SYNTHESES OF (+)-CYCLARADINE AND (+)-9-PSEUDO-β-L-XYLOFURANOSYLADENINE, TWO OPTICALLY ACTIVE CYCLOPENTANE ANALOGS OF NUCLEOSIDE

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Two optically active cyclopentane analogs of nucleoside, (+)-cyclaradine and (+)-9-pseudo-β-L-xylofuranosyladenine, were synthesized from N^6-benzoyladenine and nitro-cyclopentenes derived from pseudo-nitrofuranoses through a Michael-type addition reaction.

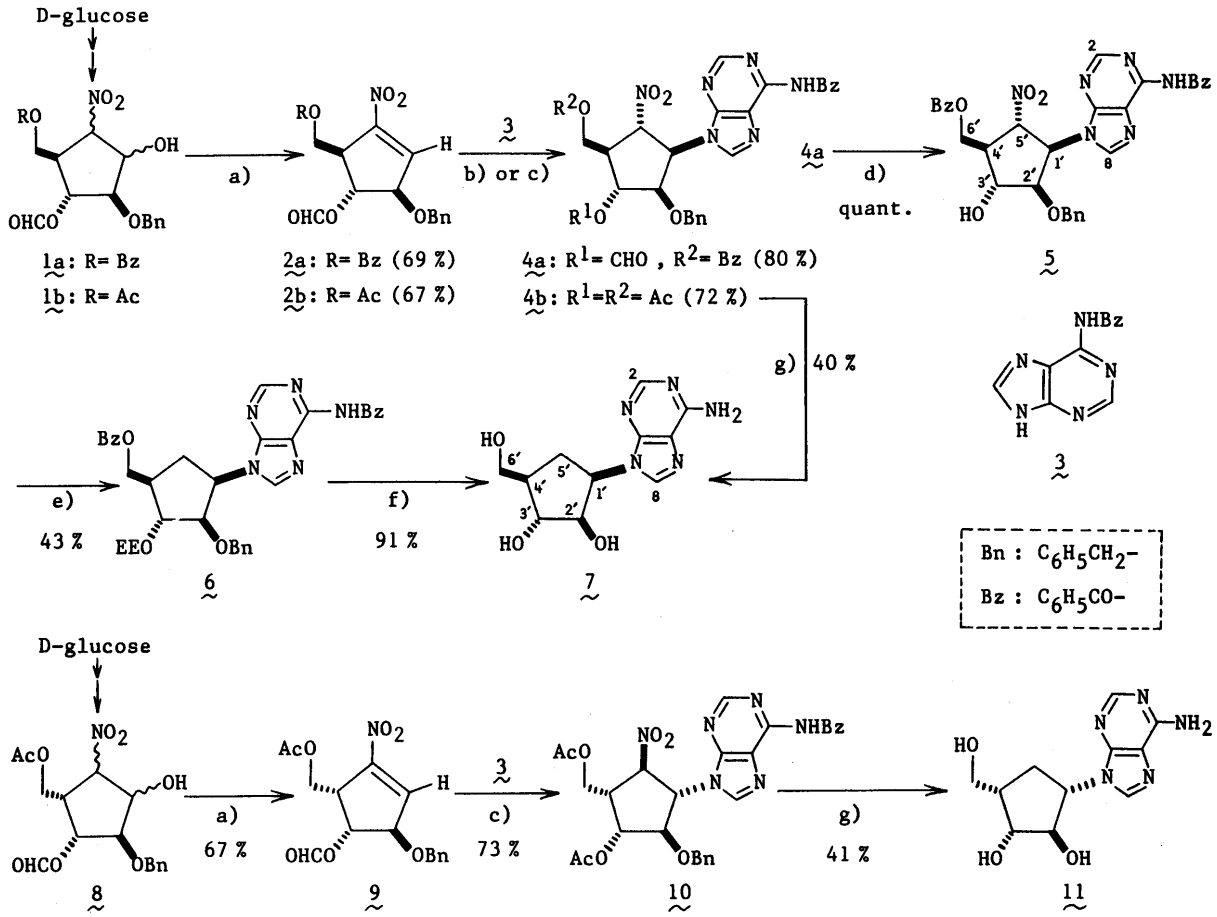
KEYWORDS (+)-cyclaradine; (+)-9-pseudo-β-L-xylofuranosyladenine; nucleoside cyclopentane analog optically active; pseudo-glycoside; nitro-cyclopentene; Michael-type addition reaction; antiviral agent; antitumor activity; D-glucose

