo* afforded a syrup (0.48 g, 95 % yield) of **5**.

^{1}H NMR (300 MHz, $CDCl_3$): (major) δ 1.30 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 3.90 (m, 2H, C-5H and C-5'H), 4.25-4.28 (m, 1H, C-4H), 4.60-4.62 (m, 1H, C-3H), 4.77-4.81 (m, 1H,

C-2H),5.41(s,1H,C-1H); $[\alpha]_D^{20}$ = -18.5° (c=1.00, H_2O); MS (EI): m/z 190 (M^+) HRMS (EI): calcd. for $C_8H_{14}O_5$:190.0841 found: 190.0831.

General procedure for hydrolysis of 2,3-*O*-isopropylidene-L-lyxose (5) to L-lyxose (6)

Amberlite IR-120H (1 g) was added to a solution of 2,3-*O*-isopropylidene-L-lyxose (0.1 g, 0.53 mmol) in water (10 mL) at room temperature and stirred overnight. After filtration, the filtrate was concentrated *in vacuo* to afford a light coloured syrup. The syrup was purified by column chromatography on silica gel.

^{13}C NMR (300 MHz, D_2O): δ C1 (93.9), C3 (72.5), C2 (70.4 and 69.9), C4 (67.4 and 66.4), C5 (64.0 and 62.9); $[\alpha]_D^{20}$ = +13.5° (c = 2.6, H_2O).

Compare: $[\alpha]_D^{20}$ = +12.7°(c = 2.6, H_2O) [4]. The ^{13}C NMR(400 MHz, D_2O) spectrum is similar to that of ref. [5]. ^1H NMR (300 MHz, D_2O) was identical to its D-isomer [5].

[4] H. Kuzuhara, H. Terayama, H. Ohrui and S. Emoto, *Carbohydr. Res.*,1971, **20**,165.

[5] S. H. Buiyan, Z. Ahmed, M. Utamura, K. Izumori, *J. Ferment. Bioeng.*,1998, **86**, 513.

General procedure for oxidation of D-lyxose (7) to D-lyxonate (8) with Pd-Bi/C catalyst

The above procedure for the oxidation of D-ribose to D-ribonate was adopted for the oxidation of D-lyxose (Carbosynth). Using HPLC, the retention time for D-lyxose is 8.35 min and that for D-lyxonate (and lyxonic acid) is 7.55 min. After 2 h, all D-lyxose was consumed giving a yield for D-lyxonate of > 92 %.

General procedure for one-pot transformation of D-lyxonate (8) to 2,3-*O*-isopropylidene -D-lyxonolactone (9)

Method 1

The crude potassium D-lyxonate (2.01 g, obtained from the oxidation of 1.5 g D-lyxose) was suspended in acetone (40 mL) and *conc.* HCl (37 %, 2 mL) was dropped into the suspension. After stirring for 1 h at room temperature, methanesulfonic acid (15 mmol) was added to suspension and the resulting mixture was stirred for 18 h. Following, $NaHCO_3$ was added to neutralize the solution. The resulting mixture was filtered and the solid was rinsed with hot acetone (10 mL). The filtrate together with the washing was rotary evaporated to give the crude product. The white solid was dissolved in ethyl acetate (20 mL) and then washed twice with deionized water (10 mL). The organic phase was rotary evaporated to dryness to afford 0.52 g (28 % overall yield from D-lyxose) of white crystalline solid. The aqueous phase was rotary evaporated to dryness followed by adding methanesulfonic acid (10 mmol) and acetone (40 mL) and stirring at room temperature for 18 h. After subjecting the unreacted D-lyxonic acid in aqueous phase to 4 cycles of reaction, a total of 1.2 g of white crystalline solid was obtained (64 % overall yield from D-lyxose)

Method 2

The crude potassium D-lyxonate (2.01 g) was dissolved in methanol (20 mL) and *conc.* HCl (2 mL). Successive concentration with methanol, toluene and methanol gave a residue to which acetone (30 mL), 2,2-dimethoxypropane (5 mL, 40 mmol) and methanesulfonic acid (0.5 mL) were added. The mixture was stirred for 20 h at room

temperature and neutralized with $NaHCO_3$. After filtration and concentration, a syrupy residue was obtained. This was dissolved in H_2O (15 mL) and extracted with diethyl ether (2 x 10 mL). The organic phase was dried with Na_2SO_4 and concentrated to give a semi-crystalline intermediate **8b**. A solution of acetic acid:H_2O (9:1, 10 mL) was added and the solution was stirred for 17 h at 28–29°C. Concentration gave a residue to which toluene was added resulting in a crystalline precipitate. The crystals were collected by filtration and dried in reduced pressure overnight to give the 2,3-acetonide **9** (0.78 g, 45 %). A light yellow syrup (**8a**) was obtained after rotary evaporating the aqueous phase. Dimethoxypropane (5 mL, 40 mmol) and MsOH (0.5 ml) were added to the syrup, followed by stirring for 20 h at room temperature. The above procedure was repeated to obtain another 0.45 g of 2,3-acetonide **9**. The total product obtained was 1.23 g (65.4 % yield from D-lyxose).

Mp 97–99°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ1.41 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 3.94-4.08 (m, 2H, C-5H and C-5'H), 4.57-4.62 (m, 1H, C-4H), 4.84-4.89 (m, 2H, C-3H and C-2H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 175.2, 113.1, 80.2, 76.1, 76.0, 60.8, 26.7, 25.4; $[\alpha]_D^{20}$ = +88.5 ^{o} (c = 1.0, acetone).

