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An expedient synthesis of L-ribulose and derivatives

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ABSTRACT

A significant improvement in the production of L-ribulose from inexpensive and commercially available starting materials, L-arabinose and sodium aluminate, is demonstrated. This has facilitated expeditious access to gram-scale quantities of L-ribulofuranoside derivatives.

1. Introduction

In the ongoing work on the search for potentially natural structural alternatives to RNA and DNA in the context of a 'Chemical Etiology of Nucleic Acid Structure', an approach pioneered and systematically implemented by Eschenmoser,[1] we needed a quick and efficient access to large quantities of L-ribulose[2] (L-erythropentulose, **1**, Fig. 1). We also realized that this investigation, though initiated in an etiological context, has an augmented significance because of the demonstrated and potential applications of L-sugars[3] and L-nucleosides[4] in the area of chemotherapeutics. From that point of view, we detail here a noteworthy enhancement to the production of L-ribulose from L-arabinose, and describe the preparation of its derivatives.

L-Sugars are used as low-calorie sweeteners,[3] and interest in L-nucleosides have greatly increased in recent years. L-Nucleosides have significant applications in antiviral, antimalarial, and antitumour chemotherapy.[5] For example, some important FDA-approved L-nucleosides are lamivudine (L-β-1,3-oxathiolanylcytosine, 3TC) as an anti-hepatitis B and an anti-HIV agent,[5] telbivudine (L-dT)[6] and clevudine[5c,7] (L-FMAU) as anti-HBV, emtricitabine[5c,6c] (FTC) as anti-HIV and troxacitabine (TRO) as anti-cancer drugs.[8]

Despite the enormities of potential applications[9] in this context (e.g., as source of L-ribose and L-ribonucleosides), the chemistry of L-ribulose has been minimally explored,[10] perhaps because of its high cost and limited availability.† Therefore, a convenient and practical method for a large-scale chemical synthesis of L-ribulose, while satisfying the needs in our etiological pursuit, would be beneficial.

L-Ribulose is produced from L-arabinose by enzymatic isomerization using L-arabinose isomerase (L-AI).[9] Apart from L-arabinose, ribitol has also been used as a precursor.[11] D-Ribulose has been chemically synthesized by the base-catalyzed isomerization of D-arabinose using pyridine (in ca. 20% yield).[12] For our needs, this method was not suitable because of low conversion (recovery of 65% of starting material) and a lengthy purification procedure. D-Ribulose has also been synthesized in ca. 20% yield starting from D-arabinose via pentose-2-ulose using cupric acetate monohydrate.[2]

More recently, L-ribulose has been synthesized in 64% yield by the base-catalyzed isomerization of L-arabinose using freshly prepared aluminate solution, followed by bromination to remove unreacted aldose from the reaction mixture (Scheme 1).[13] It was also reported by the same group that the addition of aluminum oxide to boiling pyridine solution of aldoses increases the rate of aldose–ketose transformation.[14]

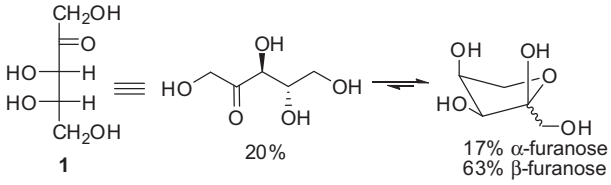

Figure 1. L-Ribulose (L-erythropentulose); percent composition from Ref. 2a; *c* = 0.3 M, 15% v/v D_2O. 50 mM acetate buffer, pH 4.0.

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† L-Ribulose is commercially available from ZuCarb™ (500 mg, $495; 2 g, $995) and Carbosynth Ltd (500 mg, $425).

