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Synthetic Studies towards (±)-Aristeromycin and its 5′-*homo*-Analogue

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Summary. A new synthetic pathway to the carbocyclic nucleoside analogues (±)-aristeromycin (**15**) and its 5′-*homo*-derivative (**17**) has been developed starting form norborn-5-en-2-one using nucleophilic substitution of a sulfonate ester group by the aglycone.

Keywords. Nucleoside, carbocyclic; Aristeromycin.

Synthesestudien zu (±)-Aristeromycin und seinem 5′-*homo*-Analogon

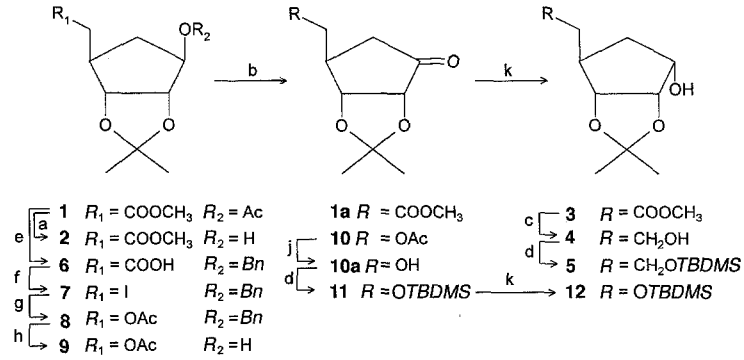
Zusammenfassung. Ausgehend von Norborn-5-en-2-on wurden neue Synthesewege für (±)-Aristeromycin (**15**) und sein 5′-*homo*-Analogon (**17**) entwickelt, wobei die Einführung der Base durch S_N2-Austausch einer Sulfonsäureestergruppe erfolgt.

Introduction

Formal substitution of the furane ring in nucleosides by a cyclopentane system leads to carbanucleosides which are stable against enzymatic and acidic hydrolysis [1]. Aristeromycin (**15**), the carbocyclic analogue of adenosine, has been synthesized first by *Shealy et al.* [2]. At about the same time, **15** was also isolated from the fermentation broth of *Streptomyces citricolor* as the first naturally occurring carbanucleoside [3]. As **15** was shown to exhibit antibacterial [3], antiviral [4], and antitumor [5] activities, synthetic pathways have been developed leading either to racemic mixtures [2, 6, 7] or to enantiomerically pure compounds [8]. In this laboratory, a synthetic pathway to carbocyclic nucleosides has been developed starting from bicyclo[2.2.1]hept-5-en-2-yl acetate which can easily be obtained in enantiomerically pure form [10]. Here we want to present synthetic transformations of this starting material leading to (±)-aristeromycin and its (±)-5′-*homo*-analogue. The latter compound has already been synthesized enantiomerically pure starting from *L*-ribonolactone [9]. Due to the promising biological activities of carbocyclic nucleosides and their substituted derivatives [1], the availability of synthetic strategies towards these compounds is of considerable importance.

Results and Discussion

This synthesis starts from diester **1**, readily obtained from norborn-5-en-2-one as described previously [11]. The removal of the acetyl group in **1** was carried out in potassium hydroxide/methanol/tetrahydrofuran solution as indicated in Scheme 1. Subsequent *Swern*-oxidation [12] and reduction of the resulting ketone with sodium borohydride in methanol at low temperature (−10°C) afforded alcohol **3** in 56% yield. In order to get a readily available model compound for the introduction of the purine system, **3** was reduced by means of lithium aluminium hydride in dry ether to give dialcohol **4**. Protection of the primary hydroxy group as *TBDMS* ether furnished **5** as a key intermediate for the preparation of (±)-5′-*homo*-aristeromycin (**17**).

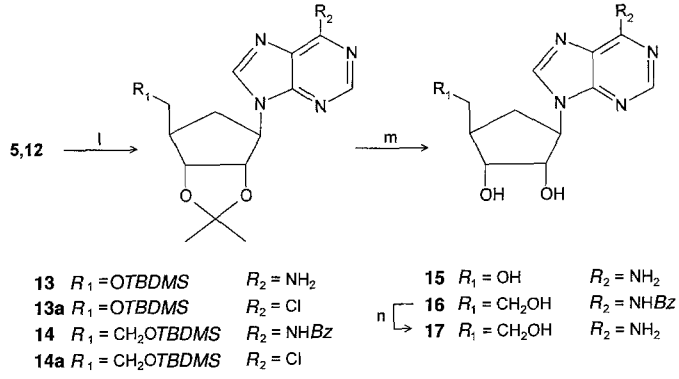


Scheme 1. Reagents and condition: (a) KOH/methanol/tetrahydrofuran/r.t.; (b) *DMSO*/$(COCl)_2$/Et_3N/CH_2Cl_2/−70°C; (c) LAH/diethyl ether/0°C; (d) *TBDMS*Cl/Et_3N/CH_2Cl_2/r.t.; (e) (i) KOH/1,4-dioxane/reflux, (ii) *Bn*Br/reflux; (f) *IBDA*/I_2/cyclohexane/hv/reflux: (g) CsOAc/DMF/reflux: (h) H_2/Pd-C/methanol: (j) CH_3ONa/methanol/r.t.: (k) $NaBH_4$/methanol/−10°C; all compounds are racemic, only one enantiomer is shown

