SYNTHESES OF PHENOLIC METABOLITES OF AN ANTIFUNGAL IMIDAZOLE DERIVATIVE (CLOCONAZOLE HYDROCHLORIDE)

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Abstract —— Syntheses of phenolic metabolites of antifungal vinylimidazole derivative 6·HCl (Cloconazole hydrochloride) are described. Phenolic compound 8 was prepared from 2 using selective mono THP protection, followed by imidazolation and deprotection. 10 was synthesized from 12 and spontaneously decomposed to 4 and 19 in acidic methanol. Synthesis of 11 started from 20 via nucleophilic aromatic substitution to introduce an oxygen function at the m-position of the chlorine substituent.

Imidazole-containing compounds, found to be active against fungi, have been extensively studied. We previously reported the synthesis of vinylimidazoles by a reaction of ketones and thionyldiimidazole or carbonyldiimidazole[1]. Since vinylimidazole 6·HCl (Cloconazole hydrochloride) has potent activity against a wide variety of fungi[2] and is now clinically useful as an antifungal agent, its metabolism in rabbits was studied[3]. In general, aromatic compounds are thought to be monooxygenated to form phenols via arene oxide[4] such as 9 in the metabolic pathway. In this article, we describe the syntheses of phenolic metabolites 8, 10, 11, and the formation of 4 and 19 from 10. (Chart 1)
First to be synthesized was phenolic compound 8, in which hydroxylation occurred at ring A. Treatment of 2,5-dihydroxyacetophenone (2) with one mol. equivalent of 2,3-dihydropyran (DHP) in the presence of pyridinium p-toluenesulfonate (PPTS)[5] selectively gave monotetrahydropyranyl (THP) ether 3 in 83% yield. Reaction of 3 with thionyldiimidazole, as reported previously[1], afforded 5 in 70% yield, which was then treated with m-chlorobenzyl chloride in the presence of sodium hydride (NaH) in dimethylformamide (DMF) yielding 7. Deprotection

