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Development of a Novel Synthetic Process for 2-Deoxy-3,5-di-*O*-*p*-toluoyl-α-L-ribofuranosyl Chloride: A Versatile Intermediate in the Synthesis of 2′-Deoxy-L-ribonucleosides

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Abstract:

A novel synthetic route to 2-deoxy-3,5-di-*O*-*p*-toluoyl-α-L-ribofuranosyl chloride (1) from inexpensive D-xylose (3) is described. 1 is a key intermediate in the synthesis of the antiviral agent 1-(2-deoxy-*β*-L-ribofuranosyl)thymine (*β*-L-thymidine) (2) and other 2′-deoxy-L-ribonucleosides. This seven-step synthesis employs a key conversion of the D to the L configuration of the sugar moiety (6 to 7 in Scheme 1) using simple reagents and reaction conditions. The entire process involves only three isolation steps. The key compound (1) was produced in 11% overall yield without chromatography.

Introduction

L-Nucleosides have attracted great interest as drugs that possess potent antiviral properties against hepatitis B virus (HBV)[1−7] and human immunodeficiency virus (HIV).[1,3,6,8,9] For instance, 2′-deoxy-*β*-L-cytidine (L-dC), 1-(2-deoxy-*β*-L-ribofuranosyl)thymine (*β*-L-thymidine or L-dT), 2′-deoxy-*β*-L-adenosine (L-dA), 2′-fluoro-5-methyl-*β*-L-arabinofuranosyluracil (L-FMAU), and 2′,3′-dideoxy-*β*-L-cytidine (L-ddC) have shown potent, selective, and specific activity against HBV replication.[2,4,5−7] 2′,3′-Dideoxy-*β*-L-5-fluorocytidine (L-FddC) and 2′,3′-dideoxy-*β*-L-adenosine (L-ddA) are found to be active against both HBV and HIV in cell cultures.[6,8,9] Therefore, the development of novel, efficient, and cost-effective processes for the synthesis of such unnatural L-nucleosides and their key precursors is essential for appropriate “cost of goods” considerations. 1-(2-Deoxy-*β*-L-ribofuranosyl)thymine or L-dT (**2**) (Figure 1) is being developed under the generic name ‘Telbivudine’ by Idenix Pharmaceuticals, Inc. (formerly Novirio Pharmaceuticals, Inc.) and Novartis Pharma AG to treat acute and chronic hepatitis B viral infections.[2,4] Currently telbivudine is in phase III clinical trials. For the synthesis of this compound and several other 2′-deoxy-L-ribonucleosides of interest, 2-deoxy-3,5-di-*O*-*p*-toluoyl-α-L-ribofuranosyl chloride or L-chlorosugar **1** is a key intermediate.[10,11] The majority of published methods[10−13] utilize L-arabinose as the starting material to make this intermediate **1**. In 1964 Smejkal and Sorm[10] reported the conversion of L-arabinose to L-chlorosugar **1** in 11 steps via diacetyl-L-arabinal as a key intermediate. The major drawbacks of their process are the extremely long reaction times of some steps, chromatographic purification of most intermediates and a very poor overall yield. In 1992 Urata et al.[11] described a 9-step synthesis of **1** from L-arabinose in overall 20% yield but their process would have difficulties in scaling up as it required several hazardous reagents. In 1999 Zhang et al.[12] described an improvement over the method of Urata et al.[11] by replacing tri-*n*-butyltin hydride with diphenylsilane as the reducing agent in a critical deoxygenation step. More recently Jung and Xu[13] prepared the L-chlorosugar **1** in six steps from L-arabinose in 30% overall yield. These processes also have limitations for the industrial manufacture of the L-chlorosugar **1** due to the use of difficult-to-handle reagents such as carbon disulfide and ethanethiol.

As our HBV program advanced to phase II and III clinical trials, the need to investigate alternative synthetic processes for L-chlorosugar **1** became increasingly important. Herein we report a novel and efficient process for the synthesis of 2-deoxy-3,5-di-*O*-*p*-toluoyl-α-L-ribofuranosyl chloride (**1**) from D-xylose (**3**). This process requires seven chemical transformations. There are only three steps where the products of reactions are isolated and purified. In all other steps

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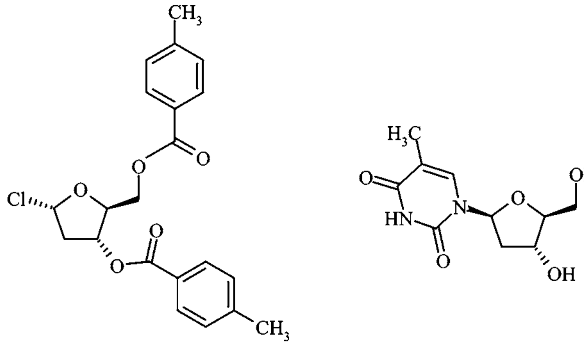

L-Chlorosugar **1**

β-L-Thymidine **2**

Figure 1.

the products are telescoped with minimal processing. The process avoids the use of any chromatographic purification.

Results and Discussion

Preparation of 2,5-Dibromo-2,5-dideoxy-D-lyxono-1,4-lactone (5). D-Xylose (**3**) was smoothly oxidized to D-xylono-1,4-lactone (**4**) by the action of bromine (Scheme 1). Initially we employed $Br_2/BaCO_3/H_2O$ as the reagent combination for this oxidation using a slight modification of the procedure of Isbell.[14] At the completion of the reaction, which typically took several hours at 0 °C followed by gradual warming to ambient temperature, the excess $BaCO_3$ was removed by filtration. The clear filtrate containing soluble $BaBr_2$ was treated with a calculated amount of diluted aqueous H_2SO_4. The precipitated $BaSO_4$ was removed by filtration, and the filtrate was concentrated in vacuo. The residue was treated with 30% HBr in acetic acid (HBA) in the subsequent step.

During the development of the above bromine-oxidation step the procedure of Okabe et al.[15] employing aqueous K_2CO_3 in place of $BaCO_3$ was found to be more practical. The use of K_2CO_3 instead of $BaCO_3$ had allowed us to employ a much higher throughput for this conversion. Since K_2CO_3 remained soluble in the reaction mixture, the processing of the product was a lot easier. Thus, an aqueous solution of D-xylose (**3**) and K_2CO_3 was treated with bromine at 0−5 °C. The mixture was gradually warmed to ambient temperature and quenched with formic acid (see Experimental Section for detail). D-Xylono-1,4-lactone (**4**) was not isolated at this stage. Instead the mixture was concentrated in vacuo at 45−50 °C, and the residual water from it was removed by coevaporation with glacial acetic acid (HOAc) in vacuo at 45−50 °C. Thus, a syrupy residue of the crude product **4** was obtained.

The crude product **4** was treated with 30% HBr in acetic acid (HBA) to get a mixture of 2,5-dibromo-2,5-dideoxy-D-lyxono-1,4-lactone (**5**) and its 3-*O*-acetyl derivative (not shown in Scheme 1). Therefore, this mixture was quenched with methanol to convert the 3-*O*-acetyl derivative of **5** back to 2,5-dibromo-2,5-dideoxy-D-lyxono-1,4-lactone (**5**). In the early stages of our research we allowed lactone **4** to react with HBA (5−6.5 equivof HBr) at room temperature according to the procedure of Lundt.[16] Under these conditions a reaction time of approximately 48−60 h was necessary for the completion of the reaction.

