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Prevalence of Oxetanose Forms in the Tautomeric Equilibrium of β-Hydroxy-1,5-dicarbonyl Monosaccharides

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Supporting Information

ABSTRACT: The synthesis of 4-deoxy- and 4-deoxy-4-*C*-methylhexos-5-uloses, starting from 4-deoxyhex-4-enopyranosides, and a nuclear magnetic resonance (NMR) study of their isomeric composition are reported. The NMR spectra show that the two δ-dicarbonyl sugars exist as two anomeric α- and β-oxetanosyl forms, derived from the hemiacetalization of the C-3 hydroxyl group with the aldehydic carbon. The observed tautomeric equilibria have been rationalized with computational calculations. Interestingly, this is the first time that dicarbonyl derivatives are mostly present in their oxetanose forms, offering a new entry into this very interesting type of scaffold.

The chemical and biological properties of common aldoses and ketoses are mainly dependent on their possible structures in solution. For this reason, their isomeric compositions in aqueous solution are well-documented[1] and have been extensively studied by NMR spectroscopy.[2−4] Solutions of aldoses and ketoses mainly consist of two pyranose and two furanose anomers, rarely accompanied by open chain or other forms. Therefore, the study of their NMR spectra is relatively straightforward. On the other hand, carbohydrates having a second carbonyl function (dialdoses, diuloses, and aldosuloses) exist as complex mixtures of isomeric forms.[5]

Among the dicarbonyl sugars, hexos-5-uloses (**A**) have long been known as intermediates in several degradation reactions as well as constituents of a few naturally occurring compounds.[6,7] Detailed NMR studies of their equilibria in aqueous solution evidenced the presence of several kinds of hemiacetalic species,[8−11] because of the hemiacetalization of either the aldehydo or the keto groups. In particular, the following forms have been reported (Figure 1): (a) two different types of furanose anomers arising from the addition of either the OH-4 group to the C-1 aldehydo group (**B**) or the OH-2 group to the C-5 keto group (**C**), (b) pyranose tautomers derived from the attack of one OH of the C-1 aldehydo hydrate form to the C-5 keto group (**D**), and (c) bicyclic heptanose forms derived from the addition of the primary OH-6 group to the C-1 aldehydo group followed by a second hemiacetalization of the anomeric OH-1 group with the C-5 keto group (**E**). In any case, the linear hydroxycarbonyl form (**A**) was not detected.

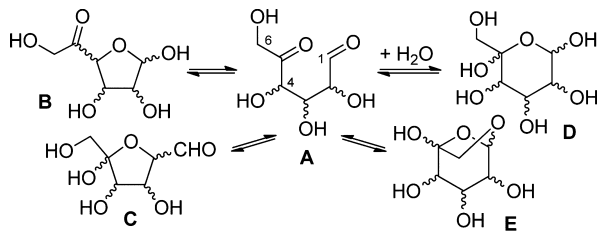

Figure 1. Prevalent anomeric species found in the hexos-5-ulose tautomeric equilibria.

Although it has been poorly investigated to date, this class of dicarbonyl hexoses recently has attracted a great deal of attention as starting materials for the synthesis of biologically interesting molecules such as 1,5-dideoxy-1,5-iminoalditols,[12−14] various kind of cyclitols, such as inososes and inositols,[15−17] and polyhydroxycyclopentanes.[18]

A useful approach to aldohexos-5-uloses, based on a selective C-5 oxidation by epoxidation of 4-deoxyhex-4-enopyranosides[19,20] or 6-deoxyhex-5-enopyranosides,[9,21] has been recently reported. In the frame of a general research project directed at the chemical valorization of lactose,[22−24] as a cheap and renewable starting material, and with the aim of obtaining new deoxy derivatives of the common aldohexos-5-ulose, we have thought that appropriate manipulations on the saccharidic skeleton may force the molecule toward the formation of oxetane tautomeric forms, rather than five-, six-, or seven-atoms rings previously reported.

In this work we report, for the first time, the synthesis of new 4-deoxy- and 4-deoxy-4-*C*-methylhexos-5-uloses and the NMR study of their isomeric composition. The observed results have been rationalized with computational calculations.

The synthesis of 2,6-di-*O*-benzyl-4-deoxy-L-*threo*-hexos-5-ulose (**3**) was achieved by acid hydrolysis of the mixture of 1,5-bis-methylglycopyranosides (**2a,b**), obtained by addition of MeOH (10 equiv) to the known hex-4-enopyranoside (**1a**)[8] in

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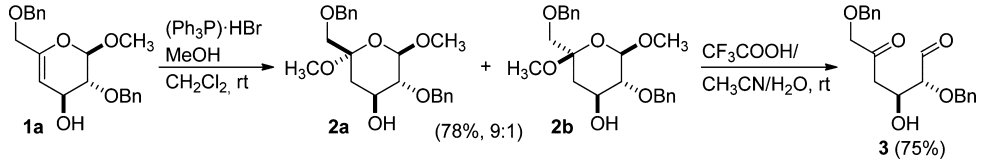
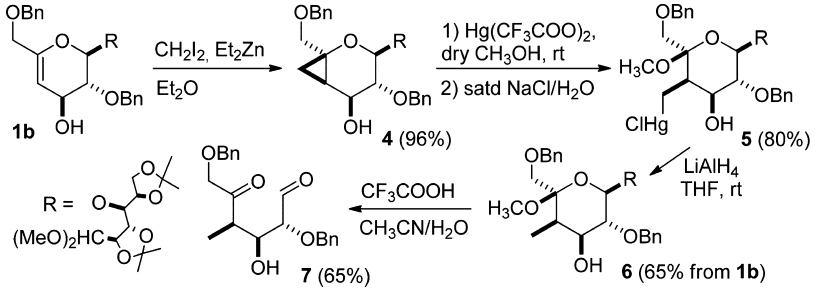
Scheme 1. Synthesis of 4-Deoxyhexos-5-ulose 3



