Manganese Tetraphenylporphyrin-Catalyzed Stereoselective Epoxidation of Thymidine Nucleosides

Pietro Tagliatesta,*[,†] Roberta Bernini,[‡] Claudia Crestini,[‡] Donato Monti,[†] Tristano Boschi,[†] Enrico Mincione,[‡] and Raffaele Saladino*[,‡]

Dipartimento di Scienze e Tecnologie Chimiche, Università degli Studi di Roma "Tor Vergata", Via della Ricerca Scientifica, 00133 Rome, Italy, and Dipartimento Agrochimico Agrobiologico, Università della "Tuscia", Via San Camillo de Lellis, 01100 Viterbo, Italy

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Manganese 2,6-disubstituted tetraphenylporphyrins, bearing halogen atoms on the β-positions, have been used as catalysts for the first described stereoselective epoxidation of thymidine nucleosides. The oxidations were carried out using dimethyldioxirane (DMDO) as the oxygen atom donor. The diastereoisomeric ratio of the final epoxides might be related to the hydrogen-bonding interaction between the OH groups of the sugar moieties and the OCH_3 groups of the catalysts during the approach of the nucleosides to the core of the macrocycles.

A number of synthetic metalloporphyrins have been studied as catalysts for the oxidation of organic substrates.[1−4] The most well studied of such compounds have been *meso*-tetraphenylporphyrins containing electron-withdrawing groups as substituents on either the four phenyl rings or the β-pyrrole positions of the macrocycle, or both.[1−6] The introduction of four or more bulky halogen substituents onto the eight β positions leads to a nonplanar conformation of the ring and to an increase in the stability of the macrocycle toward oxidative degradation.[1−8]

Updated information is not yet available on the molecular recognition that such macrocycles gravitate toward organic substrates, although many attempts have been made to rationalize these interactions.[9,10]

Several papers appeared on the interaction between DNA and metalloporphyrins, focusing the attention on the molecular recognition[11] and on the reactivity of the genetic material in the metalloporphyrin-mediated oxidation.[12] Ogoshi et al. have shown the presence of a weak interaction between ortho-substituted *meso*-tetraphenylporphyrins and several nucleosides, attributed to the presence of hydrogen bonds involving the polar groups of the macrocycles, e.g., OH, OCH_3, and the nitrogen atoms of the purine and pyrimidine bases. In these cases, all the employed nucleosides were characterized by a fully protected 2′-deoxyribose moiety.[13] Recently, Aida et al. reported the stereoselective interaction between a chiral β-octaalkyl-*meso*-methoxyphenylporphyrin and chiral carboxylic acid that was attributed to the formation of strong hydrogen bonds between the ligand and the substrates.[14]

To the best of our knowledge, no data are currently available on molecular recognition between metalloporphyrins and the OH groups in the 2′-deoxyribose residue of nucleosides or the influence of such interactions on the stereochemistry of the metalloporphyrin-catalyzed oxidations.

During the course of research on new synthetic methodologies for the oxidation of nucleic bases and nucleosides using dimethyldioxirane (DMDO), a new, powerful, and selective oxidant, we have described the epoxidation of uracil derivatives and pyrimidine nucleosides and shown the activity of such derivatives in *Sendai* virus inhibition.[15,16]

Furthermore, we have reported an improvement of the synthesis of nucleic base epoxides based on the use of manganese metalloporphyrins as catalysts.[17] Nevertheless, no stereoselectivity and only a very low yield were obtained in the epoxidation of thymidine derivatives.[16] Thymidine epoxides are important intermediates in DNA oxidative transformations because they are formed as initial photooxidation products[18] and they may be responsible for protein−nucleic acid cross-linking.[19]

We report here an efficient and stereoselective manganese tetraphenylporphyrin- catalyzed epoxidation of

† Università degli Studi di Roma "Tor Vergata".
‡ Università della "Tuscia".