To study the effect of temperature on the above bromination reaction, we carried out several experiments at 23, 40, 45, 60, 90, and 120 °C,[17] employing varied equivalents of HBr. A smooth conversion was observed at 45 °C with 5 equiv of HBr (as HBA). The reaction time was greatly reduced under these conditions (see Experimental Section for detail). Such short reaction time is a significant improvement of the process over the existing literature protocols[16,18] that require days to prepare the dibromolactones. The crude product of our new process was triturated with 20% *n*-heptane in isopropyl ether to get pure 2,5-dibromo-2,5-dideoxy-D-lyxono-1,4- lactone (**5**) as light brown crystals. This isolation of **5** was the first of the three isolation steps of the current process. The overall yield of **5** was approximately 40% for the two steps starting from D-xylose (**3**).

C-2 Debromination, Base-Induced Rearrangement, and Formation of 2-Deoxy-3,5-di-*O*-*p*-toluoyl-L-ribono-1,4-lactone (8). The C-2 debromination of **5** using iodide ion was examined in detail. This reaction was found to be sluggish when conducted at room temperature using potassium or sodium iodide and trifluoroacetic acid (TFA) in acetone,[18a−c] 2-butanone, or isopropyl acetate (IPAc). When heated at reflux, the reaction was considerably faster and required fewer equivalents of the iodide ion to go to completion. The combination of NaI/TFA/IPAc was found to be convenient because the use of IPAc (bp 85−91 °C) as the reaction solvent allowed the reaction to be completed in 2 h at 85 °C, and crude 5-bromo-2,5-dideoxy-D-*threo*-pentono-1,4-lactone (**6**) could be obtained via an IPAc/water split. Occasionally a trace amount of 5-iodo-2,5-dideoxy-D-*threo*-pentono-1,4-lactone (**6a**) was detected by NMR. There was, however, no need to separate **6a** from **6** as it would undergo the same conversion in the subsequent step. The desired monobromolactone **6** was also accessible via the catalytic hydrogenolysis[18a] of **5** in excellent yield (see Experimental Section). Considering the ease of the work-up and the higher yield and quality of the product, the hydrogenolysis method should be preferred to make the monobromolactone **6** from **5**.

The monobromolactone **6** thus obtained was then treated with 3 mol equiv of potassium hydroxide in water at ambient temperature. After complete consumption of the starting material, the mixture was briefly heated to 80 °C and then cooled to ambient temperature. Thereafter, it was treated with Amberlite IR-120 (H^+) ion-exchange resin to pH 1 to afford 2-deoxy-L-ribono-1,4-lactone (**7**). This transformation most likely involves the initial formation of an epoxyaldonic acid potassium salt **10** (Figure 2) which could ring-open via an intramolecular nucleophilic attack of the epoxide ring by the

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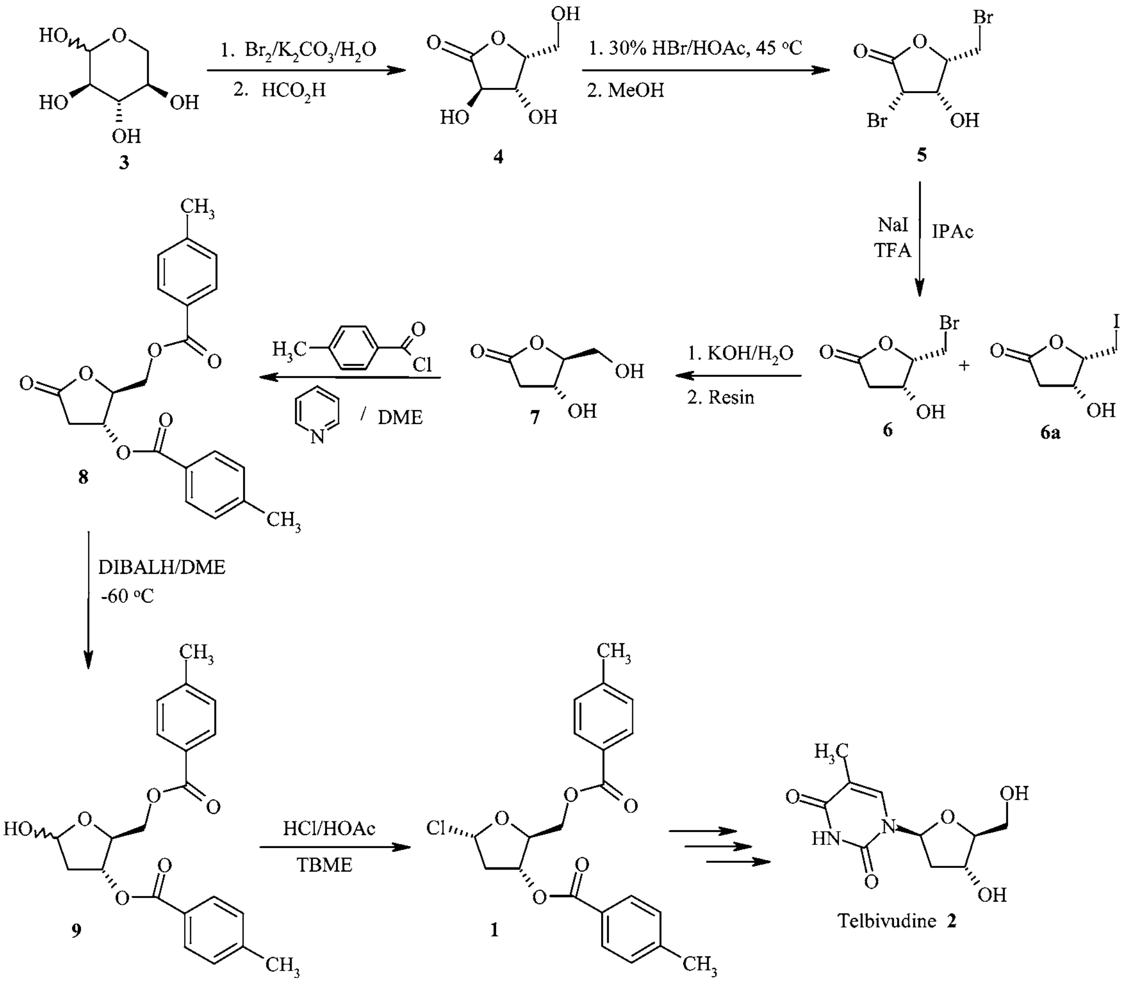
Scheme 1



carboxylate ion. According to Baldwin's rule[19] the 5-*exo* mode would be preferred to the 6-*endo* mode of opening. Hence, this would result in an inversion of configuration at the attacked carbon (C-4), producing the L-configured lactone **7** from its D-configured precursor **10**. The lactone **7** thus formed would be opened by aqueous alkali to the aldonic acid salt **11**, which however, would regenerate the lactone **7** upon acidification. The stereochemical assignment of lactone **7** was based primarily on the work of Bock et al.[18a] where **7** was synthesized from D-lyxono-1,4-lactone via a similar sequence of reactions. The stereochemistry at C-3 and C-4 of D-xylono-1,4-lactone (**4**) being respectively identical to that at C-3 and C-4 of D-lyxono-1,4-lactone, the above stereochemical assignment of lactone **7** is unequivocal. This assignment is further substantiated by a comparison of the optical rotation value of the L-chlorosugar **1** synthesized from lactone **7** (Scheme 1) with its literature value (see Experimental Section). Such stereospecific D−L interconversions of aldonolactones activated at the primary position (C-5) via the base-induced rearrangement are well documented in the literature,[20] and they provide an easy access to the synthesis of a variety of L-sugars from the D-sugar precursors. After acidification the reaction mixture was filtered, and the filtrate was concentrated at 50 ± 5 °C to a syrup. The residual water in the syrup was removed by coevaporation with 1,2-dimethoxyethane (DME), which was the solvent of choice for the subsequent reaction.

