SYNTHESIS OF FURANOID AND PYRANOID DERIVATIVES
OF 6-DEOXY-4-THIO-\(\beta\)-GALACTOSE

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(Received in USA 3 August 1969)

Abstract: The synthesis of pyranoid and furanoid derivatives of 6-deoxy-4-thio-\(\beta\)-galactose from methyl 2,3-di-\(\beta\)-glucopyranoside (1) is described. A key intermediate for the synthesis, methyl 2,3-di-\(\beta\)-benzoyl-6-deoxy-4-thio-\(\beta\)-galactopyranoside (15) was prepared by different approaches from 1. Regioselectivity for the protection or modification of the hydroxyl groups of 1 or its derivatives was achieved by employing various reagents. The thiol group at C-4 was introduced by nucleophilic substitution of a tosylate by thiocyanate followed by reduction or alkaline methanolysis of the thiocyanate group. A by-product of the latter reaction was characterized as a monothiolcarbonate derivative (17), whose conformation was studied by molecular mechanics calculations. Acetolysis of methyl 6-deoxy-4-thio-\(\beta\)-galactopyranoside (16) afforded ring sulfur containing derivatives of 6-deoxy-4-thio-\(\beta\)-galactofuranose, which are described for the first time.

In addition to the varied biological activities displayed by thio sugars they represent interesting targets for synthesis. The chemistry of thio sugars with sulfur in the ring is of particular interest, as the sulfur atom can participate in a variety of reactions and rearrangements.\(^{1,2}\) We have recently reported\(^{3}\) the synthesis of 4-thio-\(\beta\)-galactofuranose, a potential antitumor-bolite of galactofuranosidase. Some reactions of thio sugars and the possibility of converting 4-thiopyranoses into 4-thiofuranose derivatives were also examined.\(^{3}\) In order to evaluate the influence of C-6 deoxygenation on the reactivity and biological properties, we have now developed a convenient synthesis of 6-deoxy-4-thio-\(\beta\)-galactose. Although pyranoid derivatives of this sugar have been prepared starting from partially benzylated monosaccharides,\(^{4,5}\) the ring contraction to furanoid forms was not reported. We here describe the synthesis of furanose derivatives of the 4-thiosugar.

The strategy adopted for the synthesis of 6-deoxy-4-thio-\(\beta\)-galactose derivatives involves the preparation of a key intermediate: methyl 2,3-di-\(\beta\)-benzoyl-6-deoxy-4-\(\beta\)-(p-tolylsulfonyl)-\(\beta\)-glucopyranoside (13) which may be obtained from inexpensive methyl \(\alpha\)-\(\beta\)-glucopyranoside (1) by deoxygenation of the hydroxymethyl group, selective protection of HO-2 and HO-3, and conversion of HO-4 into a good leaving group. Substitution of protected
HO-4 by a nucleophile, precursor of thiol, would simultaneously produce the inversion of C-4 to give a derivative with the \textit{galacto} configuration.

The first approach for the synthesis of a precursor of 13, methyl 2,3-di-
\text{\textalpha}-benzoyl-6-bromo-6-deoxy-4-\text{\textalpha}-(p-tolylsulfonyl)-\text{\textalpha}-\text{\textbeta}-glucopyranoside (8),
involves benzoylation of the 4,6-\text{\textalpha}-benzylidene derivative of 1. Further
hydrolysis of the benzylidene gave 2, whose HO-6 and HO-4 groups were
derivatized by tritylation and tosylation respectively, to afford compound
3. Hydrolysis of the trityl ether of 3 led to compound 4, which on treatment
with \(\text{Ph}_3\text{P}-\text{CBr}_4\) underwent the substitution of the hydroxyl group at C-6 by
bromine, to give the 6-bromo-6-deoxy derivative 8, in 73% yield from 4. The
replacement of the HO-6 group by bromine was evident by the large upfield
shifting (29 ppm) showed by the C-6 signal, in the \(^{13}\text{C}\) NMR spectrum of 8 as
compared to the same signal in the spectrum of 4.

The 6-bromo-4-\text{\textalpha}-tosyl derivative 8 was also obtained from 1 by a shorter
route. Compound 1 was converted into methyl 6-bromo-6-deoxy-\text{\textalpha}-\text{\textbeta}-gluco-
pyranoside (5) by reaction with \(\text{Ph}_3\text{P}-\text{CBr}_4\). The selective protection of HO-2
and HO-3 of 5 was achieved by benzoylation of 5 with N-benzoylimidazole,
which has shown high regioselectivity for the protection of carbohydrates.