(1) Meunier, B. *Chem. Rev.* **1992**, *92*, 1411.
(2) Mansuy, D. *Coord. Chem. Rev.* **1993**, *125*, 129.
(3) Bruice, T. C. In *Mechanistic Principles of Enzyme Activity*; Liberman, J. F., Greenberg, A., Eds.; VCH: New York, 1988; Chapter 8.
(4) Grinstaff, M. W.; Hill, M. G.; Labinger, J.; Gray, H. B. *Science* **1994**, *264*, 1311.
(5) Wijesekera, T.; Matsumoto, A.; Dolphin, D.; Lexa, D. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1028.
(6) Kadish, K. M.; D'Souza, F.; Villard, A.; Van Caemelbecke, E.; Bianco, P.; Antonini, A.; Tagliatesta, P. *Inorg. Chem.* **1994**, *33*, 5169.
(7) Mandon, D.; Ochsenbein, P.; Fischer, J.; Weiss, R.; Jayaraj, K.; Austin, R. N.; Gold, A.; White, P. S.; Brigaud, O.; Battioni, P.; Mansuy, D. *Inorg. Chem.* **1992**, *31*, 2044.
(8) Ochsenbein, P.; Ayougou, K.; Mandon, D.; Fischer, J.; Weiss, R.; Austin, R. N.; Jayaraj, K.; Gold, A.; Terner, J.; Fajer, J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 348.
(9) Hayashi, T.; Miyahara, T.; Kumazaki, S.; Ogoshi, H.; Yoshihara, K. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1964.
(10) Kuroda, Y.; Ogoshi, H. *Synth. Lett.* **1994**, 319.
(11) Banville, D. L.; Marzilli, L. G.; Strickland, J. A.; Wilson, W. D. *Biopolymers* **1986**, *25*, 1837.
(12) Bernadou, J.; Pratviel, G.; Bennis, F.; Girardet, M. B.; Meunier, B. *Biochemistry* **1989**, *28*, 7268.
(13) Hogoshi, H.; Hatakeyama, H.; Kotani, J.; Kawashima, A.; Kuroda, Y. *J. Am. Chem. Soc.* **1991**, *113*, 8181.
(14) Furusho, Y.; Kimura, T.; Mizuno, Y.; Aida, T. *J. Am. Chem. Soc.* **1997**, *119*, 5267.
(15) Saladino, R.; Lupattelli, P.; Mincione, E. *Tetrahedron Lett.* **1993**, *34*, 6313.
(16) Saladino, R.; Bernini, R.; Crestini, C.; Mincione, E.; Bergamini, A.; Marini, S.; Palamara, A. T. *Tetrahedron* **1995**, *36*, 7561.
(17) Saladino, R.; Bernini, R.; Mincione, E.; Tagliatesta, P.; Boschi, T. *Tetrahedron Lett.* **1996**, *34*, 2647.
(18) Ryang, H. S.; Wang, S. Y. *J. Am. Chem. Soc.* **1978**, *100*, 1302.
(19) Smith, K. C. In *Photochemistry and Photobiology of Nucleic Acid Biology;* Wang, S. Y., Ed.; Academic Press: New York, 1976; Vol. 2, p 167.

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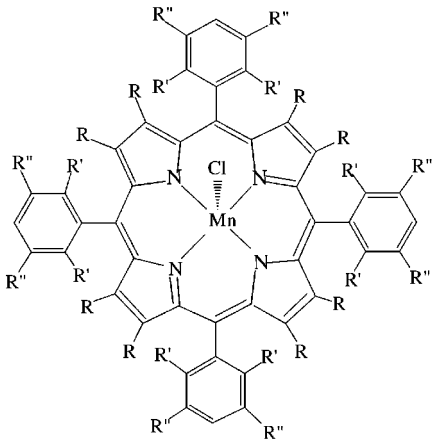


Compound 7 : R=R"=H R'=OCH_3
Compound 8 : R=R"=Cl R'=OCH_3
Compound 9 : R=R'=Cl R"=H

Figure 1. Structures of manganese porphyrins **7**−**9**.

thymidine nucleosides. A possible role of the molecular recognition processes between manganese porphyrins and OH groups in the 2′-deoxyribose moiety on the stereochemistry of the oxidation is also analyzed.

Different thymidine derivatives, 5′-*O*-acetylthymidine **1**, 3′-*O*-acetylthymidine **2**, and 3′,5′-di-*O*-acetyl thymidine **3**, have been employed. The catalysts were Mn(TDMPP)Cl (**7**), Mn[(Cl_{16})TDMPP]Cl (**8**), and Mn[(Cl_8)TDCPP]Cl (**9**),[20,21] where TDMPP is the dianion of 5,10,15,20-tetrakis(2,6-dimethoxyphenyl)porphyrin, (Cl_{16})TDMPP is the dianion of 2,3,7,8,12,13,17,18-octachloro-5,10,15,20-tetrakis(3,5-dichloro-2,6-dimethoxyphenyl)porphyrin, and (Cl_8)TDCPP is the dianion of 2,3,7,8,12,13,17,18-octachloro-5,10,15,20-tetrakis(2,6-dichlorophenyl)porphyrin. The structures of manganese porphyrins **7**−**9** are reported in Figure 1.

