SYNTHESES OF PSEUDO-α-D-GLUCOPYRANOSE, PSEUDO-β-D-GLUCOPYRANOSE, AND VALIDAMINE FROM D-GLUCURONOLACTONE

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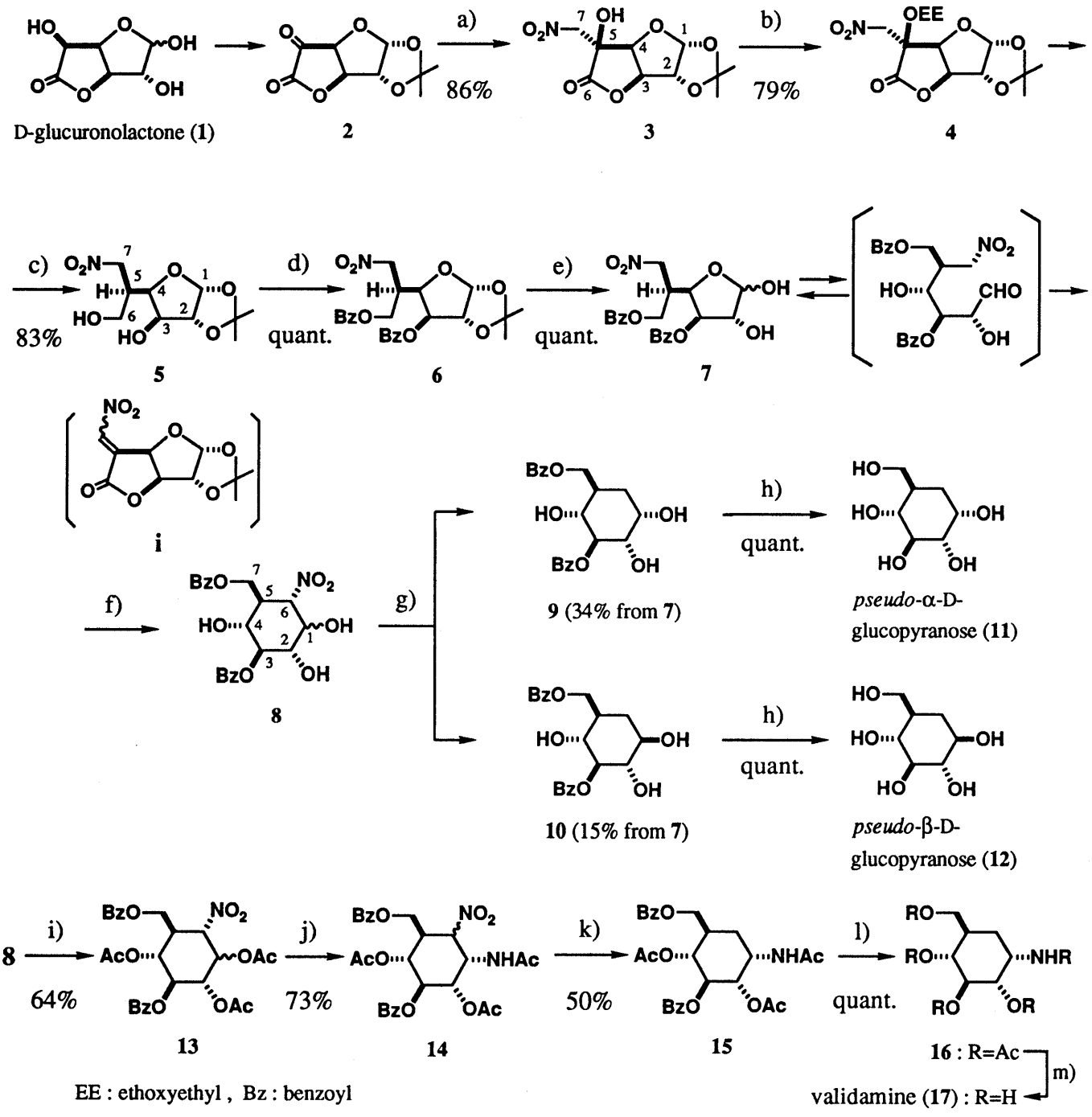
Using a stereoselective nitromethane addition and a reductive elimination of an ethoxyethoxyl moiety with $NaBH_4$ as key steps, two optically active *pseudo*-sugars, *pseudo*-α-D-glucopyranose and *pseudo*-β-D-glucopyranose, were synthesized from D-glucuronolactone in favorable overall yield. Furthermore, a biologically active *pseudo*-aminosugar, validamine, was synthesized *via* a substitution reaction for an acetoxyl group at the β-position of the nitro group in the nitrocyclitol derivative which was prepared from a synthetic intermediate of *pseudo*-D-glucopyranose.

