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5′-Methylaristeromycin and Related Derivatives

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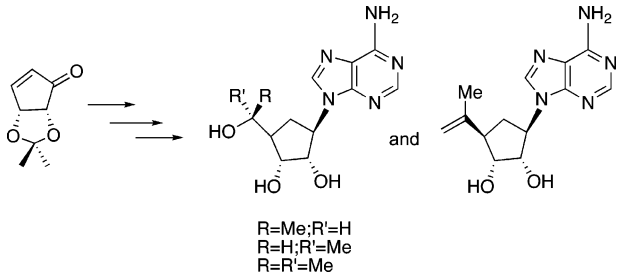


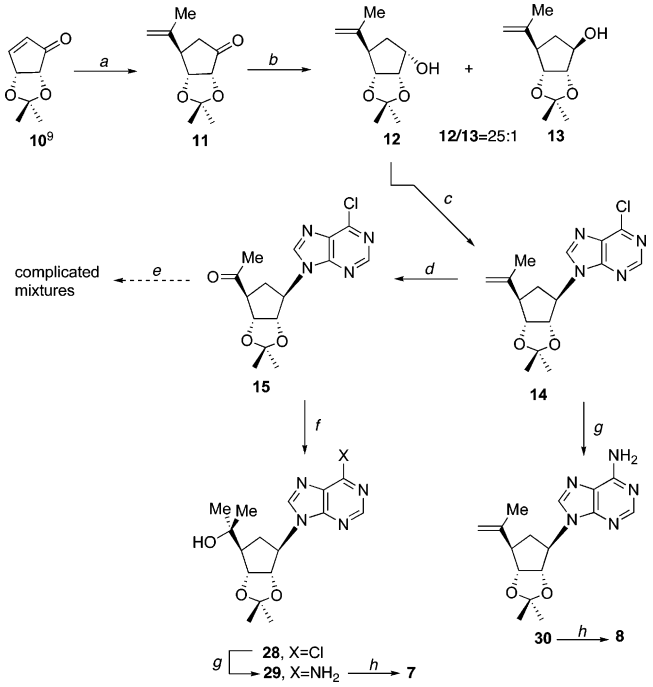
The biological versatility of aristeromycin (carbocyclic adenosine) is limited by accompanying cytotoxicity caused ostensibly by the intracellular formation of its 5′-nucleotide derivatives. Aristeromycin derivatives that offered steric interference to this transformation at the C-5′ center were sought. 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 coworkers[4] 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]

SCHEME 1[a]



[a] Reagents and conditions: (a) 2-propenylmagnesium bromide, $CuBr{\cdot}Me_2S$, LiCl, TMSCl, HMPA, THF, −20 °C, 89%; (b) DIBAL, CH_2Cl_2, −78 °C, 89%; (c) 6-chloropurine, Ph_3P, DIAD, THF, 0−50 °C; (d) OsO_4, $NaIO_4$, $MeOH/H_2O$, 0 °C to rt, 66% (two steps from **12**); (e) (*R*)MeCBS, diethylaniline borane, toluene; (f) MeMgBr, THF, 0 °C to rt, 85%; (g) NH_3, MeOH, 110 °C, 48 h, 96% (for **29**), 60% (for **30**, two steps from **12**); (h) 1 N HCl, MeOH, 90% (for **7**), 95% (for **8**).

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′-methylneplanocin (that is, a 1,2-methyl organometallic addition to a protected the 5′-aldehyde precursor)[4,6] was not an option due to the facile epimerization at the C-4′ center in the requisite aristeromycin-5′-carboxaldehye.[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) reduction[8] 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**[9] (Scheme 1) to which a 2-propenyl unit was introduced by a CuX_3Li_2-catalyzed Kharasch conjugate addition[10] to provide **11**. Luche reduction ($NaBH_4/CeCl_3$) 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

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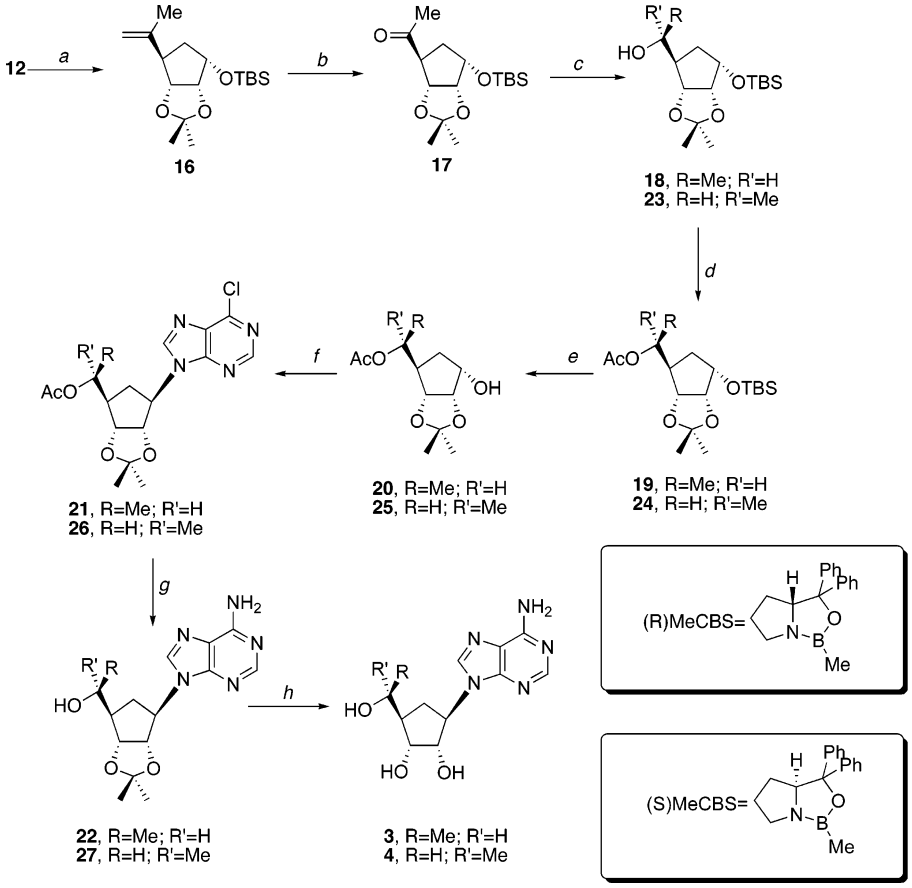
SCHEME 2[a]