The oxidations were performed by adding dimethyldioxirane (DMDO, 1.2 equiv/mol, 0.09 N acetone solution)[22] to a solution of **1**−**3** (1 mmol) in CH_2Cl_2 (5 mL) in the presence of catalytic amounts of the manganese porphyrin complexes at 25 °C. A 1:1 CH_2Cl_2/acetone solvent composition was consistentely used in all the experiments. Two chromatographically separable diastereoisomeric epoxides, **4a**,**b**, **5a**,**b**, and **6a**,**b**, were obtained from each oxidation in acceptable yields, and their ratio with unreacted substrates was determined by ^{1}H NMR analysis. Control experiments consisting of running the oxidation of thymine derivatives with DMDO in the absence of the porphyrin catalyst have been previously published.[16] In that case, *cis*- and *trans*-diols were obtained as the main products, while the corresponding epoxides were recovered only in low yields. The catalysts were recovered almost unchanged after the oxidation reactions and bleaching experiments, performed with DMDO in the same solvent mixture, showing the high stability of manganese porphyrins (90−95% of catalysts recovered).

When the oxidations were performed in the presence of catalyst **7**, a flat macrocycle, a 1:1 ratio was obtained for all the substrates (Table 1). In the case of the catalyst **8**, the stereochemical results were surprisingly different, giving a ratio of 1:5 for **4a**,**b**, 9:1 for **5a**,**b**, and 3:2 for **6a**,**b**. On the basis of these data, it is reasonable to suggest that the diastereoisomeric epoxides ratio might be related to the presence of the hydroxyl groups in the sugar residue and to the structure of the substituted porphyrin. In fact, the approach of the substrates to the core of the catalyst **8** could be influenced by formation of hydrogen bonds between the OH groups on the sugar residue and the OCH_3 groups present in the 2,6-phenyl positions of the metalloporphyrin. Because of the distortion of the macrocycle due to the saddle-shaped conformation of the β-substituted porphyrin **8**,[7,8] the methoxy groups are located closer to the reaction center than in **7**. This situation allows the formation of hydrogen bonds that could guide, in different ways, the substrates **1** and **2** during the approach to the catalyst. However, the 3:2 ratio could be reasonably ascribed to the effect of the distortion of the macrocycle **8**. The OCH_3 groups in **7** most likely cannot interact with the substrates during the reaction because they are located far from the reaction center. This hypothesis is in agreement with the low selectivity obtained in the oxidation of **3**, which is characterized by a fully protected 2′-deoxyribose moiety. Furthermore, the stereochemistry α or β to the OH groups on the 2′-deoxyribose residue seems to be an important structural feature in the stereochemistry of the oxidations catalyzed by **8**, and the diastereoisomeric epoxide ratio for **4a**,**b** and **5a**,**b** appears to be reversed depending on the presence of unprotected 3′-OH or 5′-OH groups.

Table 1. Manganese Tetraphenylporphyrin Catalyzed Epoxidations of Thymidine Derivatives 1−3[a]

substrate	catalyst[b]	product ratio[c]	R_1	R_2	yield[d] (%)
1	**7**	**4a**/**4b** = 1/1	COMe	H	51
1	**8**	**4a**/**4b** = 1/5	COMe	H	55
1	**9**	**4a**/**4b** = 2/1	COMe	H	58
2	**7**	**5a**/**5b** = 1/1	H	COMe	40
2	**8**	**5a**/**5b** = 9/1	H	COMe	57
3	**7**	**6a**/**6b** = 1/1	COMe	COMe	53
3	**8**	**6a**/**6b** = 3/2	COMe	COMe	72