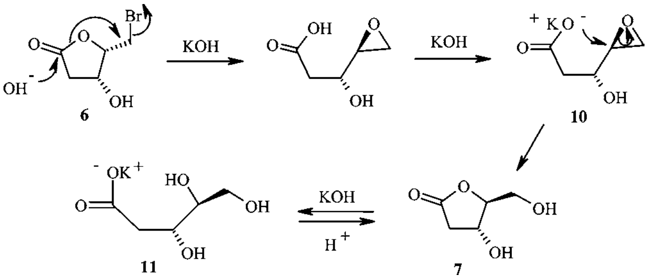


Figure 2.

The preparation of the di-*O*-*p*-toluate **8** (Scheme 1) from crude **7** was best accomplished by using 1.8 equiv of *p*-toluoyl chloride and 5 equivof pyridine in DME. The crude product of this reaction was recrystallized from *tert*-butyl methyl ether to get pure **8** as a white crystalline material. This step was the second isolation step of the current process. The yield of **8** from intermediate **5** was 37−40% for the three steps. The major by-product in this reaction was *p*-toluic anhydride. Its formation was kept minimal when the above ratio of *p*-toluoyl chloride was employed for the reaction.

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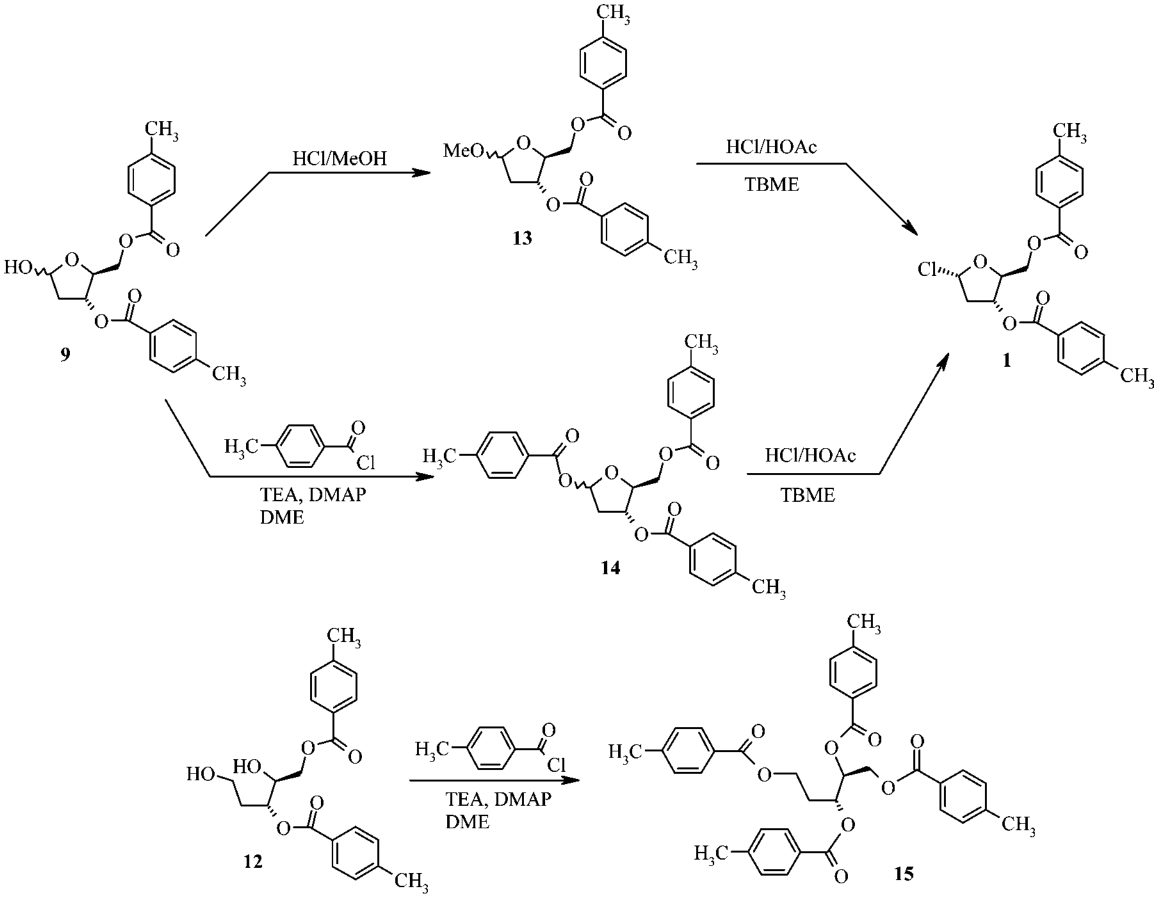
Scheme 2



Among other bases, we examined triethylamine instead of pyridine but noticed significant loss of product possibly via elimination of triethylammonium *p*-toluate involving the C-2 hydrogen atom of the protected lactone **8**.

Selective Reduction of Lactone 8 to Lactol 9 and Formation of L-Chlorosugar 1. Recently, we developed an efficient method[21] for the selective reduction of 2,3,5-tri-*O*-benzoyl-2-C-methyl-D-ribonic-γ-lactone to 2,3,5-tri-*O*-benzoyl-2-C-methyl-D-ribofuranose. The reducing agent for this reduction was generated from the reaction of sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) with an equal molar amount of C_2H_5OH in toluene. When applied to the lactone **8** in the present study, this reducing system gave a poor yield of the desired lactol, 2-deoxy-3,5-di-*O*-*p*-toluoyl-L-ribofuranose (**9**). The major product of this reaction was found to be D-*threo*-1,2,3,5-pentanetetrol 1,3-di-*p*-toluate (**12**) (Scheme 2) due to further reduction of the intermediate lactol **9**. The identity of this compound **12** was confirmed by treating the mixture with *p*-toluoyl chloride in the presence of triethylamine and 4-(dimethylamino)pyridine in anhydrous DME and isolating D-*threo*-1,2,3,5-pentanetetrol tetra-*p*-toluate (**15**) (Scheme 2). The selective reduction of the protected lactone **8** to the lactol **9** therefore required a thorough investigation to minimize the formation of the by-product **12**. In addition to the observed over-reduction, the cleavage of the labile *p*-toluoyl ester groups in the lactone **8** also led to a number of undesired by-products, thus complicating the reduction process. We needed to develop a selective and robust protocol to minimize the by-product formation so that the process could be scaled up easily. A variety of reducing agents,[22] solvents, and conditions such as Red-Al:2-propanol/toluene, Red-Al:*tert*-butyl alcohol/toluene, lithium tri-*tert*-butoxyaluminohydride/toluene, lithium tri-*tert*-butoxyaluminohydride/THF, diisobutylaluminum hydride (DIBALH)/toluene, DIBALH/THF, DIBALH/dichloromethane, DIBALH/1,2-dichloroethane, DIBALH/isopropyl ether, DIBALH/DME, DIBALH/1,2-diethoxyethane, DIBALH/diglyme, lithium borohydride/THF, sodium borohydride/THF, disiamylborane/THF, disiamylborane/DME, L-selectride/DME and borane−methyl sulfide complex/THF were screened for this conversion. These experiments were carried out at temperatures ranging from −78 °C up to +25 °C, employing varied equivalents of the reducing agents. Of these, the systems using DIBALH in either DME, THF, or diglyme appeared promising. When optimized further, it was found that the reduction of lactone **8** with 1.32 mol equiv of DIBALH in DME at -60 ± 5 °C provided the highest yield (>85% yield by HPLC, AUC @ 254 nm) of the lactol **9**

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[21] Storer, R.; Moussa, A.; Chaudhuri, N.; Waligora, F. PCT/U.S. Patent 2003/039643, WO 2004/052899.

