Synthesis of 2,6,7-Trichloro-1-(β-D-ribofuranosyl)naphtho[2,3-*d*]imidazole: A Linear Dimensional Analogue of the Antiviral Agent TCRB

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Human cytomegalovirus (HCMV) remains a significant clinical problem in neonates and immunocompromised individuals such as those undergoing transplantation as well as individuals with acquired immune deficiency syndrome (AIDS). Recently in our laboratory, 2,5,6-trichloro-1-(β-D-ribofuranosyl)benzimidazole (TCRB, **1a**) and 2-bromo-5,6-dichloro-1-(β-D-ribofuranosyl)benzimidazole (BDCRB, **1b**) were found to have better activities in cell culture studies against HCMV than the clinically used agents ganciclovir and foscarnet. These benzimidazole compounds appear to act by a unique mechanism. However, as the biological target of TCRB and BDCRB has not been completely identified, 2,6,7-trichloro-1-(β-D-ribofuranosyl)naphtho[2,3-*d*]imidazole (**2**) was designed as a linear dimensional analogue of TCRB for a study on the spatial limitation of the binding site in the target enzyme. In the synthesis, a convenient route was developed for the synthesis of 2-substituted 6,7-dichloronaphtho[2,3-*d*]imidazoles involving a Diels−Alder reaction of 4,5-dichloro-*o*-quinodimethane (**8**) as the key step. 6,7-Dichloro-1,4-dihydro-2,3-benzoxathiin 3-oxide (**15**) was found to be an ideal precursor for the generation of the elusive intermediate **8**. The ribosylation of 6,7-dichloronaphtho[2,3-*d*]imidazoles was influenced by the functional group at the 2-position and 6,7-dichloro-2-methylthionaphtho[2,3-*d*]imidazole (**3c**) was found to smoothly undergo ribosylation. The 2-methylthio group of the unprotected nucleoside **25** was converted into a chloro group under mild conditions to give nucleoside **2** in high yield.

Introduction

Human cytomegalovirus (HCMV) is a human herpes virus that has a high order of genome sequence complexity and a narrow host range.[1] Although HCMV is innocuous in the immunocompetent individual, it is a significant pathogen in neonates and immunocompromised individuals[2] such as bone marrow[3] and organ transplant[4] patients as well as individuals with acquired immune deficiency syndrome (AIDS).[5] Ganciclovir, foscarnet, and cidofovir are the only FDA approved drugs for the treatment of HCMV infections. However, all of them have exhibited poor bioavailability and undesirable side effects.[6] For ganciclovir and foscarnet, resistant virus strains are also emerging.[7] Moreover, coadministration of ganciclovir and AZT in AIDS patients was found to cause synergistic toxicity.[8] Consequently, there is a need for better, more potent, and selective antiviral drugs to treat HCMV infections.

Recently in our laboratory, a series of polyhalogenated benzimidazole ribonucleosides were found to have potent activity and high selectivity against human cytomegalovirus (HCMV).[9] The lead compounds, 2,5,6-trichloro-1-(β-D-ribofuranosyl)benzimidazole (TCRB, **1a**, Figure 1) and 2-bromo-5,6-dichloro-1-(β-D-ribofuranosyl)benzimidazole (BDCRB, **1b**) were more active and less toxic than ganciclovir and foscarnet in the cell culture studies. Furthermore, both compounds appear to act by a unique mechanism that does not involve the inhibition of DNA synthesis but does involve the inhibition of DNA processing.[10]

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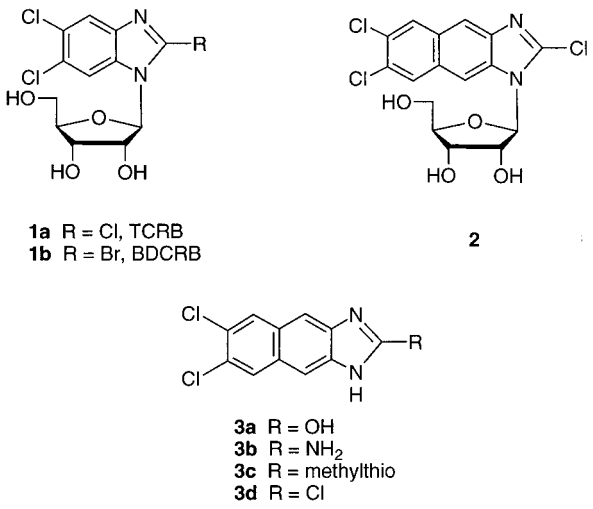


Figure 1.

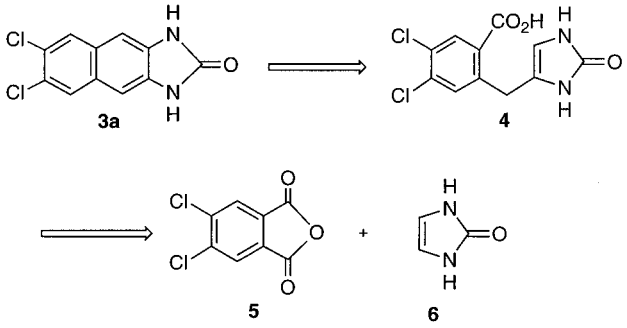
Structure−activity relationship studies of TCRB and BDCRB have demonstrated that all of the three halo groups and the ribosyl moiety are essential for antiviral activity.[11] As the target enzyme that TCRB and BDCRB inhibit has not been completely identified, we elected to explore the spatial limitation[12] of the binding site of the target enzyme by relocating the relative positions of the key structural units of TCRB with certain spacers. As part of this effort, 2,6,7-trichloro-1-(β-D-ribofuranosyl)-naphtho[2,3-*d*]imidazole (**2**) was designed as a linear dimensional analogue of TCRB with a benzene ring as the spacer. This analogue retains the relative positions of the imidazole and the ribosyl moieties while moving the *o*-dichlorobenzene moiety 2.4 Å linearly toward the periphery.

The synthesis of nucleoside **2** required the synthesis of a derivative of 6,7-dichloronaphtho[2,3-*d*]imidazole (**3**) with a functional group at the 2-position, e.g., 2-hydroxy (**3a**), 2-amino (**3b**), or 2-(methylthio) derivative (**3c**). The functional group at the 2-position could be converted to the chloro group at either the heterocycle or the nucleoside level. To the best of our knowledge, only a few 6,7-disubstituted naphtho[2,3-*d*]imidazoles have been reported.[13] Due to the unfavorable substitution pattern, the naphthalene moieties of all these 6,7-disubstituted naphtho[2,3-*d*]imidazoles have been generated either by stepwise Friedel−Crafts reactions[13a] or by Diels−Alder reactions involving *o*-quinodimethane derivatives.[13b,c] However, none of the above routes were ideal for the preparation of our target compounds. We would now like to report a new and convenient route for the preparation of certain 6,7-disubstituted naphth[2,3-*d*]imidazoles that are functionalized at the 2-position and their use in the subsequent synthesis of the nucleoside **2**.