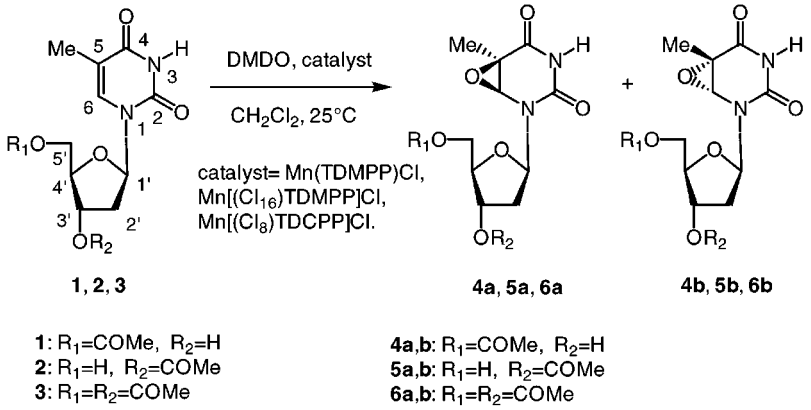
[a] Conditions: CH_2Cl_2, catalytic amount of **7**−**9**, 1.2 equiv/mol of DMDO, 2 days. [b] Mn(TDMPP)Cl (**7**), Mn[(Cl_{16})TDMPP]Cl (**8**), and Mn[(Cl_8)TDCPP]Cl (**9**). [c] The diastereoisomeric ratio was determined by ^{1}H NMR. [d] Conversions of substrates corresponded to product yields as evaluated by mass balance on recovered unreacted substrates.

To further confirm this hypothesis, a third catalyst, porphyrin **9**, lacking any acceptor of hydrogen bond, was used in the oxidation of **1**. This metalloporphyrin cannot bind the approaching substrates *via* hydrogen bond formation and thus should show a low diastereoselectivity. As expected, a low product ratio of 2:1 has been obtained in this case for **4a**,**b** (Table 1).

It was not possible to grow crystals of the different stereoisomers, suitable for the X-ray diffraction analysis; however, complete structural assignments for compounds **6a**,**b** was obtained by one- and two-dimensional ^{1}H NMR measurements and further confirmed by NOE experiments. In particular, relative to the 2′-deoxyribose moiety, the 5,6-oxiranyl-5,6-dihydrouracil base in compounds **6a**,**b** adopts an anti orientation, where no particular steric hindrance between sugar and base is present,[23] as shown by the absence of any detectable NOE effect between the H-6 and H-1′ protons.[24] In Scheme 1 the

(20) Rocha Gonsalves, A. M. d'A.; Pereira, M. M.; Serra, A. C.; Johnstone, R. W.; Nunes, M. L. P. G. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2054.
(21) Autret, M.; Ou, Z.; Antonini, A.; Boschi, T.; Tagliatesta, P.; Kadish, K. M. *J. Chem. Soc., Dalton Trans.* **1996**, 2793.
(22) Adam, W.; Bialas, J. L.; Hadjiarapoglou, L. *Chem. Ber.* **1991**, *124*, 2377.

Scheme 1



molecular structures and the stereochemistry of **6a**,**b** are reported. The sugar moiety shows the usually puckered fast conformational equilibrium between the C-3′ endo (N) and C-2′ endo (S) forms, with a prevalence of the S-type conformation.[25] In the case of compound **6b**, a deshielding effect on H-5″ (Δppm = 0.1), as well as a large shielding effect on H-2′ and H-2″ protons (Δppm = 0.23), was observed with respect to the corresponding chemical shifts of the 3′,5′-di-*O*-acetylthymidine **3**. Such shifts have been attributed to the diamagnetic anisotropy of the oxygen atom present in the oxiranyl ring.[26] Moreover, the proximity of the H-6 and H-2′ protons in **6b** was undoubtedly revealed by their mutual NOE effect, suggesting the configuration 5*S*,6*R* for the 5,6-oxyranyl-5,6-dihydrouracil ring as shown in Scheme 1. In compound **6a**, the H-5″ proton did not experience any deshielding effect, and only the shielding effect on H-2″ was still found, so indicating an endo orientation of the oxiranyl ring, corresponding to the configuration 5*R*,6*S*. Such an orientation was further confirmed by the lack of any detectable NOE effect between H-6 and H-2′ protons. The configuration of epoxides **4b** and **5b** was tentatively assigned as anti (with respect to the sugar moiety) in analogy with the diamagnetic anisotropy effect previously observed for **6b**. In fact, both **4b** and **5b** exhibited a deshielding effect on H-5′ (Δppm = 0.1 and Δppm = 0.08, respectively) and a shielding effect on H-2′, 2″ (Δppm = 0.15 and Δppm = 0.19, respectively), with respect to the parent compounds **1** and **2** (Scheme 1). Moreover, in compounds **4a** and **5a**, only a shielding effect on H-2′ (Δppm = 0.03 and Δppm = 0.10, respectively) was observed.