(+)-Cyclaradine (7) has been known as a synthetic carbocyclic analog of a well known antiviral agent 9-β-D-arabinofuranosyladenine (Ara-A).[1] Since (+)-cyclaradine (7) is resistant to adenosine deaminase, a serum enzyme which limits the clinical utility of Ara-A, it shows more superior activity against Herpes simplex virus than Ara-A. Furthermore, (+)-cyclaradine (7) is active against trifluorothymidine- or acycloguanosine(acyclovir)-resistant Herpes simplex virus mutants.[2] On the other hand, the carbocyclic analogs of 9-β-D-xylofuranosyladenine have been synthesized in racemic forms and shown to exhibit significant in vivo antitumor activity.[3]

Recently, we developed a method for synthesizing optically active pseudo-glycosides in which a Michael-type addition reaction to nitro-cyclohexenes, prepared from pseudo-nitrohexopyranoses,[4] was utilized. By this method, two optically active cyclohexane analogs of nucleoside, (-)-9-pseudo-β-D-glucopyranosyladenine and (-)-9-pseudo-β-L-idopyranosyladenine, have been synthesized from adenine and D-glucose.[5]

As a continuing study of these synthesis approaches to pseudo-glycosides, we have synthesized two optically active cyclopentane analogs of nucleoside, (+)-cyclaradine (7) and (+)-9-pseudo-β-L-xylofuranosyladenine {(+)-9-[(1'S,2'R,3'R,4'S)-2',3'-dihydroxy-4'-(hydroxymethyl)cyclopentyl]adenine, 11}, from pseudo-nitropentofuranoses (1a, 1b, 8) which were common reaction intermediates in our previous pseudo-pentofuranose synthesis.[6,7]

Treatment of a pseudo-nitrofuranose, 1a[6] or 1b[7], with Ac_2O in the presence of p-TsOH·H_2O yielded a nitro-olefin 2a (69 %), colorless oil, $[\alpha]_D^{22}$ -17° ($CHCl_3$), $C_{21}H_{19}NO_7$,[8] IR ($CHCl_3$): 1719, 1558, 1343, 1518 cm^{-1}, EI-MS (m/z): 397 (M^+) or 2b (67 %), unstable colorless oil, IR ($CHCl_3$): 1722, 1540, 1352 cm^{-1}, EI-MS (m/z): 335 (M^+). Subsequent treatment of 2a with N^6-benzoyladenine (3) in THF in the presence of KF and 18-crown-6 (2°C, 2 h) provided 4a (80 %), a white powder, $[\alpha]_D^{22}$ +36° ($CHCl_3$), $C_{33}H_{28}N_6O_8$, IR ($CHCl_3$): 1720, 1693, 1598, 1558, 1350 cm^{-1}. Deformylation of 4a with 28 % aq.NH_4OH in 95 % EtOH (23°C, 15 min) gave 5 (quant.), a white powder, $[\alpha]_D^{20}$ +45° ($CHCl_3$), $C_{32}H_{28}N_6O_7$, UV λ_{max}^{MeOH} nm (ε): 280 (24700), IR ($CHCl_3$): 3388, 1720, 1703, 1593, 1557, 1338 cm^{-1}. The detailed ^1H NMR decoupling experiments (500 MHz, $CDCl_3$) of 4a and 5 resulted in the following assignments: 4a, δ3.38 (m, 4'-H), 4.16 (d, J=5 Hz, 2'-H), 4.67 (dd, J=5, 11 Hz), 4.75 (dd, J=6, 11 Hz)(6'-H_2), 5.35 (d, J=3 Hz, 3'-H), 5.73 (dd, J=8, 11 Hz, 5'-H), 5.87 (dd, J=5, 11 Hz, 1'-H), 8.15 (s, -OCHO), 8.29, 8.71 (both s, 2,8-H); 5, δ3.08 (m, 4'-H), 4.21 (dd, J=3, 3 Hz, 2'-H), 4.58 (dd, J=3, 6 Hz, 3'-H), 4.68 (dd, J=5, 12 Hz), 4.75 (dd, J=7, 12 Hz)(6'-H_2), 5.75 (dd, J=9, 9 Hz, 5'-H), 5.90 (dd, J=3, 9 Hz, 1'-H), 8.12, 8.53 (both s, 2,8-H). The NOE's appeared between the following pairs of protons[9]: 5, 1'α-H & 2'α-H (8 %), 1'α-H & 4'α-H (3 %), 2'α-H & 1'α-H (8 %), 2'α-H & 4'α-H (2 %), 3'β-H & 5'β-H (5 %), 4'α-H & 1'α-H (6 %), 4'α-H & 2'α-H (3 %). Based on this spectral evidence, the stereostructures of 4a and 5 were determined. Treatment of 5 with ethyl vinyl ether in CH_2Cl_2 in the presence of d-camphorsulfonic acid (CSA) (23°C, 0.5 h) followed by reductive