Scheme 2. Synthesis of 4-Deoxy-4-*C*-methylhexos-5-ulose 7



the presence of triphenylphosphonium bromide (5%) in dry CH_2Cl_2 at room temperature (Scheme 1). After 1.5 h, the reaction was complete, and flash chromatography of the crude product furnished a mixture (78% yield) of **2a** and **2b** in 9:1 ratio, calculated on the basis of the relative intensities of C-1 (δ 100.6 and 96.6, respectively) and C-4 (δ 38.5 and 32.8, respectively) carbon signals.

A subsequent chromatography of the **2a**/**2b** mixture gave pure 4-deoxy-bis-glycoside **2a**, the structure of which was deduced from its ^{1}H and ^{13}C NMR spectra. The diagnostic signals appeared as a double doublet at δ 1.59 ($J_{4ax,4eq}$ = 13.1 Hz; $J_{3,4ax}$ = 11.7 Hz) for the axial H-4 proton, a double doublet at δ 2.38 ($J_{3,4eq}$ = 5.4 Hz) for the equatorial H-4 proton, a doublet at δ 4.51 ($J_{1,2}$ = 7.9 Hz) for the anomeric proton, and a singlet for the C-5 methoxy group at δ 3.25.

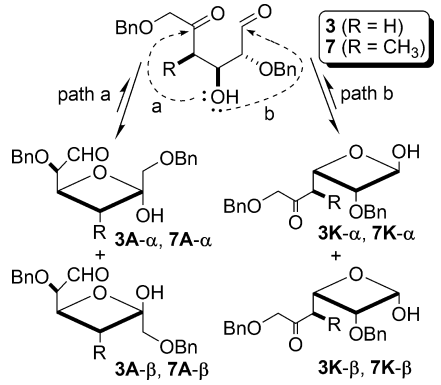
4-Deoxy-4-*C*-methyl-1,5-dicarbonyl sugar **7** was prepared from hex-4′-eno disaccharide **1b**,[23] obtained from lactose. Unsaturated sugar **1b** was subjected to a Simmons–Smith[25] cyclopropanation following our literature procedure (Scheme 2),[26,27] affording derivative **4**. **4** was then treated with mercuric trifluoroacetate (2.5 equiv) in dry methanol to give, after exchange with NaCl, organomercuric chloride **5** in high yield. It is noteworthy that the cyclopropane ring opening takes place with the same high, if not complete, regio- and stereoselectivity previously reported for the methanolysis of the analogous epoxide of **1b**.[8] The crude reaction mixture was used in the reductive demercuration with lithium aluminum hydride (5 equiv)[28] to afford 4-deoxy-4-*C*-methyl-1,5-bis-glycoside **6** in 65% yield over three steps from **1b**.

The structure and stereochemistry of compound **6** were deduced from its ^{1}H and ^{13}C NMR, COSY, and NOE spectra. In particular, in the ^{1}H NMR spectrum of **6**, diagnostic signals were a doublet ($J_{4',Me}$ = 7.1 Hz) centered at 0.92 ppm for the methyl protons at position 4′, a double quartet for the H-4′ proton at 2.39 ppm ($J_{3',4'}$ = 5.3 Hz), and a singlet for the C-5′ methoxy group at 3.22 ppm. The NOE enhancements observed between the C-5′ methoxy group and C-4′ methyl group and between the H-1′ proton and H-6′ protons confirm the reported stereochemistry.

Finally, bis-glycosides **2a,b** and **6** were subjected to the same hydrolytic conditions ($CF_3COOH/H_2O/CH_3CN$),[8] yielding the two corresponding 1,5-dicarbonyl hexoses, **3** and **7** (Schemes 1 and 2, respectively), in their oxetanose forms. The 4-deoxy-L-*threo*-5-ketoaldohexose (**3**) was isolated in 75% yield by evaporation of reagents, while 4-*C*-methyl analogue **7** required filtration on silica gel for the separation of unprotected D-glucose, derived from the hydrolysis of disaccharide **6**, and was obtained in 65% yield. Furthermore, a simpler and more effective preparation of **3** was performed by addition of H_2O to **1b** in the presence of triphenylphosphonium bromide (5%) in wet CH_2Cl_2 at room temperature. After 4 h, the reaction was complete, and flash chromatography of the crude product furnished **3** (80% yield) and the known 2,3:5,6-di-*O*-isopropylidene-D-glucose dimethyl acetal.[29]

^{1}H NMR spectra recorded in anhydrous $CDCl_3$ show that the two 1,5-dicarbonyl hexoses, **3** and **7**, exist predominantly (>99.5%) as the two anomeric α- and β-oxetanosyl forms, **3K** and **7K**, respectively, in 51:49 and 48:52 ratios, respectively, calculated from the integration of the anomeric proton signals (Scheme 3).