Compare with ref. [6]: mp 99–100 °C; $[\alpha]_D^{20}$ = +90.3° (c = 1.0, acetone).

[6] M. Godskesen, I. Lundt and I. Søtofte, *Tetrahedron: Asymmetry*, 2000, **11**, 567.

General procedure for epimerization of 2,3-*O*-isopropylidene-D-lyxonolactone (9) to 2,3-*O*-isopropylidene-L-ribonolactone (10)

Methanesulfonyl chloride (0.7 mL, 9 mmol) was added dropwise with stirring to an ice-cooled solution of 2,3-*O*-isopropylidene-D-lyxonolactone (1.5 g, 8.0 mmol) in pyridine (5 mL) and the mixture was kept for 2 h at 0 °C. The mixture was quenched with water (5 mL) and CH_2C1_2 (15 mL) was added. The organic layer was separated and the aqueous layer was extracted with CH_2C1_2 (2 x 5 mL). The organic layers were combined and concentrated to obtain the semisolid mesylate. To this crude mesylate was added a solution of KOH (1.3 g, 23.2 mmol, 2.9 equiv) in water (10 mL) maintaining at room temperature. This solution was stirred for 6 h at the same temperature and 1 M HCl was added to adjust the pH to pH 2.5 to 3.0. The acidic solution was concentrated *in vacuo* to afford a solid mass. The solid mass was triturated with acetone (15 mL) and heated to reflux for 15 min. The acetone was decanted and more acetone added followed by reflux. Following, the combined acetone was dried over Na_2SO_4 and filtered. The clear filtrate was concentrated *in vacuo* below 35 °C to afford 1.23 g (80 % yield) of product.

Mp 135°-137°; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.38 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 3.79-3.83 (dd, 1H, C-5H), 3.97-4.02 (dd, 1H, C-5H), 4.62-4.63 (m, 1H, C-4H), 4.77-4.79 (d, 1H, C-3H), 4.82-4.84 (m, 1H, C-2H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 173.3, 113.0, 82.5, 78.1, 75.5, 61.8, 26.5, 25.3; $[a]_D^{20}$ = +69.4° (c = 1.00, $CHCl_3$).

The NMR spectral data of 2,3-*O*-isopropylidene-L-ribonolactone was identical to the sample of D-isomer [7]. The optical rotation is equal but opposite to the D-isomer.

[7] T. Hudlicky, Genencor International, Inc., WIPO Patent Application WO/1991/012257, 1991.

General procedure for reduction of 2,3-*O*-isopropylidene-L-ribonolactone (10) to 2,3-*O*-isopropylidene-L-ribose (11)

2,3-*O*-isopropylidene-L-ribonolactone (0.5 g, 2.66 mmol) was dissolved into methanol (15 mL) and the resulting solution was cooled down to -20 °C. To this solution, $NaBH_4$ (0.22 g, 5.4 mmol) was very slowly added over 1 h at -20 °C. After 4 h, the solution was adjusted to pH 5-6 with 1 M HCl solution and concentrated *in vacuo* to afford a white solid. The white solid was suspended in CH_2Cl_2 (20 mL) and the resulting suspension was heated to boiling. The hot suspension was filtered and the solid was rinsed with hot CH_2Cl_2 (10 mL). The filtrate was concentrated *in vacuo* to afford syrup. Purification by column chromatography on silica gel (hexane/ethyl acetate 3:2) afforded 0.48 g (95 % yield) of 2,3-*O*-isopropylidene-L-ribose.

^{1}H NMR (300 MHz, $CDCl_3$): (major) δ1.31 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 3.68 (m, 2H, C-5H and C-5'H), 4.34-4.35 (m, 1H, C-4H), 4.53-4.55 (m, 1H, C-3H), 4.76-4.78 (m, 1H, C-2H),5.37 (s,1H,C-1H); $[a]_D^{20}$= +31.2° (c = 1.5, CH_3OH); (M^+) HRMS (EI): calcd for $C_8H_{14}O_5$: 190.0841, found: 190.0851.

Compare ref [8]: M^+ 190.0831.

[8] H. Takahashi, Y. Iwai, Y.Hitomi and S. Ikegami, *Org. Lett*., 2002, **4**, 2401.

General procedure for hydrolysis of 2,3-*O*-isopropylidene-L-ribose (11) to L-ribose (12)