[22] For reduction of lactones to lactols, see: (a) Kanazawa, R.; Tokoroyama, T. *Synthesis* **1976**, 526. (b) Kohn, P.; Samaritano, R. H.; Lerner, L. M. *J. Am. Chem. Soc.* **1965**, *87*, 5475. (c) Okabe, M.; Sun, R.-C.; Tam, S. Y.-K.; Todaro, L. J.; Coffen, D. L. *J. Org. Chem.* **1988**, *53*, 4780. (d) RajanBabu, T. V.; Nugent, W. A.; Taber, D. F.; Fagan, P. J. *J. Am. Chem. Soc.* **1988**, *110*, 7128. (e) Wolf, J.; Jarrige, J.-M.; Florent, J.-C.; Grierson, D. S.; Monneret, C. *Synthesis* **1992**, 773. (f) Zhang, Q.; Liu, H.-W. *J. Am. Chem. Soc.* **2000**, *122*, 9065.

with minimal impurity formation. The crude lactol **9** was processed via an extractive work-up and utilized without further purification.

In the final step the crude lactol **9** was treated with anhydrous HCl gas in glacial acetic acid/*tert*-butyl methyl ether at 0 °C to produce the target molecule 2-deoxy-3,5-di-*O*-*p*-toluoyl-α-L-ribofuranosyl chloride (**1**) (Scheme 1). The product crystallized out of the mixture and was collected easily by vacuum filtration. This constituted the third and the final step of isolation of goods in the current process. The yields of **1** were typically over 65% for the two steps from the protected lactone **8** and were reproducible with minimal batch-to-batch variations. To our knowledge this is the first example of the direct conversion of 2-deoxy-3,5-di-*O*-*p*-toluoyl-L-ribofuranose (**9**) to 2-deoxy-3,5-di-*O*-*p*-toluoyl-α-L-ribofuranosyl chloride (**1**). Other methods involve the intermediate formation of the methyl glycoside **13**,[11,12] or the tri-*O*-*p*-toluate **14**.[13] For the comparison of yields, we prepared the methyl glycoside **13** and the tri-*O*-*p*-toluate **14** from the protected ribose **9** and converted them to the L-chlorosugar **1** as shown in Scheme 2. Yields via these two sequences were lower than that of the direct conversion as developed in the present study. The direct conversion route thus provides a novel process for the L-chlorosugar **1** from D-xylose (**3**) in approximately 11% overall yield.

Conclusions

In summary, we have developed the chemistry of a new process for the preparation of 2-deoxy-3,5-di-*O*-*p*-toluoyl-α-L-ribofuranosyl chloride (**1**) which is a versatile intermediate in the synthesis of many unnatural 2′-deoxy-L-ribonucleosides. With an overall yield of 11%, there are only three isolation steps in the entire process. In a very critical step, the process involves an efficient and stereospecific conversion of 5-bromo-2,5-dideoxy-D-*threo*-pentono-1,4-lactone (**6**) to 2-deoxy-L-ribono-1,4-lactone (**7**). We have also developed the highly selective DIBALH-reduction of the protected lactone **8** to lactol **9** in good yield. This DIBALH-reduction of the current process may be conveniently carried out in cryogenic reactors for production batches. The process also involves the novel conversion of the lactol derivative **9** directly to the chlorosugar **1**, thus eliminating the need for going through the glycosidic intermediates **13** or **14**. Chromatographic purifications are completely avoided in any stages of the process. The present route thus offers a promising and potentially scalable process for the large-scale synthesis of L-chlorosugar **1**.

Experimental Section

General. All raw materials including solvents for HPLC were obtained from commercial sources. Moisture-sensitive reactions were carried out in an argon atmosphere. Melting points were measured on a Barnstead/Thermolyne Electrothermal Mel-Temp apparatus. NMR spectra were recorded on a Varian 400 MHz spectrometer in appropriate deuteriosolvents. Waters 2695 HPLC and 996 PDA detector were used to analyze all in-process samples and finished products that were UV-active. The HPLC data were acquired using Idenix Method 004. The data were reported in area % and were not adjusted to weight %. Thin layer chromatography (TLC) was performed on Baker Si-250-F precoated silica gel plates, and the eluted plates were viewed under UV at 254 nm or stained in appropriate TLC dips as the case might be.

HPLC conditions: column: Waters Nova-Pak C18 RP, 4 μm, 3.9 mm × 150 mm; flow rate: 1.0 mL/min; mobile phase for Idenix Method 004: gradient 40−95% acetonitrile, 60−5% water over 13 min followed by isocratic 95% acetonitrile, 5% water over 7 min and gradient 95−40% acetonitrile, 5−60% water over the next 10 min; column temperature: ambient; detection: UV 254 and 272 nm.

D-Xylono-1,4-lactone (4). A 1-L three-necked round-bottomed flask was equipped with an overhead stirrer attached to a glass stirring shaft and a Teflon blade, a digital thermometer connected to a temperature probe, a graduated addition funnel and an argon line. D-Xylose (**3**) (100 g, 0.67 mol) and deionized water (270 mL) were charged into the reaction flask, and the contents were stirred to obtain a clear solution. It was cooled to about 5 °C using an ice-bath. Potassium carbonate (113.2 g, 0.82 mol) was added to the reaction flask in portions, maintaining the temperature below 20 °C, and it was stirred for additional 30 min. When the internal temperature dropped below 5 °C, bromine (123.0 g, 0.77 mol) was added dropwise at 0−5 °C over a period of 2 h. The reaction mixture was maintained at 5−10 °C for a further 30 min and then stirred at room temperature overnight. It was quenched by dropwise addition of formic acid (8.0 g, 0.174 mol) over a period of 10 min. The mixture was stirred at room temperature for a further 40 min. In this process the bromine color was discharged, and the mixture reached a pH of approximately 3. The contents were transferred to a 1-L single-necked round-bottomed flask and concentrated under reduced pressure at 45−50 °C to a volume of approximately 50 mL. For NMR analysis an aliquot was taken to dryness at 45−50 °C under reduced pressure, and the residue was extracted with hot acetone. The acetone extract was evaporated to dryness and further dried under high vacuum to afford a sample of D-xylono-1,4-lactone (**4**); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 6.16−5.9 (1H, br s, exchangeable with D_2O, O*H*), 5.84−5.6 (1H, br s, exchangeable with D_2O, O*H*), 5.1−4.66 (1H, br s, exchangeable with D_2O, O*H*), 4.44−4.36 (1H, m, H-2), 4.28−4.14 (2H, m, H-3 and H-4), 3.72−3.56 (2H, d of an AB q, $\Delta\upsilon = 21.5$ Hz, *J* 12.2, 4.0, and 3.0 Hz, 2 × H-5; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 175.7, 80.0, 73.2, 72.3, 58.5. Glacial acetic acid (200 mL) was added to the main portion of the crude product and the mixture was concentrated again at 45−50 °C under reduced pressure to a volume of approximately 60 mL. This solution of the crude D-xylono-1,4-lactone (**4**) in acetic acid was used in the subsequent step without further purification.