Scheme 3. Anomeric α- and β-Oxetanosyl Forms 3A, 7A, 3K, and 7K



These oxetanosyl forms derive from hemiacetalyzation of the C-3 hydroxyl group (path b) onto the carbon of the aldehyde group. The α- and β-forms (**3A** and **7A**) arising from the alternative hemiacetalization path (path a) are not detected. The presence in the ^{13}C NMR spectrum of two sets of carbon signals, unequivocally ascribable to ketonic functions of **3K**-α

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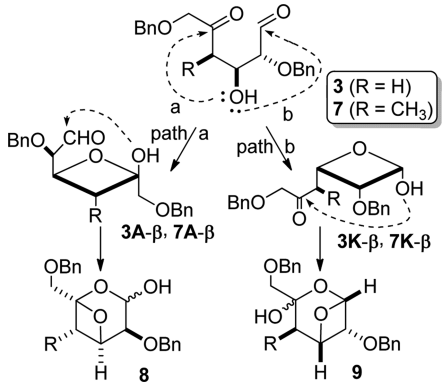
(δ 207.7), **3K**-β (δ 206.1), **7K**-α (δ 212.7), and **7K**-β (δ 212.3), further confirmed the proposed structure. In particular, in the ^{1}H and ^{13}C NMR spectra of 4-deoxy derivative **3K**, registered in $CDCl_3$, the presence of the α- and β-tautomers was confirmed by the presence of two anomeric protons at δ 5.38 ($J_{1,2}$ = 4.5 Hz, α-anomer) and δ 5.26 ($J_{1,2}$ = 1.5 Hz, β-anomer) and two anomeric carbons at δ 93.2 (α-anomer) and δ 90.7 (β-anomer). The ^{1}H NMR spectrum of 4-deoxy-4-*C*-methyl derivative **7K** registered in $CDCl_3$ showed a slight superposition of some signals, which were well resolved when CD_3CN was used (in both cases, the α:β anomeric ratio remained the same). In this last solvent, the ^{1}H and ^{13}C NMR spectra of derivative **7K** showed the two anomeric protons and carbons at δ 5.35 ($J_{1,2}$ = 5.0 Hz, α-anomer), δ 5.44 ($J_{1,2}$ = 1.3 Hz, β-anomer), δ 94.2 (α-anomer), and δ 91.1 (β-anomer), respectively.

There is no evidence, at the limit of our instrument sensitivity (0.5%), in any of the ^{1}H NMR spectra of the equilibrium product mixtures, to support the presence of alternative open chain dicarbonyl tautomers **3** and **7**, and of bicyclic 3,5- and 1,3-bridged structures **8** and **9**, which would derive from formation of a second hemiacetal ring between the hydroxyl group and the remaining carbonyl group (Scheme 4).

Scheme 4. Bicyclic 3,5- and 1,3-Bridged Structures 8 and 9



To gain further insight into the observed tautomeric equilibria and to validate the experimental results, we conducted a computational study. The obtained results are in full agreement with the experimental data, which gave the lowest Δ*H* values for **3K**-α and -β and **7K**-α and -β.

Preliminary Monte Carlo[30] simulated annealing[31] was used to sample geometries of compounds **3** and **7** (under study) from a Boltzmann-weighted distribution. The heat time was set to 1 × 10^4 steps followed by a constant-temperature simulation, i.e., 350 K, with 1 × 10^5 steps and finally a cooling time of 2 × 10^4 steps. The geometries obtained were selected within a range of 11.0 kcal/mol in terms of energy difference among the isomers, and in the next step, a full optimization of the selected geometries was conducted using the newest semiempirical PM7 Hamiltonian,[32] parametrized using experimental and high-level *ab initio* reference data, modified to further improve the description of noncovalent interactions. To consider the solvent effect, beside the gas-phase calculations, a study was conducted with the Conductor-like Screening Model (COSMO)[33] utilizing the eps parameter set to 4.81 (the dielectric constant of $CHCl_3$). The lowest Δ*H* values, both in the gas phase and in chloroform, for each compound under study, are listed in Table 1.

Results listed in Table 1 suggest that for both methylated (**7**) and nonmethylated (**3**) compounds, the preferred ring closure is that which takes place between the 3-hydroxyl group and the aldehyde moiety yielding a mixture of anomers **7K** and **3K**, respectively. In the gas phase, the β-anomers are favored over the α-anomers, whereas in chloroform, this trend is inverted only for **3K**; the results obtained in chloroform agree very well with the experimental results, obtained by recording the ^{1}H NMR spectra in chloroform. The two most stable conformers of compounds **7K** are shown in Figure 2.

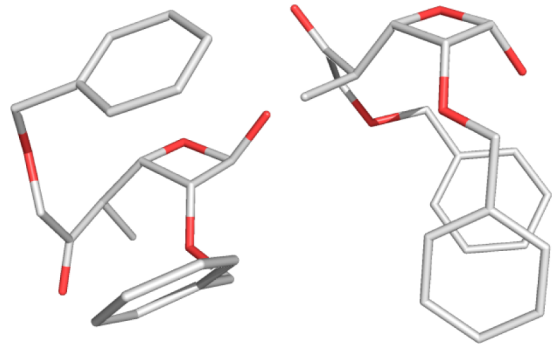


Figure 2. α- and β-anomers of compound **7K** (hydrogen atoms omitted for the sake of clarity).

