The Synthesis of Both Diastereomers of 5′-Methylhomoaristeromycin

Wei Ye and Stewart W. Schneller

Molette Laboratory for Drug Discovery, Department of Chemistry and Biochemistry, Auburn University, Auburn, Alabama

ABSTRACT
The preparation of the C-5′ diastereomers of 5′-homoaristeromycin has been achieved in 6 steps beginning with readily available (3aR,6aR)-2,2-dimethyl-2H,3aH,4H,6aH-cyclopenta[1,3]dioxol-4-one in a Michael reaction employing chiral Evans N-acyloxazolidinones that served to direct the requisite side chain stereochemistry. The two targets were evaluated against a battery of viruses and found to possess activity only towards yellow fever. Both compounds were non-cytotoxic.

INTRODUCTION
The broad-spectrum biological properties of aristeromycin (1) have been limited by its toxicity due to 5′-nucleotide formation. Several structural analogues of 1 have been investigated to either shift the C-5′ hydroxyl from its loci of phosphorylation or to sterically crowd the C-5′ site to retard phosphorylation. 5′-Noraristeromycin...
(2) and modifications of it\textsuperscript{[2]} and 5′-homoaristeromycin (3)\textsuperscript{[3]} represent the first category while 5′-methylaristeromycin (4 and 5)\textsuperscript{[4]} fall into the latter group (Figure 1). All of these variations have produced favorable outcomes for limiting the toxicity of the aristeromycin framework.

Drawing on the results for 3 and 4/5 we sought a synthetic means to the diastereomers of 5′-methylhomoaristeromycin (6 and 7) that could be adaptable to other 5′-alkylhomoaristeromycins. The results of this pursuit are described here.

**Chemistry**

Many of our studies in seeking carbocyclic nucleosides have called upon the cyclopentenone 8\textsuperscript{[5]} as the desirable and common starting point for numerous analogues. Hence, it was envisioned as a component precursor to 6 and 7.

With this in mind, we were attracted to the 1991 report of Evans and co-workers who described\textsuperscript{[6]} the stereoselective Michael reactions between the chlorotitanium enolates of chiral N-acyloxazolidinones with electrophilic alkenes that proceeded in excellent yields and stereoselectivity. An exception was the reaction with cyclohexenone that showed no diastereo-preference (d.e. = 56:44).

For the purposes of this research, we believed the bicyclic structure of 8 would bring steric hindrance control (Figure 2) that would direct the N-acyloxazolidinone enolate in such a way that the desired stereoselectivity of the two incipient chiral carbons could be expected (α-side chain methyl; β-cyclopentyl link).\textsuperscript{[7]} Thus, treating 9\textsuperscript{[6]} (Scheme 1) with titanium tetrachloride in the presence of diisopropylethylamine formed the Z-titanium enolate.\textsuperscript{[8]} This was followed by addition of 8 to provide 10 (Scheme 1) with 99% d.e. An X-ray of structure 10 confirmed its stereochemistry.

Lithium borohydride in methanol\textsuperscript{[9]} was next employed (Scheme 2) to convert 10 into 11 and its epimer 12 (ca. 5:1 by \textsuperscript{1}H NMR). Without separation, this mixture was subjected to treatment with t-butyldimethylsilyl chloride to provide selective protection of the side chain primary alcohol to 13. At this point, 13 was separated from its C-1 epimer 14 (Scheme 2). Mitsunobu coupling of 13 with 6-chloropurine provided 15, which was, in turn, converted to 16 in methanolic ammonia. The desired

![Figure 1. Selected carbocyclic nucleosides and target compounds.](image-url)
product (5′R)-5′-methylhomoaristeromycin (6) was achieved by treating 16 with 1N HCl to simultaneously remove the isopropylidene and silyl protecting groups.

The synthesis of (5′S)-5′-methylhomoaristeromycin (Scheme 3, 7) followed a similar pathway by replacing 9 with its diastereomer 17.[10]

**Antiviral results**

To gain some measure of the biological potential of 6 and 7, they were subjected to an antiviral assay.[11] No activity was found when these compounds were evaluated
against herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2), cytomegalovirus (CMV), varicella zoster virus (VZV), Epstein-Barr virus (EBV), vaccinia virus (VV), cowpox virus (CV), adenovirus type 1, measles, parainfluenza type 3 virus, yellow fever, respiratory syncytial virus (RSV), rhinovirus, influenza A and B, Venezuelan equine encephalitis (VEE), West Nile virus and Punta Toro virus. However, mild activity was found towards yellow fever (for 6, EC$_{50}$ = 18 μg/mL, CC$_{50}$ > 100 μg/mL, SI > 5.6; for 7, EC$_{50}$ = 80 μg/mL, CC$_{50}$ > 100 μg/mL, SI > 1.25). These results are similar to those for 4 and 5.[4] Neither of the compounds showed toxicity towards the host cells.[11]