KEYWORDS *pseudo*-α-D-glucopyranose ; *pseudo*-β-D-glucopyranose ; validamine ; *pseudo*-sugar ; *pseudo*-aminosugar ; D-glucuronolactone

During the course of our chemical transformation studies from carbohydrates leading to cyclitols,[1] we have found a method for synthesizing various *pseudo*-sugars,[2] *pseudo*-aminosugars,[3] and *pseudo*-nucleosides[4] such as (+)-cyclaradine[5] and (-)-aristeromycin[6] using D-glucose as a starting material. Furthermore, we have recently developed a synthetic method of *pseudo*-D-arabinofuranose and *pseudo*-β-D-arabinofuranosyl nucleosides from D-arabinose.[7] As an extension of these studies, we have found a new versatile method for synthesizing *pseudo*-α- and -β-D-glucopyranoses (**11**, **12**) from D-glucuronolactone (**1**). This synthetic pathway comprises a stereoselective addition of nitromethane to the keto-lactone derivative (**2**) and a reductive elimination of the ethoxyethoxyl moiety as the key reactions. In addition, validamine, an optically active *pseudo*-aminosugar exhibiting potent α-D-glucosidase inhibitory and antibiotic activities, was synthesized by using a substitution reaction for an acetoxyl residue at the β-position of a nitro group in the nitrocyclitol derivative (**13**) which was prepared from a synthetic intermediate (**8**) of *pseudo*-D-glucopyranoses (**11**, **12**).

Treatment of 1, 2-*O*-isopropylidene-α-D-glucofuranurono-5-ulose-6, 3-lactone (**2**)[8] with nitromethane in the presence of KF gave stereoselectively the addition product (**3**).[9] The stereostructure of C-5 position in **3** was characterized by the examination of its spectral data including the NOE observation in the following pairs of protons (7-H_2&4-H, 7-H_2&3-H). Ethoxyethylation of **3** with ethyl vinyl ether in CH_2Cl_2 in the presence of camphorsulfonic acid (CSA) furnished **4**,[10] which was subsequently treated with $NaBH_4$ in EtOH to give a epimeric mixture of branched nitrofuranoses (**5** : **5'** [5-epimar of **5**]=7:3, 58%).[11] However, treatment of **4** with $NaBH_4$ in isopropanol gave stereoselectively a single product (**5**).[12] This reaction procedure from **4** to **5** with $NaBH_4$ in isopropanol is considered to proceed in three steps: (1) elimination of the ethoxyethoxyl moiety in **4** to produce the nitro-olefin **i** ; (2) followed by reduction with hydride from the less hindered α-side (in a similar manner as nitromethane addition reaction to **2**) ; (3) and then reduction of 6, 3-lactone ring. It was presumed that, in the case of EtOH solution, the γ-lactone ring in **4** is partially cleaved prior to elimination of the ethoxyethoxyl moiety. The 5(*R*)-configuration in **5** was finally substantiated by the following conversions (*vide infra*) to *pseudo*-D-glucopyranose (**11**, **12**) and validamine (**17**).

Benzoylation of the branched nitrofuranose (**5**) with benzoyl chloride in CH_2Cl_2 containing pyridine furnished **6**,[13] which, on treatment with 80% aq. trifluoroacetic acid, was converted to **7**. Treatment of **7** with cesium fluoride (CsF) in DMF yielded the desired cyclization product **8** (a mixture of 1α-hydroxyl and 1β-hydroxyl epimers in a ca 2:1 ratio).[14] Ethoxyethylation of **8** with ethyl vinyl ether in CH_2Cl_2 in the presence of pyridinium p-toluenesulfonate (PPTS) followed by elimination of nitro group in the product with tri-n-butyltin hydride (n-Bu_3SnH) in toluene in the presence of 2, 2'-azobisisobutyronitrile (AIBN) yielded the denitro derivative which was subsequently subjected to deethoxyethylation with PPTS in 80% aq. acetone to afford **9**[15] and **10**.[16] Finally, removal of benzoyl group in **9** and **10** with 1% NaOMe-MeOH furnished *pseudo*-α-D-glucopyranose (**11**)[2a] and *pseudo*-β-D-glucopyranose (**12**),[17] respectively. Thus, *pseudo*-α- and -β-D-glucopyranoses (**11**, **12**) were synthesized from D-glucuronolactone (**1**) through 12 steps in the total yields of 11.7% and 5.2%, respectively. The present conversion method for *pseudo*-D-glucopyranoses seems to be significant due not only to the simplicity of the procedure but also to the much higher overall yield as compared with the previous methods.[2a, 17, 18]



