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Synthesis and Antiviral Evaluation of 3-Hydroxy-2-methylpyridin-4-one Dideoxynucleoside Derivatives

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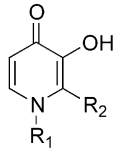
Abstract—We describe the synthesis and the antiviral evaluation of novel α and β dideoxynucleoside derivatives in which the base has been replaced by a 3-hydroxy-2-methylpyridin-4-one. The syntheses were successfully achieved by the use of the standard Vorbrüggen coupling conditions. Moderate activity of these compounds were found on herpes simplex virus (HSV) type 1 and type 2.

3-Hydroxypyridin-4-ones (HPOs) are currently one of the main candidates for the development of orally active iron chelators.[1] Indeed, the 1,2-dimethyl derivative (Deferiprone, Fig. 1), with an associated pFe^{3+} value of 19.4 is the only active iron chelator currently available for clinical use (marketed by Apotex Inc., Toronto, Canada as Ferriprox™).[2] It has been shown that iron chelation, which would make iron unavailable for redox reactions, could influence HIV replication in two possible ways:

- by inactivation of the iron-dependent cellular enzyme ribonucleotide reductase which is responsible for generating the building blocks for viral DNA.[3]
- via reduction of nuclear factor-κB (NF-κB) activation.[4]

Recently, a clear synergism in HIV-1 inhibition was observed by combining iron chelators with the anti-HIV nucleoside analogue ddI and it was suggested that in combination with existing antivirals, iron chelation could have a beneficial effect on HIV disease.[5] These findings prompted us to synthesise several 2′,3′-dideoxynucleosides



Deferiprone, Ferriprox™ $R_1 = R_2 = CH_3$

Figure 1.

in which the base has been changed to a 3-hydroxypyridin-4-one. Moreover, the base modification of these new nucleosides could confer activity against other viruses than HIV. For a start, the synthesised nucleosides contain sugar moieties similar to that of two currently FDA approved anti-HIV 2′,3′-dideoxynucleosides: ddC and 3TC (Fig. 2).

Results and Discussion

3-Hydroxybenzyl-2-methylpyridin-4-one is a requisite for the Vorbrüggen conditions in the sugar-base coupling. It was obtained starting from maltol which was benzylated with benzyl bromide in a basic media (Scheme 1). Reaction of adduct **1** with ammonia was performed by reflux in 50% aqueous ethanol. The benzylated pyridinone **2** was isolated in a crystalline form