(a) Ac_2O / p-TsOH·H_2O (b) KF / 18-crown-6 / THF (c) KF / 18-crown-6 / THF; 28 % aq.NH_4OH / EtOH; Ac_2O / p-TsOH·H_2O (d) 28 % aq.NH_4OH / EtOH (e)  / CSA / CH_2Cl_2; n-Bu_3SnH / AIBN / toluene (f) 10 % aq.AcOH; 1 % NaOMe-MeOH; Na / liq.NH_3 / THF (g) n-Bu_3SnH / AIBN / toluene; 1 % NaOMe-MeOH; Na / liq.NH_3 / THF

elimination of the nitro group (denitrohydrogenation) with n-Bu_3SnH in toluene in the presence of α,α'-azobis-iso-butyronitrile (AIBN) (110°C, 2 h), yielded 6 (43 %), a white powder, $[\alpha]_D^{20}$ +13° ($CHCl_3$), $C_{36}H_{37}N_5O_6$, IR ($CHCl_3$): 1718, 1704, 1607, 1584 cm^{-1}. After removal of the ethoxyethyl group in 6 with 10 % aq.AcOH (23°C, 12 h), the product was subjected to debenzoylation with 1 % NaOMe-MeOH (23°C, 8 h) and subsequent debenzylation with Na-liq.NH_3 in THF (-78°C, 45 min) to provide (+)-cyclaradine (7, 91 %),[10] a white powder, $[\alpha]_D^{22}$ +18° (MeOH), $C_{11}H_{15}N_5O_3$, UV $\lambda_{max}^{H_2O}$ nm (ε): 261 (11200), IR (KBr): 3330, 1640, 1595 cm^{-1}. On the other hand, treatment of 2b with N^6-benzoyladenine (3) as described above for 2a followed by deformylation (28 % aq.NH_4OH-95 % EtOH, 23°C, 15 min) and acetylation(Ac_2O, p-TsOH·H_2O, 23°C, 2 h), provided 4b (72 %),[11] colorless oil, $[\alpha]_D^{20}$ +57° ($CHCl_3$), $C_{29}H_{28}N_6O_8$, IR ($CHCl_3$): 1740, 1709, 1611, 1588, 1559, 1366 cm^{-1}. Denitrohydrogenation of 4b with n-Bu_3SnH followed by deacylation (1 % NaOMe-MeOH, 23°C, 8 h) and debenzylation (Na-liq.NH_3, THF, -78°C, 40 min) finally furnished 7 (40 %). (+)-Cyclaradine (7) synthesized via both procedures was identified by direct comparison and the structure was corroborated by its spectral data.[10]

Next, a pseudo-nitrosugar 8[7] was treated with Ac_2O in the presence of p-TsOH·H_2O to provide a nitroolefin 9 (67 %), unstable colorless oil, IR ($CHCl_3$): 1735, 1523, 1363 cm^{-1}, EI-MS (m/z): 335 (M^+). Treatment of 9 with 3 as described above for the treatment of 2a or 2b and subsequent deformylation (28 % aq.NH_4OH-95 % EtOH, 23°C, 15 min) and acetylation (Ac_2O, p-TsOH·H_2O, 23°C, 2 h), furnished 10 (73 %), colorless oil,

