SYNTHETIC STUDIES ON HETEROCYCLES FROM SUGAR DERIVATIVES I. PREPARATION OF D-MANNOPYRANO[*cis*-1, 2-*b*]DIHYDROBENZOTHIAZINE*

M. SEKIYA AND S. ISHIGURO**

Kyorin Chemical Laboratory, 1-3-32, Ukima, Kita-Ku, Tokyo (Japan)

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ABSTRACT

o-Aminophenyl 3,4,6-tri-*O*-acetyl-2-*O*-mesyl-1-thio-β-D-glucopyranoside (**3**) was prepared from the corresponding bromide by treatment with *o*-aminobenzenethiol. Refluxing a mixture of potassium acetate and sodium acetate with **3** in aqueous ethanol afforded 3,4,6-tri-*O*-acetyl-D-mannopyrano[*cis*-1,2-*b*]dihydrobenzothiazine (**14**) in 38% yield. Compound **14** was also obtainable from the corresponding deacetylated product from **3** in 75% yield. The structure was confirmed by u.v., i.r., n.m.r., and mass spectra. Attempted cyclization to prepare manno- and talopyranodihydrobenzooxazine and talopyranodihydrobenzothiazine from the corresponding aromatic glycosides and thioglycosides failed under similar conditions. The n.m.r. spectra of some *o*-substituted phenyl β-D-galactopyranosides and 1-thio-β-D-galactopyranosides are discussed.

INTRODUCTION

Much effort has been expended on the preparation from saccharide derivatives[2] of heterocycles having biological activity. In particular, there have been many reports on the synthesis of nucleosides having an anhydro bond between the glycosyl moiety and the pyrimidine or purine base (anhydro nucleosides)[3]. However, no synthetic study on aromatic anhydro glycosides† corresponding to the anhydro nucleosides has been reported.

Previously, S. Tejima and co-workers[4] have noted the anomalously high reactivity toward intramolecular, nucleophilic substitution of 2-mesyl esters of thio sugars. This observation prompted the present extention of synthetic studies on aryl glycosides and aryl thioglycosides, through nucleophilic substitution of a mesyloxy group at C-2 by an amino group in the aglycon. The present paper deals with the formation of the title compound from the new aryl thioglycoside.

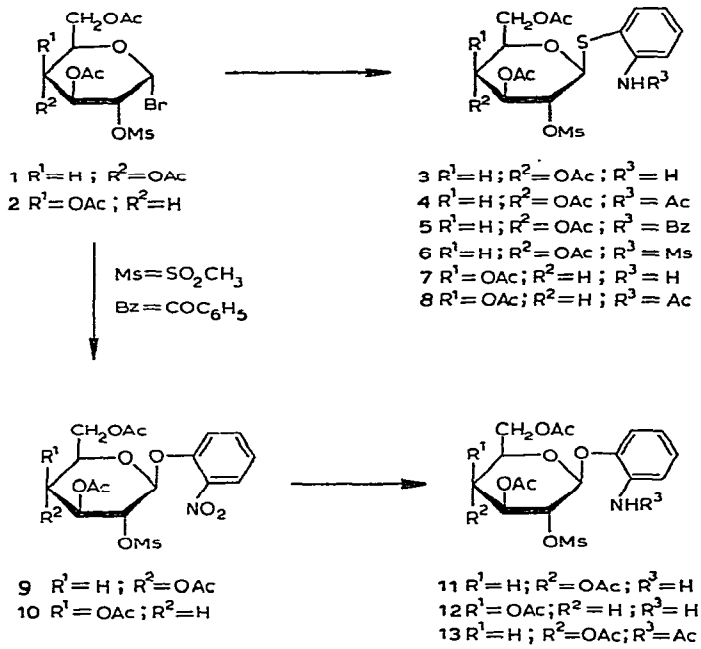
*For a preliminary communication, see ref. 1,

**Present address: Department of Biochemistry, Purudue University, Lafayette, Ind., U. S. A.

†In this case, the term "anhydro glycoside" signifies those compounds having an anhydro bond between the glycosidic moiety and the aglycon.

RESULTS AND DISCUSSION

The aryl thioglycosides were synthesized by a slight modification of the method of Purves[5]. Refluxing 2 moles of potassium *o*-aminobenzenethioxide with one mole of 3,4,6-tri-*O*-acetyl-2-*O*-mesyl-α-D-glucopyranosyl bromide[6] (**1**) in chloroform–methanol for 15 min afforded *o*-aminophenyl 3,4,6-tri-*O*-acetyl-2-*O*-mesyl-1-thio-β-D-glucopyranoside (**3**) in 82% yield and giving an acceptabie elemental analysis. The i.r. spectrum of **3** suggested the presence of mesyl and amino groups. The n.m.r. spectrum of **3** showed the H-1 doublet at τ 4.88, $J_{1,2}$ 10 Hz, in accord with the β configuration and the diaxial orientation of H-1 and H-2. Acylation of **3** with acetic

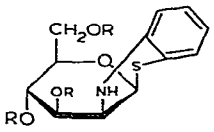


anhydride or benzoyl chloride in pyridine gave high yields of crystalline *o*-acetamidophenyl 3,4,6-tri-*O*-acetyl-2-*O*-mesyl-1-thio-β-D-glucopyranoside (**4**), and the corresponding *o*-benzamido derivative (**5**). Sulfonylation of **3** with mesyl chloride in pyridine gave a dimethanesulfonate, namely, *o*-methanesulfonamidophenyl 3,4,6-tri-*O*-acetyl-2-*O*-mesyl-1-thio-β-D-glucopyranoside (**6**), in 87% yield.

