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THE SYNTHESIS OF TWO 2'-DEOXY CARBOCYCLIC PURINE NUCLEOSIDES LACKING THE 5'-METHYLENE

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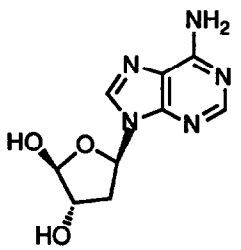
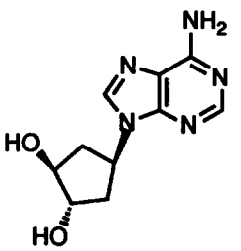
Summary: The synthesis of the adenine derivative (±)-(1α,2β,4α)-4-(6-amino-9H-purin-9-yl)-1,2-cyclopentanediol (**2**) and its hypoxanthine analogue (**3**) as carbocyclic nucleosides lacking the 5'-methylene is described in 7 steps from 3-cyclopenten-1-ylamine hydrochloride (**4**) in on overall yield of 30% for **2** and 27% for **3**.

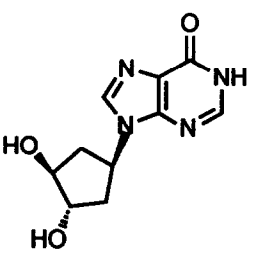
Motivated by the desire to enlighten nucleic acid structure and function and to develop biologically active agents derived therefrom, numerous analogues of the naturally occurring nucleosides and nucleotides have been prepared. However, missing from these studies is an analysis of the biochemical necessity of the 5'-methylene moiety of the ribofuranosyl unit. To conduct such an analysis, it would have been necessary to work with derivatives, such as the adenine compound **1**, that are hemiacetals and likely to be part of a mixture also containing the C-4' epimer and open chain forms. This situation can be overcome by the carbocyclic analogues (for example, **2** and **3**) in which the hydroxyl center of interest is merely a secondary alcohol. This report describes the synthesis of **2** and **3**, the former of which can also be viewed as the 5'-nor 2'-deoxy derivative of the carbocyclic nucleoside aristeromycin.[1]