Acylations of sugar derivatives having \textit{gluco} configuration have indicated a
lower reactivity for HO-4. Accordingly, benzoylation of 1 with 2.4 molar
equivalents of N-benzoylimidazole gave the 2,3-dibenzooate 6 as the main
product (75% yield), being the tribenzoate 7 a by-product (15%) of the
reaction. The structures of 6 and 7 were assigned on the basis of their
spectroscopic data (Tables I and II). Thus, the signals for H-4, H-3 and H-5
appeared shifted downfield in 7, being the signal for H-4 the more strongly
shifted (> 1.0 ppm), as expected for the benzoylation of HO-4 of 6. The
\(^{13}\text{C}\) NMR spectrum of 7, when compared with that of 6 also showed a small
displacement for the signal of the \text{\textalpha}-carbon atom (C-4), but a larger upfield
shift for the signals of the \text{\textalpha}-carbons (C-3 and C-5), as observed for the
benzoylation of a given hydroxyl group in a sugar. The structure of 6 was
further confirmed, as this compound was identical to the one obtained by
the \(\text{Ph}_3\text{P}-\text{CBr}_4\) bromination of 2. Treatment of 6 with tosyl chloride-pyridine
led to the 4-tosylate 8 in 81% yield. As observed for the sulfonylation of
other sugar derivatives, the \(^{13}\text{C}\) NMR spectrum of 8 revealed that tosylation of
the HO-4 caused a large downfield shift for the signal of C-4 (ca 6 ppm)
and an upfield displacement for the signals of C-3 and C-5. Nickel Raney
catalyzed hydrogenation of 8 gave the 6-deoxy-4-\text{\textalpha}-tosyl derivative 13 in 92%
yield. The methyl group appeared in the \(^1\text{H}\) NMR spectrum of 13 as a doublet
(J 6.0 Hz) at 1.45 ppm, and the \(^{13}\text{C}\) NMR spectrum of 13 showed the signal for
C-6 in the region of aliphatic carbons (17.6 ppm).
An alternative route for the synthesis of 13 was also developed starting from methyl 6-bromo-6-deoxy-a-D-glucopyranoside (9), which was hydrogenated using Raney Nickel as catalyst to afford methyl 6-deoxy-a-D-glucopyranoside (9), in almost quantitative yield (98%). The next step of synthesis, the selective benzylation of HO-2 and HO-3 of 9, was performed with 2.4 molar equivalents of N-benzoylimidazole. The mixture obtained was separated by column chromatography to afford, in addition to the perbenzoylated product 12 (12%), the 2,3-dibenzoate 10 (59%) and the 2,4-dibenzoate 11 (13%).

Similar yields for the dibenzoates 10 and 11 had been previously reported for the benzoylation of 9 with benzoyl chloride at low temperature (-40°C), although in this case the physical constants for the products were not given. The lower reactivity for HO-4 in 9 than in 2 may be explained by the gauche interactions of HO-4 and the C-5 substituent. The C-5 bromomethyl group of 9 being bulkier than the C-5 methyl group of 2 should produce a stronger interaction for benzoylation of the HO-4 in compound 9 than in 2.

Tosylation of the HO-4 of 10 led to the 4-O-tosyl derivative 13, in a yield
which was about 20% lower than that obtained through the sequence previously described.

Nucleophilic substitution of the sulfonyloxy group of 13 by thiocyanate in DMF took place at 110°C to afford the 4-thiocyanato derivative 14 in excellent yield (95%). We have previously described\(^3\) that among the various reagents studied, potassium thiocyanate in aprotic polar solvents such as DMF, was the most convenient nucleophile for the conversion of tosylates into thiocyanato derivatives. The substitution reaction allowed the introduction in the molecule of a group precursor of thiol and the inversion of the configuration of C-4. Thus, the coupling constants observed for the H-4 signal in the \(^1\)H NMR spectrum of 14, J\(_{3,4}\) 3.9 Hz and J\(_{4,5}\) 1.5 Hz were consistent with the change from \textit{gluco} to \textit{galacto} configuration, which was confirmed by comparing the \(^13\)C NMR spectra of 14 and 13. The shielding effect of the sulfur atom\(^11\) produces a strong upfield shifting for the C-4 signal of 14 (±25 ppm); and C-2 is also shifted upfield, as observed for related compounds having the \textit{galacto} configuration.\(^3\) Furthermore, the carbon signal for the thiocyanato group appeared at 111.6 ppm, similar to reported values for other thiocyanato derivatives.\(^3\)

\[
\begin{align*}
\text{13} & \xrightarrow{\text{NCS}} \text{14} \\
\text{15} & \quad \text{16} \\
\text{17}
\end{align*}
\]

Reduction of the thiocyanato group of 14 to thiol was conducted with zinc-acetic acid, to give compound 15 in 77% yield. The IR spectrum of 15 showed the characteristic SH absorption at 2600 cm\(^{-1}\). Moreover the \(^1\)H NMR spectrum of 15 showed a doublet at 6 1.58 and a multiplet at 6 3.73 which were assigned to SH and H-4 respectively, as on deuteration, the doublet disappeared and the multiplet collapsed to a double doublet. The \(^13\)C NMR spectrum of 15 showed the signals for two carbonyl groups and for the aromatic carbons (two benzoates); and the signals of the anomeric, methoxyl and methyl carbons at 6 97.4, 55.4 and 18.2, respectively. The signal for C-4 bonded to sulfur, appeared at higher field (6 46.5) than those for C-2 and C-3.

\begin{itemize}
\item Treatment of a carbon with \(^13\)C NMR observed. Compound T showed with the same, than that \textit{J} \(_{2,3}\) value, suggesting the conformal energy, en \\
\text{nMM2 program:} \text{ \textit{flatt:}} \text{H-4 - H-5}
\end{itemize}

