

Derivatives of 2-[[*N*-(Aminocarbonyl)-*N*-hydroxyamino]methyl]-1,4-benzodioxan as Orally Active 5-Lipoxygenase Inhibitors

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N-Hydroxyureas based on the 1,4-benzodioxan template were prepared from appropriately substituted 1,4-benzodioxan-2-methanols as the key intermediates and evaluated in the *in vitro* guinea pig polymorphonuclear leukocyte 5-lipoxygenase (5-LO) assay for their 5-LO inhibitory activity. Placement of a 7-phenoxy or 7-*p*-fluorophenoxy substituent resulted in a dramatic increase in *in vitro* potency. Selected compounds were subsequently assayed in an *ex vivo* dog model of LTB₄ synthesis at a dose of 1.0 mg/kg. The 7-phenoxy derivatives **16** and **17** showed modest duration of action (DA) in this dog model. The 6-regioisomers **21** and **22** were less potent. Replacement of the 7-phenoxy group of **16** with the *p*-fluorophenoxy moiety enhanced the DA dramatically. Compound **18** (CGS 25667), which had an IC₅₀ value of 100 nM in the *in vitro* guinea pig 5-LO assay, had a DA of 8.5 h (zileuton, DA = 8.5 h) at the oral dose of 1.0 mg/kg. Optical antipodes (**24**, **26**) of **18** were independently synthesized in high (>95%) enantiomeric purity from commercially available optically active glycidyl tosylates and evaluated. In the *in vitro* assay, the 2*S*(-)-enantiomer (**24**, CGS 25997, IC₅₀ = 85 nM) was found to be twice as active as the 2*R*(+)-counterpart (**26**, CGS 25998, IC₅₀ = 180 nM). In the *ex vivo* experiment, **24**, which dose dependently inhibited plasma 5-LO activity, was shown to be significantly longer acting than **26**, with a DA of 8.4 h when dosed orally at 1.0 mg/kg.

Introduction

It is becoming increasingly evident that leukotrienes (LT's) play extremely important roles as the major mediators of inflammatory reactions and hypersensitivity in mammalian animals, including human.¹ *In vivo*, LT's are produced from arachidonic acid (AA) by a series of enzymatic transformations. Since the oxygenation of AA by 5-lipoxygenase (5-LO) is the first committed step for the production of LT's, it has been long assumed that inhibition of 5-lipoxygenase would provide a novel therapy for human inflammatory disease conditions² such as asthma, rheumatoid arthritis, and inflammatory bowel disease. As a result of intense drug discovery efforts in the last decade, several inhibitors of 5-LO, such as zileuton,³ MK-886,⁴ MK-591,⁵ Wy-50,295,⁶ ZD2138,⁷ and so forth, have been identified and entered clinical evaluation (Figure 1). These results indicate promising therapeutic benefits of 5-lipoxygenase inhibition in certain inflammatory conditions.^{8,9}

Due to the iron-containing nature of the 5-LO enzyme, inhibitors based on metal chelators have been extensively studied. Among those tested, hydroxamate-derived inhibitors¹⁰ have met with considerable success. Conversion of lipophilic hydroxamic acids to their 'reverse' analogs¹¹ or to the *N*-hydroxyurea derivatives,¹² as demonstrated in the case of zileuton,³ was found to enhance the oral efficacy, largely due to increased *in vivo* stability.

In this article, we would like to disclose some of our continuing efforts to identify highly potent and orally available 5-lipoxygenase inhibitors.¹³ A series of *N*-hydroxyureas based on a benzodioxan template were synthesized and subsequently evaluated *in vitro* and *in vivo*. Due to the chirality of these compounds, the enantiospecificity aspect of the most potent inhibitor was also investigated.

Chemistry

Benzodioxan *N*-hydroxyureas with no substituents on the aryl ring system were conveniently prepared from commercially available 1,4-benzodioxan-2-methanol (**1**) (Scheme 1). Thus, the condensation of the bromide with a sodium salt of *N,O*-bis(*tert*-Boc)hydroxylamine gave a fully protected hydroxylamine precursor (**2**). Deprotection with TFA followed by condensation with trimethylsilyl isocyanate gave **4**. Reaction of **3** with 1 equiv of alkyl isocyanates resulted in the formation of a mixture of the desired *N*-hydroxyureas (**5–7**) and *N,O*-bis-carbamoylated derivatives. Compounds **5–7** were, therefore, prepared by first condensing **3** with 2.2 equiv of an appropriate isocyanate followed by monohydrolysis of the *O*-carbamoyl group with an aqueous base.

Regiocontrolled synthesis of 6-substituted 1,4-benzodioxan-2-methanols was carried out using 5-substituted salicyl aldehydes (**8**, **19**) as the starting materials according to the procedure described by Henning et al.¹⁴ (Scheme 2). Alkylation of **8** and **9** with epibromohydrin and subsequent Baeyer–Villiger oxidation with *m*-CPBA yielded the formoxy derivatives (**10**, **11**). Treatment of **10** and **11** with hydroxide resulted in hydrolysis of the formate and concomitant clean, regioselective intramolecular epoxide opening to their 1,4-benzodioxan derivatives (**12**, **13**). When MMPP was used in the oxidation step, free phenols instead of their formates were isolated upon workup. Compounds **12** and **13** were converted to the corresponding *N*-hydroxyureas (**16–18**) according to the procedure described in Scheme 1. It should be noted that the condensation of the hydroxylamine (**14**) with methyl isocyanate yielded *N*-hydroxyurea derivative **17**, uncontaminated with the bis-adduct, under the same conditions.

The regioisomeric benzodioxans (**21**, **22**) were prepared from the same intermediate (**8**) (Scheme 3). Thus, **8** was first protected with benzyl bromide and subjected