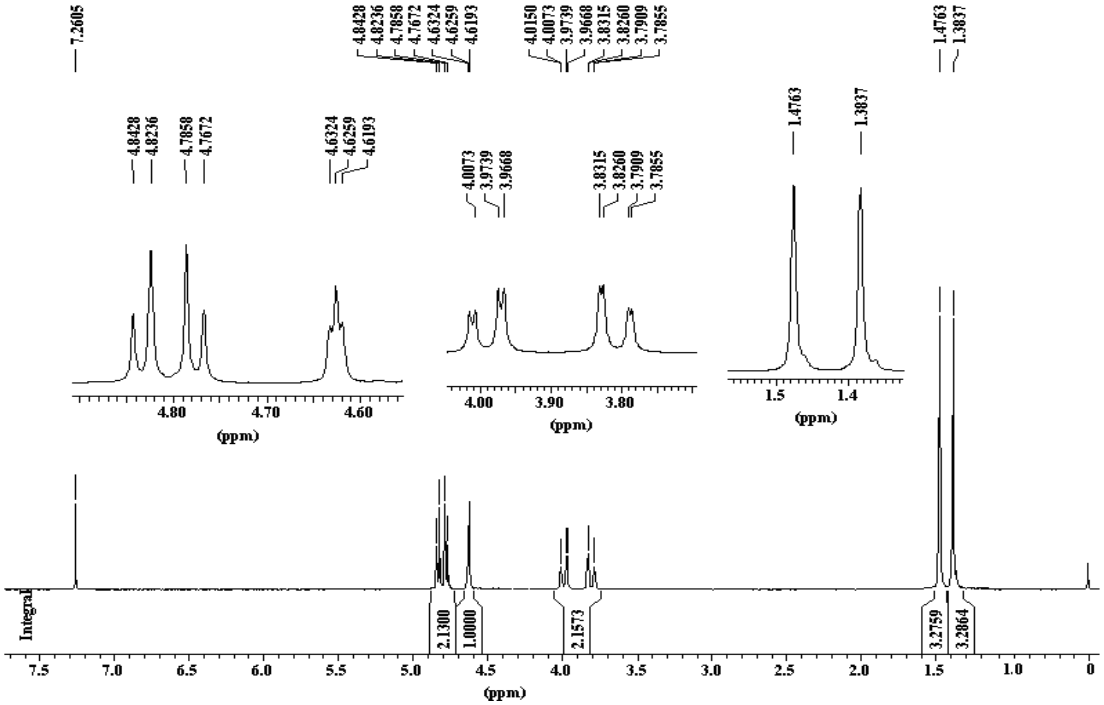
Amberlite IR-120H (1 g) was added to a solution of 2,3-*O*-isopropylidene-L-ribose (0.1 g, 0.53 mmol) in water (10 mL). The mixture was stirred overnight at room temperature, filtered and concentrated *in vacuo* to afford a light coloured syrup. Purification by

column chromatography on silica gel ($CHCl_3$/MeOH 2.5: 1) afforded 0.074 g (94 %) of L-ribose.

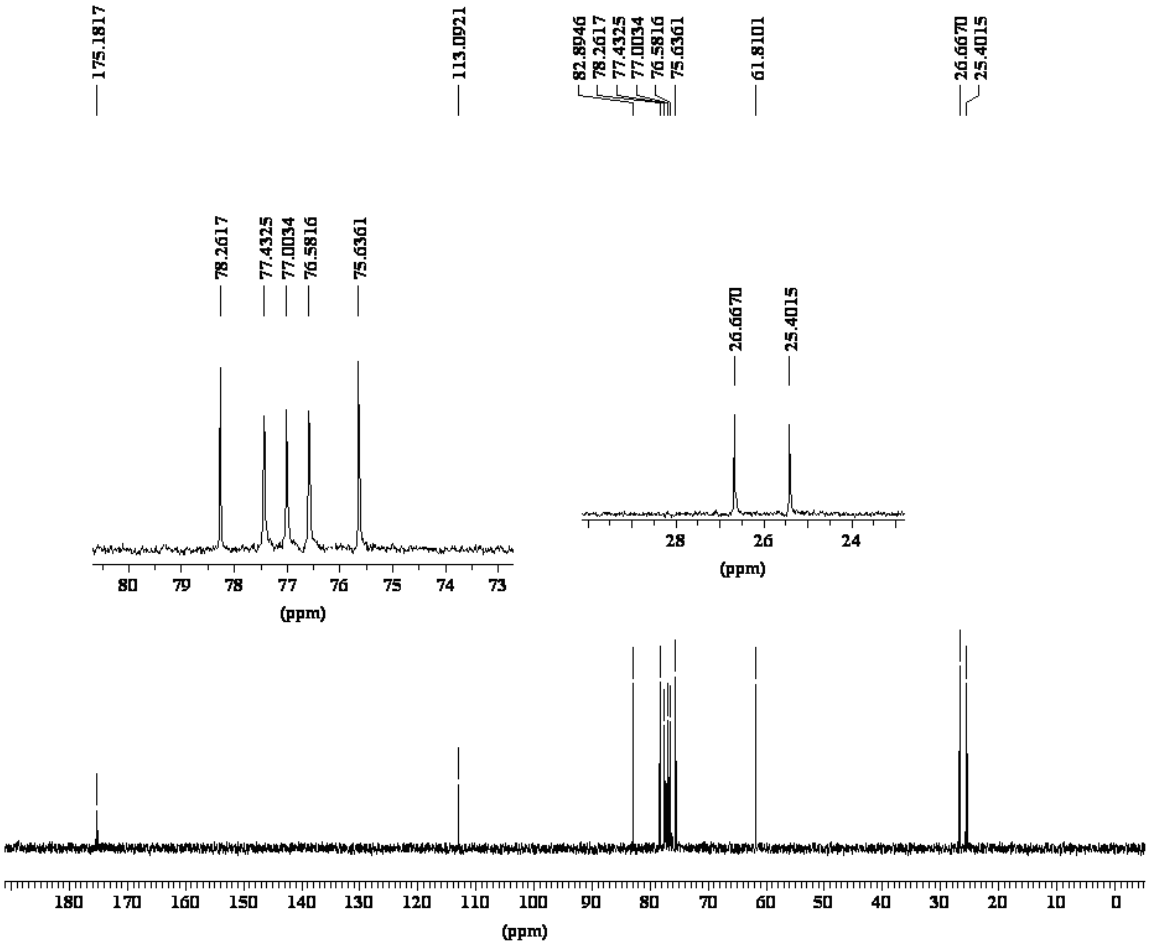
^{13}C NMR (300 MHz, CD_3OD): δ C1 (100.6), C4 (74.1), C2 (73.9), C3 (72.9), C5 (64.3).; $[\alpha]_D^{20} = +19.5°$ (c =1.0, H_2O).