**Conclusion**

By adding an α-face stereo blocking element (that is, isopropylidene) in the form of 8 it has been possible to achieve Si face and β-face diastereoselectivity with the Evans chlorotitanium enolates of chiral N-acyloxazolidinones at the start of the synthesis of 6 and 7. This scheme also opens a means to other C-5′ substituted alkyl aristeromycin targets. It can be expected that such compounds will have much reduced toxicity compared to aristeromycin and render this structural prototype available to expanded biological studies.

**Experimental**

$^1$H and $^{13}$C NMR spectra were measured on a Bruker AV-400 spectrometer or Bruker AC-250 spectrometer. $^1$H chemical shifts are reported relative to CDCl$_3$ at δ 7.27 ppm (or MeOD at δ 3.51 ppm or DMSO-d$_6$ at δ 2.51 ppm) and tetramethylsilane as an internal standard. $^{13}$C chemical shifts are reported relative to CDCl$_3$/MeOD/DMSO-d$_6$. The spin multiplicities are indicated by the symbols s.
NUCLEOSIDES, NUCLEOTIDES AND NUCLEIC ACIDS

The mass spectral data was determined using a Waters Micromass Q-TOF Premier Mass Spectrometer. Reactions were monitored by thin layer chromatography (TLC) using 0.25 mm E. Merck silica gel 60-F254 precoated silica gel plates with visualization by irradiation with a Mineral light UVGL-25 lamp or exposure to iodine vapor. Column chromatography was performed on Whatman silica gel (average particle size 5–25 mm, 60 Å) and elution with the indicated solvent system. Yields refer to chromatographically and spectroscopically (1H and 13C NMR) homogeneous materials. The reactions were generally carried out in an N2.

(2R, 3R, 4R)-4-[(1′R)-1′-((4″S)-4″-Benzyl-2″-oxo-3″-oxazolidinyl)carbonyl-ethyl]-2,3-O-isopropylidene cyclopentone (10). Titanium tetrachloride (2.48 mL, 22.6 mmol) was added dropwise to 9 (5.0 g, 21.4 mmol) in anhydrous CH2Cl2 (200 mL) at −10°C under N2 to give a yellow slurry. After 2 min, diisopropylethylamine (4.11 mL, 23.5 mmol) was added dropwise and the resulting deep red solution was stirred at −5°C for 30 min. The reaction mixture was cooled to −7°C and 8 (3.0 g, 19.5 mmol) in CH2Cl2 (20 mL) was added. The reaction was kept at −30°C for 3 h and quenched with saturated ammonia chloride solution. This aqueous solution was extracted with CH2Cl2 (2 × 30 mL) and the combined organic phases were washed with brine, dried (MgSO4) evaporated under reduced pressure. Initial purification was conducted by column chromatography (hexanes/EtOAc, 5:1) to afford 4.90 g of product. Recrystallization of this material from hexanes/EtOAc gave pure 10 as white crystals (3.03 g, 45%): 1H NMR (250 MHz, CDCl3) δ 7.34–7.18 (m, 5H), 4.79 (d, J = 5.7 Hz, 1H), 4.67–4.61 (m, 1H), 4.47 (d, J = 5.6 Hz, 1H), 4.24–4.15 (m, 2H), 3.95 (t, J = 6.5 Hz, 1H), 3.22 (d, J = 11.0 Hz, 1H), 2.85–2.66 (m, 3H), 2.14 (d, J = 18.7 Hz, 1H), 1.43 (s, 3H), 1.39 (s, 3H), 1.24 (d, J = 18.7 Hz, 3H); 13C NMR (62.9 MHz, CDCl3) δ 212.1, 175.2, 152.8, 135.0, 129.1, 128.7, 111.6, 80.0, 78.7, 66.1, 55.2, 41.0, 40.0, 38.0, 37.6, 26.5, 24.4, 14.8. Anal. calcd. for C21H25NO6: C, 65.10; H, 6.50; N, 3.62. Found: C, 64.88; H, 6.51; N, 3.65.

