SYNTHESIS OF (-)-ARISTEROMYCIN FROM D-GLUCOSE

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(-)-Aristeromycin, a carbocyclic nucleoside with various biological activities, was synthesized from D-glucose using a Michael-type addition reaction of N^6-benzoyladenine with a nitrocyclopentene derivative as its key step.

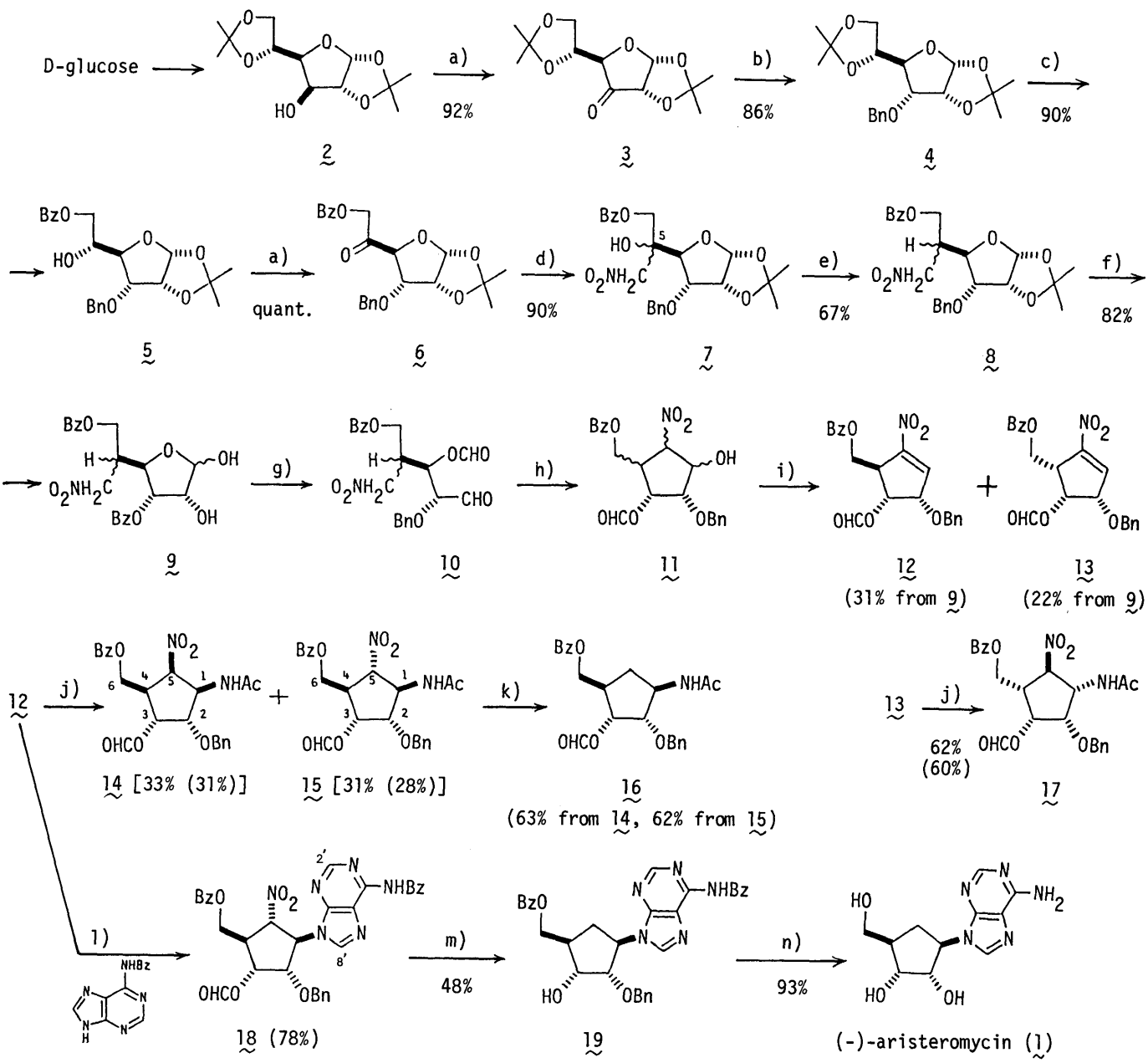
KEYWORDS (-)-aristeromycin; carbocyclic nucleoside antibiotic; pseudo-nucleoside; nitrocyclopentene; Michael-type addition reaction; pseudo-aminosugar; D-glucose; D-allofuranose

