IMPROVED SYNTHESIS OF 1,2-*trans*-ACETATES AND 1,2-*trans* ETHYL 1-THIOGLYCOSIDES DERIVED FROM 3,4,6-TRI-*O*-ACETYL-2-DEOXY-2-PHTHALIMIDO-D-HEXOPYRANOSIDES

Jan VESELÝ[a1], Miroslav LEDVINA[b1,*], Jindřich JINDŘICH[a2], David ŠAMAN[b2] and Tomáš TRNKA[a3]

[a] *Department of Organic Chemistry, Charles University, Albertov 2030, 128 40 Prague 2, Czech Republic; e-mail:* [1] *jxvesely@mail.natur.cuni.cz,* [2] *jindrich@natur.cuni.cz,* [3] *trnka@natur.cuni.cz*

[b] *Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, Flemingovo nám. 2, 166 10 Prague 6, Czech Republic; e-mail:* [1] *ledvina@uochb.cas.cz,* [2] *saman@uochb.cas.cz*

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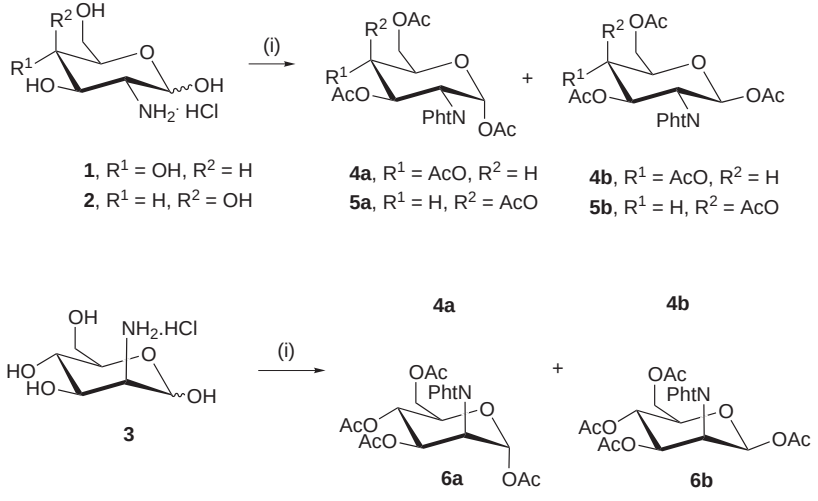
Effective one-pot synthesis of 1,2-*trans*-acetates **4b**, **5b** and **6a** derived from *N*-phthaloyl-protected D-glucosamine, D-galactosamine and D-mannosamine, respectively, is presented. Anomerisation of the corresponding 1,2-*cis*-acetates **4a**, **5a** and **6b** and direct conversion of all of them to 1,2-*trans* ethyl 1-thioglycosides **7**, **8** and **9** are also described and discussed.

Keywords: Carbohydrates; Aminosugars; Thioglycosides; Glycosyl donors; Phthalimide; Anomerisation; Protecting groups; Glycosides; Glycoconjugates.

2-Amino-2-deoxyhexopyranosides linked with 1,2-*trans*-glycosidic bonds are frequently encountered constituents of many naturally occurring oligosaccharides and glycoconjugates[1–3]. The β(1→4)-linked *N*-acetylglucosamine moieties form, *e.g.*, an important structural polysaccharide chitin[4], glycan part of peptidoglycan of bacterial cell walls[5,6] as well as the reducing end of glycan residues of *N*-glycoproteins[3]. *N*-Acetylgalactosamine residue β(1→4)-linked to 3-*O*-sialyl-β-D-galactopyranoside subunit constitutes a core unit of gangliosides[7–9]. Most commonly, introduction of the glycosidically linked 1,2-*trans*-2-amino-2-deoxyhexopyranoside residue was obtained in the oligosaccharide synthesis by the oxazoline method[10–12] or the phthalimide method introduced by Lemieux[13]. The latter is preferred, because 2-deoxy-2-phthalimidohexopyranoses with halogen, (trichloroacetimidoyl)oxy or alkylsulfanyl group at C-1 have consistently proved to be more efficient donors than the oxazolines[3]. The advantage of the latter alkyl 1-thioglycosides is that these can be used directly as glycosyl donor (by

