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SYNTHESIS OF (-)-ARISTEROMYCIN FROM D-GLUCOSE

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Abstract --- (-)-Aristeromycin (1), a typical pseudo-nucleoside exhibiting various biological activities, was synthesized from D-glucose by using an intramolecular condensation process to form a nitro-cyclopentene (12) and by subsequent employment of a stereoselective Michael-type addition reaction of ^{6}N-benzoyladenine to introduce a purine base moiety.

Pseudo-nucleosides, which contain pseudo-sugar or related cyclitols in place of a sugar moiety, often referred to as carbocyclic nucleosides, have been paid much attention from a synthetic and biological viewpoint.[1] Aristeromycin, a typical pseudo-nucleoside, was first synthesized in racemic form (also named C-Ado).[2] Afterwards, (-)-aristeromycin (1) was isolated from the ascomycete Streptomyces citricolor nov. sp. as the first naturally occurring pseudo-nucleoside.[3] (-)-Aristeromycin (1) has been shown to exhibit antibacterial, antiviral, and antitumor activities.[3,4] On the other hand, the (+)-enantiomer of 1 was completely inactive for inhibition of tumor-cell growth and virus replication.[4] Recent studies on pseudo-nucleoside have revealed that biological activities of pseudo-nucleoside reside mostly in the "natural-type" enantiomer.[5] For this reason, many efforts have been made to synthesize enantiomerically pure pseudo-nucleosides. Following several syntheses of the racemate,[2,6] enantioselective [7] and enantiospecific [8] syntheses of (-)-aristeromycin (1) have been reported recently. Furthermore, some analogs of 1 have been synthesized to investigate their antiviral activities.[9]

In the course of our studies on the effective utilization of natural carbohydrates as optically pure starting materials, we have found a versatile method for the synthesis of aminocyclitol oligoglycosides by making use of nitromethane cyclization reactions.[10] Several aminoglycoside

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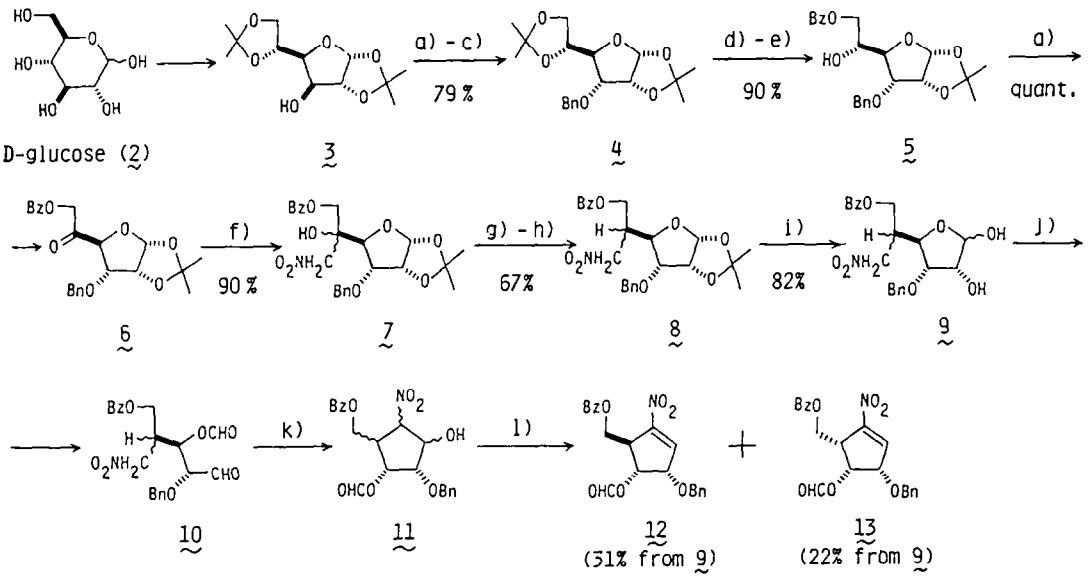
antibiotics of clinical importance such as ribostamycin and dibekacin have been synthesized.[11] As an extension of our synthetic studies for converting carbohydrates to cyclitols, we have developed an efficient method for transforming carbohydrates into pseudo-sugars by using a stereoselective deacetoxyhydrogenation and a cyclitol formation from a nitrofuranose as the key reactions. By utilizing this method, optically active pseudo-hexopyranoses,[12] pseudo-pentofuranoses,[13] and bioactive pseudo-amino-sugars[14] have been synthesized from D-glucose. Furthermore, from nitrocyclohexenes and nitro-cyclopentenes prepared from synthetic intermediates of pseudo-sugars, we have successfully synthesized three new pseudo-nucleosides : (-)-9-pseudo-β-D-glucopyranosyladenine,[15] (-)-9-pseudo-β-L-idopyranosyladenine,[15] and (+)-9-pseudo-β-L-xylofuranosyladenine,[16] and (+)-cyclaradine.[16] In this paper, we describe a full account of the synthesis of (-)-aristeromycin (1) from D-glucose (2).[17] Our approach to the construction of pseudo-nucleosides characteristically comprises initial conversion of D-glucose (2) to a substituted nitro-cyclopentene (e.g. 12) via a D-allofuranose derivative (4) and subsequent stereoselective Michael-type addition of ^{6}N-benzoyladenine to the nitro-cyclopentene.

The starting material, a D-allofuranose derivative (4), was prepared from D-glucose (2) using a modified literature procedure.[18] Namely, Swern oxidation[19] of 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (3)[12] followed by reduction with $NaBH_4$ gave 1,2:5,6-di-O-isopropylidene-α-D-allofuranose (4a)[18] which was subjected to benzylation to furnish 4 in 79% yield from 3. Bis ketal 4 was converted to alcohol 5 (90%) by treatment with 80% aqueous acetic acid at room temperature to remove only the 5,6-isopropylidene group and by subsequent selective benzoylation of the primary hydroxyl group with benzoyl chloride and pyridine under ice-cooling. Swern oxidation again of alcohol 5 quantitatively gave an unstable ketone 6 which was immediately treated with nitromethane in N,N-dimethylformamide (DMF) in the presence of KF and 18-crown-6 to provide the nitrofuranose derivative (7) in 90% yield as a mixture of epimers. Without further separation, alcohols 7 were acetylated and subjected to deacetoxyhydrogenation[12] with $NaBH_4$ to furnish ketal 8 in 67% yield. Removal of the isopropylidene group of 8 with hot 80% aqueous acetic acid gave diol 9 in 82% yield. Cleavage of this 1,2-diol with $Pb(OAc)_4$ provided a mixture of aldehydic formates (10) which was then subjected to an intramolecular condensation reaction with KF in DMF in the presence of 18-crown-6 to furnish an epimeric mixture of the cyclization products (11). Treatment of 11 with acetic anhydride and p-toluenesulfonic acid monohydrate provided two substituted nitro-cyclopentenes, i.e., a pseudo-D-ribofuranose (12, 31% overall yield from 9) and a pseudo-L-lyxofuranose (13, 22% overall yield from 9).