UV−vis spectroscopic studies aimed at the elucidation of the interaction between porphyrins and the nucleobase derivatives have been carried out. The free-base porphyrin H_2Cl_{16}TDMPP (**P**) was chosen in order to obtain information on the effects of the pure hydrogen-bond interactions on the stereochemistry of the reaction. Measurements were performed in dichloromethane−acetone (1:1 v/v) in the case of substrates **2** and **3** and in dichloromethane−acetone−tetrahydrofuran (5:4.5:0.5) in the case of nucleobase **1** for solubility reasons. The

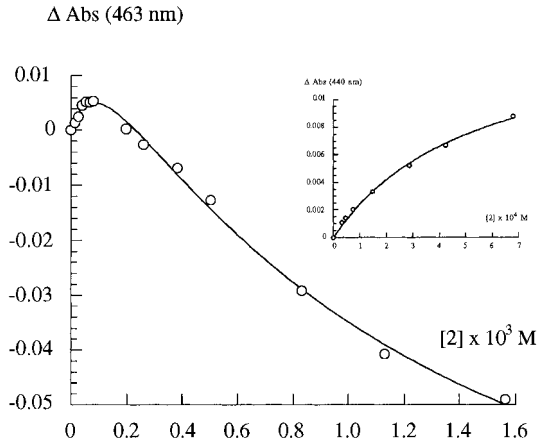


Figure 2. Spectrophotometric titration curve for the complex [**2**@**8**] and for the complex [**2**@**8-Ni**] (inset).

absorbance changes at 463 nm (Soret band) of the porphyrin receptor **8** upon addition of thymidine derivatives **1** and **2** were monitored. The spectroscopic behavior observed is dependent on the nature of the nucleobases employed. A general aspecific increase of the absorbance is observed. Moreover, no tight isosbestic point along with a biphasic absorption change was observed, indicating that the systems investigated feature not only a 1:1 but also a 1:2 porphyrin−thymidine complex formation. A small but significant wavelength shift ($\Delta\lambda$ = 4 nm) of the absorption maximum is also observed in the case of **2**. A representative result is graphically reported in Figure 2 for the formation of the complex [**2**@**8**]. This observation suggests that two thymidine molecules are bound by **8** at two independent recognition sites. The primary interaction, the one occurring at lower concentration of the added guest, could be ascribed to the hydrogen-bond formation. The nonlinear regression fitting analysis of the absorbance changes as a function of the concentration of the nucleobases gives the values of the association constants (K_{11} and K_{12}) for the molecular complex formations.[27] The results are reported in Table 2. The values obtained are strongly dependent on the nature of thymidine derivatives being 1200 (150) and 7800 (800) M^{-1} for **1** and **2**, respectively. This trend can be ascribed to the presence of the free hydroxylic groups that favorably interact with the 2,6-MeO groups on the porphyrin phenylic rings via hydrogen bonding. Ogoshi and co-

(23) De Leeuw, H. P. M.; Haasnoot, C. A. G.; Altona, C. *Isr. J. Chem.* **1980**, *20*, 108.
(24) Schirmer, R. E.; Noggle, S. H.; Hart, P. A. *J. Am. Chem. Soc.* **1972**, *94*, 2561.
(25) Altona, C.; Sumdaralingam, M. *J. Am. Chem. Soc.* **1973**, *95*, 2333.
(26) Tori, K.; Kitahonoki, K.; Takano, Y.; Tanida, H.; Tsuji, T. *Tetrahedron Lett.* **1965**, 869.
(27) Connors, K. A. *Binding Constants. The Measurements of Molecular Complex Stability*; John Wiley and Sons: New York, 1987.