activation *via* sulfonium ion) or simply converted to alternative glycosyl donors carrying on C-1 other leaving groups, such as halogen or (trichloroacetimidoyl)oxy group[14,15]. The preferred method for the preparation of alkyl 1-thioglycosides in recent years has been Lewis acid-catalyzed substitution of the anomeric acetate of peracetylated sugars with a desired alkanethiol[14,15]. In general, 1,2-*trans*-acetates react faster than their 1,2-*cis* counterparts[3,15] and the described[6,16,17] preparations of *N*-phthaloyl-protected ethyl 1-thioglycoside derived from D-glucosamine **7** and D-galactosamine **8**, using this approach, require 1,2-*trans*-acetates (β-acetates) **4b** and **5b** as starting materials (Scheme 1). These β-acetates are available from corresponding D-hexosamine hydrochlorides in five steps *via* *N*-(4-methoxybenzylidene) derivatives[6,17,18]. The "one-pot" synthesis of peracetylated 2-deoxy-2-phthalimido-D-hexopyranoses led to a mixture of α- and β-anomers[19–22]. The standard method of the conversion of α-acetates to β-acetates proceeded in two steps *via* glycosyl halide[23]. Access to 1,2-*trans*-acetates of 2-deoxy-2-phthalimidohexopyranoses was not only crucial for the preparation of target 1,2-*trans* ethyl 1-thioglycosides of 2-deoxy-2-phthalimidohexopyranoses, but these 1,2-*trans*-acetates can also directly serve as glycosyl donors for the preparation of 1,2-*trans*-*O*-glycosides in Lewis acid-catalyzed condensations with reactive glycosyl acceptors[24].



(i) conditions *A*: phthalic anhydride and $NaHCO_3$ (excess) in acetone/water, then Ac_2O in pyridine; conditions *B*: phthalic anhydride (excess) and $NaHCO_3$ in acetone/water, then Ac_2O in pyridine; conditions *C*: phthalic anhydride in pyridine/acetone/water, then Ac_2O in pyridine; conditions *D*: phthalic anhydride in pyridine/acetone/water, then Ac_2O and DMAP in pyridine

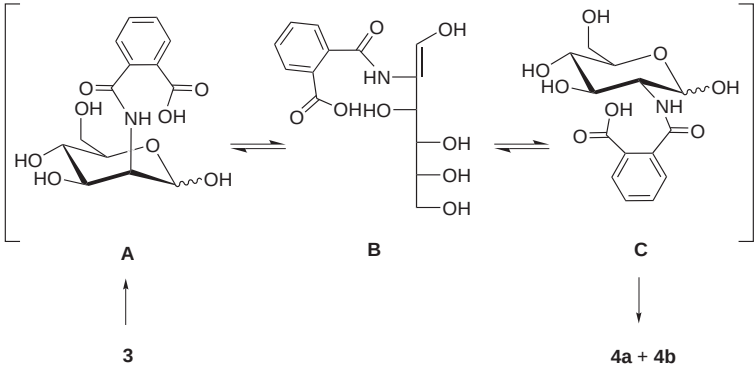
SCHEME 1

RESULTS AND DISCUSION

It stands to reason that the effective synthesis of 1,2-*trans*-acetates and 1,2-*trans* ethyl 1-thioglycosides of the 2-deoxy-2-phthalimidohexopyranoses is still a problem. These facts motivated us to focus our attention on the anomerization and one-step conversion of 1,2-*cis*-acetates to the corresponding 1,2-*trans* ethyl thioglycosides and one-pot synthesis of per-*O*-acetyl-2-deoxy-2-phthalimidohexopyranoses with preferential formation of 1,2-*trans*-acetates.

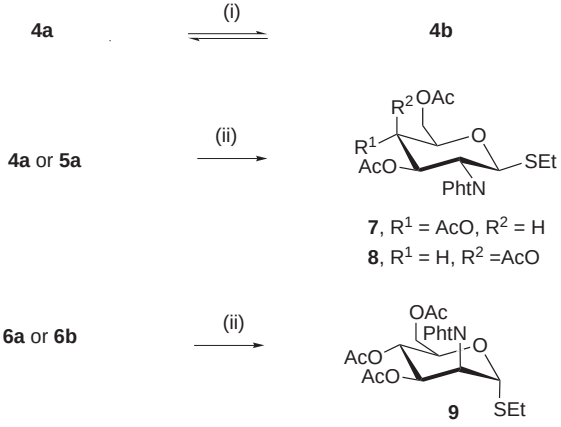
The one-pot synthesis of peracetylated 2-deoxy-2-phthalimido-D-hexopyranoses is based on the reaction of D-hexosamine hydrochloride with phthalic anhydride in the presence of base and subsequent cyclization and *O*-acetylation of intermediary phthalamic acid. It can be assumed that 1,2-*trans*- and 1,2-*cis*-acetates are obtained under the used reaction conditions. The choice of the reaction conditions can also suppress the undesired base-catalyzed epimerisation of intermediary phthalamic acid at position C-2 in the first step. By modification of the one-pot synthesis providing as main product α-acetate **4a**, described by Kochetkov *et al.*[19] (Scheme 1), *i.e.*, by the reaction of D-glucosamine hydrochloride (**1**) with phthalic anhydride in the presence of sodium hydrogencarbonate in a mixture of water–acetone and subsequent reaction of crude phthalamic acid with acetic anhydride in pyridine (conditions *A*), a mixture of α- and β-acetates **4a** and **4b** in the 1:1 ratio was obtained. An attempt to use this procedure for one-pot synthesis of α- and β-acetates derived from D-mannosamine (**3**) was not successful, because it yielded, in addition to the expected acetates with *manno* configuration, **6a** and **6b**, acetates with *gluco* configuration, **4a** and **4b**, in significant amounts. The formation of the products with *gluco* configuration can be explained by base-catalyzed epimerisation of the intermediate phthalamic acids **A** at position C-2, *via* enamine **B**, to the D-glucosamine derivative **C** (Scheme 2). Fortunately, this side reaction could be avoided by using an excess of phthalic anhydride relative to sodium hydrogencarbonate in the first step (conditions *B*), or by using pyridine as a softer base than sodium hydrogencarbonate (conditions *C*). The reaction of D-mannosamine hydrochloride (**3**) under conditions *B* yielded a mixture of α- and β-acetates **6a** and **6b** in the 1:1 ratio. D-Mannosamine hydrochloride (**3**) under conditions *C*, *i.e.*, by the reaction with phthalic anhydride in a mixture of pyridine–water–acetone, and subsequent reaction of crude phthalamic acid with acetic anhydride in pyridine afforded a mixture of α- and β-acetates **6a** and **6b** in the 5:2 ratio. D-Glucosamine hydrochloride (**1**) gave a mixture of α- and β-acetates **4a** and **4b** in the 3:4 ratio under condi-

