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CARBOCYCLIC RING-ENLARGED OXETANOCIN ANALOGUES

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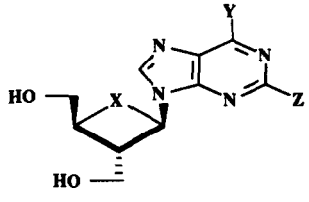
Abstract: Carbocyclic versions of 2',3'-dideoxy-3'C-hydroxymethyl nucleosides with adenine, guanine, uracil and cytosine bases were synthesized from a common cyclopentenone precursor. The extra hydroxymethyl moiety was introduced by photochemical addition of methanol to an α-enone system.

Recently, 2',3'-dideoxy-3'C-hydroxymethyl nucleosides (**5**, **6** and **9**, **10**) have been identified as potential antiviral agents.[1-4] Such compounds can be viewed as ring-expanded analogues of oxetanocin nucleosides **1** and **2**. The cytidine analogue **10** was shown to display a high level of activity against HIV and a broad range of DNA viruses.[1] Replacement of the oxetane ring by a cyclobutyl moiety produced compounds (**3** and **4**) which were very effective against both HIV and DNA-containing viruses.[5,6] These considerations provided a very strong rationale for the syntheses of carbocyclic analogues of **5** and **6** (compounds **7** and **8**), and **9** and **10** (compounds **11** and **12**). In view of the recent report by Legraverend et al.[7] on the synthesis of **7** and **8**, we were prompted to disclose our synthetic approach towards these target compounds, as well as the corresponding pyrimidine counterparts **11** and **12**.

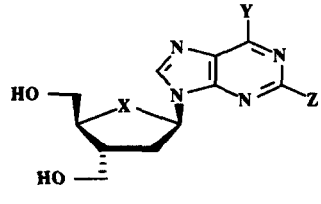


1, X = O, Y = NH_2, Z = H (Oxetanocin A)

2, X = O, Y = OH, Z = NH_2 (Oxetanocin G)

3, X = CH_2, Y = NH_2, Z = H

4, X = CH_2, Y = OH, Z = NH_2

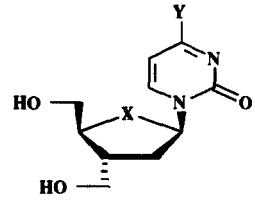


5, X = O, Y = NH_2, Z = H

6, X = O, Y = OH, Z = NH_2

7, X = CH_2, Y = NH_2, Z = H

8, X = CH_2, Y = OH, Z = NH_2



9, X = O, Y = OH

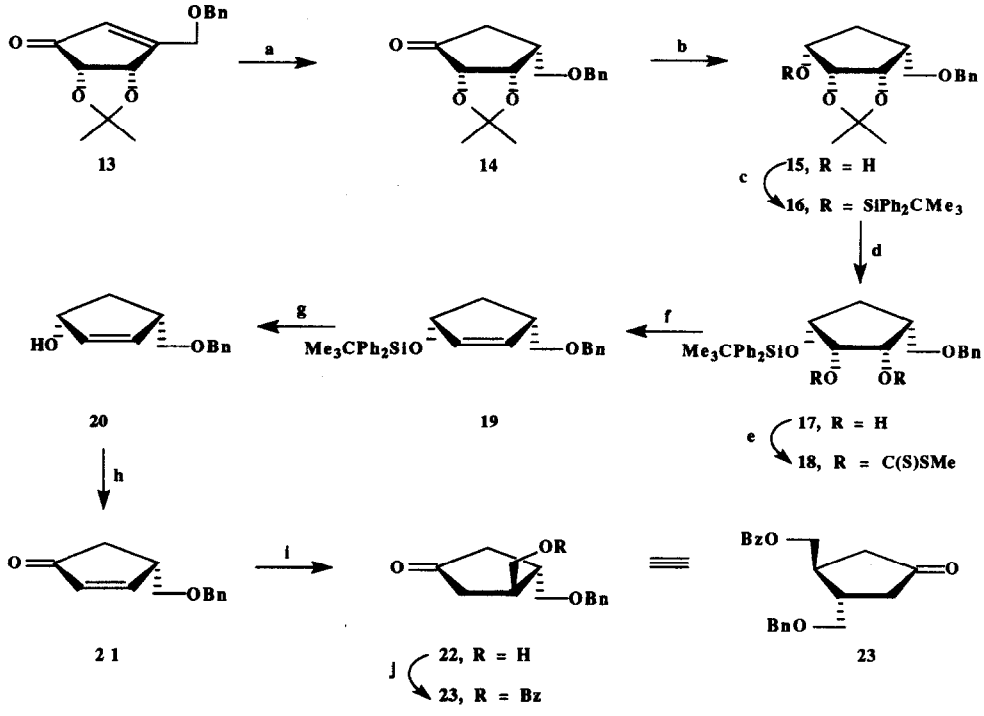
10, X = O, Y = NH_2

11, X = CH_2, Y = OH

12, X = CH_2, Y = NH_2

Our synthetic strategy in this and other projects has been to exploit the versatility of cyclopentenone **13** to access a variety of carbocyclic nucleoside structures.[8,9] As in previous cases, synthesis of the racemic compounds was first attempted with separation of the desired enantiomers to be performed later if warranted by their biological activity. The reaction sequence (Scheme 1) was designed to convert the α-enone system in **13** into a much simpler, rearranged α-enone system (**21**). The first two steps proceeded with rigorous regioselectivity and removal of the isopropylidene moiety was followed