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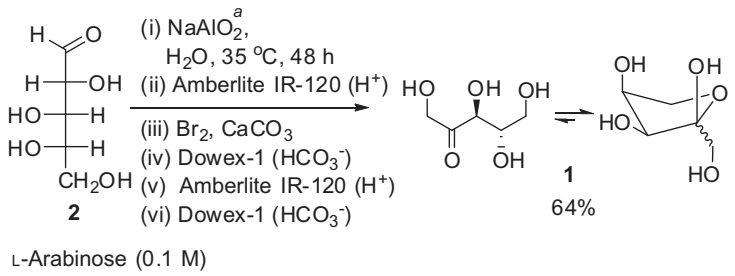


[a] Freshly prepared $NaAlO_2$ was used. 69% conversion at 35 °C after 40 h (by GC MS analysis).

Scheme 1. Literature procedure for preparation of L-ribulose.[13]

Table 1
Optimization of reaction conditions for the preparation of L-ribulose[a]

Entry	$NaAlO_2$ (g)	Deionized water (mL)	Temp (°C)	Time (h)	Conversion[b] (%)
1	1.64	60	40	64	77.8
2	1.64	30	40	64	77.8
3	1.64	30	55	24	84.2
4	1.64	30	55	48	86.5
5	1	30	45	24	86.0
6	1	30	45	48	89.7
7	**1**	**30**	**50**	**24**	**91.3**

[a] All reactions were performed on 1 g scale of L-arabinose.
[b] % conversion was calculated by the ratio of integration of L-arabinose and L-ribulose (^{1}H NMR in D_2O).‡

2. Results and discussion

Due to the relative simplicity, we chose to focus on the preparation of L-ribulose by the $NaAlO_2$-mediated keto–aldol tautomerization of L-arabinose (Scheme 1).[13] However, after many trials, a maximum yield of only 38% of L-ribulose was obtained in our hands. The procedure was found to be very time consuming due to the removal of the gelatinous precipitate that was formed during acidification with Amberlite IR-120 (H^+) ion-exchange resin. The yield of isolated material varied from one run to another probably because of (a) the varying quality of the $NaAlO_2$ that was prepared from Al metal and aq sodium hydroxide, and (b) the loss of material in successive resin exchanges and washings. Moreover, attempts to scale up the reaction were rendered impractical due to the need to evaporate huge amounts of water accumulated during the workup.

To eliminate the uncertainty posed by the quality of $NaAlO_2$, we decided to utilize the commercially available material.‡ A solution of L-arabinose and commercial $NaAlO_2$ in deionized water was heated at 40 °C for 64 h. The resulting reaction mixture was treated with Amberlite IR-120 (H^+) to remove the metal ions by ion-exchange; the pH of the solution was ~2.80. The resin was filtered, and the filtrate was evaporated to dryness to obtain a syrupy liquid. Gratifyingly, ^{1}H NMR (in D_2O) of this residue showed ca. 78% conversion of L-arabinose to L-ribulose (entry 1 of Table 1).

The use of commercially available $NaAlO_2$ was found to be very effective for the aldose–ketose isomerization reaction. Equally important was the role, and control, of pH during the ion-exchange treatment. It was observed that a pH of ~2.80 resulted in a clear solution with none of the vexing gelatinous precipitation present. This enabled the easy filtration of the solution within a matter of minutes (instead of hours). When the pH of the solution was around neutral (apart from the filtration problem), evaporation of the filtrate led to the formation of a solid material instead of the expected syrupy liquid.