tions *C*. The preferential formation of 1,2-*trans*-acetates under conditions *C* can be attributed to acetylation of the anomeric hydroxy group followed by the cyclisation of 2-carboxybenzamido group, since the 1,2-*cis* side of the pyranose ring gets shielded as soon as the phthalimido group is formed. Another significant enhancement of stereoselectivity in the formation of 1,2-*trans*-acetates was achieved by performing the second step in the presence of 4-(dimethylamino)pyridine (DMAP) (conditions *D*). D-Glucosamine hydrochloride (**1**), D-galactosamine hydrochloride (**2**) or D-mannosamine hydrochloride (**3**) under conditions *C*, *i.e.*, when reacted with phthalic anhydride in a mixture of pyridine–water–acetone, and subsequent reaction of crude phthalamic acid with acetic anhydride in pyridine in the presence of DMAP, afforded 1,2-*trans*-acetates **4b**, **5b** or **6a**, respectively, in good yields (**4b** 66%, **5b** 64%, **6a** 60%).



SCHEME 2

We found that the anomerization of 1,2-*cis*-acetates and their direct conversion to the corresponding 1,2-*trans* ethyl 1-thioglycosides can be accomplished by using stronger Lewis acid than $FeCl_3$ or $TiCl_4$, which were commonly used for the conversion of 1,2-*trans*-acetates to 1,2-*trans* ethyl 1-thioglycosides[6,16,17] (Scheme 3). The treatment of α-acetate of glucosamine derivative **4a** with trimethylsilyl trifluoromethanesulfonate (TMSOTf) in acetic anhydride led to a mixture of α- and β-anomers **4a** and **4b** in the 7:2 ratio. By TMSOTf-promoted reaction of ethanethiol with α-acetate **4a** as well as with the mentioned above mixture of anomers **4a** and **4b**, ethyl 1-thio-β-glucoside **7** was obtained in 80% yield. α-Acetates derived from D-galactosamine **5a**, which was obtained following the procedure in ref.[22], gave under identical conditions the corresponding ethyl 1-thio-β-galactoside **8** in high yield (77%). The same reaction with the above mentioned α/β-anomeric mixture of mannosamine derivatives **6a** and **6b** afforded ethyl 1-thio-α-mannoside **9** in 70% yield.



(i) TMSOTf in Ac_2O; (ii) EtSH and TMSOTf in CH_2Cl_2

SCHEME 3

The described one-pot synthesis of 1,2-*trans*-acetates derived from 2-deoxy-2-phthalimidohexopyranoses and the conversion of both 1,2-*cis*-acetates and 1,2-*trans*-acetates to the corresponding 1,2-*trans* ethyl 1-thioglycosides substantially simplifies methods for synthesis of glycosyl donors suited for the formation of 1,2-*trans*-glycosidic bonds derived from biologically important 2-amino-2-deoxyhexoses, such as, D-glucosamine, D-galactosamine and D-mannosamine, used up to now. The title 1,2-*trans*-acetates and 1,2-*trans* ethyl 1-thioglycosides of 2-deoxy-2-phthalimidohexopyranoses derived from the above mentioned aminosaccharides are glycosyl donors, which can also serve as starting materials for the preparation of other glycosyl donors tailor-made for special applications.

