

## 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<sup>6</sup>-benzoyladenine with a nitro-cyclopentene derivative as its key step.

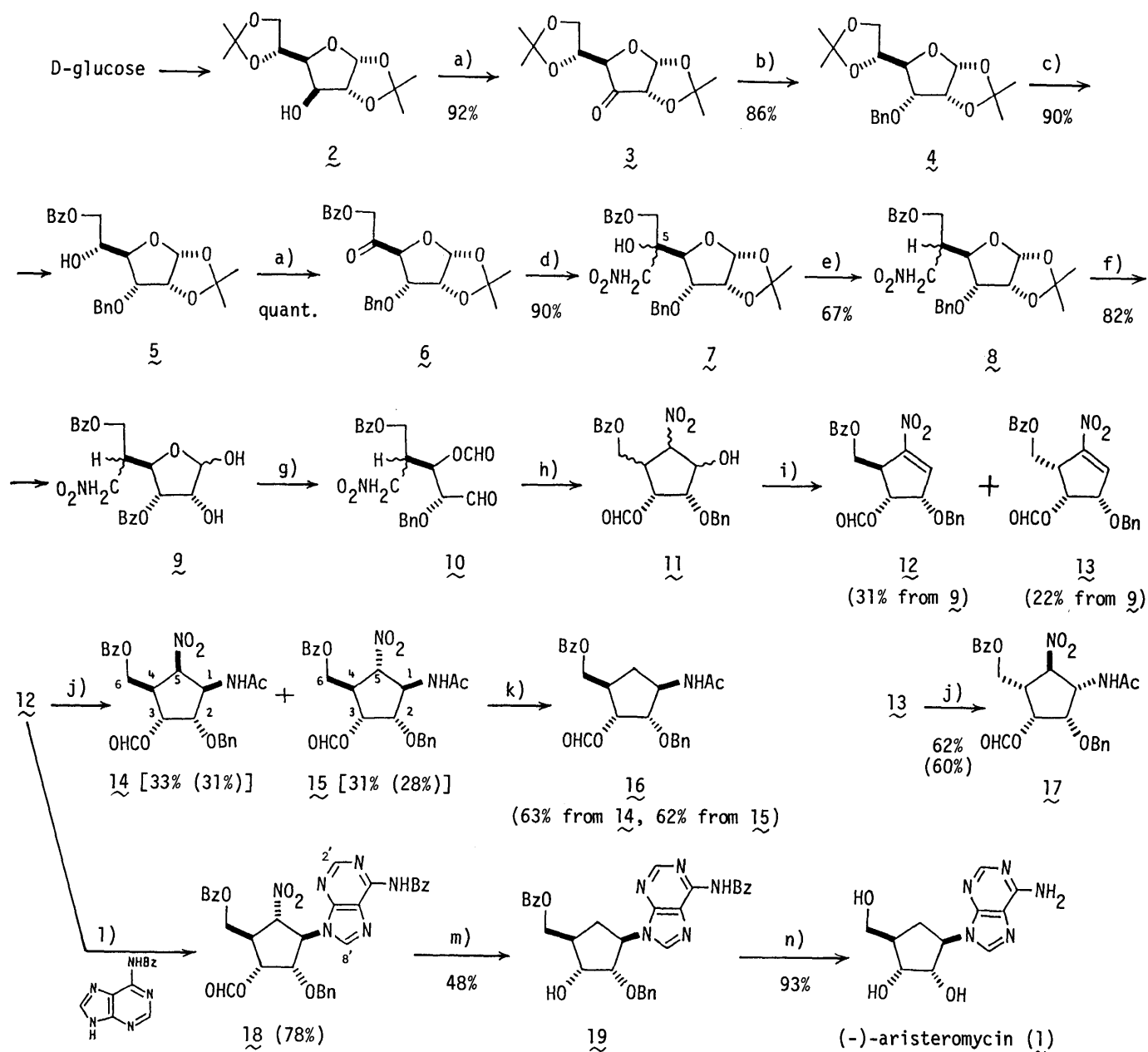
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(-)-Aristeromycin (**1**), a carbocyclic analog of adenosine, exhibits a variety of interesting biological activities such as antibacterial, antifungal, antiviral, and antitumor properties.<sup>1,2)</sup> Aristeromycin was first synthesized in a racemic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

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.<sup>7)</sup> Furthermore, we have devised a new method for synthesizing optically active pseudo-glycosides using a Michael-type addition reaction with a nitro-cyclohexene.<sup>8)</sup> 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,<sup>9)</sup> which are commonly called "pseudo-nucleosides". This paper deals with a synthesis of (-)-aristeromycin (**1**) from D-glucose.