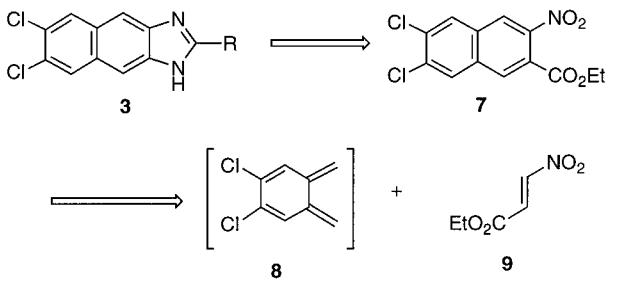
Results and Discussion

Our initial approach for the synthesis of 6,7-dichloronaphtho[2,3-*d*]imidazol-2-one (**3a**) involved sequential

Scheme 1



Scheme 2



Friedel−Crafts reactions[14] starting from 4,5-dichlorophthalic anhydride (**5**) and imidazolin-2-one[15] (**6**) (Scheme 1). Although, **6** was believed to be an exception of imidazoles and apparently possesses sufficient activity toward an electrophile under Friedel−Crafts conditions,[16] the Friedel−Crafts reaction of **5** and **6** in the presence of $AlCl_3$ in nitrobenzene was found to be very sluggish and afforded a low yield.

We then elected to pursue a route wherein the imidazole moiety would be constructed at the final stage of the synthetic route. It was envisaged that a Diels−Alder reaction between 4,5-dichloro-*o*-quinodimethane (**8**) and ethyl (*E*)-3-nitroacrylate[17] (**9**) would provide, after aromatization, ethyl 6,7-dichloro-3-nitro-2-naphthoate (**7**) with the desired functionalities for a subsequent generation of the imidazole moiety (Scheme 2).

A variety of precursors have been reported in the literature for the generation of *o*-quinodimethanes.[18] We were interested in precursors that are readily available, amenable for scale-up, and would undergo a transformation to the corresponding *o*-quinodimethanes under mild conditions. Initially, a retrosynthetic approach involving 1-acetoxy-4,5-dichlorobenzocyclobutene (**12**) was selected since the electron-donating acetoxy group would facilitate the thermal ring opening at a temperature slightly above 100 °C.[19] 1-Acetoxybenzocyclobutene has been prepared readily through a [2 + 2] cycloaddition reaction from vinyl

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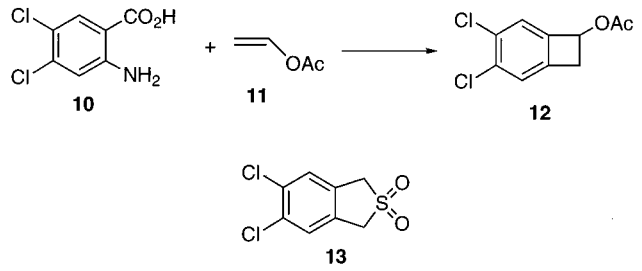
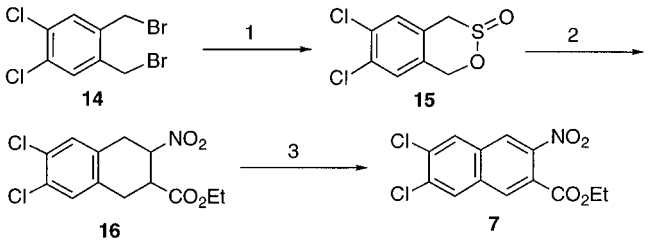
Scheme 3



acetate and benzyne generated from anthranilic acid.[20] Various reaction conditions[21] have been reported for the use of anthranilic acids in the generation of benzynes. However, our attempts to prepare **12** from 4,5-dichloroanthranilic acid (**10**) and vinyl acetate (**11**) gave less than a 7% yield of **12** (Scheme 3). This failure to obtain **12** was disappointing but not surprising since, as reported in the literature,[21d] the generation of benzynes from anthranilic acids is strongly influenced by the substituents on the benzene moiety.

This prompted us to reevaluate the other type of precursors for the generation of 4,5-dichloro-*o*-quinodimethane (**8**). One of the most attractive methods was the 1,4-elimination from *o*-xylene derivatives,[18a,b,c] such as fluoride-induced elimination from [*o*-[(trimethylsilyl)-methyl]benzyl]trimethylammonium halide[22] and dehalogenation of α,α′-dihalo-*o*-xylenes by metals.[23] However, these methods either require multistep synthesis of the precursors or use reagents that would not be compatible with reducible groups. We then evaluated an alternative method involving the thermolysis of benzofused heterocycles.[18a,b] 1,3-Dihydro-5,6-dichlorobenzo[*c*]thiophene *S*,*S*-dioxide (**13**) has been used[24] for the generation of 4,5-dichloro-*o*-quinodimethane (**8**). However, the cheletropic elimination of sulfur dioxide from this sulfone (**13**) required a temperature of 230 °C. In direct contrast to sulfones (1,3-dihydrobenzo[*c*]thiophene *S*,*S*-dioxides), the sulfinates[25] (or sultines, 1,4-dihydro-2,3-benzoxathiin 3-oxides) undergo cheletropic elimination of sulfur dioxide smoothly around 80 °C. The formation of *o*-quinodimethanes from sulfinates has not been fully explored, presumably due to the required multistep synthesis[25a,b,c]

Scheme 4[a]



[a] Key: (1) $HOCH_2SONa{\cdot}2H_2O$, TBAB, DMF, 0 °C to rt quantitative; (2) ethyl (*E*)-3-nitroacrylate, benzene, reflux, 10 h, 71%; (3) (a) NBS, chloroform, *hν*, 5 °C, (b) triethylamine, −15 °C to rt, 88% in two steps.

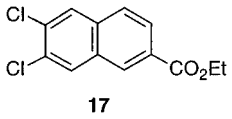


Figure 2.

for the sulfinates. However, Hoey and Dittmer have developed[25e] a convenient one-step synthesis of 1,4-dihydro-2,3-benzoxathiin 3-oxide, in high yield, from α,α′-dihalo-*o*-xylene and rongalite (sodium hydroxymethanesulfinate) under mild conditions.[26] This method made the sulfinate approach ideal for the generation of 4,5-dichloro-*o*-quinodimethane (**8**). 6,7-Dichloro-1,4-dihydro-2,3-benzoxathiin 3-oxide (**15**) was prepared by the Dittmer method in an essentially quantitative yield from 1,2-bis(bromomethyl)-4,5-dichlorobenzene[24] (**14**) and rongalite. When **15** was heated in benzene at reflux in the presence of ethyl (*E*)-3-nitroacrylate (**9**), ethyl 6,7-dichloro-3-nitro-1,2,3,4-tetrahydro-2-naphthoate (**16**) was obtained in an overall 71% yield from **14** (Scheme 4).