To the best of our knowledge, this is the first time that two oxetanose anomers have been demonstrated as prevalent forms in the tautomeric equilibrium of a monosaccharide. This result is evidently due to the presence of a sole free OH group (OH-3) and its β-relationship with two carbonyl groups (C-1 and C-5). The unexpected regioselective hemiacetalization of the OH-3 group with the aldehyde functionality, leading only to oxetanose tautomers **3K** and **7K**, could be of interest for the development of a new synthetic approach to analogues of the

Table 1. Formation Enthalpies and Percentage Distributions, at the PM7 Level of Calculation, for 3A-α, 7A-α, 3K-α, 7K-α, 3A-β, 7A-β, 3K-β, and 7K-β

compd	ΔH_f (kcal/mol)	Boltzmann distribution (%)	$\Delta H_{f\text{-}CHCl_3}$ (kcal/mol)	Boltzmann distribution (%)	experimental distribution (%)
3A-α	−145.83	0.03	−155.72	0.01	0.00
3A-β	−145.63	0.02	−155.62	0.01	0.00
3K-α	−150.14	46.21	−161.07	52.93	51.46
3K-β	−150.23	53.74	−161.00	47.06	48.54
7A-α	−152.46	0.56	−162.19	0.48	0.00
7A-β	−152.27	0.41	−161.74	0.23	0.00
7K-α	−155.07	44.96	−164.91	46.32	48.22
7K-β	−155.18	54.07	−164.99	52.97	51.78

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natural nucleoside oxetanocine, well-known for its antibiotic and antitumoral properties. Therefore, a useful alternative to the synthesis of these highly constrained oxetanose structures was discovered; this offers a straightforward entry into this very interesting type of scaffold that can be further decorated to obtain new compounds of biological interest.

EXPERIMENTAL SECTION

General Experimental Methods. Optical rotations were measured on a polarimeter at 25 ± 2 °C. All reactions were followed by thin layer chromatography (TLC) on 60 F_{254} precoated aluminum sheets (0.2 mm thick, 20 cm × 20 cm), with detection by UV light and/or with ethanolic 5% (v/v) sulfuric acid, and heating. Silica gel 60 (230−400 mesh) was used for flash chromatography. ^{1}H NMR spectra were recorded at 200 or 500 MHz in the stated solvent (Me_4Si used as the internal standard) at 27 °C. The data are reported as follows: chemical shifts in parts per million from internal tetramethylsilane on the δ scale, multiplicity (b, broad; s, singlet; d, doublet; m, multiplet; q, quartet; t, triplet), coupling constants (hertz), and integration. ^{13}C NMR spectra (27 °C) were recorded at 50 or 125 MHz, and chemical shifts are reported as δ values, using the solvent as the internal standard. The 1,5-bis-methyl-glycopyranoside **2a**:**2b** ratio was calculated on the basis of the relative intensities of C-1 and C-4 signals. The α:β ratios of oxetanose tautomers **3K** and **7K** were determined by integration of the corresponding anomeric ^{1}H NMR signals. Assignments of the respective signals were made by the combination of ^{1}H and ^{13}C NMR, COSY, HSQC, and one-dimensional NOESY experiments.

Solvents were dried by distillation according to the standard procedure[34] and stored over 4 Å molecular sieves activated for at least 24 h at 400 °C. Na_2SO_4 or $MgSO_4$ was used as the drying agent for solutions. All reagents were used without further purification.

Synthesis of 1,5-Bis-methyl-glycopyranosides 2a,b. A solution of **1a**[8] (2.57 g, 7.22 mmol) in dry CH_2Cl_2 (35 mL) containing dry MeOH (2.9 mL, 72 mmol) and PPh_3·HBr (124 mg, 0.36 mmol) was stirred under a nitrogen atmosphere at room temperature. After 1.5 h, TLC analysis (95:5 CH_2Cl_2/MeOH) showed the complete disappearance of **1a**, and the mixture was diluted with dichloromethane (25 mL) and neutralized with saturated aqueous $NaHCO_3$ (50 mL). The aqueous phase was extracted with dichloromethane (3 × 50 mL), and the combined organic extracts were treated with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Flash chromatography purification over silica gel (95:5 CH_2Cl_2/MeOH) of the residue (2.94 g) gave a syrup that consisted (^{13}C NMR) of a mixture of compounds **2a** and **2b** (2.18 g, 78% yield) in a 9:1 ratio, measured on the relative intensities of C-1 (δ 100.6 and 96.6, respectively) and C-4 (δ 38.5 and 32.8, respectively) signals. Analytically pure **2a** was obtained by subsequent flash chromatography on silica gel (95:5 CH_2Cl_2/Me_2CO) of the **2a**/**2b** mixture. Methyl 2,6-di-*O*-benzyl-4-deoxy-5-*O*-methyl-β-D-*xylo*-pyranoside (**2a**) was a syrup: R_f = 0.27 (95:5 CH_2Cl_2/Me_2CO); $[\alpha]_D^{25}$ −41.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.38−7.28 (m, 10H, Ar-H), 4.94 (d, *J* = 11.5 Hz, 1H, PhCH_2), 4.62 (d, *J* = 11.5 Hz, 1H, PhCH_2), 4.58 (s, 2H, PhCH_2), 4.51 (d, $J_{1,2}$ = 7.9 Hz, 1H, H-1), 3.99 (ddd, $J_{3,4eq}$ = 5.4 Hz, $J_{3,4ax}$= 11.7 Hz, $J_{2,3}$ = 8.9 Hz, 1H, H-3), 3.64 (d, $J_{6a,6b}$ = 10.3 Hz, 1H, H-6a), 3.30 (d, $J_{6a,6b}$ = 10.3 Hz, 1H, H-6b), 3.54 (s, 3H, OCH_3-1), 3.25 (s, 3H, OCH_3-5), 3.15 (dd, $J_{1,2}$ = 7.9 Hz, $J_{2,3}$ = 8.9 Hz, 1H, H-2), 2.38 (dd, $J_{3,4eq}$ = 5.4 Hz, $J_{4ax,4eq}$ = 13.1 Hz, 1H, H-4eq), 1.62 (bs, 1H, OH), 1.59 (dd, $J_{4ax,4eq}$ = 13.1 Hz, $J_{3,4ax}$= 11.7 Hz, 1H, H-4ax); ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.5, 137.7 (Ar-C), 128.5, 128.4, 128.0, 127.9, 127.8 (Ar-CH), 100.6 (C-1), 99.1 (C-5), 83.5 (C-2), 74.4 ($PhCH_2$), 73.4 ($PhCH_2$), 69.9 (C-6), 67.4 (C-3), 56.9 (OCH_3-1), 48.2 (OCH_3-5), 38.5 (C-4′). Anal. Calcd for $C_{22}H_{28}O_6$: C, 68.00; H, 7.30. Found: C, 68.20; H, 7.33.