9-[(1′R,2′S,3′R,4′S)-2′,3′-O-Isopropylidene-4′-(1R)-2-tert-butyldimethylsilyl-oxysopropyl)cyclopent-1′-yl]adenine (16). To a solution of 10 (1.00 g, 2.58 mmol) and MeOH (0.22 mL, 5.42 mmol) in THF (60 mL) at 0°C was slowly added a 2.0 M solution of lithium boron hydride in THF (2.71 mL, 5.42 mmol). After stirring 1 h at 0°C, the reaction was quenched by the addition of 1.0 M aqueous sodium potassium tartrate (10 mL). The reaction mixture was allowed to warm to room temperature and then stirred for an additional 30 min. The resulting cloudy white suspension was diluted with CH2Cl2 and the aqueous portion recovered. This aqueous layer was extracted with CH2Cl2 (2 × 30 mL) and the combined organic layers were washed with brine and dried (Na2SO4). The filtrate was evaporated under reduced pressure to afford 11 and epimer 12 (1H NMR). This mixture was used directly in the next step.

To a solution of 11 and 12 in CH2Cl2 (50 mL) was added imidazole (270 mg, 3.88 mmol) followed by t-butyldimethylsilyl chloride (408 mg, 2.72 mmol). This reaction mixture was diluted with CH2Cl2 and the organic layer was washed with H2O and brine until it was clear. After separating from the aqueous phase,
the organic layer was dried (MgSO\textsubscript{4}) and concentrated under reduced pressure to yield a residue that was subjected to column chromatography (hexanes/EtOAc, 20:1) purification to provide 400 mg of (1\text{S},2\text{S},3\text{R},4\text{R})-4-[(1\text{R})-2-tert-butyldimethylsilyloxyisopropyl]-2,3-O-isopropylidenecycl-opent-an-1-ol (13) (47%, 2 steps) as a clear liquid. \textsuperscript{1}H NMR (250 MHz, CDCl\textsubscript{3}) \(\delta\) 4.45–4.42 (m, 2H), 4.00 (m, 1H), 3.64–3.58 (m, 1H), 3.41–3.34 (m, 1H), 2.56–2.53 (m, 1H), 2.02–1.89 (m, 3H), 1.64–1.61 (m, 1H), 1.48 (s, 3H), 1.32 (s, 3H), 0.89–0.86 (m, 12H), −0.03 (s, 6H); \textsuperscript{13}C NMR (62.9 MHz, CDCl\textsubscript{3}) \(\delta\) 112.5, 84.2, 80.1, 70.7, 67.3, 44.8, 38.1, 35.8, 26.4, 26.1, 24.7, 18.4, 15.5, −5.2.

To a solution of 13 (870 mg, 3.05 mmol), PPh\textsubscript{3} (2.00 g, 7.62 mmol) and 6-chloropurine (942 mg, 6.10 mmol) in dry THF (100 mL) was added, dropwise, diisopropyl azodicarboxylate (DIAD, 1.55 g, 7.66 mmol) in THF (10 mL) at 0°C. This reaction mixture was kept at 0°C for 2 h followed by stirring at 50°C for 8 h. The solvent was removed under reduced pressure and the residue purified via column chromatography (hexanes/EtOAc, 10:1) to give 6-chloro-9-[(1′\text{R},2′\text{S},3′\text{R},4′\text{S})-2,3′-O-isopropylidenecyclo-4′-((1\text{R})-2-tert-butyldimethylsilyloxyisopropyl)cyclopent-1′-yl]-9H-purine (15) that was used without purification in the next step: \textsuperscript{1}H NMR (250 MHz, CDCl\textsubscript{3}) \(\delta\) 8.74 (s, 1H), 8.27 (s, 1H), 5.10–4.95 (m, 1H), 4.88–4.80 (m, 1H), 4.69–4.64 (m, 1H), 3.73–3.60 (m, 1H), 3.55–3.49 (m, 1H), 2.48–2.36 (m, 2H), 2.22–2.17 (m, 1H), 1.85–1.80 (m, 1H), 1.56 (s, 3H), 1.26 (s, 3H), 1.00–0.87 (m, 12H), 0.08 (s, 6H).

