Facile Preparation of a Phenyl 1-Thioglycoside of Allopyranosylallopyranose from Allyl *N,N'*-Diacetylchitobioside

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(Received May 18, 1994)

Synopsis. An allopyranosyl analog of allyl *N,N'*-diacetylchitobioside was converted to the corresponding *N,N'*-diphthaloylated glycosyl acetate in good yield. A thioglycosidation reaction of the glycosyl acetate gave phenyl 3,6-di-*O*-acetyl-4-*O*-(3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-allopyranosyl)-2-deoxy-2-phthalimido-1-thio-β-D-allopyranoside, the key intermediate employed in the total synthesis of an insect chitinase inhibitor, allosamidin.

In the course of our studies on the syntheses of various bioactive compounds by the utilization of oligosaccharides, we recently established an efficient method for a large-scale preparation of *N,N'*-diacetylchitobiose, and reported its chemical modifications, including the glycosidation reaction with several alcohols using the oxazoline method.[1,2] Among the obtained alkyl *N,N'*-diacetylchitobiosides, an allyl derivative **1** was readily prepared, and served as the key building block for the synthesis of a trisaccharide sequence related to the core structure of the asparagine-linked type glycoprotein.[3] In connection with the synthesis of an insect chitinase inhibitor, allosamidin (**2**), we further continued to investigate the utility of **1**. Described herein is the transformation of allyl chitobioside (**1**) into phenyl 3,6-di-*O*-acetyl-4-*O*-(3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-allopyranosyl)-2-deoxy-2-phthalimido-1-thio-β-D-allopyranoside (**9**), the key intermediate employed in our recent synthesis of **2** (Scheme 1).[4]

In a previous synthesis of **2**,[4] the phenylthio group in **9** was introduced at the early stage of the synthesis of **9**. A series of crystalline phenylthio derivatives prepared therefrom had extremely low solubility in the usual organic solvents. This made any large-scale preparation of **2** difficult. Therefore, in the present experiment, the introduction of a phenylthio group was conducted at the final step of the synthesis of **9**. Allyl *N,N'*-diacetylchitobioside (**1**) was converted to allyl 2-acetamido-4-*O*-(2-acetamido-4,6-*O*-benzylidene-2-deoxy-β-D-allopyranosyl)-2-deoxy-6-*O*-trityl-β-D-allopyranoside (**3**)[2] utilizing a neighboring group participation of the acetamido groups in high yield. The latter was treated successively with 80% acetic acid and sodium hydroxide to give diamine **4** in 94% yield. The use of hydrazine monohydrate instead of sodium hydroxide resulted in a product with a contamination of propyl glycoside. According to Lemieux's procedure,[5] diamine **4** reacted with phthalic anhydride in the presence of triethylamine to give a phthalamide derivative, which was treated with acetic anhydride in the presence of 4-dimethylaminopyridine in pyridine to give a diphthaloyl pentaacetate **5** in 66% yield.[6] As direct conversion of **5** into the thioglycoside **9** by Hanessian's method {(phenylthio)-trimethylsilane (PhSTMS)–zinc iodide (ZnI_2)}[7] was unsuccessful, the allyl group was changed to an acetyl function in order to achieve the transformation.[8] It is known that acetolysis {Ac_2O–sulfuric acid (100 : 1; v/v)} of methyl *N,N'*-diphthaloyl chitobioside pentaacetate provided the corresponding β-glycosyl acetate in high yield.[9] The acetolysis of **5** under these conditions, however, gave a mixture of unsaturated sugars formed by eliminating an allyl alcohol, and the desired glycosyl acetate was not obtained.[10] Consequently, the allyl group in **5** was removed with a 2 molar amount of palladium chloride[11] in the presence of sodium acetate in degassed aqueous acetic acid under an argon atmosphere, giving hemiacetal **6** in 70% yield along with methyl ketone **7** (21% yield) derived by Wacker oxidation.[12] The β-anomeric structure of the hemiacetal **6** was determined by ^{1}H NMR analysis, showing that the anomeric proton at C-1 was observed at 6.14 ppm as a doublet of a doublet with $J_{1,2}$=8.5 Hz. Hemiacetal **6** was acetylated with sodium acetate in acetic anhydride at 70 °C to give β-glycosyl acetate **8**. Finally, compound **8** reacted smoothly with a 3 molar amount of PhSTMS in the presence of a 3 molar amount of ZnI_2 in 1,2-dichloroethane[7] at room temperature to give **9** in high yield. In this process, no unsaturated sugars were detected on TLC.