The ^{1}H NMR data of the crude L-ribulose, obtained after Amberlite IR-120 (H^+) ion-exchange, was identical with that of D-ribulose reported in the literature.[2b] The conversion of L-arabinose to L-ribulose was optimized with respect to amount of $NaAlO_2$, concentration of L-arabinose, temperature, and time (Table 1). Reducing the concentration of the reaction volume to half did not affect the conversion efficiency (entry 2), and translated advantageously to less water removal during workup. Subsequently for all these exploratory reactions, 30 mL of deioinzed water was used. When the temperature was raised to 55 °C (entry 3), after 24 h, the ^{1}H NMR spectrum showed an 84% conversion to L-ribulose; extending the time (48 h, entry 4) led to only a marginal increase in conversion. A 1:1 wt/wt ratio of L-arabinose to $NaAlO_2$ was found to work equally well (entry 5, Fig. 2). However, lesser amounts of $NaAlO_2$ and lower temperatures led to inefficient conversions. The reaction carried out at 50 °C for 24 h with 1:1 wt/wt ratio of L-arabinose to $NaAlO_2$ (entry 7) resulted in about 91% conversion as indicated by ^{1}H NMR spectroscopy (Scheme 2, Fig. 2). The conditions described in entries 6 and 7 were found to be optimal (circumventing multiple resin exchanges, water washings, and minimizing the amount of water), and were used for preparations on larger scales (5–20 g). The quality of crude L-ribulose thus obtained was found to be satisfactory for further use.

Treatment of the crude L-ribulose (containing traces of L-arabinose) with 1% HCl in anhyd MeOH (w/w) following Tipson's procedure[12] led to a residue containing an anomeric mixture of methyl L-*erythro*-pentulofuranosides[15] (**3**) that was used in subsequent steps without purification. Benzoylation of this residue with benzoyl chloride in pyridine gave, after column chromatography, a mixture of α and β anomers (ratio 35:65 by ^{1}H NMR spectroscopy) of perbenzoylated methyl L-pentulofuranosides (**4**)[12] (Scheme 3). ^{1}H NMR spectral data for **4a** and **4b** was found to be identical that of the known β and α anomers in the D-series.[12] The α-anomer of **4b** was recrystallized from AcOEt–hexanes, and its configuration at the anomeric carbon was unambiguously proven by single-crystal X-ray structure analysis (Fig. 3), which confirmed the structural assignments based on ^{1}H and ^{13}C NMR spectral data. This three-step protocol proved amenable to scale-up; for example, starting from 5 to 15 g of L-arabinose (**2**), we could prepare about 5–18 g of compound **4** as a mixture of α and β anomers (**4a** and **4b**) in overall yield of 34–40% (av 70–73% yield per step starting from L-arabinose).

The crude methyl L-*erythro*-pentulofuranoside (**3**) could be perbenzylated under standard conditions to produce 1,3,5-tri-*O*-benzyl derivative **5** as a mixture of α and β anomers (Scheme 3), which was also amenable to scale-up. For example, starting from 5 g of L-arabinose (**2**), we obtained about 6 g of **5** in ~44% overall yield, which corresponds to an average of 76% yield per step.

In conclusion, an expedient and convenient access to L-ribulose (ca. 90% conversion starting from L-arabinose) using commercially

‡ See Supplementary data. All new compounds were fully characterized by spectroscopic methods.

