A NEW APPROACH TO THE SYNTHESIS OF OPTICALLY ACTIVE CYCLOHEXANE ANALOGS OF NUCLEOSIDE USING A MICHAEL-TYPE ADDITION REACTION TO NITRO-CYCLOHEXENES AS A KEY REACTION

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Using as a key reaction a Michael-type addition reaction to nitro-cyclohexene derivatives, two optically active cyclohexane analogs of nucleoside, (-)-9-pseudo-β-D-glucopyranosyladenine (8) and (-)-9-pseudo-β-L-idopyranosyladenine (16), were synthesized from adenine and D-glucose.

KEYWORDS (-)-9-pseudo-β-D-glucopyranosyladenine; (-)-9-pseudo-β-L-idopyranosyladenine; carbocyclic nucleoside; pseudo-glycoside; nucleoside cyclohexane analog optically active; Michael-type addition reaction; nitro-cyclohexene; D-glucose

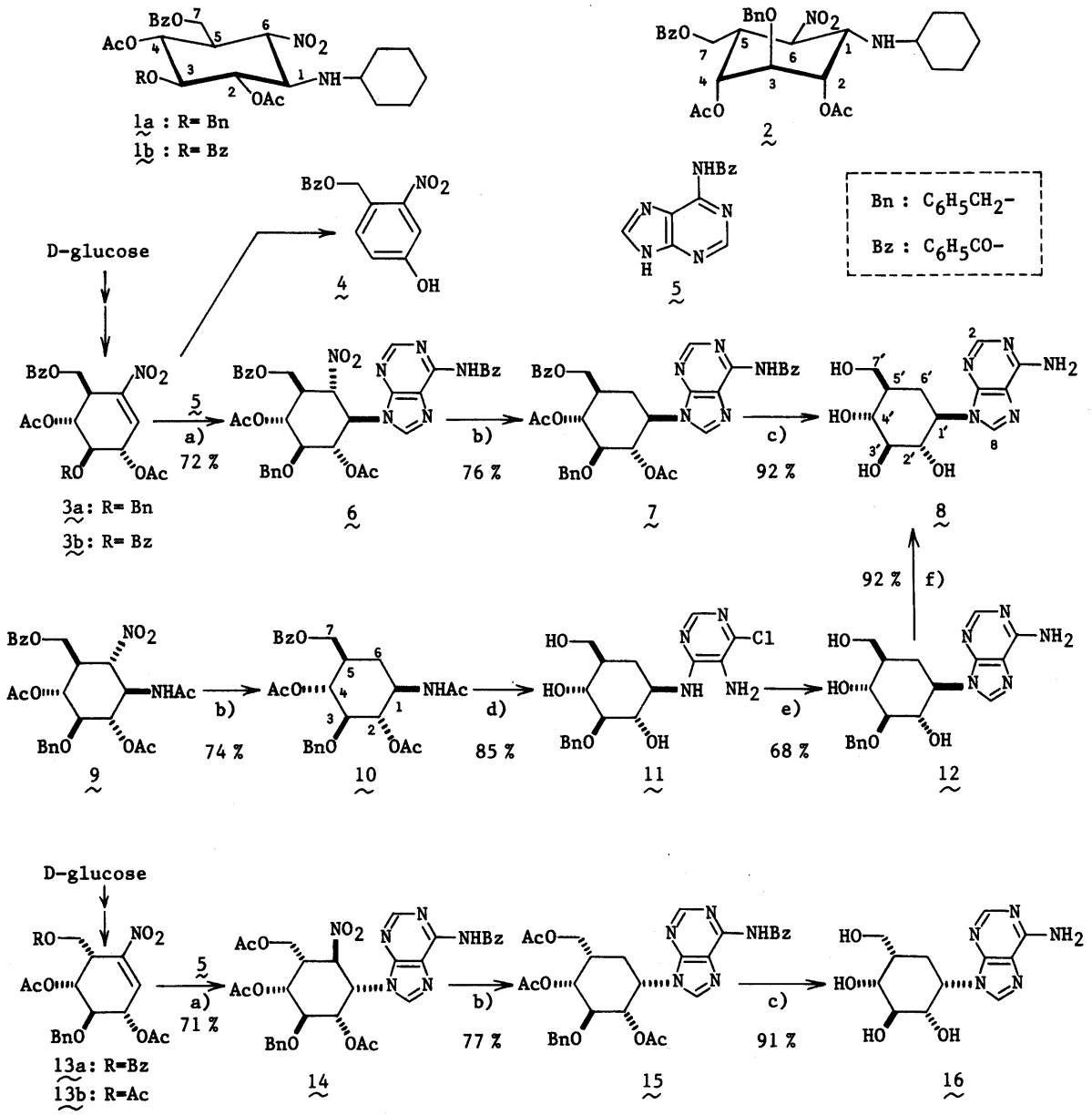
Carbocyclic nucleosides, which are nucleoside analogs having a carbocyclic ring in place of the carbohydrate moiety, exhibit interesting biological activities such as antiviral, antitumor, and antibacterial properties. These facts have made carbocyclic nucleosides attractive synthesis targets.[1)]