Cyclopropanation of Hex-4′-enopyranoside 1b. Cyclopropyl lactose derivative **4**[27] was synthetized in 96% yield and with high stereoselectivity in the Simmons−Smith[25] reaction of hex-4′-enopyranoside **1b**[23] with diethyl zinc and diiodomethane in dry diethyl ether, following our reported procedure.[27]

Synthesis of 4-*O*-[2′,6′-Di-*O*-benzyl-4′-deoxy-5′-*C*-methoxy-4′-(methylchloromercurio)-β-D-galactopyranosyl]-2,3:5,6-di-*O*-isopropylidene-*aldehydo*-D-glucose Dimethyl Acetal (5). To a stirred solution of **4** (1 g, 1.55 mmol) in dry MeOH (10 mL) was added mercury(II) trifluoroacetate (1.63 g, 3.87 mmol) at room temperature under a nitrogen atmosphere. The reaction was monitored by TLC (8:2 cyclohexane/EtOAc) until starting **4** disappeared. After ∼2 h, the reaction was quenched by the addition of brine (5 mL), and the mixture was stirred vigorously for 30 min and then extracted with dichloromethane (3 × 20 mL). The combined organic extracts were washed with water and dried (Na_2SO_4). After filtration, the solvent was removed under reduced pressure to give residual syrup that affords **5** as a pure sample (1.13 g, 80% yield) by flash chromatography (9:1 cyclohexane/EtOAc). Compound **5** was a syrup: $[\alpha]_D^{25}$ −5.8 (*c* 0.4, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38−7.29 (m, 10H, Ar-H), 4.93 (d, *J* = 11.5 Hz, 1H, CH_2Ph), 4.85 (d, $J_{1',2'}$ = 7.7 Hz, 1H, H-1′), 4.52 (d, *J* = 11.5 Hz, 1H, CH_2Ph), 4.53 (d, *J* = 12.0 Hz, 1H, CH_2Ph), 4.48 (d, *J* = 12.0 Hz, 1H, CH_2Ph), 4.38 (dd, $J_{1,2}$ = 6.6 Hz, $J_{2,3}$ = 7.7 Hz, 1H, H-2), 4.31 (d, 1H, H-1), 4.28−4.25 (m, 2H, H-5, H-3′), 4.16 (dd, $J_{5,6a}$ = 5.5 Hz, $J_{6a,6b}$ = 8.6 Hz, 1H, H-6a), 4.00 (dd, $J_{3,4}$ = 1.3 Hz, $J_{2,3}$ = 7.7 Hz, 1H, H-3), 3.97 (dd, $J_{5,6b}$ = 6.4 Hz, $J_{6a,6b}$ = 8.6 Hz, 1H, H-6b), 3.92 (dd, $J_{4,5}$ = 4.9 Hz, $J_{3,4}$ = 1.3 Hz, 1H, H-4), 3.50 (d, $J_{6'a,6'b}$ = 10.8 Hz, 1H, H-6′a), 3.26 (d, $J_{6'a,6'b}$ = 10.8 Hz, 1H, H-6′b), 3.32, 3.31 (2s, each 3H, 2 × OCH_3-1), 3.19 (s, 3H, OCH_3-5′), 3.17 (dd, $J_{2',3'}$ = 9.9 Hz, $J_{1',2'}$ = 7.7 Hz, 1H, H-2′), 3.01 (bs, 1H, OH), 2.53 (dt, $J_{3',4'}$ = 5.3, 1H, H-4′), 1.52 (dd, $J_{3',4'}$ = $J_{4',7'b}$ = 5.3 Hz, 1H, H-7′b), 1.42, 1.41, 1.40, 1.31 [4s, each 3H, 4 × C(CH_3)$_2$], 1.21 (dd, $J_{7'a,7'b}$ = 11.9 Hz, $J_{4',7'a}$ = 12.6 Hz, 1H, H-7′a); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.7, 137.2 (Ar-C), 128.7, 128.6, 128.44, 128.40, 128.3, 128.24, 128.20, 128.1 (Ar-CH), 109.9, 108.4 [2 × C(CH_3)$_2$], 105.8 (C-1), 102.6 (C-5′), 99.3 (C-1′), 78.5, 77.7, 77.3, 75.0, 74.5 (C-2, C-3, C-4, C-2′, C-5′), 74.2 (CH_2Ph), 73.4 (CH_2Ph), 67.0 (C-3′), 65.1 (C-6), 60.3 (C-6′), 55.9, 53.4 (2 × OCH_3-1), 48.4 (OCH_3-5′), 42.8 (C-4′), 27.2, 26.6, 26.5, 24.9 [4 × C(CH_3)$_2$], 20.2 (CH_2HgCl). Anal. Calcd for $C_{36}H_{51}ClHgO_{12}$: C, 47.42; H, 5.64. Found: C, 47.51; H, 5.67.

