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# SYNTHESIS OF FURANOID AND PYRANOID DERIVATIVES OF 6-DEOXY-4-THIO-D-GALACTOSE

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Abstract: The synthesis of pyranoid and furanoid derivatives of 6-deoxy-4-thio-D-galactose from methyl α-D-glucopyranoside (1) is described. A key intermediate for the synthesis, methyl 2,3-di-O-benzoyl-6-deoxy-4-thio-α-D-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 thiocyano 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-α-D-galactopyranoside (16) afforded ring sulfur containing derivatives of 6-deoxy-4-thio-D-galactofuranose, which are described for the first time.

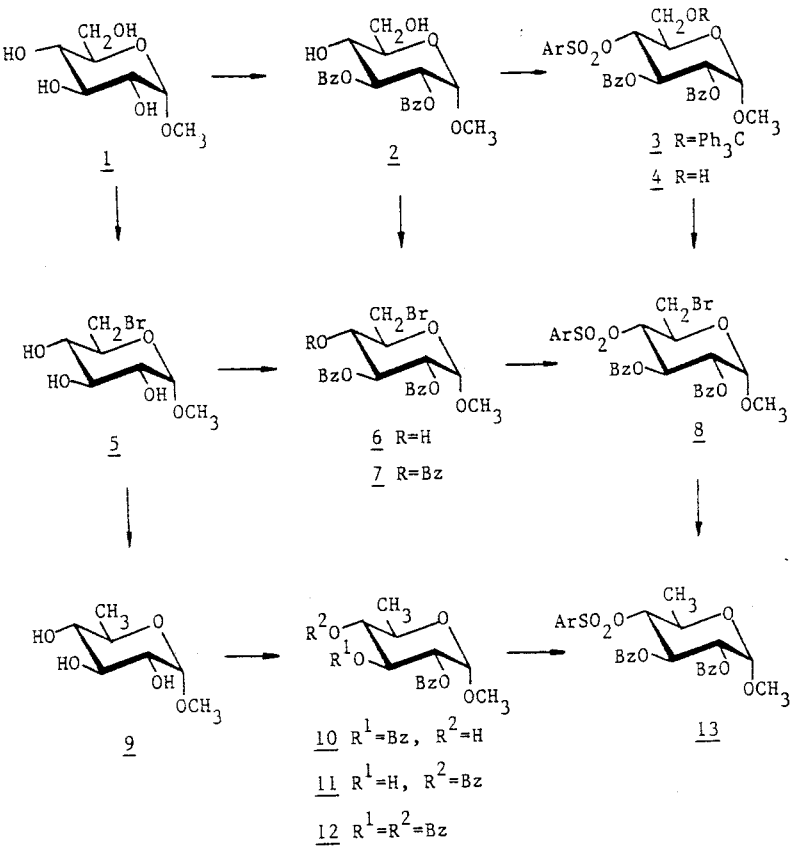
In addition to the varied biological activities displayed by thio sugars they represent interesting targets for synthesis. The chemistry of thio sugars with sulfur in the ring is of particular interest, as the sulfur atom can participate in a variety of reactions and rearrangements.[1,2] We have recently reported[3] the synthesis of 4-thio-D-galactofuranose, a potential antimetabolite of galactofuranosidase. Some reactions of thio sugars and the possibility of converting 4-thiopyranoses into 4-thio-furanose 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-D-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-D-galactose derivatives involves the preparation of a key intermediate: methyl 2,3-di-O-benzoyl-6-deoxy-4-O-(p-tolylsulfonyl)-α-D-glucopyranoside (13) which may be obtained from inexpensive methyl α-D-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 galacto configuration.

The first approach for the synthesis of a precursor of 13, methyl 2,3-di-O-benzoyl-6-bromo-6-deoxy-4-O-(p-tolylsulfonyl)-α-D-glucopyranoside (8), involves benzoylation of the 4,6-O-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 $Ph_3P$-$CBr_4$[6] 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 $^{13}C$ NMR spectrum of 8 as compared to the same signal in the spectrum of 4.