Chart 1

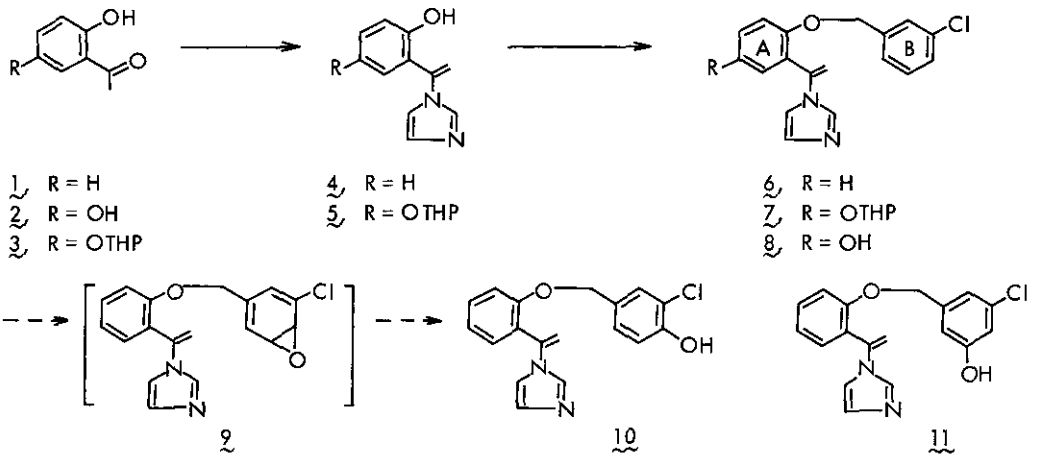


Chart 2

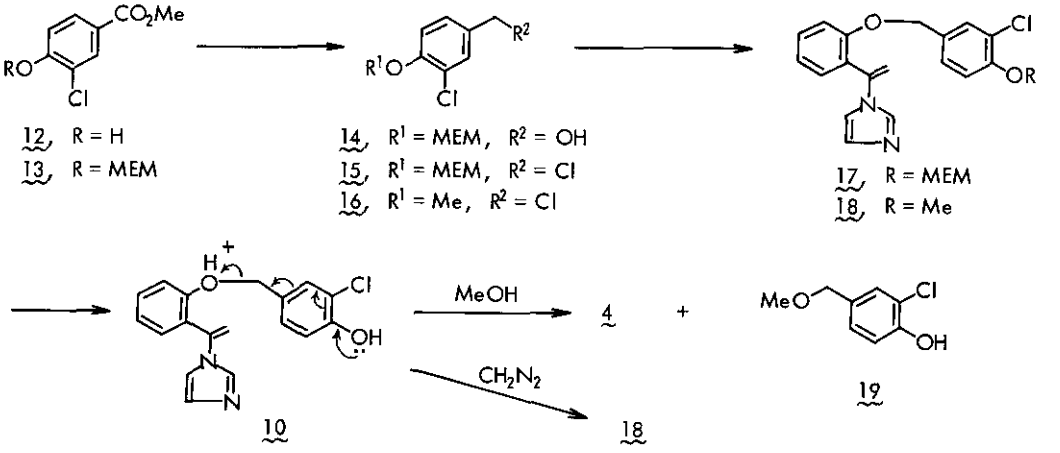
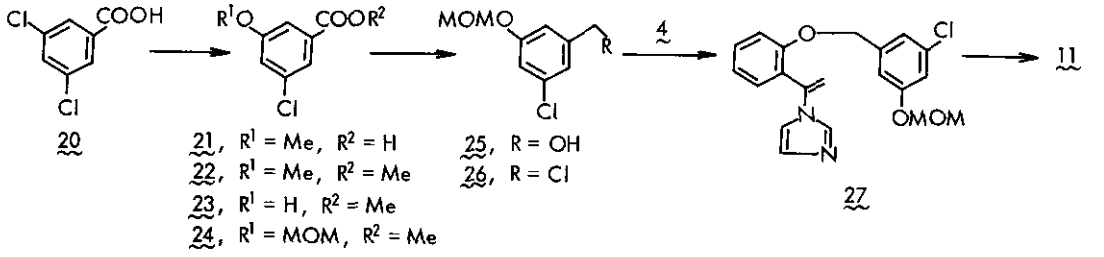


Chart 3



of the THP group of 7 with oxalic acid in aqueous methanol afforded 8, mp 155.5-156.5°C, in 80% yield; it was identical with one of the metabolites[3]. Next, the synthesis of phenolic compound 10 was examined. Protection of the hydroxy group of 12 with 2-methoxyethoxymethyl (MEM) chloride gave MEM ether 13, which was reduced with lithium aluminum hydride (LAH) to afford the alcohol 14. Treatment of the alcohol 14 with thionyl chloride ($SOCl_2$) gave the chloride 15, which when condensed with the sodium salt of phenolic compound 4 yielded 17. Although deprotection of 17 with $ZnBr_2$ in dichloromethane (CH_2Cl_2) gave a complex mixture, 4 and 19 were isolated instead of the desired 10 on treatment of 17 with methanolic hydrogen chloride. Because of instability in acidic conditions, 10 was probably decomposed to 4 and the p-quinonoid intermediate[6], which gave methyl ether 19 by reaction with methanol (MeOH)[7]. Since 4 was found to be one of the metabolites, a similar pathway might exist in the metabolism of 6. Formation of the intermediate 10 in the reaction was confirmed by treatment of the reaction mixture with diazomethane (CH_2N_2) giving 18, which was identical with a sample prepared from the chloride 16 and the phenol 4. (Chart 2)