(-)-Aristeromycin (1), a carbocyclic analog of adenosine, exhibits a variety of interesting biological activities such as antibacterial, antifungal, antiviral, and antitumor properties.[1,2] Aristeromycin was first synthesized in a racemic form named C-Ado [3] and subsequently, (-)-aristeromycin (1) was isolated from Streptomyces citricolor nov. sp. as a natural product.[1,4] Later, it was reported that the (+)-enantiomer of 1 was totally inactive in the inhibition of tumor-cell growth and virus replication.[2] Following a pioneering synthesis of (±)-aristeromycin,[3] this class of compounds have been given much attention from the synthetic and biological viewpoints,[5] and in recent years, several enantioselective syntheses of (-)-aristeromycin (1) have been reported.[6]

By use of a stereoselective deacetoxyhydrogenation and a cyclitol formation from nitrofuranose derivatives as key reactions, we have recently developed versatile methods for converting carbohydrates to optically active pseudo-hexopyranoses, pseudo-pentofuranoses, and pseudo-aminosugar.[7] Furthermore, we have devised a new method for synthesizing optically active pseudo-glycosides using a Michael-type addition reaction with a nitro-cyclohexene.[8] As an extension of this study of synthesizing pseudo-glycosides, we have successfully synthesized several optically active carbocyclic analogs of nucleosides such as (+)-cyclaradine and (+)-9-pseudo-β-L-xylofuranosyladenine,[9] which are commonly called "pseudo-nucleosides". This paper deals with a synthesis of (-)-aristeromycin (1) from D-glucose.

Swern oxidation [10] of 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (2) gave a ketone (3, 92%)[11] which was treated with $NaBH_4$ [11] and benzylated to yield a D-allofuranose derivative (4, 86%), colorless oil, $[\alpha]_D^{23}$ +107° ($CHCl_3$), $C_{19}H_{26}O_6$,[12] IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2995, 2940, 1386. Treatment of 4 with 80% aq. AcOH and subsequent selective benzoylation of the product furnished 5 (90%), colorless oil, $[\alpha]_D^{21}$ +64° ($CHCl_3$), $C_{23}H_{26}O_7$, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3524, 2993, 1711, EI-MS (m/z): 414 (M^+). Swern oxidation of 5 gave an unstable ketone 6 which was immediately treated with CH_3NO_2 in DMF in the presence of KF and 18-crown-6 to provide 7 (90%, a mixture of the 5-epimers), colorless oil, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3552, 2990, 1723, 1552, 1375, EI-MS (m/z): 458 (M^+-CH_3). The nitrofuranose derivatives (7), without separation, were acetylated and subjected to deacetoxyhydrogenation with $NaBH_4$ [7a] to furnish 8 (67%), colorless oil, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1721, 1555, 1378, EI-MS (m/z): 442 (M^+-CH_3). Removal of the isopropylidene group of 8 with 80% aq. AcOH gave 9 (82%), colorless oil, IR ν_{max}^{film} cm^{-1}: 3449, 1730, 1550, 1374, EI-MS (m/z): 417 (M^+), which was oxidized with $Pb(OAc)_4$ to provide an epimeric mixture of aldehydic formates (10). Intramolecular condensation of 10 with KF in DMF in the presence of 18-crown-6 yielded the cyclization products (11). Dehydration of 11 with Ac_2O and p-TsOH·H_2O provided two nitro-cyclopentenes, 12 (31% from 9), colorless oil, $[\alpha]_D^{20}$ +83° ($CHCl_3$), $C_{21}H_{19}NO_7$, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1728, 1556, 1523, 1345, and 13 (22% from 9), colorless oil, $[\alpha]_D^{24}$ +31° ($CHCl_3$), $C_{21}H_{19}NO_7$, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720, 1557, 1522, 1367.