EXPERIMENTAL

Melting points were determined on a Kofler block and are uncorrected. Specific rotations were measured on a Perkin–Elmer 141 polarimeter at 22 °C and are given in 10^{-1} deg cm^2 g^{-1}. Elemental analyses were performed using a Perkin–Elmer 2400 II instrument. NMR spectra were recorded on a Varian UNITY-500 spectrometer in the FT mode at 499.8 MHz (^{1}H) and at 125.6 MHz (^{13}C) in $CDCl_3$, using $(CH_3)_4Si$ as internal standard for the ^{1}H NMR spectra and $CDCl_3$ (δ 77.0) signal as standard for the ^{13}C NMR spectra. For unambiguous assignment of signals in ^{13}C NMR spectra, ^{1}H- and ^{13}C-heterocorrelated 2D NMR spectra were measured by HMQC technique using the standard pulse sequence delivered by the producer of the spectrometer. The following typical parameters were used: spectral width in both f_1 and f_2 dimensions 5000 and 17 000 Hz, respectively, number of scans 16, number of increments in f_1 dimension 256, recycle delay 1 s, acquisition time 0.2 s, 90° pulse for ^{1}H was 12.5 μs, data matrix for processing 2048 × 2048 datapoints. For processing, shifted sinebell

weighting function was used. Chemical shifts are given in ppm (δ-scale), coupling constants (*J*) in Hz. Positive-ion FAB mass spectra were measured on a BEqG geometry mass spectrometer ZAB-EQ (VG Analytical, Manchester, U.K.) using an M-Scan FAB gun (Xe, energy 8 keV) at an accelerating voltage of 8 kV. Samples were dissolved in chloroform or methanol, and a mixture of glycerol and thioglycerol or dimethyl sulfoxide was used as matrix. Thin-layer chromatography (TLC) was performed on DC-Alufolien Kieselgel 60 F_{254} (Merck, Darmstadt, Germany) or Silufol UV_{254} (Kavalier, Votice, Czech Republic) silica gel sheets. Preparative chromatography was performed on a silica gel column, particle size 40–60 μm (Fluka, Neu-Ulm, Switzerland). Analytical RP HPLC was performed using a Waters instrument (PDA detector, software Milennium 32; Milford (MA), U.S.A.) equipped with a Nova-Pak C18 column (150 × 3.9 mm), particle size 4 μm. Preparative RP HPLC was performed on a column (250 × 25 mm) filled with LiChrosorb RP-18, particle size 5 μm (Merck, Darmstadt, Germany). Solvents were evaporated on a rotary vacuum evaporator at 40 °C. Analytical samples were dried at 6.5 Pa and 25 °C for 8 h.

1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-phthalimido-D-hexopyranoses

Method A: D-Glucosamine hydrochloride (**1**) or D-mannosamine hydrochloride (**3**) (2.15 g, 10 mmol), phthalic anhydride (2.96 g, 20 mmol) and sodium hydrogencarbonate (4.20 g, 50 mmol) were stirred in a mixture of acetone–water (1:1, 100 ml) at 50 °C for 3 h. Progress of the reaction was monitored by TLC in propan-1-ol–ethyl acetate–water–25% aqueous ammonia (6:3:1:1). The solvents were evaporated *in vacuo* and to the residue pyridine (60 ml) and acetic anhydride (14.1 ml, 150 mmol) were added. The mixture was then heated under stirring at 50 °C for another 16 h. Progress of the reaction was monitored by TLC in toluene–ethyl acetate (1:1). The reaction mixture was concentrated *in vacuo* to a quarter of its volume and then diluted with toluene (30 ml). The solution was extracted with 1 M HCl (2 × 25 ml), saturated aqueous sodium hydrogencarbonate (2 × 25 ml) and water (2 × 25 ml). The organic phase was dried over anhydrous magnesium sulfate and solvents were evaporated *in vacuo*.

For **1**: The residue was chromatographed on silica gel column (45 g) in toluene–ethyl acetate (6:1) to afford **4a**, yield 1.96 g (41%) and **4b**, yield 1.95 g (41%). Both anomers were crystallized from ethanol to give **4a**, yield 1.72 g (36%) and **4b**, yield 1.62 g (34%).

For **3**: The residue was separated by HPLC on silica gel C18 column in solvent system water–methanol (linear gradient 50→100%) to give **4b**, yield 2.00 g (42%), **4a**, yield 0.24 g (5%) and a mixture of **6a** and **6b**, yield 0.72 g (15%), as white solids.