Compare: The ^{13}C NMR spectral data of L-ribose was similar to that of ref. [8]. ^1H NMR (300 MHz, D_2O) is identical to its D-isomer.

^{1}H NMR (300 MHz, $CDCl_3$) of 2,3-*O*-isopropylidene-D-ribonolactone



^{13}C NMR (300 MHz, $CDCl_3$) of 2,3-*O*-isopropylidene-D-ribonolactone



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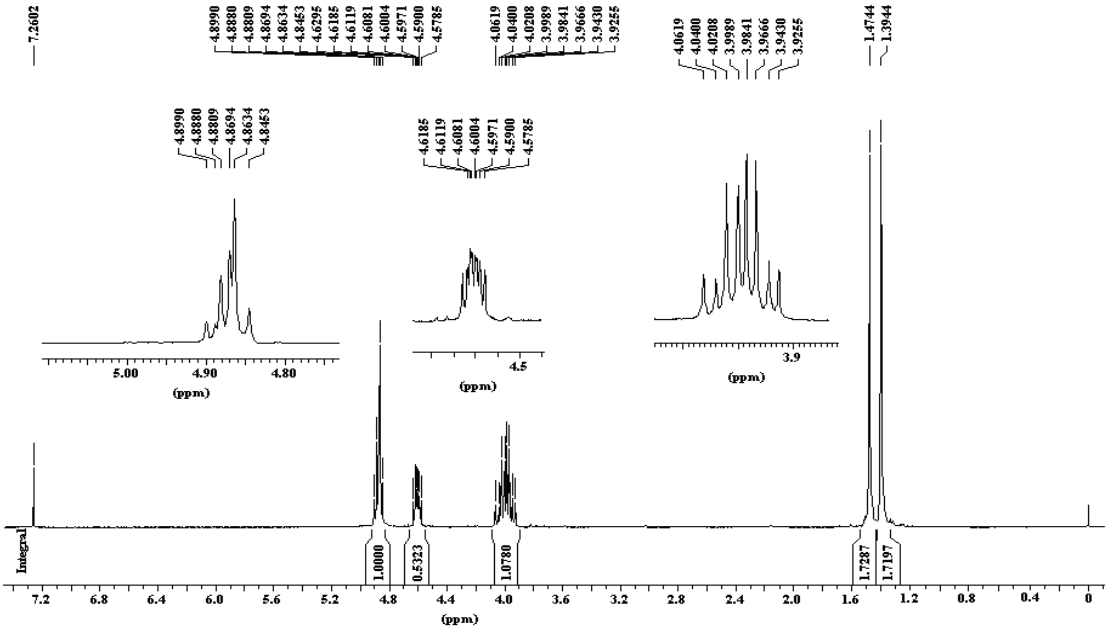