Our first attempts to aromatize[27a] **16** used the conventional Barne's method[27b] for tetralin. However, only a 40% yield of ethyl 6,7-dichloro-3-nitro-2-naphthoate (**7**) was obtained after bromination of **16** with *N*-bromosuccinimide (NBS) in the presence of benzoyl peroxide in carbon tetrachloride at reflux followed by dehydrobromination with potassium acetate. The major side product was identified as ethyl 6,7-dichloro-2-naphthoate (**17**) (Figure 2). Other aromatization methods, e.g., DDQ,[27c] trityl trifluoroacetate,[27d] and bromine in pyridine,[27e] were attempted without any major improvement. The nitro group can undergo base-induced elimination of nitrous acid if an electron-withdrawing group is present at the adjacent position.[28] However, we found that some **17** was formed during the free-radical bromination with NBS in carbon tetrachloride at reflux even before the introduction of a base. Compound **17** was also generated by NBS bromination at rt with a tungsten light as the free-radical initiator. However, by lowering the reaction temperature

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(26) We were quite surprised to find that this method has not been used for the generation of other sulfinates, except 1,4-dihydro-2,3-benzoxathiin 3-oxide, and to some extent has been neglected (see ref 25f).

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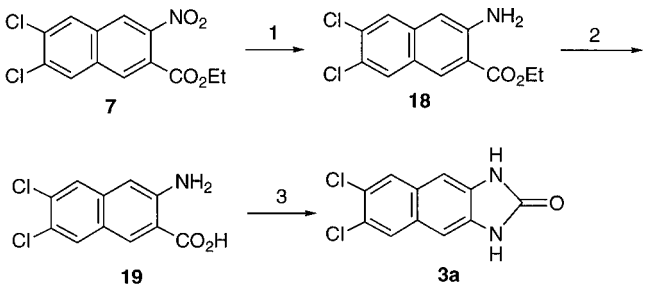
Scheme 5[a]



[a] Key: (1) $SnCl_2$, EtOH, EtOAc, 70 °C, quantitative; (2) NaOH, EtOH, 94%; (3) $(PhO)_2PON_3$, Et_3N, benzene, reflux. Overall 80% yield in three steps.

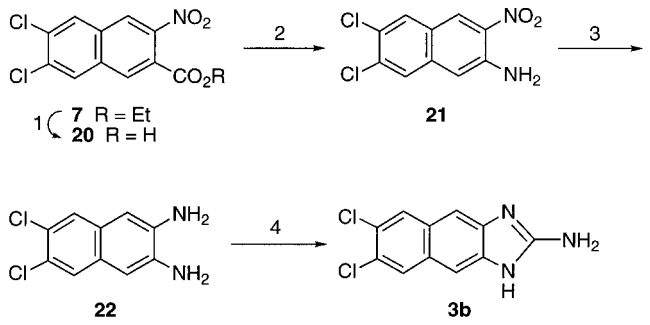
to 4 °C during the NBS bromination with tungsten light, a clean reaction was obtained to give, after dehydrobromination at −15 °C with triethylamine, compound **7** in an 88% yield.

Starting from **7**, 6,7-dichloronaphtho[2,3-*d*]imidazol-2-one (**3a**) was prepared in three steps (Scheme 5). A stannous chloride reduction of the nitro group was followed by a hydrolysis of the ester group with 10% sodium hydroxide to give 2-amino-6,7-dichloro-2-naphthoic acid (**19**). The order of reduction and hydrolysis was found to be important since the reverse order resulted in some difficulties during workup. The treatment of **19** with diphenyl phosphorazidate in benzene at reflux effected a Curtius rearrangement that was followed by a subsequent intramolecular ring closure to give **3a** in an 80% yield.

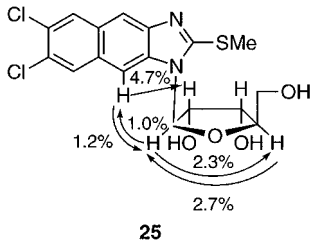
Our attempts to convert **3a** to 2,6,7-trichloronaphtho-[2,3-*d*]imidazole (**3d**) by the use of phosphorus oxychloride in the presence of *N*,*N*-dimethylaniline at reflux were found to be unsuccessful. Furthermore, ribosylations of **3a** by the Vorbruggen method[29] with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (TBAR) as well as the sodium salt method[30] with 2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl chloride[31] were unsuccessful.

We assumed that the 2-oxo group might be the cause of the unsuccessful ribosylations.[32] In an effort to overcome this problem, 2-amino-6,7-dichloronaphtho[2,3-*d*]imidazole (**3b**) was prepared in four steps (Scheme 6). Compound **7** was first converted to 2-amino-6,7-dichloro-3-nitronaphthalene (**21**) in an overall 99% yield by the hydrolysis of the ester with 10% NaOH followed by a Curtius rearrangement using diphenylphosphorazidate. Compound **21** was then reduced to the corresponding diamine (**22**) by hydrogenation followed by ring-closure using cyanogen bromide to give **3b** in quantitative yield. However, the ribosylation of **3b** was also found to be troublesome. Ribosylations by the Vorbruggen method,[29]

Scheme 6[a]



[a] (a) NaOH, EtOH, rt, quantitative; (2) (a) $(PhO)_2PON_3$, Et_3N, DMF, rt, (b) H_2O, 100 °C, 99%; (3) Pd/C, H_2; (4) CNBr, MeOH, H_2O, rt, quantitative from **21**.



25

Figure 3. NOE of compound **25**. The experiment was carried out in DMSO-d_6 at room temperature.

fusion method,[35b] and phase-transfer method[33] were unsuccessful. Ribosylation by the sodium salt method[30] with 2,3,5-tri-*O*-benzyl-D-ribofuranosyl chloride[34] gave a mixture of α- and β-anomers with the α-anomer as the major product.

The ribosylation of some 2-substituted naphtho[2,3-*d*]-imidazoles, e.g., the 2-methyl, 2-(trifluoromethyl), and 2-(methylthio) derivatives, have been reported.[35] After the unsuccessful ribosylation of both **3a** and **3b**, we prepared 6,7-dichloro-2-(methylthio)naphtho[2,3-*d*]imidazole (**3c**). The preparation of **3c** started with the ring closure of the diamine **22** by using (thiocarbonyl)-diimidazole followed by an alkylation with methyl iodide. In sharp contrast to the results for compound **3a** and **3b**, the silylated **3c** underwent ribosylation under Vorbruggen conditions with TBAR in the presence of trimethylsilyl (trifluoromethyl)sulfonate (TMSOTf) to give 6,7-dichloro-2-(methylthio)-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)naphtho[2,3-*d*]imidazole (**24**) in a 97% yield. A removal of the benzoyl groups with methanolic ammonia gave 6,7-dichloro-2-(methylthio)-1-(β-D-ribofuranosyl)naphtho[2,3-*d*]imidazole (**25**) in 96% yield. The β-configuration of **25** was established by NOE experiments as shown in Figure 3.

