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Stereoselective Conversion of D-Glucuronolactone into *Pseudo*-Sugar: Syntheses of *Pseudo*-α-D-Glucopyranose, *Pseudo*-β-D-Glucopyranose, and Validamine[1]

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Abstract: Two optically active *pseudo*-sugars, *pseudo*-α-D-glucopyranose (**12**) and *pseudo*-β-D-glucopyranose (**13**), were synthesized from D-glucuronolactone in favorable overall yields by using a stereoselective nitromethane addition reaction and a reductive elimination of an ethoxyethoxyl moiety with $NaBH_4$ as key steps. Furthermore, a biologically active *pseudo*-aminosugar, validamine (**18**) was efficiently synthesized *via* a substitution reaction for an acetoxyl group at the β-position of nitro group in a nitrocyclitol derivative (**14**) which was prepared from a synthetic intermediate (**9**) of *pseudo*-D-glucopyranoses (**12, 13**).

INTRODUCTION

Pseudo-D-glucopyranose, having a cyclohexane ring in place of the pyranose ring in D-glucose, is one of the representatives of *pseudo*-sugar which is also called carba-sugar. It has been reported that *pseudo*-DL-glucopyranose exhibited interesting biological activities such as inhibitory effects on glucokinase activity and on the expression of insulin level induced by D-glucose.[2] In addition, *pseudo*-D-glucopyranose has been found to show the sweetness similar to that of D-glucose and also, because of its property showing no tautomeric isomerization at the anomeric position in water, *pseudo*-D-glucopyranose is said to have particular potential for biochemical research of D-glucose.[3] On the other hand, *pseudo*-aminosugar validamine was reported as the partial component of antibiotic validamycins and a series of *pseudo*-oligosaccharidic α-glucosidase inhibitors such as adiposins, acarbose, and trestatins. Afterwards, validamine was isolated from the fermentation broth of *Streptomyces hygroscopicus* subsp. *limoneus* and have been found to have potent α-glucosidase inhibitory activity.[4]

In regard to synthetic studies of those *pseudo*-sugars, following a preliminary synthesis of racemate, *pseudo*-α- and β-D-glucopyranose (**12, 13**) and validamine (**18**) have so far been synthesized by means of optical resolution of synthetic intermediate[5] and by chemical transformation of natural carbohydrate precursors.[6] We have also found a versatile method for converting D-glucose to various *pseudo*-sugars including *pseudo*-D-glucopyranose and validamine.[7,8] Furthermore, from the synthetic intermediate of *pseudo*-sugar, *pseudo*-nucleosides *i.e.* such as (+)-cyclaradine and (-)-aristeromycin were synthesized by using a Michael-type addition reaction of nucleic base.[9] Recently, we have reported a facile syntheses of *pseudo*-D-arabinofuranose and two bioactive *pseudo*-β-D-arabinofuranosyl nucleosides from D-arabinose.[10] As a continuing study of a stereoselective synthesis of *pseudo*-sugar, we have developed an efficient synthetic approach to *pseudo*-D-glucopyranoses and validamine from D-glucuronolactone.

In this paper, we present a full account of the synthesis of *pseudo*-α- and β-D-glucopyranose (**12, 13**) from D-glucuronolactone (**1**) which comprises a stereoselective addition of nitromethane to the keto-derivative

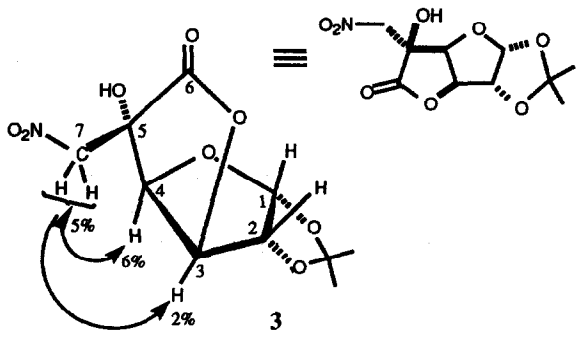
(**2**) and a reductive elimination of the ethoxyethoxyl moiety as the key reactions and also reported the synthesis of validamine (**18**) by using a substitution reaction for an acetyl residue at the β-position of nitro group by ammonia in a nitrocyclitol derivative (**14**).

RESULTS AND DISCUSSION

Syntheses of pseudo-α-D-glucopyranose (12) and pseudo-β-D-glucopyranose (13)

