A NEW APPROACH TO THE SYNTHESIS OF OPTICALLY ACTIVE *PSEUDO*-SUGAR AND *PSEUDO*-NUCLEOSIDE —SYNTHESES OF *PSEUDO*-α-D-ARABINOFURANOSE, (+)-CYCLARADINE, AND (+)-1-*PSEUDO*-β-D-ARABINOFURANOSYLURACIL FROM D-ARABINOSE —

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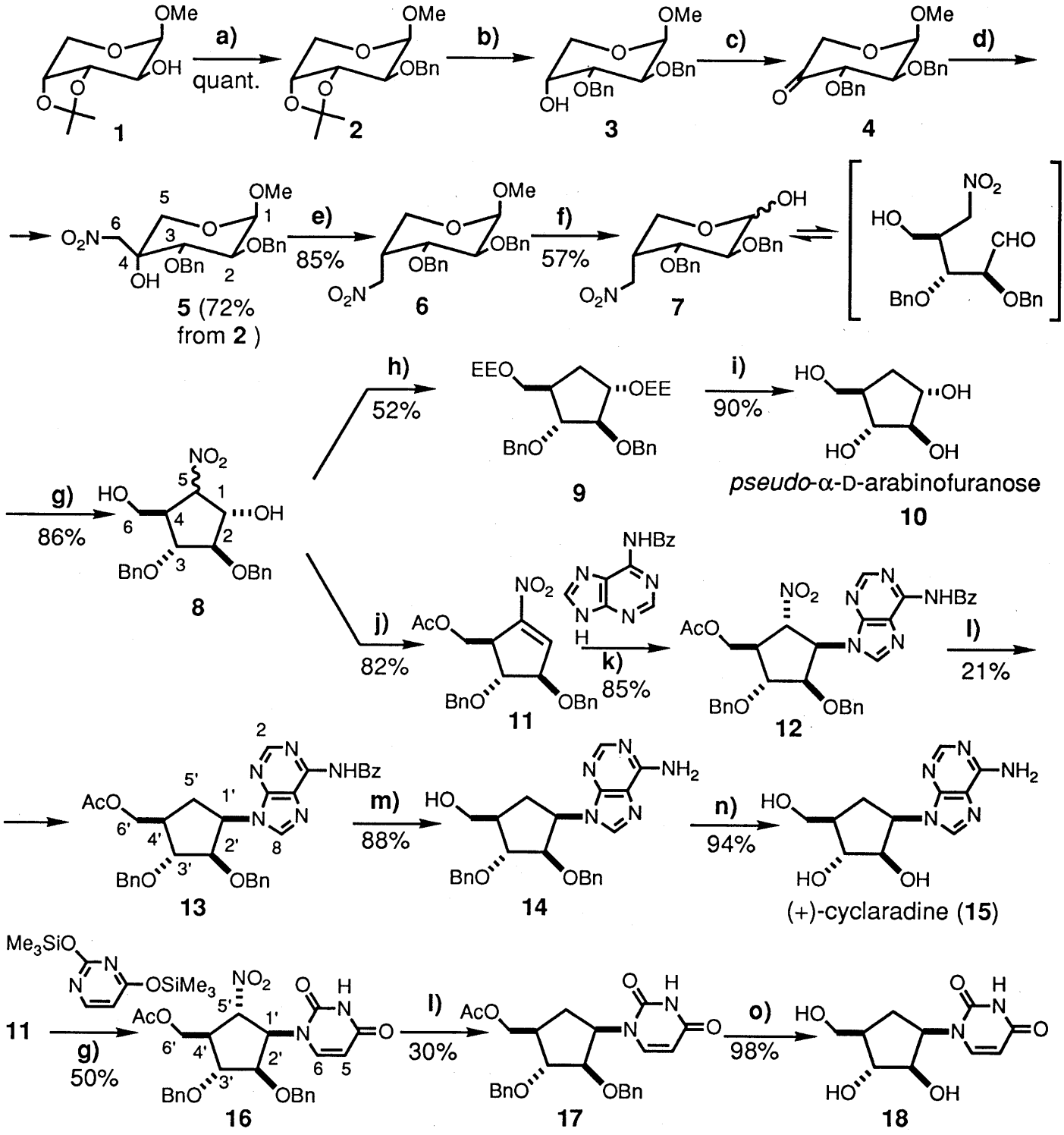
An optically active *pseudo*-sugar, *pseudo*-α-D-arabinofuranose, was synthesized from D-arabinose in favorable overall yield by using a stereoselective formation of branched nitropyranose as the key step. Furthermore, two biologically active *pseudo*-β-D-arabinofuranosylnucleosides, (+)-cyclaradine and (+)-1-*pseudo*-β-D-arabinofuranosyluracil, were synthesized *via* Michael-type reactions of nucleic acid bases and a nitrocyclopentene derivative which was prepared from a synthetic intermediate of *pseudo*-D-arabinofuranose.