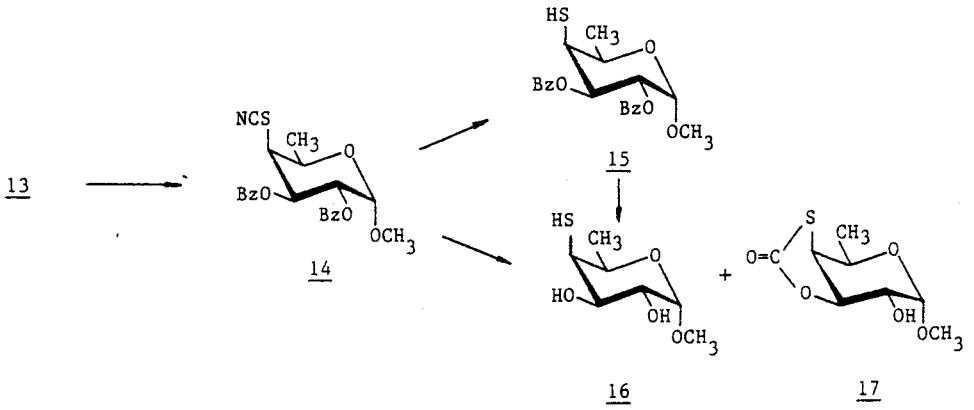
The 6-bromo-4-O-tosyl derivative 8 was also obtained from 1 by a shorter route. Compound 1 was converted into methyl 6-bromo-6-deoxy-α-D-gluco-pyranoside (5) by reaction with $Ph_3P$-$CBr_4$. The selective protection of HO-2 and HO-3 of 5 was achieved by benzoylation of 5 with N-benzoylimidazole, which has shown high regioselectivity for the protection of carbohydrates.[7] Acylations of sugar derivatives having gluco configuration have indicated[7] a lower reactivity for HO-4. Accordingly, benzoylation of 1 with 2.4 molar equivalents of N-benzoylimidazole gave the 2,3-dibenzoate 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 $^{13}C$ NMR spectrum of 7, when compared with that of 6 also showed a small displacement for the signal of the α-carbon atom (C-4), but a larger upfield shift for the signals of the β-carbons (C-3 and C-5), as observed for the benzoylation of a given hydroxyl group in a sugar.[8] The structure of 6 was further confirmed, as this compound was identical to the one obtained by the $Ph_3P$-$CBr_4$ 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,[9] the $^{13}C$ NMR spectrum of 8 revealed that tosylation of the HO-4 caused a large downfield shift for the signal of C-4 (≈ 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-O-tosyl derivative 13 in 89% yield. The methyl group appeared in the $^1H$ NMR spectrum of 13 as a doublet (J 6.0 Hz) at 1.45 ppm, and the $^{13}C$ 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-α-D-glucopyranoside (5), which was hydrogenated using Raney Nickel as catalyst to afford methyl 6-deoxy-α-D-glucopyranoside (9), in almost quantitative yield (98%). The next step of synthesis, the selective benzoylation 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[10] 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 5 than in 9 may be explained by the gauche interactions of HO-4 and the C-5 substituent. The C-5 bromomethyl group of 5 being bulkier than the C-5 methyl group of 9 should produce a stronger interaction for benzoylation of the HO-4 in compound 5 than in 9. 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-thiocyano 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 thiocyano 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 gluco to 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 galacto configuration.[3] Furthermore, the carbon signal for the thiocyano group appeared at 111.6 ppm, similar to reported values for other thiocyanate derivatives.[3]

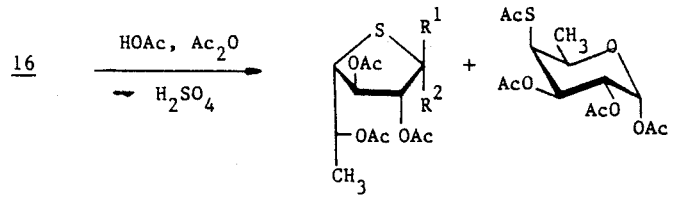



Reduction of the thiocyano group of 14 to thiol was conducted with zinc-acetic acid, to give compound 15 in 77% yield. The IR spectrum of 15 showed the characteristic SH absorption at 2600 cm$^{-1}$. Moreover the $^1$H NMR spectrum of 15 showed a doublet at δ 1.58 and a multiplet at δ 3.73 which were 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 δ 97.4, 55.4 and 18.2, respectively. The signal for C-4 bonded to sulfur, appeared at higher field (δ 46.5) than those for C-2 and C-3.