Method B: D-Mannosamine hydrochloride (**3**) (2.15 g, 10 mmol), phthalic anhydride (2.22 g, 15 mmol) and sodium hydrogencarbonate (1.01 g, 12 mmol) were stirred in a mixture of acetone–water (1:1, 100 ml) at 50 °C for 2 h. The other portions of phthalic anhydride (1.10 g, 7.4 mmol) and sodium hydrogencarbonate (0.22 g, 1.5 mmol) were then added and stirring was continued at same temperature for another 2 h. Progress of the reaction was monitored as described above in method *A*. The solvents were evaporated *in vacuo*, and pyridine (40 ml) and acetic anhydride (18.5 ml, 200 mmol) were then added to the residue. The mixture was then stirred and heated to 70 °C for 2 h. Progress of the reaction was monitored and the reaction mixture was worked up as described above in method *A*. The chromatography of the residue on a silica gel column (45 g) in toluene–ethyl acetate (6:1) afforded a mixture of **6a** and **6b** (1:1), yield 2.95 g (62%), as a white solid. The ratio of anomers was determined by ^{1}H NMR spectra.

Method C: D-Glucosamine hydrochloride (**1**) or D-mannosamine hydrochloride (**3**) (2.15 g, 10 mmol), phthalic anhydride (1.63 g, 11 mmol) and pyridine (2.0 ml, 25 mmol) were stirred in a mixture of acetone–water (1:1, 15 ml) at 50 °C for 3 h. Progress of the reaction was monitored as described above in method *A*. The solvents were evaporated *in vacuo* and pyridine (40 ml) and acetic anhydride (14.1 ml, 150 mmol) were then added to the residue. The mixture was then heated under stirring to 50 °C for 5 h. Progress of the reaction was monitored as described above in method *A*. Solvents were evaporated *in vacuo* and the residue was taken in toluene (30 ml) and 1 M HCl (25 ml). The organic phase was separated, extracted with 1 M HCl (25 ml), saturated aqueous sodium hydrogencarbonate (2 × 25 ml) and water (2 × 25 ml), dried over anhydrous magnesium sulfate and the solvent was evaporated *in vacuo*.

For **1**: The residue gave a mixture of α- and β-anomers **4a** and **4b** (3:4), yield 3.63 g (76%). The ratio of anomers was determined by ^{1}H NMR spectra. Crystallization of the α/β-anomer mixture from ethanol afforded β-anomer **4b**, yield 1.38 g (29%).

For **3**: The chromatography of the residue on a silica gel column (120 g) in toluene–ethyl acetate (8:1) afforded 3.20 g (67%) of an α/β-anomer mixture of compounds **6a** and **6b** (5:2). The ratio of anomers was determined by ^{1}H NMR spectra.

Method D: D-Glucosamine hydrochloride (**1**), D-galactosamine hydrochloride (**2**) or D-mannosamine hydrochloride (**3**) (2.15 g, 10 mmol), phthalic anhydride (1.63 g, 11 mmol) and pyridine (2.0 ml, 25 mmol) were stirred in a mixture of acetone–water (1:1, 15 ml) at 55 °C for 4 h. Progress of the reaction was monitored as described above in method *A*. The solvents were evaporated *in vacuo* and the residue was co-distilled with toluene (2 × 10 ml). To the residue, pyridine (20 ml), acetic anhydride (10.5 ml, 112 mmol) and 4-(dimethylamino)pyridine (50 mg, 0.4 mmol) were added and the mixture was then heated under stirring at 55 °C for another 5 h. Progress of the reaction was monitored as described in method *A*. Excess of acetic anhydride was decomposed by addition of methanol as follows. To the stirred reaction mixture, methanol (10 ml) was added at 0 °C and after warming to the room temperature, stirring was continued for 1 h. The solvents were then evaporated *in vacuo* and the residue was taken in toluene (30 ml) and 1 M HCl (10 ml). The organic phase was separated, extracted with saturated aqueous sodium hydrogencarbonate (10 ml) and water (10 ml), dried over anhydrous magnesium sulfate and evaporated *in vacuo*.

For **1**: The residue was crystallized from ethanol to afford β-anomer **4b**, yield 3.15 g (66%).

For **2**: The residue was crystallized from isopropanol to afford β-anomer **5b**, yield 3.05 g (64%).

For **3**: The residue was crystallized from ethanol to give α-anomer **6a**, yield 2.87 g (60%).