To shed light on the stereoselectivity in the Michael-type addition reaction of these nitro-cyclopentenes (12, 13), reactions with ammonia were first investigated. Treatment of 12 with 28% aq. NH_4OH in 95% aq. EtOH at 25 °C (or with liq. NH_3 in THF at -78 °C) and subsequent acetylation of the product, furnished two 1β-acetamide derivatives, 14 [33% (or 31%)], colorless oil, $[\alpha]_D^{24}$ +21° ($CHCl_3$), $C_{23}H_{24}N_2O_8$, IR $\nu_{max}^{CHCl_3}$ cm^{-1}:



(a) $(COCl)_2$ / DMSO / Et_3N / CH_2Cl_2 (-78 °C, 1 h) (b) $NaBH_4$ / 95% aq. EtOH (2 °C, 1.5 h) ; BnCl / NaH / DMF (25 °C, 1.5 h) (c) 80% aq. AcOH (25 °C, 24 h) ; BzCl / pyridine / CH_2Cl_2 (2 °C, 1 h) (d) CH_3NO_2 / KF / 18-crown-6 / DMF (25 °C, 3 h) (e) Ac_2O / p-TsOH·H_2O (25 °C, 3 h) ; $NaBH_4$ / 95% aq. EtOH (25 °C, 2 h) (f) 80% aq. AcOH (80 °C, 15 h) (g) $Pb(OAc)_4$ / benzene (25 °C, 40 min) (h) KF / 18-crown-6 / DMF (2 °C, 3.5 h) (i) Ac_2O / p-TsOH·H_2O (25 °C, 1.5 h) (j) 28% aq. NH_4OH / 95% aq. EtOH (25 °C, 2 h) [or liq. NH_3 / THF (-78 °C, 2 h)] ; Ac_2O / p-TsOH·H_2O (25 °C, 2 h) (k) n-Bu_3SnH / AIBN / benzene (80 °C, 3 h) (l) KF / 18-crown-6 / THF (2 °C, 1 h) (m) 28% aq. NH_4OH / 95% aq. EtOH (25 °C, 30 min) ;  / CSA / CH_2Cl_2 (25 °C, 1 h) : n-Bu_3SnH / AIBN / toluene (110 °C, 20 min) ; 10% aq. AcOH / acetone (25 °C, 14 h) (n) 5% NaOMe-MeOH (25 °C, 2 h) ; Na / liq. NH_3 / THF (-78 °C, 30 min)

1723, 1696, 1559, 1367, and 15 [31% (or 28%)], colorless oil, $[\alpha]_D^{24}$ +14 ° ($CHCl_3$), $C_{23}H_{24}N_2O_8$, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1724, 1693, 1557, 1367. The ^1H NMR decoupling experiments in detail (500 MHz) of 14 and 15 resulted in the following assignments (J in Hz): 14 (in C_6D_6), δ 3.60 (dd, J = 4, 4, 2-H), 3.73 (m, 4-H), 3.85 (dd, J = 8, 11), 4.13 (dd, J = 5, 11)(6-H_2), 4.44 (dd, J = 7, 9, 5-H), 4.54 (dd, J = 4, 10, 3-H), 4.77 (ddd, J = 4, 9, 10, 1-H),

