5'-Methyalaristeromycin and Related Derivatives

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The biological versatility of aristeromycin (carbocyclic adenosine) is limited by accompanying cytotoxicity caused ostensibly by the intracellular formation of its 5'-nucleotide derivatives. Aristeromycin derivatives that offered steric interference to this transformation at the C-5' center were sought. This paper describes the facile stereospecific synthesis, where necessary, of such C-5'-methylated aristeromycin derivatives.

S-Adenosyl-L-homocysteine hydrolase (AdoHcy hydrolase) has been recognized as an important target for inhibition in the discovery of new antiviral agents.1 Within that framework, the antiviral properties of the natural carbocyclic nucleosides aristeromycin (1) and its didehydro derivative neplanocin A (2) have been linked to their potent inhibitory effect on AdoHcy hydrolase.2 However, this antiviral potential is limited by toxicity as a result of phosphorylation of the 5' primary hydroxyl group of 1 and 2.3

In seeking ways to circumvent this undesirable transformation, the 5'-methyl epimers (3–6) offer a sterically less accessible 5'-secondary hydroxyl that could manifest in reduced or no enzymatic phosphorylation. In that regard, De Clercq and coworkers4 have found very encouraging antiviral properties for the neplanocin epimer 6 in contrast to 5. This current report adds the aristeromycin pair 3 and 4 and the tertiary alcohol 7 to the analogue collection.

Arising during this investigation was the 5'-methylene derivative 8. This compound is also included in this report since it represents a methylated derivative of 9, which Borchardt and his colleagues reported to be an inhibitor of AdoHcy hydrolase.5

The major consideration in synthesizing 5'-methylaristeromycin was, of course, control of the stereochemistry at the 5'-position. To employ conditions similar to those used for obtaining 5'-methyleneplanocin (that is, a 1,2-methyl organo-metallic addition to a protected the 5'-aldehyde precursor)6 was not an option due to the facile epimerization at the C-4' center in the requisite aristeromycin-5'-carboxaldehyde.7 Thus, an approach where the desired C-5' methyl was present prior to side chain alcohol formation led to considering the Corey–Bakshi–Shibata (CBS) reduction8 of a ketone precursor (that is, 15 shown in Scheme 1).

With that in mind, the synthesis of 3 and 4 began with the protected cyclopentenone 10 (Scheme 1) to which a 2-propenyl unit was introduced by a CuX:Li2-catalyzed Kharasch conjugate addition9 to provide 11. Luche reduction (NaBH4/CeCl3) of 11 yielded 12 and 13 (2:6:1 in 87% yield as determined by NMR). On the other hand, reduction of 11 with DIBAL gave 12 with only a trace of epimer 13 (25:1) (total yield, 89%). Mitsunobu coupling of 12 with 6-chloropurine (to 14) was


followed by treatment with OsO4 and NaIO4 to afford the desired ketone precursor 15. Unfortunately, CBS reaction of 15 with (R)-methylxazaborolidine ([R]MeCBS, structure in Scheme 2) and diethylamine—borane complex (DEANB)11 in toluene, as planned, gave a complex mixture. It was then decided to test the efficiency of the CBS reduction on a cyclopentyl unit before adding to the purine ring. This synthetic route is shown in Scheme 2. After protecting the secondary hydroxyl group of 12 with a TBS group, the 2-propenyl unit of the resultant 16 was converted to methyl ketone 17 with OsO4 and NaIO4. CBS reduction of 17 with (R)MeCBS and DEANB complex afforded 18 as the only isomer (89% yield). An X-ray single-crystal analysis of 18 was carried out to confirm its absolute configuration (see Supporting Information). The success of the CBS reduction of 17, but not with 15, suggests that the boron-mediated reduction may be limited by the basicity of the purine nitrogen atoms in the latter case.

With the enantiopure 18 in hand, protecting its hydroxyl group as an acetate (see 19) and removing the TBS group with TBAF gave the alcohol 20 in nearly quantitative yield. Coupling of 6-chloropurine with 20, under Mitsunobu conditions (to 21), followed by treatment with methanolic ammonia produced 22. The target compound (5′5′)-5′-methyleristeromycin (3) was achieved by deprotection of the isopropylidene of 22 with 1 N HCl followed by Amberlite IRA-67 resin neutralization. The epimeric CBS reagent, (S)MeCBS, was found to provide 23 from the methyl ketone precursor 17 and was used to build (5′R)-5′-methyleristeromycin (4) following the same sequence of steps used to produce 3 (Scheme 2).

The tertiary alcohol 5′,5′-dimethyleristeromycin (7) was synthesized (Scheme 1) from 15 and methylmagnesium bromide. The resultant product 28 was kept in methanolic ammonia...
solution at 110 °C for 2 days to yield 29. Treatment of 29 with 1 N HCl to remove the acetonide unit provided target 7.

Finally, preparation of the 2-propenyl analogue 8 (Scheme 1) began with ammonolysis of 14. The product of this reaction, 30, was treated with 1 N HCl solution to release the diol and afford the desired target.