Swern oxidation<sup>10)</sup> of 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (**2**) gave a ketone (**3**, 92%)<sup>11)</sup> which was treated with NaBH<sub>4</sub><sup>11)</sup> and benzylated to yield a D-allofuranose derivative (**4**, 86%), colorless oil, [α]<sub>D</sub><sup>23</sup> +107° (CHCl<sub>3</sub>), C<sub>19</sub>H<sub>26</sub>O<sub>6</sub>, IR<sub>max</sub> CHCl<sub>3</sub> cm<sup>-1</sup>: 2995, 2940, 1386. Treatment of **4** with 80% aq. AcOH and subsequent selective benzylation of the product furnished **5** (90%), colorless oil, [α]<sub>D</sub><sup>21</sup> +64° (CHCl<sub>3</sub>), C<sub>23</sub>H<sub>26</sub>O<sub>7</sub>, IR<sub>max</sub> CHCl<sub>3</sub> cm<sup>-1</sup>: 3524, 2993, 1711, EI-MS (m/z): 414 (M<sup>+</sup>). Swern oxidation of **5** gave an unstable ketone **6** which was immediately treated with CH<sub>3</sub>NO<sub>2</sub> in DMF in the presence of KF and 18-crown-6 to provide **7** (90%, a mixture of the 5-epimers), colorless oil, IR<sub>max</sub> CHCl<sub>3</sub> cm<sup>-1</sup>: 3552, 2990, 1723, 1552, 1375, EI-MS (m/z): 458 (M<sup>+</sup>-CH<sub>3</sub>). The nitrofuranose derivatives (**7**), without separation, were acetylated and subjected to deacetoxyhydrogenation with NaBH<sub>4</sub><sup>7a)</sup> to furnish **8** (67%), colorless oil, IR<sub>max</sub> CHCl<sub>3</sub> cm<sup>-1</sup>: 1721, 1555, 1378, EI-MS (m/z): 442 (M<sup>+</sup>-CH<sub>3</sub>). Removal of the isopropylidene group of **8** with 80% aq. AcOH gave **9** (82%), colorless oil, IR<sub>max</sub> film cm<sup>-1</sup>: 3449, 1730, 1550, 1374, EI-MS (m/z): 417 (M<sup>+</sup>), which was oxidized with Pb(OAc)<sub>4</sub> 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<sub>2</sub>O and p-TsOH·H<sub>2</sub>O provided two nitro-cyclopentenes, **12** (31% from **9**), colorless oil, [α]<sub>D</sub><sup>20</sup> +83° (CHCl<sub>3</sub>), C<sub>21</sub>H<sub>19</sub>NO<sub>7</sub>, IR<sub>max</sub> CHCl<sub>3</sub> cm<sup>-1</sup>: 1728, 1556, 1523, 1345, and **13** (22% from **9**), colorless oil, [α]<sub>D</sub><sup>24</sup> +31° (CHCl<sub>3</sub>), C<sub>21</sub>H<sub>19</sub>NO<sub>7</sub>, IR<sub>max</sub> CHCl<sub>3</sub> cm<sup>-1</sup>: 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<sub>4</sub>OH in 95% aq. EtOH at 25 °C (or with liq. NH<sub>3</sub> in THF at -78 °C) and subsequent acetylation of the product, furnished two β-acetamide derivatives, **14** [33% (or 31%)], colorless oil, [α]<sub>D</sub><sup>24</sup> +21° (CHCl<sub>3</sub>), C<sub>23</sub>H<sub>24</sub>N<sub>2</sub>O<sub>8</sub>, IR<sub>max</sub> CHCl<sub>3</sub> cm<sup>-1</sup>:



(a)  $(\text{COCl})_2$  / DMSO /  $\text{Et}_3\text{N}$  /  $\text{CH}_2\text{Cl}_2$  ( $-78^\circ\text{C}$ , 1 h) (b)  $\text{NaBH}_4$  / 95% aq. EtOH ( $2^\circ\text{C}$ , 1.5 h) ;  $\text{BnCl}$  / NaH / DMF ( $25^\circ\text{C}$ , 1.5 h) (c) 80% aq. AcOH ( $25^\circ\text{C}$ , 24 h) ;  $\text{BzCl}$  / pyridine /  $\text{CH}_2\text{Cl}_2$  ( $2^\circ\text{C}$ , 1 h) (d)  $\text{CH}_3\text{NO}_2$  / KF / 18-crown-6 / DMF ( $25^\circ\text{C}$ , 3 h) (e)  $\text{Ac}_2\text{O}$  /  $p\text{-TsOH}\cdot\text{H}_2\text{O}$  ( $25^\circ\text{C}$ , 3 h) ;  $\text{NaBH}_4$  / 95% aq. EtOH ( $25^\circ\text{C}$ , 2 h) (f) 80% aq. AcOH ( $80^\circ\text{C}$ , 15 h) (g)  $\text{Pb}(\text{OAc})_4$  / benzene ( $25^\circ\text{C}$ , 40 min) (h) KF / 18-crown-6 / DMF ( $2^\circ\text{C}$ , 3.5 h) (i)  $\text{Ac}_2\text{O}$  /  $p\text{-TsOH}\cdot\text{H}_2\text{O}$  ( $25^\circ\text{C}$ , 1.5 h) (j) 28% aq.  $\text{NH}_4\text{OH}$  / 95% aq. EtOH ( $25^\circ\text{C}$ , 2 h) [or liq.  $\text{NH}_3$  / THF ( $-78^\circ\text{C}$ , 2 h)] ;  $\text{Ac}_2\text{O}$  /  $p\text{-TsOH}\cdot\text{H}_2\text{O}$  ( $25^\circ\text{C}$ , 2 h) (k)  $n\text{-Bu}_3\text{SnH}$  / AIBN / benzene ( $80^\circ\text{C}$ , 3 h) (l) KF / 18-crown-6 / THF ( $2^\circ\text{C}$ , 1 h) (m) 28% aq.  $\text{NH}_4\text{OH}$  / 95% aq. EtOH ( $25^\circ\text{C}$ , 30 min) ;  $\text{CH}_2\text{O}$  / CSA /  $\text{CH}_2\text{Cl}_2$  ( $25^\circ\text{C}$ , 1 h) ;  $n\text{-Bu}_3\text{SnH}$  / AIBN / toluene ( $110^\circ\text{C}$ , 20 min) ; 10% aq. AcOH / acetone ( $25^\circ\text{C}$ , 14 h) (n) 5% NaOMe-MeOH ( $25^\circ\text{C}$ , 2 h) ; Na / liq.  $\text{NH}_3$  / THF ( $-78^\circ\text{C}$ , 30 min)

1723, 1696, 1559, 1367, and **15** [31% (or 28%)], colorless oil,  $[\alpha]_{\text{D}}^{24} +14^\circ$  ( $\text{CHCl}_3$ ),  $\text{C}_{23}\text{H}_{24}\text{N}_2\text{O}_8$ ,  $\text{IR}_{\text{max}} \nu_{\text{CHCl}_3} \text{ cm}^{-1}$ : 1724, 1693, 1557, 1367. The  $^1\text{H}$  NMR decoupling experiments in detail (500 MHz) of **14** and **15** resulted in the following assignments ( $J$  in Hz): **14** (in  $\text{C}_6\text{D}_6$ ),  $\delta$  3.60 (dd,  $J = 4, 4, 2\text{-H}$ ), 3.73 (m, 4-H), 3.85 (dd,  $J = 8, 11$ ), 4.13 (dd,  $J = 5, 11$ ) (6-H<sub>2</sub>), 4.44 (dd,  $J = 7, 9, 5\text{-H}$ ), 4.54 (dd,  $J = 4, 10, 3\text{-H}$ ), 4.77 (ddd,  $J = 4, 9, 10, 1\text{-H}$ ),