The direct transformation of a thio or methylthio group to a chloro group on unprotected nucleosides has proven to be an efficient and facile method for the generation of chloro-substituted nucleosides.[36] This appears to be an ideal way to prepare **2** from **25**. However, the naphthalene moiety of **25** could be vulnerable to chlorination under the literature reaction conditions where chlorine

(29) Vorbruggen method: (a) Vorbruggen, H.; Krolikiewicz, K.; Bennua, B. *Chem. Ber.* **1981** *114*, 1234−1255. (b) Vorbruggen, H.; Bennua, B. *Chem. Ber.* **1981**, *114*, 1279−1286. (c) Dudycz, L.; Wright, G. E. *Nucleosides Nucleotides* **1984**, *3*, 33−44.

(30) Revankar, G. R.; Robins, R. K. *Nucleosides and Nucleotides* **1989**, *8*, 709−724.

(31) Earl, R. A.; Townsend, L. B. In *Nucleic Acid Chemistry, Improved and New Synthetic Procedures, Methods and Techniques*; Wiley Interscience: New York, N.Y., 1991, Townsend, L. B., Tipson, R. S., Eds.; Part 1, pp 203−205.

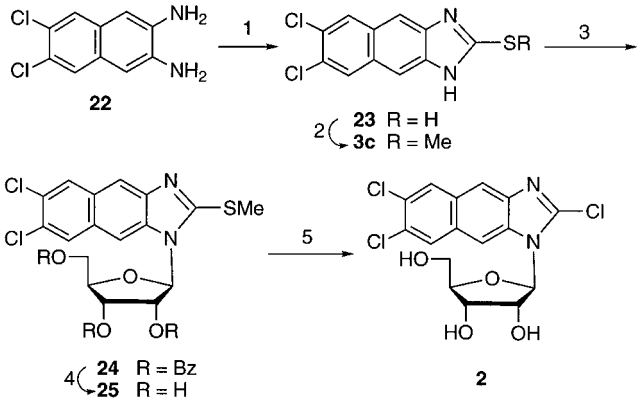
(32) However, successful examples of ribosylation of 2-oxo derivatives in benzimidazole, imidazo[4,5-*b*]quinoline, and imidazo[4, 5-*b*]-quinoxaline systems have been observed. (a) Reference 9b. (b) Zhu, Z.; Townsend, L. B. Unpublished results.

(33) Seela, F.; Bussmann, W. *Nucleosides Nucleotides* **1982**, *1*, 253−261.

(34) Mead, E. A.; Wotring, L. L.; Drach, J. C.; Townsend, L. B. *J. Med. Chem.* **1993**, *36*, 3834−3842.

(35) (a) Hijazi, A.; Pfleiderer, W. *Nucleosides Nucleotides* **1984**, *13*, 293−295. (b) Hijazi, A. *Nucleosides Nucleotides* **1986**, *5*, 529−537. (c) Hijazi, A. *Nucleosides Nucleotides* **1988**, *7*, 537−547.

Scheme 7[a]



[a] Key: (1) (thiocarbonyl)diimidazole, benzene, reflux, 80%; (2) DMF, MeI, 81%; (3) (a) BSA, $ClCH_2CH_2Cl$, rt, (b) TBAR, TMSOTf, 50 °C, 97%; (4) NH_3, MeOH, 96%; (5) Cl_2, MeOH, −78 °C, 82%.

gas was bubbled into a methanol solution at −10 °C. Indeed, when chlorine gas was bubbled into a solution of **25** in methanol at −10 °C, a complex reaction mixture was obtained with apparent overchlorination occurring on the naphthalene moiety. In an effort to avoid overchlorination of the naphthalene moiety, we elected to use a stoichiometric quantity of chlorine gas. A solution of chlorine in carbon tetrachloride was first prepared, and the concentration of chlorine was calculated through the weight increase. When approximately 1 equiv of this chlorine solution was added to a solution of **25** at −78 °C, a clean reaction was obtained and gave an 82% yield of 2,6,7-trichloro-1-(β-D-ribofuranosyl)naphtho[2,3-*d*]imidazole (**2**) with a recovery (12%) of starting material **25** (Scheme 7).

In conclusion, we have developed an efficient and convenient route for the synthesis of 2-substituted 6,7-dichloronaphtho[2,3-*d*]imidazoles. 6,7-Dichloro-1,4-dihydro-2,3-benzoxathiin 3-oxide (**15**) was found to be an ideal precursor for the generation of the corresponding *o*-quinodimethane. This *o*-quinodimethane was then used in a Diels−Alder reaction for a construction of the naphthalene moiety of 6,7-dichloronaphtho[2,3-*d*]imidazoles. The ribosylation of 6,7-dichloronaphtho[2,3-*d*]-imidazoles was found to be dependent on the substituent at the 2-position, and the 2-methylthio derivative was found to undergo the ribosylation smoothly. Mild reaction conditions for the preparation of **2** from **25** was developed in which 1 equiv of chlorine at −78 °C was used. The extremely mild reaction conditions for the transformation of a methylthio group to a chloro group on an unprotected nucleoside should increase the usefulness of this method.

Antiviral evaluation revealed that compound **2** was less active against HCMV than TCRB[9b] in plaque (IC_{50} = 16 μM) and yield (IC_{90} 9 μM) reduction assays and was more cytotoxic (IC_{50}'s = 8−16 μM). This loss of specific antiviral activity by the spatial change in the molecule is surprising and now is under further investigation in our laboratory.

(36) (a) Robins, R. K. *J. Am. Chem. Soc.* **1960** *82*, 2654−2655. (b) Gerster, J. F.; Jones, J. W.; Robins, R. K. *J. Org. Chem.* **1963**, *28*, 945−948. (c) Rousseau, R. J.; Robins, R. K.; Townsend, L. B. *J. Am. Chem. Soc.* **1968**, *90*, 2661−2668. (d) Giner-Sorolla, A.; Nanos, C.; Burchenal, J. H.; Dollinger, M.; Bendich, A. *J. Med. Chem.* **1968**, *11*, 52−54.