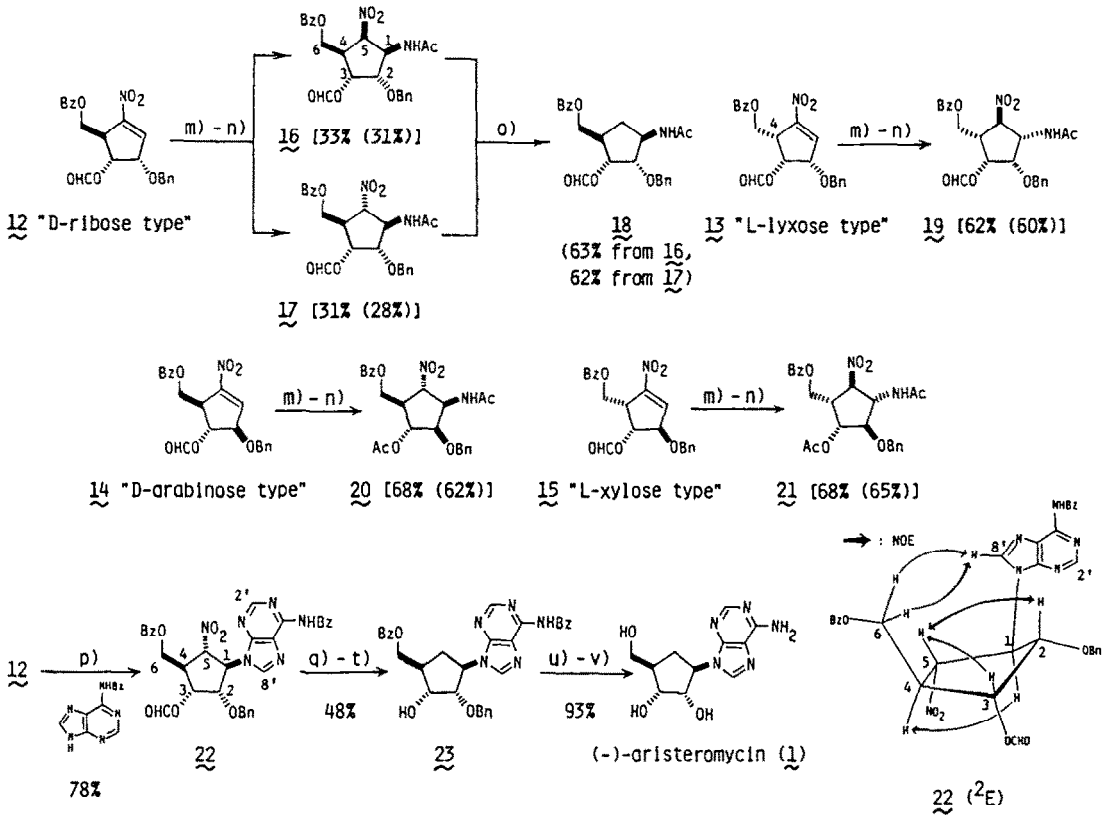
(a) $(COCl)_2$/DMSO/Et_3N/CH_2Cl_2 (-78 °C, 1 h) (b) $NaBH_4$/95% aq. EtOH (2 °C, 1.5 h) (c) BnCl/NaH/DMF (25 °C, 1.5 h) (d) 80% aq. AcOH (25 °C, 24 h) (e) BzCl/pyridine/CH_2Cl_2 (2 °C, 1 h) (f) CH_3NO_2/KF/18-crown-6/DMF (25 °C, 3 h) (g) Ac_2O/p-TsOH·H_2O (25 °C, 3 h) (h) $NaBH_4$/95% aq. EtOH (25 °C, 2 h) (i) 80% aq. AcOH (80 °C, 15 h) (j) $Pb(OAc)_4$/benzene (25 °C, 40 min) (k) KF/18-crown-6/DMF (25 °C, 3.5 h) (l) Ac_2O/p-TsOH·H_2O (25 °C, 1.5 h)

Chart 1

The structures of 12 and 13 were substantiated by detailed comparison of their physical data with those of a pseudo-D-arabinofuranose (14) and a pseudo-L-xylofuranose (15), nitro-cyclopentenes, both of which we had previously synthesized from D-glucose (2).[16]

The utility of Michael-type addition reactions to nitro-olefins in organic synthesis has been exemplified by a number of groups,[20] however the stereoselectivity of the reaction has not yet been investigated in detail. Recently, we have reported the stereoselectivity of a Michael-type addition of various nucleophiles such as ammonia, cyclohexylamine, and purine bases to substituted nitro-cyclohexenes.[14,15] On the other hand, ^{6}N-benzoyladenine is the only nucleophile to have been investigated for conjugate addition to substituted nitro-cyclopentenes, namely 14 and 15.[16] So that, prior to going on with our synthetic study of (-)-aristeromycin (1), the reactions of ammonia with electrophiles 12, 13, 14, and 15 were examined, in order to clarify the stereoselectivity of Michael-type additions to substituted nitro-cyclopentenes.

Treatment of pseudo-D-furanose type nitro-cyclopentenes having a 4β-benzoyloxymethyl group (12, 14) with 28% aqueous ammonium hydroxide in 95% ethanol at room temperature and subsequent acetylation of the products,



(m) 28% aq. NH_4OH/95% aq. EtOH (25 °C, 2 h)[or liq. NH_3/THF (-78 °C, 2 h)] (n) Ac_2O/p-TsOH·H_2O (25 °C, 2 h) (o) n-Bu_3SnH/AIBN/benzene (80 °C, 3 h) (p) KF/18-crown-6/THF (2 °C, 1 h) (q) 28% aq. NH_4OH/95% aq. EtOH (25 °C, 30 min) (r) ⩘O⩔/CSA/CH_2Cl_2 (25 °C, 1 h) (s) n-Bu_3SnH/AIBN/toluene (110 °C, 20 min) (t) 10% aq. AcOH/acetone (35 °C, 14 h) (u) 5% NaOMe-MeOH (25 °C, 2 h) (v) Na/liq. NH_3/THF (-78 °C, 30 min)

Chart 2

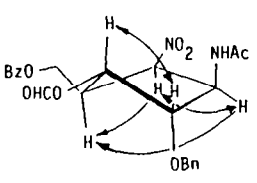
furnished 1β-acetamide derivatives : 16 (33%) and 17 (31%) from 12, or 20 [21] (68%) from 14. It was also found that treatment of 12 and 14 with liquid ammonia in tetrahydrofuran (THF) at -78 °C and acetylation of the products furnished 1β-acetamides : 16 (31%) and 17 (28%), or 20 [21] (62%). The two 5-nitro epimers (16, 17) were both reduced with tri-n-butyltin hydride (n-Bu_3SnH) in benzene in the presence of 2,2'-azobisisobutyronitrile (AIBN) to give acetate (18) as a single isomer. On the other hand, treatment of pseudo-L-furanose type nitro-cyclopentenes having a 4α-benzoyloxymethyl group (13, 15) with 28% aqueous ammonium hydroxide (or liquid ammonia) and subsequent acetylation, furnished a 1α-acetamide derivative : 19 [62% (or 60%)] or 21 [68% (or 65%)], [21] respectively.