Table 2. Binding Constant Values (*K*) of Thymidine Derivatives by Porphyrin Receptor 8[a]

ligand	K_{11}, M^{-1}	K_{12}, M^{-2}	dr (**a**/**b**)[b]
1	1200 (400)[c]	150 (60)	1/5
2	7800 (800)	800 (250)	9/1
	1800 (200)[d]		
3	3000 (350)		3/2

[a] Standard deviations are reported in parentheses. [b] dr refers to diastereomeric ratio of the obtained epoxides (see text). [c] Performed in dichloromethane/acetone/THF 5:4.5:0.5 (v/v) mixture. [d] Value for the association to **8**-**Ni**.

workers reported on the studies on the molecular recognition of functionalized metalloporphyrins toward ubiquinone analogues, pointing out the fundamental contribution of multiple hydrogen bonds to the stability of the molecular complexes. In this case, the binding constants were found to increase with the number of MeO substituents bound to the quinone ring, and two adjacent MeO substituents were found to act cooperatively.[28]

The fact that the strength of the association closely parallels the trend observed in the diastereomeric ratio for the epoxidation reaction must be emphasized. This effect appears to be dependent not only on the presence of a free hydroxylic group but also on its position. A reverse diastereomeric ratio is found in fact for the 5′- or 3′-acetylated substrate (*vide supra*). The thymidine derivative **2**, owing to the presence of the free OH in 5′-position, may more favorably interact with the methoxy partners of the meso phenylic rings. This would result in a tighter and more sterically demanding interaction. On the contrary, the thymidine derivative **1** presents a lower association constant value indicating a looser interaction, probably due to the steric crowding at the 3′-OH position. This hypothesis can explain the differences found in the diastereoselectivity of the reaction with the two different substrates.

Control experiments were performed on the nickel derivative of porphyrin **8** (**8**-**Ni**) with nucleobase **2** in order to disentangle the contribution of the pyrrolic NH coordination. In this case, only a clear 1:1 binding isotherm is observed (Figure 2) with an association constant value $K_{11} = 1800\ M^{-1}$, which can be safely assigned to that for the OMe hydrogen-bonding site. The second recognition process observed in the case of the free-base porphyrin **8**, the one occurring with a decrease of the absorbance, is then tentatively assigned to that for the interaction with the inner NH protons. The fact that the observed association constant is lower with respect to the one observed in the case of the parent **8** may be ascribed to the flattening effect of the central metal atom. The OMe moieties would be displaced apart, decreasing the extent of the coordination of the incoming ligand.

The fully protected tymidine derivative **3** gives the formation of a 1:1 molecular complex with **8**. The fact that this substrate features a low diastereomeric excess indicates the occurrence of an aspecific interaction with the macrocycle.

In conclusion, to the best of our knowledge, we have reported the first described efficient and stereoselective manganese tetraphenylporphyrin-catalyzed epoxidation of thymidine nucleosides. The stereoselectivity observed in the oxidations with catalyst **8** might be attributed to hydrogen-bond formation between the ruffled manganese porphyrin bearing methoxy groups in the 2,6 positions and halogen atoms in all the β-positions and the free hydroxy groups in the 2′-deoxyribose moiety.

Experimental Section

General Methods. Descriptions of analytical instruments and ^{1}H NMR, IR, and UV−vis spectrometers have been previously published.[16,17] Binding experiments were performed on a high-quality Perkin-Elmer λ 18 instrument equipped with a thermostated cell holders. Mass spectra were recorded on a VG 70/250S spectrometer with an electron beam of 70 eV. Chromatographic purifications were performed on silica gel columns for flash technique (Merck, 230−400 mesh). Thin-layer chromatography was carried out using Merck Kiesegel 60 F254 plates.

Materials. All reagents and solvents were of the highest grade commercially available and used purified or freshly distilled as required by literature procedures. The substrates **1**−**3** used in the present study were synthesized and purified by the methods described.[29] Manganese porphyrins **7**−**9** were synthesized according to literature procedures.[21,30]

Epoxidation Reactions. General Procedure. In a typical experiment, dimethyldioxirane (DMDO, 1.2 equiv/mol, 0.09 N acetone solution)[1] was added to a solution of the nucleoside derivative (1.0 mmol) in CH_2Cl_2 (5 mL) in the presence of the manganese porphyrin complex (1.0×10^{-2} mmol) at 25 °C. A 1:1 CH_2Cl_2/acetone solvent composition was consistently used in all experiments. The progress of the reaction was monitored by thin-layer chromatography (SiO_2; CH_2Cl_2/MeOH 95:5). The solvent was evaporated under reduced pressure, and the products were purified and separated by flash chromatography on silica gel.