a) CH_3NO_2 / KF (20°C, 6 h), b) ethyl vinyl ether / CSA / CH_2Cl_2 (r.t., 45min), c) $NaBH_4$ / iso-PrOH (r.t., 2 h), d) BzCl / CH_2Cl_2-pyridine (4:1) (r.t., 30min), e) 80% aq. CF_3COOH (40°C, 1 h), f) CsF / DMF (20°C, 30min), g) 1) ethyl vinyl ether / PPTS / CH_2Cl_2 (reflux, 2 h), 2) n-Bu_3SnH / AIBN / toluene (reflux, 1 h), 3) PPTS / 80% aq. acetone (40°C, 1 h), h) 5% NaOMe-MeOH (r.t., 15min), i) Ac_2O / *p*-TsOH (r.t., 2 h), j) 1) liq. NH_3 / THF (-78°C, 5min), 2) Ac_2O / *p*-TsOH (r.t., 2 h), k) n-Bu_3SnH / AIBN / toluene (reflux, 1 h), l) 1) 1% NaOMe-MeOH (r.t., 3 h), 2) Ac_2O / pyridine (r.t., 3 h), m) 1) 1% NaOMe-MeOH (r.t., 2 h), 2) 80% aq. NH_2NH_2 (100°C, 72 h)

Next, the cyclization product **8** was treated with Ac_2O in the presence of *p*-TsOH to provide the tri-acetate **13** (a mixture of 1α-acetoxyl and 1β-acetoxyl epimers).[19] Treatment of **13** with liquid NH_3 in THF and subsequent acetylation of the product yielded the desired 1α-acetamide derivatives **14** (a mixture of 7α-nitro and 7β-nitro epimers). The stereochemistry of C-1 position in **14** was confirmed by the completion of the synthesis presented below. Reductive elimination of the nitro group in **14** with n-Bu_3SnH and AIBN yielded **15**[20] which was treated with 1% NaOMe-MeOH and subsequent acetylation to give penta-acetylvalidamine (**16**).[3] Finally, deacetylation of **16** with 1% NaOMe-MeOH and 80% aq. NH_2NH_2 furnished validamine (**17**)[3] in a total yield of 6.3% from **1**.

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9)a)**3** : white powder, $[\alpha]_D^{25}$ +13.2° (MeOH), $C_{10}H_{13}NO_8$,[9b] IR (KBr) : 3450, 1780, 1580, 1380 cm^{-1}, ^1H NMR ($CDCl_3$) : δ4.70, 4.75 (ABq, J=13.4Hz, 7-H_2), 4.90 (d, J=3.4Hz, 2-H), 4.97 (d, J=3.7Hz, 3-H), 5.17 (d, J=3.7Hz, 4-H), 6.03 (d, J=3.4Hz, 1-H), FAB-MS m/z (%) : 298 ($[M+Na]^+$, 39), 276 ($[M+H]^+$, 22); b) The molecular composition of the compound given with the chemical formula was determined by high resolution FAB-MS measurement.

10)**4** : white powder, $C_{14}H_{21}NO_9$[9b], IR (KBr) : 2980, 2930, 1790, 1560, 1380 cm^{-1}, FAB-MS m/z (%) : 348 ($[M+H]^+$, 12).

11)An approximate ratio of the 5-isomers (**5**, **5'**) is shown by ^1H NMR (500MHz, CD_3OD).