For the synthesis of (±)-aristeromycin (**15**), the side chain in **1** had to be shortened by one carbon atom. For this degradation at C-6 we applied either conversion to a terminal olefin [11] (followed by *cis*-dihydroxylation and glycol cleavage) or synthesis of the corresponding amine by *Curtius* rearrangement with subsequent diazotation by means of sodium nitrite/acetic acid [13]. In this case, a photo-chemical decarboxylation with iodosobenzene diacetate (*IBDA*) and iodine [14] – an alternative method to the classical *Hunsdiecker* reaction – was used. Therefore, starting material **1** was transformed into carboxylic acid **6** by saponification followed by blocking of the secondary hydroxyl functionality. After decarboxylation, the resulting iodide **7** was reacted with caesium acetate to furnish the side chain degraded acetate **8**. Removal of the benzyl group was accomplished by catalytic hydrogenolysis, and the OH group was oxidized under *Swern* conditions [12]. The acetate was replaced by a *TBDMS* ether, and reduction of the ketone **11** with sodium borohydride in methanol completed the synthesis of **12**, the anticipated precursor for the preparation of (±)-aristeromycin (**15**).

The introduction of heterocyclic systems into cyclopentanoids by nucleophilic substitution of sulfonates has already been employed by many other research groups [1]. As the tosylates and mesylates of **5** and **12** proved to be non-reactive,

we synthesized the corresponding trifluoromethyl sulfonates. Those were further reacted either with the sodium salt of N-benzoyladenine or of 6-chloropurine (prepared *in situ* from N-benzoyladenine or 6-chloropurine and sodium hydride) or with adenine or 6-chloropurine, respectively, in the presence of caesium carbonate to give the carbocyclic nucleoside analogues **13**, **13a**, **14**, and **14a** in 37–50% yield as shown in Scheme 2. Further transformation of **13a** and **14a** with methanol/NH_3 can be accomplished by methods given in the literature [7]. Deprotection of **13** and **14** using standard condition [15] afforded (±)-aristeromycin (**15**) and its (±)-5′-*homo*-analogue (**17**), their analytical data being fully in accordance with the literature [9, 16].



Scheme 2. Reagents and condition: (1) (i) $(CF_3SO_2)_2O$/*pyr*/CH_2Cl_2/−70°C, (ii) N-benzoyladenine or 6-chloropurine, resp./NaH/*DMF*/r.t. or adenine/Cs_2CO_3/80°C; (m) 1 *N* HCl/70°C: (n) CH_3ONa/methanol/reflux; all compounds are recemic, only one enantiomer is shown

Experimental

Melting points were determined on a Tottoli apparatus (Büchi 530) and are uncorrected. Chromatographic separations were performed on silica gel 60 (230–400 mesh, Merck). NMR spectra were recorded on a Bruker MSL 300 spectrometer (^{1}H: 300.13 MHz, ^{13}C: 75.47 MHz); chemical shifts are given in ppm relative to internal *TMS*. For numbering of the carbon and hydrogen atoms, the molecule is considered to be a carbohydrate derivative where the methylene group is numbered 4a instead of oxygen [18]. The elemental analyses were performed at the Institute of Organic Chemistry, University of Graz.

Methyl 5-deoxy-2,3-O-isopropylidenecarba-β-DL-riburonolactone (**1a**)

2.93 ml (41.3 mmol) of dimethyl sulfoxide in 80 ml of dry dichloromethane are added carefully to a cooled solution (−70°C) of 3.3 ml (38 mmol) of oxalyl chloride in 80 ml of dry dichloromethane within 30 min under N_2. After addition of 7.32 g (31.8 mmol) of **2** in 20 ml dry dichloromethane at −70°C and stirring for 15 min, the reaction mixture is quenched with 14.0 ml (100 mmol) of dry triethylamine and allowed to warm up to room temperature. Water (50 ml) is added, and after separation of the two phases the organic layer is washed with 1 *N* HCl (100 ml) and saturated $NaHCO_3$ (20 ml) and dried (Na_2SO_4). Evaporation to dryness and flash chromatography (hexane/ethyl acetate 4/1 v/v) yields 6.53 g (90%) of **1a** as a colourless oil.

^{1}H NMR ($CDCl_3$): δ = 1.28 and 1.37 (s, 3H each, CH_3), 2.06 (d, 1H, J = 17.8 Hz, H-4a), 2.46 (dd, 2H, J_1 = 6.5 Hz, J_2 = 2.2 Hz, H-5), 2.69 (m, 1H, H-4), 2.79 (dd, 1H, J_1 = 17.8 Hz, J_2 = 9.5 Hz, H-4a), 3.62 (s, 3H, CH_3O), 4.31 (d, 1H, J = 5.4 Hz, H-2), 4.54 (d, 1H, J = 5.4 Hz, H-3); ^{13}C NMR ($CDCl_3$): δ = 24.8 and 26.8 (CH_3), 33.9 (C-4a), 37.4 (C-5), 39.7 (C-4), 51.9 (CH_3O), 78.8 (C-2), 82.0 (C-3), 112.2 ($Me_2C<$), MeOCO, 212.8 (C-1); $C_{11}H_{16}O_5$ (228.25); calcd.: C 57.89, H 7.07; found: C 58.07, H 6.87.