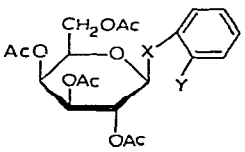
o-Aminophenyl glycosides were prepared according to the method of Latham[7]. Treatment of **1** with *o*-nitrophenol in the presence of potassium carbonate in dry acetone gave *o*-nitrophenyl 3,4,6-tri-*O*-acetyl-2-*O*-mesyl-β-D-glucopyranoside (**9**), in 14% yield. Hydrogenation of **9** with Raney nickel in methanol gave *o*-aminophenyl 3,4,6-tri-*O*-acetyl-2-*O*-mesyl-β-D-glucopyranoside (**11**), in 92% yield. The i.r. of **11** showed the presence of an amino group, and no nitro-group absorption near 1530 cm^{-1} The n.m.r. spectra of **9** and **11** showed the H-1 resonances as doublets at τ 4.62,

4,48 with $J_{1,2}$ 9 and, $J_{1,2}$ 8 Hz, respectiveiy. These large values indicate the 1,2-diaxial disposition of H-1 and H-2 and thus confirming the β configuration.

The D-galactose analogs **7**, **8**, **10**, and **12** were prepared by methods similar to those just mentioned. These aryl galactosides are considered to have the β configuration and a pyranoid ring because of (*a*) their method of synthesis from the α-galactopyranosyl bromide **2**, and (*b*) their more negative rotations when compared with *o*-substituted phenyl α-D-galactosides[8]. Their n.m.r. spectra showed a $J_{1,2}$ coupling



14 R=Ac; 15 R=H; 16 R=Bz



17 X=S; Y=NH_2
18 X=S; Y=NHAc
19 X=O; Y=NO_2

constant 2.6–3 Hz. Such small values are not consistent with the values expected from phenyl β-D-galactopyranosides. For further proof of the anomeric configuration of the galactose derivatives, the reference compounds **17**, **18**, and **19** (ref. 9), which clearly possess the β configuration, were prepared and their chemical shifts and coupling constants compared (Table I). It may be presumed that the small values (2.6–3) of the $J_{1,2}$ coupling constants, unexpected for protons oriented axial–axial, are due to ring strain caused by steric hindrance between the axial C-4 acetyl group and the *o*-substituted phenyl aglycon.

In the next step, an NH-anhydro compound was synthesized by intramolecular, nucleophilic replacement of the C-2 mesyloxy group by the amino group of the aglycon. Refluxing **3** with an excess of potassium acetate and sodium acetate in aquous ethanol for 2 h afforded crystals (**14**), in 38% yield. The same product was also obtainable from **3** in 75% yield by the following procedure: deacetylation of **3**, followed by heating under reflux with sodium hydrogen carbonate in aqueous ethanol, and then reacetylation with acetic anhydride in pyridine. The structure of **14** was assigned as 3,4,6-tri-*O*-acetyl-D-mannopyrano[*cis*-1,2-*b*] dihydrobenzothiazine*, on the basis of elementary analyses, and i.r. and n.m.r. spectra. Details are recorded in the Experimental section. It is noteworthy that the signals of the phenyl protons in **14** are observed 0.4–0.7 p.p.m. to higher field than their position in the corresponding phenyl glycosides. This upfield shift of the phenyl protons could be due to the formation of a new ring-system having some interaction between the benzene and pyranose ring.

Deacetylation of **14** with chilled sodium methoxide in methanol gave D-mannopyrano[*cis*-1,2-*b*]dihydrobenzothiazine (**15**). Pyranodihydrobenzothiazine derivatives have not yet been reported in the literature. To confirm the postulated structure,

*An officially approved system of nomenclature for such fused-ring systems does not yet exist.

TABLE I

CHEMICAL SHIFTS AND COUPLING CONSTANTS OF THE METHINE PROTON IN *o*-SUBSTITUTED PHENYL β-D-GALACTOPYRANOSIDES AND 1-THIO-β-D-GALACTOPYRANOSIDES