Experimental Section

General Procedures. Melting points were taken on a Thomas-Hoover apparatus and are uncorrected. Silica gel 60 230−400 mesh (E. Merck, Darmstadt, West Germany) was used for chromatography. Thin layer chromatography (TLC) was performed on prescored SilicAR 7GF plates (Analtech, Newark, DE). Compounds were visualized by illumination under UV light (254 nm). Evaporations were carried out under reduced pressure (water aspirator) with the bath temperature below 40 °C, unless specified otherwise. IR spectra were obtained on a Nicolet 5DXB FT-IR spectrophotometer. UV spectra were performed on a Hewlett-Packard 8450-A UV/vis spectrophotometer. Nuclear magnetic resonance (NMR) spectra were determined at 360 MHz with a Bruker WP 360 SY. The chemical shift values are expressed in δ values (parts per million) relative to the standard chemical shift of TMS or the solvent used. Elemental analyses were performed by M−H−W Laboratories, Phoenix, AZ.

6,7-Dichloro-1,4-dihydro-2,3-benzoxathiin 3-Oxide (15). Sodium hydroxymethanesulfinate dihydrate (16.4 g, 106.4 mmol) was added in one portion to a solution of 4,5-dichloro-1,2-bis(bromomethyl)benzene[24] (**14**, 17.2 g, 53.2 mmol) and tetrabutylammonium bromide (3.43 g, 10.6 mmol) in dry DMF (110 mL) in an ice bath. The suspension was stirred for 7 h in an ice bath and an additional 7 h at rt. The almost clear solution was then poured into a 1000 mL separatory funnel, and water (200 mL) was added to give a white suspension. The white suspension was shaken gently and then extracted with ether (400 mL and then 2 × 200 mL). The ether extracts were combined, washed with water (3 × 100 mL), and dried over anhydrous $MgSO_4$. This slightly cloudy ether solution was filtered to give a clear ether solution. The solvent was evaporated, and the solid was dried under vacuum by an oil pump at rt to give 6,7-dichloro-1,4-dihydro-2,3-benzoxathiin 3-oxide (**15**, 13.1 g, quantitative, contained 10% of DMF as shown by ^{1}H NMR) as a white powder. This sample was used directly for the next step without further purification. A small sample was recrystallized from ethyl acetate and hexane for analysis: ^{1}H NMR (DMSO-d_6) δ 7.70 (s, 1H), 7.66 (s, 1H), 5.16 (d, J = 14.1 Hz, 1H), 5.07 (d, J = 14 Hz, 1H), 4.51 (d, J = 15.4 Hz, 1H), 3.83 (d, J = 15.5 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 134.5, 131.7, 130.6, 129.9, 127.8, 127.7, 62.1, 54.3. Anal. Calcd for $C_8H_6O_2SCl_2$: C, 40.51; H, 2.53. Found: C, 40.72; H, 2.70.

Ethyl 6,7-Dichloro-3-nitro-1,2,3,4-tetrahydro-2-naphthoate (16). A solution of 6,7-dichloro-1,4-dihydro-2,3-benzoxathiin 3-oxide (**15**, 11 g, 45.3 mmol) and ethyl (*E*)-3-nitroacrylate (12.5 g, 86.2 mmol) in dry benzene (130 mL) was heated at reflux for 14 h. The solvent was removed under reduced pressure to give a brown solid that was recrystallized from methanol to give ethyl 6,7-dichloro-3-nitro-1,2,3,4-tetrahydro-2-naphthoate (**16**, 10.42 g, 71%) as white needles: mp 124−125 °C; ^{1}H NMR (DMSO-d_6) δ 7.51 (s, 2H), 5.32 (m, 1H), 4.15 (q, J = 7.1 Hz, 2H), 3.53−3.43 (m, 2H), 3.33−3.15 (m, 2H), 2.94 (dd, J = 11, 17 Hz, 1H), 1.20 (t, J = 7.1 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 171.4, 134.4, 133.4, 130.1, 129.9, 128.9, 128.7, 81.8, 61.1, 42, 31.9, 29.29, 13.9. Anal. Calcd for $C_{13}H_{13}NO_4Cl_2$: C, 49.06; H, 4.09; N, 4.40. Found: C, 48.89; H, 3.97; N, 4.39.

Ethyl 6,7-Dichloro-3-nitro-2-naphthoate (7). Ethyl 6,7-dichloro-3-nitro-1,2,3,4-tetrahydro-2-naphthoate (**16**, 2 g, 6.29 mmol), NBS (3.36 g, 18.78 mmol), and dry chloroform (120 mL) were stirred in a photoreaction flask with an exterior cooling jacket under an atmosphere of argon. The suspension was irradiated, with stirring, by a 60 W tungsten light 1 ft away from the reaction flask for 36 h. The cooling jacket was cooled by ice−water throughout the reaction. The orange reaction suspension was transferred to a round-bottom flask under an atmosphere of argon and immediately cooled to −15 °C. Triethylamine (2.62 mL, 18.78 mmol) was then added dropwise, and the solution was continuously stirred while the temperature was maintained under −15 °C for 3 h and then at rt for about 12 h. The solvent was removed (first by a water aspirator followed by oil pump at 0.05 mmHg), and the residue was subjected to silica gel chromatography (5 × 10 cm) with

elution by dichloromethane. The appropriate fractions were collected, and the solvents were evaporated to give ethyl 6,7-dichloro-3-nitro-2-naphthoate (**7**, 1.73 g, 88%) as a yellow solid: mp 121−123 °C; ^{1}H NMR ($CDCl_3$) δ 8.33 (s, 1H), 8.17 (s, 1H), 8.12 (s, 1H), 8.10 (s, 1H), 4.44 (q, J = 7.13 Hz, 2H), 1.39 (t, J = 7.18 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 164.7, 146.5, 135.1, 134.8, 132.4, 130.3, 129.9, 129.6, 125.5, 123.9, 62.7, 13.9. Anal. Calcd for $C_{13}H_9NO_4Cl_2$: C, 49.68; H, 2.87; N, 4.46. Found: C, 49.47; H, 2.80; N, 4.24.

Ethyl 6,7-Dichloro-2-naphthoate (17). When the aromatization reaction of ethyl 6,7-dichloro-3-nitro-1,2,3,4-tetrahydro-2-naphthoate (**16**) with NBS was carried out in the presence of benzoyl peroxide (BPO) in CCl_4 at reflux or at rt under the irradiation of a tungsten light, ethyl 6,7-dichloro-2-naphthoate (**17**) was formed as a side product. After purification by silica gel chromatography with elution by hexane/ethyl acetate (10/0.4, v/v), a solid was obtained. The solid was recrystallized from hexane to give colorless needle crystals: ^{1}H NMR ($CDCl_3$) δ 8.50 (m, 1H), 8.09 (dd, J = 8.6, 1.6 Hz, 1H), 8.06 (s, 1H), 7.99 (s, 1H), 7.79 (d, J = 8.7 Hz, 1H), 4.45 (q, J = 7.1 Hz, 2H), 1.45 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 166.1, 134.2, 132.7, 131.4, 131.1, 130, 129.7, 129, 128.7, 127.1, 126.6, 61.4, 14.3. Anal. Calcd for $C_{13}H_{10}O_2Cl_2 \cdot 0.25H_2O$: C, 57.08; H, 3.84. Found: C, 57.25; H, 4.09.