Methyl 5-deoxy-2,3-O-isopropylidenecarba-β-DL-ribo-hexafuranuronate (**2**)

A solution of 4.24 g (75.7 mmol) of KOH in 100 ml of CH_3OH is added to 19.7 g (72.2 mmol) of **1** in 100 ml of tetrahydrofuran and stirred for 40 min at room temperature. The reaction mixture is adjusted to *pH*6.0 with 2 *N* HCl, and the methanol is removed under reduced pressure at 40°C bath temperature. Extraction of the residue with dichloromethane (3 × 100 ml), drying (Na_2SO_4), and evaporation to dryness yields 12.6 g (75%) of **2** as a colourless oil.

^{1}H NMR ($CDCl_3$): δ = 1.28 and 1.43 (s, 3H each, CH_3), 1.60 (m, 1H, H-4a), 2.1–2.8 (m, 5H, H-4a, H-4, H-5, OH), 3.70 (s, 3H, CH_3O), 4.20 (m, 1H, H-1), 4.46 (s, 2H, H-2, H-3); ^{13}C NMR ($CDCl_3$): δ = 24.3 and 26.7 (CH_3), 36.7 (C-4a), 38.2 (C-5), 41.4 (C-4), 51.7 (CH_3O), 77.4 (C-1), 85.2 (C-2), 87.4 (C-3), 110.9 ($Me_2C<$), 173.4 (MeOCO); $C_{11}H_{18}O_5$ (230.26); calcd.: C 57.38, H 7.88; found: C 58.07, H 7.97.

Methyl 5-deoxy-2,3-O-isopropylidenecarba-α-DL-ribo-hexafuranuronate (**3**)

To an ice-cooled solution of 6.50 g (28.5 mmol) of **1a** in 50 ml of methanol, 1.26 g (33.3 mmol) of $NaBH_4$ are added. After quantitative turnover, the reaction mixture is acidified with 1 *N* HCl, extracted with dichloromethane (3 × 100 ml), dried (Na_2SO_4), and evaporated. Flash chromatography (hexane/ethyl acetate 2/1 v/v) yields 5.64 g (86%) of **3** as a colourless oil.

^{1}H NMR ($CDCl_3$): δ = 1.33 and 1.50 (s, 3H each, CH_3), 1.66 (m, 1H, H-4a), 1.93 (m, 2H, H-4, H-4a), 2.27 (t, 2H, J = 7.3 Hz, H-5), 2.49 (m, 2H, H-4, OH), 3.63 (s, 3H, CH_3O), 4.05 (m, 1H, H-2), 4.37 (d, 1H, J = 6.0 Hz, H-1), 4.48 (t, 1H, H-3); ^{13}C NMR ($CDCl_3$): δ = 24.5 and 26.2 (CH_3), 36.52 and 36.72 (C-4a, C-5), 38.20 (C-4), 51.8 (CH_3O), 71.2 (C-1), 79.4 (C-3), 84.38 (C-2), 112.0 ($Me_2C<$), 172.4 (MeOCO); $C_{11}H_{18}O_5$ (230.26); calcd.: C 57.38, H 7.88; found: C 56.92, H 7.95.

5-Deoxy-2,3-O-isopropylidenecarba-α-DL-ribo-hexofuranose (**4**)

15.0 g (62.0 mmol) of **3** in 100 ml of diethyl ether are added to an ice-cooled suspension of 1.80 g (46.5 mmol) of $LiAlH_4$ in 100 ml of dry diethyl ether. The resulting mixture is stirred at room temperature for 20 min, refluxed for 15 min, and quenched with 7.2 ml of saturated $MgSO_4$ solution. The inorganic salts are removed by filtration, and the precipitate is extracted with dichloromethane (3 × 100 ml). Evaporation of the combined organic layers affords 10.5 g (85%) of **4** as a colourless oil.

^{1}H NMR ($CDCl_3$): δ = 1.27 and 1.46 (s, 3H each, CH_3), 1.5–1.9 (m, 3H), 2.0–2.5 (m, 3H and 1H D_2O exchangeable), 3.74 (t, 2H, C*H*$_2$OH), 4.20 (m, 1H, C*H*OH), 4.5 (s, 2H, O–CH–CH–O); ^{13}C NMR ($CDCl_3$): δ = 24.5 and 26.2 (CH_3), 35.3 (C-4a), 37.4 (C-5), 38.7 (C-4), 61.2 (C-6), 71.0 (C-1), 79.6 (C-2), 85.3 (C-3), 112.3 ($Me_2C<$); $C_{10}H_{18}O_4$ (202.25); calcd.: C 59.39, H 8.97; found: C 58.89, H 9.06.

6-O-tert-Butyldimethylsilyl-5-deoxy-2,3-O-isopropylidenecarba-α-DL-ribo-hexofuranose (**5**)

A solution of 9.60 g (47.5 mmol) of **4**, 6.70 ml (48.1 mmol) of triethylamine, and 7.25 g (48.1 mmol) of *tert*-butyldimethylsilyl chloride in 100 ml of dichloromethane is stirred at room temperature

overnight. After washing with 0.1 *N* HCl and saturated $NaHCO_3$ solution, the organic layer is dried (Na_2SO_4) and evaporated to dryness to yield 14.3 g (95%) of **5** as a colourless oil.