Treatment of compound 15 with methanolic sodium methoxide produced O-debenzoylation to give crystalline methyl 6-deoxy-4-thio-α-D-galactopyranoside (16) in 69% yield. Since sodium methoxide has been employed[12] for the hydrolysis of the thiocyano group to thiol, the reagent was also used for the simultaneous debenzoylation and alkaline methanolysis of the thiocyanate 14. When the reaction was conducted for long periods (≥ 48hs) 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 δ 168.6 in the $^{13}C$ 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-α-D-galactopyranoside 3,4-monothiolcarbonate (17). The $^{1}H$ 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 $J_{3,4}$ in the related derivatives 14, 15 and 16, whereas the $J_{2,3}$ values for these compounds are larger than $J_{2,3}$ (8.5Hz) for 17, suggesting a distortion of the pyranoid ring by the cyclic thiolcarbonate. The conformation of compound 17 was investigated using molecular mechanics calculations. The substituted bicyclic system was minimized with respect to energy, employing the MODEL program of Still which incorporates Allinger's MM2 program.[13] The conformation of lower energy for the pyranoid ring was a $^{4}C_{1}$ flattened chair, having dihedral angles beween 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 $^{4}C_{1}$ conformation for 16. The thiolcarbonate derivative 17 may be formed from 14 by attack of the C-3 alcoxide anion, generated by debenzoylation, on the thiocyano 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 acetolysis 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 anomeric signals in the $^{1}H$ 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 $^{13}C$ 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[14] an α 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-O-acetylated analog of 18.

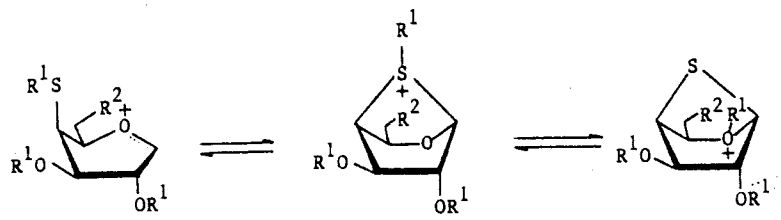



18 $R^1$=H, $R^2$=OAc 20

19 $R^1$=OAc, $R^2$=H

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 β-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 β-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 thiol-acetate (δ 193.9 and 30.7) and the C-1 signal at a δ value typical of hexo-pyranose 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 α-configuration for C-1, therefore, the compound was characterized as 1,2,3-tri-O-acetyl-4-S-acetyl-6-deoxy-4-thio-α-D-galactopyranose (20).

Acetolysis of 16 afforded a larger proportion of the pyranoid isomer than the acetolysis[3] of the 6-hydroxylated analog of 16. This result may be explained on the basis of the mechanism proposed for the acetolysis reaction of 4-thio hexopyranose derivatives,[3] which rationalizes the product distribution in terms of stabilizing or unstabilizing stereoelectronic effects operating on the ionic intermediates. Under acidic conditions, the protonation of the methoxy group of 16 would occur, promoting the cleveage 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.[15] Thus, an electron withdrawing group at C-6, such as hydroxy or acetoxy, would



21 22 23

a $R^1$=H or Ac, $R^2$=H
b $R^1$=H or Ac, $R^2$=OH or OAc

decrease the electron donation from the ring oxygen atom to the C-1 carbocation favoring the formation of 22b by participation of sulfur. 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-thiohexopyranose derivative 20, the major product in the acetolysis 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-thiosugars, according to the higher nucleophilicity of sulfur.[3,16] Thus deacylation of 20 led to an approximately 1:2 mixture of the β and α 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.[17]