Compound	*Atom at C-1*	*Substituent*		*Chemical shifts* τ^a *(Coupling constants, Hz)*				
		o-*Aryl*	*O-2*	*H-1*	*H-2*	*H-3*	*H-4*	*H-5*
7	S	NH_2	Ms	4.57 d ($J_{1,2}$ 2.7)	4.88 q ($J_{2,3}$ 8.5)	5.11 t ($J_{3,4}$ 10)	5.40 d ($J_{4,5}$ 10)	6.13 q
8	S	NHAc	Ms	4.54 d (2.6)	4.89 q (9)	5.08 t (10)	5.39 d (0)	6.08 q
10	O	NO_2	Ms	4.46 d (2.8)	4.65 q (7.6)	4.96 q (12)	4.56 d (0)	ca. 5.8
12	O	NH_2	Ms	4.50 d (2.6)	4.8～4.96			5.74～5.97
17	S	NH_2	Ac	4.58 d (2.7)	4.98 q (10)	4.82 t (10)	5.42 d (0)	6.12 q
18	S	NHAc	Ac	4.64 d (3)	5.02 q (10)	4.80 t (9.9)	5.42 d (0)	6.11 q
19	O	NO_2	Ac	4.50 d (3)	4.84 q (10)	4.42 q (7.5)	4.86 d (0)	ca. 5.8

[a]Multiplicity: d, doublet; t, triplet; q, quartet,

the mass spectra of both **14** and **15** were measured. Their major fragmentation patterns have already been tabulated[1]. Interestingly, the peaks at *m/e* 148 and 149 correspond to those expected for the benzothiazine moiety.

The mass spectra of simple glycosides have been shown[10] to indicate primary fragmentation of the molecular ion at the C-1 –aglycon. In the case of **14** and **15**, the bonds between C-1 and C-2 of the sugar moieties remain in the benzothiazine portion during the course of fragmentation. Benzoylation of **15** with benzoyl chloride in pyridine afforded the corresponding tribenzoate (**16**) in 60% yield. The u.v. spectra of **14**, **15**, and **16** show moderate absorption near 304–306 nm and a hypsochromic shift as compared with **3** and **17**. This behavior appears to be characteristic of the $-NHC_6H_4S-$ group (Table II).

TABLE II

U.V. DATA OF *o*-AMINOPHENYL 1-THIO-β-D-GLYCOPYRANOSIDES AND D-MANNOPYRANODIHYDROBENZOTHIAZINES

Compound	λ_{max} (*nm*)	$\varepsilon \times 10^{-3}$	*Solvent*
o-Aminobenzenethiol	348	2.4	EtOH
3	310	3.2	EtOH
17	309	3.2	EtOH
14	304	3.5	EtOH
15	306	3.7	EtOH
16	304	3.9	EtOH

Except for the anhydro nucleosides, there is only one report of a tricyclic ring involving a pyranose ring; this is the D-glucopyrano[*cis*-2,1-*c*]1,2,3,4-tetrahydroisoquinoline reported in 1967 by Wacker and Fritz[11].

In the next step, the preparation of talopyranodihydrobenzothiazine, and manno- and talopyranodihydrobenzooxazine derivatives corresponding to **14** was attempted, but treatment of **7** with an excess of potassium acetate and sodium acetate in aqueous ethanol did not afford the desired dihydrobenzothiazine; instead, starting material and an unidentified, syrupy product were obtained. The i.r. spectrum of the syrup showed no absorption near 1170–1180 cm^{-1} corresponding to an *O*-mesyl group, but showed the presence of an amino group. Attempted cyclization of deacetylated **11** with sodium hydrogen carbonate in aqueous ethanol, followed by acetylation, likewise did not yield a dihydrobenzooxazine, but gave instead an unidentified, crystalline product (**20**). The i.r. spectrum of this product showed no absorption near 1170–1180 cm^{-1} corresponding to an *O*-mesyl group, but showed the presence of an NHAc group. The n.m.r. spectrum revealed five singlets at τ 7.71, 7.75, 7.85, 7.87, 7.94 attributable to one *N*-acetyl and four *O*-acetyl groups. The analytical data for **20** correspond to an empirical formula of $C_{22}H_{27}NO_{11}$. The mass spectrum of **20** showed a molecular-ion peak (*m/e* 481) and a peak for a tetra-*O*-acetylhexose oxonium ion (*m/e* 331). From these data, it is speculated that **20** could be *o*-amidophenyl 2,3,4,6-tetra-*O*-acetyl-β-D-hexopyranoside. The physical constants and spectral data

of this unidentified product are not consistent with those of *o*-acetamidophenyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside, m.p. 185–187°, $[\alpha]_D^{26}$ −34° as, reported by Wagner[12].

It is noteworthy that intramolecular nucleophilic substitution on the 2-mesyloxy group occured under very mild conditions, probably via the NH-anhydro intermediate, although the intermediate could not be isolated in either case.

Cyclization attempts with **13** and with the *o*-amidophenyl 1-thioglucoside derivatives **4**, **5**, and **6** led, unexpectedly only to the starting compounds.

EXPERIMENTAL

General. — Unless stated otherwise, solvents were evaporated *in vacuo* at a bath temperature of 40° in a rotary evaporater. Reactions were monitored by t.l.c. on Silica Gel G (E. Merck, Darmstadt, Germany), with solvent systems 2:1 (*v/v*) benzene–ether, 19:1 (*v/v*) benzene–methanol, and 65:23:12 (*v/v*) ethyl acetate–isopropylalcohol–water. Detection was effected with sulfuric acid or iodine vapor. Melting points were determined with a micro melting-point apparatus and are uncorrected. Optical rotations were measured in 1-dm tubes with an Applied Electric Lab., Ltd. automatic polarimeter MP-1T. I.r. spectra were recorded with a Jasco infrared spectrophotometer DS-301. U.v. spectra were recorded with a Hitachi spectrophotometer 124. N.m.r. spectra were measured at 100 MHz in chloroform-*d* with a Jeol, JNM-4H-100 spectrometer. Chemical shifts are given on the τ scale and coupling constants (*J*) in Hz, with tetramethylsilane as the internal standard. Mass spectra were obtained with a Hitachi RMU-6-E mass spectrometer modified for direct introduction of the sample at an ionizing potential of 75 eV.