As a solution of 15 obtained from the last step was placed in MeOH (40 mL) saturated with NH\textsubscript{3} and this mixture heated at 110°C for 2 days in a Parr stainless steel sealed reaction vessel. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (hexanes/EtOAc, 10:1) to give 6-[(1′\text{R},2′\text{S},3′\text{R},4′\text{S})-2,3′-Dihydroxy-4′-((1\text{R})-2-hydroxyisopropyl)cyclopent-1′-yl]-adenine (6). To a solution of 16 (200 mg, 0.45 mmol) in MeOH (8 mL) was added 1 N HCl (12 mL) and this stirred at room temperature for 5 h. The reaction mixture was neutralized with Amberlite IR-67 resin. Filtration and evaporation of the filtrate followed by flash chromatography (EtOAc/MeOH/NH\textsubscript{4}OH, 8:1:0.5) afforded 6 (120 mg, 91%) as a white solid, mp >190°C (dec.); [\(\alpha\)]\textsubscript{D}\textsuperscript{23.6} = -32.68° (c 0.087, DMSO); \textsuperscript{1}H NMR (250 MHz, DMSO) \(\delta\) 8.20 (s, 1H), 8.11 (s, 1H), 7.19 (s, 2H), 4.95 (s, 1H), 4.70–4.52 (m, 3H), 4.28 (s, 1H), 3.82 (s, 1H), 3.30 (m, 1H), 3.24–3.22 (m, 1H), 2.02–1.67 (m, 4H), 0.85 (d, \(J\) = 6.3 Hz, 3H); \textsuperscript{13}C NMR (62.9 MHz, DMSO) \(\delta\) 155.9, 152.1, 149.7, 140.2, 119.3, 74.3, 72.3, 65.0, 59.9, 45.4, 38.2, 28.7, 14.0. HRMS-ESI \(m/z\) 294.1561 ([(M+H\textsuperscript{+})]), C\textsubscript{13}H\textsubscript{20}N\textsubscript{5}O\textsubscript{3}, calcd 294.1566. Anal.
calcd. for C_{13}H_{19}N_{5}O_{3}\cdot 1.55H_{2}O: C, 48.60; H, 6.95; N, 21.80. Found: C, 48.89; H, 6.91; N, 21.80.

(1S,2S,3R,4R)-4-[(1S)-2-tert-Butyldimethylsilyloxyisopropyl]-2,3-O-isopropylidenecyclopentan-1-ol (20). Following the same procedure for achieving 10 but replacing 9 with 17,[10] titanium tetrachloride (2.00 mL, 18.2 mmol) and 8 (2.40 g, 15.6 mmol) afforded of (2R,3R,4R)-4-[(1′S)-1′-(4″R)-4″-benzyl-2″-oxo-3″-oxazolidinyl)carbonylethyl]-2,3-O-isopropylidenecyclopentanone (18) (3.23 g, 48%), which was then used in the next step: 1H NMR (250 MHz, CDCl₃) δ 7.37–7.20 (m, 5H), 4.67–4.62 (m, 2H), 4.35–4.32 (m, 1H), 4.23–4.13 (m, 2H), 3.94–3.88 (m, 1H), 3.31–3.24 (m, 1H), 2.83–2.72 (m, 3H), 2.33–2.27 (m, 1H), 1.45 (s, 3H), 1.35 (s, 3H), 1.26 (d, J = 14.0 Hz, 3H).

Just as with the 10 to 13 conversion, 18 (2.40 g, 6.20 mmol) and a 2.0 M solution of lithium borohydride in THF (6.5 mL, 13.0 mmol) yielded, after chromatographic purification, 19 (750 mg, 60%) that was then reacted with imidazole (380 mg, 5.46 mmol) and TBSCl (580 mg, 3.86 mmol). This gave 20 (600 mg, 53%, 2 steps) as a clear liquid: 1H NMR (250 MHz, CDCl₃) δ 4.44–4.30 (m, 2H), 4.04–3.97 (m, 1H), 3.50–3.47 (m, 1H), 3.42–3.37 (m, 1H), 2.52–2.49 (m, 1H), 2.03–1.93 (m, 3H), 1.65 (m, 1H), 1.50 (s, 3H), 1.34 (s, 3H), 0.96 (d, J = 6.6 Hz, 3H), 0.89 (s, 9H), 0.02 (s, 6H); 13C NMR (62.9 MHz, CDCl₃) δ 112.6, 84.5, 80.1, 70.9, 66.6, 45.6, 38.0, 35.9, 26.4, 26.1, 24.7, 18.5, 16.3, −5.3. Anal. calcd. for C_{17}H_{34}O_{4}Si: C, 61.77; H, 10.37. Found: C, 61.93; H, 10.37.