5.50 (d, J = 10, >NH), 7.44 (s, -OCHO); 15 (in $CDCl_3$), δ 3.32 (m, 4-H), 4.28 (dd, J = 8, 12), 4.63 (dd, J = 5, 12)(6-H_2), 4.48 (dd, J = 4, 5, 2-H), 5.00 (dd, J = 5, 10, 5-H), 5.11 (ddd, J = 5, 5, 8, 1-H), 5.31 (dd, J = 4, 11, 3-H), 6.13 (d, J = 8, >NH), 8.12 (s, -OCHO). The NOE's appeared for example between the following pairs of protons[13]: 14, 1α-H & 4α-H (4%), 1α-H & 5α-H (11%), 5α-H & 4α-H (9%), 5α-H & 1α-H (11%); 15, 1α-H & 4α-H (4%), 3β-H & 5β-H (3%), 4α-H & 1α-H (4%), 5β-H & 3β-H (3%). Denitrohydrogenation of 14 and 15 with n-Bu_3SnH in benzene in the presence of α,α'-azobis-iso-butyronitrile (AIBN) gave 16 (63% from 14, 62% from 15), colorless oil, $[\alpha]_D^{24}$ +16° ($CHCl_3$), $C_{23}H_{25}NO_6$, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1717, 1684, ^1H NMR (500 MHz, $CDCl_3$): δ 1.92 (ddd, J = 7, 8, 15), 2.03 (ddd, J = 6, 6, 15)(5-H_2), 2.79 (m, 4-H), 4.10 (dd, J = 4, 5, 2-H), 4.32, 4.35 (both dd, J = 6, 11, 6-H_2), 4.54 (m, 1-H), 5.13 (dd, J = 4, 7, 3-H), 6.05 (d, J = 6, >NH), 8.11 (s, -OCHO). On the other hand, treatment of 13 with 28% aq. NH_4OH (or liq. NH_3) and subsequent acetylation, furnished 17 [62% (or 60%)], colorless oil, $[\alpha]_D^{24}$ -8° ($CHCl_3$), $C_{23}H_{24}N_2O_8$, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1706, 1667, 1555, 1379, ^1H NMR (500 MHz, $CDCl_3$): δ 3.21 (m, 4-H), 4.33 (dd, J = 4, 6, 2-H), 4.46, 4.51 (both dd, J = 5, 10, 6-H_2), 4.88 (dd, J = 7, 7, 5-H), 5.00 (ddd, J = 6, 7, 7, 1-H), 5.69 (dd, J = 4, 6, 3-H), 6.27 (d, J = 7, >NH), 8.16 (s, -OCHO), NOE (e.g.): 1β-H & 2β-H (9%), 1β-H & 4β-H (2%), 2β-H & 1β-H (13%), 2β-H & 4β-H (11%), 4β-H & 2β-H (2%), 5α-H & 1α-NH (6%). Therefore, it was inferred that the Michael-type addition reactions for nitro-cyclopentenes (12, 13) proceeded to provide thermodynamically favored addition products in which the introduced 1-NH_2 group had the same orientation as that of the 4-benzoyloxymethyl group.

Next, the Michael-type addition of N^6-benzoyladenine for 12 was examined. Treatment of 12 with N^6-benzoyladenine in THF in the presence of KF and 18-crown-6 provided 18 (78%), colorless oil, $[\alpha]_D^{25}$ -102° ($CHCl_3$), $C_{33}H_{28}N_6O_8$, UV λ_{max}^{MeOH} nm (ε): 230 (18500), 281 (12100), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1724, 1606, 1583, 1551, 1371, ^1H NMR (500 MHz, $CDCl_3$): δ 3.23 (m, 4-H), 4.76, 4.81 (both dd, J = 4, 12, 6-H_2), 4.87 (dd, J = 5, 10, 2-H), 5.37 (dd, J = 10, 10, 1-H), 5.63 (d, J = 5, 3-H), 5.94 (dd, J = 6, 10, 5-H), 7.97 (s, 8'-H), 8.16 (s, -OCHO), 8.23 (s, 2'-H), NOE (e.g.): 1α-H & 4α-H (3%), 2β-H & 3β-H (5%), 2β-H & 5β-H (6%), 3β-H & 5β-H (2%), 5β-H & 2β-H (4%).[13] Deformylation of 18 with aq. NH_4OH - EtOH followed by ethoxyethylation and denitro-hydrogenation, yielded the denitro-product from which the ethoxyethyl group was removed with 10% aq. AcOH to furnish 19 (48%), colorless oil, $[\alpha]_D^{23}$ -75° ($CHCl_3$), $C_{32}H_{29}N_5O_5$, UV λ_{max}^{MeOH} nm (ε): 281 (11600), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1706, 1690, 1580, ^1H NMR (500 MHz, $CDCl_3$): δ 2.40 (ddd, J = 4, 9, 13), 2.50 (ddd, J = 9, 9, 13)(5-H_2), 2.61 (m, 4-H), 4.28 (dd, J = 3, 5, 3-H), 4.48 (dd, J = 5, 11), 4.52 (dd, J = 3, 11)(6-H_2), 4.68 (dd, J = 5, 9, 2-H), 4.86 (ddd, J = 9, 9, 9, 1-H), 7.85 (s, 8'-H), 8.49 (s, 2'-H). Finally, removal of the benzoyl and benzyl groups furnished (-)-aristeromycin (1, 93%), mp 213-215 °C, $[\alpha]_D^{24}$ -51° (DMF), which was identified by comparing its physical data (^1H and ^{13}C NMR, etc) with those reported.[1,6a,6b]

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12) The molecular composition of the compound given with the chemical formula was determined either by elemental analysis or by high resolution mass spectrometry.
13) The magnitude of NOE (%) given in the parenthesis was observed when the underlined proton was irradiated.

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