*o-Aminophenyl 3,4,6-tri-*O*-acetyl-2-*O*-mesyl-1-thio-β-*D*-glucopyranoside* (**3**). — A solution of 3,4,6-tri-*O*-acetyl-2-*O*-mesyl-α-D-glucopyranosyl bromide (**1**) (9 g) in chloroform (50 ml) was added to a solution of *o*-aminobenzenethiol (5 g) in 50 ml of methanolic potassium hydroxide (2.25 g), and the mixture was heated for 15 min under reflux. During the course of the reaction, the mixture became turbid and potassium bromide precipitated. After cooling, the reaction mixture was poured into ice–water.

The water layer was extracted with chloroform (50 ml). The combined chloroform layers were washed with 10% potassium hydroxide solution, and water, dried (sodium sulfate), and evaporated to a syrup that crystallized from ethanol. Recrystallization from benzene afforded crystals (8.1 g, 82%), m.p. 155–156°, $[\alpha]_D^{23}$ +28° (*c* 1, chloroform); ν_{max}^{KBr} 3470, 3360 (NH_2), 1750 (OAc), 1176 (OMs), 752 cm^{-1} (phenyl); λ_{max}^{EtOH} 234 (ε 8,300), 246 (6,100) 310 nm (3,200); n.m.r. data τ 2.5, 3.3 (each 2-proton multiplets, phenyl), 4.88 (1-proton doublet, $J_{1,2}$ 10 Hz, H-1), 5.75 (2-proton singlet, NH_2), 6.78 (3-proton singlet, OMs), 7.90, 7.93, 7.98 (each 3-proton singlets, OAc); *m/e* 395 ($M^+ - 96$).

Anal. Calc. for $C_{19}H_{25}NO_{10}S_2$: C, 46.44; H, 5.13; N, 2.85; S, 13.04. Found: C, 46.70; H, 5.08; N, 2.72; S. 12.89.

*o-Acetamidophenyl 3,4,6-tri-*O*-acetyl-2-*O*-mesyl-1-thio-β-*D*-glucopyranoside* (**4**). — To a chilled mixture of acetic anhydride (10 ml) and pyridine (10 ml) was added

3 (2 g). The mixture was kept at room temperature overnight, and then poured into ice–water, and the product was extracted with chloroform. The chloroform layer was washed with dilute sulfuric acid, aqueous sodium hydrogen carbonate, and water, dried (sodium sulfate), and evaporated to a syrup that crystallized from ethanol. Recrystallization from the same solvent gave pure **4** (1.74 g, 80%), m.p. 132–133°, $[\alpha]_D^{23}$ +28° (*c* 0.35, chloroform); ν_{max}^{KBr} 3370 (NH), 1750 (OAc), 1690 (NAc), 1180 (OMs), 765 cm^{-1} (phenyl); n.m.r. data τ 2.3–2.9 (4-proton multiplet, phenyl), 1.32 (1-proton singlet, NH), 4.94 (1-proton doublet, $J_{1,2}$ 10 Hz, H-1), 6.8 (3-proton singlet, OMs), 7.80 (3-proton singlet, NAc), 7.91, 7.97, 7.98 (each 3-proton singlets, OAc); *m/e* 437 (M^+ −96).

Anal. Calc. for $C_{21}H_{27}NO_{11}S_2$: C, 47.28; H, 5.10; N, 2.63; S, 12.01. Found: C, 47.46; H, 4.94; N, 2.58; S, 11.95.

o-*Benzamidophenyl 3,4,6-tri*-O-*acetyl-2*-O-*mesyl-1-thio-β*-D-*glucopyranoside* (**5**). — To a stirred, chilled solution of **3** (2 g) in pyridine (20 ml) was added benzoyl chloride (1 ml) dropwise. The mixture, protected from moisture, was stirred for 1 h at 0°, kept overnight at room temperature, and then poured into ice–water. The product was isolated as for **3**. Recrystallization from ethanol gave pure **5** (2.2 g, 91%), m.p. 138–139°, $[\alpha]_D^{23}$ +94° (*c* 0.36, chloroform); ν_{max}^{KBr} 3380 (NH), 1750 (OAc), 1680 (NBz), 1180 (OMs), 760 cm^{-1} (phenyl); n.m.r. data τ 0.39 (1-proton singlet, NH), 1.22 (9-proton multiplet, phenyl), 4.73 (1-proton doublet, $J_{1,2}$ 10, H-1), 6.73 (3-proton singlet, OMs). 7.87, 7.98, 8.13 (each 3-proton singlet, OAc); *m/e* 499 (M^+ −96).