The IR spectra of these Michael-addition products (16, 17, 19, 20, and 21) showed absorption bands ascribable to amide, ester carbonyl, and nitro

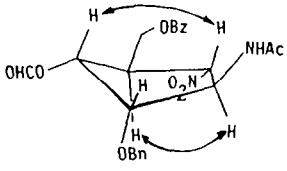
Table 1 ^{1}H NMR Data (500 MHz, δ)[a)]

	1-H	2-H	3-H	4-H	5-H	6-H	-NH 8',2'-H
16*	4.77 (ddd, J=4.6,9.2,9.7)	3.60 (dd, J=4.0,4.6)	4.54 (dd, J=4.0,9.5)	3.73 (m)	4.44 (dd, J=7.0,9.2)	3.85 (dd, J=8.2,11.3) 4.13 (dd, J=4.9,11.3)	5.50 (d, J=9.7)
17	5.11 (ddd, J=4.9,5.3,7.6)	4.48 (dd, J=4.1,5.3)	5.31 (dd, J=4.1,10.5)	3.32 (m)	5.00 (dd, J=4.9,9.5)	4.28 (dd, J=8.2,11.9) 4.68 (dd, J=5.0,11.9)	6.13 (d, J=7.6)
18	4.54 (m)	4.10 (dd, J=4.4,5.0)	5.13 (dd. J=4.4,7.2)	2.79 (m)	1.92 (ddd, J=7.0,7.8,14.8) 2.03 (ddd, J=6.0,6.3,14.8)	4.32 (dd, J=5.8,11.0) 4.35 (dd, J=5.5,11.0)	6.05 (d, J=6.1)
19	5.00 (ddd, J=6.1,6.7,6.7)	4.33 (dd, J=3.7,6.1)	5.69 (dd, J=3.7,6.4)	3.21 (m)	4.88 (dd, J=6.7,7.3)	4.46 (dd, J=5.2,10.4) 4.51 (dd, J=4.6,10.4)	6.27 (d, J=6.7)
20	5.16 (ddd, J=4.9,9.1,10.0)	3.90 (d, J=4.9)	5.00 (d, J=3.4)	3.24 (m)	4.83 (dd, J=8.4,10.0)	4.43 (dd, J=8.2,11.3) 4.56 (dd, J=5.2,11.3)	5.95 (d, J=9.1)
21	5.12 (ddd, J=5.2,8.9,9.5)	3.90 (dd, J=4.9,5.2)	5.45 (d, J=4.9)	3.89 (m)	5.21 (dd, J=7.8,9.5)	4.35 (dd, J=8.9,11.3) 4.52 (dd, J=6.1,11.3)	6.02 (d, J=8.9)
22	5.37 (dd, J=9.5,10.0)	4.87 (dd, J=5.0,10.0)	5.63 (d, J=5.0)	3.23 (m)	5.94 (dd, J=6.4,9.5)	4.76 (dd, J=4.3,11.6) 4.81 (dd, J=4.0,11.6)	7.97 (s, 8'-H) 8.23 (s, 2'-H)
23	4.86 (ddd, J=8.5,8.5,8.5)	4.68 (dd, J=5.1,8.5)	4.28 (dd, J=2.5,5.1)	2.61 (m)	2.40 (ddd, J=4.2,8.5,13.2) 2.50 (ddd, J=8.5,8.5,13.2)	4.48 (dd, J=5.4,11.2) 4.52 (dd, J=3.4,11.2)	7.85 (s, 8'-H) 8.49 (s, 2'-H)

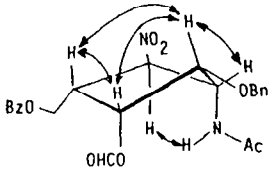
a) Spectra were recorded in $CDCl_3$ (or *in C_6D_6)



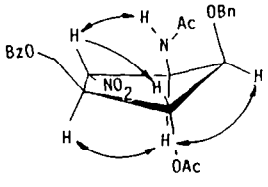
16 ($^3T_2$)



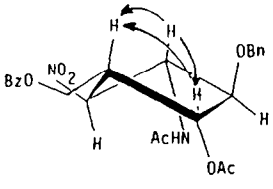
17 (^3E)



19 ($^2T_3$)



20 (^2E)



21 ($^4T_3$)

→ : NOE

^{1}H NMR (500 MHz)

Fig.

functions. Their configurations were corroborated by ^{1}H NMR examinations which included detailed decoupling and nuclear Overhauser effect (NOE) experiments, and furthermore, their conformations as shown in Fig. 1 have been presumed on the basis of the coupling constants and the dihedral angles deduced from them by using Dreiding models.[22] Based on these structural studies of the addition products, it has been presumed that the Michael-type addition reactions to nitro-cyclopentenes proceed to provide thermodynamically favored addition products in which the introduced 1-amino group possesses the same orientation as that of the 4-benzoyloxymethyl group.

Next, we carried out the addition reaction of a purine base to a pseudo-D-ribofuranose type nitro-cyclopentene (12) in order to synthesize (-)-aristeromycin (1). Treatment of nitro alkene 12 with ^{6}N-benzoyladenine in THF in the presence of KF and 18-crown-6 provided adduct 22 in 78% yield, which showed the UV absorption maximum due to the adenine moiety. The IR spectrum of 22 showed absorption bands ascribable to ester carbonyl, nitro group, and adenine moiety. Detailed comparison of the physical data for 22 with those for 16, 17, and the related compounds in the previously reported syntheses of pseudo-nucleosides,[16] has led us to determine the configuration of 22 having the ^{6}N-benzoyladenine moiety introduced at the 1β-position. Based on the ^{1}H and ^{13}C NMR examinations and the observation of NOE's between the 8'-H in the ^{6}N-benzoyladenine moiety and 6-H_2 in the pseudo-sugar portion, it has been presumed that the disposition of the purine base is anti and the cyclopentane moiety takes an ^{2}E conformation (Chart 2).

Removal of the formyl group in 22, which was unstable to direct denitrohydrogenation, with aqueous ammonium hydroxide-ethanol, ethoxyethylation, and subsequent denitrohydrogenation, provided the denitro-product, which was then treated with 10% aqueous acetic acid to furnish 23 in 48% overall yield. Finally, removal of the benzoyl and benzyl groups of 23 furnished (-)-aristeromycin (1) in 93% yield, which was identified by comparing its physical data with those reported.[3,7a,8a]

Thus, a facile and enantiospecific synthesis of (-)-aristeromycin (1) from D-glucose (2) has been accomplished. The synthetic procedure may be applied to the synthesis of modified analogs of 1, and we are currently exporing this approach for the synthesis of pseudo-nucleosides comprising other-types of nucleic acid bases and carbocyclic rings.