2,5-Dibromo-2,5-dideoxy-D-lyxono-1,4-lactone (5). The solution of the crude D-xylono-1,4-lactone (**4**) (0.67 mol for 100% conversion) in acetic acid was transferred into a 3-L three-necked round-bottomed flask whilst warm using additional acetic acid (200 mL). To this was added 30% HBr/

HOAc (896.3 g, 3.32 mol) at room temperature. The reaction mixture was stirred at 45 °C for 1 h and then at room temperature for 2 h. After this time TLC analysis (1:1, ethyl acetate:hexanes; visualized using $KMnO_4$) indicated two major products: 2,5-dibromo-2,5-dideoxy-D-lyxono-1,4-lactone (**5**), R_f 0.5; and 3-*O*-acetyl derivative of **5**, R_f 0.63. The reaction mixture was cooled to 0 °C using an ice bath, and methanol (850 mL) was added slowly over a period of 1 h, whilst maintaining the temperature below 10 °C. It was then stirred at room temperature overnight. After this time TLC analysis (1:1 ethyl acetate/hexanes) indicated conversion of one product (R_f 0.63) to the other product (R_f 0.5). The mixture was filtered through a Büchner funnel to remove the KBr salt. It was then concentrated in vacuo and coevaporated with water (2 × 250 mL). Ethyl acetate (800 mL) and water (250 mL) were added, and the layers were separated. The aqueous layer was further extracted with ethyl acetate (2 × 300 mL), and the combined organic extracts were washed with aqueous saturated sodium hydrogen carbonate solution (400 mL) followed by water (100 mL). The EtOAc layer was dried with anhydrous sodium sulfate (125 g), filtered, and concentrated in vacuo at 50 °C. Before taking to complete dryness, *n*-heptane (200 mL) was added to the thick oil and it was evaporated in vacuo at 50 °C to give a brown semisolid. A solution of 100 mL of *n*-heptane in 400 mL of isopropyl ether was added to it, and the mixture was stirred at room temperature for 4 h. Filtration of the slurry and vacuum-drying of the cake at 30−35 °C overnight yielded pure 2,5-dibromo-2,5-dideoxy-D-lyxono-1,4-lactone (**5**) as a light brown solid (71.9 g, yield 40% over 2 steps); mp 90−93°C; lit.[18b] mp 92−93°C; ^1H NMR (DMSO-d_6, 400 MHz) δ 6.37 (1H, d, *J* 6.1 Hz, exchangeable with D_2O, 3-O*H*), 5.32 (1H, d, *J* 4.6 Hz, H-2), 4.77−4.7 (1H, m, H-4), 4.43−4.37 (1H, m, H-3), 3.76−3.6 (2H, d of an AB q, $\Delta\upsilon = 36.6$ Hz, *J* 10.5, 8.1, and 5.6 Hz, 2 × H-5); ^1H NMR ($CDCl_3$, 400 MHz) δ 4.8 (1H, d, *J* 4.4 Hz, H-2), 4.73−4.66 (1H, m, H-4), 4.66−4.61 (1H, m, H-3), 3.77−3.63 (2H, m, 2 × H-5), 2.66−2.61 (1H, br s, 3-O*H*); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 171.3, 81.6, 69.2, 48.9, 29.2; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.7, 80.5, 69.0, 48.4, 26.1.

5-Bromo-2,5-dideoxy-D-*threo*-pentono-1,4-lactone (6): Sodium iodide method. 2,5-Dibromo-2,5-dideoxy-D-lyxono-1,4-lactone (**5**) (35 g, 127.8 mmol) was dissolved in isopropyl acetate (300 mL). Sodium iodide (76.6 g, 511.0 mmol) and trifluoroacetic acid (22.0 g, 192.9 mmol) were added to it at room temperature. With stirring the reaction mixture was heated at 85 °C (internal temperature) for 2 h. After this time TLC analysis (1:1, ethyl acetate:hexanes) indicated very little remaining starting material (R_f 0.5) and a new product (R_f 0.2) being formed. The reaction mixture was cooled to room temperature and stirred for 4 h. TLC analysis indicated no starting material therefore, the reaction mixture was concentrated in *vacuo* to approximately 20 mL to remove the trifluoroacetic acid. The residue was diluted with fresh isopropyl acetate (200 mL), washed with saturated aqueous sodium hydrogen carbonate solution (200 mL) and the layers were separated. The aqueous layer was further extracted with isopropyl acetate (3 × 200 mL). The combined organic extracts were treated with aqueous sodium thiosulfate solution (48 g of sodium thiosulfate in 160 mL of water). The aqueous layer was back-extracted with isopropyl acetate (2 × 200 mL), and the combined organic extracts were dried with sodium sulfate (20 g). It was filtered, and the filtrate was concentrated in vacuo to yield 5-bromo-2,5-dideoxy-D-*threo*-pentono-1,4-lactone (**6**) (16.38 g, crude) as a brown thick oil. **6** was found by NMR to contain a trace amount of the corresponding 5-iodo compound **6a**; ^1H NMR (D_2O, 400 MHz) δ 4.91−4.84 (1H, m, H-4), 4.76−4.71 (1H, m, H-3), 3.7 (2H, d, *J* 6.9 Hz, 2 × H-5), 3.54−3.4 (not integrated, m, H-5 for the iodide **6a**), 3.1 (1H, dd, *J* 18.1 and 5.6 Hz, H-2), 2.63 (1H, d, *J* 18.3 Hz, H-2); ^1H NMR (DMSO-d_6, 400 MHz) δ 5.67 (1H, d, *J* 4.8 Hz, exchangeable with D_2O, 3-O*H*), 4.7−4.62 (1H, m, H-4), 4.46−4.0 (1H, m, H-3), 3.78−3.6 (1H, d of an AB q, $\Delta\upsilon = 43.4$ Hz, *J* 10.7, 10.2, 7.8, and 5.3 Hz, 2 × H-5), 3.4−3.28 (0.1H, m, clearly seen in the D_2O-exchanged spectrum, H-5 for the iodide **6a**), 2.97 (1H, dd, *J* 17.1 Hz, *J* 6.3 Hz, H-2), 2.36 (1H, d, *J* 17.5 Hz, H-2); ^{13}C NMR (D_2O, 100 MHz) δ 179.4, 85.1, 68.4, 39.5, 27.7; TOFMS-ES$^-$ *m/z* 253 (M + AcOH); elemental analysis of a purified sample: $C_5H_7BrO_3$ requires C 30.80, H 3.62, Br 40.97; found C 30.69, H 3.55, Br 41.22.