The thiol alcoxiide followed

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Treatment of compound 15 with methanolic sodium methoxide produced O-debenzylation to give crystalline methyl 6-deoxy-4-thio-a-D-galactopyranoside (16) in 69% yield. Since sodium methoxide has been employed for the hydrolysis of the thiocyanate group to thiol, the reagent was also used for the simultaneous debenzylation and alkaline methanolyysis of the thiocyanate 14. When the reaction was conducted for long periods (48h), the expected thiol derivative 16 was obtained as the main product. However, for shorter reaction times two products were detected by TLC. Separation of the mixture by column chromatography led to the thiol 16 and a crystalline by-product. The IR spectrum of the latter showed an absorption at 1720 cm⁻¹. The presence of a carbonyl group was confirmed by the appearance of a signal at 6.168.6 in the ¹³C NMR spectrum of the product. However, no aromatic carbons were observed, which indicated that we were dealing with a completely O-debenzoylated compound. The signals for C-3 and C-4 were strongly shifted downfield with respect to those of 15, suggesting the formation of a ring involving HO-3 and HS, and therefore the by-product was formulated as methyl 6-deoxy-4-thio-a-D-galactopyranoside 3,4-monothiocarbonate (17). The ¹H NMR spectrum of 17 showed the signals for H-3 and H-4 shifted to lower fields in comparison with the same signals of 15, which supports the proposed structure. Furthermore, the coupling constant value between H-3 and H-4 (J 6.0Hz) is larger than that for J₃,₄ in the related derivatives 14, 15 and 16, whereas the J₂,₃ values for these compounds are larger than J₂,₃ (8.5Hz) for 17, suggesting a distortion of the pyranoid ring by the cyclic thiocarbonate. The conformation of compound 17 was investigated using molecular mechanics calculations. The substituted bicyclic system was minimized with respect to energy, employing the MODELL program of Still which incorporates Allinger’s MM2 program. The conformation of lower energy for the pyranoid ring was a flattened chair, having dihedral angles between H-2 - H-3; H-3 - H-4 and H-4 - H-5 of 163°, 39° and 49°, respectively. On the other hand, molecular mechanics calculations indicated an almost ideal 4₁ conformation for 16. The thiocarbonate derivative 17 may be formed from 14 by attack of the C-3 alcohode anion, generated by debenzylation, on the thiocyanate carbon atom, followed by hydrolysis of the resulting imino group.

The next step of the synthesis, the hydrolysis of the methyl glycoside 16 would allow to achieve the 4-thiohexofuranose derivatives. Thus, on acetylation of 16 a syrupy product was obtained, which showed by GLC three main components in a 2:4:4:1 ratio. The same ratio was determined by integration of the areas for the anemic signals in the ¹H NMR spectrum of the crude mixture. However, only two spots were observed by monitoring the mixture by TLC, and two fractions were obtained by column chromatography. The secondly eluted fraction afforded a crystalline product whose ¹³C NMR spectrum showed no signals for thioacetyl
and methoxyl carbons, and the signal for C-1 appeared strongly shifted upfield, suggesting a sulfur containing five membered ring. The anomeric proton in the $^1$H NMR spectrum of 18 appeared as a doublet with $J_{1,2}$ 4.4 Hz, indicating an $\alpha$ configuration. The chemical shifts and coupling constants for the other ring protons of 18 were similar to those reported$^3$ for the $1,2,3,5,6$-penta-$\alpha$-acetylated analog of 18.

The $^1$H NMR spectrum of the first chromatographic fraction indicated that it was formed by two products, which were separated by HPLC. The component having lower $t_R$ was identified as 19, the $\beta$-anomer of 18, on the basis of the spectral data; the chemical shift for H-1 and the $J_{1,2}$ value$^{14}$ (3.3 Hz) indicated a $\beta$-configuration for C-1. The component of higher $t_R$ was the major product of the mixture. Its $^{13}$C NMR spectrum showed the signals characteristic for thioacetate (4 193.9 and 30.7) and the C-1 signal at a $\delta$ value typical of hexopyranose derivatives. Furthermore, the $^1$H NMR spectrum of this compound showed for H-1 a $J_{1,2}$ of 3.8 Hz, in agreement with an $\alpha$-configuration for C-1, therefore, the compound was characterized as 1,2,3-tri-$\alpha$-acetyl-4-$\beta$-acetyl-6-deoxy-4-thio-$\alpha$-$\beta$-galactopyranose (20).

