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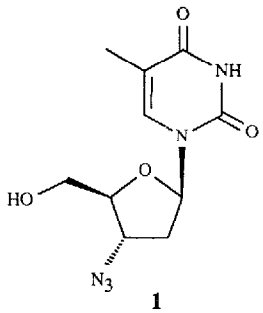
SYNTHESIS OF (±)-2'-OXA-CARBOCYCLIC -2',3'-DIDEOXYNUCLEOSIDES AS POTENTIAL ANTI-HIV AGENTS

Mark J. Bamford*, David C. Humber and Richard Storer
Department of Medicinal Chemistry, Glaxo Group Research Ltd.,
Greenford, Middlesex UB6 OHE.

Summary: Novel 2',3'-dideoxynucleosides, having the pentofuranosyl oxygen at the 2'-position, were obtained by a short synthetic route from diethyl malonate and bromoacetaldehyde dimethyl acetal. The results of biological testing against HIV-1 *in vitro* are presented.

Nucleoside analogues are currently among the most potent agents active against HIV-1[1], the causative agent of AIDS[2]. As their 5'-triphosphate metabolites they are selective inhibitors of the viral reverse transcriptase[3]. However, although AZT **1** is the only such compound approved so far for clinical use, it displays severe bone-marrow toxicity with only short term benefit[4], and resistant virus strains are now emerging[5]. Further, the potential of 2',3'-dideoxynucleosides[6], such as ddC **2**, ddA **3** and ddI **4**, as future drugs is limited due to the instability of their glycosidic bond[7], and to their toxicity (especially for ddC[8]). Recent developments have suggested that more fundamental changes to the pentofuranosyl moiety are compatible with anti-HIV activity. For example, carbovir **5**[9], iso-ddA **6**[10], dioxolane derivative **7**[11], and the cytosine 1,3-oxathiolane analogue **8**[12], have all been reported to show activity.



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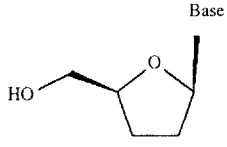
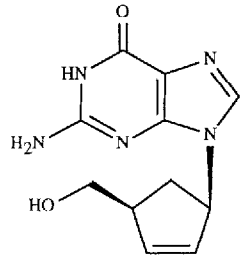


2 Base=C
3 Base=A
4 Base=I



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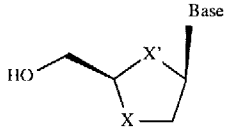
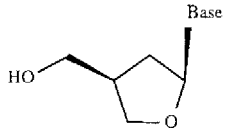
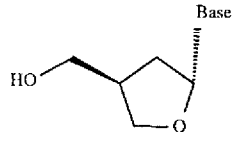


6 Base=A, X=O, X'=CH_2
7 Base=T, X=X'=O
8 Base=C, X=S, X'=O



9 Base=U
10 Base=C
11 Base=G

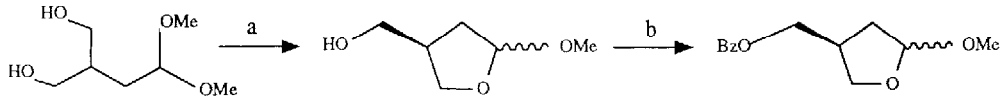


12 Base=U
13 Base=C
14 Base=G

We report herein, in a novel extension of this area, the synthesis of a series of 2'-*oxa*-carbocyclic-2',3'-dideoxynucleosides **9-11**. In the light of the reported[12] activity of α-anomers in non-ribose-based analogues, it was also of interest to investigate the corresponding α-anomers **12-14**.

The starting material 2-hydroxymethyl-4,4-dimethoxybutan-1-ol, **15**, (Scheme 1) was synthesised[13] from diethylmalonate and bromoacetaldehyde dimethyl acetal in 29% yield. Upon heating with acid, **15** was smoothly converted into a 1:1 (by NMR) anomeric mixture **16**. Benzoylation of the primary hydroxyl afforded **17** after chromatography.

Scheme 1

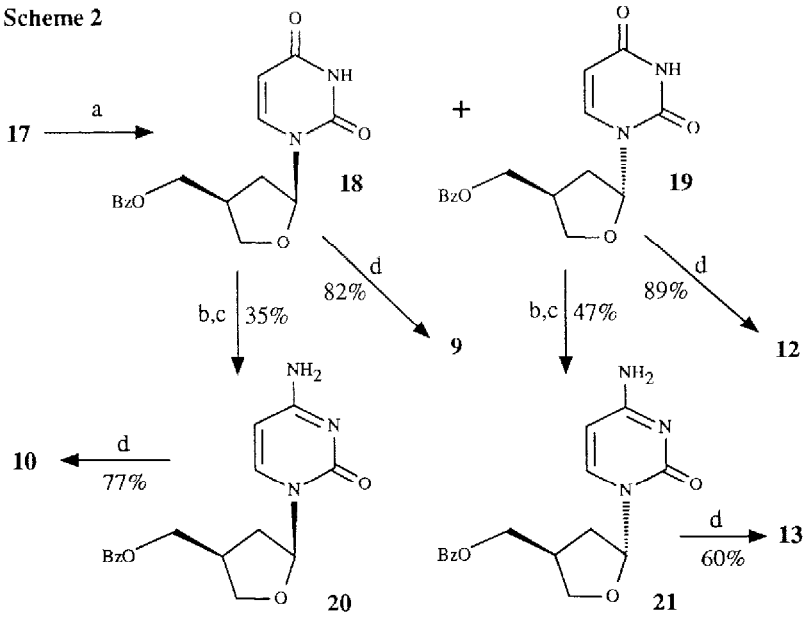


15 **16** **17**

a: Dowex 50W-8H , MeOH, Reflux, 1hr. (91%). b: Benzoyl chloride (3eq.) pyridine, 0°-RT, 2.5hrs. (82%).