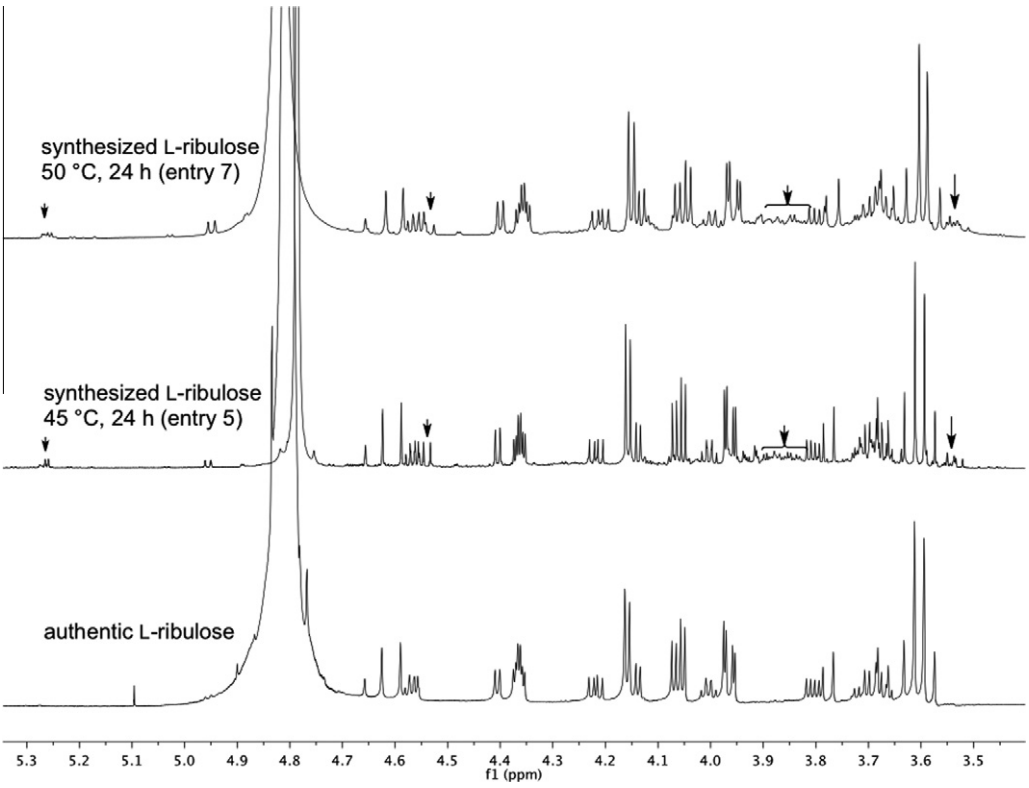
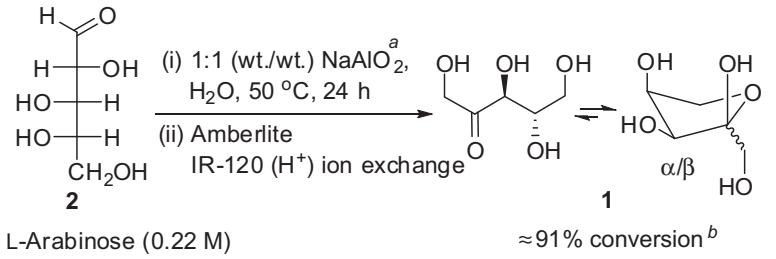


Figure 2. Comparison of ^{1}H NMR spectra of authentic L-ribulose and crude L-ribulose from entries 5 and 7 of Table 1 (peaks from L-arabinose are indicated by arrows).



[a] Commercial $NaAlO_2$ was used (contained 8% water)
[b] % Conversion calculation based on ^{1}H NMR spectroscopy (in D_2O).

Scheme 2. Improved procedure for the conversion of L-arabinose to L-ribulose.

available $NaAlO_2$ has been demonstrated. This has enabled the synthesis of derivatives of L-ribulose in large quantities. The chemistry of L-ribulose and its derivatives is under investigation.