Acetylation of 16 afforded a larger proportion of the pyranoid isomer than the acetylation$^3$ of the 6-hydroxylated analog of 16. This result may be explained on the basis of the mechanism proposed for the acetylation reaction of 4-thiohexopyranose derivatives,$^3$ which rationalizes the product distribution in terms of stabilizing or destabilizing stereoelectronic effects operating on the ionic intermediates. Under acidic conditions, the protonation of the methoxy group of 16 would occur, promoting the cleavage of the glycosidic linkage and generating a positive charge at C-1. The carbocation formed may be stabilized by participation of the ring oxygen lone pair electrons to give an oxonium ion (21), or by anchimeric assistance of sulfur affording a bicyclic sulfonium ion (22). The stereochemical course of the reaction would depend on the relative stability of these ionic species, which has been reported to be affected by the electronic properties of the C-6 substituent. Thus, an electron withdrawing group at C-6, such as hydroxy or acetoxy, would decrease the favorability of the reaction. C-1 - $\alpha$-4-thio-C-5, a: the oxonium ion of the reaction to C-1. Ring sugars of 20 $\alpha$-4-thio-sugar. peracet;
shifted upward in the spectrum indicating a more electron withdrawing C-6 substituent. The observed product of the reaction of hexopyranoside 15 with 5,6-pentandione was shown to be the 1-acetyl-D-sugar 16b. The lower degree of reactivity of the C-1, C-2, C-4 hydroxyl groups is consistent with the known reduced reactivity of this series of compounds.

Furthermore, the electron withdrawing C-6 substituent of 22b will promote the cleavage of the C-1 - O ring linkage leading, through the ion 23b, to a higher proportion of 4-thiofuranoses. Conversely, the presence of an electron-donating group at C-5, as in 16, would allow the stabilization of a positive charge at C-1 by the oxygen lone pair electrons, generating a stable oxonium ion 21a, precursor of the 4-thiogalactofuranose derivative 20, the major product in the acetylation reaction of 16. The sulfonium ion 22a could give 20 by attack of acetic acid to C-1, or 18 and 19 through the ion 23, by cleavage of the C-1 - O ring bond.

Ring contraction to the furanoid form should be expected for free 4-thiogalacto and 4-thio-2-deoxy sugars, according to the higher nucleophilicity of sulfur. Thus deacetylation of 20 led to an approximately 1:2 mixture of the 8 and 4 anomers of 6-deoxy-4-thio-D-galactofuranose, as estimated from the $^{13}$C NMR spectrum of the free sugar. Acetylation of the latter yielded the anomeric mixture of furanoid peracetylated products, as observed for other free 4-thiohexoses.
Table I. $^1$H NMR Chemical Shift and Coupling Constant Data

<table>
<thead>
<tr>
<th>Compound</th>
<th>$\delta$, ppm</th>
<th>$\Delta$</th>
<th>$\gamma$, Hz</th>
<th>$\beta$, Hz</th>
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<td>$^2$</td>
<td>5.13 5.22 5.76</td>
<td>3.70-4.10</td>
<td>7.20-8.10</td>
<td>3.8 9.8 9.0</td>
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<td>$^3$</td>
<td>5.22 5.13 5.96</td>
<td>4.08</td>
<td>6.80-7.98</td>
<td>3.9 9.6 9.9 9.9</td>
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<td>$^4$</td>
<td>5.18 5.12 5.99</td>
<td>4.18-3.80</td>
<td>6.84-7.96</td>
<td>3.6 10.7 9.2 9.2</td>
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<tr>
<td>$^5$</td>
<td>5.13 5.28 5.69</td>
<td>4.10-3.60</td>
<td>7.20-8.10</td>
<td>3.7 10.0 8.6</td>
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<tr>
<td>$^6$</td>
<td>6.17 5.49 4.29</td>
<td>7.12-8.10</td>
<td>9.9 9.9 9.8</td>
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</tr>
<tr>
<td>$^7$</td>
<td>6.08-5.17</td>
<td>4.80 4.16</td>
<td>6.82-8.02</td>
<td>3.4 9.9 9.9 9.6 2.0</td>
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<tr>
<td>$^8$</td>
<td>5.98 5.80-6.20</td>
<td>5.80-6.20</td>
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<td>$^9$</td>
<td>6.12 5.34 4.18</td>
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<td>$^{10}$</td>
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<td>$^{11}$</td>
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<td>5.30 4.23 1.33</td>
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<td>3.9 8.5 6.0 6.2</td>
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<td>$^{15}$</td>
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<td>1.98 2.00</td>
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<td>2.02 2.07</td>
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$^a$ The CH$_3$Ar appeared as a singlet (3H) at 2.17-2.09 ppm. $^b$SH gave a doublet (J 7.7 Hz) at 1.58 ppm, which disappeared on deuteration. $^c$SH gave a doublet (J 9.0 Hz) at 1.48 ppm, which disappeared on deuteration.
Table II. $^{13}$C NMR Chemical Shift Data.

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<th>Compd</th>
<th>C-1</th>
<th>C-2</th>
<th>C-3</th>
<th>C-4</th>
<th>C-5</th>
<th>C-6</th>
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<th>Ar\text{CO-} or CH$_3$\text{CO-}</th>
<th>RCO-</th>
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<td>61.7</td>
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<td>128.1-133.1</td>
<td>166.7, 165.9</td>
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<td>72.1</td>
<td>69.8*</td>
<td>75.6</td>
<td>68.8*</td>
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<td>82.9</td>
<td>55.7</td>
<td>61.3</td>
<td>20.5</td>
<td>55.6</td>
<td>21.0, 20.9, 20.8, 20.5</td>
<td>169.7-169.4</td>
</tr>
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<td>18</td>
<td>73.8*</td>
<td>76.0</td>
<td>73.1*</td>
<td>48.0</td>
<td>69.9</td>
<td>17.4</td>
<td>20.9-20.7</td>
<td>169.8-169.4</td>
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<td>19</td>
<td>79.7*</td>
<td>80.7*</td>
<td>75.9</td>
<td>53.0</td>
<td>68.1</td>
<td>18.5</td>
<td>20.9-20.7</td>
<td>193.9, 169.8, 20.5</td>
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<tr>
<td>20</td>
<td>89.8</td>
<td>67.7*</td>
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<td>50.1</td>
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<td>17.8</td>
<td>55.3</td>
<td>20.5, 169.5, 168.8</td>
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</table>