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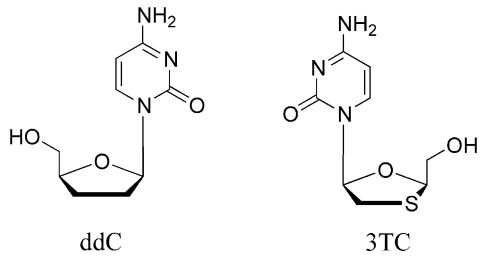
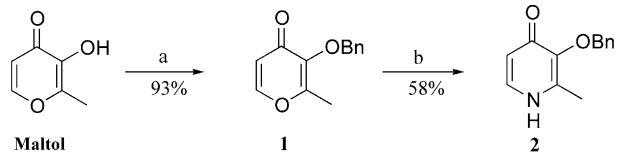
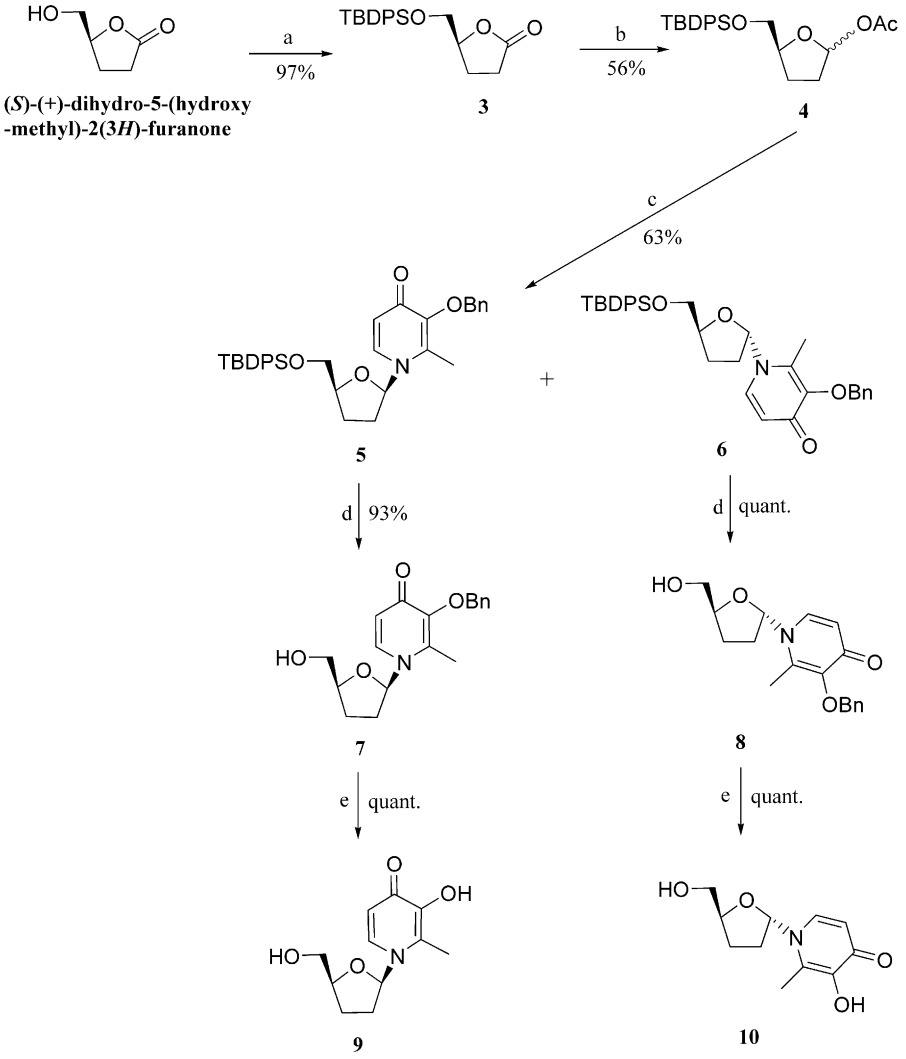


Figure 2.



Scheme 1. (a) BnBr, NaOH, MeOH, reflux, 16 h; (b) NH_3, EtOH, reflux, 24 h.

as a free base in 58% yield.[6] The primary alcohol function of the commercially available precursor (*S*)-(+)-dihydro-5-(hydroxymethyl)-2-(*3H*)-furanone was protected with TBDPSCl in THF to give the lactone **3** (Scheme 2). This latter compound was then reduced with diisobutylaluminium (DIBAL-H), followed by trapping of the resulting lactol with acetic anhydride to give **4** in 78% yield. 3-Benzyloxy-2-methylpyridin-4-one **2** was silylated under reflux for 2 h with hexamethyldisilazane (HMDS) in the presence of a catalytic amount of ammonium sulfate. After the removal of the excess of HMDS, the base was solubilised in 1,2-dichloroethane and a mixture of **4** and trimethylsilyltriflate (TMSOTf)[7] in 1,2-dichloroethane was slowly added at room temperature to afford compounds **5** and **6** in 47% yield. The β/α ratio generally was around 1, and separation of both isomers was successfully accomplished by flash silica gel chromatography. The relative stereochemistry of these compounds was assigned by 1D and 2D ^1H NMR studies (Fig. 3). NOE interactions were observed between H-1′ and H-4′ suggesting the *cis* orientation of the less polar compound **5**. The *trans* configuration was then assigned to the more polar isomer **6**. Compounds **5**



Scheme 2. (a) TBDPSCl, imidazole, dry DMF, rt, 18 h; (b) DIBAL, dry DCM, −90 °C then Ac_2O, pyridine, DMAP, rt, 72 h; (c) silylated **2**, dry DCE, TMSOTf, rt, 20 h; (d) TBAF, dry THF, rt, 72 h; (e) H_2, Pd/C, MeOH, rt, 16 h.