Recently, using a stereoselective deacetoxylation reaction and a cyclitol formation reaction for nitrofuranose derivatives at the key steps, we have developed versatile methods for converting carbohydrates to optically active pseudo-hexopyranoses and pseudo-pentofuranoses.[2,3)] During studies of the chemical behavior of the pseudo-nitrohexopyranoses, a method was developed for synthesizing optically active pseudo-aminosugar. By this method, validamine, epi-validamine, and valienamine have been synthesized from D-glucose.[4a)]

As an extension of these synthesis studies of pseudo-sugar, we have found that pseudo-glycosides such as carbocyclic nucleosides are successfully synthesized using a Michael-type addition reaction of a nucleic acid base to nitro-cyclohexene derivatives. In this paper, we report the synthesis of two new optically active cyclohexane analogs of nucleoside, (-)-9-pseudo-β-D-glucopyranosyladenine {(-)-9-[(1'R,2'S,3'S,4'R,5'R)-2',3',4'-trihydroxy-5'-(hydroxymethyl)cyclohexyl]adenine, 8} and (-)-9-pseudo-β-L-idopyranosyladenine {(-)-9-[(1'S,2'S,3'S,4'R,5'S)-2',3',4'-trihydroxy-5'-(hydroxymethyl)cyclohexyl]adenine, 16}, from adenine and nitro-cyclohexenes prepared from D-glucose.[4)]

Treatment of 3a[4a)] or 3b[4b)] with cyclohexylamine in THF in the presence of KF and 18-crown-6 (2°C, 2 h) yielded 1a (75%),[5a)] colorless oil, $[\alpha]_D^{20}$ +16° ($CHCl_3$), $C_{31}H_{38}N_2O_9$[6)] or 1b (74%),[5b)] colorless oil, $[\alpha]_D^{20}$ +37° ($CHCl_3$), $C_{31}H_{36}N_2O_{10}$. By a similar procedure, 2 (75%),[5c)] colorless oil, $[\alpha]_D^{20}$ +7° ($CHCl_3$), $C_{31}H_{38}N_2O_9$ was prepared from 13a.[4a)] Thus, we found that the Michael-type addition reactions to these nitrocyclohexenes provided thermodynamically stable products having an equatorial amino group at the 1-position.[7)] When 3a was treated with N^6-benzoyladenine (5) in DMF in the presence of KF and 18-crown-6 (2°C, 1 h), 6 (72%),[5d)] a white powder, $[\alpha]_D^{22}$ -5° ($CHCl_3$), $C_{37}H_{34}N_6O_{10}$, was obtained. But when 3b was treated under the same conditions as for 3a, an aromatic compound 4, a white powder, $C_{14}H_{11}NO_5$, was readily formed. Reductive elimination of the nitro group in 6 with n-Bu_3SnH in benzene in the presence of α,α'-azobis-iso-butyronitrile (AIBN) (80°C, 3 h), furnished 7 (76%),[5e)] a white powder, $[\alpha]_D^{22}$ -12° ($CHCl_3$), $C_{37}H_{35}N_5O_8$. After removal of the acetyl groups and the benzoyl groups in 7 with 1% NaOMe-MeOH (23°C, 8 h), the product was subjected to debenzylation (Na, liq.NH_3, THF, -78°C, 30 min) to provide (-)-9-pseudo-β-D-glucopyranosyladenine (8, 92%),[5f)] a white powder, $[\alpha]_D^{20}$ -7° (MeOH), $C_{12}H_{17}N_5O_4$. The structure 8 was further verified by the following synthesis from a pseudo-aminosugar 9.[4a)]