Ethyl 3-Amino-6,7-dichloro-2-naphthoate (18). Ethyl 6,7-dichloro-3-nitro-2-naphthoate (**7**, 1,14 g, 3.63 mmol) was dissolved in a mixture of ethanol (16 mL) and ethyl acetate (16 mL). Tin(II) chloride (3.44 g, 18.2 mmol) was added, and the yellow solution was stirred for 30 min at 70 °C under an atmosphere of argon. After being cooled to rt, the reaction solution was poured into 100 mL of ice−water and neutralized by the addition of sodium bicarbonate (solid). The yellow suspension was then extracted with ethyl acetate (3 × 100 mL), and the combined ethyl acetate extracts were washed with a saturated sodium chloride solution and dried over anhydrous sodium sulfate. The solvent was evaporated to give ethyl 3-amino-6,7-dichloro-2-naphthoate (**18**, 1.04 g, quantitative) as a yellow solid. Without further purification, this solid was used for the next step: ^{1}H NMR (DMSO-d_6) δ 8.46 (s, 1H), 8.16 (s, 1H), 7.89 (s, 1H), 7.01 (s, 1H), 6.67 (bs, 2H), 4.35 (q, J = 7.04 Hz, 2H), 1.36 (t, J = 7.07 Hz, 3H).

3-Amino-6,7-dichloro-2-naphthoic Acid (19). A 10% sodium hydroxide solution (2.5 mL) was added dropwise to a mixture of ethyl 3-amino-6,7-dichloro-2-naphthoate (**18**, 1.04 g, 3.63 mmol) in ethanol (55 mL) under an atmosphere of argon. The mixture was stirred at rt for 12 h to give a dark brown solution, at which time TLC showed the absence of starting material. A hydrogen chloride solution (5 N) was added through a syringe until the solution became acidic (as indicated by the change of the color from dark brown to yellow). The ethanol was removed under reduced pressure, and the residue was stirred in water (60 mL) while the pH was adjusted to approximately 6 by the addition of sodium bicarbonate. The solid was collected by filtration, washed with water, and dried under vacuum at rt to give 3-amino-6,7-dichloro-2-naphthoic acid (**19**, 0.874 g, 94%) as a yellow solid. Without further purification, this solid was used for the next step: mp dec above 280 °C; ^{1}H NMR (DMSO-d_6) δ 8.85 (bs, 2H), 8.46 (s, 1H), 8.14 (s, 1H), 7.87 (s, 1H), 6.97 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 168.8, 148.3, 135.9, 132.5, 131, 130.2, 125.7, 123.6, 123.3, 115.7, 107.4. Anal. Calcd for $C_{11}H_7NO_4Cl_2$: C, 51.56; H, 2.73; N, 5.47. Found: C, 51.64; H, 3.00; N, 5.33.

6,7-Dichloronaphtho[2,3-*d*]imidazol-2-one (3a). Triethylamine (0.85 mL, 6.0 mmol) was added to a suspension of 3-amino-6,7-dichloro-2-naphthoic acid (**19**, 0.78 g, 3.05 mmol) in dry benzene (90 mL), and the mixture was stirred until a clear brown solution was obtained. Diphenyl phosphorazidate (1.31 mL, 6.1 mmol) was added, and the solution was heated at reflux for 3 h to give a yellow suspension. The reaction was cooled to rt, and the solid was collected by filtration, washed with benzene and dried under vacuum to give 6,7-dichloronaphtho[2,3-*d*]imidazol-2-one (**3a**, 0.615 g, 80%) as a yellow solid. A small sample was recrystallized from DMF and acetonitrile: mp above 340 °C, ^{1}H NMR (DMSO-d_6) δ 11.02 (bs, 2H), 8.18 (s, 2H), 7.37 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 156, 132, 128.5, 127.8, 125.3, 102.8; UV [λ_{max} nm (ϵ)] (MeOH) 340.6 (10 800), 325.2 (6180), 246.8 (80 500). Anal. Calcd for $C_{11}H_6N_2OCl_2$: C, 52.17; H, 2.37; N, 11.07. Found: C, 52.16; H, 2.68; N, 11.18.

6,7-Dichloro-3-nitro-2-naphthoic Acid (20). A 10% sodium hydroxide solution (4.5 mL) was added dropwise to a suspension of ethyl 6,7-dichloro-3-nitro-2-naphthoate (**7**, 1.73 g, 5.52 mmol) in ethanol (36 mL). The mixture was stirred at rt for 6 h to give a yellow suspension, at which time TLC showed the absence of starting material. A hydrogen chloride solution (5 N) was added until the solution was completely acidic. The ethanol was removed under reduced pressure, and the residue was stirred in water (50 mL) at rt for 1 h. The solid was collected by filtration, washed with water, and dried under vacuum at 78 °C to give 6,7-dichloro-3-nitro-2-naphthoic acid (**20**, 1.58 g, quantitative) as a yellow solid. A small sample was recrystallized from a mixture of ethanol and acetonitrile for analysis: mp dec above 280 °C; ^{1}H NMR (DMSO-d_6) δ 14.0 (bs, 1H), 8.70 (s, 1H), 8.62 (s, 1H), 8.58 (s, 1H), 8.54 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 165.6, 146.5, 132.8, 132.6, 132.4, 131.7, 130.6, 130.4, 130.2, 125.4, 123.8. Anal. Calcd for $C_{11}H_5NO_4Cl_2$: C, 46.15; H, 1.75; N, 4.90. Found: C, 46.01; H, 2.07; N, 4.57.

2-Amino-6,7-dichloro-3-nitronaphthalene (21). Diphenyl phosphorazidate (1.78 mL, 8.28 mmol) was added to a solution of 6,7-dichloro-3-nitro-2-naphthoate (**20**, 1.58 g, 5.52 mmol) and triethylamine (4.5 mL, 8.28 mmol) in dry DMF (40 mL). After the mixture was stirred at 25 °C for 3 h, water (3.5 mL) was added to the solution, and the solution was then heated at 100 °C for 1 h. The solution was concentrated under reduced pressure and diluted with ethyl acetate (300 mL). The ethyl acetate solution was washed sequentially with water (3 × 100 mL), and a saturated sodium chloride solution (50 mL) and then dried over anhydrous sodium sulfate. The ethyl acetate was removed by evaporation and the solid was dried under vacuum at rt to give 2-amino-6,7-dichloro-3-nitronaphthlene (**21**, 1.4 g, 99%) as a red solid that was directly used in the next step with out further purification: ^{1}H NMR (DMSO-d_6) δ 8.77 (s, 1H), 8.25 (s, 1H), 7.98 (s, 1H), 7.24 (s, 1H), 7.00 (bs, 2H); ^{13}C NMR (DMSO-d_6) δ 142.3, 136.2, 135.1, 132.6, 130.5, 126.5, 126.2, 125, 122.8, 110.9.