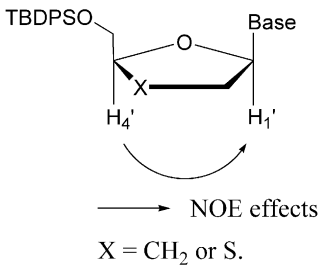
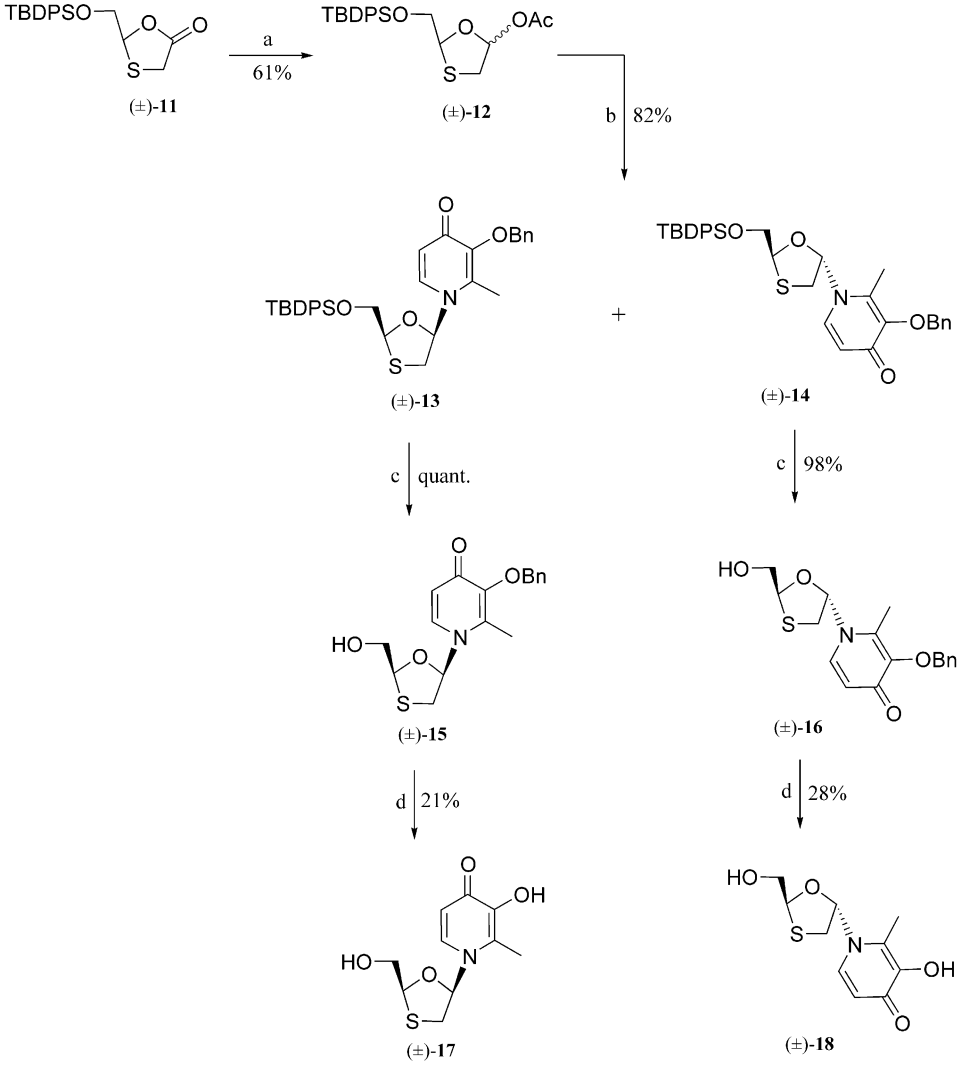


Figure 3.

