Synthesis of Natural Flutimide and Analogous Fully Substituted Pyrazine-2,6-diones, Endonuclease Inhibitors of Influenza Virus

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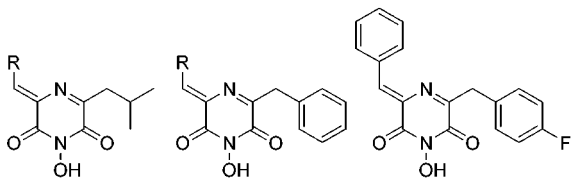
Flutimide, a fully substituted 1-hydroxy-3*H*-pyrazine-2,6-dione, is a fungal metabolite isolated from a new species of *Delitschia cofertaspora*. It has been shown to selectively inhibit cap-dependent endonuclease activity of influenza virus A. The inhibition of this activity is a target for the potential development of a therapeutic agent to treat influenza infections. A convergent total synthesis of flutimide starting from L-leucine has been described. The synthetic methodology has been extended to include the synthesis of specifically designed aromatic analogues of flutimide, some of which exhibited greater than 7-fold improvement in activity. The most potent compounds were those with *p*-fluorobenzylidene or *p*-methoxybenzylidene substitutions at C-5 of 3*H*-pyrazine-2,6-dione and showed IC_{50} values of 0.9 and 0.8 μM, respectively. The details of the rationale for the synthetic design, syntheses, and biological activities of these analogues are described.

Influenza is an acute and contagious respiratory disease that is distinguished by a severe pulmonary infection caused by influenza virus types A and B.[1] Due to periodic infections in humans of epidemic and pandemic proportions, influenza is a significant medical problem. The epidemics caused by the airborne transmission of these viruses account for thousands of deaths in the United States and millions of deaths worldwide every year.[2] Current therapies include a prophylactic annual vaccination program and therapeutic treatments with amantadine and rimantadine. More recently, neuraminidase inhibitors such as Relenza (zanamivir)[3] and Tamiflu (oseltamivir phosphate)[4] have become available for treatment, as well. However, these approaches have limited utility, and there is a significant demand for development of additional anti-influenza vaccines and therapeutic agents with potentially different mechanisms of action.[2a,5]

There are numerous potential molecular targets that can be considered for therapeutic intervention for treatment of influenza infections.[6] Primary transcription and inhibition of influenza specific endonuclease represent a unique opportunity for such interventions.[7] In 1994, we reported[7] a series of 4-substituted 2,4-dioxobutanoic acids as specific inhibitors of the endonuclease activity of transcriptase. Subsequently, we reported upon flutimide (**1a**), a novel fully substituted 3*H*-pyrazine-2,6-dione isolated from the dung-inhabiting fungus *Delitschia confertaspora* as a specific inhibitor of endonuclease.[8] This compound exhibited an IC_{50} of 5.1 μM against influenza virus transcriptase and had no activity against other transcriptases (IC_{50} >150 μM). It inhibited cap-dependent influenza endonuclease with an IC_{50} value of 6.8 μM. Although the structure of flutimide was determined by spectroscopic methods, confirmation by other methods was needed due to structural ambiguities caused by the presence of either heteroatoms or contiguous quaternary carbons. Additionally, the yield of this compound by microbial fermentation was very poor (<5 mg/L), and an additional source of production was required to provide an adequate supply for biological evaluations. Therefore, total synthesis of flutimide was undertaken and a convergent synthesis was designed to provide an easy access to a variety of analogues.[9] Details of the total synthesis of flutimide (**1a**), the synthesis of analogues **1**−**3**, and their biological activities are described.



1 **2** **3**

a: R = i-Pr
b: R = Ph
c: R = *p*-OCH_3-Ph
d: R = *p*-F-Ph
e: R = *m*-F-Ph
f: R = *o*-F-Ph

a: R = *p*-OCH_3-Ph
b: R = *p*-F-Ph
c: R = *i*-Pr

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(1) (a) Kingsbury, D. W. In *Virology*, 2nd ed.; Fields, B. N., Knipe, D. M., Eds.; Paven Press Ltd., New York, 1990; p 1075. (b) Plotch, S. J.; Bouloy, M.; Ulmanen, I.; Krug, R. M. *Cell* **1981**, *23*, 847. (c) Palese, P.; Ritchey, M. B.; Schulman, J. L. *J. Virol.* **1977**, *21*, 1187.
(2) (a) Douglas, R. G., Jr. *New Engl. J. Med.* **1990**, *322*, 443. (b) Kilbourne, E. D. *Influenza*, Plenum Press: New York, 1987.
(3) (a) Zanamivir: *Ann. Rep. Med. Chem.* **1999**, *35*, 352. (b) For a review, see: McKimm-Breschkin, J. L. *Antiviral Res.* **2000**, *47*, 1.
(4) (a) Oseltamivir phosphate: *Ann. Rep. Med. Chem.* **1999**, *35*, 346. (b) See ref 3b.
(5) Hayden, F. G.; Hay, A. J. *Curr. Top. Microbiol. Immunol.* **1992**, *176*, 1304.
(6) For reviews on various influenza targets and development of inhibitors, see: (a) Meanwell, N. A.; Krystal, M. *Drug Discovery Today* **1996**, *1*, 316. (b) Meanwell, N. A.; Krystal, M. *Drug Discovery Today* **1996**, *1*, 388. For resistance, see: (c) McKimm-Breschkin, J. L. *Antiviral Res.* **2000**, *47*, 1.

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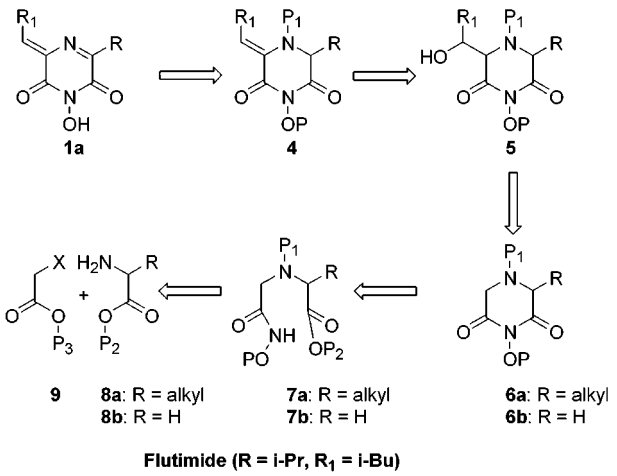
Scheme 1



Results and Discussion

Retrosynthetic Analysis. Flutimide (**1a**) is a fully substituted 1-hydroxy-3*H*-pyrazine-2,6-dione and contains the following sensitive groups: an *N*-hydroxyimide, an imine, and an exocyclic enamine with *Z*-geometry. The endocyclic imine may help in the stabilization of the exocyclic enamine via extended conjugation. The combination of such structural features is unusual and unprecedented.[10] Thus, there were two goals for the synthesis of flutimide (**1a**). The first goal was to confirm the proposed structure of natural flutimide by total synthesis, and the second goal was to generate analogues to develop a structure−activity relationship. A prerequisite of the synthetic design was that it must be convergent and provide maximal flexibility for the synthesis of analogues. The retrosynthetic analysis is shown in Scheme 1, which entailed four key operations: (i) the selection of a protecting group for the *N*-hydroxy group that could be cleaved with TFA,[11] (ii) selection of an N-protecting group that could be cleaved oxidatively and could concomitantly generate the required endocyclic imine, (iii) a cyclization step to yield a piperazine-2,6-dione either with or without one of the side chains (R_1), and (iv) easy installation of the exocyclic olefin on the piperazine-2,6-dione with various R.

In this strategy, deprotection of the enamine-installed advanced intermediate **4** provides the desired product, while **4** could be derived from putative intermediate **5** by β-elimination of a hydroxy group that could in turn be easily prepared by aldol condensation of cyclic intermediate **6a** with diverse aldehydes. Two routes could be envisioned for the key intermediate **6a**. The first, less flexible but cleaner than the second route, could be envisioned via intermediate **7a** by the N-alkylation of an α-amino acid ester (**8a**, P_2 = alkyl) with an α-halo-alkyl acetate (**9**). Alternatively, **6a** could be prepared by mono C-alkylation of a symmetrical cyclic intermediate **6b** that could be prepared by analogous N-alkylation of glycine ester (**8b**, P_2 = alkyl) with an α-halo-alkyl acetate. The cyclic intermediate **6b** provides additional flexibility for introduction of various alkyl groups from alkyl halides at a more advanced stage. However, the first route was favored for the synthesis of **6a** due to the simplicity. This route allowed for the possibility of performing multiple steps of reactions without chromatography. In both routes, the introduction of an *N*-hydroxy group was envisaged to employ hydroxylamine.[12] A *p*-methoxybenzyl (PMB) group was selected for protection of the amino group that could be oxidatively cleaved with DDQ or CAN and would be expected to also oxidize the amine to the Δ^3-imine in situ. A MOM group was selected for the protection of the *N*-hydroxy group, which later could be cleaved by TFA. The synthesis based on this approach is described below.

Synthesis of Monosubstituted Piperazine-2,6-diones. The N-alkylation of (*S*)-Leu-OMe.HCl (**10a**, R = *i*-Pr) or (*S*)-Phe-OMe (**10b**, R = Ph) at 60 °C with equimolar amounts of α-bromo-*tert*-butyl acetate in CH_3CN in the presence of diisopropylethylamine (DIPEA) gave the corresponding N-alkylated derivative **11** (Scheme 2). After completion of the reaction, the product was heated with *p*-methoxybenzyl (PMB) chloride in the same reaction vessel to afford compound **12** in a 90−97% overall two-step yield.[13] Treatment of the ester (**12**) with TFA selectively hydrolyzed the *tert*-butyl ester and produced free acid **13** in 94% yield. The acid group of **13** was activated with *N*-hydroxysuccinimide to produce active ester **14**, which was then reacted with neutralized hydroxylamine to give compound **15**, and this was subsequently heated at reflux to afford the cyclized product **16**. The *N*-hydroxy group of **16** was conveniently reacted with MOM chloride to afford MOM ether **17** in >80% purified yield based on acid **13**. This entire reaction scheme was conveniently carried out on a >0.25 mol scale without need for any purification until the last step of the Scheme 2.

Addition of the Left Side Chains. Aldol condensation of **17a** with isobutyraldehyde and lithium hexamethyldisilazide (LHMDS) at −78 °C exclusively produced the 3*S*,5*S*,11*R*-stereoisomer of flutimide advanced hydroxy intermediate **18a** in 63% yield on a 5 g scale (Scheme 3).

The stereochemistry and conformation of **18a** was deduced by NOE difference spectroscopy in C_6D_6. Selected NOE enhancements are shown in Figure 1. Irradiation of the C-7 methylene protons (δ 1.40) produced strong enhancements to H-5, indicating the 1,3-diaxial relationship between the (*S*)-leucine derived side chain and H-5, consequently establishing the *S* stereochemistry at C-5.

(7) (a) Tomassini, J.; Selnick, H.; Davies, M. E.; Armstrong, M. E.; Baldwin, J.; Bourgeois, M.; Hasting, J.; Hazuda, D.; Lewis, J.; McClements, W.; Ponticello, G.; Radzilowski, E.; Baldwin, J.; Bourgeois, M.; Ponticello, G.; Smith, G.; Tebben, A.; Wolfe, A. *Antimicrob. Agents Chemother.* **1994**, *38*, 2827. (b) Hastings, J.; Selnick, H.; Wolanski, B.; Tomassini, *Antimicrob. Agents Chemother.* **1996**, *38*, 1304.

(8) (a) Hensens, O. D.; Goetz, M. A.; Liesch, J. M.; Zink, D. L.; Helms, G. L.; Singh, S. B. *Tetrahedron Lett.* **1995**, *36*, 2005. (b) Tomassini, J. E.; Davies, M. E.; Hastings, J. C.; Lingham, R.; Mojena, M.; Raghoobar, S. L.; Singh, S. B.; Tkacz, J. S.; Goetz, M. A. *Antimicrob. Agents Chemother.* **1996**, *40*, 1189.

(9) For a brief account of the synthesis, see: Singh, S. B. *Tetrahedron Lett.* **1995**, *36*, 2009.

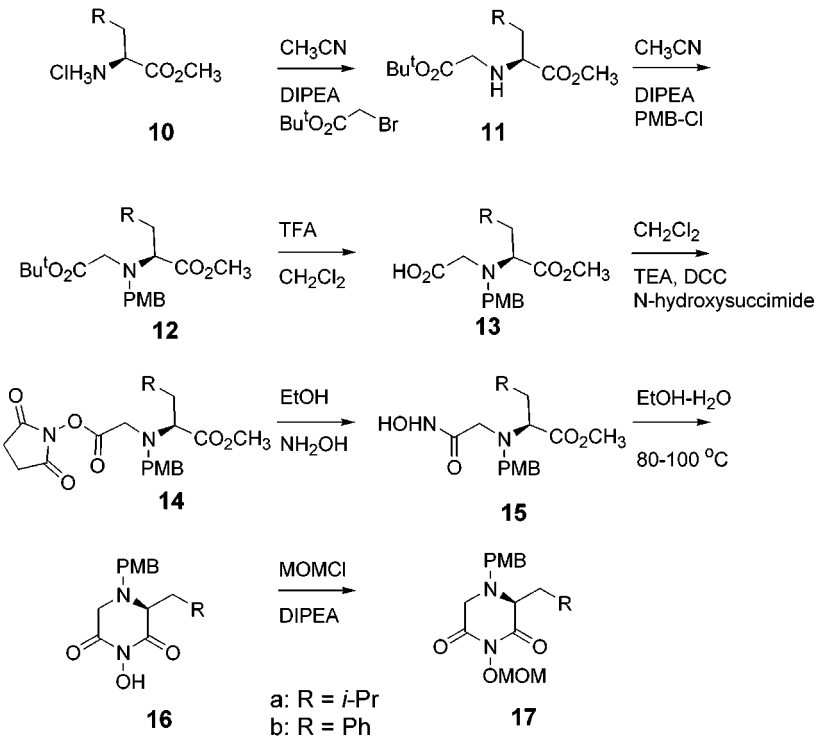
(10) At the time of the discovery of flutimide, a computer based CAS search of 3-alkyl-3*H*-pyrazine-2,6-dione showed no hits and did not change significantly when the search was performed again in January 2001 except for the report on flutimide[8] and analogues[18] and one other report of pyrazinecarboxamide.[19]

(11) Flutimide had previously been shown to be stable to TFA.[8a]

(12) It would be better if the *N*-hydroxy group could be directly introduced as a last step, but there are no methods available which will allow N-hydroxylation in good yield. We investigated MoO_5·HMPA oxidation[20] on 2,5-piperazinedione,[8a] which gave very poor yield. Therefore, we did not investigate this oxidation method in this project and decided to introduce the *N*-hydroxy group from hydroxylamine.

(13) Both alkylations could be effected in ethanol but CH_3CN proved to be much better and gave cleaner products in the large-scale reactions.