$[\alpha]_D^{20}$ +42° ($CHCl_3$), $C_{29}H_{28}N_6O_8$, IR ($CHCl_3$): 3402, 1740, 1708, 1610, 1586, 1557, 1366 cm^{-1}. The ^1H NMR decoupling experiments (500 MHz, $CDCl_3$) of 10 resulted in the following assignments: δ 3.38 (m, 4'-H), 4.37 (dd, J=6, 12 Hz), 4.40 (dd, J=6, 12 Hz)(6'-H_2), 4.72 (dd, J=5, 8 Hz, 2'-H), 5.16 (dd, J=8, 9 Hz, 1'-H), 5.37 (dd, J=5, 8 Hz, 3'-H), 5.81 (dd, J=9, 9 Hz, 5'-H), 8.34, 8.73 (both s, 2,8-H). The detailed comparisons of the ^1H NMR and ^{13}C NMR[12] data for 10 with those for 4b and 5 led us to assign the structure 10, the stereostructure of which was corroborated by examination of the NOE's.[12] Elimination of the nitro group of 10 followed by removal of the protecting groups, as mentioned above for the treatment of 4b, yielded (+)-9-pseudo-β-L-xylofuranosyladenine (11, 41 %), a white powder, $[\alpha]_D^{20}$ +5° (MeOH), $C_{11}H_{15}N_5O_3$, UV $\lambda_{max}^{H_2O}$ nm (ε): 260 (12000), IR (KBr): 3332, 1643, 1598 cm^{-1}, ^1H NMR (500 MHz, d_6-DMSO): δ 1.68 (ddd, J=6, 6, 15 Hz), 2.15 (ddd, J=6, 10, 15 Hz) (5'-H_2), 2.43 (m, 4'-H), 3.71 (dd, J=6, 11 Hz), 3.78 (dd, J=5, 11 Hz)(6'-H_2), 4.07 (dd, J=2, 3 Hz, 2'-H), 4.18 (dd, J=3, 6 Hz, 3'-H), 5.11 (ddd, J=2, 6, 10 Hz, 1'-H), 8.19, 8.27 (both s, 2,8-H), ^{13}C NMR (125 MHz, D_2O): δc 32.6 (5'-C), 46.4 (4'-C), 53.9 (1'-C), 59.5 (6'-C), 65.8 (3'-C), 74.8 (2'-C), 118.8 (5-C), 142.0 (8-C), 152.7 (4-C), 153.1 (2-C), 159.0 (6-C).

We are currently working on the further application of this method to the synthesis of other types of pseudo-glycosides.