5-Bromo-2,5-dideoxy-D-*threo*-pentono-1,4-lactone (6): Hydrogenation method.[18a] 2,5-Dibromo-2,5-dideoxy-D-lyxono-1,4-lactone (**5**) (7.5 g, 27.4 mmol) was dissolved in ethyl acetate (120 mL). Triethylamine (2.9 g, 28.7 mmol) and 5% dry palladium on carbon (1 g) were added with stirring under a blanket of argon. The argon was replaced with hydrogen via a vacuum-fill technique using a hydrogen balloon and a three-way vacuum adapter. The mixture was then stirred at room temperature under the atmosphere of hydrogen for 1.5 h. After this time TLC analysis (1:1 ethyl acetate/hexanes) indicated a new product (R_f 0.2) and residual starting material (R_f 0.5). Therefore, the reaction mixture was purged with additional hydrogen (three more times using a freshly filled balloon) and then stirred under hydrogen for a further 2 h. After this time TLC analysis indicated only a trace amount of residual starting material. Therefore, the reaction mixture was filtered through a Celite pad using ethyl acetate as the eluent (30 mL). The filtrate was washed with 4 M HCl (30 mL), and the aqueous layer was further extracted with ethyl acetate (2 × 20 mL). The combined organic extracts were dried with sodium sulfate (10 g), filtered, and concentrated in vacuo to a pale-yellow oil which was dried further in vacuo at 25 °C overnight to yield 5-bromo-2,5-dideoxy-D-*threo*-pentono-1,4-lactone (**6**): 5.15 g; crude yield 96%; ^1H NMR (D_2O, 400 MHz) δ 4.91−4.85 (1H, m, H-4), 4.77−4.72 (1H, m, H-3), 3.72 (2H, d, *J* 6.7 Hz, 2 × H-5), 3.12 (1H, dd, *J* 18.3 and 5.8 Hz, H-2), 2.65 (1H, d, *J* 18.3 Hz, H-2); ^1H NMR (DMSO-d_6, 400 MHz) δ 5.68−5.54 (1H, br, 3-O*H*), 4.68−4.6 (1H, m, H-4), 4.43−4.36 (1H, m, H-3), 3.76−3.56 (1H, d of an AB q, $\Delta\upsilon = 46.4$ Hz, *J* 10.7, 10.2, 8.3, 7.8, and 5.3 Hz, 2 × H-5), 2.94 (1H, dd, *J* 17.1 and 5.4 Hz, H-2), 2.33 (1H, d, *J* 17.1 Hz, H-2); ^{13}C NMR (D_2O, 100 MHz) δ 179.4, 85.1, 68.4, 39.5, 27.7; ^{13}C NMR (DMSO-d_6, 100 MHz) δ 175.3, 83.2, 67.1, 39.5, 29.6.

2-Deoxy-L-ribono-1,4-lactone (7). Potassium hydroxide (85%, 14.9 g, 225.7 mmol) was dissolved in water (125 mL) at 15 °C. This was added to a stirred solution of the crude 5-bromo-2,5-dideoxy-D-*threo*-pentono-1,4-lactone (**6**) (15 g, 76.9 mmol) in water (60 mL) at room temperature. After 3 h TLC analysis (2% methanol in ethyl acetate) indicated complete consumption of the starting material (R_f 0.65). The reaction mixture was then heated at 80 °C (internal temperature) for 30 min and cooled to room temperature. The pH of the reaction mixture was found to be approximately 14. Amberlite IR-120 (plus) ion-exchange acidic resin (50 g) was added and the mixture stirred at room temperature for 30 min. At this point the pH was measured to be 3. Additional resin (40 g) was charged, and the mixture was stirred at room temperature for a further 30 min. At this point the mixture registered a pH of 1. It was stirred at room temperature overnight and checked by TLC that indicated formation of a new product (R_f 0.25). The resin was then removed by filtration through a sintered glass funnel and washed with water (200 mL); the filtrate was concentrated in vacuo at 50 ± 5 °C. Before taking to complete dryness, coevaporation with 1,2-dimethoxyethane (2 × 100 mL) was performed. The residue was combined with fresh 1,2-dimethoxyethane (200 mL) and anhydrous $MgSO_4$ (10 g). The mixture was stirred at room temperature for 40 min and filtered, and the cake was washed with additional 1,2-dimethoxyethane (75 mL). A small aliquot of the filtrate was evaporated at 45 ± 5 °C under reduced pressure and dried further in the high vacuum. Thus, a sample of crude 2-deoxy-L-ribono-1,4-lactone (**7**) was obtained for NMR analysis; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 5.0−4.7 (2H, br, 2 × O*H*), 4.26 (2H, m, H-3 and H-4), 3.54 (1H, dd, *J* 12.2 and 4.2 Hz, H-5), 3.50 (1H, dd, *J* 12.2 and 3.9 Hz, H-5), 2.80 (1H, dd, *J* 18.1 and 6.3 Hz, H-2), 2.22 (1H, dd, *J* 17.6 and 2.0 Hz, H-2). The remainder of the filtrate was concentrated by rotary evaporation at 50 ± 5 °C down to approximately 100 mL and was used in the subsequent reaction without further purification.

2-Deoxy-3,5-di-*O*-*p*-toluoyl-L-ribono-1,4-lactone (8). Pyridine (30.4 g, 384.5 mmol) was added to the above solution of 2-deoxy-L-ribono-1,4-lactone (**7**) (estimated 76.9 mmol) in 1,2-DME, and the mixture was cooled between 0 and −5 °C under argon. *p*-Toluoyl chloride (21.4 g, 138.4 mmol) was added from an addition funnel over 20 min, maintaining the internal temperature between 0 and −5 °C. After stirring at 0 to −5 °C for 3.5 h, TLC analysis (2% methanol in EtOAc) indicated the formation of two new products (R_f 0.76 and 0.65). No remaining starting material (R_f 0.3) was detected. HPLC analysis also indicated that the reaction had reached completion. The reaction mixture, whilst cold (approximately 5 °C), was quenched with a solution of sodium hydrogen carbonate (25 g of $NaHCO_3$ dissolved in 300 mL of water). A brown oil separated from the mixture, and it gradually solidified upon stirring. After 2 h of stirring at room temperature the solid was collected by vacuum filtration, washed with water (150 mL), and dried in air overnight. This crude lactone (25.84 g) was dissolved in dichloromethane (150 mL), dried with $MgSO_4$ (10 g) for 1 h, and filtered. The filter cake was washed with fresh dichloromethane (50 mL), and the filtrate was concentrated at 40 °C to a volume of approximately 50 mL. *tert*-Butyl methyl ether (TBME) (100 mL) was added, and the mixture was concentrated again at 40 °C to approximately 50 mL. This concentrated solution was then stirred at room temperature to form a slurry. More TBME (50 mL) was added, and stirring was continued at room temperature for an additional 2 h. The solid was collected by vacuum filtration, washed with TBME (50 mL), and dried under vacuum at 30−35 °C overnight to yield 2-deoxy-3,5-di-*O*-*p*-toluoyl-L-ribono-1,4-lactone (**8**) (10.46 g) as a pale-brown solid; molar yield 37% over three steps from **5**; mp 115−118 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.94−7.85 (4H, 2 × d, *J* 8.4 Hz, 2 × ArH_2, ortho to -CO-); 7.3−7.23 (4H, m, 2 × ArH_2, meta to -CO-), 5.6 (1H, d, *J* 7.68 Hz, H-3), 4.99−4.93 (1H, m, H-4), 4.75−4.58 (2H, d of an AB q, $\Delta\upsilon = 39.7$ Hz, *J* 12.2, 3.7, 12.5 and 3.3 Hz, 2 × H-5), 3.17 (1H, dd, *J* 18.7 and 7.3 Hz, H-2), 2.83 (1H, dd, *J* 18.7 Hz and 1.8 Hz, H-2), 2.43 and 2.42 (6H, 2 × s, 2 × Ar-CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.2, 166.1, 166.0, 145.0, 144.6, 130.0, 129.8, 129.5, 129.5, 126.4, 126.0, 82.8, 71.8, 63.9, 35.2, 21.9.