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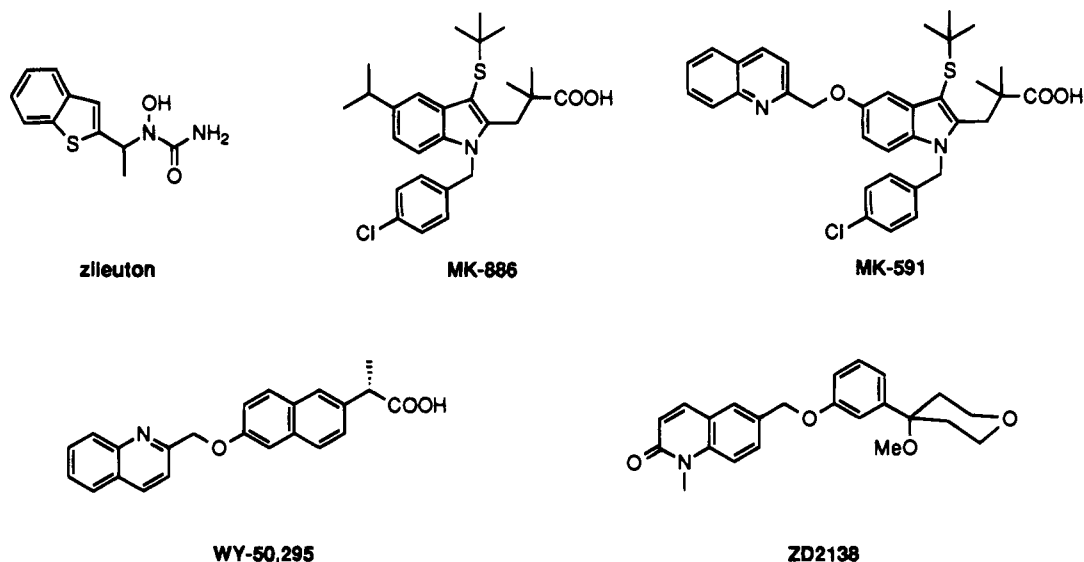
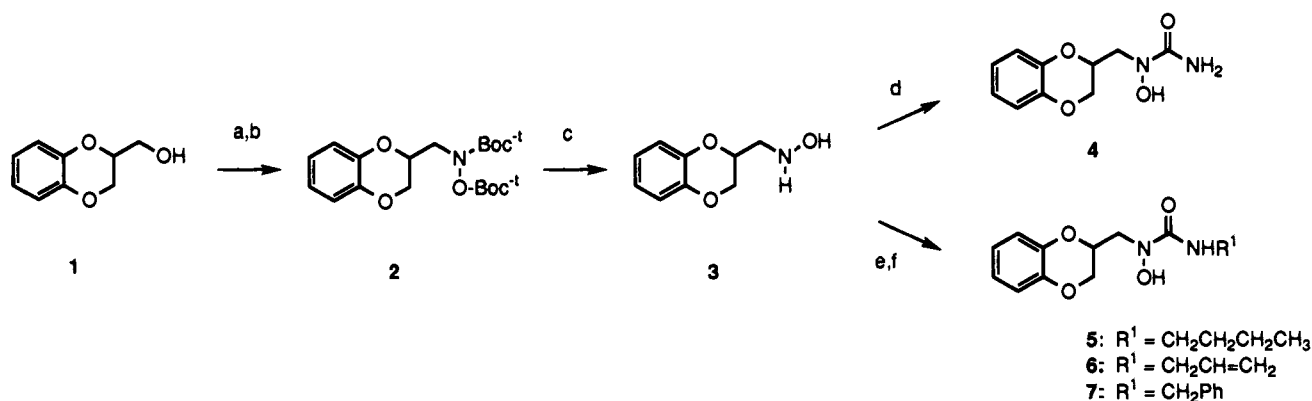
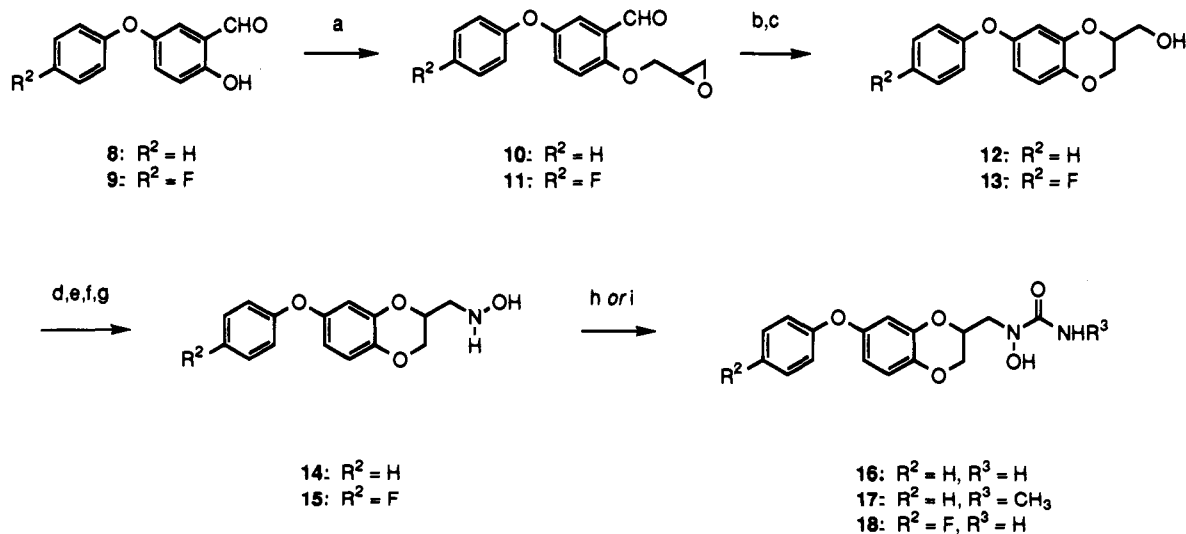


Figure 1. Representative 5-lipoxygenase inhibitors.

Scheme 1^a

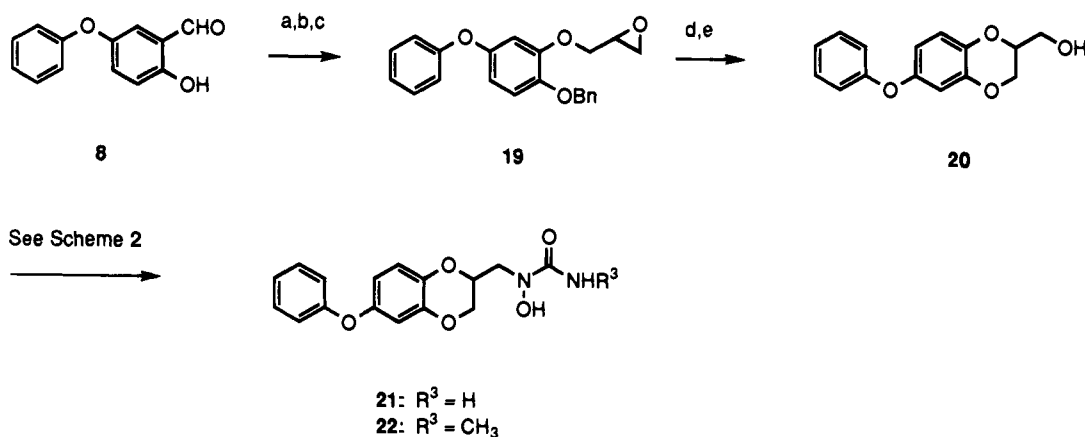
^a Reagents and conditions: (a) Ph₃PBr₂; (b) Boc^tNHOBoc^t, NaH; (c) CF₃COOH; (d) Me₃SiN=C=O, heat; (e) 2.2 equiv of R¹N=C=O, heat; (f) OH⁻.

Scheme 2^a

^a Reagents and conditions: (a) epibromohydrin, K₂CO₃, DMF; (b) MMPP or *m*-CPBA (see text); (c) OH⁻; (d) MsCl, Et₃N; (e) NaI, MEK; (f) Boc^tNHOBoc^t, NaH; (g) CF₃COOH; (h) Me₃SiN=C=O; (i) CH₃N=C=O.

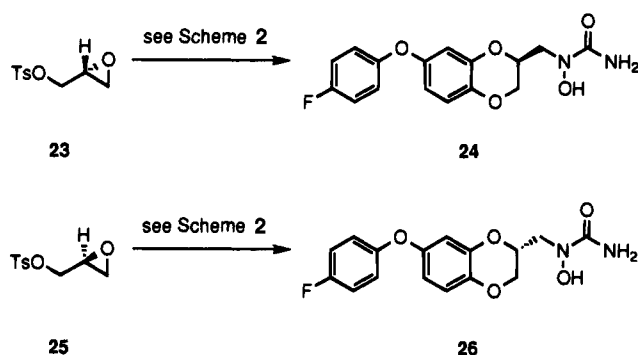
to Baeyer–Villiger oxidation with hydrogen peroxide. The phenol thus formed was treated with epibromohydrin to give the tris-ether (19). Catalytic hydrogenation of 19 with palladium hydroxide (atmospheric H₂ in ethyl acetate) gave the debenzylated phenol which cyclizes upon treatment with aqueous base to yield 20. It is

extremely important to monitor the hydrogenation closely since reductive opening of the epoxide function becomes a significant side reaction under certain conditions.¹⁵ Compound 20 was transformed into the desired *N*-hydroxyureas (21, 22) under the standard conditions described above.