^1H NMR ($CDCl_3$): $\delta = 0.02$ (s, 6H, CH_3Si), 0.87 (s, 9H, *t*-Bu–Si), 1.25 (bs, 1H, OH), 1.32 (s, 3H, CH_3), 1.41 (m, 1H), 1.47 (s, 3H, CH_3), 1.69 (m, 1H), 1.85 (m, 1H), 2.12 (m, 1H), 2.48 (m, 1H), 3.63 (m, 2H, 2× H-5), 4.05 (m, 1H, H-1), 4.38 and 4.45 (m, 1H each, H-2 and H-3); ^{13}C NMR ($CDCl_3$): $\delta = -5.2$ (CH_3Si), 18.8 (Me_3CSi), 24.5 ($CH_3C<$), 26.1 (CH_3CSi), 26.2 ($CH_3C<$), 35.5, 36.9, and 38.4 (C-4, C-4a, C-6), 61.8 (C-6), 71.4 (C-1), 79.2 (C-3), 85.3 (C-2), 111.6 ($Me_2C<$); $C_{16}H_{32}O_4Si$ (316.51); calcd.: C 60.72, H 10.19; found: C 60.34, H 10.04.

1-O-Benzyl-5-deoxy-2,3-O-isopropylidenecarba-β-DL-ribo-hexofuranuronic acid (**6**)

A mixture of 6.87 g (25.2 mmol) of **1** and 14.1 g (252 mmol) of KOH in 120 ml of 1,4-dioxane is refluxed for 1 h. After careful addition of 15.0 ml (126 mmol) of benzyl bromide, refluxing is continued overnight. Water (50 ml) is added, and the reaction mixture is washed with diethyl ether (3 × 100 ml) to remove benzyl alcohol and dibenzyl ether. The aqueous layer is acidified with HCl conc. (*pH*1) and extracted with diethyl ether (3 × 100 ml). The organic extracts are dried (Na_2SO_4) and evaporated to give 6.04 g (78%) of **6** as a slightly red oil.

^1H NMR ($CDCl_3$): $\delta = 1.32$ and 1.46 (s, 3H each, CH_3), 1.74 (d, 1H, $J = 14.0$ Hz, H-4a), 2.27 (dt, 1H, $J_1 = 13.0$ Hz, $J_2 = 6.9$ Hz, H-4a), 2.48–2.66 (m, 3H, H-4, H-5), 3.96 (t, 1H, $J = 3.8$ Hz, H-1), 4.50 (d, 1H, $J = 5.9$ Hz, H-2), 4.56 (d, 2H, $J = 2.4$ Hz, $PhCH_2$), 7.34 (m, 5H, Ph–H); ^{13}C NMR ($CDCl_3$): $\delta = 24.5$ and 26.9 (CH_3), 30.6 (C-4a), 37.9 (C-5), 41.3 (C-4), 71.4 ($PhCH_2$), 84.7 (C-1), 85.1 and 85.2 (C-2, C-3), 111.1 ($Me_2C<$), 127.8 and 128.6 (Ph–C), 178.3 (COO); $C_{17}H_{22}O_5$ (306.36); calcd.: C 66.65, H 7.24; found: C 66.20, H 7.32.

Benzyl 5-deoxy-5-iodo-2,3-O-isopropylidenecarba-β-DL-ribo-furanoside (**7**)

A solution of 1.00 g (3.33 mmol) of **6**, 0.57 g (2.3 mmol) of I_2, and 0.72 g (2.3 mmol) of iodosobenzene diacetate (*IBDA*) in 100 ml of cyclohexane is refluxed and irradiated with two 150 W photo lamps for 1 h. After addition of a second crop of I_2 (0.57 g, 2.3 mmol) of *IBDA* (0.72 g, 2.3 mmol), refluxing and irradiation is continued for an additional hour. The reaction mixture is extracted with aqueous $Na_2S_2O_3$ (1 *N*) and saturated $NaHCO_3$ solution (30 ml each), dried (Na_2SO_4), and evaporated to dryness. Purification of the residue on a silica gel column (cyclohexane/ethyl acetate 9/1 v/v) affords 1.15 g (91%) of **7** as a colourless oil.

^{13}C NMR ($CDCl_3$): $\delta = 9.9$ (C-5), 24.5 and 26.9 (CH_3), 35.5 (C-4a), 48.4 (C-4), 71.5 ($PhCH_2$), 84.3, 84.8, and 84.9 (C-1, C-2, C-3), 111.1 ($Me_2C<$), 127.8 and 128.6 (Ph-C); $C_{16}H_{21}IO_3$ (388.25); calcd.: C 49.50, H 5.45, I 32.69; found: C 49.21, H 5.27, I 31.87.

Benzyl 5-O-acetyl-2,3-O-isopropylidenecarba-β-DL-ribo-furanoside (**8**)

A mixture of 3.8 g (9.8 mmol) of **7** and 4.0 g (21 mmol) of CsOAc in 100 ml of dry N,N-dimethyl formamide is stirred vigorously at room temperature for 72 h. After addition of 250 ml of dichloromethane, the solution is washed with water (2 × 100 ml), dried (Na_2SO_4), and evaporated to dryness to yield 3.0 g (96%) of **8** as a colourless oil after flash chromatography (cyclohexane/ethyl acetate 5/1 v/v).