$^a$CH$_3$Ar appeared at 21.4 ppm, $^b$CH$_3$N appeared at 111.6 ppm, $^c$SO$_2$ appeared at 168.6 ppm. *Signals could be exchanged.
Experimental

Melting points were determined in a Thomas-Hoover apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer 141 polarimeter for 1% solutions in CHCl₃ at 25°C. ¹H and ¹³C NMR spectra were recorded with a Varian XL-100 spectrometer at 100.1 and 25.2 MHz, respectively, for solutions in CDCl₃ unless otherwise indicated. Tetramethylsilane was used as internal standard. Signal assignments for the ¹³C NMR spectra were made on the basis of selective heteronuclear decoupling experiments. Data are shown in Tables I and II. IR spectra were recorded on a Perkin-Elmer 710B spectrophotometer with the polystyrene absorption at 1602 cm⁻¹ as the reference. TLC was carried out on precoated aluminium plates (0.25 mm) of silica gel 60F₂₅₄ (Merck) with 9:1 PhMe-EtOAc. HPLC was performed with a Micromeritics liquid chromatograph equipped with a refractive-index detector and a Micromeritics 730 injector. GLC was recorded with a Hewlett-Packard HP5830 gas chromatograph, using a glass column (180 x 0.2 cm) packed with 3% OV-17 and nitrogen as carrier, flow rate 28 ml/min; T1 250°C, Tc 100-290°C, T gradient 10°C/min. Molecular mechanics calculations were performed with PCMODEL 2.0 and M0X from Serrena Software, Bloomington, IN., U.S.A.

Methyl 2,3-di-O-benzoyl-α-D-glucopyranoside ¹⁸ (2) and methyl 2,3-di-O-benzoyl-4-O-(p-tolylsulfonyl)-6-O-trityl-α-D-glucopyranoside (3). Compound 2 was synthesized by 4,6-O-benzylidene¹⁹ of methyl α-D-glucopyranoside (1), followed by 2,3-O-benzoylation and hydrolysis of the benzylidene group. Compound 3 was obtained from 2 as previously described.²⁰

Methyl 2,3-di-O-benzoyl-4-O-(p-tolylsulfonyl)-α-D-glucopyranoside (4). To a solution of 3 (3.0 g, 3.76 mmol) in dry CH₂Cl₂ (150 ml), 14% BF₃ in methanol (21 ml) was added, and the mixture was stirred for 2h at room temperature. The solution was extracted with water (3 x 50 ml), dried (MgSO₄) and concentrated to a syrup, which crystallized from EtOH to give 2.0 g (96%) of 4; m.p. 180-181°; [α]D +98°; in good agreement with reported values. ²¹

Methyl 6-bromo-6-deoxy-α-D-glucopyranoside (5). To a suspension of 1 (3.5 g, 18.04 mmol) and CBr₄ (7.5 g, 22.6 mmol) in MeCN (40 ml), Ph₃P (7.1 g, 22.6 mmol) was added in 0.5 g-portions every 10 min and the mixture was stirred at room temperature for 36h, when complete dissolution was observed. The solvent was evaporated and the residue purified by column chromatography using 2:1 AcOEt-PhMe as eluent, to give 3.4 g (73%) of compound 5, which recrystallized from ether has m.p. 126-127°, [α]D +158° (c 1, MeOH); Lit. ²² m.p. 126-127°; [α]D +137°. (Found: C, 32.96; H, 4.90; Br, 30.89. C₁₇H₁₇BrO₅ requires C, 32.70; H, 5.10; Br, 31.08).

Methyl 2,3-di-O-benzoyl-6-bromo-6-deoxy-α-D-glucopyranoside (6). a) Starting from 3. To a solution of compound 3 (0.72 g, 1.8 mmol) and CBr₄ (0.82 g, 2.47 mmol) in MeCN (5 ml), Ph₃P (0.78 g, 2.47 mmol) was slowly added, and the mixture was stirred for 48h at room temperature. The solvent was evaporated and the residue purified by column chromatography (19:1 EtOAc-PhMe) to afford 0.62 g (74%) of compound 6, which gave m.p. 146-147°; [α]D +154°. (Found: C, 16.15; H, 4.86; Br, 29.67; [α]D +154°. The m.p. of the benzoyl.