Synthesis of 11 was rather difficult because 3-chloro-5-methoxymethyloxybenzyl chloride 26 or its synthetic equivalents 21-25 were not easily available. Thus, 3,5-dichlorobenzoic acid (20) was chosen as the starting material and aromatic nucleophilic substitution[8] was employed. Heating 20 with 2 mol. equivalents of sodium methoxide (NaOMe) in hexamethylphosphoramide (HMPA)[9] gave 21 in good yield. 21 was esterified and selectively demethylated with boron tribromide (BBr_3) to the phenol 23 in 70% overall yield from 20. The phenol 23 was protected with methoxymethyl (MOM) chloride, giving 24 which was reduced with LAH, then chlorinated with $SOCl_2$ to obtain the chloride 26. Condensation of the chloride 26 with 4 followed by deprotection of the resulting MOM ether 27 gave 11, mp 151-153°C, which was identical with the authentic material of the metabolite[3,10]. (Chart 3)

EXPERIMENTAL

Melting points were determined on a Yanagimoto microapparatus or Büchi apparatus and are uncorrected. NMR spectra were obtained with a Varian T-60 or a Varian EM-390 spectrometers. A Hitachi 260-10 spectrophotometer was used to obtain IR spectra. Elemental analyses were performed by the analytical department of this laboratory. Chromatographies utilized Merck silica gel 60 (70-230 or 230-400

mesh).

2-Hydroxy-5-(tetrahydropyran-2-yloxy)acetophenone (3). A mixture of 2 (5.0 g, 32.7 mmol), DHP (4.15 g, 49.3 mmol), PPTS (100 mg, 0.4 mmol), and CH_2Cl_2 (50 mL) was refluxed for 1.5 h. The mixture was washed with aq. $NaHCO_3$ and H_2O, dried (Na_2SO_4), and evaporated to leave a solid which was recrystallized from $isoPr_2O$ yielding 3 (6.42 g, 83%). Mp 66.5-67.5°C. IR (Nujol) 3625, 1639, and 1211 cm^{-1}. NMR ($CDCl_3$) δ 11.82 (1H, bs, OH), 7.41-6.71 (3H, m, ArH), 5.38-5.17 (1H, m, OCHO), 4.16-3.24 (2H, m, OCH_2), 2.59 (3H, s, Ac), and 2.05-1.38 (6H, m, $CH_2CH_2CH_2$). Anal. Calcd. for $C_{13}H_{16}O_4$: C, 66.08; H, 6.83. Found: C, 66.19; H, 6.66.

1-[1-[2-Hydroxy-5-[(tetrahydropyran-2-yl)oxy]phenyl]vinyl]-1H-imidazole (5). The ketone 3 (3.0 g, 12.7 mmol) was added to a stirred solution of N,N'-thionyldiimidazole (19.1 mmol), prepared from imidazole (5.19 g, 76.2 mmol) and $SOCl_2$ (2.27 g, 19.1 mmol) in CH_2Cl_2 (50 mL), and stirred at r.t. for 0.5 h. The mixture was diluted with CH_2Cl_2, washed with aq. $NaHCO_3$ and H_2O, dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica gel with CH_2Cl_2/MeOH = 92/8 as the eluent to give 5 (2.50 g, 70%). Mp 153.5-155.5°C (MeOH/EtOAc). IR (Nujol) 3270 and 1644 cm^{-1}. NMR (DMSO-d_6) δ 9.37 (1H, bs, OH), 7.58 and 7.22 (each 1H, each m, 2 x ArH), 7.09-6.66 (4H, m, 4 x ArH), 5.55 and 5.14 (each 1H, each s, 2 x vinyl H), 5.49-5.17 (1H, m, OCHO), 3.86-3.42 (2H, m, OCH_2), and 1.99-1.35 (6H, m, 3 x CH_2). Anal. Calcd. for $C_{16}H_{18}N_2O_3$: C, 67.11; H, 6.34; N, 9.78. Found: C, 66.90; H, 6.17; N, 9.72.