EXPERIMENTAL

General methods IR spectra were obtained using a Hitachi 260-30 grating spectrometer. Optical rotations were measured with a JASCO DIP-181 digital polarimeter. ^{1}H NMR spectra were measured with JEOL JNM FX-500S (500 MHz) and JEOL FX-90Q (90 MHz) spectrometers with $(CH_3)_4Si$ as the internal standard. ^{13}C NMR spectra were determined on a JEOL JNM FX-500S (125 MHz) spectrometer with $(CH_3)_4Si$ (0 ppm) as the internal standard. UV spectra were obtained using a Hitachi 330 spectrometer. Low resolution and high resolu-

tion mass spectra (MS, High MS) were measured with a JEOL D-300 mass spectrometer and a JEOL OISG mass spectrometer. The following experimental conditions were used for chromatography : column chromatography, silica gel 60 (Merck, 60-230 mesh); analytical and preparative thin-layer chromatography (TLC), precoated silica gel F-254 plates (Merck, 0.25 and 0.5 mm layer thickness).

1,2:5,6-di-O-isopropylidene-3-O-benzyl-α-D-allofuranose (4) A stirred solution of $(COCl)_2$ (3.5 ml) in CH_2Cl_2 (12 ml) was cooled to -78 °C and treated with DMSO (5.8 ml) for 10 min. 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (3, 3.50 g) in CH_2Cl_2 (17 ml) was added dropwise to the solution and the whole mixture was stirred at -78 °C for 1 h. The reaction solution was then treated with Et_3N (13 ml) and stirred at -78 °C for 10 min. The reaction mixture was poured into ice-water and the whole was extracted with AcOEt. The AcOEt extract was washed with brine, then dried over $MgSO_4$ and the solvent was evaporated to dryness under reduced pressure. The residue was purified by column chromatography [using SiO_2 100 g, n-hexane-AcOEt (2:1) as eluent] to yield a ketone (3.20 g). A solution of the ketone (3.20 g) in 95% EtOH (70 ml) was treated with $NaBH_4$ (950 mg) and stirred at 2 °C (in an ice bath) for 1.5 h. After quenching of the reaction with acetone, the reaction mixture was partitioned into H_2O-AcOEt (1:1). Work-up of the AcOEt phase as described above and subsequent purification of the reduction product with column chromatography [SiO_2 100 g, n-hexane-AcOEt (2:1)] gave 1,2:5,6-di-O-isopropylidene-α-D-allofuranose (4a, 2.91 g, 83% from 3) which was identified by comparing its physical data : mp 75-76 °C, $[\alpha]_D^{23}$ +35.0 °(c = 1.03, $CHCl_3$); IR ($CHCl_3$) : 3567, 1161, 1015 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$, δ) : 1.38 (6H), 1.47, 1.58 (3H each)(all s), 3.81 (1H, dd, J = 4, 8 Hz, 4-H), 4.32 (1H, m, 5-H), 4.62 (1H, dd, J = 4, 5 Hz, 2-H), 5.82 (1H, d, J = 4 Hz, 1-H); MS (m/z, %) : 245 (M^+-CH_3, 11.0), with those reported [18] : mp 76-77 °C, $[\alpha]_D$ +37.7 °.

A solution of 4a (2.65 g) in DMF (20 ml) was treated with NaH (480 mg, defatted with dry ether before use) and stirred at room temperature (25 °C) for 30 min. After adding benzyl chloride (1.8 ml) at 2 °C, the reaction mixture was stirred at room temperature (25 °C) for 1.5 h. The reaction mixture was poured into ice-water and the whole was extracted with AcOEt. After work-up of the AcOEt extract as described above, the product was purified by column chromatography [SiO_2 100 g, n-hexane-AcOEt (4:1)] to furnish 4 (3.33 g, 95%). 4, mp 62-63 °C, $[\alpha]_D^{23}$ +107.0 °(c = 1.05, $CHCl_3$). High MS (m/z); Calcd for $C_{19}H_{26}O_6$ (M^+) : 350.173. Found : 350.175. IR ($CHCl_3$) : 2995, 1452, 1386, 1112 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$, δ) : 1.37 (9H), 1.59 (3H)(both s), 4.64, 4.73 (2H, ABq, J = 10 Hz, $-CH_2-C_6H_5$), 5.77 (1H, d, J = 4 Hz, 1-H), 7.36 (5H, br.s). MS (m/z, %) : 350 (M^+, 0.3), 335 (26.7), 91 (100).

1,2-isopropylidene-3-O-benzyl-6-O-benzoyl-α-D-allofuranose (5) A solution of 4 (2.49 g) in 80% aq. AcOH (40 ml) was stirred at room temperature (25 °C) for 24 h and then, the solvent was evaporated off under reduced pressure. The product (2.85 g) was dissolved in CH_2Cl_2 (30 ml) and the solution was treated with benzoyl chloride (1.4 ml) and pyridine (3.5 ml) at 2 °C. After stirring at 2 °C for 1 h, the reaction mixture was poured into ice-water and the whole was extracted with AcOEt. Work-up of the AcOEt extract as described above for the preparation of 4 gave the product which was purified by column chromatography [SiO_2 80 g, n-hexane-AcOEt (3:1)] to furnish 5 (2.95 g, 88%). 5, a colorless oil, $[\alpha]_D^{23}$ +64.2 °(c = 1.17, $CHCl_3$). High MS (m/z); Calcd for $C_{23}H_{26}O_7$ (M^+) : 414.168. Found : 414.168. IR ($CHCl_3$) : 3524, 2993, 1711, 1450, 1270, 1100 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$, δ) : 1.36, 1.60 (3H each, both s), 5.75 (1H, d, J = 4 Hz, 1-H), 7.27-8.11 (10H, m, aromatic protons). MS (m/z, %) : 414 (M^+, 0.3), 399 (1.3), 105 (42.3), 91(100).