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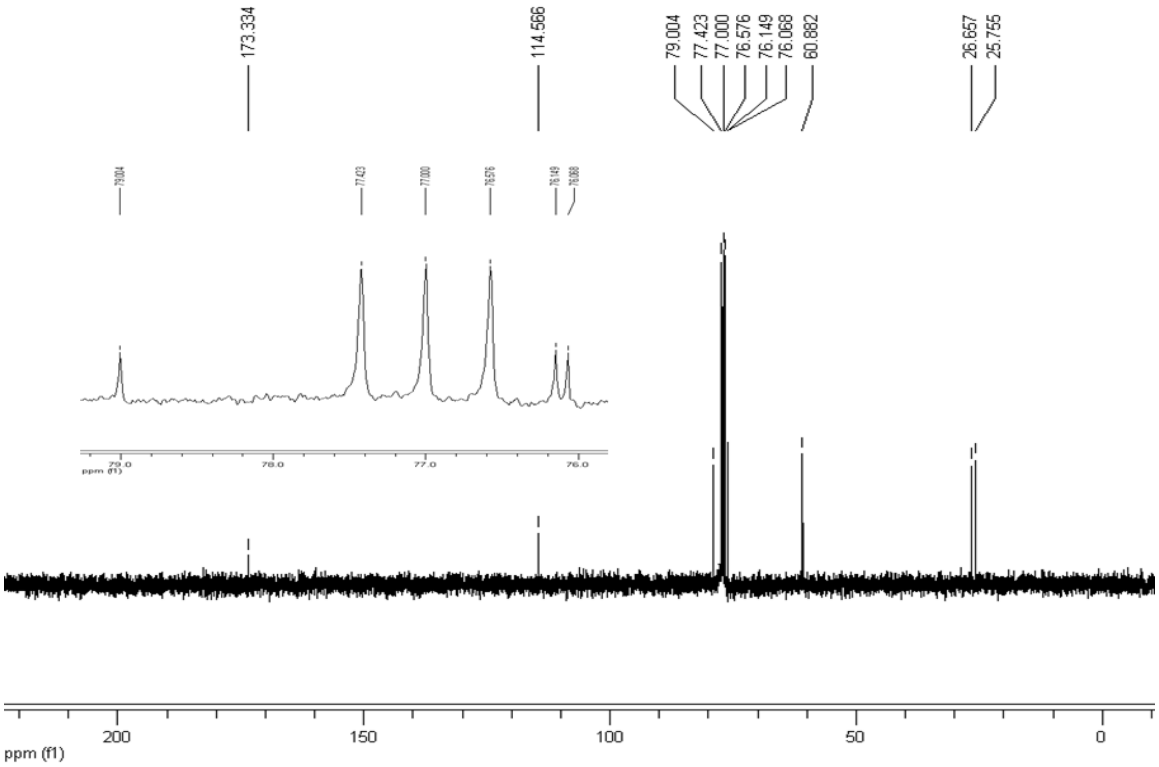
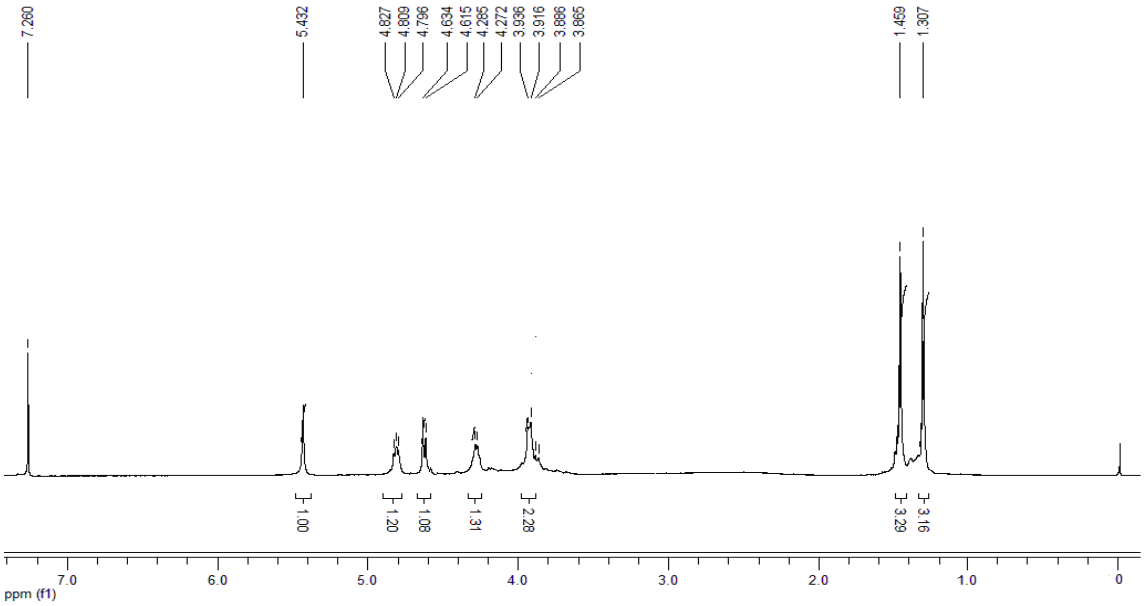
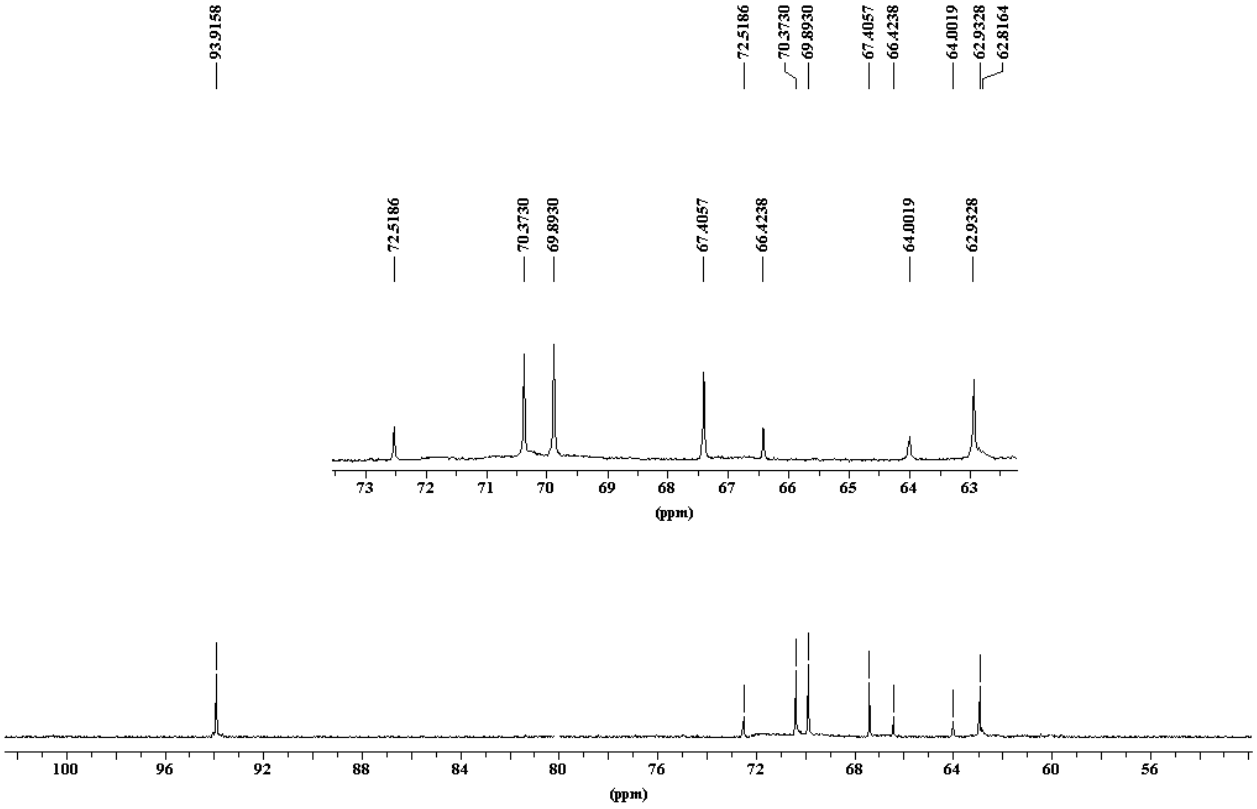