Methyl 2,3-di-O-benzoyl-4-O-(p-tolylsulfonyl)-α-D-glucopyranoside (3).
Furanoid and pyranoid derivatives

C, 54.15; H, 4.76; Br, 17.48. C_{21}H_{28}BrO_2 requires: C, 54.21; H, 4.55; Br, 17.17.

b) Starting from $\delta$. To a suspension of compound $\delta$ (0.64 g, 2.5 mmol) in 1,2-dichloroethane (20 mL), N-benzoylimidazole\(^{23}\) (1.03 g, 6.0 mmol) was added and the mixture was stirred at the reflux temperature for 24 h. The resulting solution was diluted with CH\(_2\)Cl\(_2\) (0.5 L) and extracted with 5%aq. HCl, water, aq. NaHCO\(_3\) and water. The organic layer was dried (MgSO\(_4\)) and the solvent evaporated to afford a residue, which showed two main spots on TLC ($R_f$ 0.69 and 0.41). The mixture was separated by column chromatography (19:1 PhMe-EtOAc).

The less polar component ($R_f$ 0.69) was isolated in 15% yield (0.22 g) and characterized as methyl 2,3,4-tri-O-benzoyl-6-bromo-6-deoxy-a-D-glucopyranoside ($\gamma$), which crystallized from EtOH to give m.p. 122-123°, [α]\(_D\) +100° (c 0.9, pyridine), [lit.\(^{22,24}\) m.p. 122°, [α]\(_D\) +90.9°].

The other compound ($R_f$ 0.41) isolated from the column was $\delta$ (0.87 g, 75%), which showed the same physical constants as those indicated above.

Methyl 2,3-di-O-benzoyl-6-bromo-6-deoxy-a-D-glucopyranoside ($\delta$).

a) Starting from $\delta$. Compound $\delta$ (2.1 g, 3.76 mmol) suspended in MeCN (8 mL) was allowed to react with Ph,P (1.5 g, 5.66 mmol) and CBr\(_4\) (1.57 g, 4.73 mmol) as described for the preparation of $\gamma$, to give 1.96 g (86%) of compound $\delta$, which recrystallized from EtOH had m.p. 147-148°, [α]\(_D\) +101°. (Found: C, 54.44; H, 4.63; S, 5.39. C\(_{28}\)H\(_{22}\)BrO\(_9\) requires C, 54.29; H, 4.39; S, 5.17.)

b) Starting from $\delta$. To a solution of $\delta$ (0.62 g, 1.36 mmol) in pyridine (10 mL), tosyl chloride (1.0 g, 5.24 mmol) was slowly added. The mixture was kept at 0° for 24 h, and then at room temperature for additional 24 h. A solid was obtained by pouring the solution into ice-water. Crystallization from EtOH gave 0.67 g (81%) of compound $\delta$.

Methyl 6-deoxy-a-D-glucopyranoside ($\eta$). Compound $\delta$ (2.28 g, 8.88 mmol) dissolved in MeOH (100 mL) containing Et\(_3\)N (1.5 mL) was hydrogenated in the presence of Raney Nickel (1.0 g) at 47 psi for 12 h. The catalyst was filtered and the filtrate evaporated. The resulting syrup was purified through a short column of silica gel, using EtOAc as eluent, to give 1.56 g (98.5%) of compound $\eta$. Upon crystallization from ether, $\eta$ gave m.p. 97-98°; [α]\(_D\) +153° (c 0.9, H\(_2\)O) ([lit.\(^{25}\) m.p. 98-99°, [α]\(_D\) +159°).

Methyl 2,3-di-O-benzoyl-6-deoxy-a-D-glucopyranoside ($\iota$). To a suspension of $\eta$ (1.1 g, 6.0 mmol) in 1,2-dichloroethane (40 mL) heated at the reflux temperature, N-benzoylimidazole\(^{23}\) (2.48 g, 14.4 mmol) was added following the procedure described for the preparation of $\delta$. The mixture obtained was separated by column chromatography (9:1 PhMe-EtOAc). The fastest migrating component on TLC ($R_f$ 0.55) was obtained (0.35 g, 12%) and identified as methyl 2,3,4-tri-O-benzoyl-6-deoxy-a-D-glucopyranoside ($\iota$), which had m.p. 141-142° (from EtOH), [α]\(_D\) +107° (c 1, pyridine) ([lit.\(^{24}\) m.p. 139-140°, [α]\(_D\) +107°).

The next chromatographic fraction ($R_f$ 0.34) afforded 0.30 g (13%) of methyl 2,4-di-O-benzoyl-6-deoxy-a-D-glucopyranoside ($\iota$), which upon crystallization from isopropyl ether-
hexane gave m.p. 130-131°C; [α]D +111°. (Found: C, 65.06; H, 5.96. C21H22O7 requires C, 65.28; H, 5.74).

The more polar component (RF 0.27) was characterized as the 2,3-dibenzoate (10) isomer of 11. Compound 10, which was obtained in 59% yield (1.36 g), had [α]D +167°. (Found: C, 65.37; H, 5.96. C21H22O7 requires C, 65.28; H, 5.74).

