

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 N⁶-benzoyladenine and nitro-cyclopentenones derived from pseudo-nitrofuranses through a Michael-type addition reaction.

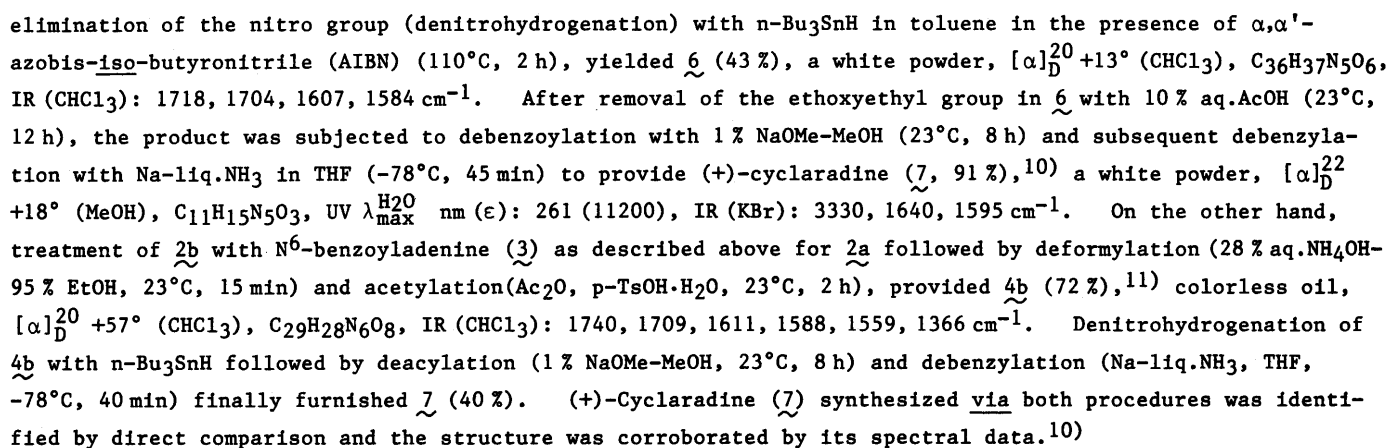
KEYWORDS (+)-cyclaradine; (+)-9-pseudo- β -L-xylofuranosyladenine; nucleoside cyclopentane analog optically active; pseudo-glycoside; nitro-cyclopentene; Michael-type addition reaction; antiviral agent; antitumor activity; D-glucose

(+)-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-nitrofuranses, 1a⁶⁾ or 1b⁷⁾, with Ac₂O in the presence of p-TsOH·H₂O yielded a nitro-olefin 2a (69 %), colorless oil, [α]_D²² -17° (CHCl₃), C₂₁H₁₉NO₇,⁸⁾ IR (CHCl₃): 1719, 1558, 1343, 1518 cm⁻¹, EI-MS (m/z): 397 (M⁺) or 2b (67 %), unstable colorless oil, IR (CHCl₃): 1722, 1540, 1352 cm⁻¹, EI-MS (m/z): 335 (M⁺). Subsequent treatment of 2a with N⁶-benzoyladenine (3) in THF in the presence of KF and 18-crown-6 (2°C, 2 h) provided 4a (80 %), a white powder, [α]_D²² +36° (CHCl₃), C₃₃H₂₈N₆O₈, IR (CHCl₃): 1720, 1693, 1598, 1558, 1350 cm⁻¹. Deformylation of 4a with 28 % aq. NH₄OH in 95 % EtOH (23°C, 15 min) gave 5 (quant.), a white powder, [α]_D²⁰ +45° (CHCl₃), C₃₂H₂₈N₆O₇, UV $\lambda_{\text{max}}^{\text{MeOH}}$ nm (ϵ): 280 (24700), IR (CHCl₃): 3388, 1720, 1703, 1593, 1557, 1338 cm⁻¹. The detailed ¹H NMR decoupling experiments (500 MHz, CDCl₃) of 4a and 5 resulted in the following assignments: 4a, δ 3.38 (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'-H₂), 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, δ 3.08 (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'-H₂), 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 protons⁹⁾: 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 CH₂Cl₂ in the presence of d-camphorsulfonic acid (CSA) (23°C, 0.5 h) followed by reductive



Next, a pseudo-nitrosugar 8⁷⁾ was treated with Ac₂O in the presence of p-TsOH·H₂O to provide a nitro-olefin 9 (67 %), unstable colorless oil, IR (CHCl₃): 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. NH₄OH-95 % EtOH, 23°C, 15 min) and acetylation (Ac₂O, p-TsOH·H₂O, 23°C, 2 h), furnished 10 (73 %), colorless oil,

$[\alpha]_D^{20} +42^\circ$ (CHCl₃), C₂₉H₂₈N₆O₈, IR (CHCl₃): 3402, 1740, 1708, 1610, 1586, 1557, 1366 cm⁻¹. The ¹H NMR decoupling experiments (500 MHz, CDCl₃) 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'-H₂), 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 ¹³C NMR¹²⁾ 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, $[\alpha]_D^{20} +5^\circ$ (MeOH), C₁₁H₁₅N₅O₃, UV $\lambda_{\max}^{H_2O}$ nm (ϵ): 260 (12000), IR (KBr): 3332, 1643, 1598 cm⁻¹, ¹H NMR (500 MHz, d₆-DMSO): δ 1.68 (ddd, J=6, 6, 15 Hz), 2.15 (ddd, J=6, 10, 15 Hz) (5'-H₂), 2.43 (m, 4'-H), 3.71 (dd, J=6, 11 Hz), 3.78 (dd, J=5, 11 Hz) (6'-H₂), 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), ¹³C NMR (125 MHz, D₂O): δ 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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- 7) 1b, colorless oil, IR (CHCl₃): 1729, 1557, 1369 cm⁻¹, EI-MS (m/z): 353 (M⁺) and 8, colorless oil, IR (CHCl₃): 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, d₆-DMSO): δ 1.98 (m, 4'-H), 2.02 (ddd, J=3, 9, 15 Hz), 2.25 (ddd, J=4, 8, 15 Hz) (5'-H₂), 3.48 (dd, J=7, 10 Hz), 3.58 (dd, J=6, 10 Hz) (6'-H₂), 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), ¹³C NMR (125 MHz, D₂O): δ 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, CDCl₃): 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'-H₂), 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%), ¹³C NMR (125 MHz, CDCl₃): δ 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, ¹³C NMR (22.5 MHz, CDCl₃): δ 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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