Table I. $^1$H NMR Chemical Shift and Coupling Constant Data

| Compound | δ, ppm | | | | | | | | | J, Hz | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | H-1 | H-2 | H-3 | H-4 | H-5 | H-6 | H-6' | $-OCH_3$ | ArCO- or $CH_3CO$- | $J_{1,2}$ | $J_{2,3}$ | $J_{3,4}$ | $J_{4,5}$ | $J_{5,6}$ |
| 2 | 5.13 | 5.22 | 5.76 | ←------- 3.70-4.10 --------→ | | | | 3.44 | 7.20-8.10 | 3.8 | 9.8 | 9.0 | | |
| 3[a] | 5.22 | 5.13 | 5.96 | 4.82 | 4.08 | ←3.86-3.30→ | | 3.54 | 6.80-7.98 | 3.9 | 9.6 | 9.9 | 9.9 | |
| 4[a] | 5.18 | 5.12 | 5.99 | 5.03 | ←--- 4.18-3.80 ----→ | | | 3.42 | 6.84-7.96 | 3.6 | 9.7 | 9.2 | 9.2 | |
| 6 | 5.13 | 5.28 | 5.69 | ←------- 4.10-3.60 --------→ | | | | 3.48 | 7.20-8.10 | 3.7 | 10.0 | 8.6 | | |
| 7 | ←5.20-5.38→ | | 6.17 | 5.49 | 4.29 | ←3.70-3.40→ | | 3.54 | 7.12-8.10 | | 9.9 | 9.9 | 9.8 | |
| 8[a] | ←5.05-5.17→ | | 5.98 | 4.90 | 4.16 | 3.87 | 3.57 | 3.46 | 6.82-8.02 | | 9.9 | 9.9 | 9.6 | 2.0 |
| 10 | 5.05 | 5.25 | 5.66 | 3.53 | 3.89 | 1.39 | | 3.42 | 7.12-8.10 | 3.9 | 9.9 | 9.8 | 9.6 | 6.4 |
| 11 | ←5.80-6.20→ | | 4.32 | 5.80-6.20 | 4.08 | 1.26 | | 3.40 | 7.20-8.18 | | 9.8 | 9.8 | 9.7 | 6.4 |
| 12 | ←5.10-5.40→ | | 6.12 | 5.34 | 4.18 | 1.33 | | 3.46 | 7.20-8.20 | | 9.7 | 9.7 | 9.8 | 6.0 |
| 13[a] | ←5.05-5.17→ | | 5.93 | 4.70 | 4.07 | 1.45 | | 3.39 | 6.79-7.97 | | 9.8 | 9.6 | 9.6 | 6.2 |
| 14 | 5.11 | 5.47 | 5.95 | 4.20 | 4.56 | 1.48 | | 3.42 | 7.18-8.14 | 3.8 | 10.5 | 3.9 | 1.5 | 6.2 |
| 15[b] | 5.11 | 5.63 | 5.79 | 3.73 | 4.47 | 1.37 | | 3.41 | 7.20-8.08 | 3.4 | 10.5 | 3.8 | 1.9 | 6.4 |
| 16[c] | 4.74 | 3.71 | 3.91 | 3.30 | 4.23 | 1.33 | | 3.42 | | 3.5 | 9.8 | 4.3 | 2.0 | 6.4 |
| 17 | 4.81 | 4.05 | 4.71 | ←4.24-4.37→ | | 1.29 | | 3.45 | | 3.9 | 8.5 | 6.0 | | 6.2 |
| 18 | 5.99 | 5.25 | 5.64 | 3.34 | 4.93 | 1.22 | | | 1.98, 2.00<br>2.02, 2.07 | 4.4 | 9.8 | 7.9 | 5.6 | 6.2 |
| 19 | 5.81 | 5.46 | 5.24 | 3.67 | 5.00 | 1.23 | | | 1.90-2.10 | 3.3 | 6.0 | 7.4 | 6.0 | 6.0 |
| 20 | 6.29 | 5.14 | 5.53 | 4.27 | 4.53 | 1.13 | | | 1.98-2.16,<br>2.42 | 3.8 | 9.9 | 4.0 | 2.1 | 6.2 |

[a]The $CH_3Ar$ 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 dissappeared 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.