1-[1-[2-[(3-Chlorobenzyl)oxy-5-hydroxy]phenyl]vinyl]-1H-imidazole (8). NaH (50% dispersion in mineral oil, 101 mg, 2.10 mmol) was added to a stirred solution of 5 (500 mg, 1.75 mmol) in DMF (5 mL) at 0°C. After 5 min, m-chlorobenzyl chloride (337 mg, 2.09 mmol) was added to the mixture at r.t. The mixture was stirred at 60°C for 0.5 h, quenched with ice, and extracted with benzene. The organic layer was washed with H_2O, dried (Na_2SO_4), and evaporated to give 7. A solution of oxalic acid (5% in MeOH/H_2O (1/9), 18 mL) was added to 7 and refluxed for 1 h. The mixture was neutralized with aq. $NaHCO_3$, extracted with CH_2Cl_2, and the organic layer was washed (H_2O), dried (Na_2SO_4) and evaporated. The residue was chromatographed on silica gel with CH_2Cl_2/MeOH (95/5) as the eluent to give 8 (456 mg, 80%). Mp 155.5-156.5°C. IR (Nujol) 3275, 1642, and 1222 cm^{-1}. NMR (DMSO-d_6) δ 9.25 (1H, bs, OH), 7.65-6.66 (10H, m, 10 x ArH), 5.58 and 5.06 (each 1H, each s, 2 x vinyl H), and 4.93 (2H, s, OCH_2). Anal.

Calcd. for $C_{18}H_{15}N_2O_2Cl$: C, 66.16; H, 4.63; N, 8.57; Cl, 10.85. Found: C, 66.29; H, 4.57; N, 8.56; Cl, 10.67.

Methyl 3-chloro-4-(β-methoxyethoxymethyl)oxybenzoate (13). MEM chloride (1.245 g, 10 mmol) was added to a mixture of the phenol 12 (1.865 g, 10 mmol) and NaH (50% dispersion in mineral oil, 0.48 g, 10 mmol) in THF (20 mL) at 0°C, then stirred at r.t. for 15 h. The mixture was poured into ice-water and extracted with Et_2O. The extract was dried (Na_2SO_4) and evaporated to leave an oil which was chromatographed on silica gel with Et_2O/n-hexane (1/5) as the eluent yielding 13 as an oil (2.50 g, 91%). NMR ($CDCl_3$)δ 8.10-7.10 (3H, m, 3 x ArH), 5.34 (2H, s, OCH_2O), 3.92 (3H, s, CO_2Me), 3.90-3.40 (4H, m, OCH_2CH_2O), and 3.35 (3H, s, $CH_2O\underline{Me}$).

3-Chloro-4-(β-methoxyethoxymethyl)oxybenzyl alcohol (14). A solution of the ester 13 (2.50 g, 9.1 mmol) was added to a stirred suspension of LAH (0.34 g, 9 mmol) in THF (10 mL) at r.t. After stirring at r.t. for 1 h, H_2O (1.5 mL) was added slowly and the mixture was extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4) and evaporated to leave an oil, which was chromatographed on silica gel with Et_2O/n-hexane (1/1) as the eluent giving 14 (1.82 g, 81%) as an oil. NMR ($CDCl_3$) δ 7.40-7.10 (3H, m, 3 x ArH), 5.26 (2H, s, OCH_2O), 4.56 (2H, bs, $C\underline{H}_2OH$), 4.00-3.40 (4H, m, OCH_2CH_2O), 3.34 (3H, s, OMe), and 2.20 (1H, bs, $CH_2O\underline{H}$). Anal. Calcd. for $C_{11}H_{15}O_4Cl$: C, 53.55; H, 6.13; Cl, 14.37. Found: C, 53.15; H, 6.20; Cl, 14.44.