9-[1′R,2′S,3′R,4′R)-2′,3′-O-Isopropylidene-4′-((1S)-2-tert-butyldimethylsilyloxyisopropyl)cyclopent-1′-yl]-adenine (7). As with the preparation of 15 via 13, 20 (560 mg, 1.69 mmol), PPh₃ (1.10 g, 4.19 mmol) and 6-chloropurine (518 mg, 3.35 mmol) in dry THF (100 mL) in the presence of diisopropyl azodicarboxylate (DIAD, 0.85 g, 4.21 mmol) gave a residue, following chromatographic purification, of 21 that was carried directly forward by being placed in NH₃ saturated MeOH (40 mL) and heated at 100°C for 2 days. This resulted in 22 (500 mg, 66% from 20 in two steps) as a white solid: 1H NMR (400 MHz, CDCl₃) δ 8.29 (s, 1H), 7.83 (s, 1H), 6.55 (s, 2H), 5.04 (t, J = 6.5 Hz, 1H), 4.60–4.57 (m, 1H), 3.52–3.50 (m, 2H), 3.47–3.45 (m, 1H), 2.40–2.34 (m, 2H), 2.12–2.08 (m, 1H), 1.73–1.67 (m, 1H), 1.53 (s, 3H), 1.27 (s, 3H), 1.05 (d, J = 6.8 Hz, 3H), 0.85 (s, 9H), 0.03 (s, 6H); 13C NMR (100 MHz, CDCl₃) δ 156.1, 152.8, 150.1, 139.8, 120.5, 113.9, 83.2, 83.1, 66.5, 62.2, 46.5, 39.2, 35.5, 27.7, 26.1, 25.3, 18.4, 15.7, −5.3; Anal. calcd. for C_{22}H_{37}N_{5}O_{4}Si: C, 59.03; H, 8.33; N, 15.64. Found: C, 59.18; H, 8.43; N, 15.59.

9-[1′R,2′S,3′R,4′S)-2′,3′-Dihydroxy-4′-((1S)-2-hydroxyisopropyl)cyclopent-1′-yl]-adenine (7). Adapting the procedure for preparing 6 from 16, 22 (420 mg, 0.94 mmol) in MeOH (8 mL) with 1 N HCl (12 mL) afforded 7 (240 mg, 82%) as a white solid. Recrystallization from MeOH/H₂O afforded pure 7, mp 206–207°C; [α]D²⁴° = −39.78° (c 0.087, DMSO); 1H NMR (250 MHz, DMSO) δ 8.20 (s, 1H), 8.11 (s, 1H), 7.18 (s, 2H), 4.94 (d, J = 6.5 Hz, 1H), 4.60–4.58 (m, 2H), 4.44–4.28 (m, 2H), 3.81 (s, 1H), 3.43–3.30 (m, 1H), 3.27–3.20 (m, 1H), 2.13–2.11 (m, 1H), 1.85–1.80 (m, 2H), 1.59–1.54 (m, 1H), 0.99 (d, J = 6.69 Hz, 3H); 13C NMR (62.9MHz,
DMSO) $\delta$ 156.0, 152.0, 149.7, 140.2, 119.3, 74.1, 71.7, 64.4, 59.7, 45.9, 38.2, 30.3, 15.2. HRMS-ESI $m/z$ 294.1560 ([M+H]+), C$_{13}$H$_{20}$N$_5$O$_3$, calcd. 294.1566. Anal. calcd. for C$_{13}$H$_{19}$N$_5$O$_3$·0.2 H$_2$O: C, 52.58; H, 6.60; N, 23.59. Found: C, 52.76; H, 6.67; N, 23.43.

**X-ray data for compound 10**

Crystallographic data for 10 have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 1008603. Copies of the data can be obtained, free of charge, on request to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033 or e mail: deposit@ccdc.cam.ac.uk).

**Acknowledgments**

This research was supported by funds from Department of Health and Human Services (AI 56540). We are grateful to the Molette Fund and Auburn University for support of this research. We are also indebted to the following individuals for providing the antiviral data following their standard protocols: Dr. Eric De Clercq, the Rega Institute, Leuven, Belgium; Drs. Donald Smee and Robert Sidwell, Utah State University; Dr. Brent Korba, Georgetown University; Drs. Mark Prichard and Earl Kern, University of Alabama at Birmingham; and, other laboratories that are part of the non-clinical evaluation program funded by the National Institute of Allergy and Infectious Diseases. We appreciate the assistance of Philip M. Almond and Dr. Thomas E. Albrecht-Schmitt, Auburn University, Auburn, AL, for providing the X-ray crystallographic data.

**References**