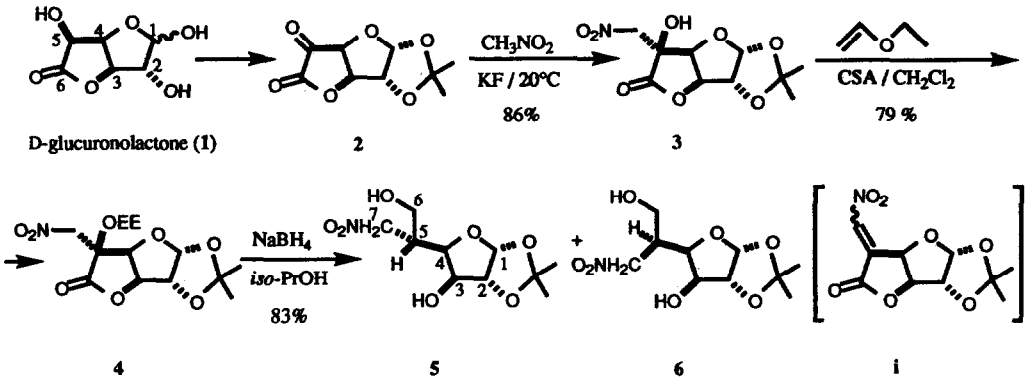
The starting material, 1,2-*O*-isopropylidene-α-D-glucofuranurono-5-ulose-6,3-lactone (**2**), was prepared from D-glucuronolactone (**1**) using a literature procedure.[11] Treatment of **2** with nitromethane in the presence of potassium fluoride (KF) at 20 °C stereoselectively furnished the addition product (**3**) in a favorable yield. On the other hand, it was found that, by the nitromethane addition condition in the presence of KF and 18-crown-6 which has hitherto been used for the nitromethane addition reaction of various keto-derivatives from D-glucose[8,9] and D-arabinose[10], **3** was obtained in a poor yield. The structure of **3** was confirmed on the basis of following evidence. Namely, the infrared spectrum of **3** showed absorption bands due to nitro and lactone groups at 1560 and 1780 cm^{-1} and its molecular formula $C_{10}H_{13}NO_8$ was confirmed from the quasimolecular ion peak $(M+Na)^+$ in the positive fast atom bombardment MS (FAB-MS) and by high resolution MS measurement. The stereostructure of C-5 position in **3** was corroborated by detailed ^1H NMR examinations of **3** including the nuclear Overhauser effect (NOE) experiments, which showed the NOEs between the 7-H_2 and the 4-H, and between the 7-H_2 and the 3-H as depicted in Fig. 1. This evidence indicated that, in the mild condition containing no 18-crown-6, the nitromethane addition reaction at C-5 took place selectively from the *exo*-side of lactone ring which is considered to be less sterically hindered.

The addition product **3** was then subjected to the elimination of its 5-hydroxyl group. We have already reported that an acetoxyl group at the β-position of nitro group in nitrocyclitol derivatives was stereoselectively eliminated by sodium borohydride ($NaBH_4$) and, by utilizing this reductive elimination reaction as a key step, various aminoglycoside antibiotics[12] and *pseudo*-sugar[7] were synthesized. However, the desired eliminated product (**5**) could not be obtained by this reaction sequence. After some preliminary examinations, we have found that the 5-ethoxyethyl derivative (**4**), which was obtained from **3** by treatment with ethyl vinyl ether in dichloromethane (CH_2Cl_2) in the presence of D-camphorsulfonic acid (CSA), provided an epimeric mixture of branched nitrofuranoses(**5**:**6** = 7:3, 58 %) by $NaBH_4$ treatment in ethanol. Since the mixture of **5** and **6** was not separated each other by using high performance liquid chromatography (HPLC), their structures were deduced to be as an epimeric mixture at C-5 by ^1H NMR examination of the mixture.



3

Fig. 1. NOEs Observed in NOE Differential Spectrum of 3



D-glucuronolactone (1) 2 3 4 5 6 i

Chart 1

After examination of $NaBH_4$ treatment in several solvents, it was found that the treatment of **4** with $NaBH_4$ in isopropanol selectively gave the desired product **5** in a favorable yield (83 %).This reaction procedure from **4** to **5** with $NaBH_4$ in isopropanol is considered to proceed in three steps: first, elimination of the ethoxyethoxyl moiety in **4** to produce the nitro-olefin **i**; second, reduction with hydride from the less hindered α-side (in a similar manner as nitromethane addition reaction to **2**); and third, reduction of the 6,3-lactone ring. It was presumed that, in the case of EtOH solution, the γ-lactone ring in **4** was partially cleaved prior to elimination of the ethoxyethoxyl moiety, so that a mixture of **5** and **6** was obtained. In the FAB-MS spectrum of **5**, the quasimolecular ion peak was observed at m/z 286 $(M+Na)^+$ and the IR spectrum of **5** showed the absorption band due to hydroxyl groups instead of lactone. The structure of **5** was clarified by ^1H NMR examination including detailed decoupling experiment. The 5-(*R*)-configuration in **5** was presumed by the above mentioned mechanism of reductive deethoxyethoxylation at β-position of the nitro group, and also eventually substantiated by the following conversions (*vide infra*) to *pseudo*-D-glucopyranose (**12**, **13**) and validamine (**18**). Thus, we have found a useful stereoselective deoxygenation method at β-position of the nitro group *via* their ethoxyethyl derivative in the case of unstable nitro-compounds.