KEYWORDS *pseudo*-α-D-arabinofuranose; (+)-cyclaradine; (+)-1-*pseudo*-β-D-arabinofuranosyluracil; *pseudo*-nucleoside; *pseudo*-sugar; D-arabinose

Recently, we have developed a method for transforming D-glucose into *pseudo*-sugars and successfully synthesized optically active *pseudo*-hexopyranoses,[1] *pseudo*-pentofuranoses,[2] and *pseudo*-aminosugars.[3] Furthermore, we have synthesized *pseudo*-nucleosides such as (-)-9-*pseudo*-β-D-glucopyranosyladenine,[4] (-)-9-*pseudo*-β-L-idopyranosyladenine,[4] (+)-9-*pseudo*-β-L-xylofuranosyladenine,[5] (+)-cyclaradine,[5] and (-)-aristeromycin [6] from nitro-cyclohexenes and nitro-cyclopentenes which were readily prepared from the synthetic intermediates of those *pseudo*-sugars. As an extension of these studies on synthesis of *pseudo*-sugar and *pseudo*-nucleoside, we have developed a new versatile conversion method starting from D-arabinose leading to *pseudo*-α-D-arabinofuranose (**10**). In addition, two biologically active *pseudo*-β-D-arabinofuranosylnucleosides, (+)-cyclaradine (**15**) and (+)-1-*pseudo*-β-D-arabinofuranosyluracil (**18**), have been synthesized by use of a Michael-type addition reaction of nucleic acid base and a nitro-cyclopentene derivative which was prepared from the synthetic intermediate of *pseudo*-D-arabinofuranose.

Benzylation of methyl 3, 4-*O*-isopropylidene-β-D-arabinopyranoside (**1**) [7] quantitatively gave **2**, colorless oil, $[\alpha]_D$-109.1° ($CHCl_3$), $C_{16}H_{22}O_5$, [8a] which was treated with 80% aq. AcOH followed by selective benzylation [9] of the product to furnish methyl 2,3-di-*O*-benzyl-β-D-arabinopyranoside (**3**), colorless oil, $[\alpha]_D$ -64.2° ($CHCl_3$), $C_{20}H_{24}O_5$. [8b] Swern oxidation [10] of **3** gave an unstable ketone **4**, colorless oil, $[\alpha]_D$ -78.2° ($CHCl_3$) , $C_{20}H_{22}O_5$ [8c] which was treated with CH_3NO_2 in DMF in the presence of KF and 18-crown-6 to provide **5**, colorless oil, $[\alpha]_D$ -20.8° ($CHCl_3$), $C_{21}H_{25}NO_7$. [8d] The nitromethane adduct **5** was acetylated and subsequently subjected to deacetoxyhydrogenation with $NaBH_4$ in EtOH to furnish **6**, colorless oil, $[\alpha]_D$ -54.0° ($CHCl_3$), $C_{21}H_{25}NO_6$. [8e] Acidic hydroysis of **6** gave a branched nitropyranose **7** [8f] which was subjected to an intramolecular condensation reaction with CsF in DMF (25°C, 3h) to furnish the desired cyclization product **8** (a mixture of 5α-nitro and 5β-nitro epimers). [8g]

