η^6-(Arene)tricarbonylchromium and Manganese Complexes Linked to 2′-Deoxyuridine

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Received July 5, 2007

Summary: Synthesis of η^6-(arene)tricarbonylchromium and manganese complexes linked to 2′-deoxyuridine via a triple-bond spacer is reported using palladium-catalyzed reactions of alkynes with halogeno derivatives, and their antiviral activity in cell-based assays studied.

Introduction

In recent years, there has been remarkable interest in nucleosides in which the base unit has been modified to provide new and unique biological and chemical properties. Of particular interest has been the generation of pyrimidine analogues substituted at the C5-position of the heterocycle, especially those in the 2′-deoxyuridine series. Indeed they have been investigated as antiviral and anticancer agents.[1] In particular, 5-alkynyl-2′deoxyuridine derivatives have been reported and evaluated as potential antiviral agents,[2] and the structure−activity relationship studies seem to indicate that the C-5 substituents likely to confer activity are those that are electron-withdrawing and conjugated to the heterocycle.[3]

It is noteworthy that, whereas ruthenium,[4,5] osmium,[5] iron,[6] rhodium,[7] technetium,[8] or platinum[9a] complexes have already been incorporated into nucleosides or nucleotides, chromium and manganese complexes have never been used as monomers before. To our knowledge, only one example of synthesis of chromium tricarbonyl derivatives has been described in the literature when spaced by a thymine PNA monomer.[10] Mann et al. have also shown recently that ruthenium complexes can serve as CO-releasing molecules *in vivo*, thereby suppressing organ graft rejection and protecting tissues from ischemic injury and apoptosis.[11] Thus, we deemed interesting trying to synthesize 2′-deoxyuridine derivatives whose C5 atom carbon would be substituted by arenetricarbonylchromium[12] and -manganese complexes,[13] as electron-withdrawing groups, via a triple bond.

Indeed, the salient feature of η^6-arenetricarbonylchromium complexes and isoelectronic cationic η^6-arenetricarbonylmanganese complexes is their very high electrophilicity due to the decreased electron density of the arene ring coordinated to the $M(CO)_3$ entity. The reactivity study of such complexes allowed the development of unprecedented reactions with significant

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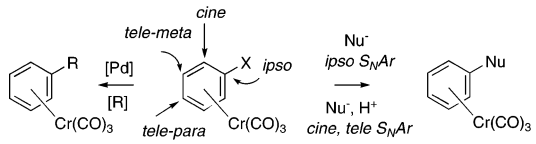
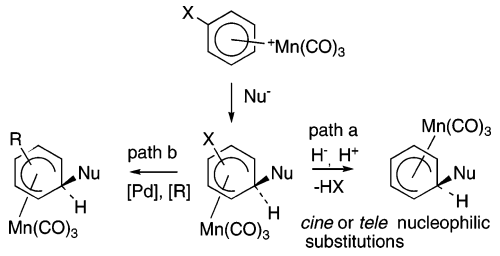
10.1021/om700674v CCC: $37.00
Publication on Web 10/05/2007

Scheme 1



Scheme 2

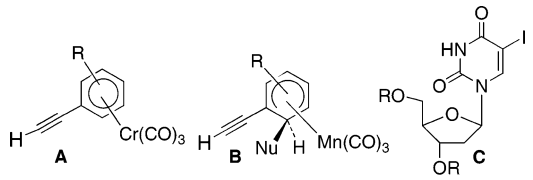


applications in organic and organometallic syntheses. Among them, in the chromium series, nucleophilic aromatic substitutions S_NAr of the X group by a nucleophile Nu^- *ipso* (on the carbon bearing the leaving group),[14] *cine* (*ortho* to the leaving group),[15] *tele-meta* (*meta* to the leaving group),[16] and *tele-para* (*para* to the leaving group)[17] have been well developed as well as palladium-catalyzed reactions,[18] which enable ready access to a large variety of substituted complexes bearing R groups such as alkyl groups, double- and triple-bond-linked to the π-system, Scheme 1.