5′-*O*-Acetyl-5,6-dihydro-5,6-oxiranylthymidine (4a): 147 mg, 49%; oil; $[\alpha]_D = -5.10°$ (*c* 0.75 in $CHCl_3$); δ_H (200 MHz, $CDCl_3/CD_3OD$) 1.29 (s, 3H, CH_3), 1.98 (s, 3H, CH_3), 2.04 and 2.20 (m, 2H, H-2′, 2″), 3.28 (m, 1H, H-3′), 3.82 (m, 3H, H-4′, 5′, 5″), 4.75 (s, 1H, H-6), 6.06 (m, 1H, H-1′); δ_C (200 MHz, $CDCl_3/CD_3OD$) 19.79 (CH_3), 21.57 (CH_3), 37.97 (CH_2), 63.70 (CH_2), 71.43 (C), 79.81 (CH), 82.65 (CH), 84.28 (CH), 84.61 (CH), 151.42 (C), 171.01 (C), 173.66 (C); MS *m*/*z* 300 (15), [M^+].

5′-*O*-Acetyl-5,6-dihydro-5,6-oxiranylthymidine (4b): 76.5 mg, 26%; oil; δ_H (200 MHz, $CDCl_3/CD_3OD$) 1.24 (s, 3H, CH_3), 1.96 (s, 3H, CH_3), 2.05 (m, 2H, H-2′, 2″), 3.20 (m, 1H, H-3′), 3.87 (m, 2H, H-5′, 5″), 4.08 (m, 1H, H-4′), 4.73 (s, 1H, H-6), 6.07 (m, 1H, H-1′); δ_C (200 MHz, $CDCl_3/CD_3OD$) 20.27 (CH_3), 22.14 (CH_3), 37.29 (CH_2), 63.97 (CH_2), 71.89 (C), 78.45 (CH), 81.60 (CH), 82.52 (CH), 83.57 (CH), 151.06 (C),171.22 (C), 174.0 (C); MS *m*/*z* 300 (19), [M^+].

3′-*O*-Acetyl-5,6-dihydro-5,6-oxiranylthymidine (5a): 60 mg, 20%; oil; δ_H (200 MHz, $CDCl_3/CD_3OD$) 1.28 (s, 3H, CH_3), 1.96 (s, 3H, CH_3), 2.18 and 2.28 (m, 2H, H-2′, 2″), 3.77 (m, 3H, H-4′, 5′, 5″), 4.80 (s, 1H, H-6), 5.09 (m, 1H, H-3′), 6.15 (m, 1H, H-1′); δ_C (200 MHz, $CDCl_3/CD_3OD$) 18.93 (CH_3), 21.96 (CH_3), 35.42 (CH_2), 61.02 (CH_2), 71.69 (C), 73.78 (CH), 79.59 (CH), 83.45 (CH), 84.54 (CH), 152.01 (C), 170.89 (C), 173.72 (C); MS *m*/*z* 300 (21), [M^+].

3′-*O*-Acetyl-5,6-dihydro-5,6-oxiranylthymidine (5b): 60 mg, 20%; $[\alpha]_D = +8.3°$ (*c* 0.6 in $CHCl_3$); oil; δ_H (200 MHz, $CDCl_3/CD_3OD$) 1.21 (s, 3H, CH_3), 1.88 (s, 3H, CH_3), 2.08−2.17 (m, 2H, H-2′, 2″), 3.88 (m, 3H, H-4′, 5′, 5″), 5.03 (s, 1H, H-6), 5.05 (m, 1H, H-3′), 5.92 (m, 1H, H-1′); δ_C (200 MHz, $CDCl_3/CD_3OD$) 20.97 (CH_3), 22.25 (CH_3), 35.71 (CH_2), 62.42 (CH_2), 72.36 (C), 74.27 (CH), 75.68 (CH), 78.96 (CH), 83.90 (CH), 151.72 (C), 171.50 (C), 174.54 (C); MS *m*/*z* 300 (25), [M^+].

3′,5′-Di-*O*-acetyl-5,6-dihydro-5,6-oxiranylthymidine (6a): 123 mg, 36%; $[\alpha]_D = -12.2°$ (*c* 0.85 in $CHCl_3$); oil; δ_H

(28) Hayashi, T.; Miyahara, T.; Koide, N.; Kato, Y.; Masuda, H.; Ogoshi, H. *J. Am. Chem. Soc.* **1997**, *119*, 7281.

(29) Verheiyden, J. P. H.; Moffatt, J. G. In *Synthetic procedures in nucleic acid chemistry*; Zorbach, W. W., Ed.; Interscience: New York, 1968; pp 383.