Benzoylation of the branched nitrofuranose (**5**) with benzoyl chloride in CH_2Cl_2 containing pyridine gave the dibenzoate (**7**), which was treated with 80 % aq. trifluoroacetic acid at 40 °C to yield the deisopropylidene product (**8**). Treatment of **8** with cesium fluoride (CsF) in N,N-dimethylformamide (DMF) furnished the desired cyclization product **9** (a mixture of 1α-hydroxyl (**9a**) and 1β-hydroxyl (**9b**) epimers in a *ca* 2:1 ratio), whose structure was supported by ^1H NMR examination including detailed decoupling experiment. Ethoxyethylation of **9** with ethyl vinyl ether in CH_2Cl_2 in the presence of pyridinium *p*-toluenesulfonate (PPTS) as a catalyst followed by removal of the nitro group radically with tributyltin hydride (*n*-Bu_3SnH) in toluene in the presence of 2, 2'-azobisisobutyronitrile (AIBN) gave the denitro derivative which was subsequently subjected to deethoxyethylation with PPTS in 80 % aq. acetone at 40 °C to furnish **10** (34 % from **8**) and **11** (15 % from **8**). Finally, removal of benzoyl group in **10** and **11** with 1 % sodium methoxide in methanol afforded *pseudo*-α-D-glucopyranose (**12**) and *pseudo*-β-D-glucopyranose (**13**), respectively

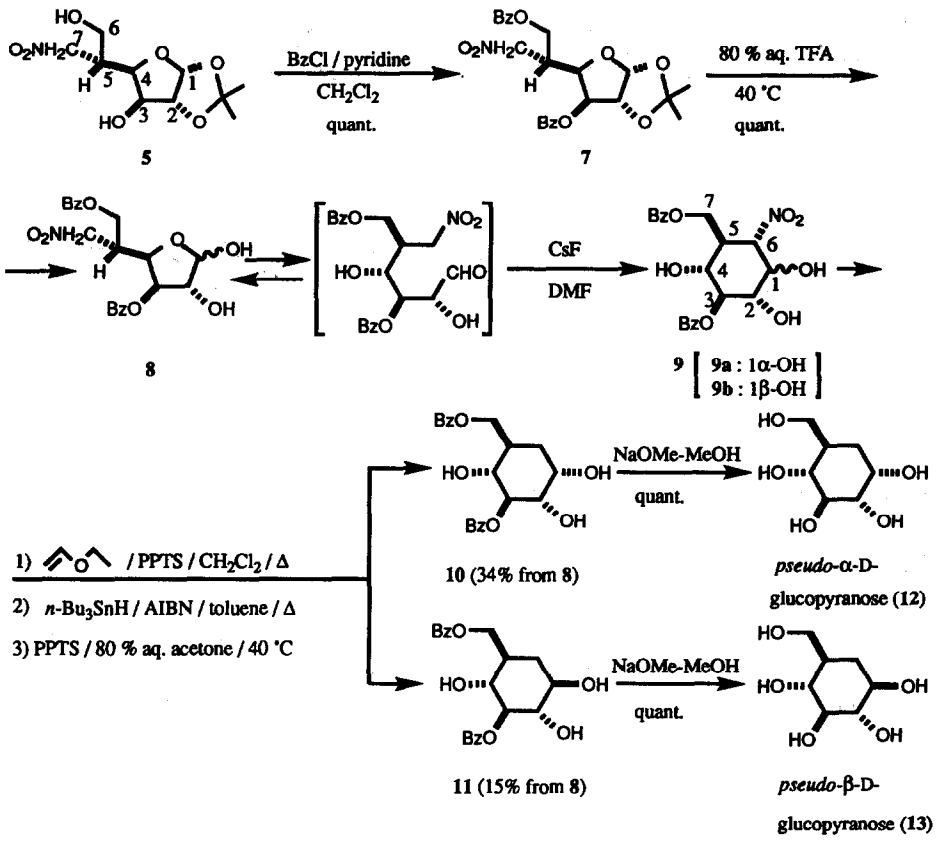


Chart 2

(Chart 2). *Pseudo*-α-D-glucopyranose (**12**) was identified by detailed comparisons of the ^1H NMR and IR data with those for authentic sample prepared in our previous synthesis.[8a] The detailed decoupling experiment in the ^1H NMR of **13** and comparison with that of **12** have led us to formulate the stereostructure of *pseudo*-β-D-glucopyranose as **13**.[13] Thus, facile syntheses of *pseudo*-α-and-β-D-glucopyranoses (**12, 13**) from D-glucuronolactone (**1**) have been accomplished through 12 steps in 11.7 % and 5.2 % overall yields, respectively. The described conversion method for *pseudo*-D-glucopyranoses seems to be significant in both the simplicity of the procedure and much higher overall yield as compared with the previous methods.[5a,6,8a]

Synthesis of validamine(18)

We have previously reported a versatile synthetic method of *pseudo*-aminosugar and *pseudo*-glycoside by using a Michael-type addition reaction to nitro-olefin and, as an application of this method, validamine (**18**) was already synthesized from D-glucose.[8c] In this paper, we describe more efficient synthesis of validamine (**18**) from the nitrocyclitol (**9**), which is a synthetic intermediate of *pseudo*-D-glucopyranose (**12, 13**), than those of the previous reports.[5b,8c] The cyclization product **9** was treated with acetic anhydride (Ac_2O) in the presence of *p*-toluenesulfonic acid (*p*-TsOH) to provide the triacetate **14** [a mixture of 1α-acetoxyl (**14a**) and