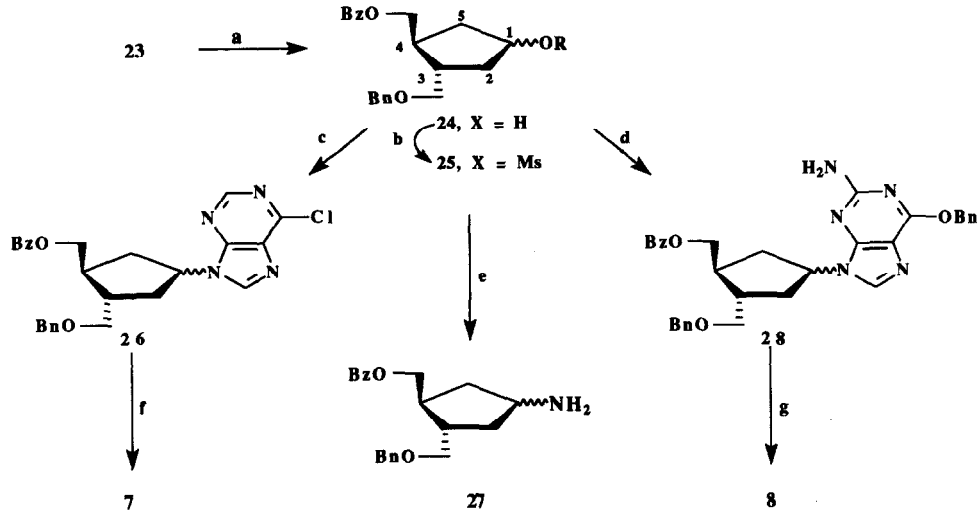
Scheme 1



Reagents : **a.** H_2, 10% Pd/C, MeOH (95%); **b.** $NaBH_4$, MeOH (94%); **c.** *t*-$BuPh_2SiCl$, imidazole, DMF (91%); **d.** H_2O, TFA (51%); **e.** NaH, CS_2, MeI, DMF (82%); **f.** Ph_2SiH_2, AIBN, toluene, Δ (88%); **g.** *n*-Bu_4NF, THF (87%); **h.** PCC, CH_2Cl_2 (77%); **i.** Ph_2CO, MeOH, *hν* (57%); **j.** PhCOCl, pyridine (87%).

by formation of a new double bond via the bis-xanthate/Ph_2SiH_2 sequence. Compound **21** was anticipated to undergo a predominantly trans benzophenone-sensitized photoaddition of methanol accross the double bond in accordance to literature precedent.[10,11] Indeed, only one product was isolated from this reaction but full confirmation of its structure became evident only at the conclusion of the synthesis (vide infra). Protection of the new alcohol function as the benzoate ester was followed by reduction of the carbonyl group and formation of the mesylate ester **25**. This compound represents a branch point from which all of the target compounds were accessed (Scheme 2). The purine analogues were obtained by a convergent approach in which the carbocyclic ring and the heterocycles were directly attached to avoid the more laborious stepwise construction of the bases.[12] The mesylate **25** reacted well with the corresponding sodium salts of the heterocyclic bases and after a few simple steps the adenosine and guanosine analogues (**7** and **8**) were obtained.[13] In all the compounds generated from **23** there exists a plane of symmetry that intersects C1 and bisects the C3 and C4 bond; therefore, in **24** and **25** the orientation of the groups at C1 is irrelevant and displacement of the mesylate from either side of the carbocycle gives the