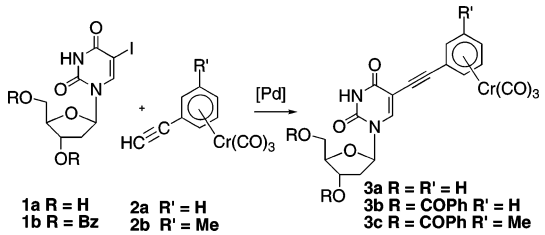
More recently, in the manganese series, analogous reactions have been established starting from neutral η^5-cyclohexadienyltricarbonylmanganese complexes, easily obtained by addition of a nucleophile to the corresponding cationic complex, Scheme 2. Thus, we reported *cine* and *tele* nucleophilic substitutions occurring when the η^5-cyclohexadienyl complex is treated with H^- and then with H^+, path a,[19] as well as Pd-cross-coupling reactions, path b,[20] R = alkyl, alkene, alkyne groups, Scheme 2.

In both cases (Cr and Mn), we reported also a general strategy to synthesize conjugated dinuclear organometallic complexes[12g,21] using a palladium-catalyzed coupling reaction. In the present work, we applied the Sonogashira coupling reaction[22] in order to link η^6-chromium complexes as well as η^5- and η^6-manganese complexes to 2′-deoxyuridine derivatives, and we report here the results of our study.

Scheme 3



Scheme 4



Results and Discussion

For our strategy of coupling reaction, we chose, as starting material, η^6-chromium **A** and η^5-manganese complexes **B**, bearing a triple bond, and, as the halogeno-substituted partner, the commercially available iodo derivative **C**, Scheme 3.

Coupling of Chromium Complexes. Sonogogashira coupling between the 5-iodo-2′-deoxyuridine **1a** with η^6-(phenylethynyl)tricarbonylchromium complex **2a**, easily obtained according to literature procedure,[21a,23,24] in the presence of $Pd(PPh_3)_4$ and CuI in Et_3N/THF at reflux or Pd_2dba_3 and $AsPh_3$ in THF/Et_3N at 50 °C, gave an intractable product mixture, Scheme 4. The use of the resin "Amberlite IRA-67" in Sonogashira cross couplings with polar nucleosides recently published[25] appeared to be promising because the separation from the reaction mixture involves only filtration. Indeed Amberlite IRA-67 is a weakly basic gel with a tertiary amine functionality and thus suitable as a heterogeneous base in the coupling reaction. However, the expected coupling product **3a** was obtained in a poor yield (13%) with decomplexed compounds in DMF as solvent, which probably decoordinates the $Cr(CO)_3$ entity. We therefore found that an appropriate mixture of MeOH in CH_2Cl_2 in a 1:4 ratio could dissolve the nucleoside and permitted performing the coupling reaction, giving complex **3a** in 40% yield with less decomplexation. Furthermore when the reaction was run with the protected nucleoside **1b** (R = Bz), Pd_2dba_3, and $AsPh_3$ in THF/Et_3N at 50 °C for 1 h, complex **3b** was isolated in 76% yield, Scheme 4.

The main spectroscopic features of arenetricarbonylchromium complexes are the presence of two strong A1 and E carbonyl ligand stretching bands[26] in the IR spectra and a remarkable

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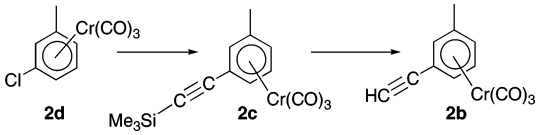
Scheme 5

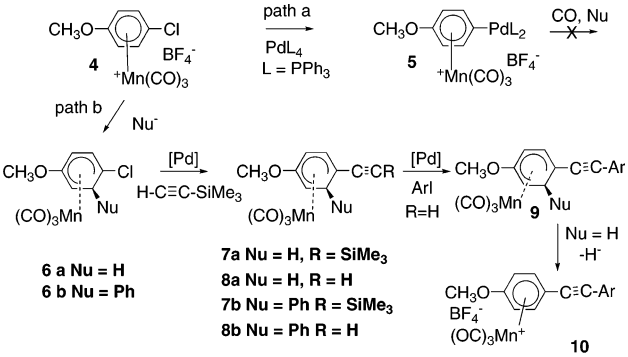


shielding effect of the $Cr(CO)_3$ entity on the aromatic proton resonances in the ^1H NMR spectra.[27] For complex **3a**, two infrared CO bands appear at 1955 and 1863 cm^{-1} in the solid state (IR ATR). The ^1H NMR spectrum displays three well-resolved signals of the five aromatic ring protons at 5.74 (*ortho* protons), 5.54 (*meta* protons), and 5.46 ppm (*para* protons) in MeOD, in good agreement with a conformation of the major conformer of the $Cr(CO)_3$ tripod anti-eclipsing the triple bond.[12e,f,28] For complex **3b**, the IR spectrum shows two stretching bands at 1961 and 1878 cm^{-1} and the ^1H NMR exhibits the five aromatic proton signals at 5.26 ppm as a broad multiplet.