1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-phthalimido-α-D-glucopyranose (**4a**)

M.p. 128 °C (ethanol), $[\alpha]_D$ +114 (*c* 1.7, chloroform); ref.[19]: m.p. 128–131°C (ethanol), $[\alpha]_D$ +112 (*c* 0.9, chloroform); ref.[25]: m.p. 131°C (methanol), $[\alpha]_D$ +98 (*c* 0.5, chloroform). ^{1}H NMR: 7.87–7.83 m, 2 H (H-arom., Pht); 7.78–7.73 m, 2 H (H-arom., Pht); 6.57 dd, 1 H, *J* = 9.2, 11.6 (H-3); 6.29 d, 1 H, *J* = 3.4 (H-1); 5.17 dd, 1 H, *J* = 9.2, 10.2 (H-4); 4.73 dd, 1 H, *J* = 3.4, 11.6 (H-2); 4.37 dd, 1 H, *J* = 3.9, 12.3 (H-6a); 4.32 ddd, 1 H, *J* = 2.0, 3.9, 10.2 (H-5); 4.14 dd, 1 H, *J* = 2.0, 12.3 (H-6b); 2.13 s, 3 H ($OCOCH_3$); 2.09 s, 3 H ($OCOCH_3$); 2.07 s, 3 H ($OCOCH_3$); 1.88 s, 3 H ($OCOCH_3$). ^{13}C NMR: 170.6 ($OCOCH_3$), 169.7 ($OCOCH_3$), 169.4 ($OCOCH_3$), 169.2 ($OCOCH_3$), 167.4 (2 C), 134.4 (2 C), 131.2 (2 C), 123.7 (2 C) (C-arom.,

Pht), 90.5 (C-1), 70.2 (C-5), 69.5 (C-4), 67.1 (C-3), 61.6 (C-6), 52.9 (C-2), 20.9 ($OCOCH_3$), 20.6 (2 × $OCOCH_3$), 20.7 ($OCOCH_3$). For $C_{22}H_{23}NO_{11}$ calculated: relative molecular mass 477.4, monoisotopic mass 477.1. FAB MS, *m/z*: 478 $[M + H]^+$, 500 $[M + Na]^+$. For $C_{22}H_{23}NO_{11}$ (477.4) calculated: 55.35% C, 4.86% H, 2.93% N; found: 55.43% C, 4.96% H, 2.95% N.

1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranose (**4b**)

M.p. 78 °C (ethanol), $[\alpha]_D$ +59 (*c* 0.6, chloroform); ref.[6]: m.p. 79–81 °C (ethanol), $[\alpha]_D$ +62 (*c* 0.6, chloroform). ^{1}H NMR spectrum agrees with that of the authentic sample prepared by the procedure described in ref.[6] For $C_{22}H_{23}NO_{11}$ calculated: relative molecular mass 477.4, monoisotopic mass 477.1. FAB MS, *m/z*: 478 $[M + H]^+$, 500 $[M + Na]^+$. For $C_{22}H_{23}NO_{11}$ (477.4) calculated: 55.35% C, 4.86% H, 2.93% N; found: 55.64% C, 4.97% H, 2.92% N.

1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-phthalimido-β-D-galactopyranose (**5b**)

M.p. 130 °C (propan-2-ol), $[\alpha]_D$ +34 (*c* 0.18, chloroform); ref.[22]: m.p. 127–131 °C (ethanol), $[\alpha]_D$ +35 (*c* 1.3, chloroform). ^{1}H NMR spectrum agrees with that of the authentic sample described in ref.[22] For $C_{22}H_{23}NO_{11}$ calculated: relative molecular mass 477.4, monoisotopic mass 477.1. FAB MS, *m/z*: 478 $[M + H]^+$, 500 $[M + Na]^+$. For $C_{22}H_{23}NO_{11}$ (477.4) calculated: 55.35% C, 4.86% H, 2.93% N; found: 55.19% C, 4.98% H, 2.89% N.

1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-phthalimido-α-D-mannopyranose (**6a**)

M.p. 136 °C (ethanol), $[\alpha]_D$ –8 (*c* 0.3, chloroform). ^{1}H NMR: 7.92–7.75 m, 4 H (H-arom., Pht); 6.59 d, 1 H, *J* = 3.9 (H-1); 5.55 dd, 1 H, *J* = 6.8, 8.2 (H-4); 5.50 dd, 1 H, *J* = 5.3, 6.8 (H-3); 4.89 dd, 1 H, *J* = 3.9, 5.3 (H-2); 4.45 dd, 1 H, *J* = 6.0, 12.2 (H-6a); 4.31 dd, 1 H, *J* = 3.3, 12.2 (H-6b); 4.23 ddd, 1 H, *J* = 3.3, 6.0, 8.2 (H-5); 2.15 s, 3 H ($OCOCH_3$); 2.13 s, 3 H ($OCOCH_3$); 2.10 s, 3 H ($OCOCH_3$); 1.96 s, 3 H ($OCOCH_3$). ^{13}C NMR: 170.8 ($OCOCH_3$), 169.9 ($OCOCH_3$), 169.5 ($OCOCH_3$), 168.5 ($OCOCH_3$), 167.6 (2 C), 134.5 (2 C), 131.3 (2 C), 123.8 (2 C) (C-arom., Pht), 90.4 (C-1), 71.1 (C-5), 69.0 (C-3), 67.8 (C-4), 62.5 (C-6), 50.5 (C-2), 21.0 ($OCOCH_3$), 20.8 (2 × $OCOCH_3$), 20.7 ($OCOCH_3$). For $C_{22}H_{23}NO_{11}$ calculated: relative molecular mass 477.4, monoisotopic mass 477.1. ESI MS, *m/z*: 500.1 $[M + Na]^+$. For $C_{22}H_{23}NO_{11}$ (477.4) calculated: 55.35% C, 4.86% H, 2.93% N; found: 57.30% C, 5.16% H, 2.67% N.