1



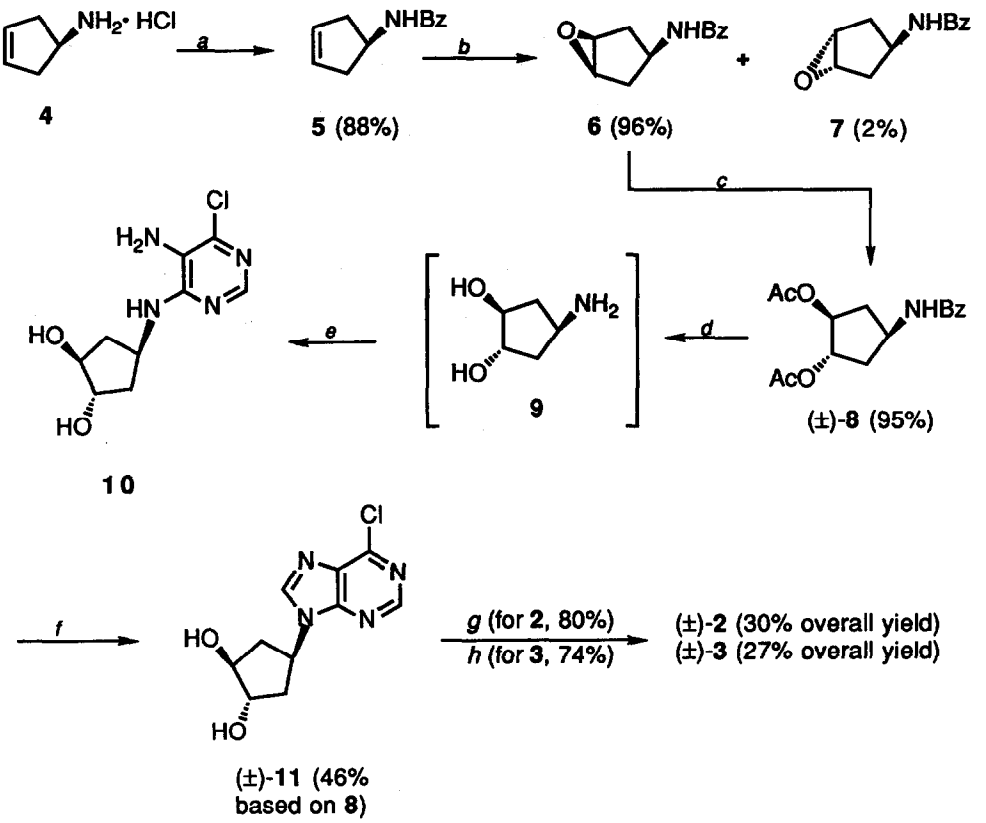
2



3

A review of the literature[2] indicated that 3-cyclopenten-1-ylamine hydrochloride (**4**)[3] would be a useful starting material. Thus, benzoylation of **4** (Scheme) yielded N-(3-cyclopenten-1-yl)benzamide (**5**,[4,5] mp 126 °C from $CHCl_3$-hexane). Oxidation of **5** using *m*-chloroperoxybenzoic acid yielded (1α,3β,5α)-N-(6-oxabicyclo[3.1.0]hex-3-yl)benzamide (**6**,[4,6] mp 84 °C from $CHCl_3$-hexane) and (1α,3α,5α)-N-(6-oxabicyclo[3.1.0]hex-3-yl)benzamide (**7**,[4,7] mp 153 °C from $CHCl_3$-hexane). The diastereomers **6** and **7** were distinguished by comparing their ^1H NMR data for the benzamide NH and the epoxide protons: the NH region for **6** (δ 7.3-7.7 ppm) is shielded by the *cis*-epoxide oxygen relative to the NH in **7** (δ 8.31 ppm) whereas the epoxide protons in **7** (δ 3.54 ppm) are shielded by the *cis*-nitrogen when compared to the epoxide protons in **6** (δ 3.57 ppm).

Scheme



Reaction conditions: *a*, BzCl/pyridine/Et_3N in $CHCl_3$; *b*, *m*-chloroperoxybenzoic acid in $CHCl_3$, room temp.; *c*, (i) 2% aq. H_2SO_4, room temp. then neutralize; (ii) Ac_2O/pyridine, room temp; *d*, 6N HCl, reflux; *e*, 5-amino-4,6-dichloropyrimidine in 1-BuOH containing Et_3N, reflux; *f*, $(EtO)_3CH$ and conc. HCl, reflux; *g*, NH_3 in MeOH, 100 °C, 48 h; *h*, 1N HCl, reflux

Ring opening of **6** with dilute sulfuric acid followed by acetylation of the resultant *trans*-vicinal diol gave (±)-(1α,3α,4β)-N-[3,4-*bis*(acetyloxy)cyclopentyl]benzamide (**8**,[4,8] mp 95 °C from hexane). Hydrolysis of **8** to (1α,2β,4α)-4-amino-1,2-cyclopentanediol (**9**, oil). Compound **9**, which was not fully characterized, was reacted with 5-amino-4,6-dichloropyrimidine to yield (±)-(1α,2β,4α)-4-[(5-amino-6-chloro-4-pyrimidinyl)amino]-1,2-cyclopentanediol (**10**,[9] mp 189 °C from $CHCl_3$-MeOH-EtOAc) that was converted into (±)-(1α,2β,4α)-4-(6-chloro-9*H*-purin-9-yl)-1,2-cyclopentanediol (**11**,[4,10] mp 202 °C from MeOH) with triethyl orthoformate. Ammonolysis of **11** gave the desired (±)-(1α,2β,4α)-4-(6-amino-9H-purin-9-yl)-1,2-cyclopentanediol (**2**,[4,11] mp 211 °C from MeOH).