^1H NMR ($CDCl_3$): $\delta = 1.32$ and 1.47 (s, 3H each, CH_3), 1.72 (dt, 1H, $J_1 = 14.0$ Hz, $J_2 = 3.4$ Hz, H-4a), 2.08 (s, 3H, CH_3CO), 2.21 (ddd, 1H, $J_1 = 14$ Hz, $J_2 = 7.8$ Hz, $J_3 = 5.5$ Hz, H-4a), 2.42 (m, 1H, H-4), 3.94 (t, 1H, $J = 4.2$ Hz, H-1), 4.12 (dd, 2H, $J_1 = 6.5$ Hz, $J_2 = 4.6$ Hz, H-5), 4.54 (d, 2H, $J = 6.1$ Hz, $PhCH_2$), 4.59 (m, 2H, H-2, H-3), 7.33 (s, 5H, Ph-H); ^{13}C NMR ($CDCl_3$): $\delta = 21.1$ (CH_3CO), 24.5 and 26.9 (CH_3), 32.1 (C-4a), 44.7 (C-4), 65.8 (C-5), 71.4 ($PhCH_2$), 82.7 (C-1), 83.4 and 84.1 (C-2 and C-3), 111.1 ($Me_2C<$), 127.7 and 128.6 (Ph-C), 171.1 (MeCO); $C_{18}H_{24}O_5$ (320.39); calcd.: C 67.48, H 7.55; found: C 67.78, H 7.44.

5-O-Acetyl-2,3-O-isopropylidenecarba-β-DL-ribo-furanose (**9**)

A solution of 0.44 g (1.38 mmol) of **8** in 10 ml of methanol is hydrogenated at 60 psi with 50 mg of Pd-C (10%) at room temperature. After removal of the catalyst by filtration, evaporation *in vacuo* yields 0.32 g (100%) of **9** as a colourless oil.

^{1}H NMR ($CDCl_3$): $\delta = 1.29$ and 1.43 (s, 3H each, CH_3), 1.57 (d, 1H, $J = 14.0$ Hz, H-4a), 2.08 (s, 3H, CH_3CO), 2.23 (ddd, 1H, $J_1 = 5.1$ Hz, $J_2 = 8.1$ Hz, $J_3 = 14.0$ Hz, H-4a), 2.41 (m, 1H, H-4), 2.51 (bs, 1H, OH, D_2O exchangeable), 4.12 (d, 2H, $J = 7.5$ Hz, H-5), 4.23 (bs, 1H, H-1), 4.46 (d, 1H, $J = 6.1$ Hz, H-3), 4.57 (d, 1H, $J = 6.1$ Hz, H-2); ^{13}C NMR ($CDCl_3$): $\delta = 21.2$ (CH_3CO), 24.4 and 26.8 (CH_3), 34.5 (C-4a), 44.9 (C-4), 66.3 (C-5), 77.2 (C-1), 83.0 (C-3), 87.4 (C-2), 110.8 ($Me_2C<$), 171.4 (MeCO); $C_{11}H_{18}O_5$ (230.26); calcd.: C 57.38, H 7.88; found: C 57.01, H 7.96.

5-O-Acetyl-2,3-O-isopropylidenecarba-DL-ribonolactone (**10**)

0.16 ml (2.2 mmol) of dimethyl sulfoxide in 5 ml of dry dichloromethane is added drop by drop to a cooled solution (−70°C) of 0.17 ml (1.9 mmol) of oxalyl chloride in 10 ml of dry dichloromethane *via* a syringe under N_2. After 20 min, 0.32 g (1.4 mmol) of **9** are added, and the cooled solution is stirred for further 15 min. The reaction mixture is quenched with 1.40 ml (13.7 mmol) of dry triethylamine and allowed to warm up to room temperature. Water (5 ml) is added, and after separation of the two phases the organic layer is washed with 1 *N* HCl (10 ml) and saturated $NaHCO_3$ solution (5 ml), dried (Na_2SO_4), and evaporated to dryness to yield 0.29 g (95%) of **10** as a slightly yellow oil.

^{1}H NMR ($CDCl_3$): $\delta = 1.34$ and 1.43 (s, 3H each, CH_3), 2.00 (CH_3CO), 2.11 (d, 1H, $J = 18.1$ Hz, H-4a), 2.72 (m, 1H, H-4), 2.82 (dd, 1H, $J_1 = 18.1$ Hz, $J_2 = 9.4$ Hz, H-4a), 4.16 (dd, 1H, $J_1 = 5.0$ Hz, $J_2 = 3.5$ Hz, H-5), 4.24 (d, 1H, $J = 5.3$ Hz, H-2), 4.66 (d, 1H, $J = 5.3$ Hz, H-3); ^{13}C NMR ($CDCl_3$): $\delta = 20.5$ (CH_3CO), 24.6 and 26.7 (CH_3), 36.5 and 37.0 (C-4, C-4a), 65.8 (C-5), 78.6 (C-2), 80.7 (C-3), 111.9 ($Me_2C<$), 170.2 (MeCO), 211.9 (C-1); $C_{11}H_{16}O_5$ (228.25); calcd.: C 57.89, H 7.07; found: C 58.64, H 7.28.

2,3-O-Isopropylidenecarba-DL-ribonolactone (**10a**)

To a freshly prepared solution of 10 mg of sodium in 10 ml of dry methanol, 0.62 g (2.7 mmol) of **10** are added and the mixture is stirred at room temperature. After complete turnover, CO_2 is bubbled through the solution. The methanol is removed *in vacuo*, and the residue is purified by flash chromatography (chloroform/methanol 19/1 v/v) to give 0.35 g (96%) of alcohol **10a**.