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.

| Compd | C-1 | C-2 | C-3 | C-4 | C-5 | C-6 | -OCH$_3$ | ArCO- or CH$_3$CO- | RCO- |
|---|---|---|---|---|---|---|---|---|---|
| 2 | 96.9 | 71.4* | 73.6 | 69.2 | 71.8* | 61.7 | 55.2 | 128.1-133.1 | 166.7, 165.9 |
| 3[a] | 96.1 | 72.1 | 69.8* | 75.6 | 68.8* | 62.9 | 55.2 | 126.8-144.1 | 165.0 |
| 4[a] | 96.7 | 72.0 | 69.7 | 75.5 | 69.7 | 60.5 | 55.5 | 127.2-144.7 | 164.9-165.4 |
| 5 | 100.3 | 72.2* | 73.8 | 72.5* | 71.2* | 34.3 | 56.2 | | |
| 6 | 96.9 | 71.2* | 74.1 | 71.7* | 70.5 | 32.9 | 55.5 | 128.3-133.4 | 167.3, 165.7 |
| 7 | 96.9 | 71.6* | 70.2 | 71.9* | 69.2 | 31.3 | 55.7 | 128.1-133.3 | 165.1-165.5 |
| 8[a] | 96.5 | 71.8 | 69.4 | 77.6 | 68.6 | 31.5 | 55.7 | 127.1-144.7 | 164.7 |
| 9 | 100.2 | 72.5 | 73.9 | 76.1 | 68.5 | 17.7 | 56.1 | | |
| 10 | 96.9 | 71.6 | 74.5 | 75.1 | 67.5 | 17.4 | 55.2 | 128.2-133.1 | 165.7 |
| 11 | 97.0 | 74.5 | 70.2 | 77.0 | 65.1 | 17.4 | 55.1 | 128.2-133.1 | 164.3 |
| 12 | 96.9 | 72.4 | 70.4 | 74.1 | 65.5 | 17.4 | 55.4 | 128.0-133.0 | 165.3-165.6 |
| 13[a] | 96.4 | 72.3 | 69.6 | 81.0 | 65.3 | 17.6 | 55.4 | 127.0-144.2 | 164.8-165.5 |
| 14[b] | 97.3 | 69.4* | 68.9* | 55.8 | 64.0 | 18.4 | 55.8 | 127.0-133.5 | 165.7 |
| 15 | 97.4 | 70.5* | 68.9* | 46.5 | 64.4 | 18.2 | 55.4 | 128.2-133.1 | 165.5-165.8 |
| 16 | 99.4 | 69.3* | 69.9* | 49.0 | 65.0 | 18.4 | 55.3 | | |
| 17[c] | 99.5 | 66.7 | 82.9 | 55.7 | 61.3 | 20.5 | 55.6 | | |
| 18 | 73.8* | 76.0 | 73.1* | 48.0 | 69.9 | 17.4 | | 21.0, 20.9, 20.8, 20.5 | 169.7-169.4 |
| 19 | 79.7* | 80.7* | 75.9 | 53.0 | 68.1 | 18.5 | | 20.9-20.7 | 169.8-169.4 |
| 20 | 89.8 | 67.7* | 68.1* | 50.1 | 67.7* | 17.8 | | 30.7, 20.9, 20.7, 20.5 | 193.9, 169.8, 169.5, 168.8 |

[a] CH$_3$Ar appeared at 21.4 ppm, [b] SCN appeared at 111.6 ppm, [c] SCOO 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 $CHCl_3$ at 25°C. $^1H$ and $^{13}C$ NMR spectra were recorded with a Varian XL-100 spectrometer at 100.1 and 25.2 MHz, respectively, for solutions in $CDCl_3$ unless otherwise indicated. Tetramethylsilane was used as internal standard. Signal assignments for the $^{13}C$ 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 60F-254 (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; Ti 250°C, Tc 100-290°C, T gradient 10°C/min. Molecular mechanics calculations were performed with PCMODEL 2.0 and MMX from Serena 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-benzylidenation[19] 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 $CH_2Cl_2$ (150 mL), 14% $BF_3$ in methanol (2.1 mL) was added, and the mixture was stirred for 2h at room temperature. The solution was extracted with water (3 x 50 mL), dried ($MgSO_4$) and concentrated to a syrup, which crystallized from EtOH to give 2.0 g (96%) of 4; m.p. 180-181°; $[\alpha]_D$ +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 $CBr_4$ (7.5 g, 22.6 mmol) in MeCN (40 mL), $Ph_3P$ (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 had m.p. 126-127°, $[\alpha]_D$ +158° (c 1, MeOH); Lit.[22] m.p. 126-127°; $[\alpha]_D$ +137°. (Found: C, 32.96; H, 4.90; Br, 30.89. $C_7H_{13}BrO_5$ 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 2. To a solution of compound 2 (0.72 g, 1.8 mmol) and $CBr_4$ (0.82 g, 2.47 mmol) in MeCN (5 mL), $Ph_3P$ (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°; $[\alpha]_D$ +154°. (Found:

C, 54.15; H, 4.76; Br, 17.48. $C_{21}H_{27}BrO_7$ requires: C, 54.21; H, 4.55; Br, 17.17).

b) Starting from 5. To a suspension of compound 5 (0.64 g, 2.5 mmol) in 1,2-dichloroethane (20 mL), N-benzoylimidazole[23] (1.03g, 6.0 mmol) was added and the mixture was stirred at the reflux temperature for 24h. The resulting solution was diluted with $CH_2Cl_2$ (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-α-D-glucopyranoside (7), which crystallized from EtOH to give m.p. 122-123°, $[\alpha]_D$ +100° (c 0.9, pyridine), [lit[22,24] m.p. 122°, $[\alpha]_D$ +90.9°].

The other compound ($R_f$ 0.41) isolated from the column was 6 (0.87 g, 75%), which showed the same physical constants as those indicated above.

Methyl 2,3-di-O-benzoyl-6-bromo-6-deoxy-4-O-(p-tolylsulfonyl)-α-D-glucopyranoside (8).

a) Starting from 4. Compound 4 (2.1 g, 3.76 mmol) suspended in MeCN (8 mL) was allowed to react with $Ph_3P$ (1.5 g, 5.66 mmol) and $CBr_4$ (1.57 g, 4.73 mmol) as described for the preparation of 5, to give 1.96 g (84%) of compound 8, which recrystallized from EtOH had m.p. 147-148°, $[\alpha]_D$ +101°. (Found: C, 54.44; H, 4.63; S, 5.39. $C_{28}H_{27}BrO_9S$ requires C, 54.29; H, 4.39; S, 5.17).

b) Starting from 6. To a solution of 6 (0.62 g, 1.34 mmol) in pyridine (10 mL), tosyl chloride (1.0 g, 5.24 mmol) was slowly added. The mixture was kept at 0° for 24h, and then at room temperature for additional 24h. A solid was obtained by pouring the solution into ice-water. Crystallization from EtOH gave 0.67 g (81%) of compound 8.

Methyl 6-deoxy-α-D-glucopyranoside (9). Compound 5 (2.28 g, 8.88 mmol) dissolved in MeOH (100 mL) containing $Et_3N$ (1.5 mL) was hydrogenated in the presence of Raney Nickel (3.0 g) at 47 psi for 12h. 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 9. Upon crystallization from ether, 9 gave m.p. 97-98°; $[\alpha]_D$ +153° (c 0.9, $H_2O$) (lit.[25] m.p. 98-99°, $[\alpha]_D$ +159°).

Methyl 2,3-di-O-benzoyl-6-deoxy-α-D-glucopyranoside (10). To a suspension of 9 (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 6. 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-α-D-glucopyranoside (13), which had m.p. 141-142° (from EtOH), $[\alpha]_D$ +107° (c 1, pyridine) (lit.[24] m.p. 139-140°, $[\alpha]_D$ +107°).

The next chromatographic fraction ($R_f$ 0.34) afforded 0.30 g (13%) of methyl 2,4-di-O-benzoyl-6-deoxy-α-D-glucopyranoside (11), which upon crystallization from isopropyl ether-

hexane gave m.p. 130–131°; $[\alpha]_D$ +111°. (Found: C, 65.06; H, 5.96. $C_{21}H_{22}O_7$ requires C, 65.28; H, 5.74).

The more polar component ($R_f$ 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 $[\alpha]_D$ +167°. (Found: C, 65.37; H, 5.96. $C_{21}H_{22}O_7$ requires C, 65.28; H, 5.74).

Methyl 2,3-di-O-benzoyl-6-deoxy-4-O-(p-tolylsulfonyl)-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°; $[\alpha]_D$ +100.5° (lit.[10] m.p. 141–142°; $[\alpha]_D$ +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°. After 72h the mixture was poured into ice-water, and extracted with $CH_2Cl_2$ (3 x 100 mL). The organic extract was washed with 5% aq. HCl, water and aq. $NaHCO_3$, dried ($MgSO_4$), filtered and evaporated. The residue crystallized from EtOH to give 0.85 g (63%) of compound 13.