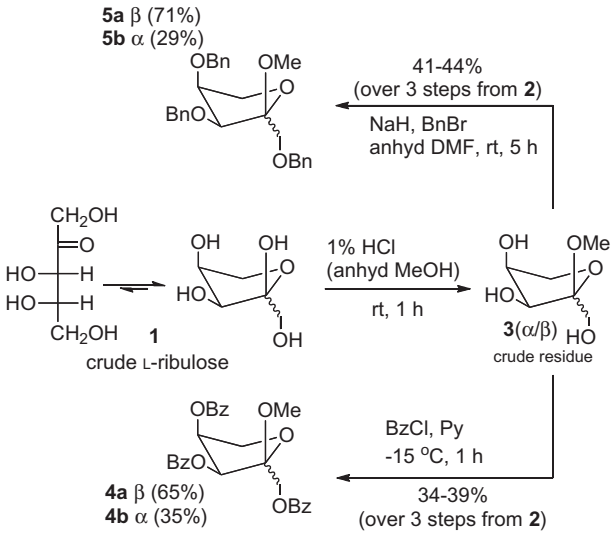
3. Experimental

3.1. Methods and materials

All reagents and solvents were obtained from commercial sources and used without purification. L(+)-Arabinose was purchased from Sigma–Aldrich Chemical Co.; $NaAlO_2$ (contained 8% H_2O) was obtained from Fisher Scientific Co. Pre-coated flexible silica gel TLC F_{254} plates were obtained from Whatman Ltd. Flash chromatography was performed using Silica Gel 60 (40–60 μm) from Fisher Scientific Co. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-600 instrument at 600 MHz for proton and 150 MHz for carbon, respectively. ^{1}H and ^{13}C NMR chemical shifts in $CDCl_3$ were referenced to chloroform at 7.26 ppm and 77.23 ppm, respectively. ^{1}H NMR chemical shifts in D_2O were referenced to HOD at 4.80 ppm. Mass analysis was performed on an Agilent ESI-TOF mass spectrometer at an ESI voltage of 4000 V and a flow rate of 200 μL/min.

3.2. Conversion of L-arabinose to L-ribulose

L-Arabinose (**2**, 5.000 g, 33.33 mmol) was added to a solution of commercial available $NaAlO_2$ (5.000 g) dissolved in 300 mL of deionized H_2O. The resulting solution was heated at 45 °C for 48 h. The reaction mixture was cooled to room temperature and treated with excess of Amberlite IR-120 (H^+) resin to exchange the metal ions (until there was no further change in the pH); the pH of the solution after ion-exchange was ~2.80. The solution was filtered and the filtrate was concentrated under vacuum to obtain a syrupy colorless liquid. This syrupy liquid was kept under vacuum (over P_2O_5) to obtain 4.295 g of a residue containing crude L-ribulose (**1**) (with ≈10% of L-arabinose), which was used in the next step without further purification.



Scheme 3. Preparation of derivatives of L-ribulose.

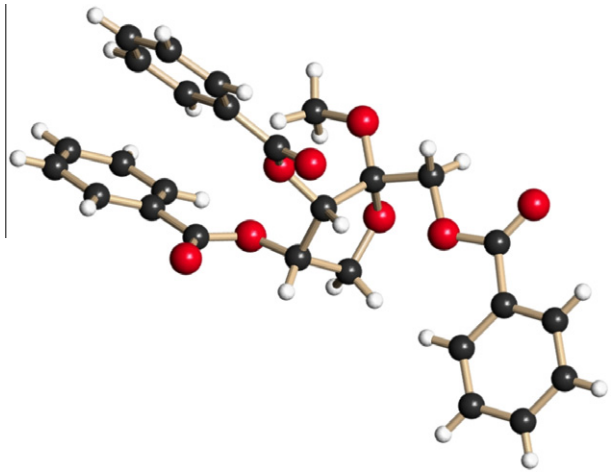


Figure 3. Ball-and-stick representation of the X-ray structure of the α-anomer **4b**.

3.3. Preparation of methyl 1,3,4-tri-*O*-benzoyl-L-*erythro*-pentulofuranoside (4)

Crude L-ribulose (**1**, 4.295 g) obtained from the previous step was dissolved in 260 mL of 1% HCl in anhyd MeOH (w/w), and the solution was kept at room temperature for 1 h. The excess HCl was bubbled off with nitrogen sparging. Ag_2CO_3 (20.62 g, 74.77 mmol) was added to the solution, and the suspension was stirred at room temperature for 1 h and filtered over a bed of Celite. The filtrate was evaporated in vacuo to obtain 4.382 g of a residue containing an anomeric mixture of methyl L-*erythro*-pentulofuranosides (**3**) (checked by ^{1}H NMR spectroscopy[15]). This crude anomeric mixture was used in the next step without further purification.