Synthesis of 4-*O*-(2′,6′-Di-*O*-benzyl-4′-deoxy-5′-*C*-methoxy-4′-methyl-β-D-galactopyranosyl)-2,3:5,6-di-*O*-isopropylidene-*aldehydo*-D-glucose Dimethyl Acetal (6). To a stirred suspension of lithium aluminum hydride (0.15 g, 3.85 mmol) in dry THF (8 mL), at the temperature of an ice bath, was slowly added a solution of **5** (0.7 g, 0.77 mmol) in dry THF (8 mL) under a nitrogen atmosphere, monitoring the reaction by TLC (8:2 cyclohexane/EtOAc). After ∼2 h, the starting material disappeared and the solution was diluted with Et_2O (10 mL) and a minimal amount of H_2O (0.25 mL), and then 0.25 mL of a NaOH 15% aqueous solution was added. The resulting mixture was stirred for an additional 30 min and then filtered over Celite; the solvent was removed under reduced pressure, and the obtained crude was purified by flash chromatography (7.5:2.5 cyclohexane/EtOAc), affording **6** (0.49 g, 65% yield, from **1b**). Compound **6** was a syrup: $[\alpha]_D^{25}$ +37.2 (*c* 0.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38−7.26 (m, 10H, Ar-H), 4.94 (d, *J* = 11.5 Hz, 1H, CH_2Ph), 4.53 (d, *J* = 11.5 Hz, 1H, CH_2Ph), 4.85 (d, $J_{1',2'}$ = 7.9 Hz, 1H, H-1′), 4.58 (d, *J* = 12.0 Hz, 1H, CH_2Ph), 4.48 (d, *J* = 12.0 Hz, 1H, CH_2Ph), 4.45 (dd, $J_{1,2}$ = 6.4 Hz, $J_{2,3}$ = 7.7 Hz, 1H, H-2), 4.32 (d, $J_{1,2}$ = 6.4 Hz, 1H, H-1), 4.28 (ddd, $J_{5,6b}$ = 5.1 Hz, $J_{5,6a}$ = 6.4 Hz, $J_{4,5}$ = 5.1 Hz, 1H, H-5), 4.16 (dd, $J_{5,6b}$ = 5.1 Hz, $J_{6a,6b}$ = 8.8 Hz, 1H, H-6b), 4.09 (dd, $J_{3',4'}$ = 5.3 Hz, $J_{2',3'}$ = 9.7 Hz, 1H, H-3′), 3.98 (dd, $J_{3,4}$ = 1.1 Hz, $J_{2,3}$ = 7.7 Hz, 1H, H-3), 3.95 (dd, $J_{5,6a}$ = 6.4 Hz, $J_{6a,6b}$ = 8.8 Hz, 1H, H-6a), 3.91 (dd, $J_{4,5}$ = 5.1 Hz, $J_{3,4}$ = 1.1 Hz, 1H, H-4), 3.50 (d, $J_{6'a,6'b}$ = 10.6 Hz, 1H, H-6′a), 3.30 (s, 6H, 2 × OCH_3-1), 3.28 (dd, $J_{1',2'}$ = 7.9 Hz, $J_{2',3'}$ = 9.7 Hz, 1H, H-2′), 3.22 (s, 3H, OCH_3-5′), 3.19 (d, $J_{6'a,6'b}$ = 10.6 Hz, 1H, H-6′b), 2.39 (dd, $J_{3',4'}$ = 5.3 Hz, $J_{4',Me}$ = 7.1 Hz, 1H, H-4′), 1.43, 1.41, 1.40, 1.31, [4s, each 3H, 4 × C(CH_3)$_2$], 0.92 (d, $J_{4',Me}$ = 7.1 Hz, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.3, 137.5 (Ar-C), 128.5, 128.4, 128.3, 128.0, 127.9, 127.8 (Ar-CH), 110.0, 108.5 [C(CH_3)$_2$], 105.6 (C-1), 101.9 (C-5′), 99.3 (C-1′), 80.2 (C-2′), 77.9, 77.6, 74.7, 74.6 (C-2, C-3, C-4, C-5), 74.4 ($PhCH_2$), 73.4 ($PhCH_2$), 69.1 (C-3′), 65.5, 65.3 (C-6, C-6′), 55.9, 52.9 (OCH_3-1), 48.2 (OCH_3-5′), 38.8 (C-4′), 27.3, 26.6, 26.5, 25.0 [4 × C(CH_3)$_2$], 8.6

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(CH_3-4′). Anal. Calcd for $C_{36}H_{52}O_{12}$: C, 63.89; H, 7.74. Found: C, 63.81; H, 7.71.