Denitrohydrogenation of 9 with n-Bu_3SnH and AIBN (benzene, 80°C, 2.5 h) yielded 10 (74%),[5g)] a white powder, $[\alpha]_D^{26}$ +18° ($CHCl_3$), $C_{27}H_{31}NO_8$. After removal of the acetyl and benzoyl groups in 10 with 1% NaOMe-



(a) KF / 18-crown-6 / DMF (b) n-Bu_3SnH / AIBN / benzene (c) 1 % NaOMe-MeOH; Na / liq.NH_3 / THF (d) 1 % NaOMe-MeOH; 80 % aq. NH_2NH_2; 5-amino-4,6-dichloropyrimidine / Et_3N / n-BuOH (e) triethyl orthoformate / conc. HCl; liq.NH_3 / MeOH (f) Na / liq.NH_3 / THF

MeOH followed by de-N-acetylation with 80 % aq.NH_2NH_2 in a sealed tube (100°C, 60 h), the product was subsequently subjected to treatment with 5-amino-4,6-dichloropyrimidine in n-BuOH in the presence of Et_3N to provide 11 (85 %),[5h] a white powder, $[\alpha]_D^{28}$ -6° (MeOH), $C_{18}H_{23}N_4O_4Cl$. Following treatment of 11 with triethyl orthoformate in the presence of conc.HCl (25°C, 3 h), the product was ammonolyzed with liq.NH_3 in a sealed tube (60°C, 2 h) to yield 12 (68 %),[5i] a white powder, $[\alpha]_D^{20}$ -3° (MeOH), $C_{19}H_{23}N_5O_4$. Debenzylation of 12 with liq.NH_3-Na in THF (-78°C, 30 min) furnished 8 (92 %), identical with the product synthesized via 6.

On the other hand, treatment of 13b[4b] with 5 as described above for 3a yielded 14 (71 %),[5j] colorless oil, $[\alpha]_D^{20}$ -15° ($CHCl_3$), $C_{32}H_{32}N_6O_{10}$. Denitrohydrogenation of 14 yielded 15 (77 %),[5k] a white powder, $[\alpha]_D^{22}$ -8° ($CHCl_3$), $C_{32}H_{33}N_5O_8$, which was subjected to deacylation and debenzylation as described above for 7

to provide (-)-9-pseudo-β-L-idopyranosyladenine (16, 91 %),[5m] a white powder, $[\alpha]_D^{20}$ -47° (MeOH), $C_{12}H_{17}N_5O_4$.