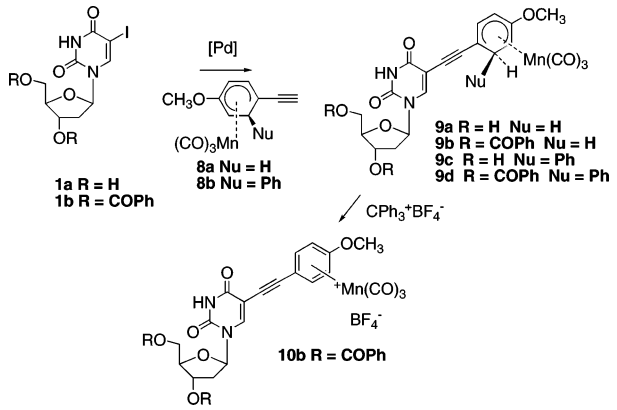
The protected nucleoside **1b**, outperforming the alcohol **1a**, was chosen as the halogeno substrate to carry out the next experiment. For this purpose, another ethynyl chromium complex was synthesized for the first time: the η^6-(3-methylphenylethynyl)tricarbonylchromium complex **2b** obtained by Pd-catalyzed reaction between η^6-(3-methylchlorobenzene)-tricarbonylchromium complex **2d**[15b] and trimethylsilylacetylene TMSA in the presence of CuI, $Pd(PPh_3)_2Cl_2$ in THF, and NEt_3, Scheme 5. The expected η^6-(1-trimetylsilylethynyl-3-methylphenyl)tricarbonylchromium complex **2c**, quantitatively obtained, was desilylated with MeOH and MeONa to afford the yellow-orange solid **2b** in 90% yield. Under the same experimental conditions as those used for the formation of **3b**, condensation of **2b** with 5-iodo-2′-deoxyuridine **1b** afforded complex **3c** in 55% yield, Scheme 4. Selected IR and NMR data display two bands at 1957 and 1871 cm^{-1} and two aromatic signals at 5.57 (1H, t) and 5.30 ppm (3H, m), respectively, in good agreement with the proposed structure.

Coupling of Manganese Complexes. Several years ago we showed that the oxidative addition of a stoichiometric amount of $Pd(PPh_3)_4$ to the C−Cl bond of the cationic η^6-(4-chloroanisole)tricarbonylmanganese complex **4**[29] proceeds readily at room temperature to give the square-planar Pd complex **5** with two *cis* phosphorus ligands. However, in contrast to the tricarbonylchromium analogue, the dinuclear complex **5** is *unreactive* toward CO and a nucleophile probably because of the strong electron-withdrawing effect of the $Mn(CO)_3^+$ entity, Scheme 6 path a. In other words, the only way to link the cationic η^6 Mn complex **4** to the iodo substrate **1b** via a triple bond was to involve the alkyne-substituted η^5-complex **8a**,[20,21a] Scheme 6. The Sonogashira coupling reaction of this last compound with the iodo deoxyuridine derivative **C**, Scheme 3, **C** = ArI, should be facilitated, giving access to the η^5-complex **9**. At this stage, the rearomatization by *exo* hydrogen abstraction, using trityl tetrafluoroborate,[21a] should form the desired η^6 Mn complex **10**, Scheme 6.