In conclusion, a facile synthesis of **9** from **1** has been developed, which in suitable for large-scale preparations. Both compounds could be of interest as useful building blocks in the synthesis of allosamidin analogs as well as nitrogen containing other complex natural sugar chains.

Experimental

General Procedures. Melting points were determined in a capillary with an Ishii melting-point apparatus, and are uncorrected. The optical rotations were determined with a JASCO DIP-370 polarimeter. The ^{1}H NMR spectra were recorded at 400 or 500 MHz with JEOL JNM-GSX 400 or

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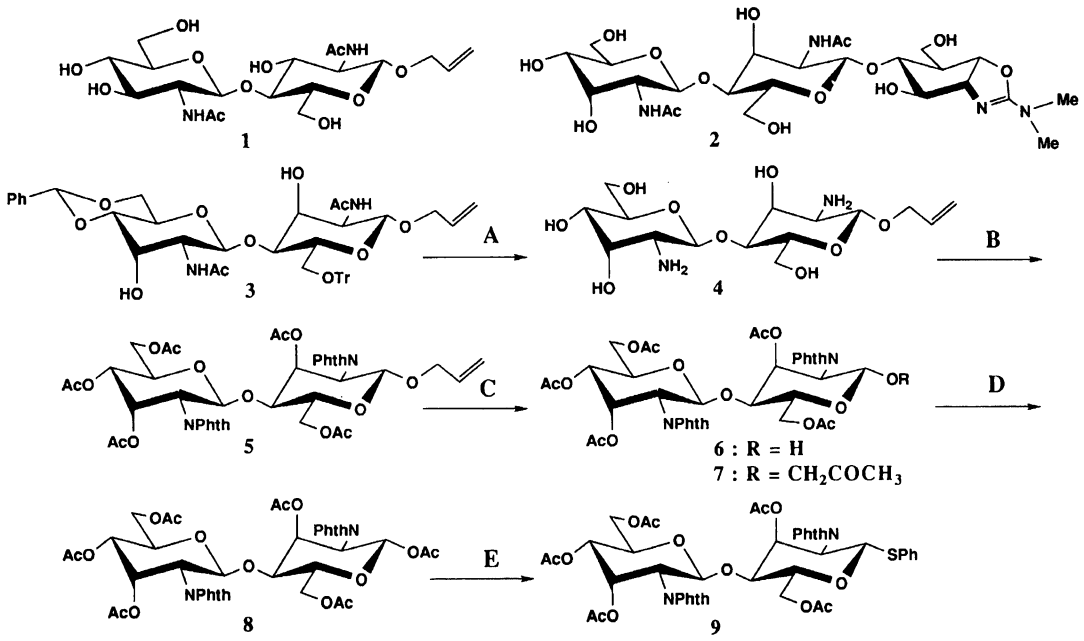

Scheme 1. Conditions: (A) i) 80% AcOH, 65 °C, ii) 1 M NaOH, 110 °C. (B) i) phthalic anhydride, Et_3N, MeOH, ii) Ac_2O, 4-dimethylaminopyridine, pyridine, RT. (C) $PdCl_2$, NaOAc, aq AcOH, 50 °C. (D) NaOAc, Ac_2O, 70 °C. (E) ZnI_2, phenylthiotrimethylsilane, 1,2-dichloroethane, RT.

500 spectrometers, using tetramethylsilane as the internal standard. Column chromatography was performed on silica gel 60 (230—400 mesh; E. Merck, Darmstadt, Germany). Merck precoated silica gel 60 F_{254} plates (0.25 or 1.0 mm thickness) were used for analytical or preparative thin-layer, chromatography, respectively.