Methyl 2,3-di-O-benzoyl-6-deoxy-4-O-(p-toluenesulfonyl)-α-D-glucopyranoside (13). a) Starting from 8. Compound 8 (1.55 g, 2.5 mmol), dissolved in 1:1 MeOH-EtOAc (30 mL) was hydrogenated using Raney Nickel (2.0 g) as described for the preparation of 9. Crystallization from EtOH afforded 1.2 g (89%) of compound 13, m.p. 138-139°C; [α]D +100.5° (lit. 10 m.p. 141-142°C; [α]D +95.8°).
b) Starting from 10. To a solution of 10 (0.96 g, 2.5 mmol) in pyridine (20 mL), tosyl chloride (1.85 g, 9.7 mmol) was slowly added at 0°C. After 72 h the mixture was poured into ice-water, and extracted with CH2Cl2 (3 x 100 mL). The organic extract was washed with 5% aq. HCl, water and aq. NaHCO3, dried (MgSO4), filtered and evaporated. The residue crystallized from EtOH to give 0.85 g (63%) of compound 13.

Methyl 2,3-di-O-benzoyl-6-deoxy-4-thiocyanato-α-D-galactopyranoside (14). To a solution of 13 (1.12 g, 2.07 mmol) in DMF (11 mL), KSCN (1.3 g, 13.25 mmol) was added and the mixture was stirred at 110°C for 36 h. The solution was poured into water and extracted with CH2Cl2. The organic extract was dried (MgSO4) and evaporated, and the residue was purified by column chromatography (9:1 PhMe-EtOAc), to afford 0.85 g (95%) of compound 14; [α]D +84°. (Found C, 61.49; H, 4.95; S, 7.16. C21H22NO6 requires C, 61.82; H, 4.95; S, 7.50).

Methyl 2,3-di-O-benzoyl-6-deoxy-4-thio-α-D-galactopyranoside (15). To a solution of 14 (0.55 g, 1.28 mmol) in acetic acid (22 mL), powdered zinc (0.9 g) was added. The mixture was heated under reflux for 40 h and then diluted with CH2Cl2 and filtered. The residue was washed with CH2Cl2 and the filtrates pooled and washed with aq. NaHCO3, and water. The organic extract was dried (MgSO4) and the solvent evaporated to give a syrup which was purified by column chromatography (4:1 hexane-EtOAc), to afford 0.40 g (77%) of compound 15; [α]D +173°. IR (film) 2600 cm⁻¹ (SH). (Found: C, 62.50; H, 5.69; S, 8.11. C21H22O6S requires C, 62.67; H, 5.51; S, 7.97).

Methyl 6-deoxy-4-thio-α-D-galactopyranoside (16). a) Starting from 14. To a solution of 14 (0.82 g, 1.93 mmol) in MeOH (60 mL) was added dropwise, at 0°C, a solution prepared by dissolving sodium (106 mg, 4.63 mmol) in MeOH (6 mL). The mixture was stirred for 0.5 h at 0°C and then for 2 h at room temperature, when no starting material was detected by TLC. The solution was neutralized with Dowex 50W(H+) resin, filtered and the solvent evaporated. The residue, which showed two spots by TLC (RF 0.58 and RF 0.47, 10:1 EtOAc-MeOH), was chromatographed using EtOAc. Evaporation of the fractions containing the product of RF 0.58 afforded 0.11 g (29%) of 16, which crystallized from CH2Cl2-hexane, gave m.p. 103-105°C; [α]D +225

C14H14O4S

From the galactopyranose compound (Found: C, 61.24; H, 5.44; S, 8.14). The TLC plate prepared from 16 yielded 1,2,3,4,5-penta-1,2,3,4,5-deoxy-p-D-galactopyranose. 

Methyl 2,3-di-O-benzoyl-6-deoxy-4-thio-α-D-galactopyranoside (17). A solution of 15 (1.12 g, 2.23 mmol) in PhMe (11 mL), KSCN (1.3 g, 13.25 mmol) was added and the mixture was stirred at 110°C for 36 h. The solution was poured into water and extracted with CH2Cl2. The organic extract was washed with 5% aq. HCl, water and aq. NaHCO3, dried (MgSO4), filtered and evaporated. The residue crystallized from EtOH to give 0.85 g (63%) of compound 17.
Furanoid and pyranoid derivatives

\[ \text{Furanoids and pyranoids are compounds with different structural motifs.} \]

\[ \text{These compounds are often used in organic synthesis and pharmaceutical research.} \]

\[ \text{IR} 3700-3100 \text{ cm}^{-1} (\text{OH}) \text{ and } 2560 \text{ cm}^{-1} \text{ (SH). (Found: C, 43.51; H, 7.31; S, 15.90.} \]

\[ \text{C}_9 \text{H}_{14} \text{O}_5 \text{S requires C, 43.28; H, 7.26; S, 16.50.} \]

\[ \text{From the fractions of } R_f 0.47, 0.08 \text{ g (19%) of crystalline methyl 6-deoxy-4-thio-α-D-galactopyranoside 3,4-monothiocarbonate (17) was obtained. Recrystallized from ether, compound 17 gave m.p. 142-143°; [α]_D^16 +83°; IR 3550-3100 (OH), and 1720 cm}^{-1} (-S=O). } \]

\[ \text{(Found: C, 43.34; H, 5.80; S, 14.85. C}_9 \text{H}_{12} \text{O}_5 \text{S requires C, 43.63; H, 5.49; S, 14.56.} \]