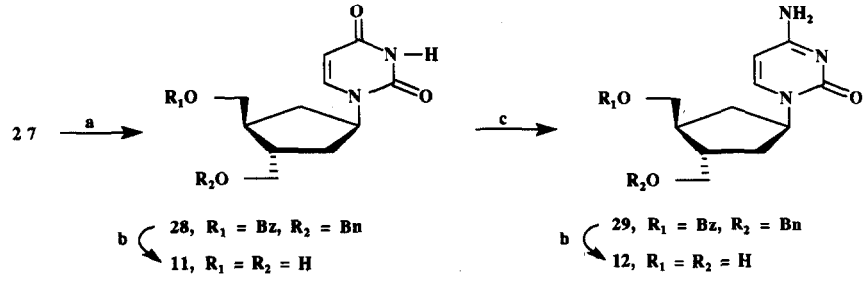
Scheme 2



Reagents: **a.** $NaBH_4$, MeOH (83%); **b.** $MeSO_2Cl$, Et_3N, CH_2Cl_2 (96%); **c.** NaH, 6-chloropurine, DMF, 70 °C (62%); **d.** NaH, 2-amino-6-benzyloxypurine, DMF, 75 °C (58%); **e.** i. NaN_3, DMSO/HMPA (80%); ii. H_2, Lindlar cat., EtOH (92%); **f.** i. NH_3, MeOH, 80 °C (91%); ii. HCO_2NH_4, 10% Pd/C, MeOH, Δ (79%); **g.** i. NaOMe, MeOH (98%); ii. H_2, 10% Pd/C, MeOH, cat. TFA (46%).

same compound. Indeed the isolation of a single compound in each case (**7** and **8**) corroborated the trans photochemical addition of methanol. Had it proceeded in a cis fashion, we would have obtained two isomers in each case depending on the relative disposition of the base and the two hydroxymethyl groups on similar or opposite sides of the carbocyclic ring. The same argument holds true for the pyrimidine analogues **11**[14] and **12**[14] which were approached linearly from the carbocyclic amine **27** by well known methods (Scheme 3).[12] Biological testing results on these new compounds will be reported elsewhere.

Scheme 3



Reagents: **a.** i. EtOCH=CHCONCO, C_6H_6, 10 °C (88%); ii. NH_4OH, DMF, 110 °C (59%); **b.** i. HCO_2NH_4, 10% Pd/C, MeOH, Δ (57%); ii. NH_3/MeOH, 60 °C (75%); **c.** i. $POCl_3$, triazole, Et_3N, CH_3CN; ii. NH_4OH, dioxane (97%).

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References and Notes

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13. These compounds and their intermediates gave correct elemental analyses for C, H, and N.
    Compound **7**: lyophilized solid. The proton NMR spectrum of this compound was identical to that reported in ref. 7; ^{13}C NMR (Me_2SO-d_6) δ 34.80, 36.20, 42.11, 43.06, 53.85, 64.22, 119.23, 139.30, 149.51, 152.11, 156.00; FAB MS *m/z* (relative intensity) 264 (MH+, 100), 136 (b+2H, 38).
    Compound **8**: mp 249-50 °C (lit.[7] mp 244 °C). The proton NMR spectrum of this compound was identical to that reported in ref. 7.; ^{13}C NMR (Me_2SO-d_6) δ 34.92, 36.46, 41.96, 42.93, 53.10, 64.17, 116.83, 135.33, 151.14, 153.33, 156.87; FAB MS *m/z* (relative intensity) 280 (MH+, 100), 152 (b+2H, 44).
14. These compounds and their intermediates gave correct elemental analyses for C, H, and N.
    Compound **11**: lyophilized solid. ^{1}H NMR (Me_2SO-d_6) δ 1.40-2.10 (m, 6 H, H-2'$_{a,b}$, H-5'$_{a,b}$, H-3', H-4'), 3.33 (m, 4 H, 2 x CH_2OH), 4.67 (br s, 2 H, OH, D_2O exchanged), 4.73 (m, 1 H, H-1'), 5.57 (d, J = 7.8 Hz, 1 H, H-5), 7.73 (d, J = 7.8 Hz, 1 H, H-6), 11.20 (br s, 1 H, NH, D_2O exchanged); ^{13}C NMR (Me_2SO-d_6) δ 33.10, 34.80, 41.92, 42.61, 54.19, 64.04, 64.13, 101.34, 142.12, 151.07, 163.14; FAB MS *m/z* (relative intensity) 241 (MH+, 100), 113 (b+2H, 42).
    Compound **12**: lyophilized solid. ^{1}H NMR (Me_2SO-d_6) δ 1.35-2.10 (m, 6 H, H-2'$_{a,b}$, H-5'$_{a,b}$, H-3', H-4'), 3.20-3.60 (m, 4 H, 2 x CH_2OH), 4.64 (m, 2 H, OH, D_2O exchanged), 4.80 (m, 1 H, H-1'), 5.67 (d, J = 7.3 Hz, 1 H, H-5), 6.98 (br s, 1 H, NH_2, D_2O exchanged), 7.64 (d, J = 7.3 Hz, 1 H, H-6); ^{13}C NMR (Me_2SO-d_6) δ 33.64, 35.35, 42.15, 42.94, 54.53, 64.23, 64.35, 93.61, 142.41, 155.80, 165.07; FAB MS *m/z* (relative intensity) 240 (MH+, 100), 112 (b+2H, 62).

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