1β-acetoxyl (**14b**) epimers]. Treatment of **14** with liquid ammonia in tetrahydrofuran (THF) at -78 °C and subsequent acetylation of the product with Ac_2O in the presence of *p*-TsOH exclusively yielded the desired 1α-acetamide derivative **15** (a mixture of 7α-nitro and 7β-nitro epimers), which suggested that the reaction proceeded to provide kinetically favorable addition product (**15**) *via* the nitro-olefin (**ii**).[8c,9a] The stereostructure of the C-1 position in **15** was confirmed by completion of the synthesis presented below. Reductive elimination of the nitro group in **15** with *n*-Bu_3SnH in toluene in the presence of AIBN yielded denitro derivative (**16**) which was treated with 1 % sodium methoxide in methanol and subsequent acetylation with Ac_2O in pyridine to give pentaacetylvalidamine (**17**). Finally, deprotection of **17** with 1 % sodium methoxide in methanol and subsequently with 80 % aq. hydrazine (NH_2NH_2) at 100 °C furnished validamine (**18**) in a total yield of 6.3 % from **1** (Chart 3). Compounds **17** and **18** were identical with the authentic samples which were prepared in our previous synthesis.[8c]

Thus, a facile and enantiospecific syntheses of *pseudo*-α-D-glucopyranose(**12**), *pseudo*-β-D-glucopyranose (**13**) and validamine (**18**) have been accomplished. The synthetic procedure may be applied to the synthesis of other 1-substituted *pseudo*-D-gulcopyranoses and *pseudo*-D-gulcopyranosylnucleosides.

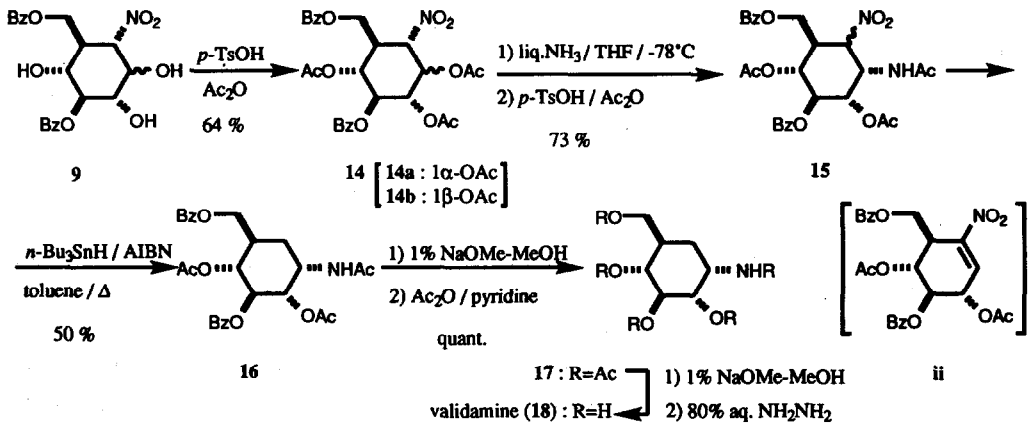


Chart 3

EXPERIMENTAL SECTION

General

Optical rotations were measured with a JASCO DIP-370 digital polarimeter and a Horiba SEPA-200 digital polarimeter. Low- and high-resolution EI mass spectra (MS) were taken on a Hitachi M-80 spectrometer. Low- and high-resolution FAB mass spectra were taken on a JEOL JMS-SX102 spectrometer. IR spectra were obtained using Shimadzu FT-IR DR-8000 or Hitachi 260-30 grating spectrometer. ^1H NMR spectra were recorded on JEOL EX-270 (270 MHz) or JEOL JNM GX-500 (500 MHz) spectrometers with $(CH_3)_4Si$ (0 ppm) as the internal standard. ^{13}C NMR spectra were determined on JEOL EX-270 (67.5 MHz) or JEOL JNM GX-500 (125 MHz) spectrometers with $(CH_3)_4Si$ (0 ppm) as the internal standard. The following experimental conditions were used for chromatography : column chromatography, silica gel BW-

200 (Fuji-Davidson Chemical) ; analytical and preparative thin-layer chromatography (TLC), precoated silica gel 60 F_{254} plates (Merck, 0.25 and 0.5 mm layer thickness).

Nitromethane treatment of 2 to give 3

i) A solution of **2**[11] (50 mg, 0.233 mmol) in CH_3NO_2 (3.0 ml) was treated with KF (12.2 mg, 0.210 mmol) and 18-crown-6 (37.0 mg, 0.140 mmol) and the whole mixture was stirred at room temperature (20 °C) for 3 h. The reaction mixture was poured into ice-water and the whole was extracted with AcOEt. The AcOEt extract was washed with brine, then dried over $MgSO_4$. After removal of the desicant by filtration, the filtrate was evaporated under reduced pressure to yield a product, which was purified by column chromatography [SiO_2 5 g, $CHCl_3$-MeOH (20:1)] to furnish **3** (23.1 mg, 36 %).

ii) A solution of **2** (50 mg, 0.233 mmol) in CH_3NO_2 (3.0 ml) was treated with KF (12.2 mg, 0.210 mmol) and 18-crown-6 (37.0 mg, 0.140 mmol) and the whole mixture was stirred at 0°C for 8 h. Work up and purification as described above furnished **3** (40.4 mg, 63%).

