Articles

Synthesis and Antiviral Evaluation of Cyclic and Acyclic 2-Methyl-3-hydroxy-4-pyridinone Nucleoside Derivatives

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A series of cyclic and acyclic nucleoside analogues derived from 3-hydroxy-4-pyridinone were synthesized using the Vorbrüggen reaction. Iron chelation studies, and antiviral evaluation against a broad panel of viruses, were performed. The pK_a value of ligand **25** and the stability constant of the corresponding iron(III) complex were compared to those of deferiprone. The pFe^{3+} values were found to be similar. Some compounds showed moderate activity against both wild-type HSV-1 and HSV-2, as well as against a thymidine kinase deficient strain of HSV-1. These results suggest a novel mode of action for this group of nucleoside analogues.

Introduction

In our efforts to identify new antiviral drugs, we have investigated the synthesis of 2-methyl-3-hydroxy-4-pyridinone (type I) and acyclic (type II) nucleoside analogues (Figure 1). There are several reasons for this strategy; first, the constant discovery of new viruses[1] which represents a continuing challenge for medicinal chemists and second, the emergence of resistance to currently FDA approved drugs[2] has highlighted the need for the search of new active nucleoside analogues. The compounds described in this study may lead to the design of new reverse transcriptase inhibitors. In addition, it has been demonstrated that iron chelation, which would make iron unavailable for redox reactions, could influence HIV replication in three possible ways: (1) by inactivation of the iron-dependent cellular enzyme ribonucleotide reductase which is responsible for generating the building blocks for viral DNA;[3] (2) by reduction of nuclear factor NF-κB activation;[4] (3) by inhibition of proliferation and the resulting onset of apoptosis.[5]

3-Hydroxy-4-pyridinones (HPOs) are currently one of the main candidates for the development of orally active iron chelators (Figure 2).[6] The 1,2-dimethyl derivative (deferiprone, Figure 2), with an associated pFe^{3+} value of 19.4, is the only orally active iron chelator currently available for clinical use (marketed by Apotex Inc., Toronto, Canada as Ferriprox).[7]

Recently, a clear synergism in HIV-1 inhibition was observed by combining iron chelators with the anti-HIV nucleoside analogues ddI, and it was suggested that in combination with existing antivirals, iron chelation could have a beneficial effect on HIV-disease.[8] So far, only three types of HPO nucleoside analogues have been synthesized, mainly with the goal of improving oral bioavailability of deferiprone[9] but also as novel nucleosides for alternative DNA base pairing through metal complexation (Figure 3).[10]

These results and hypotheses prompted us to synthesize type I and II nucleoside analogues as described in Figure 1. Type I compounds are cyclic and correspond to the class of 2′,3′-dideoxynucleosides in which the base has been changed to a 3-hydroxy-4-pyridinone. The synthesized nucleosides contain sugar moieties similar to that of two currently FDA-approved anti-HIV 2′,3′-dideoxynucleosides, namely ddC and 3TC (Figure 4). Type II compounds are acyclic nucleosides related to PMEA (Figure 4).

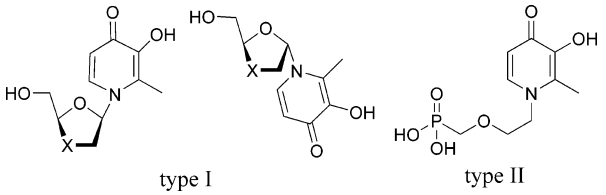

Figure 1. 3-Hydroxypyridinone nucleosides type I (cyclic analogues, X = CH_2 or S) and II (acyclic analogues);

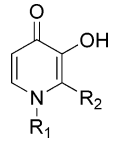

Figure 2. HPO derivative. Deferiprone (Ferriprox) $R_1 = R_2 = CH_3$.

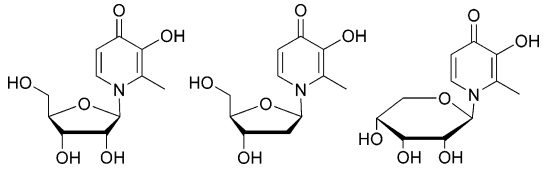

Figure 3. HPO nucleoside analogues described in the literature.

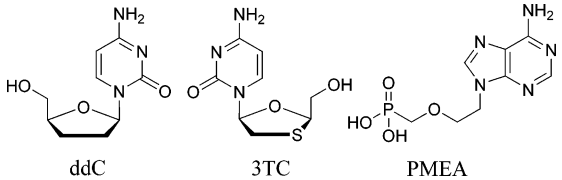

Figure 4. FDA-approved cyclic (ddC, 3TC) and acyclic (PMEA) nucleoside analogues.

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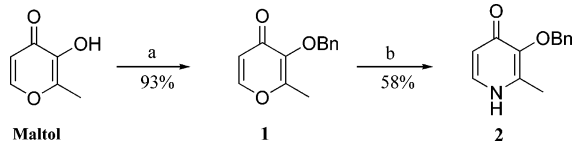
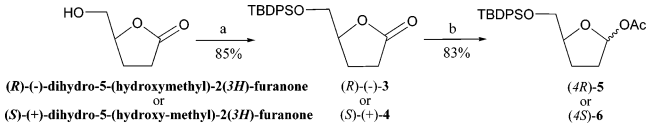
Scheme 1[a]



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

Scheme 2[a]



[a] (a) TBDPSCl, imidazole, dry DMF, rt, 18 h; (b) DIBAL, dry DCM, −90 °C then Ac_2O, pyridine, DMAP, rt, 72 h.

Iron chelation properties and antiviral evaluation on HIV, coxsackie B3, and herpes viruses (HSV-1, HSV-2, VZV, HCMV) were performed on this new class of nucleoside analogues.