Scheme 2



PMB = *p*-methoxybenzyl

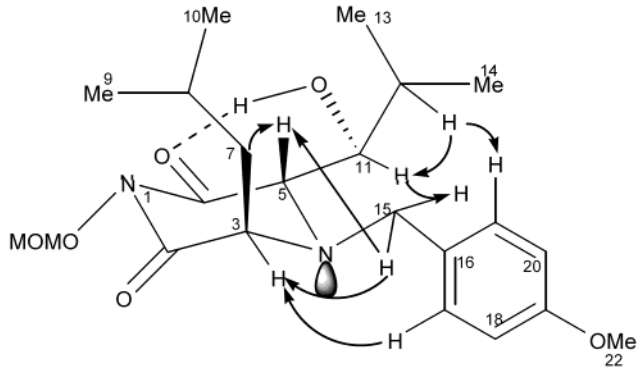
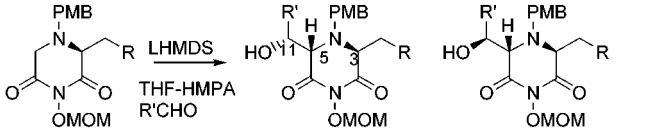


Figure 1. Structure of **18a** showing selected NOE enhancements in C_6D_6.

Scheme 3



17
a: R = *i*-Pr
b: R = Ph

18
a: R = *i*-Pr, R' = *i*-Pr
b: R = *i*-Pr, R' = Ph
c: R = *i*-Pr, R' = *p*-OCH_3-Ph
d: R = *i*-Pr, R' = *p*-F-Ph
e: R = *i*-Pr, R' = *m*-F-Ph
f: R = *i*-Pr, R' = *o*-F-Ph
g: R = Ph, R' = *i*-Pr
h: R = Ph, R' = *p*-OCH_3-Ph
i: R = Ph, R ' = *p*-F-Ph

19
f: R = *i*-Pr, R' = *o*-F-Ph
g: R = Ph, R' = *i*-Pr

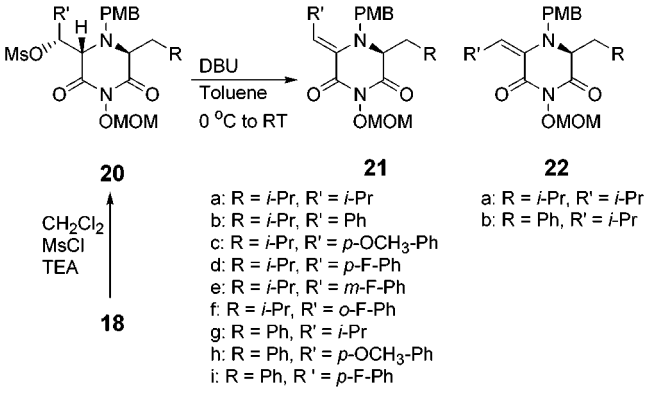
The newly generated hydroxy group (δ 3.30, brs) at C-11 appears to form a hydrogen bond with the C-6 carbonyl oxygen and tends to fix the conformation of H-11 syn to H-5 (J = 9.5 Hz). Irradiation of H-11 exhibited unambiguous strong NOE enhancements to one of the two NCH_2 protons (H-15, δ 3.55, 1H) along with H-5, H-12, and CH_3-13 (δ 1.00), indicating *R*-stereochemistry at C-11, which was further supported by formation of predominantly the *Z*-olefin as the elimination product (vide infra). The irradiation of the second NCH_2 proton (δ 3.19, 1H) gave strong enhancements to H-3 and only weak enhancements to H-5. Unfortunately, the NOE effect of the NCH_2 (δ 3.55) to either H-3 or H-5 could not be unambiguously discerned due to their proximal chemical shifts.

Similar aldol condensation reactions of **17a** with benzaldehyde, *p*-methoxybenzaldehyde, and *p*- and *m*-fluorobenzaldehyde exclusively furnished the corresponding 3*S*,5*S*,11*R*-hydroxy products **18b**−**e**. These aldol reactions were highly diastereoselective, just like **18a**, and did not produce any of the other three potential diastereomers. However, the aldol reaction of **17a** with the hindered *o*-flurorobenzaldehyde gave an approximately 2.5:1 mixture[14] of 3*S*,5*S*,11*R* and 3*S*,5*S*,11*S* isomers **18f** and **19f**, respectively, in rather poor combined yield (33%). The aldol reaction of phenylalanine-derived piperazine-2,6-dione **17b** with isobutyraldehyde surprisingly also gave a 2:1 diastereomeric mixture[14] of **18g** and **19g**, whereas the analogous aldol reactions of **17b** with *p*-methoxybenzaldehyde and *p*-fluorobenzaldehyde afforded only **18h** and **18i**, respectively.

The C-5 stereospecificity of the aldol reaction appears to be controlled by the stereochemistry at C-3, presumably due to the axial orientation of the C-3 side chain. This allows substitution at C-5 only from the equatorial side, resulting in the *S*-isomer. Stereospecificity at C-11 must result from the steric bulk of the PMB group. However, the steric bulk present near the aldehyde group appears to compete (*o*-fluorobenzaldehyde vs other benz-

(14) No attempts were made to optimize this reaction either for the diastereoselectivity or for yield.

Scheme 4



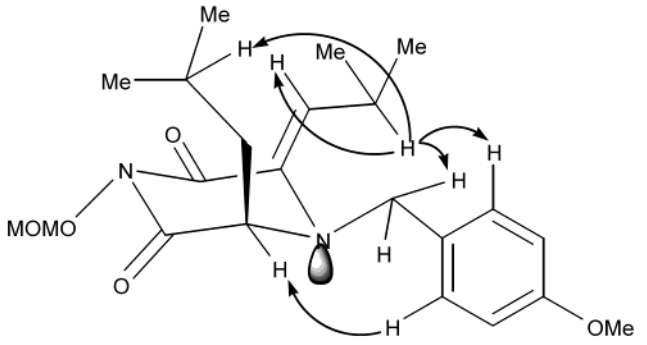


Figure 2. Structure of **21a** showing selected NOE enhancements in $CDCl_3$.

aldehydes) for the stereoselection and disturbs the stereoselectivity at C-11.

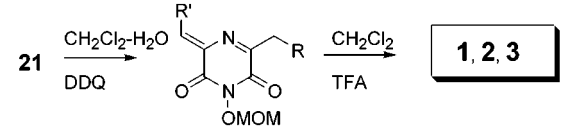
***β*-Elimination Reaction.** The aldol product **18a** was reacted with methanesulfonyl chloride (MsCl), DIPEA, and DMAP at −23 °C to give in quantitative yield the corresponding mesylate **20a**, which was directly used for the elimination reaction. The *β*-elimination reactions turned out to be challenging and required optimization. Thus, the reaction of mesylate at 0 °C with 3 equiv of DBU in toluene gave 74% combined yield of a 3:1 *Z*/*E* mixture of olefins **21a** and **22a**, respectively (Scheme 4).

The olefin geometries of **21a** and **22a** were deduced by NOE difference spectroscopic measurements of **21a** and are shown in Figure 2. Irradiation of the aromatic doublet (*δ* 7.20, J = 8.8 Hz) of **21a** exhibited strong enhancements to the vinylic methine proton (*δ* 3.11), which in turn showed enhancements to the NCH_2 protons (*δ* 3.81) indicating a *Z*-geometry of the olefin. This assignment was further supported by a Δ 1.27 ppm downfield shift of the olefinic proton of **21a** due to the oxygen proximity effect of C-6 ketone compared to the isomeric *E*-olefin **22a**.[8a] The methine protons of both isopropyl groups showed NOE enhancements to each other, indicating the spacial proximity of these protons due to their freedom of rotations.

Similar reactions of aromatic alcohols **18b**−**f** and **18h**−**i** with MsCl gave corresponding mesylates **20b**−**f**, and **20h**−**i**, which spontaneously *β*-eliminated to produce corresponding *Z*-olefins **21b**−**f** and **21h**−**i** in 70% to 99% overall yields. The elimination reaction of the mixture of **18g** and **19g** produced a mixture of *Z*/*E* isomers **21g** and **22b**.

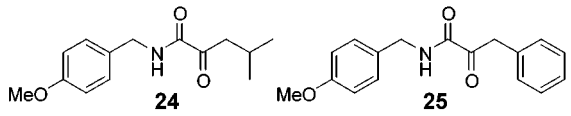
Oxidation and Deprotection Reactions. The oxidation of **21a** with DDQ in a mixture of CH_2Cl_2−H_2O (2:1)

Scheme 5



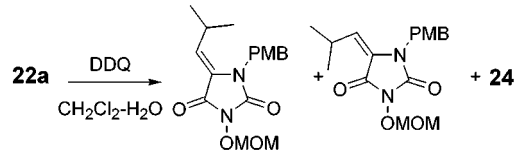
23

a: R = *i*-Pr, R' = *i*-Pr	f: R = *i*-Pr, R' = *o*-F-Ph
b: R = *i*-Pr, R' = Ph	g: R = Ph, R' = *i*-Pr
c: R = *i*-Pr, R' = *p*-OCH_3-Ph	h: R = Ph, R' = *p*-OCH_3-Ph
d: R = *i*-Pr, R' = *p*-F-Ph	i: R = Ph, R ' = *p*-F-Ph
e: R = *i*-Pr, R' = *m*-F-Ph	



24 **25**

Scheme 6



26 **27**

gave the expected oxidized product **23a** in ∼30% yield after chromatography (Scheme 5).[15] Similar oxidations of **21b**−**i** gave corresponding oxidized product **23b**−**i** in 19−50% yields. The low yields of these reactions were attributed to the decomposition of the product, presumably caused by hydration and subsequent cascade of rearrangement reactions. The oxidation reactions of **21c** and **21g** produced significant amounts of the corresponding α-ketoamides **24** and **25** along with the expected oxidized products **23c** and **23g**, respectively. Although most of these reactions produced some amounts of either **24** or **25**, the latter reaction produced equal proportions of α-ketoamide **25** and **23g**, indicating that the aromatic group facilitated the formation of α-ketoamides. Many of these oxidations also produced the corresponding aldehydes, presumably after addition of water followed by retro-aldol reactions. These side reactions were collectively responsible for the lower yields in the oxidation reactions.

The oxidation of the *E*-isomer **22a** did not give any of the expected products but instead produced a pair of isomeric[16] imidazolinediones **26** and **27**, as well as α-ketoamide **24** (Scheme 6).

Although there was decomposition observed during oxidation of *Z*-olefins, none of the reactions produced products analogous to compound **26** and **27**. It is surpris-

(15) The oxidation reaction with ceric ammonium nitrate (CAN) caused decomposition and was not successful.

(16) The geometry of the olefins was deduced by the comparison of ^{1}H NMR spectra of compounds **26** and **27** and application of oxygen proximity induced effect on the ^{1}H chemical shifts. The *Z*-olefinic proton (*δ* 5.73) of **26** showed Δ 0.5 ppm downfield shift compared to corresponding *E*-olefinic proton (*δ* 5.28) of **27** due to proximity to C-6 keto oxygen.[8a] This is supported by the observation of an analogous but more pronounced Δ 1 ppm downfield shift of the vinylic methine proton of the isopropyl group of the *E*-isomer 27 (*δ* 3.66) compared to corresponding proton of *Z*-isomer **26** (*δ* 2.64) due to the same effect.

(17) The details of the assays and the biological activity of some of the compounds have been previously reported in ref 8b.

(18) Singh, S. B. US Patent 5,624,928 (April 29, 1997).

(19) Furuta, Y.; Egawa, H. PCT Int. Appl. WO2000010569 A1 20000302, 1999.

(20) Rigby, J. H.; Qabar, M. *J. Org. Chem.* **1989**, *54*, 5852.

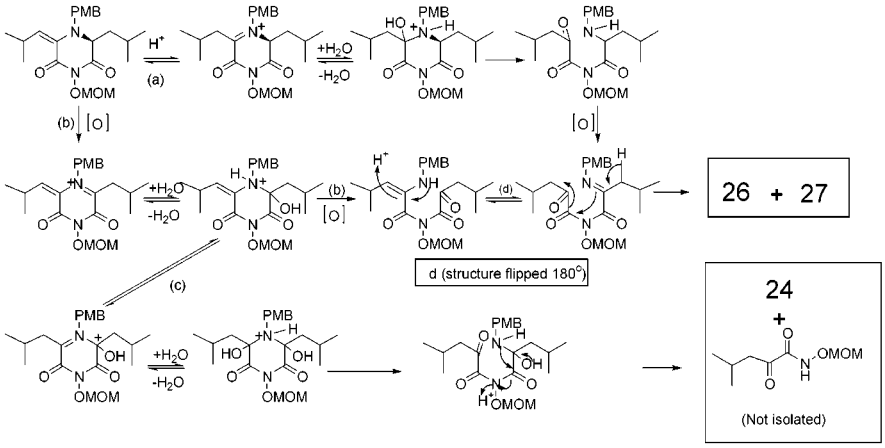


Figure 3. Plausible mechanism of formation of unexpected products.

ing that a mere difference in the olefinic geometry caused such a dramatic difference in the product composition. The process of this decomposition and formation of compounds **26** and **27** is pronounced, presumably due to decreased steric factors emanating from *E*-olefin. A plausible mechanism for the formation of the undesired products **24**−**27** is shown in Figure 3. There are two potential initial routes for the formation of isomeric compounds **26** and **27** (upper panel). However, the formation of compound **24** could be explained by a mechanism that involves the oxidation of the amine followed by addition of water and rearrangements (lower panel).

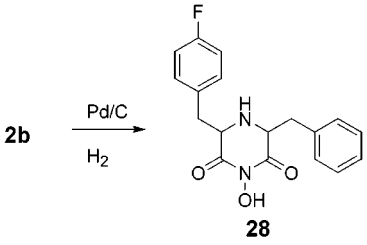
The MOM ethers **23a**−**i** were reacted with TFA in CH_2Cl_2 to give the corresponding *N*-hydroxy compounds **1**−**3** in 15−86% yields. These compounds were purified either by chromatography on reversed-phase HPLC or by recrystallization. The reaction yield was very good, but we observed a significant loss of material during chromatography. Small-scale (<10 mg) purification of synthetic flutimide could be easily accomplished by reversed-phase HPLC, but injection of larger quantities of material resulted in extremely low recoveries. Most of the aromatic pyrazinediones were crystalline and were purified by recrystallization, resulting in much better yield of the products. The NMR, MS, HPLC, and biological properties of synthetic compound **1a** were indistinguishable from the natural flutimide.

The deprotection of **23i** with TFA produced a 1:1 isomeric mixture of **2b** and **3** as a result of enamine−imine tautomerization. Surprisingly, the aromatic analogue **2a** did not produce any tautomeric products. TFA treatment of **23b** produced expected product **2c**, which spontaneously tautomerized and produced conjugated product **1b**, which was also produced by a similar reaction of **23b**.