Scheme 6



Scheme 7



Thus, the starting (η^5-cyclohexadienyl)tricarbonylmanganese complexes were prepared by adding a hydride[30] or a Grignard reagent, Scheme 6.[19,20,31,32] Addition of $LiAlH_4$ or PhMgBr to the η^6-Mn complex **4** gave regioselectively **6a**,[20] which corresponds to a *meta* addition with respect to the methoxy group in 99% yield for Nu = H, and **6b**[20] in 91% yield for Nu = Ph. A coupling reaction with trimethylsilylacetylene yielded the corresponding η^5-cyclohexadienyl$Mn(CO)_3$ **7a** (Nu = H in 97% yield) and **7b** (Nu = Ph in 91% yield. The required alkynyl-substituted cyclohexadienyl-Mn complexes **8a**,[21a] as a yellow oil in 99% yield, and **8b**,[20] as a yellow oil in 91% yield, may be prepared by literature methods as indicated in Scheme 6. The reaction of the η^5-Mn complex **8a** and the 5-iodo-2′-deoxyuridine **1a**, using the experimental procedure previously described in the case of arene$Cr(CO)_3$/$Pd(PPh_3)_4$, CuI, Amberlite IRA-67, CH_2Cl_2/MeOH as solvent at 35 °C, gave in a low yield complex **9a**, which was difficult to purify, Scheme 7. However, the reaction of **8a** or **8b** with the protected nucleoside **1b** led to the expected products **9b** and **9d** in 65% and 58% yield, respectively. IR data of the dibenzoyl manganese complexes **9b** and **9d** showed bands at 1919 and 2010 cm^{-1} and 1924 and 2011 cm^{-1}, respectively. The ^1H NMR data in $CDCl_3$ of these two complexes showed four signals at 4.97 and 5.13 (H10, 1:1 ratio of two diastereoisomers due to the presence of central and planar chiralities of the η^5-cyclohexadienyl complexes), 5.72 (H11), and 2.99 (H13) for **9b** and at 4.97 and 5.17 (H10, 1:1 ratio of two diastereoisomers), 5.57 (H11), and 3.50 (H13) for **9d**, in good agreement with shielded signals of the protons H13 at the end of the conjugated η^5-system, which have a less pronounced sp^2 character. Furthermore, only the $H14_{endo}$ proton

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of complex **9b** appears as two signals of equal importance at 2.63 and 2.76 ppm, whereas the analogous proton of complex **9d** is not affected by the planar chirality and exhibits a signal at 4.00 ppm. We recover also deprotected compounds **9a** and **9c** by hydrolysis of the esters **9b** and **9d** with MeONa in MeOH in 98% and 54% yield, respectively.

Therefore, with complex **9b** in hand, we attempted hydride abstraction of the *exo* hydrogen using $CPh_3^+BF_4^-$ in CH_2Cl_2, at room temperature for 1 h, and we were pleased to obtain the η^6-(arene)$Mn^+(CO)_3$, BF_4^- complex **10b** in 76% yield as a yellow solid, Scheme 7. The IR data are consistent with the rearomatization of the η^5-system into a η^6 one. Indeed, the stretching bands occurred at 2037 and 2011 cm^{-1}. ^1H NMR signals of the aromatic protons of this *para*-disubstituted arene complex appear at 6.62 ppm for H11 and H13 protons and at 7.06 and 7.16 ppm as two distinct doublets for the diastereotopic H10 and H14 protons.

The complexes **3a**, **9a**, and **9c** were evaluated for their antiviral activity in cell-based assays measuring the compounds' inhibitory effect on the virus-induced cytopathic effect. Unfortunately, the compounds were found to be inactive against DNA viruses such as vaccinia virus or human herpes viruses (i.e., herpes simplex virus type 1, cytomegalo virus, and varicella zoster virus) and various RNA viruses (i.e., human influenza viruses; vesicular stomatitis virus; parainfluenza virus-3 virus; Sindbis virus; Coxsackie virus B4, and Punta Toro virus). One compound, **9c**, had minimal activity against respiratory syncytial virus.

Conclusion

We successfully developed the first syntheses of η^6-(arene)-tricarbonylchromium and -manganese complexes linked to a nucleoside spaced by an alkyne using Sonogashira Pd-catalyzed reactions between η^6-(ethynylphenyl)tricarbonylchromium and η^5-(ethynylcyclohexadienyl)tricarbonylmanganese complexes and 5-iodo-2′-deoxyuridine. Although the compounds presented here were found to have no antiviral activity, the possibility to introduce at the strategic 5-position such highly electrophilic organometallic complexes, which are very useful building blocks in organic synthesis, opens new perspectives in the chemical synthesis of new nucleoside analogues.