Chemistry

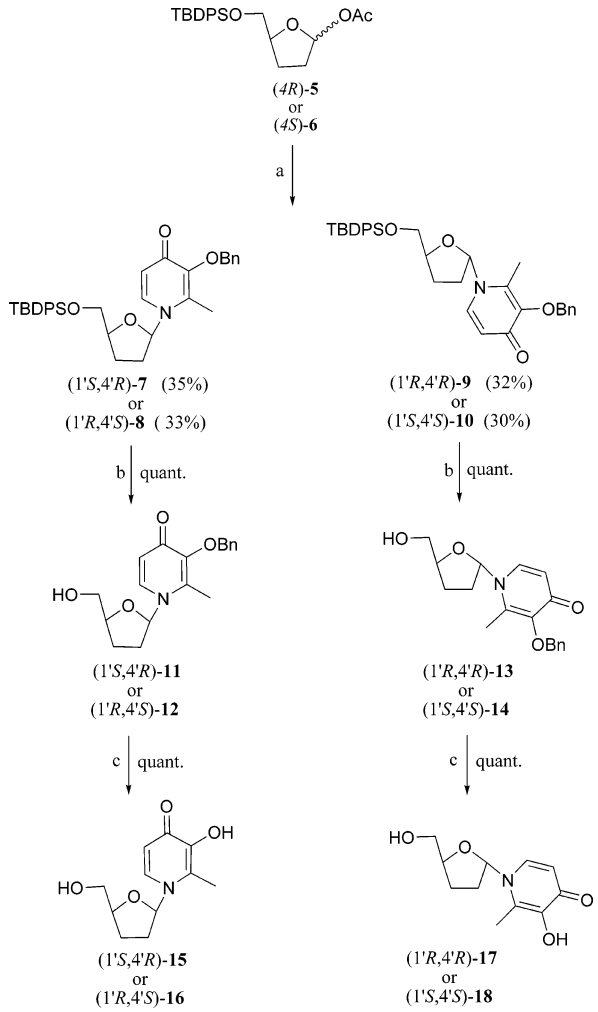
Among the different strategies used for the synthesis of cyclic nucleosides, we have investigated the straightforward Vorbrüggen procedure.[11] The 2-methyl-3-benzyloxy-4-pyridinone **2** is a requisite for the Vorbrüggen reaction together with various activated cyclic sugar derivatives. **2** was obtained from maltol which was benzylated with benzyl bromide in 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 as a free base in 58% yield.[7]

Type I analogues were obtained according to the following procedure. In the furanosyl series, the acetylated key intermediates **5** and **6** were obtained from commercially available precursors (*R*)-(−) or (*S*)-(+)-dihydro-5-(hydroxymethyl)-2-(*3H*)-furanone (Scheme 2). Standard alcohol protection of these lactones with TBDPSCl in THF gave the lactones **3** and **4** which were then reduced with diisobutylaluminum (DIBAL-H). Immediate trapping of the resulting lactol with acetic anhydride gave **5** and **6** in 83% yield. 2-Methyl-3-benzyloxy-4-pyridinone **2** was silylated under reflux for 2 h with hexamethyldisilazane (HMDS) in the presence of a catalytic amount of ammonium sulfate. After removal of excess HMDS, the base was solubilized in 1,2-dichloroethane and a mixture of **5** or **6** and trimethylsilyltriflate (TMSOTf)[11b] in 1,2-dichloroethane was slowly added at room temperature to give compounds **7**−**10** (Scheme 3).

Generally the β/α ratio was close to 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 (Figure 5). NOE interactions were observed between H-1′ and H-4′ suggesting the cis orientation of the less polar compounds **7** and **8**. The trans configuration was then assigned to the more polar isomers **9** and **10**. Compounds **7**−**10** were converted to compounds **11**−**14** by treatment with TBAF in THF. Catalytic hydrogenation in MeOH over 10% palladium on carbon gave cis nucleosides **15**−**16** and trans nucleosides **17**−**18** in quantitative yields.[12] To prepare the oxathiolanyl derivatives **25** and **26** (Scheme 4), the racemic thia-lactone **19** previously described by Choi et al.[13] was reduced with DIBAL-H and acetylated by Ac_2O in the presence of pyridine and 4-(dimethylamino)pyridine to give the corresponding acetate **20** in 61% yield.

The heterocycle base **2** was silylated and reacted with **20** in 1,2-dichloroethane using TMSOTf as a catalyst. The relative stereochemistry of the resulting compounds **21** and **22** was

Scheme 3[a]



[a] (a) Silylated 2, dry DCE, TMSOTf, rt, 20 h ; (b) TBAF, dry THF, rt, 72 h ; (c) H_2, Pd/C, MeOH, rt, 16 h.

assigned by NOESY and COSY experiments (Figure 5). NOE interactions were observed between H-1′ and H-4′ suggesting the cis configuration of the less polar **21** and the trans configuration of the more polar **22**. The racemic cis nucleoside **21** and the racemic trans nucleoside **22** were then deprotected by treatment with TBAF in THF, to give **23** and **24** in quantitative yield. Since the sulfur atom of the oxathiolane ring poisons the Pd catalyst, debenzylation of the heterocycle base was achieved by use of iodotrimethylsilane,[14] affording the racemic cis nucleoside **25** and the racemic trans nucleoside **26** in modest yields. Acyclic type II analogues were prepared according to the procedure outlined in Scheme 5. The benzylated pyranone **1** was treated in ethanol with 2-aminoethanol in basic media to afford compound **27** in 50% yield. The latter compound was treated with the diethyl phosphonate derivative **29** which was prepared by tosylation of diethyloxymethylphosphonate **28**. Condensation of **27** and **29** in the presence of sodium *tert*-butoxy