\[ \text{Treatment of compound 16 (0.43 g, 1.0 mmol) in MeOH (25 mL) with methanolic sodium methoxide prepared by dissolving sodium (83 mg, 3.61 mmol) in MeOH (3 mL) at room temperature for a longer time (48h), afforded after chromatographic isolation 0.11 g (37%) of 16. Only traces of 17 were detected by TLC.} \]

\[ \text{b) Starting from 15. To a solution of 15 (0.33 g, 0.83 mmol) in MeOH (20 mL) a 0.4 M solution of sodium methoxide (5 mL) was added dropwise, at 0°C and the mixture was stirred for 10h at room temperature. The procedure described above was followed to isolate compound 16, yielding 0.11 g (62%).} \]

\[ \text{1,2,3,5-tetra-O-acetyl-6-deoxy-4-thio-α-D-galactofuranose (18), 1,2,3,5-tetra-O-acetyl-6-}
\[ \text{deoxy-4-thio-α-D-galactofuranose (19) and 1,2,3-tri-O-acetyl-4-S-acetyl-6-deoxy-4-thio-α-D-}
\[ \text{galactopyranose (20).} \]

\[ \text{Compound 16 (75 mg, 0.39 mmol) was dissolved at 0°C in a solution of}
\[ \text{glacial acetic acid (8 mL), acetic anhydride (8 mL) and sulfuric acid (0.5 mL). The}
\[ \text{mixture was kept at 4°C for 48h and sodium acetate (0.75 g) was added. After 0.5h of stirring}
\[ \text{at room temperature, the solution was concentrated, and the residue extracted with CH}_2\text{Cl}_2
\[ \text{(2 x 100 mL), it was filtered and the filtrate was washed with aq. Na}_2\text{CO}_3
\[ \text{(2 x 150 mL) and}
\[ \text{water (150 mL), dried (MgSO}_4\text{) and evaporated. The residue was examined by G.L.C., showing}
\[ \text{three main peaks of } R_f 6.27, 6.73 \text{ and 7.16, in a ratio 2:4.4:1. The same ratio of areas was}
\[ \text{obtained by integration of the anomic region of the } ^1\text{H NMR spectrum of the mixture.} \]

\[ \text{The mixture was chromatographed on silica gel with 3:1 hexane-EtOAc. Fractions containing the lower migrating}
\[ \text{component (R_f 0.43) were pooled and evaporated affording 25 mg (19%) of compound 18, which}
\[ \text{crystallized upon addition of ether. Compound 18 had m.p. 123-124°C; [α]_D^16 +154° (Found:}
\[ \text{C, 48.34; H, 5.56; S, 9.64. C}_9 \text{H}_{14} \text{O}_5 \text{S requires C, 48.27; H, 5.79; S, 9.20.} \]

\[ \text{The fraction having R_f 0.48 contained two products, as determined on the basis of its } ^1\text{H}
\[ \text{NMR spectrum. The mixture was separated by reversed-phase HPLC [Mitsui Tech R-Sep C-18 column}
\[ \text{(10 μm), 50 x 1 cm, at a flow rate of 1.2 mL/min] with 1:1 acetonite-water. A minor fraction}
\[ \text{(10 mg, 7.5%) having } R_f 25.8, \text{ corresponded to 19. [α]_D^16 -146°.} \]

\[ \text{The fraction of } R_f 28.5 \text{ min gave, upon evaporation 41 mg (31%) of 20, [α]_D^16 +53°; IR (film)
\[ \text{1750 (CH}_2\text{CO}_2\text{), and 1700 cm}^{-1} (\text{CH}_2\text{CO}_2\text{)-. (Found: C, 48.03; H, 5.98; S, 9.16. C}_4 \text{H}_2 \text{O}_5 \text{S}
\[ \text{requires C, 48.27; H, 5.79; S, 9.20.} \]

\[ \text{Compound 20 (52 mg, 0.15 mmol) was deacetylated with a 0.01N solution of sodium methoxide}
\[ \text{(10 mL), under nitrogen, at 0°C for 2h, when a single spot of } R_f 0.57 \text{ (10:1 EtOAc-MeOH) was}
\[ \text{detected on TLC. The solution was neutralized with Dowex 50W(H) resin, filtered and}
\[ \text{concentrated. The residue was dissolved in water and extracted with ether, the aqueous layer}
was freeze-dried to afford a syrup, whose $^{13}$C NMR spectrum (1:1 D$_2$O-H$_2$O) showed signals corresponding to the carbons of the furanoid forms: 84.1 (C-1B), 79.9 (C-1a), 56.1 (C-4B), 54.3 (C-4a), 22.5 (C-6B) and 22.4 (C-6a).

Acetylation of the syrup with acetic anhydride (0.5 mL) and pyridine (0.5 mL) afforded 35 mg (67% yield) of a mixture of compounds 16 and 17 in a 2.3:1 ratio as determined by $^1$H NMR.

Acknowledgement. We are indebted to CONICET (Consejo Nacional de Investigaciones Científicas y Técnicas), the University of Buenos Aires, and UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases for financial support and to UNYMPPOR (CONICET-FCEN, Buenos Aires) for the microanalyses, and Dr. Gerardo Burton for the use of computer facilities and the PCCMEDLE programme.

References