Experimental Section

General Procedure. 3′,5′-Dibenzoyl-5-(tricarbonyl(η^6-ethynylphenyl)chromium)-2′-deoxyuridine, 3b. Tricarbonyl(ethynylbenzene)chromium (0.139 g, 0.585 mmol), $Pd_2(dba)_3$ (0.049 g, 0.053 mmol), $AsPh_3$ (0.049 g, 0.160 mmol), and 3′,5′-dibenzoyl-5-iodo-2′-deoxyuridine (**1b**) (0.299 g, 0.52 mmol) were introduced into a flask and dissolved in 20 mL of Et_3N and 10 mL of THF. The reaction mixture was stirred for 1 h at 50 °C and filtered on Celite (eluated with Et_2O and AcOEt). The solvent was evaporated under reduced pressure. The crude product was purified on a silica gel chromatography column (Merck silica gel 60, 15−40 μm, petroleum ether/AcOEt, 7:3). After evaporation under reduced pressure and drying *in vacuo*, a red complex was obtained (0.272 g, 0.400 mmol, 76%). mp = 126 °C. IR ν (cm^{-1}): 1961 (CO−Cr), 1878 (CO−Cr), 1710 (CO). $[\alpha]^{20}_D$ −130 (*c* 0.74, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 8.26 (s, 1H, NH), 8.03 (m, 4H, Ph), 7.98 (s, 1H, H_6), 7.65−7.43 (m, 6H, Ph), 6.36 (m, 1H, $H_{1'}$), 5.61 (m, 1H, $H_{3'}$), 5.40−5.10 (m, 5H, H_{10}, H_{11}, H_{12}, H_{13}, H_{14}), 4.80−4.61 (m, 3H, $H_{5'}$, $H_{4'}$), 2.83 (m, 1H, $H_{2a'}$), 2.36 (m, 1H, $H_{2b'}$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 232.0 (CO−Cr), 165.9 (CO), 160.1 (C_4), 149.1 (C_2), 142.6 (C_6), 133.8, 129.8, 129.2, 128.9, 128.8, 128.6 (Ar), 94.4, 91.6, 89.8 (C_{10}, C_{11}, C_{12}), 90.3, 89.6, 80.0 (C_7, C_8, C_9), 86.4 ($C_{1'}$), 83.4 ($C_{4'}$), 75.0 ($C_{3'}$), 65.8 (C_5), 64.4 ($C_{5'}$), 38.8 ($C_{2'}$). MS (FAB+): *m*/*z* 673 (M + 1), 537 (M + 1 − $Cr(CO)_3$)). Anal. Calcd for $C_{34}H_{25}N_2CrO_{10}$: C, 60.71; H, 3.60. Found: C, 61.03; H, 3.81.

3′,5′-Dibenzoyl-5-(tricarbonyl(η^5-1-ethynyl-4-methoxycyclohexa dienyl)manganese)-2′-deoxyuridine, 9b. Tricarbonyl(η^5-1-methoxy-4-ethynylcyclohexadienyl)manganese (**8a**)[20,21] (0.072 g, 0.264 mmol), 3′,5′-dibenzoyl-5-iodo-2′-deoxyuridine (**1b**) (0.136 g, 0,24 mmol), $Pd_2(dba)_3$ (0.022 g, 0.024 mmol), and $AsPh_3$ (0.022 g, 0.072 mmol) were introduced into a flask. Under N_2, 10.0 mL of Et_3N and 5.0 mL of THF were added and stirred at 50 °C for 1 h. The brown suspension was filtered on Celite (eluted with Et_2O and AcOEt), the solvent was evaporated under reduced pressure, and the crude product was purified on a silica gel chromatography column (Merck silica gel 60, 15−40 μm, petroleum ether/ethyl acetate, 3:2). After evaporation under reduced pressure and drying *in vacuo*, an orange-brown solid was obtained (0.110 g, 0.156 mmol, 65%). mp = 210 °C. IR: ν (cm^{-1}) 2014 (CO−Mn), 1927 (CO−Mn), 1716 (CO). ^1H NMR (200 MHz, $CDCl_3$): δ 8.24 (s, 1H, NH), 8.04 (m, 4H, Ph), 7.79 (*7.77*) (s, 1H, H_6), 7.60−7.38 (m, 6H, Ph), 6.34 (m, 1H, $H_{1'}$), 5.72 (m, 1H, H_{11}), 5.60 (m, 1H, $H_{3'}$), 5.10 (*4.96*) (m, 1H, H_{10}), 4.72 (m, 3H, $H_{4'}$, $H_{5'}$), 3.43 (s, 3H, OCH_3), 2.99 (m, 1H, H_{13}), 2.76 (*2.63*) (m, 2H, H_{14endo}, $H_{2b'}$), 2.31 (m, 2H, H_{14exo}, $H_{2a'}$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.8 (CO), 159.7 (C_4), 149.1 (C_2), 143.1 (C_6), 140.7 (C_{12}), 129.7, 129.1, 129.0, 128.7, 128.6, 128.5 (Ar), 100.9 (C_5), 97.2 (C_{10}), 95.0, 94.8 (C_7, C_8), 86.2 ($C_{1'}$), 83.2 ($C_{4'}$), 75.0 ($C_{3'}$), 68.1 (C_{11}), 64.4 ($C_{5'}$), 54.3 (OCH_3), 45.3 (C_9), 38.5 ($C_{2'}$), 36.3 (C_{13}), 31.4 (*31.6*) (C_{14}). Anal. Calcd for $C_{35}H_{27}MnN_2O_{11}$: C, 59.48; H, 3.85. Found: C, 59.32; H, 4.03. HRMS: calcd for $C_{35}H_{27}MnN_2O_{11}Na$, 729.0893; found, 729.0899 $[M + Na]^+$.