Anal. Calc. for $C_{26}H_{29}NO_{11}S_2$: C, 52.44; H, 4.91; N, 2.35; S, 10.77. Found: C, 52.43; H, 4.91; N, 2.18; S, 10.56.

o-*Methanesulfonamidophenyl 3,4,6-tri*-O-*acetyl-2*-O-*mesyl-1-thio-β*-D-*glucopyranoside* (**6**). — To a chilled, stirred solution of **3** (2 g) in pyridine (20 ml) was added mesyl chloride (1 ml) dropwise. The mixture was treated as in the preparation of **3**. Recrystallization from ethanol **6** gave (2 g, 87%), m.p. 165–167°, $[\alpha]_D^{23}$ −7.4° (*c* 0.37, chloroform); ν_{max}^{KBr} 3300 (NH), 1755 (OAc), 1180 (OMs), 1160 (NMs), 760 cm^{-1} (phenyl); n.m.r. data τ 1.9 (1-proton singlet, NH), 2.2–2.85 (4-proton multiplet, phenyl), 4.97 (1-proton doublet, $J_{1,2}$ 10 NHz, H-1), 6.8 (3-proton singlet, OMs), 7.02 (3-proton singlet, NMs), 7.92, 7.94, 8.00 (each 3-proton singlets, OAc); *m/e* 569 (M^+), 473 (M^+ −96).

Anal. Calc. for $C_{20}H_{27}NO_{12}S_3$: C, 42.19; H, 4.78; N, 2.46; S, 16.88. Found: C, 41.83; H, 4.69; N, 2.30, S. 16.64.

o-*Aminophenyl 3,4,6-tri*-O-*acetyl-2*-O-*mesyl-1-thio-β*-D-*galactopyranose* (**7**). — A solution of 3,4,6-tri-*O*-acetyl-2-*O*-mesyl-α-D-galactopyranosyl bromide[6] (**2**) (9 g) in chloroform (50 ml) was added to a solution of *o*-aminobenzenethiol (5 g) in 50 ml of methanolic potassium hydroxide (2.25 g) and the mixture was heated for 20 min under reflux. The reaction mixture was treated as in the preparation of **3**, to give **7** as a slightly yellow syrup (9 g, 91%), $[\alpha]_D^{11}$ +11° (*c* 1.44, chloroform); ν_{max}^{KBr} 3480, 3370 (NH_2), 1750 (OAc), 1175 (OMs), 750 cm^{-1} (phenyl); n.m.r. data τ 5.73 (2-proton singlet, NH_2), 6.80 (3-proton singlet, OMs), 7.84, 7.94, 7.99 (each 3-proton singlets, OAc); *m/e* 395 (M^+ −96).

o-Acetamidophenyl 3,4,6-tri-O-acetyl-2-O-mesyl-1-thio-β-D-galactopyranoside (**8**). — To a chilled mixture of acetic anhydride (30 ml) and pyridine (30 ml) was added **7** (9 g). The mixture was treated as in the preparation of **4**, to give a colorless, syrupy **8** (8 g, 82%), $[\alpha]_D^{11}$ +26° (*c* 0.92, chloroform); ν_{max}^{KBr} 3360 (NH), 1750 (OAc), 1690 (NAc), 1175 (OMs), 755 cm^{-1} (phenyl); n.m.r. data τ 1.3 (1-proton singlet, NH), 6.80 (3-proton singlet, OMs), 7.84, 7.94, 7.99 (each 3-proton singlets, OAc).

o-Nitrophenyl 3,4,6-tri-O-acetyl-2-O-mesyl-β-D-glucopyranoside (**9**). — A mixture of o-nitrophenol (13 g), anhydrous potassium carbonate (13 g), and **1** (26 g) in dry acetone (400 ml) was heated for 20 h under reflux. After the solvent had been evaporated to dryness, the residue was dissolved in chloroform, and then poured into ice–water. The chloroform layer was treated as in the preparation of **3**. Recrystallization from ethanol gave needles (3.8 g, 14%), m.p. 164–165°, $[\alpha]_D^{14}$ +35° (*c* i, chloroform); ν_{max}^{KBr} 1745 (OAc), 1525 (OAc), 1175 (OMs), 740 cm^{-1} (phenyl); n.m.r. data τ 2.08–2.8 (4-proton multiplet, phenyl), 4.62 (1-proton doublet, $J_{1,2}$ 9 Hz, H-1), 6.87 (3-proton singlet, OMs) 7.88, 7.93 (9-proton singlets, OAc); *m/e* 367 ($M^+ - 138$).

Anal. Calc. for $C_{19}H_{23}NO_{13}S$: C, 45.33; H, 4.58; N, 2.77; S, 6.34. Found: C, 45.76; H, 4.55; N, 2.80; S, 6.05.

o-Nitrophenyl 3,4,6-tri-O-acetyl-2-O-mesyl-β-D-galactopyranoside (**10**). — A mixture of *o*-nitrophenol (15 g), anhydrous potassium carbonate (15 g) and **2** (30 g) in dry acetone (450 ml) was treated as in the preparation of **9**. Recrystallization from ethanol gave pure **10** (13 g, 38%), m.p. 149–150°, $[\alpha]_D^{14}$ +17° (*c* 1, chloroform); ν_{max}^{KBr} 1750 (OAc), 1530 (NO_2), 1175 (OMs), 768 cm^{-1} (phenyl); n.m.r. data τ 6.86 (3-proton singlet, OMs), 7.79, 7.81, 7.85 (each 3-proton singlets, OAc); *m/e* 367 ($M^+ - 138$).