^{1}H NMR ($CDCl_3$): $\delta = 1.29$ and 1.37 (s, 3H each, CH_3), 2.12 (d, 1H, $J = 18.3$ Hz, H-4a), 2.50 (m, 1H, H-4), 2.69 (dd, 1H, $J_1 = 18.3$ Hz, $J_2 = 9.1$ Hz, H-4a), 2.93 (bs, 1H, OH), 3.64 and 3.78 (dd, 1H, $J_1 = 10.2$ Hz, $J_2 = 3.3$ Hz, 2× H-5), 4.25 (d, 1H, $J = 4.8$ Hz, H-2), 4.68 (d, 1H, $J = 4.8$ Hz, H-3); ^{13}C NMR ($CDCl_3$): $\delta = 24.8$ and 26.9 (CH_3), 37.3 (C-4a), 39.0 (C-4), 64.2 (C-5), 79.1 (C-2), 81.5 (C-3), 111.4 ($Me_2C<$), 214.8 (C-1); $C_9H_{14}O_4$ (186.21); calcd.: C 58.05, H 7.58; found: C 58.07, H 7.27.

5-O-tert-Butyldimethylsilyl-2,3-O-isopropylidenecarba-DL-ribonolactone (**11**)

0.29 g (1.56 mmol) of **10a** are dissolved in 10 ml of dry dichloromethane; 0.31 g (2.0 mmol) of *tert*-butyldimethylsilyl chloride and 0.30 ml of dry triethylamine are added. The solution is kept at room temperature overnight, extracted with 0.1 *N* HCl and saturated $NaHCO_3$, dried (Na_2SO_4), and evaporated. Purification on silica gel yields 0.34 g (73%) of **11** as a colourless oil.

^{1}H NMR ($CDCl_3$): $\delta = 0.02$ and 0.04 (s, 3H each, 2× CH_3Si), 0.86 (s, 9H, *t*-Bu-Si), 1.36 and 1.44 (s, 3H each, CH_3), 2.09 (d, 1H, $J = 18.2$ Hz, H-4a), 2.51 (d, 1H, $J = 8.2$ Hz, H-4), 2.74 (dd, 1H, $J_1 = 18.2$ Hz, $J_2 = 9.0$ Hz, H-4a), 3.63 (dd, 1H, $J_1 = 9.8$ Hz, $J_2 = 3.0$ Hz, H-5), 3.82 (dd, 1H,

$J_1 = 9.8$ Hz, $J_2 = 3.0$ Hz, H-5), 4.23 (d, 1H, $J = 5.4$ Hz, H-2), 4.64 (d, 1H, $J = 5.4$ Hz, H-3); ^{13}C NMR ($CDCl_3$): $\delta = -5.50$ (CH_3Si), 18.5 (Me_3CSi), 24.9 ($CH_3C<$), 26.1 (CH_3CSi), 27.1 ($CH_3C<$), 37.5 (C-4a), 39.4 (C-4), 65.6 (C-5), 79.3 (C-2), 82.2 (C-3), 83.3 (C-2), 111.3 ($Me_2C<$), 212.9 (C-1); $C_{15}H_{28}O_4Si$ (300.47); calcd.: C 59.96, H 9.39; found: C 59.88, H 9.47.

5-O-tert-Butyldimethylsilyl-2,3-O-isopropylidenecarba-α-DL-ribo-furanose (**12**)

38 mg (1.0 mmol) of $NaBH_4$ are added to an ice-cooled solution of 200 mg (1.5 mmol) of **11** in 5 ml of methanol. The reaction mixture is acidified with 1 *N* HCl, extracted with dichloromethane (3 × 15 ml), dried (Na_2SO_4), and evaporated. Purification on silica gel (hexane/ethyl acetate 2/1 v/v) affords 200 mg (100%) of **12** as a colourless oil.

^{1}H NMR ($CDCl_3$): $\delta = 0.03$ (s, 3H each, CH_3Si), 0.89 (s, 9H, *t*-Bu-Si), 1.35 and 1.49 (s, 3H each, CH_3), 1.85 (m, 2H, H-4a), 2.19 (t, 1H, $J = 5.0$ Hz, H-4), 2.47 (d, 1H, $J = 8.5$ Hz, OH), 3.48 (dd, 1H, $J_1 = 4.7$ Hz, $J_2 = 10.0$ Hz, H-5), 3.60 (dd, 1H, $J_1 = 4.7$ Hz, $J_2 = 10.0$ Hz, H-5), 4.20 (dt, 1H, $J_1 = 13.4$ Hz, $J_2 = 2.0$ Hz, H-1), 4.46 (m, 2H, H-2, H-3); ^{13}C NMR ($CDCl_3$): $\delta = -5.28$ (CH_3Si), 18.5 (Me_3CSi), 24.6 ($CH_3C<$), 26.2 (CH_3CSi), 26.5 ($CH_3C<$), 36.0 (C-4a), 44.3 (C-4), 64.9 (C-5), 72.2 (C-1), 80.1 (C-3), 83.3 (C-2), 111.3 ($Me_2C<$); $C_{15}H_{30}O_4Si$ (302.49); calcd.: C 59.56, H 10.00; found: C 59.04, H 9.71.