Methyl 2,3-di-O-benzoyl-4,6-dideoxy-4-thiocyano-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° for 36h. The solution was poured into water and extracted with $CH_2Cl_2$. The organic extract was dried ($MgSO_4$) and evaporated, and the residue was purified by column chromatography (99:1 PhMe-EtOAc), to afford 0.85 g (95%) of compound 14; $[\alpha]_D$ +84°. (Found C, 61.49; H, 4.95; S, 7.16. $C_{22}H_{21}NO_6S$ 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 40h and then diluted with $CH_2Cl_2$ and filtered. The residue was washed with $CH_2Cl_2$ and the filtrates pooled and washed with aq. $NaHCO_3$, and water. The organic extract was dried ($MgSO_4$) 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; $[\alpha]_D$ +173°. IR (film) 2600 $cm^{-1}$ (SH). (Found: C, 62.50; H, 5.69; S, 8.11. $C_{21}H_{22}O_6S$ 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 0.5h at 0°C and then for 2h 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 ($R_f$ 0.58 and $R_f$ 0.47, 10:1 EtOAc-MeOH), was chromatographed using EtOAc. Evaporation of the fractions containing the product of $R_f$ 0.58 afforded 0.11 g (29%) of 16, which crystallized from $CH_2Cl_2$-hexane, gave m.p. 103–105°;

$[\alpha]_D$ +225°; IR 3700-3100 (OH) and 2560 $cm^{-1}$ (SH). (Found: C, 43.51; H, 7.31; S, 15.90. $C_7H_{11}O_4S$ requires C, 43.28; H, 7.26; S, 16.50).

From the fractions of $R_f$ 0.47, 0.08 g (19%) of crystalline methyl 6-deoxy-4-thio-α-D-galactopyranoside 3,4-monothiolcarbonate (17) was obtained. Recrystallized from ether, compound 17 gave m.p. 142-143°; $[\alpha]_D$ +83°; IR 3550-3100 (OH), and 1720 $cm^{-1}$ (-SCOO-). (Found: C, 43.34; H, 5.80; S, 14.85. $C_8H_{12}O_5S$ requires C, 43.63; H, 5.49; S, 14.56).

Treatment of compound 14 (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 (57%) of 16. Only traces of 17 were detected by TLC.

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 (69%).

1,2,3,5-tetra-O-acetyl-6-deoxy-4-thio-α-D-galactofuranose (18), 1,2,3,5-tetra-O-acetyl-6-deoxy-4-thio-β-D-galactofuranose (19) and 1,2,3-tri-O-acetyl-4-S-acetyl-6-deoxy-4-thio-α-D-galactopyranose (20). Compound 16 (75 mg, 0.39 mmol) was dissolved at 0°C in a solution of glacial acetic acid (8 mL), acetic anhydride (8 mL) and sulfuric acid (0.5 mL). The mixture was kept at 4°C for 48h and sodium acetate (0.75 g) was added. After 0.5h of stirring at room temperature, the solution was concentrated, and the residue extracted with $CH_2Cl_2$ (2 x 100 mL), it was filtered and the filtrate was washed with aq. $NaHCO_3$ (2 x 150 mL) and water (150 mL), dried ($MgSO_4$) and evaporated. The residue was examined by G.L.C., showing three main peaks of $t_R$ 6.27, 6.73 and 7.16, in a ratio 2:4.4:1. The same ratio of areas was obtained by integration of the anomeric region of the $^1H$ NMR spectrum of the mixture. However only two spots (Rf 0.48 and Rf 0.43, 2:1 PhMe-EtOAc) were detected by TLC. The mixture was chromatographed on silica gel with 3:1 hexane- EtOAc. Fractions containing the lower migrating component ($R_f$ 0.43) were pooled and evaporated affording 25 mg (19%) of compound 18, which crystallized upon addition of ether. Compound 18 had m.p. 123-124°C; $[\alpha]_D$ +154° (Found: C, 48.34; H, 5.56; S, 9.64. $C_{14}H_{20}O_8S$ requires C, 48.27; H, 5.79; S, 9.20).