[a] Reagents and conditions: (a) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 95%; (b) OsO_4, $NaIO_4$, MeOH/H_2O, 0 °C to rt, 91%; (c) for **18**, (*R*)-MeCBS, diethylaniline borane, toluene, 90%; for **23**, (*S*)MeCBS, 83%; (d) Ac_2O, DMAP, pyridine, CH_2Cl_2, 0 °C to rt, 99% (for 19); (e) TBAF, THF, 99% (for **20**), 92% (for **25**, two steps); (f) 6-chloropurine, Ph_3P, DIAD, THF, 0 °C to rt, 77% (for **21**); (g) NH_3/MeOH, 110 °C, 48 h, 90% (for **22**); 56% (for **27**, two steps); (h) 1 N HCl, MeOH, 98% (for **3**), 89% (for **4**).

followed by treatment with OsO_4 and $NaIO_4$ to afford the desired ketone precursor **15**. Unfortunately, CBS reaction of **15** with (*R*)-methyloxazaborolidine ((*R*)MeCBS, structure in Scheme 2) and diethylaniline−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 ofthe resultant **16** was converted to methyl ketone **17** with OsO_4 and $NaIO_4$. 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′*S*)-5′-methylaristeromycin (**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′-methylaristeromycin (**4**) following the same sequence of steps used to produce **3** (Scheme 2).

The tertiary alcohol 5′,5′-dimethylaristeromycin (**7**) was synthesized (Scheme 1) from **15** and methylmagnesium bromide. The resultant product **28** was kept in methanolic ammonia

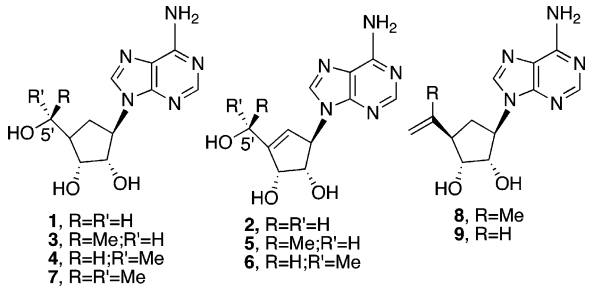


FIGURE 1.

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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 potent effects of **4** toward yellow fever (EC_{50} 0.32 μg/mL, CPE inhibition in Vero cell; positive drug control EC_{50} 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 flaviviruses[14a,b] (for example, West Nile,[14c] dengue,[14d] and hepatitis C[14e]), which were unaffected by **4**.

Experimental Section

For complete details, see the Supporting Information.

9-[(1′*R*,2′*S*,3′*R*,4′*R*)-2′,3′-Dihydroxy-4′-((1*S*)-1-hydroxyethyl)-cyclopent-1′-yl]adenine (3): white solid; mp 206−208 °C; $[\alpha]^{23.5}_D$ −39.50 (*c* 0.01, MeOH); ^{1}H 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); ^{13}C 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 $C_{12}H_{18}N_5O_3$ [M + H]$^+$ 280.1409, found 280.1410.

9-[(1′*R*,2′*S*,3′*R*,4′*R*)-2′,3′-Dihydroxy-4′-((1*R*)-1-hydroxyethyl)-cyclopent-1′-yl]adenine (4): white solid; mp 166−168 °C; $[\alpha]^{23.5}_D$ −53.18 (*c* 0.18, MeOH); ^{1}H 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); ^{13}C 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 $C_{12}H_{18}N_5O_3$ [M + H]$^+$ 280.1409, found 280.1400.

9-[(1′*R*,2′*S*,3′*R*,4′*S*)-2′,3′-Dihydroxy-4′-(1-hydroxyisopropyl)-cyclopent-1′-yl]adenine (7): white solid; mp 128−130 °C; $[\alpha]^{23.6}_D$ −43.03 (*c* 0.13, MeOH); ^{1}H 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), 1.18 (s, 3H), 1.09 (s, 3H); ^{13}C NMR (62.5 MHz, DMSO) δ 156.0, 152.0, 149.8, 139.8, 119.3, 94.4, 74.6, 69.9, 69.4, 59.2, 54.1, 28.0, 27.7. HRMS calcd for $C_{13}H_{20}N_5O_3$ [M + H]$^+$ 294.1566, found 294.1558.

9-[(1′*R*,2′*S*,3′*R*,4′*R*)-2′,3′-Dihydroxy-4′-(2-propenyl)cyclopent-1′-yl]adenine (8): white solid; mp >196 °C dec; $[\alpha]^{23.5}_D$ −24.25 (*c* 0.09, MeOH); ^{1}H 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); ^{13}C 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 $C_{13}H_{18}N_5O_2$ [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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