3-Chloro-4-(β-methoxyethoxymethyl)oxybenzyl chloride (15). $SOCl_2$ (1.2 g, 10 mmol) was added to a stirred solution of the alcohol 14 (1.23 g, 5 mmol) in CH_2Cl_2 (10 mL) at 0°C, and then stirred at 0°C for 0.5 h. The mixture was evaporated and the residue was chromatographed on silica gel with n-hexane/Et_2O (1/1) as the eluent to give 15 (1.02 g, 77%) as an oil. NMR ($CDCl_3$) δ 7.50-7.22 (3H, m, 3 x ArH), 5.38 (2H, s, OCH_2O), 4.54 (2H, s, CH_2Cl), 4.10-3.46 (4H, m, OCH_2CH_2O), and 3.40 (3H, s, OMe).

1-[1-[2-[3-Chloro-4-(β-methoxyethoxymethyl)oxybenzyloxy]phenyl]vinyl]-1H-imidazole (17). NaH (50% mineral oil dispersion, 96 mg, 2 mmol) was added to a stirred solution of the phenol 4 (372 mg, 2 mmol) in DMF (2 mL) at r.t. A solution of the chloride 15 (530 mg, 2 mmol) in DMF (2 mL) was added to the mixture and stirred at r.t. for 2 h. The mixture was poured into ice-H_2O and extracted (CH_2Cl_2). The organic layer was dried (Na_2SO_4) and evaporated. The residue was chromatographed on silica gel with CH_2Cl_2/MeOH (95/5) as the eluent to give 17

(516 mg, 62%) as a syrup. NMR ($CDCl_3$) δ 7.70-6.90 (10H, m, 10 x ArH), 5.38 and 5.08 (each 1H, each s, 2 x vinyl H), 5.26 (2H, s, OCH_2O), 4.82 (2H, s, $ArCH_2O$), 4.00-3.40 (4H, m, OCH_2CH_2O), and 3.32 (3H, s, OMe).

1-[1-[2-[(3-Chloro-4-methoxybenzyl)oxy]phenyl]vinyl]-1H-imidazole (18). (a). NaH (50% dispersion in mineral oil, 144 mg, 3 mmol) was added to a solution of 4 (558 mg, 3 mmol) in DMF (3 mL) at r.t. A solution of the chloride 16 (573 mg, 3 mmol) in DMF (2 mL) was added to the mixture and stirred at r.t. for 2 h. The mixture was poured into ice-water and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4), evaporated to leave an oil which was chromatographed on silica gel with CH_2Cl_2/MeOH (95/5) as the eluent to give 18 (615 mg, 60%) as a syrup. NMR ($CDCl_3$) δ 7.70-6.90 (10H, m, 10 x ArH), 5.38 and 5.06 (each 1H, each s, 2 x vinyl H), 4.84 (2H, s, CH_2O), and 3.84 (3H, s, OMe). Hydrochloride of 18: mp 153-155°C (MeOH/Et_2O, hygroscopic). Anal. Calcd. for $C_{19}H_{18}N_2O_2Cl_2 \cdot H_2O$/3: C, 59.54; H, 4.91; N, 7.31; Cl, 18.50. Found: C, 59.79; H, 5.03; N, 7.38; Cl, 18.03.

(b). A solution of HCl (10% in AcOEt, 1 mL) was added to a solution of 17 (100 mg, 0.24 mmol) in CH_2Cl_2 (2 mL) and stirred at r.t. for 2 h. The mixture was neutralized with aq. $NaHCO_3$, and the organic layer was dried (Na_2SO_4) and evaporated. The residue was dissolved in MeOH and treated with a solution of CH_2N_2 in Et_2O to give 18 (56 mg, 67%) after chromatography on silica gel, which was identical with the authentic sample of 18, prepared in (a).

Reaction of 17 with HCl in MeOH. A mixture of the MEM ether 17 (200 mg, 0.48 mmol), HCl (10% in AcOEt, 1 mL), and MeOH (2 mL) was stirred at r.t. for 8 h. The mixture was basified with aq. $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4), concentrated, and chromatographed on silica gel with CH_2Cl_2/MeOH (95/5) as the eluent to give 19 (34 mg, 41%) as an oil. NMR ($CDCl_3$) δ 7.40-6.80 (3H, m, 3 x ArH), 6.10 (1H, bs, OH, D_2O exchanged), 4.35 (2H, s, CH_2O), and 3.35 (3H, s, OMe). Further elution afforded 4 (51 mg, 57%) which was identical with the authentic material of 4 in every respect.