Reaction of **11** with dilute hydrochloric acid produced the hypoxanthine analogue (±)-(1α,3α,4β)-9-(3,4-dihydroxycyclopentyl)-1,9-dihydro-6*H*-purin-6-one (**3**,[4,12] mp 283 °C from H_2O-MeOH).

Acknowledgments. We are appreciate the assistance of Ms. Linda Morgan in the synthesis of **4**.

References and Notes

1. See, for example, Yoshikawa, M.; Okaichi, Y.; Cha, B.C.; Kitagawa, I. *Chem Pharm. Bull.* **1989**, *37*, 2555.
2. (a) Murdock, K.C.; Angier, R.B. *J. Am. Chem. Soc.* **1962**, *84*, 3748. (b) Murdock, K.C.; Angier, R.B. *J. Org. Chem.* **1962**, *27*, 3317.
3. [redacted]
5. The spectral data[13] for **5** is as follows: IR (Nujol, cm^{-1}) 3300 (NH), 1630 (C=O), 1575, 1550 and 1540 (C=C); ^1H NMR (DMSO-d_6, ppm) δ 2.2-2.9 (m, 4 H, H-2' and H-5'), 4.4-4.8 (m, 1 H, H-1'), 5.73 (s, 2 H, H-3' and H-4'), 7.3-7.6 and 7.8-8.0 (m, 5 H, H of phenyl), 8.52 (d, 1 H, J=7 Hz, NH); ^{13}C NMR (DMSO-d_6, ppm) δ 39.17 (C-2' and C-5'), 49.19 (C-1'), 127.42, 128.18, 131.05, and 134.73 (C of phenyl), 129.10 (C-3' and C-4'), 166.21 (C=O).
6. The spectral data[13] for **6** is as follows: IR (Nujol, cm^{-1}) 3400 (NH), 1660 (C=O), 1575, 1530, and 1520 (C=C); ^1H NMR (DMSO-d_6, ppm) δ 1.9-2.2 (m, 4 H, H-2' and H-4'), 3.57 (s, 2 H, H-1' and H-5'), 4.2-4.5 (m, 1 H, H-3'), 7.3-7.7 (m, 4 H, NH and H-3, H-4, and H-5 of phenyl), 7.7-8.0 (m, 2 H, H-2 and H-6 of phenyl); ^{13}C NMR (DMSO-d_6, ppm) δ 34.94 (C-2' and C-4'), 46.48 (C-3'), 56.94 (C-1' and C-5'), 127.09, 128.23, 131.05, and 134.62 (C of phenyl), 165.01 (C=O).
7. The spectral data[13] for **7** is as follows: IR (Nujol, cm^{-1}) 3285 (NH), 1630 (C=O), 1575 and 1555 (C=C); ^1H NMR (DMSO-d_6, ppm) δ 1.5-1.9 and 2.2-2.5 (m, 4 H, H-2' and H-4'), 3.54 (s, 2 H, H-1' and H-5'), 3.9-4.2 (m, 1 H, H-3'), 7.3-7.6 (m, 3 H, H-3, H-4, and H-5 of phenyl), 7.7-7.9 (m, 2 H, H-2 and H-6 of phenyl), 8.31 (d, J=8 Hz, 1 H, NH); ^{13}C NMR (DMSO-d_6, ppm) δ 33.21 (C-2' and C-4'), 44.85 (C-3'), 55.04 (C-1' and C-5'), 127.31, 128.28, 131.15, and 134.57 (C of phenyl), 166.04 (C=O).
8. The spectral data[13] for **8** is as follows: IR (Nujol, cm^{-1}) 3370 (NH), 1735 (C=O of acetyl), 1635 (C=O of benzoyl), 1580 and 1515 (C=C); ^1H NMR (DMSO-d_6, ppm) δ 2.04 (s, 6 H, 2 x CH_3) overlapped by 1.5-2.7 (m, 4 H, H-2' and H-5'), 4.3-4.6 (m, 1 H, H-1'), 4.9-5.3 (m, 2 H, H-3' and H-4'), 7.2-7.5 (m, 3 H, H-3, H-4, and H-5 of phenyl), 7.6-7.9 (m, 2 H, H-2 and H-6 of phenyl), 8.52 (d, J=7 Hz, 1 H, NH); ^{13}C NMR (DMSO-d_6, ppm) δ 20.80 (2 x CH_3), 36.24 (C-2' and C-5'), 46.97 (C-1'), 76.93 (C-3' and C-4'), 127.36, 128.23, 131.21, and 134.46 (C of phenyl), 166.15 (C=O of benzoyl), 169.78 (C=O of acetyl).
9. The spectral data[13] for **10** is as follows: IR (Nujol, cm^{-1}) 3400-3100 (NH and OH), 1650 and 1580 (C=N and C=C); ^1H NMR (DMSO-d_6, ppm) δ 1.1-2.6 (m, 4 H, H-3 and H-5), 3.8-4.0 (m, 2 H, H-1 and H-2), 4.4-4.8 (m, 1 H, H-4), 4.75 and 4.88 (2 d, J=3 Hz, 2 H, 1-OH and 2-OH), 5.08 (s, 2 H, NH_2), 6.74 (d, J=7 Hz, 1 H, NH), 8.06 (s, 1 H, H-2 of pyrimidine); ^{13}C NMR (DMSO-d_6, ppm) δ 38.95 (C-3 and C-5), 48.92 (C-4), 76.82 (C-1 and C-2), 123.41, 136.79, 145.78, and 151.63 (C of pyrimidine).
10. The spectral data[13] for **11** is as follows: IR (Nujol, cm^{-1}) 3345 (OH), 1595 and 1560 (C=N and C=C); ^1H NMR (DMSO-d_6, ppm) δ 1.8-2.8 (m, 4 H, H-3 and H-5), 4.0-4.2 (m, 2 H, H-1 and H-2), 5.0-5.5 (m, 3 H, H-4, 1-OH, and 2-OH), 8.79 (br s, 2 H, H-2 and H-8 of purine); ^{13}C NMR (DMSO-d_6, ppm) δ 38.95 and 39.38 (C-3 and C-5), 52.71 (C-4), 76.49 and 76.71 (C-1 and C-2), 131.10, 146.22, 148.98, 151.25, and 151.69 (C of purine).