^{1}H NMR (300 MHz, $CDCl_3$) of 2,3-*O*-isopropylidene-L-lyxose



^{13}C NMR (300 MHz, D_2O) of L-lyxose



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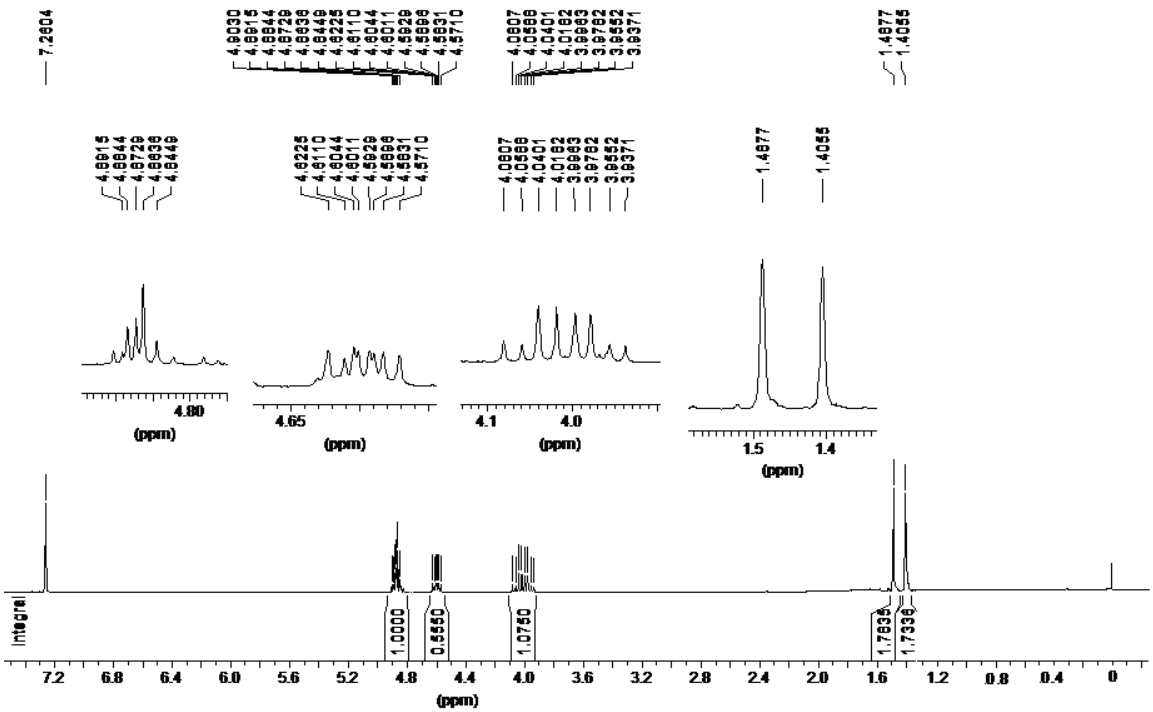

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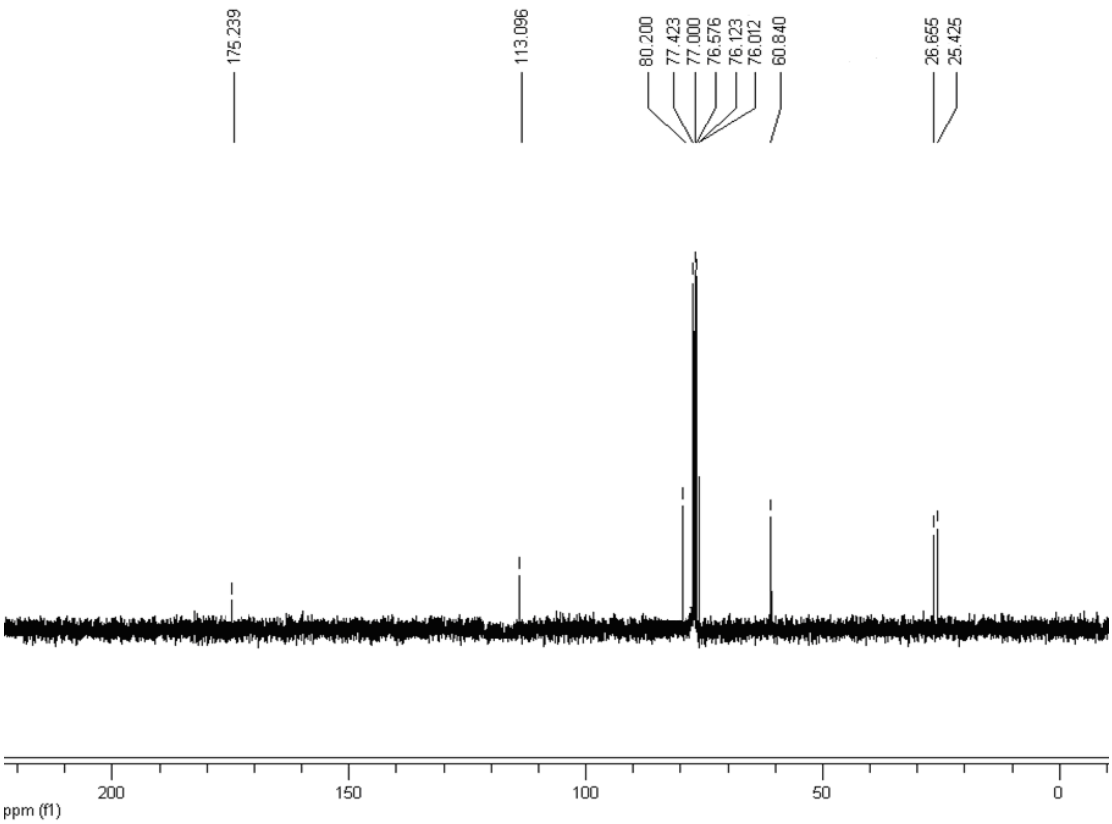