Crude **3** (4.278 g) was dissolved in anhyd pyridine (30 mL). The solution was cooled with an ice–salt bath, and benzoyl chloride (10.3 mL, 89.3 mmol) was added with vigorous stirring. The reaction mixture was stirred in an ice salt bath for 15 min, then further stirred for 1 h at room temperature and cooled again with the ice–salt bath. Moist pyridine (40 mL containing few drops of water) was added, and the solution was stirred for 40 min with ice–salt bath cooling. Satd aq $NaHCO_3$ (20 mL) was added, and the reaction mixture was stirred for 30 min with ice–salt bath cooling. The reaction mixture was evaporated to dryness in vacuo, and the residue was partitioned between CH_2Cl_2 (300 mL) and H_2O (300 mL). The organic layer was separated, washed successively with satd aq $KHSO_4$ (3 × 100 mL), H_2O (2 × 100 mL), satd aq $NaHCO_3$ (2 × 100 mL), H_2O (100 mL), and finally with brine solution (100 mL). The organic layer was dried over anhyd $MgSO_4$ and concentrated in vacuo to obtain 11.0 g of a crude mixture of anomers of methyl 1,3,4-tri-*O*-benzoyl-L-*erythro*-pentulofuranosides (**4**). The residue was subjected to column chromatography (silica gel, 3–8% AcOEt–hexanes) to obtain 3.73 g of the β anomer **4a** as syrup, 0.876 g of the α anomer **4b** as white solid and 0.733 g of a mixture (**4a** + **4b**). The overall yield of **4** from L-arabinose over the three steps was 5.341 g (33.6%). The ^{1}H NMR spectra of both the anomers were found to be identical to the ones reported in the literature for the D-series.[12]

3.3.1. Methyl 1,3,4-tri-*O*-benzoyl-β-L-*erythro*-pentulofuranoside (4a)

Syrupy liquid; R_f 0.47 (20:80 AcOEt–hexanes); $[\alpha]_D^{24}$ +96.5 (*c* 1.0, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.40 (s, 3H, OMe), 4.16 (dd, *J* = 10.2, 4.8 Hz, 1H, H-5), 4.46 (d, *J* = 12.0 Hz, 1H, H-1), 4.48 (dd, *J* = 10.2, 6.6 Hz, 1H, H-5′), 4.92 (d, *J* = 12.6 Hz, 1H, H-1′), 5.85 (d, *J* = 5.4 Hz, 1H, H-3), 5.84–5.89 (m, 1H, H-4), 7.27–7.30 (m, 2H, arom.), 7.34–7.40 (m, 4H, arom.), 7.46–7.50 (m, 1H, arom.), 7.50–7.54 (m, 2H, arom.), 7.80–7.84 (m, 2H, arom.), 7.94–8.00 (m, 4H, arom.); ^{13}C NMR (150 MHz, $CDCl_3$): δ 49.3 (OMe), 59.3 (C-1), 70.7 (C-5), 72.9 (C-4), 75.6 (C-3), 107.2 (C-2), 128.6, 128.6, 128.7, 129.3, 129.4, 129.6, 129.8, 129.9, 130.0, 133.4, 133.5, 133.6, 165.2, 165.9, 166.1 (arom. C); HRMS (ESI-TOF high-acc); calcd for $C_{27}H_{24}O_8$ (M+Na$^+$), *m/z* 499.1363; found, *m/z* 499.1361.