2-Deoxy-3,5-di-*O*-*p*-toluoyl-L-ribofuranose (9). A solution of 2-deoxy-3,5-di-*O*-*p*-toluoyl-L-ribono-1,4-lactone (**8**) (9.0 g, 24.42 mmol) in 1,2-dimethoxyethane (90 mL) was cooled to approximately −60 °C under argon with overhead stirring. A 1 M solution of diisobutylaluminum hydride in hexanes (32.4 mL, 32.4 mmol) was added dropwise via an addition funnel over a period of 15 min. The internal temperature was maintained at −60 ± 5 °C for 1 h, and HPLC analysis after this period indicated completion of the reaction. The cold reaction mixture was quenched by addition of acetone (10 mL) over 2 min followed by 5 N HCl (30 mL) over 5 min. The mixture was stirred at room temperature for an additional 30 min and concentrated in vacuo at 35 °C. The residual oil was combined with a solution of NaCl (24 g) in water (60 mL) and extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were dried with anhydrous sodium sulfate (10 g, 30 min), concentrated to a volume of 40 mL, and coevaporated with TBME (2 × 125 mL) to yield 2-deoxy-3,5-di-*O*-*p*-toluoyl-L-ribofuranose (**9**) as a solution in TBME. The second coevaporation above was stopped when the volume in the distilling flask was approximately 40 mL. This product was used crude in the next step. An aliquot of this solution was concentrated in vacuo to dryness for NMR analysis; ^{1}H NMR ($CDCl_3$, 400 MHz, mixture of α- and β-anomers) δ 7.98−7.88 (4H, m, 2 × ArH_2, ortho to -CO- for α- and β-anomers), 7.28−7.18 (4H, m, 2 × ArH_2, meta to -CO- for α- and β-anomers), 5.78−5.44 (2H, 3 × m, 1 × d, H-1 and H-3 for α- and β-anomers), 4.74−4.44 (3H, m, H-4 and 2 × H-5 for α- and β-anomers), 2.58−2.23 (8H, m, 2 × H-2 and 2 × Ar-CH_3 for α- and β-anomers).

2-Deoxy-3,5-di-*O*-*p*-toluoyl-α-L-ribofuranosyl Chloride (1): Directly from Lactol 9. A solution of 2-deoxy-3,5-di-*O*-*p*-toluoyl-L-ribofuranose (**9**) (24.4 mmol approximately) in TBME (40 mL approximately) as obtained in the previous step was further diluted with additional TBME (15 mL) and stirred for 20 min at room temperature. Some white precipitates appeared. Glacial acetic acid (5 mL) was added with stirring until a clear solution was obtained. This solution was cooled to 0 °C under argon, and anhydrous HCl gas (total 20.4 g, 559.5 mmol, measured by difference of weights of the HCl tank) was passed into it in a steady stream for 25 min. A white solid crystallized out of the solution. After an additional 10 min of stirring at 0−5 °C an aliquot (0.2 mL) was quenched with anhydrous ethanol (1.2 mL), and it was allowed to sit at room temperature with occasional shaking for 10 min until a clear solution was obtained. HPLC analysis of this sample detected <1% of unreacted lactol **9**. The reaction mixture was maintained at 0−5 °C for an additional 30 min while being stirred. It was then filtered, and the solid cake was washed with TBME (50 mL). The product was dried in a vacuum over KOH for 5 h at room temperature to yield 2-deoxy-3,5-di-*O*-*p*-toluoyl-α-L-ribofuranosyl chloride (**1**) as an off-white crystalline solid; yield 6.24 g, 65% over two steps from the lactone **8**; mp 114−116 °C (lit.[12] mp 118−121 °C); $[\alpha]_D^{25} = -117°$ ($c = 1.0$, $CHCl_3$) [lit.[23] $[\alpha]_D^{25} = -125.7°$ ($c = 0.811$, DMF)]; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.99 (2H, d, *J* 8.4 Hz, ArH_2, ortho to -CO-), 7.9 (2H, d, *J* 8.0 Hz, ArH_2, ortho to -CO-), 7.3−7.2 (4H, m, 2 × ArH_2, meta to -CO-), 6.48 (1H, d, *J* 5.1 Hz, H-1), 5.56 (1H, dd, *J* 7.3 and 2.6 Hz, H-3), 4.85−4.83 (1H, m, H-4), 4.72−4.56 (2H, d of an AB q, $\Delta\upsilon = 36.1$ Hz, *J* 12.1, 4.4 and 3.3 Hz, 2 × H-5), 2.92−2.82 (1H, ddd, *J* 15.2, 7.5, and 5.3 Hz, H-2), 2.75 (1H, pseudo d, *J* 15.0 Hz, H-2), 2.42 (3H, s, Ar-CH_3), 2.41 (3H, s, Ar-CH_3).

2-Deoxy-3,5-di-*O*-*p*-toluoyl-α-L-ribofuranosyl Chloride (1): via the Methyl Glycoside 13. A solution of 1% HCl in methanol was prepared by the reaction of acetyl chloride (215 mg, 2.738 mmol) with a measured excess of anhydrous methanol (10 mL) at 5 °C and stirring the mixture at 5 °C to room temperature for 40 min. In a separate round-bottomed flask, 2-deoxy-3,5-di-*O*-*p*-toluoyl-L-ribofuranose (**9**) (470 mg, 1.27 mmol) was dissolved in anhydrous methanol (9 mL) and cooled to 10 °C. To this, was added 1% HCl in methanol (1 mL, 0.274 mmol)) as prepared above, and the reaction mixture was stirred under argon at 10−15 °C for 1.5 h. After this time HPLC analysis detected 18.4% of unreacted ribofuranose **9**. Therefore, another portion of 1% HCl in methanol (1 mL, 0.274 mmol) was added, and stirring continued at room temperature for a further 1.5 h. HPLC analysis after this time indicated that the reaction was close to completion. The reaction mixture was then concentrated in vacuo at 30 °C, and any methanol left in it was coevaporated with TBME (10 mL) at 30 °C. The residue was taken up in fresh TBME (10 mL), and since some suspended white solids were observed, ethyl acetate (15 mL) was added to dissolve the suspension. This solution was dried with anhydrous sodium sulfate (2 g) and filtered. The filtrate was concentrated in vacuo at 30 °C and further dried in high vacuum at room temperature for 2 h to yield a thick oil of methyl 2-deoxy-3,5-di-*O*-*p*-toluoyl-L-ribofuranoside (**13**). The product **13** was found to be a 1:1 mixture of α- and *β*-anomers by HPLC; yield 480 mg, 98% based on the crude. An analytical sample of **13** was obtained by flash chromatography on silica gel using 15% EtOAc/*n*-heptane (v/v) as the eluent; ^1H NMR ($CDCl_3$, 400 MHz, approximately 1:1 mixture of α- and *β*-anomers) δ 8.0−7.88 (4H, m, 2 × ArH_2, ortho to -CO-), 7.28−7.18 (4H, m, 2 × ArH_2, meta to -CO-), 5.64−5.56 (0.5H, m, H-3 for one anomer), 5.44−5.38 (0.5H, m, H-3 for the other anomer), 5.23 (0.5H, dd, *J* 5.4 and 2.0 Hz, H-1 for one anomer), 5.19 (0.5H, d, *J* 5.4 Hz, H-1 for the other anomer), 4.68−4.36 (3H, m, H-4 and 2 × H-5 for α- and *β*-anomers), 3.42 (1.5H, s, OCH_3 for one anomer), 3.36 (1.5H, s, OCH_3 for the other anomer), 2.6−2.16 (8H, m containing CH_3 singlets, 2 × H-2 and 2 × Ar-CH_3 for α- and *β*-anomers); ^{13}C NMR ($CDCl_3$, 100 MHz, mixture of α- and *β*-anomers) δ 166.7, 166.6, 166.5, 166.3, 144.2, 144.1, 144.0, 143.8, 130.0, 130.0, 129.9, 129.3, 129.3, 127.4, 127.3, 127.2, 127.1, 105.8, 105.2, 82.1, 81.1, 75.6, 74.8, 65.3, 64.5, 55.4, 55.2, 39.5, 21.8.