Scheme 3^a

^a Reagents and conditions: (a) BnBr, K₂CO₃; (b) MMPP; (c) epibromohydrin, K₂CO₃; (d) H₂, Pd/C; (e) OH⁻.

Scheme 4



This method is easily applicable for the synthesis of optically active 2-substituted 1,4-benzodioxans.^{16,17} Thus, commercially available (2*R*)-(-)-glycidyl tosylate (**23**) and its 2*S*-(+)-antipode (**25**) were converted to the corresponding optically active *N*-hydroxyureas **24** and **26** (Scheme 4), through the key intermediates 2*S*- and 2*R*-13, respectively. The stereochemical consequence was assigned on the basis of well-precedented S_N2 substitution of glycidyl arenesulfonates with phenoxides¹⁸ and the inversion of the stereochemistry upon intramolecular epoxide opening.^{16c} The optical purity of 2*S*- and 2*R*-13 was estimated to be 95% by the comparison of their Mosher esters by ¹H NMR.¹⁹ This methodology appears to be highly useful for the synthesis of unsymmetrically substituted, optically active 1,4-benzodioxan-2-methanols with predictable stereochemical outcome.

Biological Results and Discussion

In vitro 5-LO inhibitory activity was determined by measuring production of 5-hydroxyeicosatetraenoic acid (5-HETE) and LTB₄ in guinea pig polymorphonuclear leukocytes (PMN's).¹³ The assay is based on A23187-stimulated conversion of [¹⁴C]AA in leukocytes to form the desired products, which are measured by a radiometric thin-layer chromatographic assay. The IC₅₀ values for both products were calculated as the concentration of the test compound at which the synthesis of 5-HETE and LTB₄ were reduced to 50% of their respective control values. The results are summarized in Table 1.

Our previous results in the chromene-based *N*-hydroxyurea series¹³ indicated either the phenoxy or *p*-fluorophenoxy substituents on the core substituent

Table 1. *In Vitro* Guinea Pig PMN 5-LO Assay

compd	molecular formula	mp, °C	anal. ^a	IC ₅₀ , μM ^b	
				5-HETE	LTB ₄
4	C ₁₀ H ₁₂ N ₂ O ₄	126	C, H, N	18	15
5	C ₁₄ H ₂₀ N ₂ O ₄	59	C, H, N	1.2	1.4
6	C ₁₃ H ₁₆ N ₂ O ₄	oil	C, H, N	5.0	6.0
7	C ₁₇ H ₁₈ N ₂ O ₄	126	C, H, N	2.7	2.9
16	C ₁₆ H ₁₆ N ₂ O ₅	146	C, H, N	0.12	0.14
17	C ₁₇ H ₁₈ N ₂ O ₅	60	C, H, N	0.098	0.11
18	C ₁₆ H ₁₅ FN ₂ O ₅	168	C, H, N	0.10	0.12
21	C ₁₆ H ₁₆ N ₂ O ₅	136	H, N; C ^c	0.39	0.45
22	C ₁₇ H ₁₈ N ₂ O ₅	150	C, H, N	0.48	0.42
24	C ₁₆ H ₁₅ FN ₂ O ₅	173	C, H, N, F	0.085	0.097
26	C ₁₆ H ₁₅ FN ₂ O ₅	175	C, H, N, F	0.18	0.17
zileuton				1.8 ± 0.17	2.2 ± 0.36

^a Elemental analyses were within ±0.4% of the calculated values unless otherwise noted. The ¹H NMR, ¹³C NMR, IR, and MS data for all the compounds are fully consistent with the assigned structures. ^b *In vitro* 5-LO inhibitory activity was determined on the basis of A23187-stimulated conversion of [¹⁴C]AA to the 5-LO products in guinea pig peritoneal PMN's. The IC₅₀ values reported are calculated for both 5-HETE and LTB₄ production and represent the means of at least two independent experiments. The SEM values are given for zileuton (*n* = 3). ^c C: calcd, 60.76; found, 60.34.

were optimal for inhibitory activity. In the present study, potent inhibitors were identified through the same approach. A brief effort was made to investigate inhibitors where the pharmacophore was placed in the center part of the molecule rather than at the termini (compounds **5–7**) without much success, though the positive correlation between the potency and overall lipophilicity of the molecule is evident (cf. **4** vs **5–7**).²⁰ The position of the aryloxy substituent appears to be critical since the 7-phenoxy isomers (**16**, **17**) are about 3–5 times more potent than the 6-phenoxy isomers (**21**, **22**). We previously observed the same tendency in the benzoxepin series.²¹ The *p*-fluoro group does not seem to exert any significant effects on intrinsic potency (cf. **16** vs **18**). Due to the *ex vivo* efficacy of the 7-*p*-fluorophenoxy derivative **18** as compared to the phenoxy analog **16** (see below), both enantiomers of **18** were prepared with their optical purity exceeding 95% (see the Chemistry section). The negative enantiomer (**24**) was found to be twice as active as its optical isomer (**26**) in this assay.

Selected compounds were subsequently evaluated following a single intravenous (*iv*) or oral (*po*) dose in an *ex vivo* dog model,¹³ which was used to determine *in vivo* 5-LO inhibition using *ex vivo* stimulation of whole blood with the calcium ionophore, A23187. The method allows for the calculation of the time that the test

Table 2. *Ex Vivo* Inhibition of 5-LO Following Intravenous or Oral Administration in Dog

compd	dose, mg/kg ^c	n ^b	inhibition, % ^c								DA, h ^d
			0.08 h	0.25 h	0.5 h	1.0 h	3.0 h	6.0 h	9.0 h	24 h	
5	1.0 (iv)	1	100	100	64	45	12	0	ND ^e	ND ^e	0.7
16	1.0 (iv)	1	100	100	100	100	92	22	0	4	4.0
17	1.0 (iv)	1	100	100	98	74	19	0	9	0	1.5
18	1.0 (iv)	2	94	98	94	92	91	63	34	17	8.2
	1.0 (po)	2	ND ^e	87	94	97	97	90	48	38	8.5
21	1.0 (iv)	1	100	100	100	98	14	1	9	2	1.7
24	1.0 (iv)	1	100	94	92	92	100	76	46	0	8.4
	0.3 (po)	2	ND ^e	52	79	76	35	43	0	0	3.5
	1.0 (po)	2	ND ^e	80	100	100	100	85	45	7	8.4
	3.0 (po)	2	ND ^e	100	100	100	100	97	91	40	19
26	1.0 (iv)	1	100	100	100	100	84	15	0	0	3.8
	1.0 (po)	2	ND ^e	64	95	83	80	19	20	3	3.7
zileuton	1.0 (iv)	3	96	94	91	87	81	56	47	27	8.5 ± 0.6
	1.0 (po)	3	ND ^e	89	94	91	87	74	49	25	9.8 ± 1.2