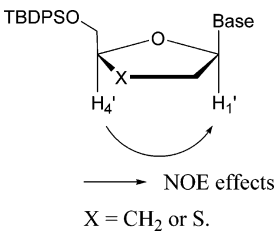
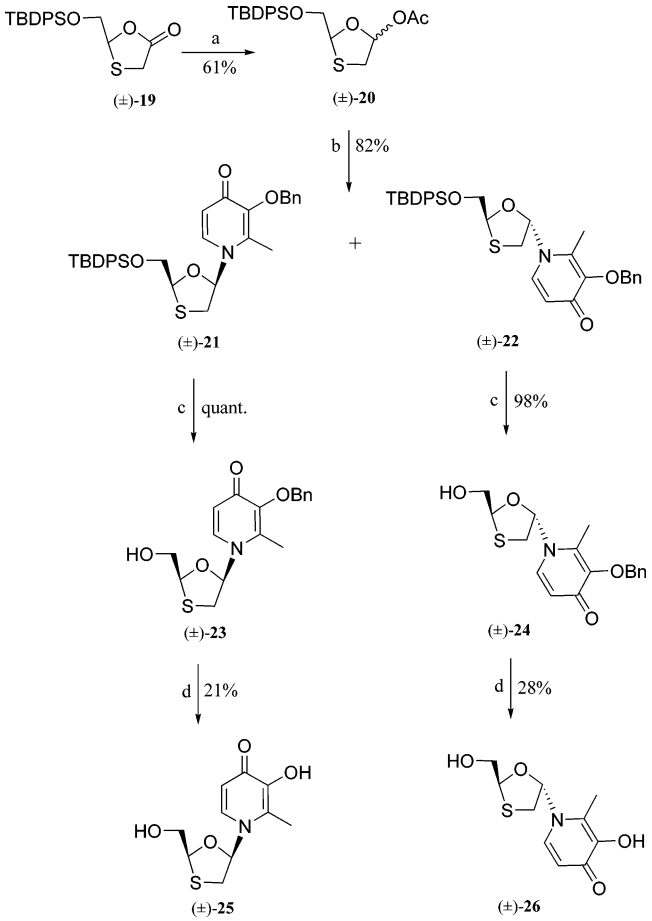


Figure 5. NOE interactions of cis type I nucleosides.

Scheme 4[a]



[a] (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.

in DMF yielded the desired compound **30** as well as the side product **31**. Although hydrolysis of compound **30** with trimethylsilyl bromide[15] gave the target compound, subsequent hydrogenation was necessary to obtain **32** in quantitative yield.

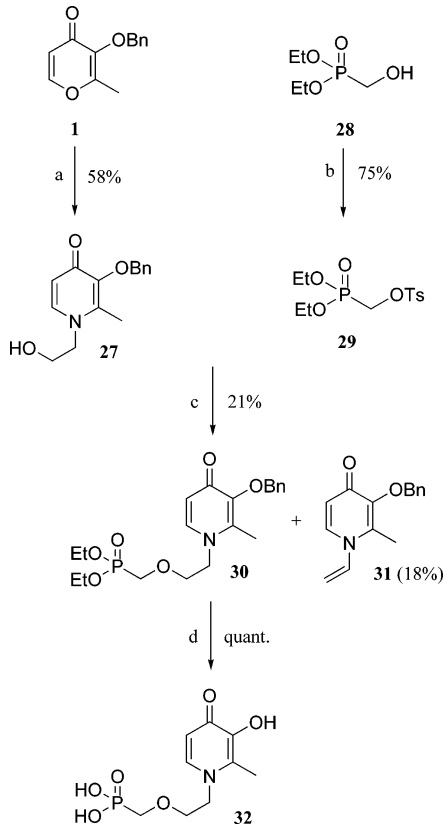
Iron Chelation Properties. Determination of the pK_a Values and Affinity Constants of Compound 25 and Deferiprone. Complex formation of iron(III) by bidentate 3-hydroxy-4-pyridinones has been previously described[6b] and follows the equations presented in Scheme 6.

pH titration curves were evaluated by spectrophotometry in the presence of iron(III) for the ligands **15**−**18**, **25**, **26**, **32** as well as for the standard deferiprone. As all the curves produced similar profiles, only two examples are presented; Figure 6 (ligand = deferiprone) and Figure 7 (ligand = **25**). The optimized pK_a values and affinity constant determined for both compounds are presented in Table 1. These values have been determined using a previously described procedure.[6b]

As previously described for deferiprone,[6b] a clear shift in λ_{max} was observed in the full speciation spectra of all the tested ligands:iron(III) complexes over pH range 2.2−11.3 which displays the pH dependence of the different metal/ligand equilibria. At low pH values the λ_{max} of the iron(III) complex (545 nm) corresponds to the two species $[Fe^{III}L]^{2+}$ and $[Fe^{III}L_2]^{+}$. Above pH 3.3 the neutral $[Fe^{III}L_3]^{0}$ complex ($\lambda_{max,}$ 460 nm) dominates.

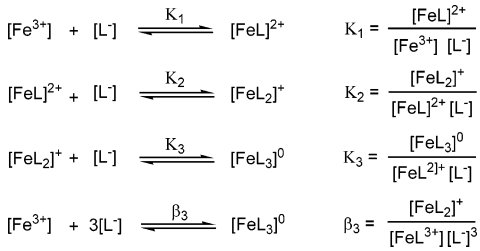
Antiviral Evaluation. Evaluation of antiviral activity was undertaken as described in the Experimental Section. The compounds were evaluated against HIV-1(III_B), HIV-2 (ROD),

Scheme 5[a]



[a] (a) $NH_2CH_2CH_2OH$, EtOH, NaOH, reflux, 16 h; (b) TsCl, NEt_3, Et_2O, −10 °C − 0 °C, 16 h; (c) tBuONa, DMF, rt, 48 h; (c) TMSBr, DCM, rt, 18 h then H_2, Pd/C 10%, rt, 16 h.

Scheme 6[a]



[a] Complex formation of iron(III) by a bidentate 3-hydroxy-4-pyridinone.

herpes simplex virus type 1 (HSV-1), herpes simplex virus type 2 (HSV-2), vaccinia virus, and vesicular stomatitis virus in Hela cells, parainfluenza-3 virus, reovirus-1, Sindbis virus, coxsackie

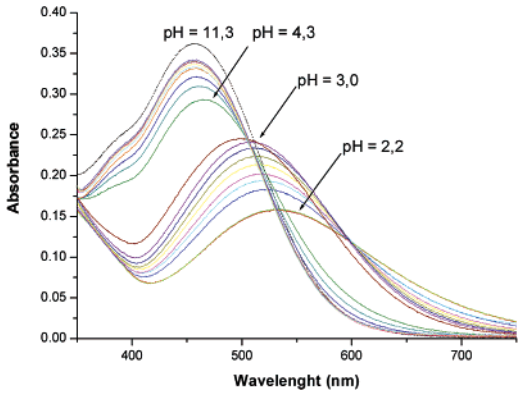


Figure 6. pH dependence of the spectrum of deferiprone in the presence of iron(III) over the pH range of 2.2−11.3. [Fe(III)] = 2.55×10^{-4} M; [deferiprone] = 0.63×10^{-4} M.