iii) A solution of **2** (803 mg, 3.75 mmol) in CH_3NO_2 (50 ml) was treated with KF (195 mg, 3.36 mmol) and the whole mixture was stirred at room temperature (20 °C) for 6 h. Work up as described above furnished **3** (887 mg, 86 %). **3**, white powder, $[\alpha]_D^{25}$ +13.2° (*c*=1.1, MeOH). High resolution FAB MS (m/z); Calcd for $C_{10}H_{13}NO_8Na$ $(M+Na)^+$:298.0539. Found: 298.0511. IR (KBr): 4450, 1780, 1580, 1380 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, δ): 1.38, 1.58 (3H each, both s, isopropylidene), 4.70, 4.75 (2H, ABq, *J*=13.4 Hz, CH_2NO_2), 4.90 (1H, d, *J*=3.4 Hz, 2-H), 4.97 (1H, d, *J*=3.7 Hz, 3-H), 5.17 (1H, d, *J*=3.7 Hz, 4-H), 6.03 (1H, d, *J*=3.4 Hz, 1-H). MS (m/z, %): 260 (M^+-CH_3, 3.2), 215 (M^+-CH_2NO_2, 0.1), 89 (100). FAB MS (m/z): 298 $(M+Na)^+$.

Ethoxyethylation of 3 to give 4

A solution of **3** (540 mg, 1.96 mmol) in CH_2Cl_2 (20 ml) was treated with ethyl vinyl ether (1.6 ml, 17 mmol) and CSA (2.4 mg, 0.010 mmol) in an ice-cooling bath and the whole mixture was stirred at room temperature (25 °C) for 45 min. The reaction mixture was poured into ice-water and the whole was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with sat. aq. $NaHCO_3$, brine and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave a product, which was purified by column chromatography [SiO_2 25 g, $CHCl_3$-MeOH (40:1)] to furnish **4** (536 mg, 79 %). **4**, white powder, High resolution FAB MS (m/z); Calcd for $C_{14}H_{22}NO_9$ $(M+H)^+$: 348.1295. Found: 348.1268. IR (KBr): 2980, 2930, 1790, 1560 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, δ): 1.13 -1.52 (12H, s, CH_3 x4), 3.30-3.70 (2H, m, OCH_2CH_3), 4.76-5.20 (5H, m, 2, 3, 4-H, CH_2NO_2), 5.36-5.57 (1H, m, $OCHCH_3OC_2H_5$), 6.02 (1H, d, *J*=4.0 Hz, 1-H), 6.06 (1H, d, *J*=4.0 Hz, 1-H). MS (m/z, %): 332 (M^+-CH_3, 2.4), 73 (100). FAB MS (m/z): 348 $(M+H)^+$.

Conversion from 4 to 5

i) A solution of **4** (320 mg, 0.922 mmol) in *iso*-PrOH (25 ml) was treated with $NaBH_4$ (160 mg, 4.23 mmol) and the whole mixture was stirred at room temperature (25 °C) for 2 h. The reaction mixture was neutralized with DOWEX 50Wx8 (H^+ form) and the resin was removed by filtration. Removal of the solvent from the filtrate under reduced pressure gave a product, which was purified by column chromatography [SiO_2 15 g, $CHCl_3$-MeOH (20:1)] to give **5** (202 mg, 83 %). **5**, white powder, $[\alpha]_D^{25}$ -23.8° (*c*=1.0, MeOH). High resolution FAB MS (m/z); Calcd for $C_{10}H_{27}NO_7Na$ $(M+Na)^+$: 286.0903. Found: 286.0883. IR (KBr): 3380, 1530 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, δ): 1.29, 1.44 (3H each, both s, isopropylidene), 2.71(1H, m, 5-H),

3.75 (1H, dd, *J*=5.8, 11.3 Hz, 6-H), 3.77 (1H, dd, *J*=4.3, 11.3 Hz, 6-H), 4.10 (1H, d, *J*=2.8 Hz, 3-H), 4.16 (1H, dd, *J*=2.8, 8.9 Hz, 4-H), 4.48 (1H, d, *J*=3.7 Hz, 2-H), 4.63 (2H, m, 7-H_2), 5.86 (1H, d, *J*=3.7 Hz, 1-H). MS (m/z, %): 248 (M^+-CH_3, 7.7), 59 (100). FAB MS (m/z): 286 $(M+Na)^+$.

ii) A solution of **4** (40 mg, 0.115 mmol) in EtOH (3.1 ml) was treated with $NaBH_4$ (20 mg, 0.529 mmol) and the whole mixture was stirred at room temperature. Work up as described above gave a mixture of **5** and **6** (17.6 mg, 58 %). ^1H NMR ($CDCl_3$, δ) : 2.71 (7/10H, m, 5-H of **5**), 2.81 (3/10H, m, 5-H of **6**).

Benzoylation of 5

A solution of **5** (100 mg, 0.380 mmol) in CH_2Cl_2 (2.5 ml) was treated with pyridine (0.6 ml, 7.4 mmol) and benzoyl chloride (0.45 ml, 3.9 mmol) in an ice-cooling bath. After stirring at room temperature (25 °C) for 30 min, the reaction mixture was poured into ice-water and the whole was extracted with AcOEt. The AcOEt extract was successively washed with 5 % aq. HCl, sat. aq. $NaHCO_3$ and brine, then dried over $MgSO_4$. The solvent was evaporated under reduced pressure to give a product, which was purified by column chromatography [SiO_2 30 g, *n*-hexane-AcOEt (8:1-4:1)] to furnish **7** (178 mg, quant.). **7**, white powder, $[\alpha]_D^{22}$ -33.2° (*c*=1.1, $CHCl_3$). High resolution FAB MS (m/z); Calcd for $C_{24}H_{25}NO_9Na$ $(M+Na)^+$: 494.1428. Found: 494.1391. IR ($CHCl_3$): 1720, 1560 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, δ): 1.32, 1.53 (3H each, both s, isopropylidene), 3.22 (1H, m, 5-H), 4.49 -4.75 (6H, m, 2, 4-H, 6, 7-H_2), 5.52 (1H, d, *J*=2.6 Hz, 3-H), 6.00 (1H, d, *J*=3.6 Hz, 1-H), 7.45 -8.07 (10H, m, PhCO x2). FAB MS (m/z): 494 $(M+Na)^+$.