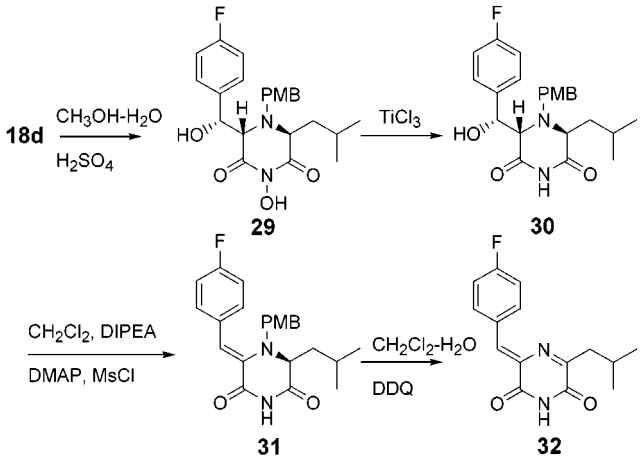
Tetrahydro- and *N*-Deoxy Derivatives. To test the role of the enamine−imine or *N*-hydroxy group on the transcriptase activity, compounds **28** (Scheme 7) and **32** (Scheme 8) were synthesized. Hydrogenation of compound **2b** produced tetrahydro compound **28** without reductive elimination of the *N*-hydroxy group.

For synthesis of the *N*-deoxy compound with an intact enamine−amine group, we elected to synthesize the corresponding deoxy analogue **32** of the most active *p*-fluorobenzylidene analogue **1d** and began the synthesis from the advanced intermediate **29**. Deprotection of

Scheme 7



Scheme 8



MOM ether with methanolic sulfuric acid gave **29**, which was reacted with titanium trichloride to give *N*-deoxy compound **30** in moderate yield. Compound **30** was reacted with methanesulfonyl chloride to give the mesylate derivative which concomitantly β-eliminated to give 63% yield of enamine **31**. This was oxidized with DDQ, giving 36% yield of pyrazine-2,6-dione **32** (Scheme 8).

Biological Activity. Flutimide (**1a**) inhibited cap1 ALMV primed influenza transcriptase with an IC_{50} value of 5.1 μM.[8b] There was no difference in the activities of the natural and synthetic samples of flutimide (**1a**). The substitution of the left side isopropyl group of flutimide with *p*-substituted phenyl groups (**1c** and **1d**) produced some of the most active compounds of the series and yielded IC_{50} values of 0.8 and 0.9 μM, respectively (Table 1).[17] Surprisingly, there was no significant difference in the activities between *p*-methoxyphenyl (**1c**) and *p*-fluorophenyl (**1d**) substituted compounds. However, there

Table 1. ALMV Primed Transcriptase Inhibitory Activities of Compounds

compd	IC_{50} (μM)	compd	IC_{50} (μM)
1a	5.1	**2a**	2.8
1b	4.8	**2b**	3.5
1c	0.8	**3**	6.5
1d	0.9	**18**−**22**	>200
1e	1.5	**23**	>200
1f	7.3	**28**	85
		32	>365

was a marked difference in the activity when compared with phenyl (**1b**), *m*- (**1e**), and *o*-fluorophenyl (**1f**) analogues. Substitution of both of the isopropyl groups with phenyl and/or *p*-methoxyphenyl (**2a**), *p*-fluorophenyl (**2b**), and **3** produced compounds with activity slightly greater than or equivalent to that of flutimide, but not as potent as **1c**. The reduction of olefins (compound **28**) caused a 17-fold loss of activity, and the reduction of the *N*-hydroxy group (compound **32**) completely obliterated the transcriptase activity. All other pyrazine-2,6-diones (**23**) and piperazine-2,6-diones (**18**−**22**) were inactive (>200 μM).

Flutimide-inhibited influenza virus infection of MDCK cells with an IC_{50} of 5.9 μM without any toxicity at 100 μM concentrations. The more potent in vitro active compounds **1c** and **1d** also appeared to be more potent in the antiviral assay but showed overt cytotoxicity to the cells at >10 μM concentrations. The SAR indicated that the substitution of both side chains was tolerated and produced 5−6-fold more potent compounds. This suggests that the preparation of further derivatives can potentially lead to superior analogues; however, the *N*-hydroxy group and both olefins appear to be necessary for the potency.

Summary

In this paper, we have described the convergent total synthesis of natural flutimide, which was successfully extended to the synthesis of additional analogues with substitutions at positions 1, 3, and 5 of 3*H*-pyrazine-2,6-dione. The *p*-substituted phenyl-substituted analogues showed activity (IC_{50}) in sub μM levels that are 6−7-fold better than flutimide.

Experimental Section

General Procedure. All reagents were purchased from Sigma-Aldrich Co. and were used without further purification. Optical rotations were measured on a Perkin-Elmer model 241 polarimeter. All NMR spectra were recorded on Varian Inova instruments operating at 400 and 500 MHz for ^{1}H and 100 and125 MHz for ^{13}C nuclei or on a Varian XL300 operating at 300 MHz for ^{1}H and 75 MHz for ^{13}C nuclei. FAB-MS was performed on JEOL instrument. LC-MS was performed on a Thermo Quest LCQ instrument using electrospray ionization (ESI) or atmospheric pressure chemical ionization (APCI). High-resolution mass spectral analysis was performed on a Thermo Quest FTMS using electrospray ionization. LCMS and ^{1}H NMR spectral analysis was used to determine the purity of all compounds.

Synthesis of *N*-*p*-Methoxybenzyl-*N*-*tert*-butylacetyl-(*S*)-leucine Methyl Ester (12a). A solution of α-bromo-*tert*-butyl acetate (44.4 mL, 0.275 mol), (*S*)-leucine methyl ester hydrochloride (50 g, 0.275 mol), and DIPEA (191 mL, 1.1 mol) in CH_3CN (400 mL) was stirred at room temperature for 16 h and heated at 60 °C for 4 h. After completion of the reaction (TLC, hexanes−EtOAc, 9:1), a small aliquot (5 mL) was taken out and CH_3CN was removed under reduced pressure. EtOAc (100 mL) was added, and the solution was washed with water (2 × 100 mL), 10% aqueous citric acid (100 mL), and water (100 mL). The EtOAc extract was dried over Na_2SO_4, evaporated under reduced pressure, and chromatographed over silica gel column. Elution with 5% EtOAc in hexane gave pure *N*-*tert*-butyl acetyl -(*S*)-leucine methyl ester (**11a**) as colorless oil: $[\alpha]^{25}_D$ −17.2° (*c* 2.9, MeOH); ^{1}H NMR ($CDCl_3$) δ 0.88 (3H, d, J = 6.6 Hz), 0.89 (3H, d, J = 6.6 Hz), 1.42 (9H, s), 1.48 (2H, m), 1.70 (1H, apparent hept, J = 6.6 Hz), 3.24 (2H, ABq, J = 18 Hz), 3.29 (1H, t, J = 7.2 Hz), 3.68 (3H, s); ^{13}C NMR ($CDCl_3$) δ 22.3, 22.7, 24.8, 28.1, 42.4, 49.9, 51.7, 59.2, 81.3, 170.9, 175.4. Anal. Calcd for $C_{13}H_{25}NO_4$: C, 60.20; H, 9.72; N, 5.40. Found: C, 60.05; H, 9.44; N, 5.32.

p-Methoxybenzyl chloride (56 mL, 0.41 mol) was added to the aforementioned reaction mixture, which was then heated at 70 °C for 24 h. After completion of the reaction, the solution was allowed to cool to room temperature. CH_3CN and DIPEA were removed under reduced pressure, and the residue was suspended in 500 mL of water. The product was extracted with EtOAc (3 × 600 mL). The EtOAc extract was sequentially washed with water (2 × 400 mL), 10% aqueous citric acid (400 mL), and water (400 mL) and dried (Na_2SO_4). The EtOAc was removed under reduced pressure, and the product was chromatographed over silica gel and eluted with 5% EtOAc−hexane to yield colorless oil of *N*-*p*-methoxybenzyl-*N*-*tert*-butylacetyl-(*S*)-leucine methyl ester **12a** (101.5 g, 97.3%): $[\alpha]^{25}_D$ −67.8° (*c* 3.43, MeOH); ^{1}H NMR ($CDCl_3$) δ 0.73 (3H, d, J = 6.6 Hz), 0.86 (3H, d, J = 6.6 Hz), 1.43 (9H, s), 1.48 and 1.57 (2H, m), 1.76 (1H, apparent hept, J = 6.6 Hz), 3.34 (2H, ABq, J = 17.4 Hz), 3.42 (1H, t, J = 6.6 Hz), 3.66 (1H, ABd, J = 13.5 Hz), 3.69 (3H, s), 3.78 (3H, s), 3.90 (1H, ABd, J = 13.5 Hz), 6.83 (2H, d, J = 8.7 Hz), 7.30 (2H, d, J = 8.7 Hz); ^{13}C NMR ($CDCl_3$) δ 21.9, 23.1, 24.3, 28.1, 39.2, 51.14, 52.4, 55.3, 55.5, 60.5, 80.5, 113.6, 130.2, 131.0, 158.8, 171.1, 173.9. Anal. Calcd for $C_{21}H_{33}NO_5$: C, 66.46; H, 8.76; N, 3.69. Found: C, 66.75; H, 8.93; N, 3.64.

Synthesis of *N*-*p*-Methoxybenzyl-*N*-*tert*-butylacetyl-(*S*)-phenylalanine Methyl Ester (12b). (*S*)-Phenylalanine methyl ester hydrochloride (20 g, 92.7 mmol) was reacted with α-bromo-*tert*-butyl acetate (16.07 mL, 98 mmol) in CH_3CN for 6 h before addition of *p*-methoxybenzyl chloride (18.85 mL, 139 mmol) and then heated at 70 °C overnight. The reaction was worked up and chromatographed as described above to give pure *N*-*p*-methoxybenzyl-*N*-*tert*-butyl acetyl-(*S*)-leucine methyl ester **12b** (34.0 g, 89.1%): $[\alpha]^{25}_D$ −52.8° (*c* 1.88, MeOH); ^{1}H NMR ($CDCl_3$) δ 1.44 (9H, s), 2.95 (1H, dd, J = 13.5, 7.2 Hz), 3.04 (1H, dd, J = 13.8, 8.1 Hz), 3.40 (2H, ABq, J = 17.4 Hz), 3.64 (3H, s), 3.64 (1H, dd, J = 7.2, 8.1 Hz), 3.74 (1H, d, J = 13.5 Hz), 3.78 (3H, s), 3.94 (1H, d, J = 13.5 Hz), 6.76 (2H, d, J = 9.0 Hz), 7.10 (2H, d, J = 8.7 Hz), 7.11 (2H, dd, J = 8.1, 1.5 Hz), 7.22 (3H, m); ^{13}C NMR ($CDCl_3$) δ 28.1, 36.4, 51.3, 52.2, 55.2, 55.4, 64.3, 80.8, 113.5, 126.3, 128.2, 129.4, 130.0, 130.6, 138.0, 158.7, 170.8, 172.7; HRESI−FTMS calcd for $C_{24}H_{32}NO_5$ (M + H) 414.2280, found 414.2263. Anal. Calcd for $C_{24}H_{31}NO_5$: C, 69.71; H, 7.56; N, 3.39. Found: C, 69.79; H, 7.49; N, 3.16.

Synthesis of *N*-*p*-Methoxybenzyl-*N*-carboxymethyl-(*S*)-leucine Methyl Ester (13a). To a solution of *tert*-butyl ester (**12a**, 114 g, 0.3 mol) in methylene chloride (200 mL) at −78 °C was added trifluoroacetic acid (160 mL). After the solution was stirred for 20 min at −78 °C, it was allowed to warm to room temperature and stirred for 70 h. Volatile material was removed under reduced pressure. EtOAc (2.0 L) was added to the residue followed by 100 mL of water. The pH of the solution was 1.0, which was basified to pH 4.0 by addition of 10% aqueous solution of $NaHCO_3$. The layers were separated, and the EtOAc solution was washed once with 400 mL of water. The product was extracted from EtOAc solution by extraction with 10% aqueous $NaHCO_3$ (3 × 300 mL), 4 N NaOH (400 mL), and water (200 mL). The EtOAc extract was dried over Na_2SO_4 and concentrated to give unreacted starting material (30 g). All of the basic extracts containing the product were combined and acidified to pH 4.0 by addition of aqueous citric acid and extracted with EtOAc (3 × 500 mL). The combined EtOAc extract was washed with water (400 mL), dried over Na_2SO_4, and evaporated under reduced pressure

followed by drying at 60 °C under vacuum for 48 h to give pure acid **13a** (67 g, 93.7%, based on recovery of the starting material) as a gum. A small aliquot of the acid was purified on a preparative Zorbax RX C-8 (22.5 × 250 mm) HPLC column and eluted with 30% aqueous CH_3CN at a flow rate of 10 mL/min to give an analytical sample: $[\alpha]^{25}_D$ −33.8 (*c* 0.32, MeOH); ^{1}H NMR ($CDCl_3$) δ 0.85 (3H, d, J = 6.3 Hz), 0.90 (3H, d, J = 6.0 Hz), 1.68 (2H, m), 1.83 (1H, m), 3.81 (3H, s), 3.82 (3H, s), 3.96 (2H, ABq, J = 17.4), 4.05 (1H, dd, J = 8.7, 4.8 Hz), 4.27 (2H, s), 6.92 (2H, d, J = 8.7 Hz), 7.33 (2H, d, J = 8.7 Hz); FABMS *m*/*z* 330 (M + Li), 324 (M + H). Anal. Calcd for $C_{17}H_{25}NO_5$.0.7 TFA: C, 54.81; H, 6.42; N, 3.49. Found: C, 54.89; H, 6.25; N, 3.83.

Synthesis of *N*-*p*-Methoxybenzyl-*N*-carboxymethyl-(*S*)-phenylalanine Methyl Ester (13b). *tert*-Butyl ester (**12b**, 33 g, 80 mmol) in methylene chloride (160 mL) was deprotected with trifluoroacetic acid (40 mL) by stirring at room temperature for 48 h. The solvents were removed under reduced pressure, the product was thoroughly dried under vacuum for 48 h, and the acid (**13b**) was used for next step without any purification: ^{1}H NMR ($CDCl_3$) δ 3.24 (1H, dd, J = 13.5, 8.1 Hz), 3.34 (1H, dd, J = 13.5, 7.5 Hz), 3.74 (3H, s), 3.79 (3H, s), 4.14 (2H, s), 4.34 (2H, ABq, J = 12.9 Hz), 4.40 (1H, dd, J = 8.1, 7.5 Hz), 6.86 (2H, d, J = 8.7 Hz), 7.07 (2H, m), 7.18 (2H, d, J = 9.0 Hz), 7.31 (3H, m); HRESI−FTMS calcd for $C_{20}H_{24}NO_5$ (M + H) 358.1649, found 358.1634.