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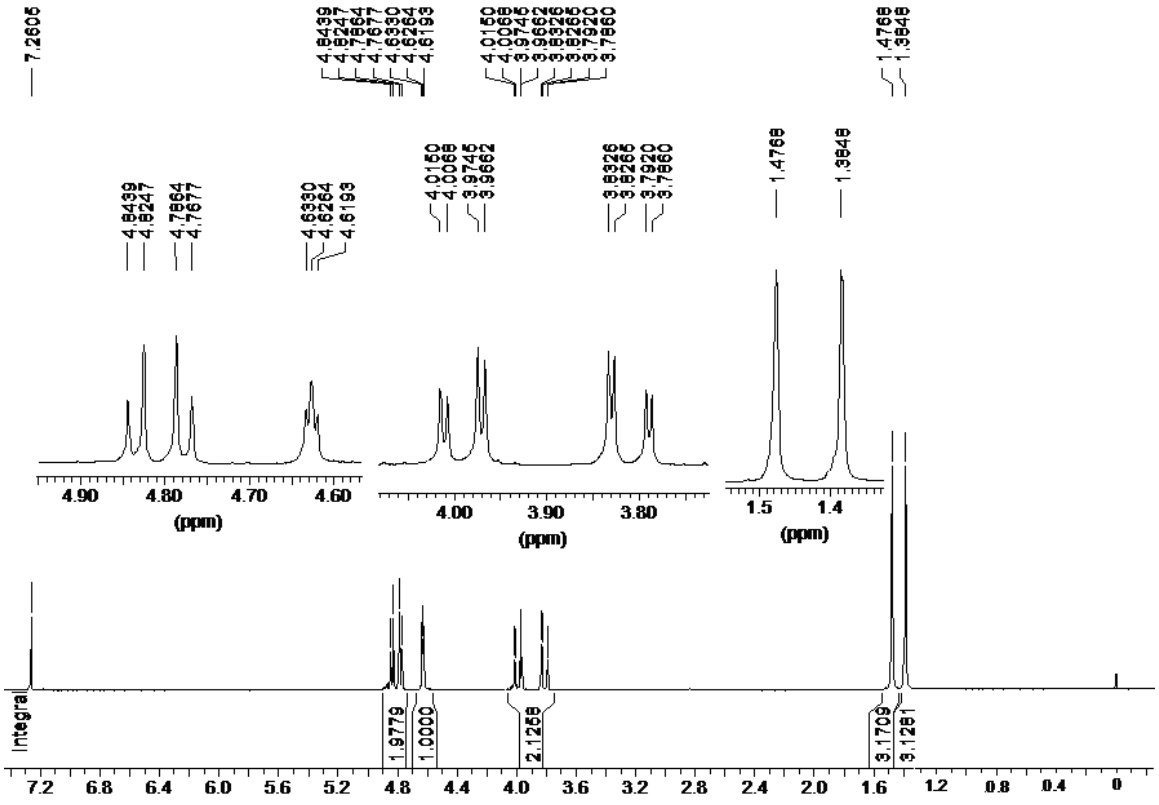