^a Test compounds and zileuton were administered either intravenously (iv) or orally (po) at the dose specified. ^b n = number of experiments. ^c *Ex vivo* inhibition was determined by the measurement of A23187-stimulated LTB₄ production in dog blood at the time specified following administration of the drug. ^d Duration of action (DA) was defined as the period of time from maximum inhibition of A23187-stimulated LTB₄ formation to the time point where 50% of maximum inhibition is reached. The DA was determined graphically from a plot of percent inhibition vs time. The SEM values are given for zileuton. ^e ND = not determined.

compounds are biologically active in the circulation, which is a function of plasma clearance or inactivation. The product, LTB₄, was quantitated by radioimmunoassay. Inhibition of A23187-stimulated LTB₄ formation was calculated as the change in LTB₄ at each time point following compound administration (iv or po) compared to the value of LTB₄ before dosing. The duration of action (DA) following iv or po administration was defined as the period of time from maximum inhibition of A23187-stimulated LTB₄ formation to the time point where 50% of maximum inhibition is reached. The DA was determined graphically from a plot of percent inhibition of A23187-stimulated LTB₄ formation vs time.

Compound **16**, to our disappointment, showed rather modest DA of 4.0 h following iv administration of 1.0 mg/kg in the *ex vivo* dog model. Its *N'*-methyl analog (**17**) was even shorter acting (1.5 h). However, placement of the *p*-fluoro group to the distal aryloxy substituent (compound **18**) led to a significant increase in the intravenous DA (8.2 h) at 1.0 mg/kg. The data suggests that, at least in dog, *p*-hydroxylation of the phenoxy ring could be a significant metabolic pathway *in vivo*, although further studies are needed to clarify this aspect. Upon oral dosing, **18** exhibited the DA of 8.5 h with sustained maximal inhibition at earlier time points. The 6-phenoxy regioisomer **21** and the non-aryloxy-substituted derivative **5** were less active in the *ex vivo* study, probably due to weaker enzyme inhibitory potency as demonstrated in the *in vitro* assay (see above).

In accord with the aforementioned *in vitro* studies, the 2*S*-isomer **24** was considerably more potent following iv and po administration than its enantiomer (**26**). Compound **24** was therefore selected for further examination. The *ex vivo* inhibition of 5-LO was found to be dose dependent (Table 2). The inhibitory potency compares favorably with zileuton in our dog model.

In conclusion, we have identified potent, orally active *N*-hydroxyurea inhibitors of 5-LO based on the 1,4-benzodioxan template (**18**, CGS 25667) employing the *in vitro* guinea pig PMN 5-LO assay and the *ex vivo* dog model. *In vitro* and *in vivo* inhibitory potency was found to be dependent on the absolute stereochemistry, indicated by the fact that the 2*S*-enantiomer (**24**, CGS 25997) is twice as active as its antipode (**26**, CGS 25998). A general method for the preparation of unsymmetri-

cally substituted benzodioxans from salicyl aldehydes is disclosed. Use of optically active glycidyl derivatives allows chiral synthesis of such 1,4-benzodioxans in high optical purity.

Experimental Section

General. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. ¹H NMR spectra were recorded on a Bruker AC-250 or Bruker AC-300 spectrometer. A Bruker AC-300 spectrometer was used for ¹³C NMR spectra. IR and MS spectra were measured on a Nicolet 5SXB FTIR spectrometer and a Hewlett-Packard GC/MS 5985B spectrometer, respectively. Microanalyses were carried out at Robertson Laboratory, Inc., Madison, NJ.

DMF, dioxane, methylene chloride, and acetonitrile used were all of anhydrous grade obtained from Aldrich Chemicals. THF was distilled from benzophenone ketyl just prior to use. All the other chemicals were from commercial suppliers and used as received, unless otherwise mentioned. As a general rule, all the reactions were carried out under an inert atmosphere.

Biological assay methods are described previously in full detail.¹³

2-[[*N*-(*tert*-Butylcarbonyl)-*N*-[(*tert*-butylcarbonyl)oxy]amino]methyl]-1,3-benzodioxan (2). 2-(Hydroxymethyl)-1,4-benzodioxan (**1**; 17.9 g, 107 mmol) was taken in acetonitrile (200 mL) and treated with dibromotriphenylphosphorane (50 g, 119 mmol). The mixture was stirred for 30 min and evaporated. The residue was taken up in a 1:1 mixture of ether/hexane, and triphenylphosphine oxide was removed by filtration. The solvent was removed by evaporation to give 2-(bromomethyl)-1,4-benzodioxan (24.7 g, 67%), contaminated with a small amount of triphenylphosphine oxide (~5%), as a brownish oil. This material was used without further purification: ¹H NMR (250 MHz, CDCl₃) δ 3.70 (dd, *J* = 5.2 and 11.0 Hz, 1 H), 3.77 (dd, *J* = 3.2 and 11.0 Hz, 1 H), 4.20 (dd, *J* = 3.6 and 8.4 Hz, 1 H), 4.36 (dd, *J* = 1.0 and 8.4 Hz, 1 H), 4.42 (m, 1 H), 6.99 (m, 4 H).

N,O-bis-(*tert*-Butoxycarbonyl)hydroxylamine (14.0 g, 61 mmol) was dissolved in DMF (150 mL) and treated with sodium hydride (2.64 g, 60% in mineral oil, 66 mmol). The mixture was stirred for 30 min. To this was added 2-(bromomethyl)-1,4-dioxane (10.6 g, 46 mmol) in DMF (30 mL), and the mixture was stirred overnight at room temperature. This was diluted with ether and washed with saturated aqueous ammonium chloride solution. The organic layer was dried over magnesium sulfate and evaporated. The residue was purified by silica gel flash chromatography (3% ethyl acetate in hexane) to give **2** (10.2 g, 58%) as a pale yellow oil: ¹H NMR (250 MHz, CDCl₃) δ 1.48 (s, 9 H), 1.52 (s, 9H), 3.90 (m, 2 H), 4.09 (dd, *J* = 6.0 and 8.9 Hz, 1 H), 4.85 (dd, *J* = 1.0 and 8.9 Hz, 1 H), 4.42 (m, 1 H), 6.68 (m, 4 H).

2-[(*N*-Hydroxyamino)methyl]-1,4-benzodioxan (3). The protected hydroxylamine **2** (2.0 g, 5.3 mmol) was taken in 20 mL of methylene chloride and treated with trifluoroacetic acid (2.45 g, 21.5 mmol) at room temperature for 30 min. The excess trifluoroacetic acid was evaporated, and the residue was diluted with ether. The organic phase was washed twice with aqueous 1 N sodium hydroxide, dried over magnesium sulfate, and evaporated to give **3** (0.86 g, 91%) as a colorless oil: $^1\text{H NMR}$ (250 MHz, $\text{DMSO-}d_6$) δ 2.92 (dd, $J = 5.2$ and 11.9 Hz, 1 H), 3.02 (dd, $J = 4.0$ and 11.9 Hz, 1 H), 3.97 (dd, $J = 5.2$ and 7.2 Hz, 1 H), 4.28 (m, 1 H), 4.36 (dd, $J = 1.0$ and 7.2 Hz, 1 H), 6.78 (m, 4 H), 7.47 (br s, 1 H).