12)**5** : white powder, $[\alpha]_D^{25}$ -23.8° (MeOH), $C_{10}H_{17}NO_7$,[9b] IR (KBr) : 3380, 1530, 1380 cm^{-1}, ^1H NMR (CD_3OD) : δ2.71 (m, 5-H), 3.75 (dd, J=5.8, 11.3Hz), 3.77 (dd, J=4.3, 11.3Hz) (6-H_2), 4.10 (d, J=2.8Hz, 3-H), 4.16 (dd, J=2.8, 8.9Hz, 4-H), 4.48 (d, J=3.7Hz, 2-H), 4.63 (m, 7-H_2), 5.86 (d, J=3.7Hz, 1-H), FAB-MS m/z (%) : 286 ($[M+Na]^+$, 24), 264 ($[M+H]^+$, 85).

13)**6** : white powder, $[\alpha]_D^{22}$ -33.2° ($CHCl_3$), $C_{24}H_{25}NO_9$,[9b] IR ($CHCl_3$) : 1720, 1560, 1380 cm^{-1}, FAB-MS m/z (%) : 494 ($[M+Na]^+$, 75).

14)**8** : white powder, $C_{21}H_{21}NO_9$,[9b] IR (KBr) : 3500, 1700, 1540, 1380 cm^{-1}, ^1H NMR (CD_3OD) : (1α-epimer) δ3.00 (m, 5-H), 3.66 (dd, J=9.9, 9.9Hz, 4-H), 3.87 (dd, J=2.6, 9.9Hz, 2-H), 5.52 (dd, J=9.9, 9.9Hz, 3-H) ; (1β-epimer) 2.60 (m, 5-H), 3.80 (dd, J=9.6, 11.2Hz, 2-H), 4.07 (dd, J=9.9, 9.9Hz, 4-H), 5.23 (dd, J=9.6, 9.9Hz, 3-H), FAB-MS m/z (%) : 454 ($[M+Na]^+$, 25), 432 ($[M+H]^+$, 38).

15)**9** : white powder, $[\alpha]_D^{22}$ +48.0° (MeOH), $C_{21}H_{22}O_7$,[9b] IR (film) : 3400, 1710, 1280 cm^{-1}, ^1H NMR (CD_3OD) : δ1.63, 2.05 (m, 6-H_2), 2.41 (m, 5-H), 4.10 (br s, 1-H), 4.48 (m, 7-H_2), 5.43 (dd, J=9.6, 9.9Hz, 3-H), FAB-MS m/z (%) : 387 ($[M+H]^+$, 27).

16)**10** : white powder, $[\alpha]_D^{22}$ +12.9° (MeOH), $C_{21}H_{22}O_7$,[9b] IR (film) : 3430, 1700, 1280 cm^{-1}, ^1H NMR (CD_3OD) : δ2.00 (m, 5-H), 2.12 (m, 6-H_2), 3.46 (dd, J=9.2, 9.6Hz, 2-H), 3.63 (m, 1-H), 3.65 (dd, J=9.7, 10.2Hz, 4-H), 4.43 (dd, J=5.6, 10.9Hz), 4.54 (dd, J=3.0, 10.9Hz) (7-H_2), 5.07 (dd, J=9.2, 9.7Hz, 3-H), FAB-MS m/z (%) : 387 ($[M+H]^+$, 27).

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19)**13** : white powder, IR (film) : 1730, 1700, 1540, 1380, 1270 cm^{-1}, ^1H NMR ($CDCl_3$) : (1α-epimer) δ3.27 (m, 5-H), 4.40-4.52 (m, 7-H_2), 5.22 (dd, J=2.6, 10.4Hz, 2-H), 6.09 (dd, J=2.6, 2.6Hz, 1-H) ; (1β-epimer) 2.92 (m, 5-H), 4.20-4.52 (m, 7-H_2), 5.59 (dd, J=9.9, 9.9Hz, 3-H), 5.79 (t-like, 1-H).

20)**15** : white powder, $[\alpha]_D^{22}$ +43.0° ($CHCl_3$), $C_{27}H_{29}NO_9$,[9b] IR (film) : 1750, 1680, 1270cm^{-1}, ^1H NMR ($CDCl_3$) : δ1.79 (m, 6-H), 2.34 (m, 5, 6-H), 4.31 (m, 7-H_2), 4.61 (m, 1-H), 5.21(dd, J=4.6, 10.6Hz, 2-H), 5.28 (dd, J=9.7, 10.6Hz, 4-H), 5.52 (dd, J=9.7, 10.6Hz, 3-H), 5.78 (d, J=6.9Hz, NH), FAB-MS m/z (%) : 512 ($[M+H]^+$, 32).

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