Synthesis of 1-Methoxymethoxy-3*S*-isobutyl-4-*p*-methoxybenzylpiperazine-2,6-dione (17a). *N*-Hydroxysuccinimide (23.0 g, 0.2 mol) and TEA (27.8 mL, 0.2 mol) was added to a soultion of acid **13a** (64.6 g, 0.2 mol) in methylene chloride (500 mL). The solution was cooled to 0 °C, and DCC (41.2 g, 0.2 mol) was added in small portions over a period of 5 min. The solution was stirred under nitrogen for 20 h at room temperature. The precipitated urea was removed by filtration, and the filtrate was concentrated to dryness under reduced pressure to give 90 g of chromatographically homogeneous (TLC, hexanes−EtOAc, 7:3) succinimide ester (**14a**) as a gum that was used in the next step without purification: ^{1}H NMR ($CDCl_3$) δ 0.70 (3H, d, J = 6.6 Hz), 0.86 (3H, d, J = 6.6 Hz), 1.54 and 1.61 (2H, m), 1.73 (1H, m), 2.84 (4H, s), 3.46 (1H, dd, J = 9.0, 6.3 Hz), 3.69 (1H, d, J = 12.9 Hz), 3.71 (3H, s), 3.79 (3H, s), 3.86 (2H, ABq, J = 18 Hz), 3.94 (1H, d, J = 13.2 Hz), 6.84 (2H, d, J = 8.7 Hz), 7.28 (2H, d, J = 8.7 Hz); FABMS *m*/*z* 421 (M + H).

To a solution of succinimide ester **14a** (84 g, 0.2 mol) in a mixture of ethanol (250 mL) and THF (200 mL) was added a neutralized solution of hydroxylamine [hydroxylamine hydrochloride (20.85 g, 0.3 mol) was dissolved in 100 mL of water and was mixed with a 100 mL solution of 0.3 mol NaOH]. The mixture, which had a pH of 6.0, was stirred at room temperature for 3 h. TLC examination (hexanes−EtOAc, 7:3) indicated consumption of the succinimide ester and formation of an $FeCl_3$ positive product **15a**. Precipitated NaCl was removed from the reaction mixture by filtration, and the precipitate was washed with 20 mL of ethanol. The combined filtrate was refluxed overnight to give almost clean (HPLC, Zorbax RX C-8, 4.6 × 250 mm, 40% aqueous CH_3CN containing 0.1% TFA, flow rate 1 mL/min at 40 °C, t_R of the product 15.19 min) cyclized *N*-hydroxy compound (**16a**). After removal (under reduced pressure) of most of the solvents from the reaction mixture (pH 5.3), it was poured onto 200 mL water giving a total volume of 600 mL, which was extracted with EtOAc (4 × 900 mL). The EtOAc extract was washed with water (300 mL), dried over Na_2SO_4, and evaporated under reduced pressure to give ∼70 g of crude product as a gum. A small aliquot of the product was purified on preparative Zorbax RX C-8 (22.5 × 250 mm) HPLC column and eluted with 30% aqueous CH_3CN containing 0.1% TFA at a flow rate of 10 mL per min followed by lyophilization of the fractions gave **16a** as a semisolid: $[\alpha]^{25}_D$ −21.2° (*c* 0.61, CH_3OH); ^{1}H NMR ($CDCl_3$) δ 0.80 (3H, d, J = 6.3 Hz), 0.94 (3H, d, J = 6.3 Hz), 1.28 (2H, m) 1.60 (1H,m), 3.35 (1H, brt), 3.58 (1H, d, J = 18 Hz), 3.72 (2H, ABq, J = 12.9 Hz), 3.80 (3H, s), 3.87 (1H, d, J = 18 Hz), 5.90 (1H, br, OH), 6.86 (2H, d, J = 8.7 Hz), 7.17 (2H, d, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 21.2, 22.9, 24.7, 37.8, 50.3, 55.3, 58.5, 61.4, 114.1, 128.1, 130.3, 159.4, 165.4, 169.0; FABMS *m*/*z* 367 (M + Na + K − H), 351 (M + 2Na − H), 336 (M + Na + Li − H), 319 (M + 2Li − H). Anal. Calcd for $C_{16}H_{22}N_2O_4$·0.3 TFA: C, 58.54; H, 6.60; N, 8.23. Found: C, 58.85; H, 6.51; N, 8.50.

To a cooled (−40 °C) and stirred (under nitrogen) solution of just prepared *N*-hydroxy compound **16a** (66.8 g, 0.2 mol) in methylene chloride (600 mL) was added DIPEA (76 mL, 0.4 mol) followed by addition of methoxymethyl chloride (33.1 mL, 0.4 mol) over 15 min. The solution was stirred at the same temperature for 2 h. After completion (TLC, hexanes−EtOAc, 9:1) of the reaction, methylene chloride was removed under reduced pressure, water (500 mL) was added to the residue, and product was extracted with EtOAc (3 × 600 mL). The EtOAc layer was washed with 10% aqueous citric acid (2 × 400 mL) and water (2 × 400 mL), dried over Na_2SO_4, and evaporated under reduced pressure to give ∼80 g of an oily product that was chromatographed on a silica gel column. Elution with 5−10% of EtOAc in hexane gave MOM ether **17a** (54 g, 80% based on starting acid) as an oil: $[\alpha]^{25}_D$ −33.8° (*c* 0.65, CH_3OH); ^{1}H NMR ($CDCl_3$) δ 0.81 (3H, d, J = 6.6 Hz), 0.95 (3H, d, J = 6.3 Hz), 1.57 and 1.75 (2H, m), 1.87 (1H,m), 3.52 (1H, dd, J = 18, 1.2 Hz), 3.61 (1H, dd, J = 5.4, 1.2 Hz), 3.63 (3H, s), 3.72 (2H, ABq, J = 12.9 Hz), 3.81 (3H, s), 3.82 (1H, d, J = 18 Hz), 5.01 (2H, ABq, J = 7.0 Hz), 6.86 (2H, d, J = 9.0 Hz), 7.17 (2H, d, J = 9.0 Hz); ^{13}C NMR ($CDCl_3$) δ 21.3, 23.0, 24.5, 37.9, 51.2, 55.3, 58.3, 58.3, 62.4, 100.6, 114.0, 128.4, 130.3, 159.4, 167.2, 170.4; HRESI−FTMS calcd for $C_{18}H_{27}N_2O_5$ (M + H) 351.1914, found 351.1911. Anal. Calcd for $C_{18}H_{26}N_2O_5$: C, 61.70; H, 7.47; N, 7.99. Found: C, 61.85; H, 7.73; N, 8.16.

Synthesis of 1-Methoxymethoxy-3*S*-benzyl-4-*p*-methoxybenzylpiperazine-2, 6-dione (17b). The acid **13b** (79.9 mmol), DCC (16.5 g, 79.9 mmol), *N*-hydroxysuccinimide (9.2 g, 79.9 mmol), and TEA (22.4 mL, 160 mmol) was reacted in methylene chloride (200 mL) as described above to give succinimide ester (**14b**), which was reacted similarly with hydroxylamine hydrochloride (8.21 g, 120 mmol) for 48 h. The reaction mixture was concentrated under reduced pressure to a volume of 100 mL. The precipitated product (18 g) was collected by filtration and washed with water. The filtrate was extracted with EtOAc (3 × 400 mL), and the EtOAc layer was washed with water, dried (Na_2SO_4), and evaporated under reduced pressure to give 7 g of additional product **16b** (total 25 g, yield 92.0%). Recrystallization from methylene chloride−hexane gave colorless granules: mp 161−163 °C; $[\alpha]^{25}_D$ −49.4° (*c* 0.65, MeOH−CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 3.09 (1H, dd, J = 14.1, 9.3 Hz), 3.16 (1H, dd, J = 14.1, 5.4 Hz), 3.57 (1H, dd, J = 18, 0.9 Hz), 3.68 (2H, ABq, J = 13.2 Hz), 3.77 (3H, s), 3.87 (1H, ddd, J = 9.3, 5.4, 0.9 Hz), 3.97 (1H, d, J = 18 Hz), 6.73 (2H, d, J = 8.7 Hz), 6.87 (2H, d, J = 8.7 Hz), 7.15 (2H, dd, J = 7.8, 2.4 Hz), 7.28 (3H, m), 8.50 (1H, broad signal, OH); ^{13}C NMR ($CDCl_3$) δ 35.2, 50.9, 55.3, 58.2, 64.6, 113.9, 127.0, 128.0, 128.5, 129.2, 130.0, 136.7, 159.2, 166.3, 168.5; HRESI−FTMS calcd for $C_{19}H_{21}N_2O_4$ (M + H) 341.1496, found 341.1497. Anal. Calcd for $C_{19}H_{20}N_2O_4$: C, 67.05; H, 5.92; N, 8.23. Found: C, 66.86; H, 5.67; N, 8.20.

A cooled (−40 °C) solution of *N*-hydroxy compound **16b** (23 g, 67.6 mmol) in methylene chloride (200 mL) was reacted with methoxymethyl chloride (10.3 mL, 135 mmol). The reaction was worked up and chromatographed in an analogous manner as described before to give 15 g (57.8%) of the MOM ether **17b** as oil: $[\alpha]^{25}_D$ −36.3° (*c* 1.48, MeOH−CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 3.09 (1H, dd, J = 14.4, 9.3 Hz), 3.16 (1H, dd, J = 14.4, 5.7 Hz), 3.54 (1H, dd, J = 18.0, 1.2 Hz), 3.64 (3H, s), 3.69 (2H, ABq, J = 13.2 Hz), 3.83 (1H, ddd, J = 9.0, 5.7, 1.2 Hz), 3.92 (1H, d, J = 18.0 Hz), 5.02 (2H, ABq, J = 7.2 Hz), 6.75 (2H, d, J = 8.7 Hz), 6.90 (2H, d, J = 8.7 Hz), 7.16 (2H, dd, J = 7.8, 2.1 Hz), 7.23 (3H, m); ^{13}C NMR ($CDCl_3$) δ 35.2, 51.7, 55.3, 58.0, 58.3, 65.4, 100.9, 113.9, 126.9, 128.1, 128.5, 129.2, 130.0, 136.8, 159.2, 167.1, 169.1; HRESI−FTMS calcd for $C_{21}H_{25}N_2O_5$ (M + H) 385.1758, found 385.1765. Anal. Calcd for $C_{21}H_{24}N_2O_5$: C, 65.61; H, 6.29; N, 7.29. Found: C, 65.83; H, 6.24; N, 6.99.

Synthesis of 1-Methoxymethoxy-3*S*-isobutyl-4-*p*-methoxybenzyl-5*S*-(1*R*-hydroxy-2-methylpropyl)piperazine-

2,6-dione (18a). To a cooled (−78 °C) solution of MOM ether **17a** (5.5 g, 15.7 mmol) in THF (60 mL) and HMPA (10 mL) was added a 1 M THF solution of lithium hexamethyldisilazide (18.85 mL, 18.85 mmol) under nitrogen over a period of 10 min. The dark yellow solution thus obtained was stirred at the same temperature for 3 h. Isobutyraldehyde (5.7 mL, 62.8 mmol) was added slowly (10 min) via a syringe. The pale solution was stirred for 2 h. The reaction was monitored by TLC (hexanes−EtOAc, 3:1), and after complete consumption of the starting MOM ether it was quenched with 20 mL of 10% aqueous NH_4Cl. The reaction mixture was allowed to warm to room temperature and poured onto EtOAc (800 mL). The organic layer was washed with water (3 × 300 mL), dried (Na_2SO_4), and evaporated under reduced pressure to give a gum that was chromatographed over a silica gel column. Elution of the column with 5−20% EtOAc in hexane afforded 4.2 g (63.3%) of aldol product **18a** as a gum: $[\alpha]^{25}_D$ −24.2° (*c* 0.54, MeOH); ^{1}H NMR (C_6D_6) δ 0.52 (3H, d, J = 6.5 Hz), 0.74 (3H, d, J = 7.0 Hz), 0.88 (3H, d, J = 6.5 Hz), 1.03 (3H, d, J = 7.0 Hz), 1.41 (2H, t, J = 7.5 Hz), 1.73 (1H,nonet, J = 6.5 Hz), 2.10 (1H, doublet of heptet, J = 7.0, 3.5 Hz), 3.19 (1H, d, J = 13 Hz), 3.25 (3H, s), 3.30 (1H, brs, OH), 3.49 (3H, s), 3.58 (1H, d, J = 13 Hz), 3.62 (1H, d, J = 7.5 Hz), 3.72 (1H, t, J = 7.5 Hz), 3.91 (1H, brdd, J = 7.0, 2.5 Hz), 4.92 (1H, d, J = 7.5 Hz), 5.02 (1H, d, J = 7.5 Hz), 6.66 (2H, d, J = 8.5 Hz), 6.98 (2H, d, J = 9.0 Hz); HRESI−FTMS calcd for $C_{22}H_{35}N_2O_6$ 423.2489, found 423.2500. Anal. Calcd for $C_{22}H_{34}N_2O_6$: C, 62.54; H, 8.11; N, 6.62. Found: C, 62.65; H, 8.36; N, 6.33.

Synthesis of 1-Methoxymethoxy-3*S*-isobutyl-4-*p*-methoxybenzyl-5*S*-[(phenyl)-1*R*-hydroxymethyl]piperazine-2,6-dione (18b). The aldol reaction performed with MOM ether **17a** (3.5 g, 10 mmol) and benzaldehyde (2.03 mL, 20 mmol), as described above, gave 3.08 g (67.5%) of *R*-hydroxy compound **18b** as a foam: $[\alpha]^{25}_D$ −17.7° (*c* 1.9, MeOH); ^{1}H NMR ($CDCl_3$) δ 0.37 (3H, d, J = 6.0 Hz), 0.81 (3H, d, J = 6.3 Hz), 1.43 (3H, m), 3.23 (1H, d, J = 12.6 Hz), 3.52 (1H, dd, J = 10.5, 3.6 Hz), 3.65 (3H, s), 3.73 (3H, s), 3.78 (1H, brs, OH), 3.87 (1H, d, J = 12.6 Hz), 4.09 (1H, d, J = 7.8 Hz), 5.05 (2H, ABq, J = 7.5 Hz), 5.26 (1H, dd, J = 7.8, 1.2 Hz), 6.62 (2H, d, J = 8.7 Hz), 6.68 (2H, d, J = 9 Hz), 7.38 (5H, m); ^{13}C NMR ($CDCl_3$) δ 20.7, 23.3, 23.8, 37.1, 52.0, 55.2, 58.4, 59.8, 63.8, 72.9, 100.8, 113.8, 127.5, 127.9, 128.5, 128.7, 130.3, 139.1, 159.2, 169.9, 170.3; HRESI−FTMS calcd for $C_{25}H_{33}N_2O_6$ (M + H) 457.2333, found 457.2328. Anal. Calcd for $C_{25}H_{32}N_2O_6$: C, 65.77; H, 7.07; N, 6.14. Found: C, 65.61; H, 6.80; N, 6.01.