5.50 (d,  $J=10$ ,  $>NH$ ), 7.44 (s,  $-OCHO$ ); 15 (in  $CDCl_3$ ),  $\delta$  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<sup>13</sup>): 14,  $\underline{1\alpha-H}$  &  $4\alpha-H$  (4%),  $\underline{1\alpha-H}$  &  $5\alpha-H$  (11%),  $\underline{5\alpha-H}$  &  $4\alpha-H$  (9%),  $\underline{5\alpha-H}$  &  $1\alpha-H$  (11%); 15,  $\underline{1\alpha-H}$  &  $4\alpha-H$  (4%),  $\underline{3\beta-H}$  &  $5\beta-H$  (3%),  $\underline{4\alpha-H}$  &  $1\alpha-H$  (4%),  $\underline{5\beta-H}$  &  $3\beta-H$  (3%). Denitrohydrogenation of 14 and 15 with  $n-Bu_3SnH$  in benzene in the presence of  $\alpha, \alpha'$ -azobis-iso-butyronitrile (AIBN) gave 16 (63% from 14, 62% from 15), colorless oil,  $[\alpha]_D^{24} +16^\circ$  ( $CHCl_3$ ),  $C_{23}H_{25}NO_6$ ,  $IR \nu_{max}^{CHCl_3} cm^{-1}$ : 1717, 1684,  $^1H$  NMR (500 MHz,  $CDCl_3$ ):  $\delta$  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,  $[\alpha]_D^{24} -8^\circ$  ( $CHCl_3$ ),  $C_{23}H_{24}N_2O_8$ ,  $IR \nu_{max}^{CHCl_3} cm^{-1}$ : 1706, 1667, 1555, 1379,  $^1H$  NMR (500 MHz,  $CDCl_3$ ):  $\delta$  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.):  $\underline{1\beta-H}$  &  $2\beta-H$  (9%),  $\underline{1\beta-H}$  &  $4\beta-H$  (2%),  $\underline{2\beta-H}$  &  $1\beta-H$  (13%),  $\underline{2\beta-H}$  &  $4\beta-H$  (11%),  $\underline{4\beta-H}$  &  $2\beta-H$  (2%),  $\underline{5\alpha-H}$  &  $1\alpha-NH$  (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,  $[\alpha]_D^{25} -102^\circ$  ( $CHCl_3$ ),  $C_{33}H_{28}N_6O_8$ ,  $UV \lambda_{max}^{MeOH} nm (\epsilon)$ : 230 (18500), 281 (12100),  $IR \nu_{max}^{CHCl_3} cm^{-1}$ : 1724, 1606, 1583, 1551, 1371,  $^1H$  NMR (500 MHz,  $CDCl_3$ ):  $\delta$  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.):  $\underline{1\alpha-H}$  &  $4\alpha-H$  (3%),  $\underline{2\beta-H}$  &  $3\beta-H$  (5%),  $\underline{2\beta-H}$  &  $5\beta-H$  (6%),  $\underline{3\beta-H}$  &  $5\beta-H$  (2%),  $\underline{5\beta-H}$  &  $2\beta-H$  (4%).<sup>13</sup> Deformylation of 18 with aq.  $NH_4OH$ -EtOH followed by ethoxyethylation and denitrohydrogenation, yielded the denitro-product from which the ethoxyethyl group was removed with 10% aq. AcOH to furnish 19 (48%), colorless oil,  $[\alpha]_D^{23} -75^\circ$  ( $CHCl_3$ ),  $C_{32}H_{29}N_5O_5$ ,  $UV \lambda_{max}^{MeOH} nm (\epsilon)$ : 281 (11600),  $IR \nu_{max}^{CHCl_3} cm^{-1}$ : 1706, 1690, 1580,  $^1H$  NMR (500 MHz,  $CDCl_3$ ):  $\delta$  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  $^\circ C$ ,  $[\alpha]_D^{24} -51^\circ$  (DMF), which was identified by comparing its physical data ( $^1H$  and  $^{13}C$  NMR, etc) with those reported.<sup>1,6a,6b</sup>

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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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