1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-phthalimido-β-D-mannopyranose (**6b**)

^{1}H NMR and ^{13}C NMR spectra of β-anomer **6b** were extracted from NMR spectra of the α/β-anomer mixture of compounds **6a** and **6b** obtained under conditions *B*. ^{1}H NMR: 7.92–7.75 m, 4 H (H-arom., Pht); 6.06 t, 1 H, *J* = 9.5, 9.5 (H-4); 5.99 d, 1 H, *J* = 2.8 (H-1); 5.37 dd, 1 H, *J* = 6.8, 9.4 (H-3); 5.06 dd, 1 H, *J* = 2.8, 6.8 (H-2); 4.48 dd, 1 H, *J* = 6.0, 12.2 (H-6a); 4.27 dd, 1 H, *J* = 2.3, 12.2 (H-6b); 3.93 ddd, 1 H, *J* = 2.3, 6.0, 9.7 (H-5); 2.16 s, 3 H ($OCOCH_3$); 2.07 s, 3 H ($OCOCH_3$); 1.97 s, 3 H ($OCOCH_3$); 1.91 s, 3 H ($OCOCH_3$). ^{13}C NMR: 170.7 ($OCOCH_3$), 169.7 ($OCOCH_3$), 169.5 ($OCOCH_3$), 168.4 ($OCOCH_3$), 168.0 (2 C), 134.3 (2 C), 131.2 (2 C), 123.6 (2 C) (C-arom., Pht), 90.3 (C-1), 73.9 (C-5), 69.8 (C-3), 66.7 (C-4), 62.5 (C-6), 49.9 (C-2), 20.7 (2 × $OCOCH_3$), 20.5 ($OCOCH_3$), 20.4 ($OCOCH_3$).

Anomerization of Compound **4a**

To a stirred solution of α-anomer **4a** (70 mg, 0.15 mmol) in acetic anhydride (2 ml), trimethylsilyl trifluoromethanesulfonate (5 μl, 0.025 mmol) was added and stirring was continued at 35 °C for 1 h. Progress of the reaction was monitored by TLC in toluene–ethyl acetate (1:1). The mixture was poured into a stirred mixture of toluene–saturated aqueous sodium hydrogencarbonate (1:1, 8 ml) cooled in an ice bath. After 1 h stirring, the organic layer was separated, extracted with water (2 × 3 ml) and poured on a column of silica gel (3 g). The product was desorbed with a mixture of toluene–ethyl acetate (1:1). The eluent was evaporated *in vacuo* to obtain a mixture of α- and β-anomers **4a** and **4b** (2:7). The ratio of anomers was determined by ^{1}H NMR spectra.

Preparation of Ethyl 3,4,6-Tri-*O*-acetyl-2-deoxy-2-phthalimido-1-thio-1,2-*trans*-D-hexopyranosides

Glucosamine derivative **4a** (4.77 g, 10 mmol), α/β-anomer mixture of galactosamine derivative **5a** and **5b** (4.77 g, 10 mmol), obtained by the procedure in ref.[22], or α/β-anomer mixture of mannosamine derivatives **6a** and **6b** (1:1), obtained by method *B* (4.77 g, 10 mmol), was dried with crushed molecular sieves 4A (0.5 g) in an apparatus equipped with a septum at room temperature and 20 Pa for 5 h. The apparatus was flushed with argon twice and then dry dichloromethane (120 ml) was added through the septum. After dissolution of the starting material, ethanethiol (13.1 ml, 17.3 mmol) and trimethylsilyl trifluoromethanesulfonate (1.9 ml, 10.7 mmol) were added through the septum under stirring and stirring was then continued at room temperature for 1 h. Progress of the reaction was monitored by TLC in toluene–ethyl acetate (1:1). The mixture was filtered over a short column of Celite and the column was washed with chloroform (270 ml). The filtrate was washed with saturated aqueous sodium hydrogencarbonate (3 × 100 ml), water (3 × 100 ml), dried over anhydrous magnesium sulfate and evaporated *in vacuo*. The residue was chromatographed on a silica gel column (200 g) in toluene–ethyl acetate (6:1).