Synthesis of 1-Methoxymethoxy-3*S*-isobutyl-4-*p*-methoxybenzyl-5*S*-[(*p*-methoxyphenyl)-1*R*-hydroxymethyl]-piperazine-2,6-dione (18c). Under reaction conditions identical to those described above, MOM ether **17a** (1.55 g, 4.42 mmol) was reacted with *p*-methoxybenzaldehyde and LHMDS in THF−HMPA and chromatographed over silica gel column to give *R*-hydroxy product **18c** (1.2 g, 56%) as a gum: $[\alpha]^{25}_D$ −1.76° (*c* 1.02, MeOH); ^{1}H NMR ($CDCl_3$) δ 0.40 (3H, d, J = 6.0 Hz), 0.83 (3H, d, J = 6.3 Hz), 1.44 (2H, m), 1.75 (1H, m), 3.23 (1H, d, J = 13.8 Hz), 3.53 (1H, dd, J = 10.5, 3.9 Hz), 3.66 (3H, s), 3.75 (3H, s), 3.85 (3H, s), 3.87 (1H, d, J = 12.9 Hz), 4.08 (1H, d, J = 7.8 Hz), 5.05 (2H, ABq, J = 7.5 Hz), 5.24 (1H, d, J = 7.8 Hz), 6.66 (2H, d, J = 9.0 Hz), 6.71 (2H, d, J = 9.0 Hz), 6.93 (2H, d, J = 9.0 Hz), 7.29 (2H, d, J = 8.7 Hz); ^{13}C NMR ($CDCl_3$) δ 20.7, 23.3, 23.8, 37.2, 52.0, 55.3, 55.5, 58.4, 59.8, 63.8, 72.5, 100.8, 113.8, 113.9, 127.9, 128.7, 130.3, 131.4, 159.2, 159.8, 170.0, 170.2; FABMS *m*/*z* 487 (M + H), 493 (M + Li); HRESI−FTMS calcd for $C_{26}H_{35}N_2O_7$ (M + H) 487.2438, found 487.2414. Anal. Calcd for $C_{26}H_{34}N_2O_7$: C, 64.18; H, 7.04; N, 5.76. Found: C, 64.52; H, 6.89; N, 5.52.

Synthesis of 1-Methoxymethoxy-3*S*-isobutyl-4-*p*-methoxybenzyl-5*S*-[(*p*-fluorophenyl)-1*R*-hydroxymethyl]piperazine-2,6-dione (18d). The aldol reaction was repeated with MOM ether **17a** (3.5 g, 10 mmol) and *p*-fluorobenzaldehyde (2.15 mL, 20 mmol), as described above, to give 3.17 g (67.5%) of *R*-hydroxy fluoro compound **18d** as a foam: $[\alpha]^{25}_D$ −18.8° (*c* 2.87, MeOH); ^{1}H NMR ($CDCl_3$) δ 0.41 (3H, d, J = 6.0 Hz), 0.82 (3H, d, J = 6.6 Hz), 1.43 (2H, m), 1.71 (1H, m), 3.23 (1H, d, J = 12.9 Hz), 3.54 (1H, dd, J = 10.5, 3.9 Hz), 3.64 (3H, s), 3.74 (3H, s), 3.83 (1H, d, J = 12.6 Hz), 3.84 (1H, d, J = 2.7 Hz, OH), 4.02 (1H, d, J = 7.8 Hz), 5.04 (2H, ABq, J = 7.5 Hz), 5.23 (1H, dd, J = 7.8, 2.7 Hz), 6.66 (2H, d, J = 9.0 Hz), 6.70 (2H, d, J = 9.0 Hz), 7.07 (2H, t, J = 8.7 Hz), 7.31 (2H, dd, J = 8.7, 5.4 Hz); ^{13}C NMR ($CDCl_3$) δ 20.7, 23.2, 23.9, 37.1, 52.0, 55.3, 58.4, 59.7, 63.9, 72.2, 100.8, 113.9, 115.4 (d, J = 25.7 Hz), 127.7, 129.1 (d, J = 9.8 Hz), 130.2, 135.2 (d, J = 3.8 Hz), 159.3, 162.8 (d, J = 294.8 Hz), 169.8, 170.1; HRESI−FTMS calcd for $C_{25}H_{32}FN_2O_6$ (M + H) 475.2238, found 475.2222. Anal. Calcd for $C_{25}H_{31}FN_2O_6$: C, 63.28; H, 6.58; N, 5.90. Found: C, 63.52; H, 6.47; N, 5.72.

Synthesis of 1-Methoxymethoxy-3*S*-isobutyl-4-*p*-methoxybenzyl-5*S*-[(*m*-fluorophenyl)-1*R*-hydroxymethyl]piperazine-2,6-dione (18e). Reaction of MOM ether **17a** (1.75 g, 5 mmol) with *m*-fluorobenzaldehyde (1.06 mL, 10 mmol), as described above, gave 0.95 g (40%) of *R*-hydroxy *m*-fluoro compound **18e** as a gum: $[\alpha]^{25}_D$ −20.7° (*c* 1.61, MeOH); ^{1}H NMR ($CDCl_3$) δ 0.44 (3H, d, J = 6.6 Hz), 0.82 (3H, d, J = 6.3 Hz), 1.44 (2H, m), 1.80 (1H, m), 3.23 (1H, d, J = 12.9 Hz), 3.58 (1H, dd, J = 10.8, 4.2 Hz), 3.63 (3H, s), 3.73 (3H, s), 3.85 (1H, d, J = 12.9 Hz), 3.99 (1H, d, J = 7.8 Hz), 5.02 (2H, ABq, J = 7.5 Hz), 5.22 (1H, d, J = 7.5 Hz), 6.70 (4H, brs), 7.07 (3H, m), 7.30 (1H, m); HRESI−FTMS calcd for $C_{25}H_{32}FN_2O_6$ (M + H) 475.2238, found 475.2227. Anal. Calcd for $C_{25}H_{31}FN_2O_6$: C, 63.28; H, 6.58; N, 5.90. Found: C, 63.18; H, 6.51; N, 5.55.

Synthesis of 1-Methoxymethoxy-3*S*-isobutyl-4-*p*-methoxybenzyl-5*S*-[(*o*-fluorophenyl)-1*R*- and -1*S*-hydroxymethyl]piperazine-2,6-dione (18f and 19f). MOM ether **17a** (1.75 g, 5 mmol) and *o*-fluorobenzaldehyde (1.05 mL, 10 mmol) were reacted as described above to give after chromatography 220 mg of *S*-hydroxy (**19f**) and 570 mg of *R*-hydroxy (**18f**) compounds (combined yield 33.3%) both as a gum. **18f**: $[\alpha]^{25}_D$ −22.8° (*c* 0.93, MeOH); ^{1}H NMR ($CDCl_3$) δ 0.34 (3H, d, J = 6 Hz), 0.81 (3H, d, J = 6 Hz), 1.38 (2H, m), 1.76 (1H, m), 3.24 (1H, d, J = 13.9 Hz), 3.54 (1H, dd, J = 10.5, 3.6 Hz), 3.65 (3H, s), 3.74 (3H, s), 3.75 (1H, brd, J = 3.3 Hz, OH), 3.85 (1H, d, J = 12.6 Hz), 4.25(1H, d, J = 8.1 Hz), 5.05 (2H, ABq, J = 7.5 Hz), 5.59 (1H, dd, J = 8.1, 3.0 Hz), 6.60 (2H, d, J = 9.0 Hz), 6.68 (2H, d, J = 9.0 Hz), 7.10 (1H, m), 7.19 (1H, dt, J = 7.5, 2.1 Hz), 7.40 (2H, m); ^{13}C NMR ($CDCl_3$) δ 20.6, 23.2, 23.9, 37.3, 52.3, 55.2, 58.4, 60.1, 62., 67.7, 100.8, 113.8, 115.7 (d, J = 26.5 Hz), 124.4 (d, J = 4.1 Hz), 126.3 (d, J = 15.5 Hz), 127.9, 129.3 (d, J = 4.0 Hz), 130.2 (d, J = 10.3 Hz), 130.3, 159.2, 160.9 (d, J = 294.3 Hz), 169.9, 170.3; HRESI−FTMS calcd for $C_{25}H_{32}FN_2O_6$ (M + H) 475.2238, found 475.2228. Anal. Calcd for $C_{25}H_{31}FN_2O_6$: C, 63.28; H, 6.58; N, 5.90. Found: C, 63.13; H, 6.42; N, 5.80. **19f**: $[\alpha]^{25}_D$ −49.2° (*c* 0.61, MeOH); ^{1}H NMR ($CDCl_3$) δ 0.78 (3H, brd, J = 6 Hz), 0.94 (3H, d, J = 6 Hz), 1.28 (2H, m), 1.73 (1H, m), 3.21 (1H, d, J = 13.2 Hz), 3.45 (1H, m), 3.64 (3H, s), 3.78 (3H, s), 4.00 (1H, d, J = 5.4 Hz), 4.10 (1H, d, J = 13.2 Hz), 4.17 (1H, brs, OH), 5.03 (2H, ABq, J = 7.2 Hz), 5.63 (1H, dd, J = 5.7, 2.7 Hz), 6.70 (2H, d, J = 8.4 Hz), 6.76 (2H, d, J = 8.4 Hz), 6.95 (1H, dd, J = 10.5, 8.1 Hz), 7.20 (1H, dt, J = 7.2, 0.6 Hz), 7.30 (1H, m), 7.53 (1H, dt, J = 7.5, 1.5 Hz); HRESI−FTMS calcd for $C_{25}H_{32}FN_2O_6$ (M + H) 475.2238, found 475.2219. Anal. Calcd for $C_{25}H_{31}FN_2O_6$: C, 63.28; H, 6.58; N, 5.90. Found: C, 63.23 H, 5.99; N, 5.63.

Synthesis of 1-Methoxymethoxy-3*S*-benzyl-4-*p*-methoxybenzyl-5*S*-[(*p*-methoxyphenyl)-1*R*-hydroxymethyl]-piperazine-2,6-dione (18h). Reaction of the MOM ether **17b** (2.5 g, 6.5 mmol) with *p*-methoxybenzaldehyde (2 equiv) after chromatography gave *R*-hydroxy product **18h** (1.2 g, 56%) as a gum: $[\alpha]^{25}_D$ −22.4° (*c* 1.2, MeOH); ^{1}H NMR ($CDCl_3$) δ 2.94 (1H, dd, J = 14.7, 10.5 Hz), 3.16 (1H, dd, J = 14.4, 4.2 Hz), 3.27 (1H, d, J = 12.9 Hz), 3.67 (3H, s), 3.74 (3H, s), 3.76 (1H, d, J = 12.9 Hz), 3.84 (3H, s), 3.86 (1H, dd, J = 10.8, 4.5 Hz), 3.97 (d, J = 13.2 Hz), 4.01 (1H, d, J = 7.5 Hz), 5.08 (2H, ABq, J = 7.5 Hz), 5.14 (1H, brd, J = 7.5 Hz), 6.43 (2H, d, J = 8.7 Hz), 6.56 (2H, d, J = 9.0 Hz), 6.79 (2H, d, J = 8.7 Hz), 6.8 (2H, d, J = 8.1 Hz), 7.07−7.22 (5H, m); ^{13}C NMR ($CDCl_3$) δ 34.1, 52.0, 55.2, 55.4, 58.5, 63.1, 64.9, 71.9, 100.9, 113.7, 113.9, 126.6, 127.3, 128.3, 128.3, 129.3, 130.0, 131.4, 136.5, 159.0, 159.6, 169.0, 169.8; HRESI−FTMS calcd for $C_{29}H_{33}N_2O_7$ (M + H) 521.2282, found 521.2287. Anal. Calcd for $C_{29}H_{32}N_2O_7$: C, 66.91; H, 6.20; N, 5.38. Found: C, 66.81; H, 6.03; N, 5.30.

Synthesis of 1-Methoxymethoxy-3*S*-benzyl-4-*p*-methoxybenzyl-5*S*-[(p-fluorophenyl)-1*R*-hydroxymethyl]piperazine-2,6-dione (18i). Reaction of the MOM ether **17b** (1.9 g, 4.95 mmol) with *p*-fluorobenzaldehyde (1.5 equiv) after chromatography gave *R*-hydroxy product **18i** (1.62 g, 64.5%) as a foam that turned into a gum: $[\alpha]^{25}_D$ −27.7° (*c* 1.24, MeOH); ^{1}H NMR ($CDCl_3$) δ 2.94 (1H, dd, J = 14.7, 10.8 Hz), 3.20 (1H, dd, J = 15.0, 4.5 Hz), 3.28 (1H, d, J = 13.2 Hz), 3.67 (3H, s), 3.74 (3H, s), 3.89 (1H, dd, J = 10.8, 4.5 Hz), 3.956 (1H, d, J = 7.8 Hz), 3.957 (1H, d, J = 13.2 Hz), 5.08 (2H, ABq, J = 7.2 Hz), 5.13 (1H, dd, J = 7.8, 1.8 Hz), 6.41 (2H, d, J = 8.4 Hz), 6.57 (2H, d, J = 8.7 Hz), 6.84 (2H, dd, J = 6.9, 1.5 Hz), 6.91 (2H, dd, J = 8.4, 5.4 Hz), 7.23 (3H, m); ^{13}C NMR ($CDCl_3$) δ 34.0, 52.0, 55.2, 58.5, 63.1, 64.9, 71.6, 100.9, 113.7, 115.2 (d, J = 25.7 Hz), 126.8, 127.1, 128.4, 128.9 (d, J = 9.8 Hz), 129.2, 129.9, 135.1 (d, J = 3.9 Hz), 136.5, 159.1, 162.6 (d, J = 294.4 Hz), 168.8, 169.6; HRESI−FTMS calcd for $C_{28}H_{30}FN_2O_6$ (M + H) 509.2082, found 509.2080. Anal. Calcd for $C_{28}H_{29}N_2O_6$: C, 66.13; H, 5.75; N, 5.51. Found: C, 66.43; H, 5.74; N, 5.53.

Synthesis of 1-Methoxymethoxy-3*S*-isobutyl-4-*p*-methoxybenzyl-5-(2-methyl-*Z*- and -*E*-prop-1-enyl)piperazine-2,6-dione (21a and 22a). To a cooled (−23 °C) solution of hydroxy compound **18a** (3.8 g, 9 mmol) in methylene chloride (50 mL) were added DIPEA (3.13 mL, 18 mmol) and DMAP (2.2 g, 18 mmol) under nitrogen. After 10 min, methanesulfonyl chloride (1.39 mL, 18 mmol) was slowly added via a syringe, and the mixture was stirred for 20 min at −23 °C followed by 1 h at room temperature. The reaction mixture was conveniently monitored on TLC (hexanes−EtOAc 7:3) and formation of a slightly polar product was observed. Water (100 mL) was added to the mixture and extracted with EtOAc (800 mL). The EtOAc layer was washed sequentially with water (2 × 200 mL), 10% aqueous citric acid (2 × 200 mL), water (200 mL), 20% aqueous $NaHCO_3$ (2 × 200 mL), and finally with water (2 × 200 mL), dried over Na_2SO_4, and evaporated to give chromatographically homogeneous mesylate **20a** (4.5 g) as a gum that was used without purification.