2-[[*N*-(Aminocarbonyl)-*N*-hydroxyamino]methyl]-1,4-benzodioxan (4). The hydroxylamine **3** (950 mg, 5.3 mmol) was taken in 1,4-dioxane (20 mL) and treated with trimethylsilyl isocyanate (910 mg, 7.1 mmol). The mixture was heated at reflux for 30 min and cooled to room temperature. The mixture was diluted with saturated aqueous ammonium chloride and extracted with ethyl acetate. The combined organic layer was dried over magnesium sulfate and evaporated. The residue was crystallized from ether/hexane to give **4** (0.70 g, 60%) as a colorless solid: mp 126 °C; $^1\text{H NMR}$ (300 MHz, $\text{DMSO-}d_6$) δ 3.52 (dd, $J = 6.5$ and 14.2 Hz, 1 H), 3.69 (dd, $J = 5.6$ and 14.2 Hz, 1 H), 3.98 (dd, $J = 6.9$ and 11.9 Hz, 1 H), 4.31 (dd, $J = 2.2$ and 11.9 Hz, 1 H), 4.35 (m, 1 H), 6.43 (br s, 2 H), 6.82 (m, 4 H), 9.57 (s, 1 H); $^{13}\text{C NMR}$ (75.47 MHz, $\text{DMSO-}d_6$) δ 161.47, 142.99, 142.82, 121.39, 121.15, 117.14, 116.89, 70.54, 65.81, 50.15; IR (KBr) 1653, 1594, 1578, 1037, 750 cm^{-1} ; MS (CI/CH₄) 225 (M + 1). Anal. (C₁₀H₁₂N₂O₄) C, H, N.

2-[[*N*'-(*N*-Butylamino)carbonyl]-*N*-hydroxyamino]methyl]-1,4-benzodioxan (5). 2-[(*N*-Hydroxyamino)methyl]-1,4-benzodioxan (**3**; 860 mg, 4.75 mmol) was dissolved in 20 mL of 1,4-dioxane and treated with butyl isocyanate (710 mg, 7.1 mmol). The mixture was heated at reflux for 30 min and cooled. The mixture was diluted with ether and washed with saturated aqueous ammonium chloride solution. The organic layer was dried over magnesium sulfate and evaporated to give a mixture (1.24 g) of **5** and 2-[[*N*'-(*N*-butylamino)carbonyl]-*N*'-[(*N*'-butylamino)carbonyl]oxy]amino]methyl]-1,4-dioxane as an oil. This was not fully characterized and used as obtained in the next step. The crude material was dissolved in a 1:1 mixture of water/2-propanol and treated with lithium hydroxide monohydrate (1.38 g, 32.8 mmol) for 30 min. The mixture was made acidic with 1 N hydrochloric acid and diluted with ethyl acetate. The organic layer was washed with saturated aqueous ammonium chloride solution, dried over magnesium sulfate, and evaporated. Silica gel flash chromatography (2:1 hexane/ethyl acetate) gave **5** (0.35 g, 26%) as a colorless solid: mp 59 °C; $^1\text{H NMR}$ (300 MHz, $\text{DMSO-}d_6$) δ 0.86 (t, $J = 7.2$ Hz, 3 H), 1.26 (sextet, $J = 7.2$ Hz, 2 H), 1.40 (quintet, $J = 7.2$ Hz, 2 H), 3.03 (dt, $J = 5.8$ and 7.2 Hz, 2 H), 3.49 (dd, $J = 6.4$ and 14.1 Hz, 1 H), 3.64 (dd, $J = 5.9$ and 14.1 Hz, 1 H), 3.98 (dd, $J = 7.0$ and 11.6 Hz, 1 H), 4.30 (dd, $J = 2.1$ and 11.6 Hz, 1 H), 4.35 (m, 1 H), 6.82 (m, 4 H), 7.01 (t, $J = 5.8$ Hz, 1 H), 9.50 (s, 1 H); $^{13}\text{C NMR}$ (75.47 MHz, $\text{DMSO-}d_6$) δ 160.66, 142.99, 142.82, 121.39, 121.14, 117.12, 116.89, 70.53, 65.83, 50.92, 38.99, 31.90, 19.47, 13.72; IR (KBr) 1634, 1592, 1547, 1263, 740 cm^{-1} ; MS (CI/CH₄) 281 (M + 1). Anal. (C₁₄H₂₀N₂O₄) C, H, N.

2-[[*N*'-(*N*-Benzylamino)carbonyl]-*N*-hydroxyamino]methyl]-1,4-benzodioxan (6). This compound was prepared from **3** by the reaction with allyl isocyanate according to the procedure described for **5** and isolated as a tan solid: mp 120 °C; $^1\text{H NMR}$ (300 MHz, $\text{DMSO-}d_6$) δ 3.52 (dd, $J = 6.4$ and 14.3 Hz, 1 H), 3.6–3.8 (m, 3 H), 3.98 (dd, $J = 7.0$ and 11.5 Hz, 1 H), 4.31 (dd, $J = 2.2$ and 11.5 Hz, 1 H), 4.37 (m, 1 H), 5.05 (dd, $J = 1.5$ and 10.3 Hz, 1 H), 5.10 (dd, $J = 1.5$ and 17.2 Hz, 1 H), 5.79 (m, 1 H), 6.83 (m, 4 H), 7.17 (t, $J = 5.9$ Hz, 1 H), 9.58 (s, 1 H); $^{13}\text{C NMR}$ (75.47 MHz, $\text{DMSO-}d_6$) δ 160.45, 142.98, 142.81, 136.30, 121.39, 121.14, 117.14, 116.88, 114.54, 70.47, 65.80, 54.88, 50.84; IR (KBr) 1657, 1649, 1594, 1530, 1275, 1227 cm^{-1} ; MS (CI/CH₄) 264 (M + 1). Anal. (C₁₃H₁₆N₂O₄) C, H, N.

2-[[*N*'-(*N*-Allylamino)carbonyl]-*N*-hydroxyamino]methyl]-1,4-benzodioxan (7). This compound was prepared from **3** by the reaction with benzyl isocyanate according to the

procedure described for **5** and isolated as a pale yellow oil: $^1\text{H NMR}$ (300 MHz, $\text{DMSO-}d_6$) δ 3.53 (dd, $J = 6.3$ and 14.3 Hz, 1 H), 3.74 (dd, $J = 5.0$ and 14.3 Hz, 1 H), 3.99 (dd, $J = 7.0$ and 11.5 Hz, 1 H), 4.24 (d, $J = 6.3$ Hz, 2 H), 4.30 (dd, $J = 2.2$ and 11.5 Hz, 1 H), 4.37 (m, 1 H), 6.81 (m, 4 H), 7.1–7.3 (m, 5 H), 7.61 (t, $J = 6.3$ Hz, 1 H), 9.61 (s, 1 H); $^{13}\text{C NMR}$ (75.47 MHz, $\text{DMSO-}d_6$) δ 160.66, 142.98, 142.79, 140.52, 128.10, 127.14, 126.55, 121.39, 121.14, 117.15, 116.89, 70.54, 65.78, 50.83, 42.94; IR (KBr) 1635, 1539, 1264 cm^{-1} ; MS (CI/CH₄) 315 (M + 1). Anal. (C₁₇H₁₈N₂O₄) C, H, N.