Swern oxidation of 5 followed by nitromethane treatment A solution of 5 (770 mg) in CH_2Cl_2 (10 ml) was treated with the reagents of Swern oxidation [$(COCl)_2$ (0.81 ml) and DMSO (1.3 ml) in CH_2Cl_2 (10 ml)] as described above for the oxidation of 2 and stirred at -78 °C for 1 h. The reaction solution was treated with Et_3N (4.5 ml) and stirred at -78 °C for 10 min. The whole mixture was poured into ice-water and the whole was extracted with AcOEt. Work-up of the AcOEt extract in the usual manner gave an unstable ketone (6, 770 mg) which was dissolved in a solution of CH_3NO_2 (8 ml), KF (163 mg), and 18-crown-6 (492 mg), and the whole mixture was stirred at room temperature (25 °C) for 3 h. The reaction mixture was poured into ice-water and the whole was extracted with AcOEt. After work-up of the AcOEt extract in the usual manner, the product was purified by column chromatography [SiO_2 30 g, n-hexane-AcOEt (3:1)] to furnish 7 (795 mg, 90%). 7, a colorless oil, IR ($CHCl_3$) : 3552, 2990, 1723, 1552, 1375, 1026 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$, δ) :

1.35, 1.57 (3H each, both s), 5.62 (ca.1/2H, d, J = 4 Hz), 5.75 (ca.1/2H, d, J = 3 Hz)(1-H), 7.25-8.16 (10H, m, aromatic protons). MS (m/z, %) : 458 (M^+-CH_3, 0.2), 105 (23.2), 91 (100).

Acetylation of 7 followed by deacetoxyhydrogenation A solution of 7 (4.30 g) and p-TsOH·H_2O (1.70 g) in Ac_2O (45 ml) was stirred at room temperature (25 °C) for 3 h. The reaction mixture was poured into ice-water and the whole was extracted with AcOEt. Work-up of the AcOEt extract in the usual manner gave the acetylation product which was dissolved in 95% EtOH (50 ml). The solution was treated with $NaBH_4$ (414 mg) and stirred at room temperature (25 °C) for 2 h. After decomposition of excess $NaBH_4$ with acetone, the reaction mixture was poured into ice-water and the whole was extracted with AcOEt. After work-up of the AcOEt extract in the usual manner, the product was purified by column chromatography [SiO_2 120 g, n-hexane-AcOEt (4:1)] to furnish 8 (2.78 g, 67%). 8, a colorless oil, IR ($CHCl_3$) : 1721, 1555, 1378, 1023 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$, δ) : 1.36, 1.56 (3H each, both s), 3.05 (1H, m, 5-H), 3.76 (1H, dd, J = 4, 9 Hz, 3-H), 5.72 (1H, d, J = 4, 1-H), 7.25-8.00 (10H, m, aromatic protons). MS (m/z) : 442 (M^+-CH_3, 0.9), 105 (60.1), 91 (100).

Conversion from 8 to 9 A solution of 8 (1.82 g) in 80% aq. AcOH (50 ml) was stirred at 80 °C for 15 h and then the solvent was evaporated off under reduced pressure. The product was purified by column chromatography [SiO_2 60 g, benzene-acetone (5:1)] to furnish 9 (1.36 g, 82%). 9, a colorless oil, IR (film) : 3449, 1730, 1550, 1374, 1271 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$, δ) : 2.94 (1H, m, 5-H), 5.30 (1H, d, J = 4 Hz, 1-H), 7.10-8.01 (10H, m, aromatic protons). MS (m/z, %) : 417 (M^+, 0.1), 400 (0.4), 105 (35.0), 91 (100).

Nitro-cyclopentenes (12 and 13) A solution of 9 (290 mg) in benzene (7 ml) was treated with $Pb(OAc)_4$ (310 mg) and stirred at room temperature (25 °C) for 40 min. The reaction mixture was diluted with $CHCl_3$ and the whole was washed successively with H_2O, sat. aq. $NaHCO_3$, and brine, then dried over $MgSO_4$. Removal of the solvent from the organic phase under reduced pressure gave a mixture of unstable aldehydic formates (10) which was dissolved in DMF (3 ml). The solution was treated with KF (81 mg) and 18-crown-6 (185 mg), and stirred at 2 °C for 3.5 h. The reaction mixture was poured into ice-water and the whole was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with brine and dried over $MgSO_4$. Removal of the solvent from the $CHCl_3$ extract under reduced pressure gave the cyclization products (11). A solution of 11 and p-TsOH·H_2O (130 mg) in Ac_2O (18 ml) was stirred at room temperature (25 °C) for 1.5 h and the whole was poured into ice-water, then extracted with AcOEt. Work-up of the AcOEt extract in the usual manner gave the products which were purified by column chromatography [SiO_2 25 g, n-hexane-AcOEt (5:1-4:1)] to furnish 12 (86 mg, 31%) and 13 (61 mg, 22%). 12, a colorless oil, $[\alpha]_D^{24}$ +82.9 °(c = 1.11, $CHCl_3$). High MS (m/z) ; Calcd for $C_{21}H_{19}NO_7$ (M^+) : 397.116. Found : 397.116. IR ($CHCl_3$) : 1728, 1600, 1523, 1345, 1269 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, δ) : 3.70 (1H, br.s, 4-H), 4.53, 4.64 (1H each, both d, J = 11.8 Hz, -CH_2-C_6H_5), 4.64 (1H, dd, J = 3.4, 11.6 Hz), 4.72 (1H, dd, J = 4.3, 11.6 Hz)(6-H_2), 4.85 (1H, ddd, J = 1.8, 1.8, 5.5 Hz, 2-H), 5.65 (1H, dd, J = 1.0, 5.5 Hz, 3-H), 6.94 (1H, br.s, 1-H), 7.25-7.87 (10H, m, aromatic protons), 8.13 (1H, s, -OCHO). MS (m/z, %) : 397 (M^+, 0.1), 307 (1.8), 105 (57.0), 91 (100). 13, a colorless oil, $[\alpha]_D^{24}$ +31.2 °(c = 0.86, $CHCl_3$). High MS (m/z) ; Calcd for $C_{21}H_{19}NO_7$ (M^+) : 397.116. Found : 397.117. IR ($CHCl_3$) : 1720, 1601, 1522, 1367, 1270 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, δ) : 3.86 (1H, ddd, J = 4.9, 6.1, 6.4 Hz, 4-H), 4.53, 4.66 (1H each, both d, J = 11.9 Hz, -CH_2-C_6H_5), 4.65 (1H, dd, J = 4.9, 11.3 Hz), 4.72 (1H, dd, J = 6.1, 11.3 Hz)(6-H_2), 4.73 (1H, dd, J = 2.8, 6.1 Hz, 2-H), 5.54 (1H, dd, J = 6.1, 6.4 Hz, 3-H), 6.93 (1H, m, 1-H), 7.25-8.00 (10H, m, aromatic protons), 8.14 (1H, s, -OCHO). MS (m/z, %) : 397 (M^+, 0.2), 105 (60.0), 91 (100).