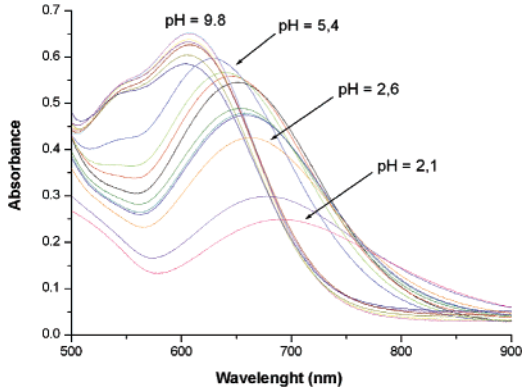


Figure 7. pH dependence of the spectrum of ligand **25** in the presence of iron(III) over the pH range of 2.1−9.8. [Fe(III)] = 2.55×10^{-4} M; [**25**] = 0.63×10^{-4} M.

Table 1. Spectrophotometric Determined pK_a Values for Ligands **25** and Deferiprone and Affinity Constants for the Corresponding Fe(III) Complexes

	compd **25**	deferiprone
pK_{a1}	3.1	3.6
pK_{a2}	9.5	9.6
log K_1	14.3	14.6
log K_2	11.8	12.2
log K_3	9.5	9.7
log β_3[a]	35.6	36.4
pFe^{3+} (at pH 7.4)	19.9	19.4

[a] log β_3 = log K_1 + log K_2 + log K_3.

B4 virus, Punta Toro virus in Vero cells, and respiratory syncytial virus in Hela cell cultures. None of the compounds described in this study were active against any of the tested viruses with the exception of herpes simplex virus. The anti-HIV and HSV activities of compounds **12**, **16**−**18**, **25**, and **26** are presented in Table 2. Compounds **16**−**18** displayed moderate activity against wild-type HSV-1. Compounds **25** and **26** showed moderate activity against both wild-type HSV-1 and HSV-2, as well as against a thymidine kinase deficient strain (TK^-) of HSV-1 that is 270-fold less sensitive to acyclovir than the wild-type virus.

Discussion

None of the nucleoside analogues described in this study were active against HIV, whereas moderate activity was shown against HSV-1 and HSV-2. The absence of anti-HIV activity may arise due either to a lack of intracellular phosphorylation or to difficulties associated with crossing the cellular membrane. It seems likely that with the type II acyclic derivative **32**, the negative charge associated with the phosphate group is responsible for its general inactivity. As a result, the synthesis of phosphonate derivatives, acting as prodrugs of compound **32** might be expected to improve the potential of this analogue. This work is currently in progress in our laboratory. Concerning HSV, chelation properties of the type I cyclic nucleoside analogues seem to be a prerequisite for the antiviral activities. Hydroxypyridinones form five-membered chelate rings in which iron is coordinated by the two vicinal oxygen atoms.[16] As shown in Table 1, benzyl protection of the 3-hydroxy group in compound **12** abolishes the anti-HSV properties. It is unlikely that the ether link would be hydrolyzed in the cell culture medium. This assumption was confirmed by replacing ester function by ethers in reverse transcriptase nucleoside inhibitors.[17] The affinity constant pFe^{3+} for the representative nucleoside analogue **25** was similar to that of deferiprone, indicating that the replacement of the methyl group by an oxathiolane ring does not inhibit the iron chelating properties of these analogues. Not much difference in the HSV activities was observed for the stereoisomers **17** and **18**, although the D-enantiomer **18**-(1′*S*,4′*S*) was slightly less cytotoxic that its L-counterpart **17**. Since both are active against HSV-1 and HSV-2, oxathiolane derivatives **25** and **26** represent the most interesting compounds. Unlike their analogues **16**−**18**, they are both active on a thymidine kinase deficient strain of HSV-1. This mechanism needs to be further explored, it would appear that these analogues do not need to be phosphorylated in order to be active. Interestingly, the activity observed for the α epimers (**26**) is quite unusual and few such molecules have been reported. This may indicate a new mode of action for these compounds. Although compounds **25** and **26** were tested as racemates, it would be interesting to synthesize and test the pure enantiomers, mainly in order to compare their cytotoxicity profile. In conclusion, the weak activity of these compounds against HSV-1 and HSV-2 is encouraging and may suggest that these nucleosides are either metabolized to their 5′-triphosphates in a HSV TK-independent manner or recognized in a nonphosphorylated form by the viral DNA polymerases or another yet unidentified viral target. How iron chelation is associated with the relative activities of these analogues is not known. At the present time, insufficient data are available to understand the mechanism of action, but the compounds described in this study may represent a new lead. Further work is required both to design analogues with an improved anti-herpes virus activity and to unravel their mechanism of action.

Experimental Section

General Methods. Melting points were determined in capillary tubes with a 9100 Electrothermal (Fisher Scientific) apparatus and are uncorrected. The ^1H NMR and ^{13}C NMR spectra were

Table 2. Antiviral Activity of Type I and II Nucleosides **12**, **16**, **17**, **18**, **25**, **26**, and **32** in Comparison with Standard and Approved Antiviral Drugs

compound	EC_{50}, μM HSV-1 KOS (Hel cells)	EC_{50}, μM HSV-1 TK^- (Hel cells)	EC_{50}, μM HSV-2 G (Hel cells)	MTC, μM	EC_{50}, μM HIV-1, HIV-2 (CEM)	CC_{50}, μM
(1′*R*,4′*S*)-**12**	>200	>200	>200	>900	>150	>150
(1′*R*,4′*S*)-**16**	40 ± 4.4	500 ± 4.3	>900	>900	>50	>50
(1′*R*,4′*R*)-**17**	177 ± 7.5	>177	>177	>900	>90	84 ± 21
(1′*S*,4′*S*)-**18**	177 ± 6.3	>177	>177	>900	>50	101 ± 6
(±)-β **25**	32 ± 8.6	80 ± 1.6	81 ± 3.6	>400	>80	188 ± 11
(±)-α **26**	40 ± 5.7	95 ± 6.5	90 ± 29	>400	>80	188 ± 2.0
32	>200	−	>200	>200	>50	>50
acyclovir	1.12 ± 1.10	86.6 ± 23	1.76 ± 1.10	>1700	>50	−
gancyclovir	0.06 ± 0.012	−	0.06 ± 0.08	−	>50	−
cidofovir	0.57 ± 0.04	−	−	>350	>10	−
AZT	−	−	−	−	0.0055 ± 0.0007	>100