3.3.2. Methyl 1,3,4-tri-*O*-benzoyl-α-L-*erythro*-pentulofuranoside (4b)

Colorless blades; TLC: R_f 0.40 (20:80 AcOEt–hexanes); mp 94–95 °C; $[\alpha]_D^{24}$ +121.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.52 (s, 3H, OMe), 4.18 (dd, *J* = 10.8, 3.6 Hz, 1H, H-5), 4.52 (dd, *J* = 10.8, 6.0 Hz, 1H, H-5′), 4.57 (d, *J* = 12.0 Hz, 1H, H-1), 4.64 (d, *J* = 11.4 Hz, 1H, H-1′), 5.68 (d, *J* = 6.6 Hz, 1H, H-3), 5.77–5.81 (m, 1H, H-4), 7.27–7.33 (m, 4H, arom.), 7.36–7.41 (m, 2H, arom.), 7.46–7.57 (m, 2H, arom.), 7.52–7.57 (m, 1H, arom.), 7.92–7.98 (m, 4H, arom.), 7.98–8.03 (m, 2H, arom.); ^{13}C NMR (150 MHz, $CDCl_3$): δ 49.8 (OMe), 63.0 (C-1), 70.3 (C-4), 71.2 (C-5), 73.6 (C-3), 103.1 (C-2), 128.5, 128.5, 128.6, 129.3, 129.7, 129.8, 129.9, 130.0, 130.1, 133.3, 133.4, 133.4 (arom. C), 165.6, 166.0 (CO); HRMS (ESI-TOF high-acc): calcd for $C_{27}H_{24}O_8$ (M+Na$^+$), *m/z* 499.1363; found, *m/z* 499.1371.

3.4. Preparation of anomers of methyl 1,3,4-tri-*O*-benzyl-L-*erythro*-pentulofuranoside (5)

L-Arabinose **2** (5.000 g, 33.33 mmol) was added to a solution of commercially available $NaAlO_2$ (5.000 g) dissolved in 150 mL of deionized H_2O. The resulting solution was heated at 50 °C for 24 h. The reaction mixture was cooled to room temperature and treated with an excess of Amberlite IR-120 (H^+) resin to exchange the metal ions (until there was no further change in the pH); the pH of the solution after ion-exchange was ~2.80. The solution was filtered and concentrated under vacuum to obtain a syrupy liquid. This syrupy liquid was kept under vacuum over a P_2O_5 in a desiccator to obtain 4.675 g of crude L-ribulose (**1**) (containing ~10% of L-arabinose), and was used in the next step without any further purification.

Crude L-ribulose (**1**, 4.675 g) obtained from the previous step was dissolved in 260 mL of 1% HCl in anhyd MeOH (w/w). The solution was kept at room temperature for 1 h. The excess HCl was bubbled off with nitrogen sparging. Ag_2CO_3 (12.00 g, 43.52 mmol)

was added to the solution, and the suspension was stirred at room temperature for 1 h and filtered over a bed of Celite. The filtrate was evaporated under vacuum to obtain 4.700 g of a residue containing a mixture of anomers of methyl L-*erythro*-pentulofuranosides (**3**, checked by ^{1}H NMR spectroscopy[15]), and was used in the next step without any further purification.

A crude mixture of **3** (4.614 g) was dissolved in anhyd DMF (230 mL). The solution was cooled to 0 °C, followed by addition of NaH (60% dispersion in oil, 6.752 g, 168.80 mmol) with vigorous stirring. The reaction mixture was stirred for 30 min at 0 °C, followed by dropwise addition of benzyl bromide (30 mL, 253.20 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirring was continued for 5 h. The reaction mixture was quenched by addition of MeOH and evaporated to dryness under reduced pressure. The residue obtained was dissolved in AcOEt (250 mL) and washed with water (3 × 250 mL). The organic layer was washed with brine solution (100 mL), dried over anhyd $MgSO_4$ and concentrated under vacuum to obtain 20.10 g of a residue containing a crude mixture of anomers of methyl 1,3,4-tri-*O*-benzyl-L-*erythro*-pentulofuranosides (**5**). The residue was subjected to column chromatography (silica gel, 8–15% AcOEt–hexanes) to obtain 4.499 g of the β anomer **5a**, and 1.825 g of the α anomer **5b** as syrupy liquids (2.5:1 ratio). The overall yield of **5** from L-arabinose over the three steps was 6.324 g (43.7%).