Synthesis of 2,6-Di-*O*-benzyl-4-deoxy-L-*threo*-hexos-5-ulose (3). *Method A (from **2a,b**).* To a solution of bis-glycosides **2a,b** (305 mg, 0.78 mmol) in a 2:1 (v/v) CH_3CN/H_2O mixture (10 mL) was added CF_3COOH (2.5 mL) and the mixture stirred at room temperature until the TLC analysis (95:5 CH_2Cl_2/MeOH) showed the complete disappearance of the starting material (2 h). The mixture was concentrated and repeatedly coevaporated with toluene (5 × 10 mL) under reduced pressure, and the crude residue was directly subjected to a flash chromatographic purification (2:8 hexane/EtOAc) to give **3** (200 mg, 75% yield) as a colorless syrup.

*Method B (from **1b**).* A solution of **1b** (239 mg, 0.38 mmol) in CH_2Cl_2 containing 0.2% water (6.0 mL) was treated with PPh_3·HBr (7 mg, 0.06 mmol) and stirred at room temperature until the starting material disappeared (TLC analysis, 2:3 hexane/EtOAc). After 4 h, the mixture was diluted with CH_2Cl_2 (20 mL) and neutralized with saturated aqueous $NaHCO_3$ (20 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL), and the combined organic extracts were treated with brine (30 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Flash chromatography of the crude residue eluting first with a 3:2 hexane/EtOAc mixture and then with a 2:3 hexane/EtOAc mixture gave the known[29] 2,3:5,6-di-*O*-isopropylidene-D-glucose dimethyl acetal (64 mg, 55% yield) and **3** (104 mg, 80% yield), identical to the sample described above.

*2,6-Di-O-benzyl-4-deoxy-L-threo-hexos-5-ulose (**3**).* $[\alpha]_D^{25}$ −7.63 (*c* 2.50, CH_3OH). Anal. Calcd for $C_{20}H_{22}O_5$: C, 70.16; H, 6.48. Found: C, 70.21; H, 6.52. The NMR spectrum of **3** revealed the exclusive presence of a mixture of α- and β-oxetanose forms **3K**-α and **3K**-β, respectively, in a 51:49 ratio calculated from the integration of the anomeric proton signals.

*Anomer **3K**-α:* ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35−7.24 (m, 10H, Ar-H), 5.40 (d, $J_{1,2}$ = 4.5 Hz, 1H, H-1), 4.83 (d, J = 11.7 Hz, 1H, PhCH_2), 4.55 (d, J = 11.7 Hz, 1H, PhCH_2), 4.51 (s, 2H, PhCH_2), 4.29 (m, 1H, H-3), 3.98 (m, 2H, H-6a, H-6b), 3.40 (dd, $J_{2,3}$ = 3.8 Hz, $J_{1,2}$ = 4.5 Hz, 1H, H-2), 2.75 (dd, $J_{3,4b}$ = 8.5 Hz, $J_{4a,4b}$ = 16.5 Hz, 1H, H-4b), 2.44 (dd, $J_{3,4a}$ = 4.5 Hz, $J_{4a,4b}$ = 16.5 Hz, 1H, H-4a); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.7 (C-5), 137.5, 137.1 (2 × Ar-*C*), 128.3−127.7 (Ar-CH), 93.2 (C-1), 80.3 (C-2), 75.2 (C-6), 73.8 (PhCH_2), 73.1 (PhCH_2), 67.1 (C-3), 42.1 (C-4).

*Anomer **3K**-β:* ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35−7.24 (m, 10H, Ar-H), 5.26 (d, $J_{1,2}$ = 1.5 Hz, 1H, H-1), 4.50 (s, 2H, PhCH_2), 4.65 (d, J = 12.0 Hz, 1H, PhCH_2), 4.48 (m, 1H, H-3), 4.38 (d, J = 12.0 Hz, 1H, PhCH_2), 3.99 (m, 2H, H-6a, H-6b), 3.16 (t, $J_{1,2}$ = $J_{2,3}$ = 1.5 Hz, 1H, H-2), 2.90 (dd, $J_{3,4b}$ = 8.0 Hz, $J_{4a,4b}$ = 17.5 Hz, 1H, H-4b), 2.49 (dd, $J_{3,4a}$ = 5.5 Hz, $J_{4a,4b}$ = 17.5 Hz, 1H, H-4a); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.1 (C-5). 138.2, 137.2, (2 × Ar-*C*), 128.4−127.7 (Ar-CH), 90.7 (C-1), 75.2 (C-6), 73.2 (PhCH_2), 72.7 (C-2), 72.4 (PhCH_2), 70.5 (C-3), 40.2 (C-4).