Conversion from 7 to 8

A solution of **7** (90 mg, 0.19 mmol) in 80 % aq. trifluoroacetic acid (2 ml) was stirred at 40 °C for 1 h. The reaction mixture was poured into ice-water followed by salting out with NaCl, and the whole was extracted with CH_2Cl_2. The CH_2Cl_2 extract was washed with sat. aq. $NaHCO_3$, brine, then dried over $MgSO_4$. Removal of the solvent under reduced pressure gave **8** (84 mg, quant.). **8**, white powder, High resolution FAB MS (m/z); Calcd for $C_{27}H_{30}NO_9$ $(M+H)^+$: 512.1921. Found: 512.1898. IR ($CHCl_3$): 3520, 1720, 1560 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$, δ): 3.25 (1H, m, 5-H), 4.35 -4.72 (6H, m, 2, 4-H, 6, 7-H_2), 5.40 (1H, m, 3-H), 5.60 (1H, m, 1-H), 7.43 -8.03 (10H, m, PhCO x2). FAB-MS (m/z): 512 $(M+H)^+$.

Nitro-cyclohexane (9)

A solution of **8** (140 mg, 0.325 mmol) in DMF (10 ml) was treated with CsF (100 mg, 0.658 mmol) and the whole mixture was stirred at room temperature (25 °C) for 30 min. The reaction mixture was poured into ice-water followed by salting out with NaCl and the whole was extracted with AcOEt. Work-up of the AcOEt extract as described above for the preparation of **3** gave **9** (a mixture of **9a** and **9b**, 140 mg). **9**, white powder, High resolution FAB MS (m/z); Calcd for $C_{21}H_{21}NO_9Na$ $(M+Na)^+$: 454.1114. Found: 454.1096. IR ($CHCl_3$): 3500, 1700, 1540 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$, δ): signals due to **9a**, 2.60 (1H, m, 5-H), 3.66 (1H, dd, *J*=9.9, 9.9 Hz, 4-H), 3.87 (1H, dd, *J*=2.6, 9.9 Hz, 2-H), 4.42-4.97 (4H, m, 1,6-H, 7-H_2), 5.52 (1H, dd, *J*=9.9, 9.9 Hz, 3-H), 7.42 -8.15 (10H, m, PhCO x2); signals due to **9b**, 3.00 (1H, m, 5-H), 3.80 (1H, dd, *J*=9.6, 11.2 Hz, 2-H), 4.07 (1H, dd, *J*=9.9, 9.9 Hz, 4-H), 4.42-4.97 (4H, m, 1, 6-H, 7-H_2), 5.23 (1H, dd, *J*=9.6, 9.9 Hz, 3-H), 7.42 -8.15 (10H, m, PhCO x2). FAB MS (m/z): 454 $(M+Na)^+$

Conversion from 9 to 10 and 11

A solution of **9** (5.0 mg, 0.012 mmol) in CH_2Cl_2 (1.0 ml) was treated with ethyl vinyl ether (0.03 ml,