Anal. Calc. for $C_{19}H_{23}NO_{13}S$: C, 45.33; H, 4.58; N, 2.77; S, 6.34. Found: C, 45.09; H, 4.51; N, 2.80; S, 6.12.

o-Aminophenyl 3,4,6-tri-O-acetyl-2-O-mesyl-β-D-glucopyranoside (**11**). — To a suspension of **9** (4 g) in dry methanol (100 ml) was added Raney nickel (4 g). The mixture was agitated for 4 h at room temperature under hydrogen. After the catalyst had been removed by filtration, the filtrate was concentrated to dryness to give a crystalline residue. Recrystallization from ethanol gave **11** (3.6 g, 92%), m.p. 156–158°, $[\alpha]_D^{14}$ −45° (*c* 1, *N,N*-dimethylformamide); ν_{max}^{KBr} 3480, 3380 (NH_2), 1745 (OAc), 1173 (OMs), 745 cm^{-1} (phenyl); n.m.r. data (in dimethyl sulfoxide-d_6) τ 3.0–3.50 (4-proton multiplet, phenyl), 4.48 (1-proton doublet, $J_{1,2}$ 8 Hz, H-1), 5.16 (2-proton singlet, NH_2), 6.76 (3-proton singlet, OMs), 7.96, 7.98 (9-proton singlets, OAc); *m/e* 475 (M^+), 367 ($M^+ - 108$).

Anal. Calc. for $C_{19}H_{25}NO_{11}S$: C, 47.99; H, 5.30; N, 2.95; S, 6.74. Found: C, 47.45; H, 5.32; N, 2.91; S, 6.58.

o-Aminophenyl 3,4,6-tri-O-acetyl-2-O-mesyl-β-D-galactopyranoside (**12**). — To a suspension of **10** (10 g) in dry methanol (250 ml) was added Raney nickel (10 g). The mixture was agitated for 4 h at room temperature under hydrogen. The reaction solution was treated as in the preparation of **11**. Recrystallization from ethanol gave needles (9 g, 90%), m.p. 126.5–128°, $[\alpha]_D^{14}$ −11° (*c* 1, chloroform); ν_{max}^{KBr} 3470, 3360 (NH_2), 1745 (OAc), 1172 (OMs), 737 cm^{-1} (phenyl); n.m.r. data τ 6.25 (2-proton

singlet, NH_2), 6.88 (3-proton singlet, OMs), 7.80, 7.91, 7.93 (each 3-proton singlets, OAc); *m/e* 475 (M^+), 367 ($M^+ - 108$).

Anal. Calc. for $C_{19}H_{25}NO_{11}S$: C, 47.99; H, 5.30; N, 2.95; S, 6.74. Found: C, 48.21; H, 5.55; N, 2.89; S, 6.70.

o-*Acetamidophenyl 3,4,6-tri*-O-*acetyl-2*-O-*mesyl-β*-D-*glucopyranoside* (**13**). — To a chilled mixture of acetic anhydride (10 ml) and pyridine (10 ml) was added **11** (1 g). The mixture was treated as in the preparation of **4**. Recrystallization from ethanol gave needles (1 g, 92%), m.p. 177–183.5°, $[\alpha]_D^{14}$ −44° (*c* 1, chloroform); ν_{max}^{KBr} 3370 (NH), 1750 (OAc), 1690 (NAc), 1175 cm^{-1} (OMs); n.m.r. data τ 1.6 (2-proton multiplet, NH and phenyl), 2.97 (3-proton multiplet, phenyl), 4.82 (1-proton doublet, H-1), 6.91 (3-proton singlet, OMs), 7.82 (3-proton singlet, NAc), 7.88, 7.90, 7.92 (each 3-proton singlets, OAc); *m/e* 517 (M^+), 367 ($M^+ - 150$).

Anal. Calc. for $C_{21}H_{27}NO_{12}S$: C, 48.73; H, 5.26; N, 2.71; S, 6.19. Found: C, 48.73; H, 5.16; N, 2.66; S, 6.14.

3,4,6-Tri-O-*acetyl*-D-*mannopyrano*[cis-*1,2*-b]*dihydrobenzothiazine* (**14**). — *A*. A mixture of **3** (10 g), potassium acetate (10 g), and sodium acetate trihydrate (10 g) in 90% ethanol (200 ml) was heated for 2 h under reflux. After cooling the reaction mixture and adding chloroform (100 ml) thereto, it was poured into ice–water and the water layer was extracted with chloroform. The combined chloroform layers were washed with water, dried (sodium sulfate), and evaporated to give a syrup that crystallized from ethanol. Recrystallization from ethanol gave colorless needles (3 g, 38%), m.p. 152–154°, $[\alpha]_D^{14}$ +3° (*c* 1, chloroform); ν_{max}^{KBr} 3380 (NH_2) 1740 (OAc), 750 (phenyl), no absorption near 1170–1180 cm^{-1} (OMs); λ_{max}^{EtOH} 230 (ε 13,000), 265 (3,100), 304 nm (3,500); n.m.r. data τ 2.9–3.53 (4-proton multiplet, phenyl), 4.85 (1-proton singlet, NH), 7.90, 7.97 (9-proton singlets, OAc); *m/e* 395 (M^+), 149.