Ethoxyethylation of **8** followed by denitrohydrogenation with n-Bu_3SnH in toluene in the presence of α, α'-azobis-*iso*-butyronitrile (AIBN) gave **9**. [8h] Finally, removal of the benzyl and ethoxyethyl groups of **9** furnished *pseudo*-α-D-arabinofuranose (**10**).[2] The present conversion method for *pseudo*-D-arabinose seems to be significant due not only to the simplicity of the procedure but also to the improved overall yield (14% from D-arabinose) as compared with yields in most of the previous methods. [2, 11] Next, the cyclization product **8** was treated with Ac_2O in the presence of *p*-TsOH·H_2O to provide a nitro-cyclopentene **11**, colorless oil, $[\alpha]_D$ -82.5° ($CHCl_3$), $C_{22}H_{23}NO_6$. [8i] Treatment of **11** with N^6-benzoyladenine in DMF in the presence of CsF (0°C, 1h) provided **12**, white powder, $[\alpha]_D$ +65.7° ($CHCl_3$), $C_{34}H_{32}N_6O_7$,[8j] which was subjected to denitrohydrogenation, as described above for the conversion from **8** to **9**, to furnish **13**, white powder, $[\alpha]_D$ +47.7° ($CHCl_3$), $C_{34}H_{33}N_5O_5$. [8k] Removal of the acetyl and N-benzoyl groups of **13** yielded **14**, white powder, $[\alpha]_D$ +60.2° ($CHCl_3$), $C_{25}H_{27}N_5O_3$, [8l] from which the benzyl groups were finally removed to furnish (+)-cyclaradine (**15**).[5] On the other hand, treatment of **11** with a silylated uracil[12] in CsF-DMF (25°C, 1h) gave **16**, white powder, $[\alpha]_D$ +91.3° ($CHCl_3$), $C_{26}H_{27}N_3O_8$. [8m] Reductive elimination of the nitro group in **16** gave **17**, white powder,



Bn : $C_6H_5CH_2$- , EE : ethoxyethyl , Bz : C_6H_5CO- , PPTS : pyridinium *p*-toluenesulfonate

a) BnCl / NaH / DMF, **b)** 1) 80% aq. AcOH (50°C) 2) Bu_2SnO / toluene (110°C) 3) BnBr / CsF / DMF, **c)** Swern oxid., **d)** CH_3NO_2 / KF / 18-crown-6 / DMF, **e)** 1) Ac_2O / *p*-TsOH · H_2O 2) $NaBH_4$ / EtOH, **f)** c-HCl / AcOH (30°C), **g)** CsF / DMF (25°C), **h)** 1) ethyl vinyl ether / PPTS / CH_2Cl_2 2)n-Bu_3SnH / AIBN / toluene (110°C), **i)** 1) H_2 / Pd-black / AcOEt 2) PPTS / 80% aq. acetone (40°C), **j)** 1) Ac_2O / *p*-TsOH · H_2O 2) pyridine, **k)** CsF / DMF (0°C), **l)** n-Bu_3SnH /AIBN / toluene (110°C), **m)** 10% NaOMe-MeOH, **n)** H_2 (6 atm) / Pd-black / 10% AcOH-EtOH, **o)** 1) 1% NaOMe-MeOH 2) H_2 / Pd-black / 10% AcOH-EtOH.

$[\alpha]_D$ +120.5° ($CHCl_3$), $C_{26}H_{28}N_2O_6$ [8n], which was subjected to successive deprotection to furnish the final product, 1-(+)-*pseudo*-β-D-arabinofuranosyluracil (**18**), white powder, $[\alpha]_D$ +112.3° (CH_3OH), $C_{10}H_{14}N_2O_5$.[8o]