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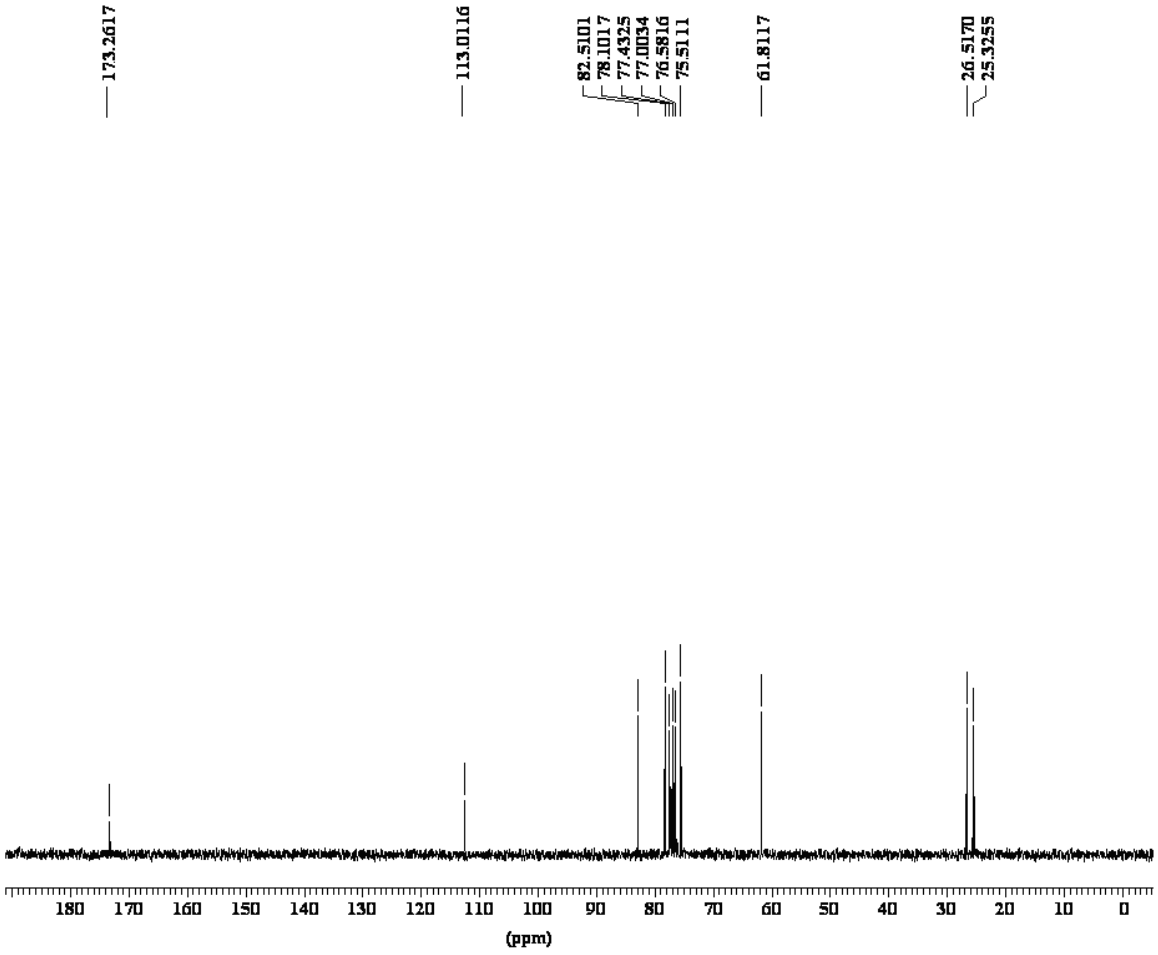
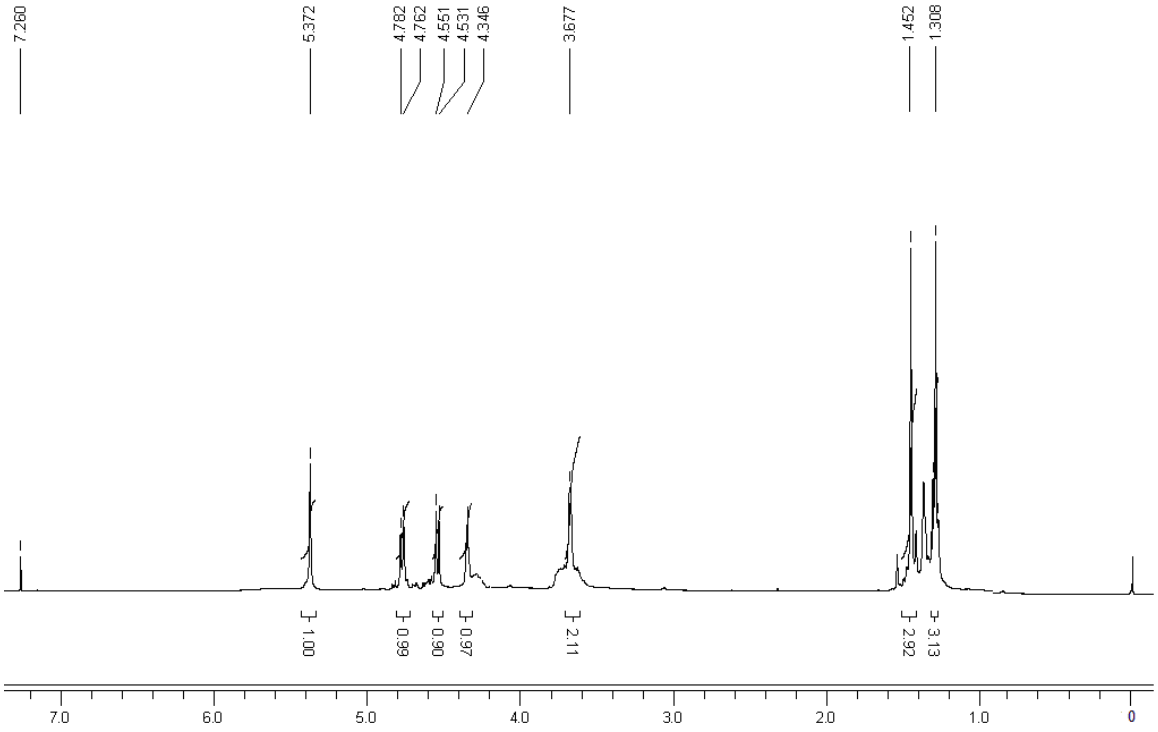


^{1}H NMR (300 MHz, $CDCl_3$) of 2,3-*O*-isopropylidene-L-ribose



^{13}C NMR (300 MHz, CD_3OD) of L-ribose