0.31 mmol) and catalytic amount of PPTS, and the whole mixture was heated under reflux for 2 h. The reaction mixture was poured into ice-water and the whole was extracted with AcOEt. Work-up of the AcOEt extract as described above for the preparation of **4** gave a crude product, which was purified by column chromatography [SiO_2 2 g, *n*-hexane-AcOEt (5:1)] to yield the ethoxyethylated product (5.3 mg, 71 %). A solution of this ethoxyethyl derivative (16 mg, 0.025 mmol) in toluene (2.5 ml) was treated with *n*-Bu_3SnH (0.07 ml, 0.26 mmol) and AIBN (6.2 mg, 0.038 mmol), and then the whole mixture was heated under reflux for 1 h. The reaction mixture was cooled to room temperature (25 °C), then added $CHCl_3$ and the solvent was evaporated to dryness under reduced pressure. The residue was purified by column chromatography [SiO_2 2 g, *n*-hexane-acetone (5:1)] to give the denitro-product (10.6 mg, 71 %). A solution of the product (25 mg, 0.042 mmol) in 80 % aq. acetone (2.0 ml) was treated with PPTS (30 mg, 0.12 mmol) and the whole mixture was stirred at 40 °C for 1 h. The reaction mixture was neutralized with Amberlite IRA-400 (^-OH form) and the resin was removed by filtration. Removal of the solvent from the filtrate under reduced pressure gave products, which were purified by preparative TLC [benzene-acetone (1:1)] to furnish **10** (11 mg, 69 %) and **11** (5 mg, 31 %). **10**, white powder, $[\alpha]_D^{22}$ +48.0° (*c*=0.20, MeOH). High resolution FAB MS (m/z); Calcd for $C_{21}H_{23}O_7$ $(M+H)^+$: 387.1444. Found: 387.1439. IR (film): 3400, 1710, 1280, 710 cm^{-1}. ^1H NMR (270 MHz, CD_3OD, δ): 1.63, 2.05 (2H, m, 6-H_2), 2.41 (1H, m, 5-H), 3.65 (2H, m, 2, 4-H), 4.10 (1H, br s, 1-H), 4.48 (2H, m, 7-H_2), 5.43 (1H, dd, *J*=9.6, 9.9 Hz, 3-H), 7.42-8.16 (10H, m, PhCO x2). FAB MS (m/z): 387 $(M+H)^+$. **11**, white powder, $[\alpha]_D^{22}$ +12.9° (*c*=0.30, MeOH). High resolution FAB MS (m/z); Calcd for $C_{21}H_{23}O_7$ $(M+H)^+$: 387.1444. Found: 387.1434. IR (film): 3430, 1700, 1280, 710 cm^{-1}. ^1H NMR (270 MHz, CD_3OD, δ): 2.00 (1H, m, 5-H), 2.12 (2H, m, 6-H_2), 3.46 (1H, dd, *J*=9.2, 9.6 Hz, 2-H), 3.63 (1H, m, 1-H), 3.65 (1H, dd, *J*=9.7, 10.2 Hz, 4-H), 4.43 (1H, dd, *J*=5.6, 10.9 Hz, 7-H), 4.54 (1H, dd, *J*=3.0, 10.9 Hz, 7-H), 5.07 (1H, dd, *J*=9.2, 9.7 Hz, 3-H), 7.45 -8.15 (10H, m, PhCO x2). FAB MS (m/z): 387 $(M+H)^+$.

Conversion from 10 to pseudo-α-D-glucopyranose (12)

A solution of **10** (3.0 mg, 0.0078 mmol) in 5 % NaOMe-MeOH (0.2 ml) was stirred at room temperature (25 °C) for 15 min. The reaction mixture was neutralized with Amberlite IR-120B (H^+ form) and the resin was removed by filtration. Removal of the solvent from the filtrate under reduced pressure gave a product, which was purified by column chromatography [SiO_2 1 g, $CHCl_3$-MeOH-H_2O (6:4:1)] to furnish *pseudo*-α-D-glucopyranose (**12**, 1.4 mg, quant.). **12** was identical with an authentic samples[8a] by comparisons of TLC behavior, mixed mp (150 - 152 °C), ^1H NMR (pyridine-d5) and ^{13}C NMR (pyridine-d5) spectra.

Conversion from 11 to pseudo-β-D-glucopyranose (13)

A solution of **11** (5.0 mg, 0.013 mmol) in 5 % NaOMe-MeOH (0.5 ml) was stirred at room temperature (25 °C) for 15 min. The reaction mixture was neutralized with Amberlite IR-120B (H^+ form) and the resin was removed by filtration. Removal of the solvent from the filtrate yielded *pseudo*-β-D-glucopyranose (**13**, 2.5 mg, quant.). **13**, white powder, $[\alpha]_D^{22}$ +6.7° (*c*=0.15, MeOH). IR (film): 3350, 2930 cm^{-1}. ^1H NMR (270 MHz, CD_3OD, δ): 1.18 (1H, dd, *J*=11.9, 12.9 Hz, 6-H), 1.53 (1H, m, 5-H), 1.96 (1H, ddd, *J*=3.6, 4.6, 12.9 Hz, 6-H), 3.16 (3H, m, 2, 3, 4-H), 3.42 (1H, ddd, *J*=4.6, 8.6, 13.2 Hz, 1-H), 3.57 (1H, dd, *J*=6.1, 10.7 Hz, 7-H), 3.74 (1H, dd, *J*=4.1, 10.7 Hz, 7-H).

Acetylation of 9 to give 14

A solution of **9** (55 mg, 0.13 mmol) in acetic anhydride (0.7 ml) was treated *p*-TsOH (14 mg, 0.081

mmol) and the whole mixture was stirred at room temperature (25 °C) for 2 h. The reaction mixture was poured into ice-water and the whole was extracted with AcOEt. Work-up of the AcOEt extract as described above for the preparation of **4** gave a product, which was purified by column chromatography [SiO_2 7 g, *n*-hexane-acetone (50:1)] to furnish **14** (a mixture of **14a** and **14b**, 45 mg, 64 %). **14**, white powder, High resolution FAB MS (m/z); Calcd for $C_{27}H_{28}NO_{12}$ $(M+H)^+$: 558.1611. Found: 558.1630. IR (film): 1730, 1700, 1540, 1380, 1270 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$, δ): signals due to **14a**, 1.93, 1.97, 2.21 (3H each, s, OAc x3), 3.27 (1H, m, 5-H), 4.96 (1H, dd, *J*=2.6, 11.9 Hz, 6-H), 5.22 (1H, dd, *J*=2.6, 10.4 Hz, 2-H), 5.43 (1H, dd, *J*=10.0, 11.2 Hz, 4-H), 5.79 (1H, dd, *J*=10.0, 10.4 Hz, 3-H), 6.02 (1H, dd, *J*=2.6, 2.6 Hz, 1-H); signals due to **14b**, 1.92, 1.94, 2.04 (3H each, s, OAc x3), 2.92 (1H, m, 5-H), 4.96 (1H, dd, *J*=10.6, 10.6 Hz, 2-H), 5.40 (1H, dd, *J*=10.6, 11.6 Hz, 1-H), 5.43 (1H, dd, *J*=10.2, 10.6 Hz, 3-H), 5.58 (1H, dd, *J*=9.8, 11.6 Hz, 6-H). FAB MS (m/z): 558 $(M+H)^+$.