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REFERENCES AND NOTES

1) T.L.Nagabhushan, P.Reichert, H.Tsai, M.Ortrander, M.Lieberman, J.Schwartz, R.Vince, and G.H.Miller, Program Abstr. Am. Chem. Soc. Natl. Meet. 185, Seattle, Wash., Abstr. No. CARB 27, 1983.
2) a) R.Vince and S.Daluge, J. Med. Chem., 20, 612 (1977);
b) R.Vince, S.Daluge, H.Lee, W.M.Shannon, G.Arnett, T.W.Schafer, T.L.Nagabhushan, P.Reichert, and H.Tsai, Science, 221, 1405 (1983);
c) W.M.Shannon, L.Westbrook, G.Arnett, S.Daluge, H.Lee, and R.Vince, Antimicrob. Agents Chemother., 24, 538 (1983);
d) J.Schwartz, M.Ostrander, N.J.Butkiewicz, M.Lieberman, C.Lin, J.Lim, and G.H.Miller, Antimicrob. Agents Chemother., 31, 21 (1987).
3) R.Vince, J.Brownell, and S.Daluge, J. Med. Chem., 27, 1358 (1984).
4) a) M.Yoshikawa, B.C.Cha, T.Nakae, and I.Kitagawa, Chem. Pharm. Bull., 36, 3714 (1988).
b) M.Yoshikawa, B.C.Cha, Y.Okaichi, Y.Takinami, Y.Yokokawa, and I.Kitagawa, Chem. Pharm. Bull., 36, 4236 (1988).
5) I.Kitagawa, B.C.Cha, T.Nakae, Y.Okaichi, Y.Takinami, and M.Yoshikawa, the preceding paper.
6) M.Yoshikawa, B.C.Cha, Y.Okaichi, and I.Kitagawa, Chem. Pharm. Bull., 36, 3718 (1988).
7) 1b, colorless oil, IR ($CHCl_3$): 1729, 1557, 1369 cm^{-1}, EI-MS (m/z): 353 (M^+) and 8, colorless oil, IR ($CHCl_3$): 1735, 1552, 1369 cm^{-1}, EI-MS (m/z): 353 (M^+), were prepared from D-glucose as described for the synthesis of 1a.[6]
8) The molecular composition of the compound given with the chemical formula was determined either by elemental analysis or by high resolution mass spectrometry.
9) The magnitude of NOE (%) given in the parenthesis was observed when the underlined proton was irradiated.
10) (+)-Cyclaradine (7), ^1H NMR (500 MHz, d_6-DMSO): δ 1.98 (m, 4'-H), 2.02 (ddd, J=3, 9, 15 Hz), 2.25 (ddd, J=4, 8, 15 Hz)(5'-H_2), 3.48 (dd, J=7, 10 Hz), 3.58 (dd, J=6, 10 Hz)(6'-H_2), 3.75 (dd, J=2, 6 Hz, 3'-H), 3.87 (dd, J=2, 5 Hz, 2'-H), 4.95 (ddd, J=3, 5, 8 Hz, 1'-H), 8.01, 8.29 (both s, 2,8-H), ^{13}C NMR (125 MHz, D_2O): δc 32.4 (5'-C), 47.3 (4'-C), 57.6 (1'-C), 65.5 (6'-C), 79.4 (3'-C), 81.3 (2'-C), 121.1 (5-C), 144.5 (8-C), 152.1 (4-C), 155.2 (2-C), 158.1 (6-C), EI-MS (m/z): 265 (M^+).
11) 4b, ^1H NMR (500 MHz, $CDCl_3$): δ 3.20 (m, 4'-H), 4.10 (dd, J=3, 4 Hz, 2'-H), 4.40 (dd, J=6, 12 Hz), 4.51 (dd, J=8, 12 Hz)(6'-H_2), 5.10 (dd, J=3, 3 Hz, 3'-H), 5.50 (dd, J=8, 11 Hz, 5'-H), 5.87 (dd, J=4, 11 Hz, 1'-H), 8.36, 8.74 (both s, 2,8-H), NOE (%): 1'α-H & 2'α-H (9 %), 1'α-H & 4'α-H (5 %), 2'α-H & 1'α-H (7 %), 2'α-H & 3'β-H (5 %), 3'β-H & 2'α-H (5 %), 3'β-H & 5'β-H (2 %), 4'α-H & 1'α-H (3 %), 5'β-H & 3'β-H (2 %), ^{13}C NMR (125 MHz, $CDCl_3$): δc 47.8 (4'-C), 58.9 (1'-C), 63.1 (6'-C), 72.6 (2'-C), 80.1 (3'-C), 87.8 (5'-C), 122.7 (5-C), 141.9 (8-C), 150.0 (4-C), 152.4 (2-C), 152.6 (6-C), 165.1 (-NHCO-φ).
12) 10, ^{13}C NMR (22.5 MHz, $CDCl_3$): δc 42.5 (4'-C), 60.5 (1'-C), 63.6 (6'-C), 73.0 (2'-C), 80.5 (3'-C), 84.6 (5'-C), 123.9 (5-C), 143.2 (8-C), 150.0 (4-C), 151.3 (2-C), 152.2 (6-C), 164.6 (-NHCO-φ), ^1H NMR, NOE (%): 1'β-H & 4'β-H (5 %), 2'α-H & 5'α-H (3 %), 2'α-H & 3'β-H (3 %), 3'β-H & 2'α-H (8 %), 4'β-H & 1'β-H (3 %), 5'α-H & 2'α-H (5 %).

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