Synthesis of 2,6-Di-*O*-benzyl-4-deoxy-4-*C*-methyl-L-*arabino*-hexos-5-ulose (7). To a solution of bis-glycosides **6** (0.9 g, 1.32 mmol) in a 2:1 (v/v) CH_3CN/H_2O mixture (10 mL) was added CF_3COOH (3.5 mL) and the mixture stirred at 50 °C until the TLC analysis (1:1 cyclohexane/EtOAc) showed the complete disappearance of the starting material (5 h). The mixtures were concentrated and repeatedly coevaporated with toluene (5 × 10 mL) under reduced pressure. The crude residue was partitioned between brine (10 mL) and EtOAc (20 mL) and the aqueous phase extracted with EtOAc (3 × 20 mL). The organic phases that were collected and dried ($MgSO_4$) were concentrated under reduced pressure to give a residue that was directly purified by flash chromatography (70:30 cyclohexane/EtOAc) to give **7** (305 mg, 65% yield) as a colorless syrup.

*2,6-Di-O-benzyl-4-deoxy-4-C-methyl-L-arabino-hexos-5-ulose (**7**).* $[\alpha]_D^{25}$ +2.19 (*c* 1.82, CH_3OH). Anal. Calcd for $C_{21}H_{24}O_5$: C, 70.77; H, 6.79. Found: C, 70.81; H, 6.72. The NMR analysis, in both $CDCl_3$ and CD_3CN solvents, revealed that δ-dicarbonyl hexose **7** exists almost exclusively in the two anomeric α- and β-oxetanosyl forms **7K**-α and **7K**-β, respectively, in 48:52 ratio, calculated from the integration of the anomeric proton signals. Only in CD_3CN was it possible to assign all signals for each anomer.

*Selected data for the anomeric mixture of **7K**-α and **7K**-β:* ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.31 (d, $J_{1,2}$ = 4.8 Hz, 1H, H-1α), 5.30 (d, $J_{1,2}$ = 1.3 Hz, 1H, H-1β), 3.83 (m, 1H, H-3β), 3.45 (m, 1H, H-2α), 3.36 (m, 1H, H-3α), 3.28 (m, 2H, H-2β and H-4β), 2.97 (dd, 1H, $J_{3,4}$ = 7.2 Hz, $J_{4,Me}$ = 7.0 Hz, H-4α), 0.86 (d, $J_{4,Me}$ = 7.0 Hz, 3H, CH_3), 0.73 (d, $J_{4,Me}$ = 7.0 Hz, 3H, CH_3).

*Anomer **7K**-α:* ^{1}H NMR (500 MHz, CD_3CN) δ 7.45−7.29 (m, 10H, Ar-H), 5.35 (d, $J_{1,2}$ = 5.0 Hz, 1H, H-1), 4.76 (d, J = 11.5 Hz, 1H, PhCH_2), 4.54 (d, J = 11.5 Hz, 1H, PhCH_2), 4.47 (s, 2H, PhCH_2), 4.30 (d, J = 13.5 Hz, 1H, H-6b), 4.22 (d, J = 13.5 Hz, 1H, H-6a), 3.78 (dd, $J_{2,3}$ = 1.3 Hz, Hz, $J_{3,4}$ = 9.0 Hz, 1H, H-3), 3.37 (dd, $J_{2,3}$ = 1.3 Hz, $J_{1,2}$ = 5.0 Hz, 1H, H-2), 2.94 (dq, $J_{4,Me}$ = 7.0 Hz, $J_{3,4}$ = 9.0 Hz, 1H, H-4), 0.84 (d, $J_{4,Me}$ = 7.0 Hz, 3H, CH_3); ^{13}C NMR (125 MHz, CD_3CN) δ 212.7 (C-5), 139.8, 139.2 (Ar-CH), 129.7−128.8 (Ar-CH), 94.2 (C-1), 79.1 (C-2), 74.6 (C-6), 74.0 (C-3), 73.7 (PhCH_2), 73.1 (PhCH_2), 44.8 (C-4), 13.8 (CH_3).

*Anomer **7K**-β:* ^{1}H NMR (500 MHz, CD_3CN) δ 7.45−7.29 (m, 10H, Ar-H), 5.44 (d, $J_{1,2}$ = 1.3 Hz, 1H, H-1), 4.89 (d, J = 11.5 Hz, 1H, PhCH_2), 4.55 (d, J = 11.5 Hz, 1H, PhCH_2), 4.48 (s, 2H, PhCH_2), 4.21 (d, $J_{6a,6b}$ = 13.5 Hz, 1H, H-6b), 4.17 (d, $J_{6a,6b}$ = 13.5 Hz, 1H, H-6a), 4.12 (dd, $J_{2,3}$ = 1.3 Hz, $J_{3,4}$ = 9.5 Hz, 1H, H-3), 3.28 (t, $J_{2,3}$ = 1.3 Hz, 1H, H-2), 3.18 (dq, $J_{4,Me}$ = 7.0 Hz, $J_{3,4}$ = 9.5 Hz, 1H, H-4), 0.87 (d, $J_{4,Me}$ = 7.0 Hz, 3H, CH_3); ^{13}C NMR (125 MHz, CD_3CN) δ 212.3 (C-5), 139.4, 139.3 (Ar-CH), 129.7−128.8 (Ar-CH), 91.1 (C-1), 77.9 (C-3), 76.8 (C-6), 74.6 (PhCH_2), 73.7 (PhCH_2), 72.8 (C-2), 42.9 (C-4), 12.2 (CH_3).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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