[a] Data are the mean ± SD (standard deviation) of at least three independent experiments. EC_{50}, μM: effective concentration or concentration required to inhibit 50% of virus induced cytopathicity. MTC, μM: minimal toxic concentration (or concentration that is required to cause a microscopically detectable alteration of normal cell morphology). CC_{50}, μM: cytotoxic concentration or concentration required to reduce cell viability by 50%. − = not determined

determined with a BRUKER AMX 200 MHz and referenced to the solvent. Chemical shifts are expressed in ppm and coupling constants (*J*) are in hertz (*s* = singlet, d = doublet, dd = double doublet, ddd = double double doublet, t = triplet, dt = double triplet, tt = triple triplet, m = multiplet, dm = double multiplet, triple multiplet). FAB^+ mass spectra were obtained on a JEOL DX-100 mass spectrometer (Laboratoire de Mesures Physiques RMN, Dr. Astier, USTL, Montpellier, France) using a cesium ion source and a glycerol/thioglycerol matrix. Elemental microanalysis were determined by Service Central d'Analyse CNRS Vernaison-Lyon France and gave combustion values for C, H, N within 0.4% of the theoretical values. Preparative flash column chromatography was performed using silica gel (Merck) G60 230−240 mesh. Analytical thin layer chromatographies were performed on silica gel 60F 254 aluminum plates (Merck) of 0.2 mm thickness. The spots were examined with UV light and Cericdip spray. Preparative TLC was done on EM Science glass plates silica gel 60F 254 (1.0 mm or 2.0 mm layer).

2-Methyl-3-benzyloxy-4(*1H*)-pyranone (1). To a stirred solution of 2-methyl-3-hydroxy-4-pyranone**1** (2 g, 15.85 mmol) in methanol (17 mL) were successively added sodium hydroxide (700 mg, 17.44 mmol) in water (1.6 mL) and benzyl bromide (2.18 mL, 18.22 mmol). The mixture was heated at reflux for 16 h. Removal of the solvent under reduced pressure gave an orange oil which was then taken up in dichloromethane and washed with 5% aqueous sodium hydroxide and water. Organic fractions were dried over anhydrous $MgSO_4$ and filtered. Evaporation of the volatiles and purification by recrystallization (Et_2O) yielded **1** (3.26 g, 93%) as colorless needles: mp 53 °C (lit.[18] mp 53−55 °C).

2-Methyl-3-benzyloxy-4(*1H*)-pyridinone (2). 2-Methyl-3-benzyloxy-4-pyranone **1** (3.80 g, 17.57 mmol) dissolved in ethanol (10 mL) was treated with a 28% ammonium hydroxide solution-(40 mL). The resulting suspension was refluxed for 16 h. Solvent was removed under reduced pressure, and water (30 mL) was added. The resulting mixture was adjusted to pH 1 with concentrated hydrochloric acid and extracted with EtOAc. The aqueous solution was then adjusted to pH 10 with 2 M sodium hydroxide solution and extracted with $CHCl_3$. The organic extracts were combined, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Recrystallization from ethanol afforded **2** (2.17 g, 58%) as a white powder: mp 165−166 °C (lit.[18] mp 162−163 °C).

(*R*)-(−)-5-[(*tert*-Butyldiphenylsilyl)oxymethyl]-4,5-dihydrofuran-2(*3H*)-one (3). To a stirred solution of (*R*)-(−)-5-(hydroxymethyl)-4,5-dihydrofuran-2(*3H*)-one (2 g, 17.22 mmol) in dry DMF (30 mL) under argon was added at 0 °C imidazole (1.75 g, 25.83 mmol) followed by the slow addition of *tert*-butyldiphenylsilyl chloride (5.30 mL, 20.66 mmol). The reaction mixture was stirred for 14 h at room temperature, and the DMF was removed under reduced pressure. The residue was dissolved in Et_2O, washed with saturated $NaHCO_3$, water, and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (cyclohexane/EtOAc: 8/2) afforded **3** (5.91 g, 85%) as a white solid: mp 74−75 °C.

An analogous procedure using (*S*)-(+)-5-(hydroxymethyl)-4,5-dihydrofuran-2(*3H*)-one gave (*S*)-(+)-5-[(*tert*-butyldiphenylsilyloxy)methyl]-4,5-dihydro-2(*3H*)-furanone (**4**) as white solid (85%): mp 74−75 °C (lit.[19] mp 70−72 °C).

(4*R*)-1-*O*-Acetyl-5-*O*-*tert*-butyldiphenylsilyl-2,3-dideoxy-L-ribofuranose (5). To a stirred solution of **3** (2 g, 5.64 mmol) in dry dichloromethane (70 mL) at −90 °C under argon was added a 1 M solution of DIBAL-H in hexane (17 mL, 16.92 mmol) over a 15 min period. The mixture was allowed to stir for 2 h at −90 °C before being quenched with methanol (20 mL) and stirred for 2 h at room temperature. The reaction mixture was successively washed with saturated sodium tartrate solution, water, and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting crude lactol was acetylated with acetic anhydride (800 μL, 8.46 mmol), pyridine (920 μL, 11.28 mmol), and DMAP (206 mg, 1.69 mmol) in dry dichloromethane (35 mL) at 0 °C for 2 h. The reaction was quenched by addition of a saturated solution of $NaHCO_3$, extracted with dichloromethane, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (cyclohexane/EtOAc: 9/1) yielded **5** as a colorless oil (1.96 g, 83%). SM (GT, FAB^+): 281 $(M - OAc\text{-}tBu)^+$, 339 $(M - OAc)^+$, 399 $(M + 1H)^+$.