Anal. Calc. for $C_{18}H_{21}NO_7S$: C, 54.68; H, 5.35; N, 3.54; S, 8.11. Found: C, 54.60; H, 5.50; N, 3.43; S, 8.06.

B. To a suspension of **3** (10 g) in methanol (100 ml) was added methanol (100 ml) saturated with dry hydrogen chloride gas at 0°, and the reaction mixture was refrigerated overnight. Complete removal of the solvent afforded a syrup that was suspended in saturated sodium hydrogen carbonate solution (50 ml). Ethanol (50 ml) was added, and the mixture was heated for 20 min under reflux. Removal of the solvent gave a crystalline mass, which was acetylated with 1:1 (*v/v*) pyridine–acetic anhydride (100 ml) in the usual manner. The mixture was treated as described in the preparation of **3** to afford crystals. Recrystallization from ethanol gave pure **14** (6 g, 75%), m.p. 152–154°. The product was identical with **14** prepared by method *A* by mixed m.p. and i.r. spectrum.

D-*Mannopyrano*[cis-*1,2*-b]*dihydrobenzothiazine* (**15**). — A mixture of **14** (2 g) in dry methanol (25 ml) containing sodium (0.2 g) was stirred for 5 min at 0°, and then kept for 2 h at room temperature. After addition of glacial acetic acid (1 ml), the mixture was poured into ice–water and the resulting precipitate was filtered off, washed with water, and dried. Recrystallization from absolute ethanol gave **15** as

colorless crystals (1 g, 73%), m.p. 205–207°, $[\alpha]_D^{14}$ −5° (*c* 0.2, *N*,*N*-dimethylformamide) ν_{max}^{KBr} 3400 (NH), 740 cm^{-1} (phenyl); *m/e* 269 (M^+), 149.

Anal. Calc. for $C_{12}H_{15}NO_4S$: C, 53.52; H, 5.61; N, 5.20; S, 11.90. Found: C, 53.62; H, 5.71; N, 4.87; S, 11.48.

Compound **15** (1 g) was acetylated with 1:1 (*v/v*) pyridine–acetic anhydride (10 ml) to afford a crystalline product (1 g, 68%), m.p. 152–153° identical wity **15** by mixed m.p. and i.r. spectrum.

*3,4,6-Tri-*O*-benzoyl-*D*-mannopyrano*[cis-*1,2*-b]*dihydrobenzothiazine* (**16**). — To a chilled, stirred solution of **15** (2 g) in pyridine (30 ml) was added benzoyl chloride (4.2 g) dropwise. The mixture, protected from moisture, was stirred for 1 h at 0°, kept overnight at room temperature, and then poured into ice– water (300 ml). The product was extracted with chloroform, the chloroform layer was washed with dilute sulfuric acid, aqueous sodium hydrogen carbonate solution, and water, dried (sodium sulfate), and evaporated to give a syrup, which was triturated with ethanol to afford crystals. Recrystallization from ethanol gave pure **16** (2.6 g, 60%), m.p. 190° $[\alpha]_D^{18}$ +41° (*c* 1, chloroform); ν_{max}^{KBr} 3390, (NH), 1723 (OBz), 1600, 1587, 740 cm^{-1} (phenyl); λ_{max}^{EtOH} 304 nm (ε 3,900); n.m.r. data τ 1.94–2.77 (15-proton multiplet, benzoyl), 2.94–3.53 (4-proton multiplet, phenyl), 4.85 (1-proton, NH); mass-spectral data, M^+ not observed.

Anal. Calc. for $C_{33}H_{27}NO_7S$: C, 68.15; H, 4.68; N, 2.41; S, 5.52. Found: C, 68.45; H, 4.63; N, 2.37; S, 5.49.

o-*Aminophenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-*D*-galactopyranoside* (**17**). — A solution of tetra-*O*-acetyl-α-D-galactopyranosyl bromide (4.5 g) in chloroform (30 ml) was added to a solution of *o*-aminobenzenethiol (2.5 g) in 30 ml of methanolic potassium hydroxide (1.12 g), and the mixture was heated for 20 min under reflux. The reaction mixture was treated as in the preparation of **3** to give slightly yellow crystals (9.7 g, 55%). Recrystallization from ethanol gave pure **14**, m.p. 101–103°, $[\alpha]_D^{11}$ +26° (*c* 1.1, chloroform); ν_{max}^{KBr} 3480, 3360 (NH_2), 1745, 1730 (OAc), 750 cm^{-1} (phenyl); n.m.r. data τ 2.55–3.4 (4-proton multiplet, phenyl), 5.6 (2-proton broad singlet, NH_2), 7.85 (6-proton singlet, OAc), 7.97, 8.01 (each 3-proton singlet, OAc); mass-spectral data: *m/e* 455 (M^+).