To a cooled (0 °C) solution of the mesylate (4.5 g, 9 mmol) in toluene (25 mL) was added DBU (4.0 mL, 27 mmol) via a syringe under nitrogen. The solution was stirred at 0 °C for 10 min, room temperature for 30 min, and at 50 °C for 1 h. The reaction mixture was allowed to cool to room temperature before adding EtOAc (700 mL). The EtOAc solution was sequentially washed with water, aqueous citrtic acid, water, aquoues $NaHCO_3$, and water, dried over Na_2SO_4, and evaporated under reduced pressure to give the crude product as a gum that was chromatographed over a silica gel column and eluted with 2−15% of EtOAc in hexane to give 400 mg of *E*-isomer **22a**, 800 mg of a mixture of *E* and *Z* isomers, and finally 1.53 g of *Z*-isomer **21a** all as gums. The ismeric ratio *Z*/*E* was measured to be ∼3/1 and overall two step yield 74.3%. **21a**: $[\alpha]^{25}_D$ +37.6° (*c* 0.21, CH_3OH); ^{1}H NMR ($CDCl_3$) δ 0.63 (3H, d, J = 6.4 Hz), 0.84 (3H, d, J = 6.8 Hz), 0.99 (3H, d, J = 6.8 Hz), 1.03 (3H, d, J = 6.8 Hz), 1.29 (1H, ddd, J = 14, 9.6, 4.4 Hz), 1.49 (1H, ddd, J = 13.6, 10.8, 4.4 Hz), 1.77 (1H,m), 3.11 (1H, m), 3.55 (1H, dd, J = 11.2, 4.4 Hz), 3.62 (3H, s), 3.78 (1H, d, J = 12.8 Hz), 3.79 (3H, s), 3.81 (2H, s), 4.95 (2H, ABq, J = 7.2 Hz), 6.71 (1H, d, J = 11.2 Hz), 6.86 (2H, d, J = 8.4 Hz), 7.20 (2H, d, J = 8.8 Hz); ^{13}C NMR ($CDCl_3$) δ 20.8 (CH_3), 21.3 (CH_3), 22.1 (CH_3), 23.1 (CH_3), 24.1 (CH), 26.8 (CH), 41.1 (CH_2), 55.3 (OCH_3), 58.1 (CH_2), 60.0 (OCH_3), 60.8 (CH), 100.7 (OCH_2O), 114.0 (2 × CH), 128.3, 130.6 (2 × CH), 132.7, 147.6 (CH), 159.4, 160.8, 170.78: FABMS *m*/*z* 427 (M + Na), 405 (M + H). Anal. Calcd for $C_{22}H_{32}N_2O_5$: C, 65.31; H, 7.97; N, 6.92. Found: C, 65.61; H, 7.65; N, 6.63. *E*-isomer **22a**: $[\alpha]^{25}_D$ +76° (*c* 0.25, CH_3OH); ^{1}H NMR ($CDCl_3$) δ 0.81 (3H, d, J = 6.4 Hz), 0.83 (3H, d, J = 6.4 Hz), 0.93 (3H, d, J = 6.4 Hz), 0.98 (3H, d, J = 6.4 Hz), 1.41 (1H, ddd, J = 14, 7.0, 7.0 Hz), 1.50 (1H, ddd, J = 14, 7.0, 7.0 Hz), 1.74 (1H, nonet, J = 6.4 Hz), 3.58 (1H, m), 3.63 (3H, s), 3.65 (1H, t, J = 8.0 Hz), 3.78 (1H, d, J = 12.8 Hz), 3.79 (3H, s), 4.00 (1H, d, J = 13.2 Hz), 5.00 (2H, ABq, J = 7.2 Hz), 5.44 (1H, d, J = 10 Hz), 6.84 (2H, d, J = 8.8 Hz), 7.15 (2H, d, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 22.2 (CH_3), 22.4 (CH_3), 22.7 (CH_3), 23.1 (CH_3), 24.3 (CH), 26.6 (CH), 38.3 (CH_2), 55.3 (OCH_3), 56.3 (CH_2), 58.2 (OCH_3), 60.2 (CH), 100.6 (OCH_2O), 113.9 (2 × CH), 128.2, 130.2 (2 × CH), 130.4, 143.6 (CH), 159.2, 160.3, 169.3; FABMS *m*/*z* 427 (M + Na), 405 (M + H).

Synthesis of 1-Methoxymethoxy-3*S*-isobutyl-4-*p*-methoxybenzyl-5-*Z*-benzylidenepiperazine-2,6-dione (21b). *R*-Hydroxy benzyl compound **18b** (1.42 g, 3.1 mmol) was reacted with methanesulfonyl chloride (2 equiv) under identical conditions as described above to give mesylate **20b**, which spontaneously produced *Z*-olefin **21b** (1.0 g, 73.3%) as a yellow gum: $[\alpha]^{25}_D$ +27.5° (*c* 0.16, MeOH); ^{1}H NMR ($CDCl_3$) δ 0.83 (3H, d, J = 6.6 Hz), 0.87 (3H, d, J = 6.6 Hz), 1.47 (1H, ddd, J = 14.1, 8.7, 5.1 Hz), 1.64 (1H, ddd, J = 13.8, 9.9, 5.4 Hz), 1.84 (1H, m), 3.60 (3H, s), 3.72 (1H, dd, J = 9.9, 5.1 Hz), 3.78 (3H, s), 3.95 (2H, ABq, J = 13.8 Hz), 4.80 (2H, ABq, J = 7.2 Hz), 6.83 (2H, d, J = 8.7 Hz), 7.12 (2H, d, J = 8.7 Hz), 7.44 (3H, m), 7.56 (1H, s), 7.96 (2H, dd, J = 8.7, 1.8 Hz); ^{13}C NMR ($CDCl_3$) δ 21.4 (CH_3), 23.0 (CH_3), 24.8 (CH), 42.7 (CH_2), 55.3 (OCH_3), 58.1 (CH), 59.0 (CH_2), 60.1 (OCH_3), 100.9 (OCH_2O), 114.2 (2 × CH), 127.7, 128.8 (2 × CH), 129.9 (CH), 130.5 (2 × CH), 130.9 (2 × CH), 131.1 (CH), 133.3, 133.8, 159.6, 161.3, 170.0; HRESI−FTMS calcd for $C_{25}H_{31}N_2O_5$ (M + H) 439.2227, found 439.2224.

Synthesis of 1-Methoxymethoxy-3*S*-isobutyl-4-*p*-methoxybenzyl-5-*Z*-*p*-methoxybenzylidenepiperazine-2,6-dione (21c). To a cooled (−23 °C) and stirred solution of the hydroxy compound **18c** (720 mg, 1.48 mmol) in methylene chloride (10 mL) were added DIPEA (0.52 mL, 2.96 mmol) and DMAP (361 mg, 2.96 mmol) followed by slow addition of methanesulfonyl chloride (0.23 mL, 2.96 mmol) via a syringe. The reaction mixture was stirred for 30 min at −23 °C followed by stirring at room temperature for 1 h. The mesylate (**20c**) formed in this reaction was short-lived and produced almost instantaneously the elimination product (**21c**). The mixture was poured on to EtOAc (200 mL) and was washed with water, 10% aqueous citric acid, water, aqueous $NaHCO_3$, and finally with water. The organic layer was dried over Na_2SO_4, evaporated under reduced pressure, and chromatographed over a silica gel column. Elution with 5−20% EtOAc in hexane afforded (528 mg, 76%) pure product **21c** as a yellow gum: $[\alpha]^{25}_D$ 0° (*c* 0.98, MeOH); ^{1}H NMR ($CDCl_3$) δ 0.80 (3H, d, J = 6.6 Hz), 0.84 (3H, d, J = 6.6 Hz), 1.43 (1H, ddd, J = 13.8, 9.0, 5.1 Hz), 1.62 (1H, ddd, J = 13.8, 10.2, 5.4 Hz), 1.81 (1H, m), 3.59 (3H, s), 3.70 (1H, dd, J = 10.2, 5.4 Hz), 3.78 (3H, s), 3.88 (3H, s), 3.93 (2H, ABq, J = 13.8 Hz), 4.80 (2H, ABq, J = 7.2 Hz), 6.84 (2H, d, J = 8.7 Hz), 6.98 (2H, d, J = 8.7 Hz), 7.15 (2H, d, J = 8.4 Hz), 7.54 (1H, s), 7.99 (2H, d, J = 9.0 Hz); ^{13}C NMR ($CDCl_3$) δ 21.3, 23.0, 24.8, 42.3, 55.3, 55.4, 58.0, 58.7, 60.0, 100.8, 114.2, 114.2, 126.5, 127.8, 130.7, 131.0, 132.1, 133.0, 159.6, 161.0, 161.6, 170.2; FABMS *m*/*z* 475 (M + Li); HRESI−FTMS calcd for $C_{26}H_{33}N_2O_6$ (M + H) 479.2333, found 469.2319. Anal. Calcd for $C_{26}H_{32}N_2O_6$: C, 66.65; H, 6.88; N, 5.98. Found: C, 66.65; H, 6.80; N, 5.92.

Synthesis of 1-Methoxymethoxy-3*S*-isobutyl-4-*p*-methoxybenzyl-5-*Z*-*p*-fluorobenzylidenepiperazine-2,6-dione (21d). An elimination reaction similar to the one just described from *R*-hydroxy *p*-fluorobenzyl compound **18d** (1.42 g, 3.1 mmol) via mesylate **20d** gave *Z*-olefin **21d** (1.05 g, 78%) as a yellow gum: $[\alpha]^{25}_D$ +12.3° (*c* 1.32, MeOH); ^{1}H NMR ($CDCl_3$) δ 0.82 (3H, d, J = 6.6 Hz), 0.85 (3H, d, J = 6.6 Hz), 1.45 (1H, ddd, J = 14.1, 8.7, 5.4 Hz), 1.61 (1H, ddd, J = 13.8, 9.6, 5.4 Hz), 1.77 (1H, m), 3.58 (3H, s), 3.71 (1H, dd, J = 9.6, 5.4 Hz), 3.77 (3H, s), 3.92 (2H, ABq, J = 13.8 Hz), 4.80 (2H, ABq, J = 7.2 Hz), 6.82 (2H, d, J = 8.7 Hz), 7.11 (2H, d, J = 8.7 Hz), 7.14 (2H, t, J = 8.4 Hz), 7.51 (1H, s), 7.98 (2H, dd, J = 8.7, 5.4 Hz); ^{13}C NMR ($CDCl_3$) δ 21.4, 22.9, 24.8, 42.5, 55.3, 58.1, 58.9, 60.1, 100.8, 114.2, 115.9 (d, J = 25.8 Hz), 127.5, 130.0 (d, J = 4.3 Hz), 130.2, 130.6 (2C), 133.0 (d, J = 9.8 Hz), 159.6, 161.3, 163.2 (d, J = 301.2 Hz), 169.9; HRESI−FTMS calcd for $C_{25}H_{30}FN_2O_5$ (M + H) 457.2133, found 457.2109. Anal. Calcd for $C_{25}H_{29}FN_2O_5 \cdot 0.5H_2O$: C, 64.51; H, 6.49; N, 6.01. Found: C, 64.29; H, 6.16; N, 5.95.

Synthesis of 1-Methoxymethoxy-3*S*-isobutyl-4-*p*-methoxybenzyl-5-*Z*-*m*-fluorobenzylidenepiperazine-2,6-dione (21e). Elimination reaction of hydroxy-*m*-fluorobenzyl

compound **18e** (0.75 g, 1.58 mmol) gave *Z*-olefin **21e** (0.53 g, 73.5%) as a yellow gum: $[\alpha]^{25}_D$ +44.8° (*c* 0.67, MeOH); ^{1}H NMR ($CDCl_3$) δ 0.84 (3H, d, J = 6.6 Hz), 0.88 (3H, d, J = 6.6 Hz), 1.47 (1H, ddd, J = 14.1, 8.7, 5.4 Hz), 1.62 (1H, ddd, J = 14.1, 9.9, 5.4 Hz), 1.81 (1H, m), 3.60 (3H, s), 3.73 (1H, dd, J = 9.9, 5.4 Hz), 3.77 (3H, s), 3.90 (1H, d, J = 13.5 Hz), 3.98 (1H, d, J = 13.5 Hz), 4.80 (2H, ABq, J = 7.2 Hz), 6.83 (2H, d, J = 8.7 Hz), 7.10 (1H, m), 7.11 (2H, d, J = 8.7 Hz), 7.41 (1H, dt, J = 8.1, 6.0 Hz), 7.49 (1H, s), 7.57 (1H, d, J = 7.5 Hz), 7.83 (1H, ddd, J = 10.5, 2.4, 1.5 Hz); ^{13}C NMR ($CDCl_3$) δ 21.4, 22.9, 24.9, 42.8, 55.3, 58.1, 59.2, 60.1, 100.9, 114.2, 116.7 (d, J = 27.4 Hz), 116.7 (d, J = 27.4 Hz), 127.1 (d, J = 3.3 Hz), 127.4, 129.24 (d, J = 3.4 Hz), 130.2 (d, J = 10 Hz), 130.3, 134.5, 135.8 (d, J = 9.9 Hz), 159.7, 161.0, 162.8 (d, J = 293.2 Hz), 169.7; HRESI−FTMS calcd for $C_{25}H_{30}FN_2O_5$ (M + H) 457.2133, found 457.2143. Anal. Calcd for $C_{25}H_{29}FN_2O_5 \cdot 0.5\ H_2O$: C, 64.51; H, 6.49; N, 6.01. Found: C, 64.91; H, 6.26; N, 6.08.