Analogous procedures using furanone **4** gave (4*S*)-1-*O*-acetyl-5-*O*-*tert*-butyldiphenylsilyl-2,3-dideoxy-D-ribofuranose (**6**) as a colorless oil (83%).

(1′*S*,4′*R*)-1-[5′-*tert*-Butyldiphenylsilyl-2′,3′-dideoxy-β-L-ribofuranosyl]-2-methyl-3-benzyloxy-4-pyridinone (7) and (1′*R*,4′*R*)-1-[5′-*tert*-Butyldiphenylsilyl-2′,3′-dideoxy-α-L-ribofuranosyl]-2-methyl-3-benzyloxy-4-pyridinone (9). A suspension of pyridinone **2** (1.50 g, 7.11 mmol) and ammonium sulfate (cat.) in hexamethyldisilazane (15 mL, 71.1 mmol) was refluxed until a clear solution was obtained (2 h). The reaction mixture was cooled to room temperature and HMDS was removed under reduced pressure in anhydrous conditions. To the resulting residue was added, under argon, the acetate **5** (1.96 g, 4.91 mmol) in dry 1,2-DCE (30 mL). The reaction mixture was cooled to 0 °C, treated with TMSOTf (1.77 mL, 9.82 mmol), and allowed to stir successively at 0 °C for 10 min and 18 h at room temperature. It was then diluted in dichloromethane, washed with saturated $NaHCO_3$ solution, water, and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (EtOAc/MeOH: 9/1) yielded **7** as a white solid (950 mg, 35%) and **9** as a colorless oil (880 mg, 32%). (**7**): mp 128 °C; SM (GT, FAB^+): 216 $(B + 1H)^+$; 339 $(M - B)^+$; 554 $(M + 1H)^+$. (**9**): SM (GT, FAB^+): 216 $(B + 1H)^+$, 339 $(M - B)^+$, 554 $(M + 1H)^+$.

Analogous procedures using acetate **6** gave (1′*R*,4′*S*)-1-[5′-*O*-*tert*-butyldiphenylsilyl-2′,3′-dideoxy-β-D-ribofuranosyl]-2-methyl-3-benzyloxy-4-pyridinone (**8**) as a white powder (33%) and (1′*S*,4′*S*)-1-[5′-*O*-*tert*-butyldiphenylsilyl-2′,3′-dideoxy-α-D-ribofuranosyl]-2-methyl-3-benzyloxy-4-pyridinone (**10**) as a colorless oil (30%). (**8**): mp 131 °C.

(1′*S*,4′*R*)-1-[2′,3′-Dideoxy-β-L-ribofuranosyl]-2-methyl-3-benzyloxy-4-pyridinone (11). To a solution of**7** (950 mg, 1.71 mmol) in dry THF (10 mL) was added a 1 M solution of TBAF in THF (2.57 mL, 2.57 mmol). The reaction mixture was stirred at room temperature for 72 h. and the solvent was removed under reduced pressure. Purification by flash chromatography (dichloromethane/MeOH: 9/1) gave **11** (540 mg, quantitative) as a white powder: mp 116 °C. SM (GT, FAB^+): 216 $(B + 1H)^+$, 316 $(M + 1H)^+$.

Analogous procedure using compounds **8**, **9**, and **10** gave respectively (1′*R*,4′*S*)-1-[2′,3′-dideoxy-β-D-ribofuranosyl]-2-methyl-3-benzyloxy-4-pyridinone (**12**) as a white powder (quantitative), (1′*R*,4′*R*)-1-[2′,3′-dideoxy-α-L-ribofuranosyl]-2-methyl-3-benzyloxy-4-pyridinone (**13**) as a colorless oil (quantitative), and (1′*S*,4′*S*)-1-[2′,3′-dideoxy-α-D-ribofuranosyl]-2-methyl-3-benzyloxy-4-pyridinone (**14**) as a white foam (quantitative). (**12**): mp 118−120 °C; Anal. ($C_{18}H_{21}NO_4$) C, H, N, O. (**14**): mp 104 °C.

(1′*S*,4′*R*)-1-[2′,3′-Dideoxy-β-L-ribofuranosyl]-2-methyl-3-hydroxy-4-pyridinone (15). A suspension of compound **11** (200 mg, 0.63 mmol) and 5% Pd/C (20 mg) in methanol (10 mL) was hydrogenated for 16 h under atmospheric pressure. The reaction mixture was filtered through Celite and concentrated to afford compound **15** as an orange powder (140 mg, quantitative): mp 172−173 °C. Anal. ($C_{11}H_{15}NO_4$) C, H, N, O. SM (GT, FAB^+): 126 $(B + 1H)^+$, 226 $(M + 1H)^+$, 451 $(2M + 1H)^+$.

An analogous procedure using compounds **12**, **13**, and **14** gave respectively (1′*R*,4′*S*)-1-[2′,3′-dideoxy-β-D-ribofuranosyl]-2-methyl-3-hydroxy-4-pyridinone (**16**) as an orange powder (quantitative), (1′*R*,4′*R*)-1-[2′,3′-dideoxy-α-L-ribofuranosyl]-2-methyl-3-hydroxy-4-pyridinone (**17**) as an orange powder (quantitative), and (1′*S*,4′*S*)-1-[2′,3′-dideoxy-α-D-ribofuranosyl]-2-methyl-3-hydroxy-4-pyridinone (**18**) as an orange powder (quantitative). (**16**): mp 176 °C. Anal. ($C_{11}H_{15}NO_4$) C, H, N, O. SM (GT, FAB^+): 126 $(B + 1H)^+$, 226 $(M + 1H)^+$, 451 $(2M + 1H)^+$. (**17**): mp 94 °C. Anal. ($C_{11}H_{15}NO_4$) C, H, N, O. SM (GT, FAB^+): 126 $(B + 1H)^+$, 226 $(M + 1H)^+$, 451 $(2M + 1H)^+$. (**18**): mp 92 °C. Anal. ($C_{11}H_{15}NO_4$) C, H, N, O. SM (GT, FAB^+): 126 $(B + 1H)^+$, 226 $(M + 1H)^+$, 451 $(2M + 1H)^+$.