Treatment of 12 with 28% aq. NH_4OH followed by acetylation A solution of 12 (30 mg) in 95% EtOH (2.5 ml) was treated with 28% aq. NH_4OH (5 ml) and stirred at room temperature (25 °C) for 2 h. Removal of the solvent and ammonia under reduced pressure gave the products which were dissolved in a solution of Ac_2O (3 ml) and p-TsOH·H_2O (10 mg). The reaction mixture was stirred at room temperature (25 °C) for 2 h and poured into ice-water. The whole mixture was extracted with AcOEt and the AcOEt extract was worked up in the usual manner. The products were purified by column chromatography [SiO_2 4 g, benzene-acetone (4:1)] and subsequently by HPLC (Zorbax ODS, 9.4 mm X 25 cm, CH_3CN-H_2O (1:1)] to furnish 16 (12 mg, 33%) and 17 (11 mg, 31%). 16, a colorless oil, $[\alpha]_D^{24}$ +20.8 °(c = 0.48, $CHCl_3$). High MS (m/z) ; Calcd for $C_{23}H_{24}N_2O_8$ (M^+) : 456.153. Found : 456.155. IR ($CHCl_3$) : 1723, 1696, 1559, 1367 cm^{-1}. ^1H NMR (500 MHz, C_6D_6, δ) : 1.65 (3H, s, -NHAc), 4.15, 4.43 (1H each, both d, J = 12.2 Hz, -CH_2-C_6H_5), 7.02-8.08 (10H, m, aromatic protons), 7.44 (1H, s,

-OCHO), and as given in Table 1. NOE (%) : 1α-H, 4α-H (3.7); 1α-H, 5α-H (10.8); 2β-H, 3β-H (9.1); 3β-H, 2β-H (8.0); 5α-H, 4α-H (8.8); 5α-H, 1α-H (11.4).[23] MS (m/z, %) : 456 (M^+, 0.2), 105 (30.0), 91 (100). 17, a colorless oil, $[\alpha]_D^{24}$ +13.8 °(c = 0.11, $CHCl_3$). High MS (m/z) ; Calcd for $C_{23}H_{24}N_2O_8$ (M^+) : 456.153. Found : 456.152. IR ($CHCl_3$) : 1724, 1693, 1557, 1367 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, δ) : 2.09 (3H, s, -NHAc), 4.47, 4.77 (1H each, both d, J = 11.3 Hz, $-CH_2-C_6H_5$), 7.23-7.98 (10H, m, aromatic protons), 8.12 (1H, s, -OCHO), and as given in Table 1. NOE (%) : 1α-H, 4α-H (3.8); 3β-H, 5β-H (2.8); 4α-H, 1α-H (4.3), 5β-H, 3β-H (2.6).[23] MS (m/z, %) : 456 (M^+, 0.2), 105 (32.0), 91 (100).

Treatment of 12 with liq. NH_3 followed by acetylation A solution of 12 (14 mg) in THF (1 ml) was treated with liq. NH_3 (ca. 5 ml) and stirred at -78 °C for 2 h. After removal of liq. NH_3 at room temperature and then the solvent under reduced pressure, the product was dissolved in a solution of Ac_2O (2 ml) and p-TsOH·H_2O (5 mg) and the whole was stirred at room temperature (25 °C) for 2 h. The reaction mixture was poured into ice-water and the whole was extracted with AcOEt. Work-up of the AcOEt extract in the usual manner gave the products which were purified by column chromatography [SiO_2 2 g, benzene-acetone (4:1)] and then by HPLC [same conditions as described above on the treatment of 12 with aq. NH_4OH] to furnish 16 (5 mg, 31%) and 17 (4.5 mg, 28%). 16 and 17 thus obtained were shown to be identical with respective authentic samples which were obtained by aq. NH_4OH treatment of 12 by HPLC [Zorbax ODS, 9.4 mm X 25 cm, CH_3CN-H_2O (1:1)], IR ($CHCl_3$), and ^1H NMR ($CDCl_3$) comparisons.

Denitrohydrogenation of 16 and 17 A solution of 16 (10 mg) in benzene (2 ml) was treated with n-Bu_3SnH (0.14 ml) and AIBN (3 mg), and stirred at 80 °C for 3 h. Removal of the solvent from the reaction mixture under reduced pressure gave the residue which was purified by preparative TLC [benzene-acetone (2:1)] to furnish 18 (5.7 mg, 63%). 18, a colorless oil, $[\alpha]_D^{24}$ +15.6 °(c = 0.42, $CHCl_3$). High MS (m/z) ; Calcd for $C_{23}H_{25}NO_6$: 411.148. Found : 411.146. IR ($CHCl_3$) : 1717, 1684, 1272 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, δ) : 2.04 (3H, s, -NHAc), 4.51, 4.69 (1H each, both d, J = 11.6 Hz, $-CH_2-C_6H_5$), 7.24-8.09 (10H, m, aromatic protons), 8.11 (1H, s, -OCHO), and as given in Table 1. MS (m/z, %) : 411 (M^+, 1.1), 368 (1.2), 123 (94.6), 105 (100), 91 (83.6). Under the same reaction conditions, 17 (10 mg) was converted to 18 (5.6 mg, 62%) which was shown to be identical with an authentic sample obtained above by TLC [benzene-acetone (3:1), n-hexane-AcOEt (1:1)], IR ($CHCl_3$), and ^1H NMR ($CDCl_3$) comparisons.

Treatment of 13 with 28% aq. NH_4OH followed by acetylation A solution of 13 (55 mg) in 95% EtOH (2.5 ml) was treated with 28% aq. NH_4OH (0.5 ml) and stirred at room temperature (25 °C) for 2 h. After removal of the solvent and ammonia under reduced pressure, the product was dissolved in a solution of Ac_2O (3 ml) and p-TsOH·H_2O (10 mg) and the whole mixture was stirred at room temperature (25 °C) for 2 h. The reaction mixture was poured into ice-water and the whole was extracted with AcOEt. Work-up of the AcOEt extract in the usual manner gave the product which was purified by column chromatography [SiO_2 5 g, benzene-acetone (4:1)] to furnish 19 (39 mg, 62%). 19, a colorless oil, $[\alpha]_D^{24}$ -8.3 ° (c = 0.36, $CHCl_3$). High MS (m/z) ; Calcd for $C_{23}H_{24}N_2O_8$ (M^+) : 456.153. Found : 456.155. IR ($CHCl_3$) : 1706, 1667, 1555, 1379 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, δ) : 2.12 (3H, s, -NHAc), 4.52, 4.72 (1H each, both d, J = 11.0 Hz, $-CH_2-C_6H_5$), 8.16 (1H, s, -OCHO), and as given in Table 1. NOE (%) : 1β-H, 2β-H (9.0); 1β-H, 4β-H (1.4); 2β-H, 1β-H (13.4); 2β-H, 3β-H (7.9); 2β-H, 4β-H (4.7); 3β-H, 1β-H (3.8); 3β-H, 2β-H (9.7); 3β-H, 4β-H (11.1); 4β-H, 1β-H (3.4); 4β-H, 2β-H (1.8); 4β-H, 3β-H (9.3); 5α-H, 1α-NH (5.7); 1α-NH, 5α-H (8.6).[23] MS (m/z, %) : 456 (M^+, 0.2), 105 (100), 91 (91).