Synthesis of 1-Methoxymethoxy-3*S*-isobutyl-4-*p*-methoxybenzyl-5-*Z*-*o*-fluorobenzylidenepiperazine-2,6-dione (21f). Hydroxy-*o*-fluorobenzyl compound **18f** (0.42 g, 0.9 mmol) gave *Z*-olefin **21f** (0.4 g, 99%) as a yellow gum: $[\alpha]^{25}_D$ +11.5° (*c* 0.6, MeOH); ^{1}H NMR ($CDCl_3$) δ 0.84 (3H, d, J = 6.6 Hz), 0.89 (3H, d, J = 6.6 Hz), 1.49 (1H, ddd, J = 13.8, 8.4, 5.4 Hz), 1.65 (1H, ddd, J = 13.8, 9.6, 5.7 Hz), 1.81 (1H, m), 3.59 (3H, s), 3.72 (1H, dd, J = 9.6, 5.7 Hz), 3.77 (3H, s), 3.87 (1H, d, J = 13.8 Hz), 3.99 (1H, d, J = 13.8 Hz), 4.83 (2H, ABq, J = 7.2 Hz), 6.81 (2H, d, J = 8.7 Hz), 7.07 (2H, d, J = 8.7 Hz), 7.13 (1H, ddd, J = 10.2, 8.4, 1.2 Hz), 7.23 (1H, dt, J = 7.2, 0.9 Hz), 7.36 (1H, m), 7.71 (1H, s), 8.27 (1H, dt, J = 7.8, 1.8 Hz); ^{13}C NMR ($CDCl_3$) δ 21.6, 22.8, 24.8, 43.0, 55.3, 58.1, 59.0, 60.1, 100.8, 114.2, 115.9 (d, J = 26.4 Hz), 120.4 (d, J = 7.4 Hz), 122.2 (d, J = 13.8 Hz), 124.1 (d, J = 4.4 Hz), 127.7, 130.1 (d, J = 2.3 Hz), 130.3, 131.2 (d, J = 10.4 Hz), 134.8 (d, J = 1.9 Hz), 159.6, 160.7, 161.2 (d, J = 302.5 Hz), 169.6; HRESI−FTMS calcd for $C_{25}H_{30}FN_2O_5$ (M + H) 457.2133, found 457.2124. Anal. Calcd for $C_{25}H_{29}FN_2O_5 \cdot 0.25H_2O$: C, 65.78; H, 6.40; N, 6.14. Found: C, 65.41; H, 6.07; N, 6.02.

Synthesis of 1-Methoxymethoxy-3*S*-benzyl-4-*p*-methoxybenzyl-5-(2-methyl-*Z*- and *E*-prop-1-enyl)piperazine-2,6-dione (21g and 22b). Aldol condensation of MOM ether **17b** (2.7 g, 7 mmol) using 3 equiv of isobutyrlaldehyde after chromatography gave an inseparable ~2:1 mixture of *R*- and *S*-hydroxy compounds **18g** and **19g** (1.8 g, 56%) as a gum that was used for the elimination reaction without any further characterization: HRESI−FTMS calcd for $C_{25}H_{33}N_2O_6$ (M + H) 457.2333, found 457.2318. Anal. Calcd for $C_{25}H_{32}N_2O_6$: C, 65.77; H, 7.07; N, 6.14. Found: C, 65.44; H, 6.82; N, 5.93.

Mesylation of the mixture of the hydroxy compounds **18g** and **19g** (1.6 g, 3.5 mmol) gave corresponding mesylates that upon elimination reaction using DBU gave a 4:1 mixture of *Z* and *E* isomers, which were separated by chromatography on silica gel to give *Z*-isomer **21g** (810 mg, total two step yield of 57%) as a gum. *E*-isomer (**22b**) was not stable and was not characterized. **21g**: $[\alpha]^{25}_D$ −0.2° (*c* 1.55, MeOH); ^{1}H NMR ($CDCl_3$) δ 0.99 (3H, d, J = 6.9 Hz), 1.09 (3H, d, J = 6.6 Hz), 2.74 (1H, dd, J = 13.8, 10.8 Hz), 2.88 (1H, m), 2.98 (1H, dd, J = 13.8, 4.5 Hz), 3.63 (3H, s), 3.78 (3H, s), 3.78 (1H, dd, J = masked due to overlap), 3.80 (2H, ABq, J = 13.8 Hz), 4.96 (2H, ABq, J = 7.5 Hz), 6.72 (2H, d, J = 8.7 Hz), 6.73 (1H, d, J = 10.8 Hz), 6.88 (2H, d, J = 8.4 Hz), 7.01 (2H, m), 7.25 (3H, m); ^{13}C NMR ($CDCl_3$) δ 21.5, 22.2, 26.7, 38.8, 55.3, 58.2, 61.0, 63.2, 100.8, 114.0, 126.8, 128.0, 128.2, 129.2, 129.9, 132.7, 146.5, 159.3, 160.8, 169.6; HRESI−FTMS calcd for $C_{25}H_{31}N_2O5$ (M + H) 439.2227, found 439.2233. Anal. Calcd for $C_{25}H_{30}N_2O_5 \cdot 0.25\ H_2O$: C, 67.78; H, 6.88; N, 6.32. Found: C, 67.53; H, 6.77; N, 6.46.

Synthesis of 1-Methoxymethoxy-3*S*-benzyl-4-*p*-methoxybenzyl-5-*Z*-*p*-methoxybenzylidenepiperazine-2,6-dione (21h). This reaction was performed identical to other aromatic analogues, and the hydroxy compound **18h** (2.0 g, 3.85 mmol) was reacted with methanesulfonyl chloride to give directly after silica gel chromatography the *Z*-olefin **21h** (1.32 g, 68.4%) as a yellow gum: $[\alpha]^{25}_D$ + 77.3° (*c* 1, MeOH); ^{1}H NMR ($CDCl_3$) δ 2.83 (1H, dd, J = 14.1, 11.4 Hz), 3.12 (1H, dd, J = 13.8, 3.9 Hz), 3.61 (3H, s), 3.72 (1H, d, J = 13.8 Hz), 3.77 (3H, s), 3.83 (3H, s), 3.87 (1H, d, J = 14.1 Hz), 4.00 (1H, dd, J = 10.8, 3.9 Hz), 4.83 (2H, ABq, J = 7.2 Hz), 6.77 (2H, d, J = 8.7 Hz), 6.78 (2H, d, J = 9.0 Hz), 6.93 (2H, d, J = 8.7 Hz), 7.03 (1H, dd, J = 7.5, 1.2 Hz), 7.18−7.24 (5H, m), 7.54 (1H, s), 7.59 (2H, d, J = 8.7 Hz); ^{13}C NMR ($CDCl_3$) δ 39.5, 55.3, 55.4, 58.1, 58.6, 63.5, 100.9, 113.9, 114.1, 126.1, 126.9, 127.7, 128.5, 129.5, 130.2, 130.3, 131.7, 133.4, 136.7, 159.5, 160.9, 161.5, 169.3; HRESI−FTMS calcd for $C_{29}H_{31}N_2O_6$ (M + H) 503.2176, found 503.2158. Anal. Calcd for $C_{29}H_{30}N_2O_6 \cdot 0.8\ H_2O$: C, 67.38; H, 6.16; N, 5.41. Found: C, 67.42; H, 5.84; N, 5.60.

Synthesis of 1-Methoxymethoxy-3*S*-benzyl-4-*p*-methoxybenzyl-5-*Z*-*p*-fluorobenzylidenepiperazine-2,6-dione (21i). In an identical reaction condition starting with hydroxy compound **18i** (1.2 g, 2.36 mmol), the elimination reaction gave product **21i** as a yellow powder (0.81 g, 70.7%): $[\alpha]^{25}_D$ + 10.7° (*c* 0.48, MeOH−CH_2Cl_2, 1:1); ^{1}H NMR ($CDCl_3$) δ 2.83 (1H, dd, J = 14.7, 10.8 Hz), 3.17 (1H, dd, J = 14.1, 4.2 Hz), 3.61 (3H, s), 3.70 (1H, d, J = 14.1 Hz), 3.86 (1H, d, J = 14.4 Hz), 4.05 (1H, dd, J = 11.4, 4.2 Hz), 4.84 (2H, ABq, J = 6.9 Hz), 6.78 (2H, d, J = 8.7 Hz), 6.92 (2H, d, J = 8.7 Hz), 6.93 (2H, t, J = 9 Hz), 7.05 (1H, dd, J = 8.1, 1.2 Hz), 7.20−7.33 (3H, m), 7.49 (1H, s), 7.55 (2H, dd, J = 9.9, 5.7 Hz), 7.63 (1H, dd, J = 7.5, 1.5 Hz); HRESI−FTMS calcd for $C_{28}H_{27}FN_2O_5$ (M + H) 491.1977, found 491.1963. Anal: Calcd for $C_{28}H_{27}FN_2O_5 \cdot H_2O$: C, 66.13; H, 5.74; N, 5.50. Found: C, 65.82; H, 5.64; N, 5.65.

Synthesis of 1-Methoxymethoxy-3-isobutyl-5-(2-methyl-*Z*-prop-1-enyl)-3*H*-pyrazine-2,6-dione (23a). To a solution of *N*-*p*-methoxybenzyl compound **21a** (96 mg, 0.24 mmol) in methylene chloride (5 mL) were added water (2.5 mL) and DDQ (197 mg, 0.84 mmol, 3.5×), and the reaction mixture was stirred at room temperature overnight. The reaction mixture was filtered through a small bed of silica gel and Celite and eluted with 50% EtOAc−hexane. The product mixture was rechromatographed over a small silica gel column and eluted with 5% EtOAc−hexane to give 20 mg (30%) chromatographically homogeneous imine product **23a** as an oil: ^{1}H NMR ($CDCl_3$) δ 0.99 (3H, d, J = 6.8 Hz), 1.13 (3H, d, J = 6.4 Hz), 2.19 (1H, heptet, J = 6.4 Hz), 2.64 (1H, d, J = 6.8 Hz), 3.54 (1H, m), 3.66 (3H, s), 5.08 (2H, s), 7.13 (1H, d, J = 10.4 Hz); ^{13}C NMR ($CDCl_3$) δ 21.9, 22.6, 26.4, 27.4, 41.8, 58.4, 100.7, 133.9, 155.3, 157.5, 158.4, 159.8; FABMS *m*/*z* 283 (M + H). Anal. Calcd for $C_{14}H_{22}N_2O_4$: C, 59.56; H, 7.85; N, 9.92. Found: C, 59.62; H, 7.48; N, 9.60.

Scale-up Reaction. *N*-*p*-Methoxybenzyl compound **21a** (1.5 g, 3.7 mmol) in methylene chloride (40 mL), water (20 mL), and DDQ (2.1 g, 2.5 equiv) was reacted under similar conditions to give 200 mg (20%) of the product **23a**. In this reaction, the isobutylaldehyde was also present in significant quantities (NMR).

Synthesis of 1-Methoxymethoxy-3-isobutyl-5-*Z*-benzylidene-3*H*-pyrazine-2,6-dione (23b). To a solution of the PMB derivative **21b** (800 mg, 1.83 mmol) in methylene chloride (10 mL) and water (2 mL) was added DDQ (1.66 g, 4 eq) and the mixture stirred overnight. The reaction mixture was filtered, diluted with 300 mL of methylene chloride, washed with water, 10% aqueous $NaHCO_3$, and water, dried (Na_2SO_4), evaporated under reduced pressure, and chromatographed over a silica gel column. Elution with 10% EtOAc in hexane yielded 128 mg (22.2%) of product **23b** as a yellow powder. ^{1}H NMR spectrum of crude reaction mixture indicated the presence of a significant amount of benzaldehyde, which was confirmed by co-TLC. **23b**: mp 90−92 °C; ^{1}H NMR ($CDCl_3$) δ 1.04 (6H, d, J = 6.6 Hz), 2.28 (1H, nonet, J = 6.6 Hz), 2.75 (2H, d, J = 6.9 Hz), 3.69 (3H, s), 5.13 (2H, s), 7.47 (3H, m), 7.83 (1H, s), 8.20 (2H, m); ^{13}C NMR ($CDCl_3$) δ 22.6, 26.5, 42.1, 58.5, 100.7, 128.8, 132.0, 133.0, 133.7, 134.1, 142.8, 155.0, 158.3, 160.5; HRESI−FTMS calcd for $C_{17}H_{21}N_2O_4$ (M + H) 317.1496, found 317.1495. Anal. Calcd for $C_{17}H_{20}N_2O_4$: C, 64.54; H, 6.37; N, 8.85. Found: C, 64.57; H, 6.32; N, 8.53.

Synthesis of 1-Methoxymethoxy-3-isobutyl-5-*Z*-*p*-methoxybenzylidene- 3*H*-pyrazine-2,6-dione (23c). PMB derivative **21c** (235 mg) was reacted in methylene chloride (10 mL) and water (5 mL) with 3 equiv of DDQ under identical conditions overnight. The reaction mixture was filtered, diluted

with 200 mL of methylene chloride, washed with water, 10% aqueous $NaHCO_3$, and water, dried (Na_2SO_4), evaporated under reduced pressure, and chromatographed over a silica gel column. Elution with 10% EtOAc in hexane yielded 45 mg (26%) of required product **23c** as a yellow solid and 5 mg of product **24** as a gum. **23c**: ^{1}H NMR ($CDCl_3$) δ 1.04 (6H, d, J = 6.9 Hz), 2.26 (1H, nonet, J = 6.9 Hz), 2.73 (2H, d, J = 6.9 Hz), 3.68 (3H, s), 3.88 (3H, s), 5.12 (2H, s), 6.96 (2H, d, J = 9.0 Hz), 7.78 (1H, s), 8.20 (2H, d, J = 8.4 Hz); FABMS m/z 353 (M + Li); HRESI−FTMS calcd for $C_{18}H_{22}N_2O_5$ (M + H) 347.1601, found 347.1603. **24**: ^{1}H NMR ($CDCl_3$) δ 0.95 (6H, d, J = 6.9 Hz), 2.18 (1H, nonet, J = 6.6 Hz), 2.82 (2H, d, J = 6.6 Hz), 3.80 (3H, s), 4.40 (2H, d, J = 5.7 Hz), 6.87 (2H, d, J = 8.7 Hz), 7.21 (2H, d, J = 8.4 Hz); FABMS m/z 250 [M + H].

Synthesis of 1-Methoxymethoxy-3-isobutyl-5-*Z*-*p*-fluorobenzylidene-3*H*-pyrazine-2,6-dione (23d). Oxidation of PMB derivative **21d** (700 mg, 1.5 mmol) in methylene chloride (10 mL) and water (2 mL) with DDQ (1.60 g, 4 equiv) overnight followed by filtration through silica gel and Celite and washing of the methylene chloride solution with aqueous sodium bicarbonate and crystallization of the residue from acetone−hexane afforded (180 mg, 35.1%) desired product **23d** as yellow needles: mp 138−140 °C; ^{1}H NMR ($CDCl_3$) δ 1.04 (6H, d, J = 6.6 Hz), 2.26 (1H, nonet, J = 6.9 Hz), 2.75 (2H, d, J = 6.9 Hz), 3.69 (3H, s), 5.13 (2H, s), 7.15 (2H, t, J = 8.7 Hz), 7.78 (1H, s), 8.23 (2H, dd, J = 8.7, 5.7 Hz); ^{13}C NMR ($CDCl_3$) δ 22.6, 26.5, 42.1, 58.5, 100.7, 116.2 (d, J = 25.9 Hz), 130.1 (d, J = 3.9 Hz), 132.5 (d, J = 3.2 Hz), 136.3 (d, J = 10.6 Hz), 141.3 (d, J = 1.7 Hz), 154.9, 158.4 (d, J = 1.7 Hz), 160.5, 164.8 (d, J = 306.1 Hz); HRESI−FTMS calcd for $C_{17}H_{20}N_2O_4F$ (M + H) 335.1401, found 335.1402. Anal. Calcd for $C_{17}H_{19}FN_2O_4$: C, 61.07; H, 5.73; N, 8.38. Found: C, 60.84; H, 5.77; N, 8.30.