(30) Rocha Gonsalves, A. M. d'A.; Varejao, J. M. T. B.; Pereira, M. M. *J. Heterocycl. Chem.* **1991**, 28, 635.

(200 MHz, $CDCl_3/CD_3OD$) 1.25 (s, 3H, CH_3), 1.99 (s, 6H, CH_3), 2.24 and 2.44 (m, 2H, H-2′, 2″), 4.09 (m, 1H, H-4′), 4.27 (m, 2H, H-5′, 5″), 4.76 (s, 1H, H-6), 5.16 (m, 1H, H-3′), 6.22 (m, 1H, H-1′); δ_C (200 MHz, $CDCl_3/CD_3OD$) 19.01 (CH_3), 20.73 (CH_3), 22.26 (CH_3), 35.71 (CH_2), 64.11 (CH_2), 72.05 (C), 74.22 (CH), 80.06 (CH), 81.23 (CH), 84.95 (CH), 151.83 (C), 170.94 (C), 171.38 (C), 171.38 (C); MS 342 (38), [M^+].

3′,5′-Di-*O*-acetyl-5,6-dihydro-5,6-oxiranylthymidine (6b): 123 mg, 36%; $[\alpha]_D = +23.3°$ (*c* 0.85 in $CHCl_3$); oi; δ_H (200 MHz, $CDCl_3/CD_3OD$) 1.29 (s, 3H, CH_3), 1.94 (s, 6H, CH_3), 2.22 (m, 2H, H-2′, 2″), 4.13 (m, 1H, H-4′), 4.29 and 4.39 (m, 2H, H-5′, 5″), 4.65 (s, 1H, H-6), 5.15 (m, 1H, H-3′), 6.36 (m, 1H, H-1′); δ_C (200 MHz, $CDCl_3/CD_3OD$) 20.67 (CH_3), 20.96 (CH_3), 22.63 (CH_3), 34.82 (CH_2), 64.21 (CH_2), 72.30 (C), 74.88 (CH), 78.72 (CH), 80.92 (CH), 84.10 (CH), 151.54 (C), 171.24 (C), 171.42 (C), 174.35 (C); MS *m*/*z* 342 (41), [M^+].

Evaluation of the Binding Constants (K_{assoc}) and Stoichiometry of the Complex Formation. The binding constants were measured by UV−vis spectroscopy. Experiments were performed in dichloromethane/acetone (1:1 v/v) mixture unless otherwise indicated, recording the absorbance changes at fixed wavelength (typically at the Soret band absorption maxima) upon addition of aliquots (5−250 μL) of a 3−5 mM solution of thymidine derivative to 2 mL of a 0.8−1.2 μM porphyrin solution. All measurements were performed in a 1.0 cm quartz cell mantained at 25.0 °C. Solutions of thymidines were prepared by addition of a stock solution of the porphyrin to a weighted amount of nucleobases in a 2 mL volumetric flask. This procedure ensures a constant concentration of the receptor throughout the spectrophotometric titration. Binding constant values were obtained by nonlinear curve fitting analysis of the apparent molar absorbitivity as a function of the concentration of the added ligand.[27] In the case of two multiple equilibria, the equation used is as follows (eq 1)

$$\Delta A/S_t b = (\beta_{11}\Delta\epsilon_{11}[L] + \beta_{12}\Delta\epsilon_{12}[L]^2)/(1 + \beta_{11}[L] + \beta_{12}[L]^2) \quad (1)$$

where β_{11} is K_{11}, β_{12} is $K_{11}K_{12}$, and $\Delta\epsilon_{11}$ and $\Delta\epsilon_{12}$ are the related differences of the molar extinction coefficients of the species involved in the equilibria. S_t is the analytical concentration of the porphyrin receptor, b is the cuvette path length, and [L] is the concentration of the added host. In the case of simple 1:1 equilibria, eq 2 is used:

$$\Delta A/S_t b = K_{11}\Delta\epsilon_{11}[L]/(1 + K_{11}[L]) \quad (2)$$

The nonlinear least-squares calculations were carried out by the program Kaleidagraph. Duplication of a single set of measurements were reproducible within the experimental errors.

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Supporting Information Available: ^{1}H NMR correlated spectra for all the final oxidation products. This material is available free of charge via the Internet at http://pubs.acs.org.

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