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4) a) M. Yoshikawa, B. C. Cha, Y. Okaichi, Y. Takinami, Y. Yokokawa, and I. Kitagawa, Chem. Pharm. Bull., 36, 4236 (1988) ;
b) 3b, colorless oil, $[\alpha]_D^{22}$ +62° ($CHCl_3$), $C_{25}H_{23}NO_{10}$, and 13b, colorless oil, $[\alpha]_D^{20}$ +3° ($CHCl_3$), $C_{20}H_{23}NO_9$, were prepared from D-glucose as for 3a and 13a.[4a]
5) All new compounds were fully characterized by IR ($CHCl_3$), ^1H NMR (500 MHz, $CDCl_3$, with decoupling experiments), and MS spectra (unless specified otherwise):
a) 1a ; IR: 1724, 1560 cm^{-1}, ^1H NMR: δ 2.66 (m, 5α-H), 3.34 (dd, J=10, 10 Hz, 3α-H), 3.70 (dd, J=10, 10 Hz, 1α-H), 4.13 (dd, J=2, 13 Hz), 4.29 (dd, J=4, 13 Hz)(7-H_2), 4.50 (dd, J=10, 10 Hz, 6β-H), 4.99 (dd, J=10, 10 Hz, 2β-H), 5.19 (dd, J=10, 12 Hz, 4β-H), MS (m/z): 582 (M^+) ;
b) 1b ; IR: 1725, 1559 cm^{-1}, ^1H NMR: δ 2.83 (m, 5α-H), 3.53 (dd, J=10, 10 Hz, 1α-H), 4.14 (dd, J=3, 12 Hz), 4.44 (dd, J=4, 12 Hz)(7-H_2), 4.60 (dd, J=10, 10 Hz, 6β-H), 5.13 (dd, J=10, 10 Hz, 2β-H), 5.34 (dd, J=10, 11 Hz, 4β-H), 5.50 (dd, J=10, 10 Hz, 3α-H), MS (m/z): 596 (M^+) ;
c) 2 ; IR: 1737, 1555 cm^{-1}, ^1H NMR: δ 3.14 (m, 5β-H), 3.66 (dd, J=3, 11 Hz, 1β-H), 3.91 (dd, J=3, 3 Hz, 3β-H), 4.26 (dd, J=7, 12 Hz), 4.39 (dd, J=7, 12 Hz)(7-H_2), 4.73 (dd, J=11, 11 Hz, 6α-H), 5.20 (dd, J=3, 3 Hz, 2β-H), 5.25 (dd, J=3, 3 Hz, 4β-H), MS (m/z): 582 (M^+) ;
d) 6 ; IR: 1753, 1722, 1611, 1594 cm^{-1}, ^1H NMR: δ 2.86 (m, 5'α-H), 3.91 (dd, J=9, 9 Hz, 3'α-H), 4.28 (dd, J=3, 12 Hz), 4.44 (dd, J=4, 12 Hz)(7'-H_2), 5.03 (dd, J=10, 11 Hz, 1'α-H), 5.52 (dd, J=9, 11 Hz, 4'β-H), 5.95 (dd, J=9, 10 Hz, 2'β-H), 6.34 (dd, J=10, 11 Hz, 6'β-H), 7.84, 8.82 (both s, 2,8-H), CI-MS(methane)m/z: 723 (M^++H);
e) 7 ; IR: 1741, 1712, 1611, 1592 cm^{-1}, ^1H NMR: δ 2.31 (m, 5'α-H), 2.36 (ddd, J=10, 10, 12 Hz, 6'β-H), 2.39 (ddd, J=6, 6, 12 Hz, 6'α-H), 3.82 (dd, J=10, 10 Hz, 3'α-H), 4.23 (dd, J=6, 11 Hz), 4.45 (dd, J=4, 11 Hz)(7'-H_2), 4.77 (ddd, J=6, 10, 10 Hz, 1'α-H), 5.35 (dd, J=10, 10 Hz, 4'β-H), 5.62 (dd, J=10, 10 Hz, 2'β-H), 8.05, 8.82 (both s, 2,8-H), MS (m/z): 677 (M^+) ;
f) 8 ; UV $\lambda_{max}^{H_2O}$ nm (ε): 261 (8400), IR (KBr): 3330, 1640, 1590 cm^{-1}, ^1H NMR (CD_3OD): δ 1.75 (m, 5'α-H), 2.10 (ddd, J=5, 5, 13 Hz, 6'α-H), 2.12 (ddd, J=11, 11, 13 Hz, 6'β-H), 3.37 (dd, J=9, 9 Hz, 3'α-H), 3.44 (dd, J=9, 11 Hz, 4'β-H), 3.65 (dd, J=6, 11 Hz), 3.81 (dd, J=4, 11 Hz)(7'-H_2), 4.03 (dd, J=9, 11 Hz, 2'β-H), 4.41 (ddd, J=5, 11, 11 Hz, 1'α-H), 8.16, 8.18 (both s, 2,8-H), ^{13}C NMR (125 MHz, D_2O): δ_C 32.7 (6'-C), 44.3 (5'-C), 60.3 (1'-C), 64.9 (7'-C), 75.2, 76.5, 80.4 (2'-C, 3'-C, 4'-C), 121.6 (5-C), 143.9 (8-C), 152.0 (4-C), 155.2 (2-C), 158.4 (6-C), MS (m/z): 295 (M^+) ;