2-[(2,3-Oxopropyl)oxy]-5-phenoxybenzaldehyde (10). 2-Hydroxy-5-phenoxybenzaldehyde (**8**; 4.23 g, 19.8 mmol) and cesium carbonate (32.2 g, 98.8 mmol) were taken in DMF (200 mL) and treated with epibromohydrin (3.25 g, 23.7 mmol). The mixture was stirred overnight at room temperature. This was diluted with ether, washed with water and brine, dried over magnesium sulfate, and evaporated. Purification by silica gel flash chromatography (4:1 hexane/ethyl acetate) gave **10** (4.18 g, 78%) as a colorless oil: $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 2.79 (dd, $J = 2.6$ and 4.5 Hz, 1 H), 2.95 (t, $J = 4.5$ Hz, 1 H), 3.41 (m, 1 H), 4.04 (dd, $J = 5.9$ and 11.2 Hz, 1 H), 4.40 (dd, $J = 2.7$ and 11.2 Hz, 1 H), 6.95 (d, $J = 8.1$ Hz, 2 H), 6.99 (d, $J = 9.0$ Hz, 1 H), 7.09 (t, $J = 7.4$ Hz, 1 H), 7.24 (dd, $J = 3.1$ and 9.0 Hz, 1 H), 7.31 (t, $J = 8.0$ Hz, 2 H), 7.47 (d, $J = 3.1$ Hz, 1 H); IR (CH₂Cl₂) 2717, 1685, 1591, 1488, 1215, 836, 817 cm^{-1} ; MS (CI/CH₄) 271 (M + 1).

2-(Hydroxymethyl)-7-phenoxy-1,4-benzodioxan (12). The epoxy aldehyde **10** (4.5 g, 11.6 mmol) was dissolved in chloroform (100 mL) and treated with *m*-chloroperbenzoic acid (4.36 g, 80%, 25.2 mmol). The mixture was heated at reflux for 3 h. Ether was added, and the organic phase was washed three times with saturated aqueous sodium bicarbonate solution, dried over magnesium sulfate, and evaporated. Purification with silica gel flash chromatography (10% ethyl acetate/hexane) gave 2-[(2,3-oxopropyl)oxy]-5-phenoxyphenol (2.76 g, 69%) as a colorless oil: $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 2.75 (dd, $J = 2.5$ and 4.5 Hz, 1 H), 2.87 (t, $J = 4.5$ Hz, 1 H), 3.25 (m, 1 H), 3.96 (dd, $J = 6.0$ and 11.2 Hz, 1 H), 4.19 (dd, $J = 2.5$ and 11.2 Hz, 1 H), 6.26 (s, 1 H), 6.40 (dd, $J = 2.7$ and 8.8 Hz, 1 H), 6.58 (d, $J = 2.7$ Hz, 1 H), 6.77 (d, $J = 8.8$ Hz, 1 H), 6.90 (d, $J = 8.0$ Hz, 2 H), 6.99 (t, $J = 8.0$ Hz, 1 H), 7.22 (t, $J = 8.0$ Hz, 2 H).

The phenol thus formed (2.76 g, 10.7 mmol) was taken in 1,4-dioxane (30 mL) and treated with aqueous 1 N sodium hydroxide (22 mmol). The reaction mixture was stirred at room temperature for 2 h. The mixture was diluted with ether, extracted with saturated aqueous sodium chloride solution, dried over magnesium sulfate, and evaporated. Purification with silica gel flash chromatography (1:2 ethyl acetate/hexane) gave **12** (2.76 g, 73%) as a colorless oil: $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 3.83 (dd, $J = 5.2$ and 11.2 Hz, 1 H), 3.90 (dd, $J = 4.2$ and 11.2 Hz, 1 H), 4.11 (m, 1 H), 4.29 (m, 2 H), 6.55 (dd, $J = 2.7$ and 8.8 Hz, 1 H), 6.60 (d, $J = 2.7$ Hz, 1 H), 6.85 (d, $J = 8.8$ Hz, 1 H), 6.97 (d, $J = 7.7$ Hz, 2 H), 7.06 (t, $J = 7.7$ Hz, 1 H), 7.31 (t, $J = 7.7$ Hz, 2 H); IR (film) 1594, 1217, 1146, 1139 cm^{-1} .

2-[(*N*-Hydroxyamino)methyl]-7-phenoxy-1,4-benzodioxan (14). The cyclization product **12** (1.42 g, 5.50 mmol) and triethylamine (1.11 g, 11.0 mmol) were dissolved in methylene chloride (50 mL) and treated with methanesulfonyl chloride (0.94 g, 8.26 mmol) at 0 °C. The mixture was stirred at 0 °C for 30 min and diluted with ether. This was washed with aqueous sodium bicarbonate, aqueous 1 N hydrochloric acid, and saturated aqueous ammonium chloride, dried over magnesium sulfate, and evaporated. The residue was purified by silica gel flash chromatography (1:3 ethyl acetate/hexane) to give 2-[(methylsulfonyl)oxy]methyl]-7-phenoxy-1,4-benzodioxan (1.85 g, 100%) as a tan oil which partially solidified upon standing: $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 3.06 (s, 3 H), 4.10 (dd, $J = 6.0$ and 11.7 Hz, 1 H), 4.29 (dd, $J = 4.2$ and 11.7 Hz, 1 H), 4.4–4.6 (m, 3 H), 6.55 (m, 2 H), 6.84 (d, $J = 8.7$ Hz, 1 H), 6.95 (d, $J = 7.7$ Hz, 2 H), 7.05 (t, $J = 7.7$ Hz, 1 H), 7.30 (t, $J = 7.7$ Hz, 2 H); IR (film) 1594, 1501, 1365, 1217, 1147 cm^{-1} ; MS (CI/CH₄) 337 (M + 1).

The mesylate (1.85 g, 5.5 mmol) and sodium iodide (1.54 g, 11.0 mmol) were taken in methyl ethyl ketone (60 mL) and heated at reflux for 3 h. The mixture was cooled and diluted with ethyl acetate. This was washed with aqueous sodium

bicarbonate, dried over magnesium sulfate, and evaporated. Purification of the residue by silica gel flash chromatography (hexane) gave **14** (1.83 g, 90%) as a tan oil: $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 3.32 (m, 2 H), 4.12 (dd, $J = 5.8$ and 11.1 Hz, 1 H), 4.26 (m, 1 H), 4.34 (dd, $J = 2.2$ and 11.1 Hz, 1 H), 6.53 (dd, $J = 2.7$ and 8.7 Hz, 1 H), 6.59 (d, $J = 2.7$ Hz, 1 H), 6.83 (d, $J = 8.7$ Hz, 1 H), 6.96 (d, $J = 7.7$ Hz, 2 H), 7.05 (d, $J = 7.7$ Hz, 1 H), 7.29 (t, $J = 7.7$ Hz, 2 H); IR (film) 1595, 1500, 1285 cm^{-1} ; MS (Cl/CH_4) 369 ($M + 1$).