11. The spectral data[13] for **2** is as follows: IR (Nujol, cm^{-1}) 3340 and 3165 (NH and OH), 1660, 1595, and 1575 (C=N and C=C); ^1H NMR (DMSO-d_6, ppm) δ 1.8-2.8 (m, 4 H, H-3 and H-5), 4.0-4.2 (m, 2 H, H-1 and H-2), 4.9-5.6 (m, 3 H, H-4, 1-OH, and 2-OH), 7.35 (br s, 2 H, NH_2), 8.21 (br s, 2 H, H-2 and H-8 of purine); ^{13}C NMR (DMSO-d_6, ppm) δ 39.17 and 39.33 (C-3 and C-5), 51.95 (C-4), 76.66 and 76.98 (C-1 and C-2), 119.24, 139.99, 149.14, 152.23, and 156.18 (C of purine).
12. The spectral data[13] for **3** is as follows: IR (Nujol, cm^{-1}) 3220-3430 (NH and OH), 1680 (C=O), 1595, 1550, and 1515 (C=N and C=C); ^1H NMR (DMSO-d_6, ppm) δ 1.7-2.8 (m, 4 H, H-2' and H-5'), 3.8-4.2 (m, 2 H, H-3' and H-4'), 4.8-5.3 (m, 3 H, H-1', 3'-OH, and 4'-OH), 8.09 and 8.2 (2 s, 2 H, H-2 and H-8 of purine), 12.31 (br s, 1 H, NH of purine); ^{13}C NMR (DMSO-d_6, ppm) δ 39.44 and 39.76 (C-2' and C-5'), 52.06 (C-1'), 76.55 and 76.82 (C-3' and C-4'), 124.17, 138.96, 145.46, 148.22, and 156.83 (C of purine).
13. Refer to the compound name in the narrative to determine atom numbering for spectra assignments.

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