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8) All new compounds were fully characterized by IR (neat), ^{1}H-NMR (270 MHz, $CDCl_3$) and MS spectra (unless specified otherwise), a) **2** : IR : 2930, 1460 cm^{-1}, ^{1}H-NMR : δ 3.52 (dd, *J*=3, 8Hz, 2-H), 3.91 (br s, 5-H_2), 4.21 (m, 4-H), 4.33 (dd, *J*=6, 8Hz, 3-H), 4.64 (d, *J*=3 Hz, 1-H), EI-MS (%) : *m* / *z* 294 (M^+, 0.4) ; b) **3** : IR : 3480, 2930 cm^{-1}, ^{1}H-NMR : δ 3.71 (m, 5-H_2), 3.87 (m, 2, 3-H), 3.98 (m, 4-H), 4.68 (d, *J*=3Hz, 1-H), EI-MS (%) : *m* / *z* 312 (M^+-MeOH, 2); c) **4** : IR : 3030, 1730 cm^{-1}, ^{1}H-NMR : δ 3.80 (dd, *J*=3, 10Hz, 2-H), 3.90, 4.14 (ABq, *J*=15Hz, 5-H_2), 4.44 (d, *J*=10Hz, 3-H), 4.76 (d, *J*=3Hz, 1-H), EI-MS (%) : *m* / *z* 342 (M^+, 0.1); d) **5** : IR : 3470, 1560, 1380 cm^{-1}, ^{1}H-NMR : δ 3.47 (dd, *J*=3, 8Hz, 2-H), 3.60, 3.70 (ABq, *J*=12Hz, 5-H_2), 3.89 (d, *J*=8Hz, 3-H), 4.60 (d, *J*=3Hz, 1-H), 4.70 (br s, 6-H_2), NOEs : 1-H & 2-H, 3-H & 6-H_2, EI-MS (%) : *m* / *z* 342 (M^+-CH_3NO_2, 0.1); e) **6** : IR : 1560, 1380 cm^{-1}, ^{1}H-NMR : δ 2.91 (m, 4-H), 3.36 (dd, *J*=4, 10Hz, 2-H), 3.51 (dd, *J*=3, 12Hz), 3.84 (dd, *J*=2, 12Hz) (5-H_2), 4.01 (dd, *J*=6, 10Hz, 3-H), 4.52 (dd, *J*=10, 13Hz), 4.69 (dd, *J*=5, 13Hz) (6-H_2), 4.61 (d, *J*=4Hz, 1-H), EI-MS (%) : *m* / *z* 355 (M^+-MeOH, 0.1); f) **7** : colorless oil, IR : 3400, 3030, 1560, 1380 cm^{-1}, ^{1}H-NMR : 2.93-2.98 (m, 4-H), 3.39-3.91 (m, 2,3-H, 5-H_2), EI-MS (%) : *m* / *z* 282 (3) ; g) **8** : colorless oil , IR (KBr) : 3400, 3030, 1560, 1380 cm^{-1}, ^{1}H-NMR : 2.70-3.11 (m, 4-H), 3.57-4.05 (m, 2,3-H, 6-H_2), 4.47-4.95 (m, 1,5-H), EI-MS (%) : *m* / *z* 355 (M^+-H_2O, 0.1); h) **9** : colorless oil, IR : 2980, 1130, 1060 cm^{-1}, ^{1}H-NMR : δ 1.78-2.40 (m, 4,5-H), 3.35-4.16 (m, 1,2,3-H, ,6-H_2), EI-MS (%) : *m* / *z* 399 (M^+-CH_3CHOEt, 1); i) **11** : IR : 3030, 1740, 1530 cm^{-1}, ^{1}H-NMR : δ 3.38 (m, 4-H), 4.12 (m, 3-H), 4.38 (d, *J*=5Hz, 6-H_2), 4.57 (m, 2-H), 6.95 (br s, 1-H), EI-MS (%) : *m* / *z* 397 (M^+, 0.1); j) **12** : IR (KBr) : 1740, 1700, 1610, 1590, 1560, 1370, 1240 cm^{-1}, ^{1}H-NMR : δ 2.02 ($COCH_3$), 3.20 (m, 4'-H), 3.89 (dd, *J*=1, 3Hz, 3'-H), 4.15 (*br* d, 2'-H), 4.33 (d, *J*=7Hz, 6'-H_2), 5.46 (dd, *J*=8, 10Hz, 5'-H), 5.93 (dd, *J*=5, 10Hz, 1'-H), 8.24 (s, 8-H), 8.77 (s, 2-H), 9.10 (br s, NH), NOEs : 1'-H & 2'-H, 1'H & 8-H, 5'-H & 6'-H_2, 5'-H & 8-H, EI-MS (%) : *m* / *z* 398 (0.2) ; k) **13** : IR (KBr) : 1740, 1700, 1610, 1580 cm^{-1}, ^{1}H-NMR : δ 2.05 ($COCH_3$), 2.13 (m, 5'-H), 2.48 (m, 4', 5'-H), 3.85 (br s, 3'-H), 4.08 (d, *J*=5Hz, 2'-H), 4.19 (d, *J*=7Hz, 6'-H), 5.30 (m, 1'-H), 8.25 (s, 8-H), 8.77 (s, 2-H), 9.12 (br s, NH). NOEs : 1'-H & 2'-H, 1'-H & 8-H, EI-MS (%) : *m* / *z* 591 (M^+, 2); l) **14** : IR (KBr) : 3300, 1650, 1600 cm^{-1}, ^{1}H-NMR : δ 2.20 (m, 5'-H), 2.40 (m, 4', 5'-H), 3.72 (dd, *J*=6, 11Hz), 3.79 (dd, *J*=5, 11Hz)(6'-H_2), 3.93 (br s, 3'-H), 4.08 (dd, *J*=1, 5Hz, 2'-H), 5.21 (m, 1'-H), 5.65 (br s, NH_2), 8.04 (s, 8-H), 8.33 (s, 2-H), EI-MS (%) : *m* / *z* 445 (M^+, 0.7); m) **16** : UV ($CHCl_3$) : 263 nm (ε 14000), IR (KBr) : 3060, 3030, 1740, 1690, 1560, 1370 cm^{-1}, ^{1}H-NMR : δ 2.99 (m, 4'-H), 3.69 (dd, *J*=2, 4Hz, 3'-H), 4.00 (*br* d, 2'-H), 4.18 (d, *J*=8Hz, 6'-H_2), 5.01 (dd, *J*=8, 11Hz, 5'-H), 5.59 (dd, *J*=5, 11Hz, 1'-H), 5.63 (d, *J*=8Hz, 5-H), 7.35 (d, *J*=8Hz, 6-H), 8.36 (br s, NH), EI-MS (%) : *m* / *z* 397 (4) ; n) **17** : UV ($CHCl_3$) : 266nm (ε 8500), IR (KBr) : 3460, 3220, 1740, 1690, 1250 cm^{-1}, ^{1}H-NMR : δ 2.02 ($COCH_3$), 1.84 (dd, *J*=10, 13Hz), 2.15 (dd, *J*=7, 12Hz) (5'-H_2), 2.39 (m, 4'-H), 3.70 (dd, *J*=1, 4Hz, 3'-H), 3.99 (*br* d, 2'-H), 4.14 (d, *J*=7Hz, 6'-H_2), 5.10 (ddd, *J*=5, 7, 13Hz, 1'-H), 5.65 (dd, *J*=2, 8Hz, 5-H), 7.46 (d, *J*=8Hz, 6-H), 8.53 (br s, NH), NOEs : 1'-H & 2'-H, 1'-H & 4'-H, 1'-H & 6-H, EI-MS (%) : *m* / *z* 373 (M^+-CH_2Ph, 9) ; o) **18** : UV (MeOH) : 268 nm (ε 10000), IR (KBr) : 3350, 1690 cm^{-1}, ^{1}H-NMR (CD_3OD) : δ 1.88, 2.12 (both m, 5'-H_2), 1.99 (m, 4'-H), 3.63 (dd, *J*=7, 11Hz), 3.74 (dd, *J*=5, 11Hz) (6'-H_2), 3.77 (dd, *J*=3, 5Hz, 3'-H), 3.99 (dd, *J*=3, 6Hz, 2'-H), 4.96 (ddd, *J*=6, 7, 12Hz, 1'-H), 5.62 (d, *J*=8Hz, 5-H), 7.72 (d, *J*=8Hz, 6-H), EI-MS (%) : *m* / *z* 242 (M^+, 5).
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