3-Chloro-5-methoxybenzoic acid (21). A mixture of 3,5-dichlorobenzoic acid (20) (5.73 g, 30 mmol), NaOMe (5.0 g, 93 mmol), and HMPA (100 mL) was heated at 115-120°C for 15 h. The mixture was poured into ice-water and acidified with conc. HCl to give 21 (5.01 g) as a precipitate which was collected by suction and used in the next step without purification. NMR ($CDCl_3$/DMSO-d_6) δ 7.50, 7.40, and 7.00 (each 1H, each dd, $J_1 = J_2$ = 2Hz, 3 x ArH), and 3.80 (3H, s, OMe).

Methyl 3-chloro-5-methoxybenzoate (22). Acetyl chloride (10 mL) was added dropwise to a solution of 21 (5.01 g) in MeOH (200 mL) at 0°C, then stirred at r.t. for 15 h. The mixture was evaporated and the residue was chromatographed on silica gel with Et_2O/n-hexane (1/5) as the eluent yielding 22 (4.23 g, 70% from 20) as an oil. NMR ($CDCl_3$) δ 7.50, 7.38, and 7.00 (each 1H, each m, 3 x ArH), 3.86 and 3.76 (each 3H, each s, 2 x OMe).

Methyl 3-chloro-5-hydroxybenzoate (23). BBr_3 (2.35 mL, 25 mmol) was added dropwise to a solution of 22 (5.0 g, 25 mmol) in CH_2Cl_2 (100 mL) at 0°C and the mixture was stirred at 0°C for 3 h. The mixture was poured into ice-H_2O-MeOH and extracted with CH_2Cl_2. The organic layer was washed (aq. $NaHCO_3$), dried (Na_2SO_4), and evaporated to give 23 (4.35 g, 93%). Mp 138-139°C (Et_2O/n-hexane). IR (Nujol) 3560 and 1720 cm^{-1}. NMR ($CDCl_3$) δ 8.30 (1H, bs, OH), 7.45-7.35 (2H, m, 2 x ArH), 6.98 (1H, m, ArH), and 3.80 (3H, s, OMe). Anal. Calcd. for $C_8H_7O_3Cl$: C, 51.49; H, 3.78; Cl, 19.00. Found: C, 51.32; H, 3.76; Cl, 19.09.

Methyl 3-chloro-5-methoxymethyloxybenzoate (24). MOM chloride (1.88 g, 23.3 mmol) was added to a mixture of 23 (4.35 g, 23.3 mmol) and NaH (50% dispersion in mineral oil, 1.12 g, 23.3 mmol) in THF (40 mL), and stirred at r.t. for 3 h. The mixture was poured into ice-H_2O and extracted with Et_2O. The organic layer was dried (Na_2SO_4) and evaporated and the residue was chromatographed on silica gel with Et_2O/n-hexane (1/4) as the eluent to give 24 (5.0 g, 93%) as an oil. NMR ($CDCl_3$) δ 7.60-7.35 (2H, m, 2 x ArH), 7.15 (1H, m, ArH), 5.12 (2H, s, CH_2O), 4.80 (3H, s, CO_2Me), and 3.40 (3H, s, $CH_2O\underline{Me}$).