Treatment of 13 with liq. NH_3 followed by acetylation A solution of 13 (11 mg) in THF (1 ml) was treated with liq. NH_3 (ca. 5 ml) and stirred at -78 °C for 2 h. Work-up of the reaction mixture as described above on the liq. NH_3 treatment of 12 gave the product which was dissolved in a solution of Ac_2O (2 ml) and p-TsOH·H_2O (5 mg) and the whole was stirred at room temperature (25 °C) for 2 h. The reaction mixture was poured into ice-water and the whole was extracted with AcOEt. After work-up of the AcOEt extract in the usual manner, the product was purified by preparative TLC [benzene-acetone (2:1)] to furnish 19 (7.6 mg, 60%). 19 thus obtained was shown to be identical with an authentic sample which was obtained above by aq. NH_4OH treatment of 13 by TLC (as described above for 18), IR ($CHCl_3$), and ^1H NMR ($CDCl_3$) comparisons.

Treatment of 14 with 28% aq. NH_4OH followed by acetylation A solution of 14 (21 mg)

in 95% EtOH (2.5 ml) was treated with 28% aq. NH_4OH (0.5 ml) and stirred at room temperature (25 °C) for 2 h. After work-up of the reaction mixture as described above on the aq. NH_4OH treatment of 12, the product was dissolved in a solution of Ac_2O (2 ml) and p-TsOH·H_2O (5 mg) and then, the whole mixture was stirred at room temperature (25 °C) for 2 h. The reaction mixture was worked up as described above on the aq. NH_4OH treatment of 12 to give the product which was purified by column chromatography [SiO_2 2.5 g, benzene-acetone (5:1)] to furnish 20 (17 mg, 68%). 20, a colorless oil, $[\alpha]_D^{23}$ +54.5 °(c = 0.58, $CHCl_3$). High MS (m/z) ; Calcd for $C_{24}H_{26}N_2O_8$ (M^+) : 470.169. Found : 470.169. IR ($CHCl_3$) : 1720, 1684, 1556, 1368 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, δ) : 1.93 (3H, s, -NHAc), 2.14 (3H, s, OAc), 4.54, 4.80 (1H each, both d, J = 11.9 Hz, $-CH_2-C_6H_5$), 7.26-7.96 (10H, m, aromatic protons), and as given in Table 1. NOE (%) : 1α-H, 2α-H (12.6); 1α-H, 4α-H (6.1); 2α-H, 1α-H (12.8); 4α-H, 1α-H (6.4); 5β-H, 3β-H (8.8); 5β-H, 1β-NH (7.6); 1β-NH, 5β-H (5.6).[23] MS (m/z, %) : 470 (M^+, 0.3), 105 (73.8), 91 (100).

Treatment of 14 with liq. NH_3 followed by acetylation A solution of 14 (53 mg) in THF (2 ml) was treated with liq. NH_3 (ca. 10 ml) and stirred at -78 °C for 2 h. Work-up of the reaction mixture and subsequent acetylation as described above on the liq. NH_3 treatment of 12 gave the product which was purified by column chromatography [SiO_2 15 g, benzene-acetone (5:1)] to furnish 20 (39 mg, 62%). 20 thus obtained was shown to be identical with an authentic sample which was obtained by aq. NH_4OH treatment of 14 by TLC (as described above for 18), IR ($CHCl_3$), and ^1H NMR ($CDCl_3$) comparisons.

Treatment of 15 with aq. NH_4OH followed by acetylation A solution of 15 (25 mg) in 95% EtOH (2.5 ml) was treated with 28% aq. NH_4OH (0.5 ml) and stirred at room temperature (25 °C) for 2 h. Work-up of the reaction mixture and subsequent acetylation as described above on the aq. NH_4OH treatment of 12 gave the product which was purified by preparative TLC [benzene - acetone (3:1)] to furnish 21 (20 mg, 68%). 21, a colorless oil, $[\alpha]_D^{24}$ +9.0 °(c = 1.84, $CHCl_3$). High MS (m/z) ; Calcd for $C_{24}H_{26}N_2O_8$ (M^+) : 470.169. Found : 470.166. IR ($CHCl_3$) : 1719, 1678, 1557, 1370 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, δ) : 1.93 (3H, s, -NHAc), 2.06 (3H, s, OAc), 4.62, 4.86 (1H each, both d, J = 12.2 Hz, $-CH_2-C_6H_5$), 7.23-7.96 (10H, m, aromatic protons), and as given in Table 1. NOE (%) : 1β-H, 3β-H (3.9); 1β-H, 4β-H (3.1); 3β-H, 1β-H (3.7); 3β-H, 4β-H (12.0).[23] MS (m/z, %) : 470 (M^+, 0.2), 105 (40.5), 91 (100).

Treatment of 15 with liq. NH_3 followed by acetylation A solution of 15 (18 mg) in THF (1 ml) was treated with liq. NH_3 (ca. 5 ml) and stirred at -78 °C for 2 h. After work-up of the reaction mixture and subsequent acetylation as described above on the liq. NH_3 treatment of 13, the product was purified by preparative TLC [benzene-acetone (3:1)] to furnish 21 (14 mg, 65%) which was shown to be identical with an authentic sample obtained by aq. NH_4OH treatment of 15 by TLC (as described above for 18), IR ($CHCl_3$), and ^1H NMR ($CDCl_3$) comparisons.

Michael-type addition reaction of 12 with ^{6}N-benzoyladenine to give 22 A solution of 12 (264 mg) in THF (5 ml) was treated with ^{6}N-benzoyladenine (160 mg), KF (58 mg), and 18-crown-6 (180 mg) and stirred at 2 °C for 1 h. The reaction mixture was poured into ice-water and the whole was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with brine, then dried over $MgSO_4$ and the solvent was removed under reduced pressure to give a product which was purified by column chromatography [SiO_2 30 g, benzene-acetone (5:1)] to furnish 22 (330 mg, 78%). 22, a colorless oil, $[\alpha]_D^{25}$ -102.2 °(c = 0.54, $CHCl_3$). High MS (m/z) ; Calcd for $C_{33}H_{28}N_6O_8$ (M^+) : 636.197. Found : 636.199. UV (MeOH) : 230 (ε 18500), 281 (ε 12100) nm. IR ($CHCl_3$) : 1724, 1606, 1583, 1551, 1371 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, δ) : 4.20, 4.51 (1H each, both d, J = 12.4 Hz, $-CH_2-C_6H_5$), 6.76-8.17 (15H, m, aromatic protons), 8.16 (1H, s, -OCHO), and as given in Table 1. NOE (%) : 1α-H, 4α-H (2.2); 1α-H, 8'-H (20.2); 2β-H, 3β-H (5.1); 2β-H, 5β-H (5.9); 3β-H, 2β-H (6.3); 3β-H, 6-Ha (2.5); 3β-H, 5β-H (2.3); 5β-H, 2β-H (4.0); 5β-H, 6-Ha (2.7); 6-Ha, 3β-H (4.8); 6-Ha, 5β-H (4.5); 6-Ha, 8'-H (11.2); 6-Hb, 5β-H (7.6); 6-Hb, 8'-H (8.9); 8'-H, 1α-H (8.2).[23] ^{13}C NMR (125 MHz, $CDCl_3$, δc) : 46.6 (4-C), 62.8 (6-C), 63.4 (1-C), 70.7 (2-C), 72.7 (3-C), 74.8 ($-CH_2-C_6H_5$), 80.9 (5-C), 123.7 (5'-C), 143.7 (8'-C), 149.6 (4'-C), 151.0 (2'-C), 152.0 (6'-C), 159.5 (-OCHO), 164.5, 166.2 ($-CO-C_6H_5$ X 2). MS (m/z, %) : 636 (M^+, 0.1), 105 (100), 91 (92.3).