2-[[*N*-(Aminocarbonyl)-*N*-hydroxyamino]methyl]-7-phenoxy-1,4-benzodioxan (16). This compound was obtained as a colorless solid from **14** according to the procedure described for **4**: mp 146°C ; $^1\text{H NMR}$ (300 MHz, $\text{DMSO}-d_6$) δ 3.51 (dd, $J = 6.4$ and 14.4 Hz, 1 H), 3.69 (dd, $J = 5.9$ and 14.4 Hz, 1 H), 3.98 (dd, $J = 5.8$ and 11.6 Hz, 1 H), 4.31 (dd, $J = 2.1$ and 11.6 Hz, 1 H), 4.35 (m, 1 H), 6.42 (br s, 2 H), 6.52 (m, 2 H), 6.89 (d, $J = 9.5$ Hz, 1 H), 6.94 (d, $J = 7.4$ Hz, 2 H), 7.08 (t, $J = 7.4$ Hz, 1 H), 7.35 (t, $J = 7.4$ Hz, 2 H), 9.55 (s, 1 H); $^{13}\text{C NMR}$ (75.47 MHz, $\text{DMSO}-d_6$) δ 161.44, 157.48, 150.21, 143.33, 139.30, 129.90, 122.91, 117.80, 117.56, 112.02, 108.20, 70.81, 65.66, 50.05; IR (KBr) 1648, 1217 cm^{-1} ; MS (Cl/CH_4) 317 ($M + 1$). Anal. ($\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_5$) C, H, N.

2-[[*N*-(*N*'-Methylamino)carbonyl]-*N*-hydroxyamino]methyl]-7-phenoxy-1,4-benzodioxan (17). 2-[[*N*-Hydroxyamino]methyl]-7-phenoxy-1,4-benzodioxan (**14**; 200 mg, 0.73 mmol) was taken in acetonitrile (10 mL) and treated with methyl isocyanate (42 mg, 0.73 mmol) at room temperature. This was stirred for 3 h at room temperature and diluted with ethyl acetate. The organic phase was washed with saturated aqueous ammonium chloride, dried over magnesium sulfate, and evaporated. Crystallization of the residue from ethyl acetate/hexane gave the title compound **17** (93 mg, 38%) as a glossy solid: mp 60°C ; $^1\text{H NMR}$ (300 MHz, $\text{DMSO}-d_6$) δ 2.59 (d, $J = 3.6$ Hz, 3 H), 3.49 (dd, $J = 6.2$ and 14.3 Hz, 1 H), 3.70 (dd, $J = 6.2$ and 14.3 Hz, 1 H), 3.99 (dd, $J = 6.9$ and 11.6 Hz, 1 H), 4.30 (dd, $J = 2.2$ and 11.6 Hz, 1 H), 4.37 (d of quartet, $J = 2.2$ and ~ 6.5 Hz, 1 H), 6.5 (m, 2 H), 6.8–7.0 (m, 4 H), 7.08 (t, $J = 7.4$ Hz, 1 H), 7.34 (t, $J = 7.4$ Hz, 2 H), 9.49 (s, 1 H); $^{13}\text{C NMR}$ (75.47 MHz, $\text{DMSO}-d_6$) δ 161.21, 157.49, 150.18, 143.30, 139.30, 129.89, 122.89, 117.77, 117.56, 112.03, 108.24, 70.77, 65.62, 50.84, 26.51; IR (KBr) 1645, 1541, 1500, 1216, 1251, 1145 cm^{-1} ; MS (Cl/CH_4) 331 ($M + 1$). Anal. ($\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_5$) C, H, N.

2-[[*N*-(Aminocarbonyl)-*N*-hydroxyamino]methyl]-7-(4-fluorophenoxy)-1,4-benzodioxan (18). This compound was obtained as a colorless solid from **15** according to the procedure described for **4**: mp 168°C ; $^1\text{H NMR}$ (300 MHz, $\text{DMSO}-d_6$) δ 3.51 (dd, $J = 6.4$ and 14.3 Hz, 1 H), 3.69 (dd, $J = 5.9$ and 14.3 Hz, 1 H), 3.98 (dd, $J = 6.9$ and 11.6 Hz, 1 H), 4.30 (dd, $J = 2.0$ and 11.6 Hz, 1 H), 4.35 (m, 1 H), 6.43 (br s, 2 H), 6.50 (m, 2 H), 6.88 (d, $J = 9.4$ Hz, 1 H), 6.99 (dd, $J = 4.6$ and 8.9 Hz, 2 H), 7.18 (t, $J = 8.9$ Hz, 2 H), 9.55 (s, 1 H); $^{13}\text{C NMR}$ (75.47 MHz, $\text{DMSO}-d_6$) δ 161.36, 157.77 ($^1J_{\text{C-F}} = 238.8$ Hz), 153.37 ($^4J_{\text{C-F}} = 2.2$ Hz), 150.59, 143.23, 139.13, 119.62 ($^3J_{\text{C-F}} = 8.4$ Hz), 117.49, 116.30 ($^2J_{\text{C-F}} = 23.4$ Hz), 111.47, 70.70, 65.54, 49.93; IR (KBr) 1662, 1615, 1595, 1575, 1251, 1191, 1142 cm^{-1} ; MS (Cl/CH_4) 335 ($M + 1$). Anal. ($\text{C}_{16}\text{H}_{16}\text{FN}_2\text{O}_5$) C, H, N.

2-[(2,3-Oxopropyl)oxy]-4-phenoxyphenyl Benzyl Ether (19). 5-Phenoxy-2-hydroxybenzaldehyde (**8**; 20 g, 94 mmol) and potassium carbonate (26.1 g, 188 mmol) were taken in DMF (250 mL) and treated with benzyl bromide (16.1 g, 94 mmol). The mixture was stirred at room temperature overnight. This was diluted with ethyl acetate, washed three times with saturated aqueous ammonium chloride, dried over magnesium sulfate, and evaporated to give 2-(benzyloxy)-5-phenoxybenzaldehyde (25.2 g, 88%) as a colorless solid. This was used without further purification: mp $64\text{--}65^\circ\text{C}$; $^1\text{H NMR}$ (250 MHz, CDCl_3) δ 5.17 (s, 2 H), 6.93 (d, $J = 7.6$ Hz, 2 H), 7.03 (d, $J = 8.9$ Hz, 2 H), 7.09 (d, $J = 7.6$ Hz, 1 H), 7.2–7.6 (m, 8 H), 10.48 (s, 1 H).

The benzyl ether (**22.25** g, 73 mmol) was dissolved in methanol (200 mL) and treated with hydrogen peroxide (31% in water, 32.0 mL) and concentrated sulfuric acid (15.0 mL). The mixture was stirred overnight at room temperature and evaporated. The residue was dissolved in saturated aqueous sodium chloride solution and extracted with ether. The organic phase was dried over magnesium sulfate and evapo-

rated. Purification of the residue by silica gel flash chromatography (5% ethyl acetate/hexane) gave 2-(benzyloxy)-5-phenoxyphenol (16.5 g, 77%) as a colorless solid: mp $36\text{--}37^\circ\text{C}$; $^1\text{H NMR}$ (250 MHz, CDCl_3) δ 5.07 (s, 2 H), 5.71 (s, 1 H), 6.44 (dd, $J = 2.8$ and 8.8 Hz, 1 H), 6.61 (d, $J = 2.8$ Hz, 1 H), 6.84 (d, $J = 8.8$ Hz, 1 H), 6.9–7.1 (m, 5 H), 7.39 (m, 5 H).