and **6** were converted to compounds **7** and **8** by treatment with TBAF in THF. Catalytic hydrogenation in MeOH over 10% palladium on carbon gave the *cis* nucleoside **9** and the *trans* nucleoside **10** in quantitative yields.[8] In order to prepare the oxathiolane derivatives **17** and **18** (Scheme 3) the racemate thialactone **11** previously described by Choi et al.[9] was reduced with DIBAL-H and acetylated by Ac_2O in presence of pyridine and 4-(dimethylamino)pyridine to give the corresponding acetate **12** in 64% yield. The heterocycle base **2** was silylated and reacted with **12** in 1,2-dichloroethane and TMSOTf as catalyst. The relative stereochemistry of these compounds was assigned by NOESY and COSY experiments (Fig. 3). NOE interactions were observed between H-1′ and H-4′ suggesting the *cis* configuration of the less polar **13** and the *trans* configuration of the more polar **14**. The racemic *cis* nucleoside **13** and the racemic *trans* nucleoside **14** were then deprotected by treatment with TBAF in THF, to give **15** and **16** in quantitative yields. Since the sulphur atom, contained in the oxathiolane ring, poisons the Pd catalyst, debenzylation of the heterocycle base was successfully achieved with the use of iodotrimethylsilane[10,11] to afford the racemic *cis* nucleoside **17** and the racemic *trans* nucleoside **18** in modest yields.

Evaluation of antiviral activity was done as described previously.[12] The compounds were evaluated against HIV-1 and HIV-2, herpes simplex virus type 1 (HSV-1)



Scheme 3. (a) DIBAL, dry DCM, −90 °C then Ac_2O, pyridine, DMAP, rt, 72 h; (b) silylated **2**, dry DCE, TMSOTf, rt, 24 h; (c) TBAF, dry THF, rt, 3 h; (d) NaI, TMSCl, dry $CHCl_3$, rt, 18 h.

Table 1. Anti-HIV and anti-HSV activities of compounds **9**, **10**, (±)-**17**, and (±)-**18**

Compd	Anti-HIV activity			Anti-HSV activity			
	EC_{50} (μM) HIV-1 in CEM cells	EC_{50} (μM) HIV-2 in CEM cells	CC_{50} (μM)	EC_{50} (μM) HSV-1 (KOS) in HEL cells	EC_{50} (μM) HSV-2 (G) in HEL cells	EC_{50} (μM) HSV-1 TK neg in HEL cells	CC_{50} (μM)
9	>50	>50	101±6.2	40	>900	500	>900
10	>50	>50	>50	177	500	500	>900
(±)-**17**	>80	>80	203±2.5	32	81	80	>100
(±)-**18**	>80	>80	203±11.9	40	90	95	>400
ACV (acyclovir)	>200	>200	>200	0.32	1.3	88	>1700
DHPG (ganciclovir)	>200	>200	>200	—	0.06	—	>400
HPMPC (cidofovir)	>200	>200	>200	0.57	—	—	>350

EC_{50}, effective concentration or concentration required to inhibit 50% of virus induced cytopathicity; CC_{50}, cytotoxic concentration or concentration required to reduce cells viability by 50%; —not determined.

and type 2 (HSV-2), vaccinia virus and vesicular stomatitis virus in HEL cells, parainfluenza-3 virus, reovirus-1, Sindbis virus, coxsackie B4 virus, Punta Toro virus in Vero cells and respiratory syncytial virus in HeLa cell cultures. The anti-HIV and HSV activities of compounds **9**, **10**, **17** and **18** are represented in Table 1. None of these compounds were active against any of the tested viruses except for herpes simplex virus (Table 1). Compound **10**, **17** and **18** displayed moderate activity against both wild-type HSV-1 and HSV-2, as well as against a thymidine kinase deficient strain of HSV-1 that has a 270 fold reduced sensitivity for acyclovir than the wild-type virus. The weak but consistent activity of these compounds against HSV-1 and HSV-2 is encouraging and may suggest that these new nucleosides are metabolised to their 5′-triphosphates or as such recognised by the viral DNA polymerases. The (moderate) activity of an form of a nucleoside (**10** and **18**) is quite unusual, few such molecules have been reported. Further work is needed both to design analogues with an improved anti-herpes virus activity and to unravel their mechanism of action.

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