Compounds 3, 4, and 7 lacked cytoxicity, as hoped, but this was accompanied by limited antiviral activity (for 8 also).12 A particularly relevant exception to this was the potently effective 4 toward yellow fever (EC50 0.32 µg/mL, CPE inhibition in Vero cell; positive drug control EC50 55 µg/mL), a flavivirus of much recent interest.13 This latter observation is under further study from both a therapeutic standpoint and to enlighten possibly subtle biochemical differences between yellow fever and other flaviviruses14−16 (for example, West Nile,14 dengue,14 and hepatitis C14b), which were unaffected by 4.

**Experimental Section**

For complete details, see the Supporting Information.

9-[(1R,2S,3R,4R)-2,3-Dihydroxy-4’-(1S)-1-hydroxyethyl)cyclopent-1’-yl]adenine (3): white solid; mp 206–208 °C; [α]23 −39.50 (c 0.01, MeOH); 1H NMR (250 MHz, DMSO) δ 8.18 (s, 1H), 8.12 (s, 1H), 7.19 (s, 2H), 4.93 (d, J = 6.6 Hz, 1H), 4.66–4.58 (m, 3H), 4.27–4.23 (m, 1H), 3.80–3.75 (m, 2H), 2.15–2.11 (m, 1H), 1.94–1.86 (m, 2H), 1.10 (d, J = 6.2 Hz, 3H); 13C NMR (62.5 MHz, DMSO) δ 156.0, 152.1, 149.8, 139.7, 120.9, 74.8, 72.0, 66.9, 59.3, 50.4, 27.2, 22.1; HRMS calcd for C15H15N2O3 [M + H]+ 280.1409, found 280.1410.

9-[(1R,2S,3R,4R)-2,3-Dihydroxy-4’-(1R)-1-hydroxyethyl)cyclopent-1’-yl]adenine (4): white solid; mp 166–168 °C; [α]23 +53.18 (c 0.18, MeOH); 1H NMR (250 MHz, DMSO) δ 8.18 (s, 1H), 8.11 (s, 1H), 7.18 (s, 2H), 4.90 (d, J = 6.9 Hz, 1H), 4.72–4.55 (m, 3H), 4.31–4.27 (m, 1H), 3.97–3.95 (m, 1H), 3.63–3.60 (m, 1H), 2.17–2.12 (m, 1H), 1.87–1.77 (m, 2H), 1.09 (d, J = 6.2 Hz, 3H); 13C NMR (62.5 MHz, DMSO) δ 156.0, 152.0, 150.0, 140.0, 119.3, 74.6, 70.4, 67.6, 59.1, 50.3, 29.3, 21.6. HRMS calcd for C17H15N2O3 [M + H]+ 280.1409, found 280.1400.

9-[(1R,2S,3R,4R)-2,3-Dihydroxy-4’-(1-hydroisopropyl)cyclopent-1’-yl]adenine (7): white solid; mp 128–130 °C; [α]23 −43.03 (c 0.13, MeOH); 1H NMR (250 MHz, DMSO) δ 8.18 (s, 1H), 8.11 (s, 1H), 7.17 (s, 2H), 4.92 (d, J = 6.9 Hz, 1H), 4.59–4.52 (m, 2H), 4.33 (s, 1H), 4.22–4.18 (m, 1H), 3.91 (s, 1H), 2.06–1.87 (m, 3H), 1.38 (s, 3H), 1.09 (s, 3H); 13C NMR (62.5 MHz, DMSO) δ 156.0, 152.0, 149.8, 139.8, 119.3, 94.4, 76.4, 69.9, 64.9, 59.2, 54.1, 28.0, 27.7. HRMS calcd for C15H19N2O3 [M + H]+ 294.1566, found 294.1558.

9-[(1R,2S,3R,4R)-2,3-Dihydroxy-4’-(2-propenyl)cyclopent-1’-yl]adenine (8): white solid; mp >196 °C dec; [α]23 −24.25 (c 0.09, MeOH); 1H NMR (250 MHz, DMSO) δ 8.21 (s, 1H), 8.11 (s, 1H), 7.19 (s, 2H), 5.00 (m, 1H), 4.86 (m, 3H), 4.78 (m, 1H), 4.67–4.62 (m, 1H), 4.30 (m, 1H), 2.16–2.07 (m, 3H), 1.80 (s, 3H); 13C NMR (62.5 MHz, DMSO) δ 156.0, 152.1, 149.6, 145.7, 140.3, 119.4, 110.3, 74.2, 72.8, 60.1, 50.3, 30.5, 21.0; HRMS calcd for C17H19N2O3 [M + H]+ 276.1460, found 276.1466.

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**Supporting Information Available:** Experimental procedures, physical properties, and spectral data for all new compounds (3, 4, 7, 8, 11–13, 15–20, 22, 23, 25, and 27–30). X-ray structural information (CIF) and ORTEP drawing for compound 18. This material is available free of charge via the Internet at http://pubs.acs.org.

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