2,3-Diamino-6,7-dichloronaphthalene (22). 2-Amino-6,7-dichloro-3-nitronaphthalene (**21**, 1.11 g, 4.3 mmol), Raney nickel (0.1 g), ethyl acetate (80 mL) and ethanol (30 mL) were placed in a Parr hydrogenation apparatus under hydrogen (40 psi) for 15 h to give a yellow suspension. Acetone (50 mL) was added to the suspension, and a clear brown solution was obtained. The Raney nickel was removed by filtration through a bed of Celite. The filtrate was evaporated under reduced pressure, and the solid was dried under vacuum by an oil pump at rt to give 2,3-diamino-6,7-dichloronaphthalene (**22**, 0.97 g, quantitative) as a brown solid that was used directly in the next step without further purification: ^{1}H NMR (DMSO-d_6) δ 7.61 (s, 2H), 6.77 (s, 2H), 5.3 (bs, 4H); ^{13}C NMR (DMSO-d_6) δ 138.8, 127.7, 125.1, 122.7, 105.3. **2,3-Diamino-6,7-dichloronaphthalene was found to undergo oxidation very easily, and side products were generated after exposure to air for a short period of time.**

2-Amino-6,7-dichloronaphtho[2,3-*d*]imidazole (3b). 2,3-Diamino-6,7-dichloronaphthalene (**22**, 0.97 g, 4.27 mmol) was suspended in freshly distilled THF (10 mL), and then methanol (25 mL) and water (25 mL) were added sequentially. Cyanogen bromide (0.94 mL, 4.7 mmol) was added dropwise to this suspension over a period of 15 min. The mixture was stirred at rt for 36 h, and an additional amount of cyanogen bromide (0.3 mL, 1.5 mmol) was then added. The reaction mixture was stirred at rt for an additional 2 d. Another portion of cyanogen bromide (0.03 mL, 0.15 mmol) was added, and the reaction mixture was stirred continuously for an additional day to give an almost clear solution. TLC showed that the reaction was complete, and the insoluble solid was removed by filtration. The orange filtrate was concentrated under reduced pressure to about 20 mL and diluted with water (50 mL) to give an orange suspension. The orange suspension was neutralized

by the addition of a saturated sodium bicarbonate solution to give a yellow suspension. The solid was collected by filtration, washed with water, and then dried under vacuum at 78 °C to give 2-amino-6,7-dichloronaphtho[2,3-*d*]imidazole (**3b**, 1.08 g, quantitative) as a slightly brown solid: mp dec above 250 °C; ^{1}H NMR (DMSO-d_6) δ 12.90 (bs, 1H), 9.10 (bs, 2H), 8.36 (s, 2H), 7.84 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 152.9, 131.2, 128.7, 128.2, 126.6, 106.4; UV [λ_{max} nm (ϵ)] (MeOH) 345.6 (8560), 338.2 (7920), 255.2 (59 300), 230.2 (27 300). Anal. Calcd for $C_{11}H_7N_3Cl_2$: C, 52.38; H, 2.78; N, 16.67. Found: C, 52.16; H, 2.91; N, 16.51.

6,7-Dichloronaphtho[2,3-*d*]imidazol-2-thione (23). 2,3-Diamino-6,7-dichloronaphthalene (**22**, 1.3 g, 5.7 mmol) and (thiocarbonyl)diimidazole (1.23 g, 6.9 mmol) were heated for 8 h in dry benzene at reflux under an atmosphere of argon. The orange suspension was cooled to rt and allowed to stand at 5 °C overnight. The yellow solid was collected by filtration and washed with benzene. The crude solid product was stirred in 70 mL of water for 2 h, collected by filtration, washed with water and then dried under vacuum over P_2O_5 at 78 °C to give 6,7-dichloronaphtho[2,3-*d*]imidazol-2-thione (**23**, 1.23 g, 80%) as a brown solid: mp above 320 °C; ^{1}H NMR (DMSO-d_6) δ 12.80 (bs, 2H), 8.31 (s, 2H), 7.26 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 172.8, 133.9, 128.9, 128.4, 126.3, 104; UV [λ_{max} nm (ϵ)] (MeOH) 357.2 (35 000), 342.0 (19 400, shoulder), 282.0 (61 400), 230.2 (47 500), 203.0 (16 800). Anal. Calcd for $C_{11}H_6N_2SCl_2 \cdot 1.5\ H_2O$: C, 44.59; H, 3.04; N, 9.46. Found: C, 44.73; H, 3.27; N, 9.10.

6,7-Dichloro-2-(methylthio)naphtho[2,3-*d*]imidazole (3c). Methyl iodide (0.449 mL, 7.2 mmol) was added to a solution of 6,7-dichloronaphtho[2,3-*d*]imidazole-2-thione (**23**, 1.76 g, 6.55 mmol) in dry DMF (25 mL) in an ice bath and stirred for 30 min in an ice bath and then about 12 h at rt. The reaction solution was concentrated under reduced pressure to about 5 mL and diluted with ethyl acetate (300 mL). The ethyl acetate solution was washed with a saturated sodium carbonate solution (3 × 100 mL), water (2 × 100 mL), and a saturated sodium chloride solution (50 mL) and then dried over anhydrous sodium sulfate. The solvent was evaporated, and the residue was subjected to silica gel chromatography (5 × 10 cm) with elution first by 0.5% methanol in chloroform and then by 3% methanol in chloroform. The appropriate fractions, as determined by TLC (R_f = 0.4, 0.2% methanol in chloroform), were collected, and the solvents were removed under reduced pressure to give 6,7-dichloro-2-(methylthio)naphtho[2,3-*d*]imidazole (**3c**, 1.5 g, 81%) as a yellow solid: mp 215−217 °C; ^{1}H NMR [DMSO-d_6 (50 °C)] δ 12.77 (bs, 1H), 8.27 (s, 2H), 7.96 (s, 2H), 2.76 (s, 3H); UV [λ_{max} nm (ϵ)] (MeOH) 346.4 (18 500), 331.4 (13 600), 267.8 (63 200), 261.2 (63 800), 235.4 (38 400). Anal. Calcd for $C_{12}H_8N_2SCl_2$: C, 50.88; H, 2.83; N, 9.89. Found: C, 50.73; H, 2.76; N, 9.69.