The above-obtained methyl 2-deoxy-3,5-di-*O*-*p*-toluoyl-L-ribofuranoside (**13**) (1:1 mixture of α- and *β*−anomers, 480 mg, 1.25 mmol) was dissolved in TBME (3 mL) and glacial acetic acid (1 mL). This solution was cooled to 0 °C under argon. Anhydrous HCl gas was bubbled into this solution for 15 min, and the reaction mixture was stirred at 0−5 °C for an additional 10 min. HPLC detected about 6% remaining starting material. This number decreased marginally after the reaction had continued for an additional 45 min. The white solid that crystallized out of the reaction mixture was collected by vacuum filtration, washed with TBME (5 mL) and dried under high vacuum at room temperature for 4 h to get 2-deoxy-3,5-di-*O*-*p*-toluoyl-α-L-ribofuranosyl chloride (**1**): mp 113−115 °C; yield 228 mg, 47% over three steps from the lactone **8**; its ^1H NMR in $CDCl_3$ was identical to that of the chlorosugar **1** obtained directly from the lactol **9** above.

2-Deoxy-3,5-di-*O*-*p*-toluoyl-α-L-ribofuranosyl Chloride (1): via the Tri-*O*-*p*-toluate 14. For this reaction a batch of crude 2-deoxy-3,5-di-*O*-*p*-toluoyl-L-ribofuranose (**9**) (550 mg, 1.484 mmol) was prepared via the reduction of the protected lactone **8** with 2.0 mol equiv of Red-Al:C_2H_5OH reagent. To a solution of this crude 2-deoxy-3,5-di-*O*-*p*-toluoyl-L-ribofuranose (**9**) (550 mg, 1.484 mmol) in anhydrous DME (15 mL) were added triethylamine (728 mg, 7.194 mmol) and 4-(dimethylamino)pyridine (18 mg, 0.147 mmol). It was cooled to 0 °C under argon, and *p*-toluoyl chloride (445 mg, 2.878 mmol) dissolved in DME (2 mL) was added over a period of 10 min. The mixture was stirred at 0−20 °C for 2 h and heated at 45 °C for 4 h. When the reaction was complete, the mixture was cooled to 5 °C and quenched with aqueous $NaHCO_3$ (1.25 g dissolved in 20 mL of water). The crude product was isolated via extractive work-up using ethyl acetate. This product was found to contain three main compounds in the ratio of 5:2:15 as determined by HPLC area %; one of these compounds originated from an over-reduced by-product **12** generated in the previous step. Flash chromatography of this mixture on silica gel using 15% ethyl acetate/hexanes as the eluent afforded a thick oil (480 mg), which was found to be still a

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[23] Fujimori, S.; Iwanami, N.; Hashimoto, Y.; Shudo, K. *Nucleosides Nucleotides* **1992**, *11*, 341.

mixture of the same three compounds in the same ratio. Mass spectral data of this mixture confirmed these compounds as 2-deoxy-L-ribofuranose 1,3,5-tri-*p*-toluate (**14**, α- and *β*-anomers) and D-*threo*-1,2,3,5-pentanetetrol tetra-*p*-toluate (**15**); TOFMS-ES$^+$ *m*/*z* 506.4 (M + NH_4^+ for **14**), 507.4 (M + NH_4^+ + 1 for **14**), 626.3 (M + NH_4^+ for **15**), 627.3 (M + NH_4^+ + 1 for **15**) and 628.3 (M + NH_4^+ + 2 for **15**).

To a solution of the above compounds (480 mg, **14** and **15**) in glacial acetic acid/TBME (4 mL, 1:1, v/v) at 5−10 °C was bubbled an excess of anhydrous HCl gas. After 1 h at 5−10 °C a white solid crystallized out. The reaction was continued for additional 2 h at 10−15 °C under argon. The white solid was collected by vacuum filtration, washed with TBME (5 mL), and dried in high vacuum at room-temperature overnight to obtain pure 2-deoxy-3,5-di-*O*-*p*-toluoyl-α-L-ribofuranosyl chloride (**1**); mp 116−117 °C; mmp 114−116 °C; yield 40 mg, 7.2% over three steps from the protected lactone **8**; its ^{1}H NMR in $CDCl_3$ was identical to that of the chlorosugar **1** obtained directly from the lactol **9** (described before); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ* 166.6, 166.2, 144.5, 144.2, 130.1, 129.8, 129.4, 129.4, 126.9, 126.8, 95.5, 84.9, 73.7, 63.6, 44.7, 21.9, 21.8.

Recovery of D-*threo*-1,2,3,5-Pentanetetrol Tetra-*p*-toluate (15). The filtrate from the above step was concentrated at 30 °C by rotary evaporation under reduced pressure, and the residue was treated with a solution of $NaHCO_3$ (2.0 g) in water (20 mL) until effervescence of CO_2 ceased. The mixture was then extracted with EtOAc (2 × 25 mL). The EtOAc layer was washed with water (20 mL) and brine (20 mL), dried over anhydrous Na_2SO_4 (5 g), filtered, and evaporated to dryness. The residue was further dried under high vacuum at 20 °C overnight to obtain 320 mg (0.52 mmol, 54% recovery) of D-*threo*-1,2,3,5-pentanetetrol tetra-*p*-toluate (**15**). This compound **15** was found to be 97% pure by HPLC, t_R 14.5 min; ^{1}H NMR ($CDCl_3$, 400 MHz) *δ* 7.92−7.82 (8H, m, 4 × ArH_2, ortho to -CO-), 7.24−6.09 (8H, m, 4 × ArH_2, meta to -CO-), 5.86−5.76 (2H, m, H-2 and H-3), 4.82−4.34 (4H, three complex m, 2 × H-1 and 2 × H-5), 2.44−2.34 (14H, m containing singlets at *δ* 2.39, 2.38, and 2.36, 2 × H-4, 4 × Ar-CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ* 166.6, 166.4, 165.8, 165.8, 144.2, 144.2, 144.0, 143.6, 130.4, 130.0, 130.0, 129.9, 129.8, 129.4, 129.3, 129.1, 127.3, 126.9, 72.4, 70.1, 62.7, 61.1, 30.0, 21.8; TOFMS-ES$^+$ *m*/*z* 473.2 (MH$^+$ − *p*-toluic acid), 609.3 (MH$^+$), 626.3 (M + NH_4^+), 627.3 (M + NH_4^+ + 1).

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