Allyl 2-Amino-4-*O*-(2-amino-2-deoxy-β-D-allopyranosyl)-2-deoxy-β-D-allopyranoside (4). A solution of **3** (1.0 g, 1.26 mmol) in 80% AcOH (15 cm^3) was stirred at 65 °C for 1.5 h under Ar, and then concentrated. The residue was co-evaporated with ethanol–toluene, then heated in a 1 M (1 M=1 mol dm^{-3}) NaOH solution (40 cm^3) while stirring at 110 °C for 2 d under argon. After cooling, the resulting suspension was filtered through a Celite pad. The filtrate was applied to a column of Dowex 50W-X8 (H^+) ion-exchange resin, which was eluted with 1 M aqueous ammonia; the eluate was concentrated in vacuo to give 450 mg (94%) of **4**. This amine was employed in the next step without further purification. ^{1}H NMR (D_2O–DCl) δ=3.27 (1H, dd, $J_{1,2}$=8.9 and $J_{2,3}$=3.0 Hz, H-2), 3.33 (1H, dd, $J_{1',2'}$=8.2 and $J_{2',3'}$=3.0 Hz, H-2'), 3.69 (1H, dd, $J_{4',5'}$=10 and $J_{3',4'}$=3.0 Hz, H-4'), 3.73—3.76 (2H, m, H-6a, 6'a), 3.81 (1H, m, H-5'), 3.85 (2H, br.d, J=12 Hz, H-6b, 6'b), 3.88—3.94 (2H, m, H-4, 5), 4.18 (1H, dd, J=13 and 6.4 Hz, OC*H*HC_2H_3), 4.27 (1H, t, H-3'), 4.36 (1H, dd, J=13 and 5.8 Hz, OCH*H*C_2H_3), 4.62 (1H, br.s, H-3), 4.94 (1H, d, H-1), 5.04 (1H, d, H-1'), 5.26 (1H, br.d, J_{cis}=10 Hz, $OCH_2CHCH_ZH_E$), 5.34 (1H, br.d, J_{trans}=17 Hz, $OCH_2CHCH_ZH_E$), 5.94 (1H, m, OCH_2CHCH_2).

Allyl 3,6-Di-*O*-acetyl-4-*O*-(3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-allopyranosyl)-2-deoxy-2-phthalimido-β-D-allopyranoside (5). Compound **4** (435 mg, 1.15 mmol) was treated with phthalic anhydride (680 mg, 4.59 mmol) and triethylamine (0.48 cm^3, 3.44 mmol) in methanol to give the phthalamide derivative, which was reacted with acetic anhydride (5 cm^3) and 4-dimethylaminopyridine (56 mg, 0.46 mmol) in pyridine (20 cm^3) at room temperature for 18 h. The reaction mixture was poured into ice-water, and allowed to stand overnight. The resulting solution was extracted with ethyl acetate. The extracts were successively washed with 10% hydrochloric acid, aqueous sodium hydrogencarbonate, water, and brine, dried ($MgSO_4$), and concentrated. Column chromatography with hexane–ethyl acetate (1:1, v/v) as the eluant gave 645 mg (66%) of **5**: $[\alpha]_D^{25}$ −24° (*c* 0.61, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ=1.97, 1.99, 2.00, 2.05, 2.07 (15H, each s, Ac), 3.65 (1H, dd, $J_{5,6a}$=3.9 and $J_{6a,6b}$=12 Hz, H-6a), 3.99 (1H, br.d, H-6b), 3.98—4.10 (5H, m, H-4, 5, 6a, 6b, OC*H*HC_2H_3), 4.23 (1H, m, H-5'), 4.25—4.28 (1H, m, OCH*H*C_2H_3), 4.26 (1H, dd, $J_{1,2}$=8.6 and $J_{2,3}$=2.5 Hz, H-2), 4.30 (1H, dd, $J_{1',2'}$=8.6 and $J_{2',3'}$=2.5 Hz, H-2'), 4.94 (1H, dd, $J_{3',4'}$=2.9 and $J_{4',5'}$=11 Hz, H-4'), 5.07 (1H, br.d, J_{cis}=10 Hz, $OCH_2CHCH_ZH_E$), 5.15 (1H, dd, J=1.5 and J_{trans}=17 Hz, $OCH_2CHCH_ZH_E$), 5.55 (1H, dd, H-3'), 5.75—5.85 (1H, m, OCH_2CHCH_2), 5.81 (1H, d, H-1), 5.82 (1H, dd, $J_{3,4}$=2.4 Hz, H-3), 6.07 (1H, d, H-1'), 7.69—7.80 (8H, m, Ph).

Found: C, 57.83; H, 4.97; N, 3.30%. Calcd for $C_{41}H_{42}O_{18}N_2$: C, 57.88; H, 4.98; N, 3.29%.