6,7-Dichloro-2-(methylthio)-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)naphtho[2,3-*d*]imidazole (24). *N*,*O*-Bis(trimethylsilyl)acetamide (BSA, 0.45 mL, 1.86 mmol) was added to a suspension of 6,7-dichloro-2-(methylthio)naphtho[2,3-*d*]imidazole (**3c**, 0.262 g, 0.93 mmol) in dry 1,2-dichloroethane (13 mL) under an atmosphere of argon and stirred at rt for 30 min. 1-*O*-Acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (0.68 g, 1.39 mmol) was added to this mixture, followed by the addition of trimethylsilyl (trifluoromethyl)sulfonate (TMSOTf, 0.287 mL, 1.48 mmol), and the reaction was stirred at 50 °C for 3 d. The reaction solution was diluted with ethyl acetate (100 mL). The ethyl acetate solution was washed with a saturated sodium bicarbonate solution (2 × 100 mL) and a saturated sodium chloride solution (50 mL) and then dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the residue was subjected to silica gel chromatography (5 × 10 cm) with elution by 0.5% methanol in chloroform. The appropriate fractions, as determined by TLC (R_f = 0.4, chloroform), were collected, and the solvents were removed under reduced pressure to give 6,7-dichloro-2-(methylthio)-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)naphtho[2,3-*d*]imidazole (**24**, 0.65 g, 96.6%) as a brown solid. A small sample was recrystallized from a mixture of chloroform and methanol for analysis: mp 241−243 °C; ^{1}H NMR (DMSO-d_6) δ 8.31−6.92 (m, 19H), 6.46 (d, J = 7.36 Hz, 1H), 6.19−6.10 (m, 2H), 5.00 (q, J = 12.4, 2.0 Hz), 4.85 (q, J = 12.4, 2.9 Hz), 4.77 (m, 1H), 2.83 (s, 3H). Anal. Calcd for $C_{38}H_{28}N_2O_7SCl_2$: C, 62.72; H, 3.85; N, 3.85. Found: C, 62.80; H, 3.67; N, 3.74.

6,7-Dichloro-2-(methylthio)-1-(β-D-ribofuranosyl)naphtho[2,3-*d*]imidazole (25). 6,7-Dichloro-2-(methylthio)-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)naphtho[2,3-*d*]imidazole (**24**, 0.32 g) was added to saturated methanolic ammonia (140 mL) and stirred at rt for 24 h. The solvent was evaporated, and the solid was triturated with hexane (3 × 50 mL). The hexane was decanted, and the solid was dried under 0.01 mmHg/78 °C for 24 h to give 6,7-dichloro-2-(methylthio)-1-(β-D-ribofuranosyl)naphtho[2,3-*d*]imidazole (**25**, 0.173 g, 96.3%) as a brown solid. A small sample was recrystallized from 2-propanol for analysis: mp 244−246 °C; ^{1}H NMR (DMSO-d_6) δ 8.38 (s, 1H), 8.33 (s, 1H), 8.23 (s, 1H), 8.12 (s, 1H), 5.76 (d, J = 7.46 Hz, 1H), 5.46 (d, J = 6.29 Hz, 1H), 5.34 (m, 1H), 5.27 (d, J = 4.31 Hz, 1H), 4.62 (q, J = 6.57, 6.23 Hz, 1H), 4.18 (m, 1H), 4.01 (m, 1H), 3.78 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 159.5, 144.5, 135.6, 128.8, 128.6, 128.5, 128.2, 126.2, 125.8, 113.2, 107.6, 88.9, 85.8, 70.6, 70, 61.5, 14.5; UV [λ_{max} nm (ϵ)] (MeOH) 347.0 (18 100), 330.5 (14 900), 269.0 (75 000), 262.5 (71 100), 237.0 (40 300). Anal. Calcd for $C_{17}H_{16}N_2O_4SCl_2$: C, 49.16; H, 3.86; N, 6.75. Found: C, 49.17; H, 4.04; N, 6.66.

2,6,7-Trichloro-1-(β-D-ribofuranosyl)naphtho[2,3-*d*]imidazole (2). Chlorine in carbon tetrachloride (0.92 mL, 0.972 M, 0.88 mmol) was added through a gastight syringe to a suspension of 6,7-dichloro-2-(methylthio)-1-(β-D-ribofuranosyl)-naphtho[2,3-*d*]imidazole (**25**, 0.33 g, 0.795 mmol) in dry methanol (33 mL) at −78 °C under an atmosphere of argon. The suspension became clear a short while after the addition of chlorine. The solution was stirred at −78 °C for 1 h and diluted with ethyl acetate (300 mL). The ethyl acetate solution was washed with a mixture of a saturated sodium chloride solution and a saturated sodium bicarbonate solution (3 × 100 mL, 1/1, v/v), and a saturated sodium chloride solution (50 mL) and then dried over anhydrous sodium sulfate. The solution was evaporated, and the residue was subjected to silica gel chromatography (5 × 18 cm) and eluted with 4% methanol in chloroform. The appropriate fractions, as determined by TLC (R_f = 0.35, chloroform/methanol, 10/0.5, v/v), were collected, and the solvents were removed under reduced pressure to give 2,6,7-trichloro-1-(β-D-ribofuranosyl)naphtho[2,3-*d*]imidazole (**2**, 0.262 g, 81.9%) as a white solid. Some starting material (0.042 g, 12.1%) was also recovered from the column. The total yield, after the recovery of the starting material, was 90.4%: mp 179−182 °C; ^{1}H NMR (DMSO-d_6) δ 8.609 (s, 1H), 8.408 (s, 1H), 8.287 (s, 1H), 8.266 (s, 1H), 5.973 (d, J = 7.57 Hz, 1H), 5.525 (d, J = 6.37 Hz, 1H), 5.415 (t, J = 4.45 Hz, 1H), 5.309 (d, J = 4.22 Hz, 1H), 4.635 (q, 1H), 4.200 (m, 1H), 4.047 (m, 1H), 3.801 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 145.4, 142.2, 133.9, 129.1, 128.8, 128.7, 128.7, 127.1, 126.5, 115.2, 109, 89.3, 86.1, 70.7, 69.9, 61.4; UV [λ_{max} nm (ϵ)] (MeOH) 323.0 (8730), 249.0 (93 900); MS EI *m/e* 402 (M^+, 8.9%); HRMS calcd for $C_{16}H_{13}N_2O_4Cl_3$ 401.9941, found 401.9928. Anal. Calcd for $C_{16}H_{13}N_2O_4Cl_3$: C, 47.58; H, 3.22; N, 6.94. Found: C, 47.39; H, 3.10; N, 6.75.

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