5-Acetoxy-2-[(*tert*-butyldiphenylsilyl)oxymethyl]-1,3-oxathiolane (20). To a stirred solution of **19** (3.80 g, 10.20 mmol) in dry toluene (100 mL) at −90 °C under argon was added over a 15 min period a 1 M solution of DIBAL-H in hexane (25.50 mL, 25.50 mmol). The reaction mixture was stirred for 2 h at −90 °C, quenched with methanol (30 mL), and allowed to stir at room temperature for 2 h. It was then successively washed with saturated sodium tartrate solution, water, and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting crude lactol was acetylated with acetic anhydride (1.20 mL, 12.69 mmol), pyridine (1.37 mL, 16.92 mmol), and DMAP (310 mg, 2.53 mmol) in dry dichloromethane (50 mL) at 0 °C for 16 h. The reaction was quenched by the addition of a saturated solution of $NaHCO_3$, extracted with dichloromethane, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (cyclohexane/EtOAc: 8/2) yielded **20** as a colorless oil (2.60 g, 61%).

(±)-1-[5′-*O*-*tert*-Butyldiphenylsilyl-2′,3′-dideoxy-3′-thia-β-ribofuranosyl]-2-methyl-3-benzyloxy-4-pyridinone (21) and (±)-1-[5′-*O*-*tert*-Butyldiphenyl-silyl-2′,3′-dideoxy-3′-thia-α-ribofuranosyl]-2-methyl-3-benzyloxy-4-pyridinone (22). A suspension of pyridinone **2** (2.00 g, 9.36 mmol) and ammonium sulfate (cat.) in hexamethyldisilazane (15 mL, 71.1 mmol) was refluxed until a clear solution was obtained (2 h). The reaction mixture was cooled to room temperature, and HMDS was removed under reduced pressure in anhydrous conditions. To the resulting residue was added under argon the acetate **20** (2.60 g, 6.24 mmol) in dry 1,2-DCE (30 mL). The reaction mixture was cooled to 0 °C, treated with TMSOTf (1.70 mL, 9.32 mmol), and allowed to stir at 0 °C for 10 min and then 24 h at room temperature. It was then diluted in dichloromethane, washed with saturated $NaHCO_3$ solution, water, and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (EtOAc/MeOH: 95/5) yielded **21** as a white powder (1.60 g, 45%) and **22** as a colorless oil (1.32 g, 37%). (**21**): mp 146−147 °C; SM (GT, FAB^+): 216 (**2** + 1H)$^+$, 357 (M − 2)$^+$, 572 (M + 1H)$^+$, 1143 (2M + 1H)$^+$. (**22**): SM (GT, FAB^+): 216 (2 + 1H)$^+$, 357 (M − 2)$^+$, 572 (M + 1H)$^+$, 1143 (2M + 1H)$^+$.

(±)-1-[2′,3′-Dideoxy-3′-thia-β-ribofuranosyl]-2-methyl-3-benzyloxy-4-pyridinone (23). To a solution of **21** (1.07 g, 1.87 mmol) in dry THF (15 mL) was added a 1 M solution of TBAF in THF (3.74 mL, 3.74 mmol). The reaction mixture was stirred at room temperature for 72 h, and the solvent was removed under reduced pressure. Purification by flash chromatography (dichloromethane/MeOH: 9/1) gave **23** (621 mg, quantitative) as a white foam: mp 116 °C; SM (GT, FAB^+): 216 (2 + 1H)$^+$, 242 (M − Bn)$^+$, 334 (M + 1H)$^+$.

An analogous procedure using compound **22** gave (±)-1-[2′,3′-dideoxy-3′-thia-α-ribofuranosyl]-2-methyl-3-benzyloxy-4-pyridinone (**24**) as a colorless oil (quantitative). SM (GT, FAB^+): 216 (**2** + 1H)$^+$, 242 (M − Bn)$^+$, 334 (M + 1H)$^+$.

(±)-1-[2′,3′-Dideoxy-3′-thia-β-ribofuranosyl]-2-methyl-3-hydroxy-4-pyridinone (25). Iodotrimethylsilane was generated, in situ, by addition at room temperature of NaI (900 mg, 5.9 mmol) and chlorotrimethylsilane (750 μL, 5.9 mmol) in dry chloroform (10 mL). Compound **23** (200 mg, 0.59 mmol) diluted in dry chloroform (10 mL) was then slowly added. The reaction mixture was stirred 16 h at room temperature and refluxed for 6 h. The reaction was quenched by the addition of methanol (10 mL), filtered, and concentrated under reduced pressure. The residue obtained was successively triturated with EtOAc and Et_2O. Purification by flash chromatography (dichloromethane/methanol: 85/15) yielded **25** (30 mg, 21%) as an orange powder: mp 222 °C. Anal. ($C_{10}H_{13}NO_4S$) C, H, N, O. SM (GT, FAB^+): 126 (B + 1H)$^+$, 244 (M + 1H)$^+$.

Analogous procedure using compound **24** gave (±)-1-[2′,3′-dideoxy-3′-thia-α-ribofuranosyl]-2-methyl-3-hydroxy-4-pyridinone (**26**) as an orange powder (28%): mp 207 °C. Anal. ($C_{10}H_{13}NO_4S$) C, H, N, O. SM (GT, FAB^+): 126 (B + 1H)$^+$, 244 (M + 1H)$^+$.

1-(2-Hydroxyethyl)-2-methyl-3-benzyloxy-4-pyridinone (27). To a solution of 2-methyl-3-benzyloxy-4-pyranone**1** (3.20 g, 14.79 mmol) in ethanol (30 mL) were successively added 2-aminoethanol (1.34 mL, 22.19 mmol) and 2 M sodium hydroxide solution (1.50 mL, 2.95 mmol). The mixture was refluxed for 16 h. The solvent was then removed under reduced pressure, and water (40 mL) was added. The mixture was adjusted to pH 1 with concentrated hydrochloric acid and washed with Et_2O. The resultant aqueous solution was then adjusted to pH 7 with 10 M sodium hydroxide solution and extracted with chloroform. The organic extracts were combined, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Recrystallization from EtOH/Et_2O afforded pyridinone **27** as white crystals (1.88 g, 50%): mp 208−210 °C; SM (GT, FAB^+): 125 (M − Bn − OEt)$^+$, 168 (M − Bn)$^+$, 260 (M + 1H)$^+$, 519 (2M + 1H)$^+$.