General Procedures for the Introduction of Aglycons

To a cooled (−20°C) solution of 5.84 g (19.3 mmol) of **12** or 6.12 g (19.3 mmol) of **5** and 1.9 ml (23.2 mmol) of pyridine in 50 ml of dichloromethane, 3.4 ml (20 mmol) of trifluoromethanesulfonic anhydride in 10 ml of dichloromethane are added. After 5 min, the reaction mixture is extracted with 0.5 *N* HCl and aq. $NaHCO_3$ (50 ml each) and washed with water (2 × 50 ml). The combined organic layers are dried (Na_2SO_4) and evaporated at room temperature to yield the corresponding triflates.

Method A

To a suspension of 38.7 mmol of the heterocyclic base in 100 ml of N,N-dimethyl formamide, 1.06 g (39 mmol) of sodium hydride (80% dispersion in mineral oil) are added. The trifluoromethanesulfonic esters of **5** or **12** are added, and the resulting solution is stirred at 50°C for 48 h. After quenching with acetic acid, water is added until dissolution is obtained, and the reaction mixture is extracted with dichloromethane (3 × 150 ml). The combined organic layers are dried (Na_2SO_4), evaporated, and purified on silica gel (chloroform/methanol 19/1 v/v).

Method B

A mixture of the sulfonic ester of **5** or **12** (19 mmol), the heterocyclic base (39 mmol), and caesium carbonate (39 mmol) in 100 ml of N,N-dimethyl formamide is stirred at 40°C for 48 h. After addition of water (200 ml), the reaction mixture is extracted with dichloromethane (3 × 200 ml). Drying, evaporation *in vacuo*, and purification on silica gel (chloroform/methanol 19/1 v/v) yields the protected nucleoside analogues.

9-(5-O-tert-Butyldimethylsilyl-2,3-O-isopropylidenecarba-β-DL-ribo-furanosyl)adenine (**13**)

Method B; 3.56 g (44%); colourless oil; ^{1}H NMR ($CDCl_3$): $\delta = 0.08$ (s, 3H each, CH_3Si), 0.91 (s, 9H, *t*-Bu-Si), 1.31 and 1.57 (s, 3H each, CH_3), 2.39 (m, 2H, H-4′a), 2.48 (dd, 1H, $J_1 = 11.2$ Hz, $J_2 = 13.8$ Hz, H-4′), 3.78 (d, 2H, H-5′), 4.66 (dd, 1H, $J_1 = 4.4$ Hz, $J_2 = 7.0$ Hz, H-3′), 4.85 (dt, 1H,

$J_1 = 7.3$ Hz, $J_2 = 11.4$ Hz, H-1′), 4.99 (t, 1H, $J = 6.4$ Hz, H-2′), 6.18 (bs, 2H, NH_2), 7.88 (s, 1H, H-8), 8.33 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$): $\delta = -5.18$ (CH_3Si), 18.5 (Me_3CSi), 25.5 ($CH_3C<$), 26.1 (CH_3CSi), 27.9 ($CH_3C<$), 33.8 (C-4′a), 46.1 (C-4′), 62.2 (C-5′), 63.3 (C-1′), 81.1 (C-3′), 84.1 (C-2′), 113.7 ($Me_2C<$), 120.6 (C-5), 139.7 (C-8), 150.5 (C-4), 153.0 (C-2), 156.0 (C-6); $C_{20}H_{33}N_5O_3Si$ (419.60); calcd.: C 57.25, H 7.93, N 16.69; found: C 57.34, H 7.81, N 16.32.

9-(5-O-tert-Butyldimethylsilyl-2,3-O-isopropylidenecarba-β-DL-ribo-furanosyl)-6-chloro-9H-purine (**13a**)

Method A: 4.07 g (48%); method B: 3.14 g (37%); colourless oil; ^{1}H NMR ($CDCl_3$): $\delta = 0.07$ (s, 3H each, CH_3Si), 0.91 (s, 9H, *t*-Bu-Si), 1.30 and 1.56 (s, 3H each, CH_3), 2.41 (m, 2H, H-4′a), 2.56 (dd, 1H, $J_1 = 11.6$ Hz, $J_2 = 4.4$ Hz, H-4′), 3.77 (m, 2H, H-5′), 4.69 (dd, 1H, $J_1 = 7.1$ Hz, $J_2 = 4.2$Hz, H-3′), 4.85 (dt, 1H, $J_1 = 11.5$ Hz, $J_2 = 6.2$ Hz, H-1′), 4.99 (t, 1H, $J = 5.5$ Hz, H-2′), 8.21 (s, 1H, H-8), 8.72 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$): $\delta = -5.24$ (CH_3Si), 18.46 (Me_3CSi), 25.38 ($CH_3C<$), 26.06 (CH_3CSi), 27.84 ($CH_3C<$), 33.21 (C-4′a), 45.76 (C-4′), 62.95 (C-5′), 63.04 (C-1′), 80.96 (C-3′), 83.95 (C-2′), 113.88 ($Me_2C<$), 132.56 (C-5), 144.53 (C-8), 151.45 (C-4), 151.91 (C-2), 152.06 (C-6); $C_{20}H_{31}ClN_4O_3Si$ (439.03); calcd.: C 54.72, H 7.12, N 12.76; found: C 54.61, H 6.94, N 12.21.