g) 10 ; IR: 1728, 1669, 1502 cm^{-1}, ^1H NMR: δ 1.40 (ddd, J=12, 13, 13 Hz, 6β-H), 2.13 (m, 5α-H), 2.20 (ddd, J=4, 4, 13 Hz, 6α-H), 3.65 (dd, J=10, 10 Hz, 3α-H), 4.09 (dddd, J=4, 8, 11, 12 Hz, 1α-H), 4.15 (dd, J=6, 11 Hz), 4.32 (dd, J=3, 11 Hz)(7-H_2), 4.91 (dd, J=10, 11 Hz, 2β-H), 5.12 (dd, J=10, 11 Hz, 4β-H), 5.91 (d, J=8 Hz, -NH), MS (m/z): 497 (M^+) ;
h) 11 ; IR (KBr): 3478, 2992, 1692 cm^{-1}, ^1H NMR (CD_3OD): δ 1.63 (ddd, J=11, 11, 13 Hz, 6'β-H), 1.70 (m, 5'α-H), 2.12 (ddd, J=4, 4, 13 Hz, 6'α-H), 3.34 (dd, J=10, 10 Hz, 3'α-H), 3.43 (dd, J=10, 10 Hz, 4'β-H), 3.53 (dd, J=10, 11 Hz, 2'β-H), 3.63 (dd, J=6, 11 Hz), 3.76 (dd, J=4, 11 Hz)(7'-H_2), 4.18 (ddd, J=4, 11, 11 Hz, 1'α-H), 7.79 (s, 2-H), MS (m/z): 394, 396 (3:1, M^+) ;
i) 12 ; IR (KBr): 3392, 1703, 1602, 1589 cm^{-1}, ^1H NMR (CD_3OD): δ 1.79 (m, 5'α-H), 2.10 (ddd, J=6, 6, 13 Hz, 6'α-H), 2.11 (ddd, J=12, 12, 13 Hz, 6'β-H), 3.38 (dd, J=9, 9 Hz, 3'α-H), 3.58 (dd, J=9, 11 Hz, 4'β-H), 3.65 (dd, J=6, 11 Hz), 3.82 (dd, J=4, 11 Hz)(7'-H_2), 4.19 (dd, J=9, 11 Hz, 2'β-H), 4.44 (ddd, J=6, 11, 12 Hz, 1'α-H), 8.16, 8.18 (both s, 2,8-H), MS (m/z): 385 (M^+) ;
j) 14 ; IR: 1746, 1711, 1612, 1586 cm^{-1}, ^1H NMR: δ 3.28 (m, 5'β-H), 4.04 (dd, J=3, 3 Hz, 3'α-H), 4.07 (dd, J=6, 12 Hz), 4.33 (dd, J=7, 12 Hz)(7'-H_2), 5.23 (dd, J=3, 3 Hz, 2'β-H), 5.31 (dd, J=3, 3 Hz, 4'β-H), 5.77 (dd, J=12, 12 Hz, 6'α-H), 5.88 (dd, J=3, 12 Hz, 1'β-H), 8.09, 8.82 (both s, 2,8-H), CI-MS (methane)m/z: 661 (M^++H) ;
k) 15 ; IR: 1732, 1703, 1605, 1583 cm^{-1}, ^1H NMR: δ 1.93-2.02 (m, 6'β-H), 2.51 (ddd, J=13, 13, 13 Hz, 6'α-H), 2.69 (m, 5'β-H), 4.04 (dd, J=3, 3 Hz, 3'α-H), 4.03 (dd, J=7, 11 Hz), 4.17 (dd, J=3, 11 Hz)(7'-H_2), 5.16 (dd, J=3, 3 Hz, 2'β-H), 5.25 (br. s, 4'β-H), 5.38 (ddd, J=3, 3, 13 Hz, 1'β-H), 8.11, 8.82 (both s, 2,8-H), MS (m/z): 615 (M^+) ;
m) 16 ; UV $\lambda_{max}^{H_2O}$ nm (ε): 261 (7400), IR (KBr): 3318, 1636, 1596 cm^{-1}, ^1H NMR (CD_3OD): δ 1.80 (ddd, J=8, 9, 14 Hz, 6'α-H), 2.32 (m, 5'β-H), 2.33 (ddd, J=3, 3, 14 Hz, 6'β-H), 3.63 (dd, J=6, 11 Hz), 3.77 (dd, J=6, 11 Hz) (7'-H_2), 3.99 (br. s, 4'β-H), 4.01 (br. s, 2'β-H), 4.11 (dd, J=3, 3 Hz, 3'α-H), 5.07 (ddd, J=3, 4, 9 Hz, 1'β-H), 8.19, 8.35 (both s, 2,8-H), ^{13}C NMR (125 MHz, D_2O): δ_C 24.9 (6'-C), 41.1 (5'-C), 55.7 (1'-C), 65.6 (7'-C), 72.1, 73.6, 73.6 (2'-C, 3'-C, 4'-C), 121.0 (5-C), 144.3 (8-C), 151.3 (4-C), 155.0 (2-C), 158.2 (6-C), MS (m/z): 295 (M^+) .
6) The molecular composition of the compound given with the chemical formula was determined either by elemental analysis or by high resolution mass spectrometry.
7) When 3a or 13a was treated with aniline or cyclohexanol as described above for the treatment with cyclohexylamine, an addition product, having an equatorial substitiuent at the 1-position the same as in 1a, 1b, and 2a, was obtained.

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