3.4.1. Methyl 1,3,4-tri-*O*-benzyl-β-L-*erythro*-pentulofuranoside (5a)

Syrupy liquid; TLC: R_f 0.45 (20:80 AcOEt–hexanes); $[\alpha]_D^{24}$ −10.96 (*c* 1, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.21 (s, 3H, OMe), 3.63 (d, *J* = 10.2 Hz, 1H, H-1), 3.74 (d, *J* = 10.8 Hz, 1H, H-1′), 3.89–3.92 (m, H-5), 3.95–4.01 (m, 2H, H-3 and H-5′), 4.38–4.44 (m, 2H, H-4 and C*H*$_2$OBn), 4.51 (d, *J* = 12.0 Hz, 1H, C*H*$_2$OBn), 4.53 (d, *J* = 12.0 Hz, 1H, C*H*$_2$OBn), 4.62 (d, *J* = 12.0 Hz, 1H, C*H*$_2$OBn), 4.73 (s, 2H, C*H*$_2$OBn), 7.24–7.39 (m, 15H, arom.); ^{13}C NMR (150 MHz, $CDCl_3$): δ 48.7 (OMe), 65.2 (C-1), 69.5 (C-5), 72.6 (*C*H$_2$OBn), 73.7 (*C*H$_2$OBn), 74.0 (*C*H$_2$OBn), 78.7 (C-4), 80.2 (C-3), 108.9 (C-2), 127.8, 127.8, 127.9, 128.0, 128.3, 128.3, 128.5, 128.6, 128.6, 137.9, 138.2, 138.5 (arom. C); HRMS (ESI-TOF high-acc): calcd for $C_{27}H_{30}O_5$ $(M+H)^+$, *m/z* 435.2166; found, *m/z* 435.2170; calcd for $C_{27}H_{30}O_5$ $(M+Na)^+$, *m/z* 457.1985; found *m/z* 457.2006.

3.4.2. Methyl 1,3,4-tri-*O*-benzyl-α-L-*erythro*-pentulofuranoside (5b)

Syrupy liquid, TLC: R_f 0.35 (20:80 AcOEt–hexanes); $[\alpha]_D^{24}$ −3.02 (*c* 1, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.43 (s, 3H, OMe), 3.53 (d, *J* = 10.2 Hz, 1H, H-1), 3.56 (d, *J* = 10.2 Hz, 1H, H-1′), 3.94–4.01 (m, 3H, H-4, H-5 and H-5′), 4.06 (d, *J* = 6.0 Hz, 1H, H-3), 4.46 (d, *J* = 12.0 Hz, 1H, C*H*$_2$OBn), 4.52 (d, *J* = 12.0 Hz, 1H, C*H*$_2$OBn), 4.55 (d, *J* = 12.0 Hz, 1H, C*H*$_2$OBn), 4.62 (d, *J* = 12.0 Hz, 1H, C*H*$_2$OBn), 4.65 (s, 2H, (C*H*$_2$OBn)), 7.22–7.37 (m, 15H, arom.); ^{13}C NMR (150 MHz, $CDCl_3$): δ 50.2 (OMe), 70.3 (C-1), 71.0 (C-5), 72.4 (*C*H$_2$OBn), 72.9 (*C*H$_2$OBn), 73.7 (*C*H$_2$OBn), 74.9 (C-4), 78.3 (C-3), 104.7 (C-2), 127.8, 127.9, 127.9, 127.9, 128.1, 128.4, 128.5, 128.5, 128.6, 138.1, 138.3, 138.4 (arom. C); HRMS (ESI-TOF high-acc): calcd for $C_{27}H_{30}O_5$ $(M+Na)^+$, *m/z* 457.1985; found *m/z* 457.1997.

Acknowledgments

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Supplementary data

^{1}H NMR spectra for the L-arabinose to L-ribulose conversion reactions, ^{1}H and ^{13}C NMR spectra of compounds and X-ray data for **4b**. Complete crystallographic data for the structural analysis for **4b** have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 800959. Copies of this information may be obtained free of charge from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK. (fax: +44 1223 336033, e-mail: deposit@ccdc.cam.ac.uk or via: www.ccdc.cam.ac.uk). Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2011.01.013.

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