For **4a**: The reaction afforded **7**, yield 3.84 g (80%), as a syrupy residue, which was crystallized from toluene to give **7**, yield 3.21 g (67%).

For **5a** and **5b**: The reaction gave **8**, yield 3.69 g (77%).

For **6a** and **6b**: The reaction afforded **9**, yield 3.34 g (70%), as a syrupy residue, which was crystallized from toluene, yield 2.86 g (67%).

Ethyl 2,4,6-Tri-*O*-acetyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (**7**)

M.p. 117–118 °C (toluene), $[\alpha]_D$ +42 (*c* 0.7, chloroform); ref.[6] m.p. 115–118 °C, $[\alpha]_D$ +46 (*c* 0.8, dichloromethane). ^{1}H NMR spectrum agrees with that of the authentic sample prepared by the procedure described in ref.[6] For $C_{22}H_{25}NO_9S$ calculated: relative molecular mass 479.5, monoisotopic mass 479.1. FAB MS, *m/z*: 480 $[M + H]^+$, 502 $[M + Na]^+$. For $C_{22}H_{25}NO_9S$ (479.5) calculated: 55.11% C, 5.26% H, 2.92% N, 6.69% S; found: 55.24% C, 5.34% H, 2.98% N, 6.57% S.

Ethyl 2,4,6-Tri-*O*-acetyl-2-deoxy-2-phthalimido-1-thio-β-D-galactopyranoside (**8**)

Syrup, $[\alpha]_D$ +17 (*c* 0.3, chloroform); ref.[17] $[\alpha]_D$ +18 (*c* 1.0, chloroform). ^{1}H NMR spectrum agrees with that of the authentic sample described in ref.[17] For $C_{22}H_{25}NO_9S$ calculated: rela-

tive molecular mass 479.5, monoisotopic mass 479.1. FAB MS, *m/z*: 480 $[M + H]^+$, 502 $[M + Na]^+$. For $C_{22}H_{25}NO_9S$ (479.5) calculated: 55.11% C, 5.26% H, 2.92% N, 6.69% S; found: 55.24% C, 5.34% H, 2.98% N, 6.57% S.

Ethyl 2,4,6-Tri-*O*-acetyl-2-deoxy-2-phthalimido-1-thio-α-D-mannopyranoside (**9**)

M.p. 129 °C (toluene), $[\alpha]_D$ +24 (*c* 1.5, chloroform). ^{1}H NMR: 7.86–7.73 m, 4 H (H-arom., Pht); 5.96 d, 1 H, *J* = 7.0 (H-1); 5.39 dd, 1 H, *J* = 4.3, 5.2 (H-3); 4.28 dd, 1 H, *J* = 5.2, 6.4 (H-4); 4.79 dd, 1 H, *J* = 4.3, 7.0 (H-2); 4.56 dd, 1 H, *J* = 7.0, 12.0 (H-6a); 4.37 dt, 1 H, *J* = 3.7, 6.6, 6.6 (H-5); 4.30 dd, 1 H, *J* = 3.7, 12.0 (H-6b); 2.70 dq, 1 H, *J* = 7.4, 7.4, 7.4, 12.9 ($SC\mathbf{H}_2CH_3$); 2.62 dq, 1 H, *J* = 7.4, 7.4, 7.4, 12.9 ($SC\mathbf{H}_2CH_3$); 2.14 s, 3 H ($OCOCH_3$); 2.13 s, 3 H ($OCOCH_3$); 2.00 s, 3 H ($OCOCH_3$); 1.28 t, 3 H, *J* = 7.4 ($SCH_2C\mathbf{H}_3$). ^{13}C NMR: 170.7 ($O\mathbf{C}OCH_3$), 169.8 ($OCO\mathbf{C}H_3$), 168.2, 168.0, 167.7 ($O\mathbf{C}OCH_3$), 134.3 (2 C), 131.5 (2 C), 123.6 (2 C) (C-arom., Bn, Pht), 78.0 (C-1), 70.9 (C-5), 69.6 (C-3), 68.6 (C-4), 62.1 (C-6), 51.5 (C-2), 24.9 ($SCH_2\mathbf{C}H_3$), 20.9, 20.8 ($OCO\mathbf{C}H_3$), 20.8 ($OCO\mathbf{C}H_3$), 14.9 ($S\mathbf{C}H_2CH_3$). For $C_{22}H_{25}NO_9S$ calculated: relative molecular mass 479.5, monoisotopic mass 479.1. FAB MS, *m/z*: 480 $[M + H]^+$, 502 $[M + Na]^+$, 524 $[M + 2\ Na]^+$. For $C_{22}H_{25}NO_9S$ (479.5) calculated: 55.11% C, 5.26% H, 2.92% N, 6.69% S; found: 55.23% C, 5.31% H, 2.87% N, 6.58% S.

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