Condensation of **17** with *bis*(trimethylsilyl)uracil using the procedure established by Vorbruggen[14] gave a 1:1 diastereomeric mixture of (±)-nucleoside derivatives (Scheme 2).

Scheme 2

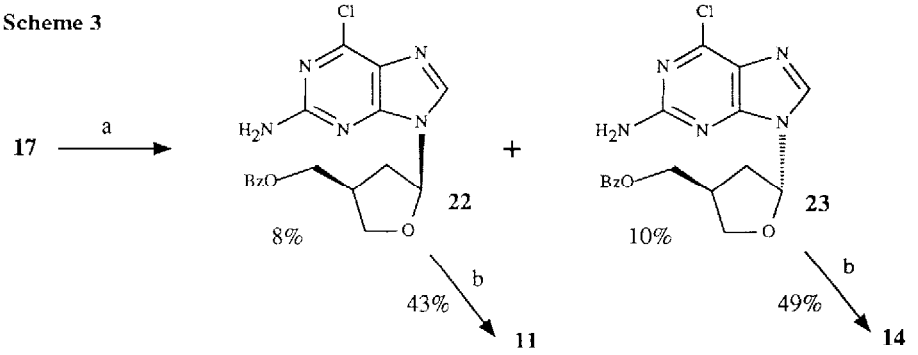


a: $(TMS)_2$Uracil, CH_3CN, TMSOTf, O °C, 10 min. (80%). b: $POCl_3$, Triazole, Et_3N, CH_3CN.
c: NH_4OH, Dioxan. d: NH_3 /MeOH, 20 °C, 16 hr.

Separation by chromatography on silica gel (7:3 / ethyl acetate:cyclohexane) afforded both the β- and α-anomers **18**[15] and **19**[16], respectively, the relative stereochemistries of which were assigned by NOE difference spectra. Compounds **18** and **19** were each converted by established[17] chemistry into their respective ddC analogues **20** and **21**. Debenzoylation of **18**, **19**, **20** and **21** yielded **9**, **12**, **10** and **13**, respectively.

Similar condensation of **17** with *bis*(trimethylsilyl)-2-amino-6-chloropurine[18] (Scheme 3) gave a mixture in modest yield which, following chromatography on silica, afforded the pure β-anomer **22** and α-anomer **23** which could not be freed by further chromatography or crystallisation from contaminating β-isomer (ca. 10% by NMR).

Scheme 3



a: $(TMS)_2$2-Amino-6-chloropurine, TMSOTf, CH_3CN, 0°C, 25min.
b: 1M NaOH, H_2O, reflux, 1hr.

Relative stereochemistries were assigned by comparison of their NMR spectra with those of their uracil counterparts. Refluxing of **22** and **23** in 1M NaOH[19] followed by chromatography and crystallisation yielded guanine derivatives **11** and **14**, respectively, although the latter again contained β-anomer impurity which could not be removed, even by HPLC.

None of the 2'-*oxa*-nucleosides described above were inhibitory to HIV-1 *in vitro* at concentrations up to 100μM. In marked contrast to the potent activity reported[10-12] for certain 3'-heteroatom-substituted derivatives, it appears that similar modification at the 2'-position is not compatible with anti-HIV activity. This is probably due to such structures not being recognised by the highly selective cellular kinases.

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15. 250 *MHz* ^{1}HNMR (±)-**18**: (d_6DMSO, TMS=δ 0.00) δ 11.25(s,1H,H3), 7.95(d,2H,o-phenyl), 7.70(d,1H,H6), 7.65(t,1H,*p*-phenyl), 7.55(t,2H,*m*-phenyl), 6.00(t,1H,H1'), 5.60(d,1H,H5), 4.40-4.30(2dd,2H,H5'), 4.05 and 3.95(2t,2H,H3'), 2.85(m,1H,H4'), 2.50 and 1.85(2ddd,2H,H6').
16. 250 *MHz* ^{1}NMR (±)-**19**: (d_6DMSO, TMS=δ 0.00) δ 11.25(s,1H,H3), 8.00(d,2H,*o*-phenyl), 7.65(d and t,2H,H6 and *p*-phenyl), 7.55(t,2H,*m*-phenyl), 6.05(t,1H,H1'), 5.60(d,1H,H5), 4.40-4.20(m,3H,H5' and 0.5H3'), 3.75(t,1H,0.5H3'), 2.85(m,1H,H4'), 2.20(t,2H,H6').
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