6-Benzoyl-9-(5-O-tert-butyldimethylsilyl-2,3-O-isopropylidenecarba-β-DL-ribo-furanosyl)adenine (**14**)

Method A; 5.19g (50%); colourless oil; ^{1}H NMR ($CDCl_3$): $\delta = -0.03$ and 0.01 (s, 3H each, CH_3Si), 0.83 (s, 9H, *t*-Bu-Si), 1.24 and 1.49 (s, 3H each, CH_3), 1.66 (m, 1H, H-5), 1.81 (s, 1H, H-5′), 2.25 (m, 2H, H-4′, H-4′a), 2.43 (m, 1H, H-4′a), 3.66 (t, 2H, $J = 6.3$ Hz, H-6′), 4.47 (dd, 1H, $J_1 = 7.2$ Hz, $J_2 = 5.1$ Hz, H-3′), 4.72 (m, 1H, H-1′), 5.00 (dd, 1H, $J_1 = 7.2$ Hz, $J_2 = 5.1$ Hz, H-2′), 7.36, 7.46, and 7.94 (m, 5H, Ph-H), 7.98 (s, 1H, H-8), 8.64 (s, 1H, H-2), 9.77 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): $\delta = -5.27$ (CH_3Si), 18.3 (Me_3CSi), 25.25 ($CH_3C<$), 25.98 (CH_3CSi), 27.6 ($CH_3C<$), 36.5 and 36.9 (C-4′a, C-5′), 41.1 (C-4′), 61.4 (C-6′), 62.2 (C-1′), 83.4 and 84.7 (C-2′, C-3′), 113.9 ($Me_2C<$), 124.1 (C-5), 128.1 and 128.7 (Ph-C), 132.6 (C-8), 133.9 (C-4), 142.5 (*ipso*-Ph), 149.8 (C-6), 152.2 (C-2), 165.1 (PhCONH); $C_{28}H_{39}N_5O_4Si$ (537.73); calcd.: C 62.54, H 7.31, N 13.02; found: C 61.27, H 7.54, N 11.93.

9-(5-O-tert-Butyldimethylsilyl-2,3-O-isopropylidenecarba-β-DL-ribo-furanosyl)-6-chloro-9H-purine (**14a**)

Method A; 4.20 g (48%); white crystals; m.p.: 168–171°C; ^{1}H NMR ($CDCl_3$): $\delta = 0.07$ (s, 2× 3H, CH_3Si), 0.89 (s, 9H, *t*-Bu-Si), 1.22 and 1.36 (s, 3H each, CH_3), 1.32 (m, 1H, H-5′), 1.62 (m, 1H, H-5′), 1.97 (m, 1H, H-4′), 2.21 (m, 2H, H-4′a), 3.66 (t, 2H, H-6′), 4.50 and 4.92 (m, 2H, H-1′, H-3′), 5.46 (dt, 1H, H-2′), 8.38 and 8.50 (s, 1H each, H-2 and H-6); $C_{21}H_{33}ClN_4O_3Si$ (453.06); calcd.: C 55.67, H 7.34, N 12.37; found: C 55.72, H 7.16, N 12.31.

(±)-Aristeromycin (**15**)

A solution of 2.94 g (7.0 mmol) of **13** and 5.9 g (23 mmol) of Bu_4NF in 100 ml of tetrahydrofuran is stirred at room temperature for 2 h. The solvent is removed *in vacuo*, and the residue is purified on a silica gel column (chloroform/methanol 19/1 v/v) to give 1.64 g of the intermediate alcohol. This compound is treated with 50 ml 1 *N* HCl at 70°C for 30 min. The solution is neutralized with a strong alkali anion exchange resin and evaporated after filtration. Purification of the gummy residue by crystallization from methanol affords 0.93 g (47%) of **15** as white crystals. Analytical data are in accordance with the literature [16].

6-Benzoyl-9-(5-deoxy-2,3-O-isopropylidenecarba-β-DL-ribo-hexofuranosyl)adenine (**16**)

3.83 g (7.1 mmol) of **14** are treated in the same manner as described above for the preparation of **15** to give 1.47 g (54%) of **16** as a colourless oil.

^{1}H NMR ($CDCl_3$): $\delta = 1.19$ and 1.32 (s, 3H each, CH_3), 1.32–1.62 (m, 2H, H-4a′), 1.97 (m, 1H, H-4′), 2.21 (m, 2H, H-3′), 3.43 (s, 1H, OH), 3.48 (dt, 2H, H-6′), 4.43 (m, 1H, H-2′), 4.88 (m, 2H, H-3′), 5.42 (dt, 1H, H-1′), 7.97 (s, 1H, H-8), 9.77 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): $\delta = 25.75$ and 26.30 (CH_3), 35.13 (C-4′), 37.20 (C-5′), 59.37 (C-6′), 75.47, 77.85, and 84.61 (C-1′, C-2′, C-3′), 110.69 ($Me_2C<$), 124.91 (C-5), 128.55, 128.68, and 142.52 (Ph-C), 132.58 (C-8), 133.95 (C-4), 149.84 (C-6), 152.23 (C-2), 165.14 (CO); $C_{19}H_{21}N_5O_4$ (383.41); calcd.: C 59.52, H 5.52, N 18.27; found: C 58.82, H 5.68, N 17.68.

(±)-5′-homo-Aristeromycin (**17**)

1.20 g (3.1 mmol) of **16** are treated with a freshly prepared solution of 0.1 g of sodium in 20 ml of methanol. The resulting solution is refluxed for 6 h and neutralized with a weakly acidic exchange resin (Amberlite IRC-84). Filtration, evaporation, and flash chromatography on silica gel (chloroform/methanol 3/1 v/v) yields 0.64 g (74%) of **17** as a colourless foam, the analytical data being in accordance with the literature [9].

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