3,6-Di-*O*-acetyl-4-*O*-(3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-allopyranosyl)-2-deoxy-2-phthalimido-β-D-allopyranose (6), and 2-Oxopropyl 3,6-Di-*O*-acetyl-4-*O*-(3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-allopyranosyl)-2-deoxy-2-phthalimido-β-D-allopyranoside (7). To a stirred suspension of allyl glycoside **5** (200 mg, 0.24 mmol), sodium acetate (88 mg, 1.07 mmol) in degassed 95% acetic acid (3 cm^3) was added palladium chloride (88 mg, 0.50 mmol) at room temperature. The mixture was stirred at 50 °C for 2 h under Ar, and then cooled, filtered through a Celite pad, and concen-

trated. The residue was diluted with chloroform, washed with aqueous sodium hydrogencarbonate, water, and brine, dried ($MgSO_4$), and concentrated. Column chromatography with chloroform–ethyl acetate (2 : 1, v/v) as the eluant gave 134 mg (70%) of the hemiacetal **6** and 42 mg (21%) of the methyl ketone **7**.

6: Mp 177—178 °C (EtOH); $[\alpha]_D^{25}$ −16° (*c* 0.67, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ=1.97, 1.99, 2.01, 2.05, 2.07 (15H, each s, Ac), 3.39 (1H, d, $J_{1,OH}$=6.1 Hz, OH), 3.63 (1H, dd, $J_{5,6a}$= 3.4 and $J_{6a,6b}$=12 Hz, H-6a), 4.02 (1H, br.d, H-6b), 4.03 (1H, dd, $J_{5',6'a}$=2.0 and $J_{6'a,6'b}$=12 Hz, H-6'a), 4.05 (1H, dd, $J_{3,4}$=2.1 and $J_{4,5}$=9.5 Hz, H-4), 4.07 (1H, ddd, H-5), 4.09 (1H, dd, $J_{5',6'b}$=5.0 Hz, H-6'b), 4.21 (1H, dd, $J_{1,2}$=8.5 and $J_{2,3}$=2.4 Hz, H-2), 4.22 (1H, ddd, H-5'), 4.30 (1H, dd, $J_{1',2'}$=8.6 and $J_{2',3'}$=2.4 Hz, H-2'), 4.95 (1H, dd, $J_{3',4'}$=3.1 and $J_{4',5'}$=10 Hz, H-4'), 5.54 (1H, dd, H-3'), 5.84 (1H, dd, H-3), 6.09 (1H, d, H-1'), 6.14 (1H, dd, H-1), 7.69—7.80 (8H, m, Ph).

Found: C, 56.05; H, 4.69; N, 3.39%. Calcd for $C_{38}H_{38}O_{18}N_2$: C, 56.30; H, 4.72; N, 3.46%.

7: $[\alpha]_D^{25}$ −22° (*c* 0.26, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ= 1.97, 1.98, 2.01, 2.03, 2.04, 2.07 (18H, each s, Ac), 3.65 (1H, dd, $J_{5,6a}$=3.5 and $J_{6a,6b}$=12 Hz, H-6a), 3.97 (1H, br.d, H-6b), 4.00—4.10 (4H, m, H-4, 5, 6a', 6b'), 4.09, 4.23 (2H, each d, J_{AB}=17 Hz, CH_2O-1), 4.18—4.24 (1H, m, H-5'), 4.30 (1H, dd, $J_{1',2'}$=8.5 and $J_{2',3'}$=3.0 Hz, H-2'), 4.32 (1H, dd, $J_{1,2}$=8.9 and $J_{2,3}$=3.0 Hz, H-2), 4.95 (1H, dd, $J_{3',4'}$=3.0 and $J_{4',5'}$=10 Hz, H-4'), 5.55 (1H, t, H-3'), 5.82 (1H, d, H-1), 5.83 (1H, br.t, H-3), 6.08 (1H, d, H-1'), 7.69—7.80 (8H, m, Ph).

Found: C, 55.60; H, 4.76; N, 3.08%. Calcd for $C_{41}H_{42}O_{19}N_2 \cdot H_2O$: C, 55.66; H, 5.01; N, 3.17%.