3-Chloro-5-methoxymethyloxybenzyl alcohol (25). A solution of the ester 24 (5.0 g, 21.7 mmol) in THF (25 mL) was added to a suspension of LAH (0.824 g, 21.7 mmol) in THF (25 mL) at r.t. After stirring at r.t. for 0.5 h, H_2O was added slowly at 0°C and the mixture was filtered through Celite. The filtrate was concentrated and chromatographed on silica gel with Et_2O/n-hexane (1/1) as the eluent to afford 25 (3.08 g, 70%) as an oil. NMR ($CDCl_3$) δ 7.20 (1H, m, ArH), 7.00-6.90 (2H, m, 2 x ArH), 5.12 (2H, s, OCH_2O), 4.58 (2H, d, J = 6 Hz, $C\underline{H}_2OH$), and 3.40 (3H, s, OMe). Anal. Calcd. for $C_9H_{11}O_3Cl$: C, 53.34; H, 5.47; Cl, 17.50. Found: C, 53.21; H, 5.47; Cl, 17.62.

3-Chloro-5-methoxymethyloxybenzyl chloride (26). A mixture of the alcohol 25 (1.0 g, 4.9 mmol), $SOCl_2$ (1 mL), and benzene (6 mL) was refluxed for 0.5 h and evaporated. The residue was extracted with CH_2Cl_2, washed (aq. $NaHCO_3$), dried (Na_2SO_4), concentrated, and chromatographed on silica gel with Et_2O/n-hexane

(1/1) as the eluent to give 26 (310 mg, 29%) as an oil. NMR ($CDCl_3$) δ 7.00-6.80 (3H, m, 3 x ArH), 5.10 (2H, s, OCH_2O), 4.40 (2H, s, CH_2Cl), and 3.40 (3H, s, OMe).

1-[1-[2-[(3-Chloro-5-methoxymethyloxybenzyl)oxy]phenyl]vinyl]-1H-imidazole (27). NaH (50% dispersion in mineral oil, 65 mg, 1.36 mmol) was added to a solution of the phenol 4 (252 mg, 1.36 mmol) in DMF (2.5 mL). After hydrogen evolution had ceased, a solution of the chloride 26 (300 mg, 1.36 mmol) in DMF (2 mL) was added and the mixture was stirred at r.t. for 15 h. The mixture was poured into ice-H_2O, extracted with CH_2Cl_2, and the organic layer was dried (Na_2SO_4) and evaporated to leave an oil which was chromatographed on silica gel. Elution with CH_2Cl_2/MeOH (95/5) yielded 27 (320 mg, 64%) as an oil. NMR ($CDCl_3$) δ 7.65-6.60 (10H, m, 10 x ArH), 5.40 (1H, s, vinyl H), 5.10 (3H, s, vinyl H and OCH_2O), 4.85 (2H, s, $ArCH_2$), and 3.38 (3H, s, OMe).

1-[1-[2-[(3-Chloro-5-hydroxybenzyl)oxy]phenyl]vinyl]-1H-imidazole (11). A mixture of 27 (200 mg, 0.54 mmol), HCl (10% in AcOEt, 1 mL), CH_2Cl_2 (1 mL), and MeOH (1 mL) was stirred at r.t. for 2 h and evaporated to leave a solid, which was recrystallized from MeOH/Et_2O yielding 11·hydrochloride (120 mg, 61%). Mp 183-185°C. Anal. Calcd. for $C_{18}H_{16}N_2O_2Cl_2$: C, 59.51; H, 4.44; N, 7.71; Cl, 19.52. Found: C, 59.31; H, 4.20; N, 7.63; Cl, 19.59.

The hydrochloride was basified (aq. $NaHCO_3$), extracted (CH_2Cl_2), dried (Na_2SO_4), and evaporated to afford 11. Mp 151-152°C (AcOEt/Et_2O). IR (Nujol) 3500 cm^{-1}. NMR ($CDCl_3$) δ 7.70-6.50 (10H, m, 10 x ArH), 6.10 (1H, bs, OH), 5.40 and 5.15 (each 1H, each d, J = 1 Hz, 2 x vinyl H), and 4.78 (2H, s, CH_2). Anal. Calcd. for $C_{18}H_{15}N_2O_2Cl$: C, 66.15; H, 4.63; N, 8.57; Cl, 10.85. Found: C, 65.93; H, 4.47; N, 8.48; Cl, 10.71.

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