Diethyl [[(*p*-Toluenesulfonyl)oxy]methyl]phosphonate (29). Triethylamine (3.38 mL, 24.04 mmol) was added dropwise to a stirred solution of diethyl hydroxymethylphosphonate **28** (3.85 g, 22.89 mmol) in dry Et_2O (30 mL). The mixture was cooled to −10 °C, and a solution of toluene-*p*-sulfonylchoride (4.58 g, 24.04 mmol) in dry Et_2O (10 mL) was added dropwise. The solution was stirred at 0 °C for 3 h and at room temperature for 16 h. Et_2O (80 mL) was then added, and a solid was filtered off. Solvents were removed under reduced pressure, and the resulting oil was purified by flash chromatography (dichloromethane/EtOAc: 9/1) to afford **29** (5.57 g, 75%) as a colorless oil. SM (GT, FAB^+): 155 (Ts)$^+$, 267 (M − 2Et)$^+$, 295 (M − Et)$^+$, 323 (M + 1H)$^+$, 645 (2M + 1H)$^+$.

1-[2′-(Diethylphosphonomethoxy)ethyl]-2-methyl-3-benzyloxy-4-pyridinone (30). To a solution of pyridinone **27** (200 mg, 0.771 mmol) in dry DMF (10 mL) was added, at room temperature, sodium *tert*-butoxide (222 mg, 2.31 mmol). The mixture was stirred 10 min, and a solution of diethyl phosphonate **29** (373 mg, 1.15 mmol) in dry DMF (3 mL) was added. The reaction mixture was stirred for 48 h and then quenched with water (10 mL), extracted with $CHCl_3$, and washed with brine. The organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (dichloromethane/methanol: 9/1) yielded **30** as a colorless oil (67 mg, 21%). SM (GT, FAB^+): 290 (M − Bn − Et)$^+$, 318 (M − Bn)$^+$, 382 (M − Et)$^+$, 410 (M + 1H)$^+$, 819 (2M + 1H)$^+$.

1-[2′-(Phosphonomethoxy)ethyl]-2-methyl-3-hydroxy-4-pyridinone (32). Bromotrimethylsilane (322 μL, 2.44 mmol) was added dropwise to compound **30** (100 mg, 0.24 mmol) dissolved in dry dichloromethane (10 mL). The mixture was stirred at room temperature for 18 h, and the reaction was quenched with methanol (5 mL). After evaporation to dryness, the residue was coevaporated three times with methanol and toluene. The residue was resuspended in methanol (5 mL) and hydrogenated over 5% Pd/C (8 mg) for 16 h under atmospheric pressure. The reaction mixture was filtered through Celite and concentrated to afford compound **32** as an orange powder (63 mg, quantitative): mp 146 °C. Anal. ($C_9H_{14}NO_6P$) C, H, N, P. SM (GT, FAB^+): 264 (M − Bn)$^+$, 354 (M + 1H)$^+$.

Iron(III) Complexes. Determination of Physicochemical Properties of Ligand 25 and Deferiprone. Spectra UV were determined with a spectrophotometer Varian Cary 1E. A solution containing the ligand and iron(III) in Milli-Q water ([ligand] = 1.8×10^{-3} M, [Fe(III)] = 1.8×10^{-4} M; ligand/Fe (III) 10/1) was adjusted to pH 2 with concentrated hydrochloric acid. A 0.2 M potassium hydroxide solution was added by fractions to visualize the formation of the metal/ligand complexes according to the pH.

pK_a and iron(III) affinity constant values were determined according to a previously published procedure.[6b]

Antiviral Assays. Cells and Viruses. The origins of HSV-1 KOS and HSV-2 G, have been described before.[20] TK HSV-2 (HS-44) is a plaque-purified TK^- strain isolated from a patient refractory to ACV treatment.[21] Human embryonic lung (HEL) cells (ATCC-CCL 137) were propagated in minimal essential medium (MEM) supplemented with 10% fetal calf serum (FCS), l-glutamine, and bicarbonate. The human T-cell line CEM was propagated in RPMI medium supplemented with 10% FCS, L-glutamine, and bicarbonate.

Compounds. Acyclovir and zidovudine were from GlaxoSmith-Kline, ganciclovir from Hoffmann-La−Roche, and cidofovir from Gilead.

Anti-HSV Assays and Effect of the Compounds on Uninfected Cells. HEL cells were grown to confluency in microtiter trays and were inoculated with one of the different HSV strains at 100 times the 50% cell culture infective dose. Compounds, either alone or in combination, were added after a 2-h virus adsorption period. The virus-induced cytopathic effect (CPE) was recorded microscopically at 2 to 3 days postinfection and were expressed as percentage of the untreated controls. The 50% effective concentrations (EC_{50}) were derived from graphical plots. The minimal toxic concentration (MTC) was defined as the minimal concentration that resulted in a microscopically detectable alteration of cell morphology. The MTC was determined in uninfected confluent cultures of HEL cells that were incubated, akin to the cultures used for the antiviral assays, with serial dilutions of the compounds for the same period. Cultures were inspected microscopically for alteration of cell morphology.

Anti-HIV Assays. The methodology has been described previously.[22] In brief, CEM cells (4.5×10^5 cells per mL) were suspended in fresh culture medium and infected with HIV-1(III_B) or HIV-2(ROD) at 100 $CCID_{50}$ per mL of cell suspension. Then, 100 μL of the infected cell suspension was transferred to microplate wells, mixed with 100 μL of the appropriate dilutions of the test compounds, and further incubated at 37 °C. After 4 to 5 days, giant cell formation was recorded microscopically in the CEM cell cultures. The 50% effective concentration (EC_{50}) corresponds to the compound concentrations required to prevent syncytium formation by 50% in the virus-infected CEM cell cultures. The 50% cytostatic concentration (CC_{50}) corresponds to the compound concentration required to inhibit cell proliferation by 50%.

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Supporting Information Available: Elemental analysis and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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