1,3,6-Tri-*O*-acetyl-4-*O*-(3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-allopyranosyl)-2-deoxy-2-phthalimido-β-D-allopyranose (8). Compound **6** (54 mg, 0.07 mmol) was acetylated with sodium acetate (54 mg, 0.66 mmol) in acetic anhydride (1 cm^3) at 70 °C for 4 h. After cooling, the reaction mixture was diluted with xylene, concentrated, and then mixed with ice-water. The resulting suspension was extracted with dichloromethane. The extract was washed with aqueous sodium hydrogencarbonate, water, and brine, dried ($MgSO_4$), and concentrated. Crystallization of the residual syrup with ethanol gave 38 mg of the acetate **8**. The mother liquid was further purified by preparative TLC (hexane–ethyl acetate 1 : 1) to give additional **8** (11 mg); total yield (86%). Mp 225—226 °C (EtOH); $[\alpha]_D^{25}$ −1.8° (*c* 0.40, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ=1.97, 1.98, 2.01, 2.06, 2.07 (18H, each s, Ac), 3.65 (1H, dd, $J_{5,6a}$=3.5 and $J_{6a,6b}$=12 Hz, H-6a), 3.98 (1H, br.d, H-6b), 4.03 (1H, br.d, $J_{6'a,6'b}$=12 Hz, H-6'a), 4.06—4.10 (2H, m, H-4, 6'b), 4.17 (1H, m, H-5), 4.21 (1H, m, H-5'), 4.30 (1H, dd, $J_{1',2'}$=8.6 and $J_{2',3'}$=2.1 Hz, H-2'), 4.38 (1H, dd, $J_{1,2}$=9.2 and $J_{2,3}$=2.1 Hz, H-2), 4.95 (1H, dd, $J_{3',4'}$=2.7 and $J_{4',5'}$=10 Hz, H-4'), 5.54 (1H, dd, H-3'), 5.88 (1H, dd, $J_{3,4}$=2.7 Hz, H-3), 6.09 (1H, d, H-1'), 6.94 (1H, d, H-1), 7.72—7.83 (8H, m, Ph).

Found: C, 55.94; H, 4.67; N, 3.25%. Calcd for $C_{40}H_{40}O_{19}N_2$: C, 56.34; H, 4.73; N, 3.29%.

Phenyl 3,6-Di-*O*-acetyl-4-*O*-(3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-allopyranosyl)-2-deoxy-2-phthalimido-1-thio-β-D-allopyranoside (9). To a stirred solution of **8** (100 mg, 0.12 mmol) and (phenylthio)trimethylsilane (70 μl, 0.37 mmol) in 1,2-dichloroethane (6 cm^3) was added zinc iodide (112 mg, 0.35 mmol). The mixture was stirred at room temperature under Ar for 4 h, and then filtered through a Celite pad. The filtrate was washed with 10% hydrochloric acid, aqueous sodium hydrogencarbonate, water, and brine, dried ($MgSO_4$), and concentrated. Column chromatography with benzene–ethyl acetate (2 : 1, v/v) as the eluant gave 95 mg (90%) of **9**; $[\alpha]_D^{26}$ +12° (*c* 1.0, $CHCl_3$); {$[\alpha]_D^{23}$ +11.3° (*c* 0.40, $CHCl_3$)[4]}, ^{1}H NMR ($CDCl_3$) δ=1.96, 1.97, 1.98, 2.05, 2.06 (15H, each s, Ac), 3.64 (1H, dd, $J_{6a,6b}$=12 and $J_{5,6a}$=4.9 Hz, H-6a), 3.94—4.08 (5H, m, H-4, 5, 6b, 6'a, 6'b), 4.18 (1H, m, H-5'), 4.23 (1H, dd, $J_{1,2}$=10 and $J_{2,3}$=2.2 Hz, H-2), 4.29 (1H, dd, $J_{1',2'}$=8.5 and $J_{2',3'}$=2.4 Hz, H-2'), 4.93 (1H, dd, $J_{4',5'}$=10 and $J_{3',4'}$=3.0 Hz, H-4'), 5.54 (1H, dd, H-3'), 5.79 (1H, dd, $J_{3,4}$=3.0 Hz, H-3), 6.04 (1H, d, H-1'), 6.05 (1H, d, H-1), 7.26—7.40 (5H, m, Ph), 7.72—7.84 (8H, m, Ph).

Found: C, 58.43; H, 4.66; N, 2.93; S, 3.38%. Calcd for $C_{44}H_{42}N_2O_{17}S$: C, 58.53; H, 4.69; N, 3.10; S, 3.55%.

We thank Ms. Mutsuko Yoshida and her collaborators in RIKEN for the elemental analyses.

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