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

The fraction of $t_R$ 28.5 min gave, upon evaporation 41 mg (31%) of 20, $[\alpha]_D$ +53°; IR (film) 1750 ($CH_3CO_2$-), and 1700 $cm^{-1}$ ($CH_3COS$-). (Found: C, 48.03; H, 5.98; S, 9.14. $C_{14}H_{20}O_8S$ requires C, 48.27; H, 5.79; S, 9.20).

Compound 20 (52 mg, 0.15 mmol) was deacetylated with a 0.01N solution of sodium methoxide (10 mL), under nitrogen, at 0°C for 2h, when a single spot of $R_F$ 0.57 (10:1 EtOAc-MeOH) was detected on TLC. The solution was neutralized with Dowex 50W($H^+$) resin, filtered and 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 $D_2O$-$H_2O$) showed signals corresponding to the carbons of the furanoid forms: 84.1 (C-1β), 79.9 (C-1α), 56.1 (C-4β), 54.3 (C-4α), 22.5 (C-6β) and 22.4 (C-6α).

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 18 and 19 in a 2.3:1 ratio as determined by $^1H$ NMR.

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References

1. Hashimoto, H.; Hideya, Y. *Tetrahedron Lett.* 1988, *29*, 1939-1942.
2. Al-Masoudi, N. A. L.; Hughes, N. A. *J. Chem. Soc., Perkin Trans. I* 1987, 2061-2067. Hughes, N. A.; Wood, C. *Ibid.* 1986, 695-700.
3. Varela, O.; Cicero, D.; de Lederkremer, R. M. *J. Org. Chem.* 1989, *54*, 1884-1890.
4. Fügedi, P.; Lipták, A. *J. Chem. Soc. Chem. Commun.* 1980, 1234-1235.
5. Simon, P.; Ziegler, J-C.; Gross, B. *Carbohydr. Res.* 1978, *64*, 257-262.
6. Castro, B. R. *Org. React.* 1983, *29*, 1-162.
7. Haines, A. H. *Adv. Carbohydr. Chem. Biochem.* 1976, *33*, 11-109.
8. Bock, K; Pedersen, C. *Adv. Carbohydr. Chem. Biochem.* 1983, *41*, 27-66.
9. Lipták, A.; Nánási, P.; Neszmélyi, A.; Wagner, H. *Carbohydr. Res.* 1980, *86*, 133-136.
10. Kondo, Y.; Miyahara, K.; Kashimura, N. *Can. J. Chem.* 1973, *51*, 3272-3276.
11. Berman, E.; Daman, M. E.; Dill, K. *Carbohydr. Res.* 1983, *116*, 144-149.
12. Witczack, Z. J. *Adv. Carbohydr. Chem. Biochem.* 1986, *44*, 91-145.
13. Burkert, U.; Allinger, N. L. *Molecular Mechanics*, ACS Monograph No *177*, American Chemical Society, Washington, DC 1982.
14. Bundle, D. R.; Lemieux, R. U. *Methods Carbohydr. Chem.* 1976, *7*, 79-86.
15. Horton, D.; Priebe, W.; Varela, O. *J. Org. Chem.* 1986, *51*, 3479-3485.
16. Horton, D.; Wander, J. *The Carbohydrates: Chemistry and Biochemistry*; Pigman, W. and Horton, D. Eds.; Academic, New York, 1980, Vol. *IB*, 799-842.
17. Shah, R. H.; Bose, J. L.; Bahl, O. P. *Carbohydr. Res.* 1979, *77*, 107-115.
18. Mathers, D. S.; Robertson, G. J. *J. Chem. Soc.* 1933, 696-698.
19. Evans, M. E. *Carbohydr. Res.* 1972, *21*, 473-475.
20. Oldham, J. W. H.; Robertson, G. J. *J. Chem. Soc.* 1935, 685-689.
21. Cook, A. F.; Overend, W. G. *J. Chem. Soc. C* 1966, 1549-1556.
22. Hanessian, S.; Plessas, N. R. *J. Org. Chem.* 1969, *34*, 1035-1044.
23. Staab, H. A. *Angew. Chem. Int. Ed. Engl.* 1962, *1*, 351-367.
24. Helferich, B.; Klein, W.; Schäfer, W. *Ann.* 1926, *449*, 19-26.
25. Lehmann, J. *Carbohydr. Res.* 1966, *2*, 486-499.