Treatment of 14 with liq. NH_3 followed by acetylation to give 15

A solution of **14** (15 mg, 0.027 mmol) in THF (0.5 ml) was treated with liq. NH_3 (*ca.* 1 ml) and the whole mixture was stirred at -78 °C for 9 min. After removal of liq. NH_3 at room temperature (25 °C) and then the solvent under reduced pressure, the product was dissolved in a solution of acetic anhydride (0.25 ml) and *p*-TsOH•H_2O (2.5 mg, 0.013 mmol) and the whole mixture was stirred at room temperature (25 °C) for 2 h. The reaction mixture was poured into ice-water and the whole was extracted with AcOEt. Work-up of the AcOEt extract in the usual manner gave a product, which was purified by preparative TLC [benzene-acetone (2:1)] to furnish **15** (7 mg, 73 %). **15**, white powder, High resolution FAB MS (m/z); Calcd for $C_{27}H_{29}N_2O_{11}$ $(M+H)^+$: 557.1771. Found: 557.1758. IR (film): 1730, 1680, 1540, 1380, 1270 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$, δ): 1.90 (3H, s), 1.98 (6H, s)(OAc x2, NHAc), 2.75 (1H, m, 5-H), 4.20-4.54 (2H, m, 7-H_2), 5.00-6.10 (6H, m, 1, 2, 3, 4, 6-H, NH), 7.43 -8.08 (10H, m, PhCO x2). FAB MS (m/z): 557 $(M+H)^+$.

Denitration of 15 to give 16

A solution of **15** (8.0 mg, 0.014 mmol) in toluene (1.4 ml) was treated with *n*-Bu_3SnH (0.04 ml, 0.15 mmol) and AIBN (3.4 mg, 0.021 mmol) and the whole mixture was stirred at 110 °C for 1 h. Removal of the solvent from the reaction mixture under reduced pressure gave the residue, which was purified by preparative TLC [*n*-hexane-acetone (1:1)] to furnish **16** (3.7 mg, 50 %). **16**, white powder, $[\alpha]_D^{22}$ +43.0° (*c*=0.18, $CHCl_3$). High resolution FAB MS (m/z); Calcd for $C_{27}H_{30}NO_9$ $(M+H)^+$: 512.1921. Found: 512.1898. IR (film): 1750, 1680, 1270 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$, δ): 1.87, 1.91, 2.09 (3H each, s, OAc x2, NHAc), 1.79(1H, m, 6-H), 2.34 (2H, m, 5, 6-H), 4.31 (2H, m, 7-H_2), 4.61 (1H, m, 1-H), 5.21 (1H, dd, *J*=4.6, 10.6 Hz, 2-H), 5.28 (1H, dd, *J*=9.7, 10.6 Hz, 4-H), 5.52 (1H, dd, *J*=9.7, 10.6 Hz, 3-H), 5.78 (1H, d, *J*=6.9 Hz, NH), 7.45 -8.10 (10H, m, PhCO x2). FAB MS (m/z): 512 $(M+H)^+$.

Conversion from 16 to pentaacetylvalidamine (17)

A solution of **16** (8.0 mg, 0.016 mmol) in 1 % NaOMe-MeOH (0.8 ml) was stirred at room temperature (25 °C) for 3 h. The reaction mixture was neutralized with Amberlite IR-120B (H^+ form) and the resin was removed by filtration. Removal of the solvent from the filtrate under reduced pressure gave the product. A solution of the product (3.9 mg) in acetic anhydride-pyridine (1:1, 1 ml) was stirred at room temperature (25 °C) for 12 h. The reaction mixture was poured into ice-water and the whole was extracted with AcOEt. Work-up of the AcOEt extract as described above for the preparation of **7** yielded pentaacetylvalidamine (**17**, 6.3 mg,

quant.), which was identical with an authentic sample[8c] by comparisons of TLC behavior and IR ($CHCl_3$) and ^1H NMR ($CDCl_3$) spectra.

Conversion from 17 to validamine (18)

A solution of **17** (5.0 mg, 0.013 mmol) in 1 % NaOMe-MeOH (0.5 ml) was stirred at room temperature (25 °C) for 2 h. The reaction mixture was neutralized with Amberlite IR-120B (H^+ form) and the resin was removed by filtration. Removal of the solvent from the filtrate under reduced pressure gave a product, which was dissolved in 80 % aq. NH_2NH_2 (0.5 ml) and the whole mixture was stirred at 100 °C for 72 h. Removal of the solvent from the reaction mixture under reduced pressure yielded validamine (**18**, 2.3 mg, quant.), which was identical, by comparisons of TLC behavior, $[\alpha]_D$ value and IR spectrum, with an authentic sample.[8c]

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