The phenol (16 g, 55 mmol) and cesium carbonate (26.9 g, 82.5 mmol) were taken in DMF (200 mL) and treated with epibromohydrin (11.2 g, 83 mmol). The mixture was stirred at room temperature for 2 h and diluted with ether. The organic phase was washed several times with saturated aqueous sodium chloride solution, dried over magnesium sulfate, and evaporated. Purification of the residue by silica gel flash chromatography (10% ethyl acetate/hexane) gave **19** (14.9 g, 78%) as a colorless oil: $^1\text{H NMR}$ (250 MHz, CDCl_3) δ 2.72 (dd, $J = 2.6$ and 4.7 Hz, 1 H), 2.86 (t, $J = 4.7$ Hz, 1 H), 3.34 (m, 1 H), 3.96 (dd, $J = 5.6$ and 11.3 Hz, 1 H), 4.22 (dd, $J = 2.8$ and 11.3 Hz, 1 H), 5.08 (s, 2 H), 6.47 (dd, $J = 2.8$ and 8.7 Hz, 1 H), 6.64 (d, $J = 2.8$ Hz, 1 H), 6.85 (d, $J = 8.7$ Hz, 1 H), 6.9–7.1 (m, 5 H), 7.3–7.5 (m, 5 H).

2-(Hydroxymethyl)-6-phenoxy-1,4-benzodioxan (20). The benzyl ether **19** (3.68 g, 10.6 mmol) and palladium on charcoal (10%, 1.84 g) were taken in ethyl acetate and subjected to hydrogenation at atmospheric pressure. The reaction was terminated in 15 min. The catalyst was removed by filtration over a bed of Celite, and the solvent was evaporated. Purification of the residue by silica gel flash chromatography (15% ethyl acetate/hexane) gave 2-[(2,3-oxopropyl)oxy]-4-phenoxyphenol (2.19 g, 50%) as a colorless oil: $^1\text{H NMR}$ (250 MHz, CDCl_3) δ 2.76 (dd, $J = 2.6$ and 4.6 Hz, 1 H), 2.90 (t, $J = 4.6$ Hz, 1 H), 3.34 (m, 1 H), 3.93 (dd, $J = 5.7$ and 11.3 Hz, 1 H), 4.26 (dd, $J = 2.7$ and 11.3 Hz, 1 H), 6.53 (dd, $J = 2.6$ and 8.5 Hz, 1 H), 6.59 (d, $J = 2.6$ Hz, 1 H), 6.8–7.1 (m, 6 H).

The resultant phenol (6.0 g, 23 mmol) was taken in ethanol (250 mL) and treated with aqueous 1 N sodium hydroxide (23 mL). The mixture was stirred for 30 min and diluted with ether. The organic phase was washed with 1 N hydrochloric acid and water, dried over magnesium sulfate, and evaporated. Purification of the residue by silica gel flash chromatography (25% ethyl acetate/hexane) gave **20** (4.29 g, 71%) as a colorless oil: $^1\text{H NMR}$ (250 MHz, CDCl_3) δ 3.82 (dd, $J = 4.7$ and 12.0 Hz, 1 H), 3.91 (dd, $J = 3.8$ and 12.0 Hz, 1 H), 4.09 (dd, $J = 7.5$ and 10.7 Hz, 1 H), 4.22 (m, 1 H), 4.28 (dd, $J = 1.6$ and 10.7 Hz, 1 H), 5.62 (m, 2 H), 6.83 (d, $J = 8.5$ Hz, 1 H), 6.85–7.05 (m, 5 H).

2-[[*N*-Hydroxyamino]methyl]-6-phenoxy-1,4-benzodioxan (21). This compound was prepared from **20** according to the procedure described for **16** and obtained as a colorless solid: mp 136°C ; $^1\text{H NMR}$ (300 MHz, $\text{DMSO}-d_6$) δ 3.53 (dd, $J = 6.4$ and 14.3 Hz, 1 H), 3.70 (dd, $J = 5.6$ and 14.3 Hz, 1 H), 4.00 (dd, $J = 7.4$ and 11.8 Hz, 1 H), 4.32 (m, 2 H), 6.44 (br s, 2 H), 6.51 (dd, $J = 2.8$ and 8.7 Hz, 1 H), 6.56 (d, $J = 2.8$ Hz, 1 H), 6.87 (d, $J = 8.7$ Hz, 1 H), 6.94 (d, $J = 7.6$ Hz, 2 H), 7.07 (t, $J = 7.6$ Hz, 1 H), 7.34 (t, $J = 7.6$ Hz, 2 H), 9.57 (s, 1 H); $^{13}\text{C NMR}$ (75.47 MHz, $\text{DMSO}-d_6$) δ 161.47, 157.50, 149.94, 143.46, 139.15, 129.89, 122.87, 117.79, 117.72, 112.29, 108.05, 70.43, 66.00, 50.10; IR (KBr) 1667, 1590, 1501, 1232, 1216, 1143 cm^{-1} ; MS (Cl/CH_4) 317 ($M + 1$). Anal. ($\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_5$) C, H, N.

2-[[*N*-(*N*'-Methylamino)carbonyl]-*N*-hydroxyamino]methyl]-6-phenoxy-1,4-benzodioxan (22). This compound was prepared according to the procedure described for **17** and obtained as a colorless solid: mp 150°C ; $^1\text{H NMR}$ (300 MHz, $\text{DMSO}-d_6$) δ 2.60 (d, $J = 4.6$ Hz, 3 H), 3.50 (dd, $J = 6.4$ and 14.2 Hz, 1 H), 3.70 (dd, $J = 5.7$ and 14.2 Hz, 1 H), 4.00 (dd, $J = 7.4$ and 11.8 Hz, 1 H), 4.3 (m, 2 H), 6.51 (dd, $J = 2.8$ and 8.7 Hz, 1 H), 6.56 (d, $J = 2.8$ Hz, 1 H), 6.86 (d, $J = 8.7$ Hz, 1 H), 6.93 (d, $J = 7.5$ Hz, 2 H), 7.00 (quartet, $J = 4.6$ Hz, 1 H), 7.07 (t, $J = 7.5$ Hz, 1 H), 7.34 (t, $J = 7.5$ Hz, 2 H), 9.50 (s, 1 H); $^{13}\text{C NMR}$ (75.47 MHz, $\text{DMSO}-d_6$) δ 161.22, 157.51, 149.94, 143.46, 139.15, 129.89, 122.87, 117.80, 117.71, 112.31, 108.06, 70.43, 65.99, 50.93, 26.53; IR (KBr) 1653, 1649, 1211, 1147 cm^{-1} ; MS (Cl/CH_4) 331 ($M + 1$). Anal. ($\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_5$) H, N; C: calcd, 60.76; found, 60.34.

(2S)-(-)-2-[[*N*-(Aminocarbonyl)-*N*-hydroxyamino]methyl]-7-(4-fluorophenoxy)-1,4-benzodioxan (24). This compound was prepared according to the procedure described for

16, using (2*R*)-(-)-glycidyl tosylate (**23**) and **9** as the starting materials: mp 173 °C; $[\alpha]_D^{25}$ -46.50° (c 0.92, DMSO). Anal. (C₁₆H₁₅FN₂O₅) C, H, N, F.

(2*R*)-(+)-2-[[*N*-(Aminocarbonyl)-*N*-hydroxyamino]methyl]-7-(4-fluorophenoxy)-1,4-benzodioxan (**26**). This compound was prepared according to the procedure described for **16**, using (2*S*)-(+)-glycidyl tosylate (**25**) and **9** as the starting materials: mp 175 °C; $[\alpha]_D^{25}$ +39.09° (c 0.74, DMSO). Anal. (C₁₆H₁₅FN₂O₅) C, H, N, F.

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