3′,5′-Dibenzoyl-5-(tricarbonyl(η^6-1-ethynyl-4-methoxybenzene)manganese)-2′-deoxyuridine Tetrafluroborate, 10b. To a solution of 3′,5′-dibenzoyl-5-(tricarbonyl(η^5-1-ethynyl-4-methoxycyclohexadienyl)manganese)-2′-deoxyuridine (**9b**) (0.159 g, 0.225 mmol) in 5 mL of CH_2Cl_2 was added CPh_3BF_4 (0.148 g, 0.45 mmol) in 5 mL of CH_2Cl_2. The mixture was stirred at rt for 1 h. The product was precipitated by adding 30 mL of dry Et_2O, filtered, washed with Et_2O, and dried in *vacuo*. A pale yellow, oily solid was obtained (0.120 g, 0.170 mmol, 76%). IR ν (cm^{-1}): 2037 (CO−Mn), 2011 (CO−Mn), 1717 (CO), 1690 (CO). $[\alpha]^{20}_D$ −89 (*c* 0.82, $CHCl_3$). ^1H NMR (400 MHz, $(CD_3)_2CO$)): δ 10.59 (s, 1H, NH), 8.36 (s, 1H, H_6), 8.13 (m, 4H, Ph), 7.80−7.50 (m, 6H, Ph), 7.22−7.01 (m, 2H, H_{10}, H_{14}), 6.62 (m, 2H, H_{11}, H_{13}), 6.41 (t, J = 6.8 Hz, 1H, $H_{1'}$), 5.80 (m, 1H, $H_{3'}$), 4.79 (m, 3H, $H_{4'}$, $H_{5'}$), 4.26 (s, 3H, OCH_3),2.89 (m, 2H, $H_{2'}$). ^{13}C NMR (100 MHz, $(CD_3)_2$-CO)): δ 215.1 (CO−Mn), 165.0 (CO), 160.0 (C_4), 148.4 (C_2), 146.4 (C_{12}), 142.0 (C_6), 133.6, 133.0, 129.7, 128.9 (Ar), 114.2 (C_9), 105.0 (C_{10}, C_{14}), 92.8, 92.0, 89.9 (C_5, C_7, C_8), 87.1 ($C_{1'}$), 83.1 (C_{11}, C_{13}), 83.0 ($C_{4'}$), 75.2 ($C_{3'}$), 64.6 ($C_{5'}$), 55.0 (OCH_3), 37.9 ($C_{2'}$). Anal. Calcd for $C_{35}H_{26}BF_4N_2MnO_{11}$: C, 53.02; H, 3.31. Found: C, 53.28; H, 3.42. HRMS-ES: calcd for $C_{35}H_{26}BF_4N_2MnO_{11}$, 792.0946; calcd for $C_{35}H_{26}N_2MnO_{11}$ 705.0917; found 705.0912 $[M - BF_4]$; found 566.1581 $[M - BF_4 - Mn(CO)_3 + Na]^+$.

Acknowledgment. We thank Jasmin Nitsche, Hamburg, University and Ulrike Ziffels, Bonn University, for helpful synthesis and the CNRS for financial support.

Supporting Information Available: Syntheses of the new compounds except complexes **3b**, **9b**, and **10b**. The activity of the test compounds against a variety of DNA viruses and RNA viruses was evaluated in cell-culture-based assays using the virus-induced cytopathic effect as the parameter for virus replication; see Supporting Information.[1e] Tables giving cytotoxicity and antiviral activity of complexes **3a**, **9a**, and **9c** in HEL, Vero, and HeLa cell cultures. This material is available free of charge via the Internet at http://pubs.acs.org.

OM700674V