Conversion of 22 to 23 A solution of 22 (215 mg) in 95% EtOH (1 ml) was treated with 28% aq. NH_4OH (6 ml) and stirred at room temperature (25 °C) for 30 min. After

removal of the solvent and ammonia from the reaction mixture under reduced pressure, the product was dissolved in CH_2Cl_2 (10 ml) and the solution was treated with ethyl vinyl ether (0.07 ml) and d-camphorsulfonic acid (CSA)(30 mg). The reaction mixture was stirred at room temperature (25 °C) for 1 h and poured into ice-water. The whole mixture was extracted with $CHCl_3$ and the $CHCl_3$ extract was washed with aq. sat. $NaHCO_3$ and brine, then dried over $MgSO_4$. Removal of the solvent from the extract under reduced pressure gave a product which was dissolved in a solution of toluene (8 ml), n-Bu_3SnH (0.9 ml), and AIBN (60 mg). The solution was stirred at 110 °C for 20 min and then worked up as described above for the denitrohydrogenation of 16. The product was dissolved in acetone (0.5 ml) and 10% aq. AcOH (8 ml), and the solution was stirred at 35 °C for 14 h. Removal of the solvent from the reaction mixture under reduced pressure gave the product which was purified by column chromatography [SiO_2 7 g, $CHCl_3$ - MeOH (50:1)] to furnish 23 (92 mg, 48%). 23, a colorless oil, $[\alpha]_D^{23}$ -75.4 °(c = 0.49, $CHCl_3$). High MS (m/z) ; Calcd for $C_{32}H_{29}N_5O_5$ (M^+) : 563.217. Found : 563.218. UV (MeOH) : 230 (ε 19200), 281 (ε 11600). IR ($CHCl_3$) : 1706, 1690, 1580, 1453, 1269 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, δ) : 4.32, 4.54 (1H each, both d, J = 12.0 Hz, -CH_2-C_6H_5), 6.95-8.15 (15H, m, aromatic protons), and as given in Table 1. NOE (%) : 1α-H, 4α-H (1.2); 1α-H, 8'-H (9.2); 2β-H, 3β-H (4.0); 3β-H, 2β-H (7.8); 4α-H, 1α-H (3.3).[23] MS (m/z, %) : 563 (M^+, 0.2), 336 (53.8), 136 (91.2), 105 (96.3), 91 (100).

Conversion of 23 to (-)-aristeromycin (1) A solution of 23 (8 mg) in MeOH (1 ml) was treated with 10% NaOMe - MeOH (1 ml) and stirred at room temperature (25 °C) for 2 h. The reaction mixture was neutralized with Dowex 50W X 8 (H^+ form) and the resin was removed by filtration. Removal of the solvent from the filtrate under reduced pressure gave the product which was dissolved in THF (4 ml). The solution was treated with liq. NH_3 (ca. 5 ml) and Na (10 mg), and then stirred at -78 °C for 30 min. After decomposition of excess Na with MeOH at -78 °C and removal of NH_3 at room temperature (25 °C), the resulting reaction mixture was neutralized with Dowex 50W X 8 (H^+ form) and the resin was removed by filtration. After removal of the solvent from the filtrate under reduced pressure, the product was purified by column chromatography [SiO_2 1.5 g, $CHCl_3$ - MeOH - H_2O (7:3:1, lower phase)] and then by crystallization from aq. EtOH to furnish (-)-aristeromycin (1, 3.5 mg, 93%). 1, mp 213-215 °C, $[\alpha]_D^{24}$ -51.2 °(c = 0.23, DMF). ^1H NMR (500 MHz, d_6-DMSO + D_2O, δ) : 1.74 (1H, ddd, J = 8.3, 10.4, 12.8 Hz), 2.26 (1H, ddd, J = 8.6, 8.6, 12.8 Hz)(5-H_2), 2.07 (1H, m, 4-H), 3.46 (1H, dd, J = 6.1, 10.7 Hz), 3.51 (1H, dd, J = 7.0, 10.7 Hz)(6-H_2), 3.85 (1H, dd, J = 3.0, 5.3 Hz, 3-H), 4.34 (1H, dd, J = 5.3, 9.0 Hz, 2-H), 4.70 (1H, ddd, J = 8.3, 8.6, 8.6 Hz, 1-H), 8.13 (1H, s, 8'-H), 8.19 (1H, s, 2'-H). ^{13}C NMR (125 MHz, d_6-DMSO, δc) : 29.3 (5-C), 45.3 (4-C), 59.3 (1-C), 63.0 (6-C), 71.7 (3-C), 74.6 (2-C), 119.3 (5'-C), 140.0 (8'-C), 149.7 (4'-C), 152.0 (2'-C), 155.9 (6'-C). [lit. mp 213-215 °C,[3] $[\alpha]_D$ -52.5 °,[3] -53.0 °,[7a] ^1H NMR (100 MHz, δ) : 1.5-2.5 (3H, m, 4-H, 5-H_2), 3.50 (2H, d, J = 5 Hz, 6-H_2), 3.85 (1H, dd, J = 2.5, 5 Hz), 4.29 (1H, dd, J = 2.5, 5 Hz) (2, 3-H), 4.73 (1H, dt, J = 9, 9 Hz, 1-H), 8.12, 8.20 (1H each, both s, 2', 8'-H).[7a] (300 MHz) : 1.74, 2.25 (1H each, both m, 5-H_2), 2.05 (1H, m, 4-H), 3.40 (2H, m, 6-H_2), 3.86 (1H, dd, J = 3, 5 Hz, 3-H), 4.34 (1H, dd, J = 5, 9 Hz, 2-H), 4.70 (1H, q, J = 9 Hz, 1-H), 8.12 (1H, s, 8'-H), 8.18 (1H, s, 2'-H).[8a] ^{13}C NMR (75.453 MHz, δc) : 29.28, 45.39, 59.41, 62.98, 71.71, 74.62, 119.35, 140.00, 149.75, 152.01, 155.96.[8a)]

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