Anal. Calc. for $C_{20}H_{25}NO_9S$: C, 52.72; H, 5.50; N, 3.08; S, 7.04. Found: C, 52.62; H, 5.41; N, 3.06; S, 7.01.

o-*Acetamidophenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-*D*-galactopyranoside* (**18**). — To a chilled mixture of acetic anhydride (10 ml) and pyridine (10 ml) was added **17** (1 g). The mixture was treated as in the preparation of **4** to give **18** as colorless syrup (1 g, 92%), $[\alpha]_D^{15}$ +34° (*c* 2, chloroform); i.r. ν_{max}^{KBr} 3460 (NH), 1750 (OAc), 1695 (NAc), 755 cm^{-1} (phenyl); n.m.r. τ: 1.3 (1-proton singlet, NH), 1.66 (1-proton doublet, phenyl), 2.42–3.05 (3-proton multiplet, phenyl), 7.82, 7.86, 7.91, 8.01, 8.04 (each 3-proton singlet, NAc and OAc).

o-*Nitrophenyl 2,3,4,6-tetra-*O*-acetyl-β-*D*-galactopyranoside* (**19**). — To a solution of sodium hydroxide (4.2 g) and *o*-nitrophenol (10 g) in water (105 ml) was added the solution of tetra-*O*-acetyl-α-D-galactopyranosyl bromide (22 g) in acetone (154 ml).

The mixture was kept for 5 h at room temperature and the solvent was removed to give long needles. Recrystallization from 95% ethanol gave pure **19** (15 g, 60%), m.p. 175–176°, $[\alpha]_D^{20}$ +60° (*c* 1, chloroform). lit.[9] m.p. 172–172.5°, $[\alpha]_D^{18}$ +69.9° (*c* 1.9, chloroform).

Attempted cyclization of o-*aminophenyl 3,4,6-tri*-O-*acetyl-2*-O-*mesyl-1-thio-β*-D-*galactopyranoside* (**7**). — A mixture of **7** (5 g), potassium acetate (5 g), and sodium acetate trihydrate (5 g) in 90% ethanol (100 ml) was heated for 2 h under reflux. The reaction mixture was treated as described in the preparation of **9** to give a syrupy residue (4 g), which was dissolved in chloroform and chromatographed on silica gel (120 g). Elution was performed using benzene, 7.5% ether–benzene (*v/v*), and 10% ether–benzene (*v/v*). From the last effluent, two syrupy products were obtained. No structure could be assigned to the yellow syrup obtained from the first portion of the effluent (1 g): i.r. ν_{max}^{KBr} 3460, 3360 (NH_2), 1750 (OAc), 750 cm^{-1} (phenyl), no absorption near 1170–1180 cm^{-1} (OMs). The second syrup (3 g), obtained from the later portion of the effluent, was identical with the starting material (**7**).

Attempted cyclization of o-*aminophenyl 3,4,6-tri*-O-*acetyl-2*-O-*mesyl-β*-D-*glucopyranoside* (**11**). — To a suspension of **11** (3 g) in methanol (40 ml) was added methanol (40 ml) saturated with dry hydrogen chloride gas at 0° and the mixture was kept for 3 h at room temperature. Complete removal of the solvent afforded a syrup, which was suspended in saturated sodium hydrogen carbonate solution (30 ml). After ethanol (30 ml) had been added, the reaction mixture was heated for 30 min under reflux. Removal of the solvent gave a crystalline mass, which was acetylated 1:1 (*v/v*) pyridine–acetic anhydride (40 ml). The mixture was treated as described in the preparation of **3** to afford a crystalline residue, which was separated by column chromatography on silica gel (50 g). Elution with 10% ether–benzene and 5% methanol–benzene, successively gave, after removal of the solvent from the former effluent and addition of ethanol, crystals **20**, (0.8 g), m.p. 180–183°, $[\alpha]_D^{14}$ −19° (*c* 1, chloroform); i.r. ν_{max}^{KBr} 3360 (NH), 1740 (OAc), 1690 (NAc), 1600, 745 cm^{-1} (phenyl), no absorption near 1170 cm^{-1} (OMs); n.m.r. data: τ 1.5–3.05 (4-proton multiplet, phenyl), 1.9 (1-proton singlet, NH), 4.4–4.8 (4-proton multiplets, sugar protons), 5.67 (3-proton multiplets, sugar protons), 7.71, 7.75, 7.85, 7.87, 7.94 (each 3-proton singlets, NHAc and four OAc); mass-spectral data: *m/e* 481 (M^+), 331.

Anal. Calc. for $C_{22}H_{27}NO_{11}$: C, 54.89; H, 5.65; N, 2.91. Found: C, 54.84; H, 5.45; N, 2.83.

The later effluent was evaporated to give a crystalline product (1.5 g) identical with **13** by t.l.c. and i.r. and n.m.r. spectra.

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