Synthesis of 1-Methoxymethoxy-3-isobutyl-5-*Z*-*m*-fluorobenzylidene-3*H*-pyrazine-2,6-dione (23e). A similar oxidation of PMB derivative **21e** (475 mg, 1.08 mmol) with 4 equiv of DDQ and crystallization of the residue from methylene chloride−hexane followed by acetone−hexane yielded (125 mg, 36%) desired product **23e** as pale rosettes: mp 98−102 °C; ^{1}H NMR ($CDCl_3$) δ 1.04 (6H, d, J = 6.9 Hz), 2.28 (1H, nonet, J = 6.6 Hz), 2.76 (2H, d, J = 6.9 Hz), 3.68 (3H, s), 5.12 (2H, s), 7.17 (1H, m), 7.40 (1H, dt, J = 8.1, 6.0 Hz), 7.71 (1H, brd, J = ~6.0 Hz), 7.75 (1H, s), 8.16 (1H, brd, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 22.6, 26.4, 42.2, 58.5, 100.7, 118.9 (d, J = 25.9 Hz), 119.7 (d, J = 27.8 Hz), 130.1 (d, J = 9.6 Hz), 133.7, 125.4 (d, J = 10.3 Hz), 140.8 (d, J = 3.7 Hz), 154.8, 159.2, 160.3, 162.6 (d, J = 193.9 Hz); HRESI−FTMS calcd for $C_{17}H_{20}FN_2O_4$ (M + H) 335.1401, found 335.1399. Anal. Calcd for $C_{17}H_{19}FN_2O_4$: C, 61.07; H, 5.73; N, 8.38. Found: C, 60.76; H, 5.48; N, 8.20.

Synthesis of 1-Methoxymethoxy-3-isobutyl-5-*Z*-*o*-fluorobenzylidene-3*H*-pyrazine-2,6-dione (23f). A similar oxidation of PMB derivative **21f** (360 mg, 0.82 mmol) with DDQ (0.75 g, 4 equiv) overnight and crystallization of the residue from methylene chloride−hexane followed by acetone-hexane furnished (50 mg, 19%) desired product **23f** as fine pale needles: mp 86−90 °C; ^{1}H NMR ($CDCl_3$) δ 1.04 (6H, d, J = 6.6 Hz), 2.26 (1H, nonet, J = 6.9 Hz), 2.75 (2H, d, J = 7.2 Hz), 3.69 (3H, s), 5.13 (2H, s), 7.14 (1H, ddd, J = 9.5, 8.4, 1.2 Hz), 7.23 (1H, t, J = 7.2 Hz), 7.46 (1H, m), 8.16 (1H, s), 7.73 (1H, dt, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$) δ 22.6, 26.5, 42.2, 58.5, 100.7, 115.7 (d, J = 26.6 Hz), 121.9 (d, J = 11.6 Hz), 124.5 (d, J = 4.3 Hz), 133.3 (d, J = 9.3 Hz), 133.7 (d, J = 11.1 Hz), 133.8 (d, J = 2.2 Hz), 134.0, 154.9, 159.1, 160.1, 162.7 (d, J = 307.3 Hz); HRESI−FTMS calcd for $C_{17}H_{20}FN_2O_4$ (M + H) 335.1401, found 335.1409. Anal. Calcd for $C_{17}H_{19}FN_2O_4$: C, 61.07; H, 5.73; N, 8.38. Found: C, 61.10; H, 5.61; N, 8.13.

Synthesis of 1-Methoxymethoxy-3-benzyl-5-(2-methyl-*Z*-prop-1-enyl)-3*H*-pyrazine-2,6-dione (23g). DDQ oxidation of *Z*-olefin **21g** (660 mg) and purification on silica gel gave the desired imine **23g** (40 mg) as an oil and 65 mg of diketoamide **25** as a semisolid. **23g**: ^{1}H NMR ($CDCl_3$) δ 1.12 (6H, d, J = 6.9 Hz), 3.50 (1H, m), 3.64 (3H, s), 4.06 (2H, s), 5.06 (2H, s), 7.15 (1H, d, J = 9.9 Hz), 7.24−7.36 (5H, m); ^{13}C NMR ($CDCl_3$) δ 21.8, 27.5, 39.8, 58.4, 100.6, 126.9, 128.5, 129.5, 134.0, 135.7, 155.0, 156.4, 159.3, 159.7; HRESI−FTMS calcd for $C_{17}H_{21}N_2O_4$ (M + H) 317.1495, found 317.1483. Anal. Calcd for $C_{17}H_{20}N_2O_4 \cdot 0.5\ H_2O$: C, 62.76; H, 6.50; N, 8.61. Found: C, 62.67; H, 6.10; N, 8.43. **25**: ^{1}H NMR ($CDCl_3$) δ 3.79 (3H, s), 4.24 (2H, s), 4.39 (2H, d, J = 6.0 Hz), 6.86 (2H, d, J = 8.7 Hz), 7.18 (2H, d, J = 8.7 Hz), 7.24−7.34 (5H, m); ^{13}C NMR ($CDCl_3$) δ 43.1, 43.2, 55.3, 114.3, 127.3, 128.7, 128.9, 129.4, 129.9, 132.7, 159.3, 159.8, 196.0.

Synthesis of 1-Methoxymethoxy-3-benzyl-5-*Z*-*p*-methoxybenzylidene-3*H*-pyrazine-2,6-dione (23h). DDQ oxidation of 1.1 g of the PMB derivative (**21h**) under the conditions described above and crystallization from acetone−hexane gave (400 mg, 48%) of desired product **23h** as a yellow granular solid: mp 160−162 °C; ^{1}H NMR ($CDCl_3$) δ 3.70 (3H, s), 3.86 (3H, s), 4.18 (2H, s), 5.14 (2H, s), 6.79 (2H, d, J = 9.0 Hz), 7.34 (5H, m), 7.72 (1H, s), 7.86 (2H, d, J = 9.0 Hz); ^{13}C NMR ($CDCl_3$) δ 39.8, 55.5, 58.5, 100.7, 114.4, 126.7, 126.8, 128.6, 130.1, 131.0, 136.0, 136.8, 143.5, 155.0, 155.8, 160.5; HRESI−FTMS calcd for $C_{21}H_{21}N_2O_5$ (M + H) 381.1445, found 381.1446. Anal. Calcd for $C_{21}H_{20}N_2O_5 \cdot 0.5H_2O$: C, 64.77; H, 5.43; N, 7.19. Found: C, 65.02; H, 5.18; N, 7.20.

Synthesis of 1-Methoxymethoxy-3-benzyl-5-*Z*-*p*-fluorobenzylidene-3*H*-pyrazine-2,6-dione (23i). DDQ oxidation of protected compound **21i** (0.70 g, 1.43 mmol) followed by trituration by acetone-hexane gave imine product **23i** (150 mg, 28.5%) as a yellow powder: mp 142−144 °C; ^{1}H NMR ($CDCl_3$) δ 3.69 (3H, s), 4.20 (2H, s), 5.13 (2H, s), 6.94 (2H, t, J = 9.0 Hz), 7.27−7.43 (5H, m), 7.70 (1H, s), 7.85 (2H, dd, J = 9,0, 5.7 Hz); HRESI−FTMS calcd for $C_{20}H_{18}FN_2O_4$ (M + H) 369.1245, found 369.1242. Anal. Calcd for $C_{20}H_{17}FN_2O_4$: C, 65.21; H, 4.65; N, 7.60. Found: C, 64.97; H, 4.57; N, 7.48.

DDQ Oxidation of *E*-Isomer 22a. DDQ (202 mg, 3 equiv) was added to a biphasic mixture of *p*-methoxybenzyl derivative **22a** (120 mg, 0.30 mmol) at 0 °C in methylene chloride (5 mL) and water (2.5 mL). After being stirred at 0 °C for 20 min, the starting compound was consumed in favor of two major products. The crude reaction mixture was filtered through a small bed of Celite and silica gel and then purified by preparative TLC developing in hexanes−EtOAc (4:1). Three major bands were eluted to give 6 mg of **24** and 15 mg each of compounds **26** and **27** all as gum. **26**: ^{1}H NMR ($CDCl_3$) δ 0.84 (6H, d, J = 6.3 Hz), 2.64 (1H, m), 3.70 (3H, s), 3.79 (3H, s), 4.90 (2H, s), 5.11 (2H, s), 5.73 (1H, d, J = 11.4 Hz), 6.88 (2H, d, J = 8.7 Hz), 7.07 (2H, d, J = 8.7 Hz); ^{13}C NMR ($CDCl_3$) δ 22.8, 26.2, 44.9, 55.3, 57.9, 101.1, 114.3, 123.6, 124.6, 127.2, 127.8, 151.7, 159.1; FABMS m/z 357 [M + Na]; HRESI−FTMS calcd for $C_{17}H_{23}N_2O_5$ (M + H) 335.1601, found 335.1594. **27**: ^{1}H NMR ($CDCl_3$) δ 0.97 (6H, d, J = 6.6 Hz), 3.66 (1H, m), 3.70 (3H, s), 3.80 (3H, s), 4.68 (2H, s), 5.09 (2H, s), 5.28 (1H, d, J = 10.2 Hz), 6.87 (2H, d, J = 8.7 Hz), 7.16 (2H, d J = 8.7 Hz); ^{13}C NMR ($CDCl_3$) δ 22.9, 25.4, 43.1, 55.3, 57.8, 101.2, 114.2, 124.2, 127.1, 128.5, 129.1, 150.3, 158.2, 159.2; FABMS m/z 357 [M + Na]; HRESI−FTMS calcd for $C_{17}H_{23}N_2O_5$ (M + H) 335.1601, found 335.1594.

Synthesis of 1-Hydroxy-3-isobutyl-5-(2-methyl-*Z*-prop-1-enyl)-3*H*-pyrazine-2,6-dione (Flutimide, 1a). To a cooled (0 °C) solution of MOM ether **23a** (6 mg, 0.025 mmol) in anhydrous methylene chloride (1 mL) was added TFA (0.3 mL), and the solution was stirred under nitrogen for 30 min followed by at room temperature for 5 h. The progress of the reaction was monitored by TLC (hexanes−EtOAc, 7:3) and reversed-phase HPLC (Zorbax RX C-8, 4.6 × 250 mm, 50% aqueous CH_3CN +0.1%TFA at 40 °C at a flow rate of 1 mL/min). After completion of the reaction the volatile materials were evaporated under stream of nitrogen which gave almost pure (NMR and HPLC) product. The product was purified on a same analytical HPLC column to give pure product **1a** (2 mg) as a gum which was identical[6a] with the natural products in all respect (UV, NMR, and HPLC).

In a similar reaction 190 mg of the MOM ether **23a** was deprotected and purified on a Zorbax RX C-8 (22 × 250 mm) column and eluted with 50% aqueous CH_3CN containing 0.1% TFA at a flow rate of 8 mL/min to give the clean *N*-hydroxy product (20 mg, 12.5%). It was difficult to improve the yield due to hydrolysis of imine bond and other enamine reactions in larger scale preparations.

Synthesis of 1-hydroxy-3-isobutyl-5-*Z*-benzylidene-3*H*-pyrazine-2,6-dione (1b). To a cooled (0 °C) solution of MOM ether **23b** (35 mg) in methylene chloride (2.0 mL) was added TFA (0.5 mL), and the solution was stirred for 30 min under nitrogen followed by 5 h at room temperature. Solvents were removed under a stream of nitrogen and then dried under vacuum overnight. The residue was crystallized from methylene chloride−hexane to give the *N*-hydroxy compound **1b** (25 mg, 83.3%) as a yellow powder: mp 138−140 °C; ^{1}H NMR ($CDCl_3$) δ 1.05 (6H, d, J = 6.6 Hz), 2.31 (1H, nonet J = 6.6 Hz), 2.79 (2H, d, J = 7.2 Hz), 7.48 (3H, m), 7.90 (1H, s), 8.23 (2H, dd, J = 8.1, 1.8 Hz); ^{13}C NMR ($CDCl_3$) δ 22.6, 26.5, 42.1, 129.0, 131.6, 132.5, 133.5, 134.5, 144.2, 152.1, 157.4, 159.2; HRESI−FTMS calcd for $C_{15}H_{17}N_2O_3$ (M + H) 273.1233, found 273.1244. Compound **1b** was also produced upon deprotection of **23g**.

Synthesis of 1-Hydroxy-3-isobutyl-5-*Z*-*p*-methoxybenzylidene-3*H*-pyrazine-2,6-dione (1c). TFA (0.3 mL) was added to a cooled (0 °C) solution of MOM ether **23c** (25 mg) in methylene chloride (1.0 mL), and the solution was stirred for 30 min under nitrogen followed by overnight at room temperature. The solvents were removed under a stream of nitrogen, and the residue was triturated with CH_3CN and filtered to give 5 mg of product **1c** as a yellow solid. The filtrate was chromatographed on a Zorbax RX C-8 (9.4 × 250 mm) column and eluted with 50% aqueous CH_3CN at a flow rate of 4 mL/min to give additional 4 mg of the product (total yield 41%): mp 152−156 °C; ^{1}H NMR ($CDCl_3$) δ 1.05 (6H, d, J = 6.6 Hz), 2.30 (1H, nonet, J = 6.6 Hz), 2.77 (2H, d, J = 7.2 Hz), 3.91 (3H, s), 6.99 (2H, d, J = 9.3 Hz), 7.86 (1H, s), 8.27 (2H, d, J = 8.7 Hz); FABMS m/z 315 (M + 2Li − H); HRESI−FTMS calcd for $C_{16}H_{19}N_2O_4$ (M + H) 303.1339, found 303.1350.

Synthesis of 1-Hydroxy-3-isobutyl-5-*Z*-*p*-fluorobenzylidene-3*H*-pyrazine-2,6-dione (1d). MOM ether **23d** (60 mg) was deprotected with TFA and crystallized from methylene chloride-hexane to afford the *N*-hydroxy compound **1d** (45 mg, 86.5%) as a yellow needles: mp 168−170 °C; ^{1}H NMR ($CDCl_3$) δ 1.04 (6H, d, J = 6.6 Hz), 2.28 (1H, nonet, J = 6.9 Hz), 2.78 (2H, d, J = 6.9 Hz), 7.26 (2H, t, J = 9.0 Hz), 7.85 (1H, s), 8.27 (2H, dd, J = 9.0, 5.7 Hz); ^{13}C NMR ($CDCl_3$) δ 22.6, 26.5, 42.1, 116.4 (d, J = 26.1 Hz), 129.9 (d, J = 3.9 Hz), 131.2 (d, J = 3.2 Hz), 136.8 (d, J = 10.9 Hz), 142.5, 152.3, 157.6 (d, J = 1.6 Hz), 159.3, 165.1 (d, J = 307 Hz); HRESI−FTMS calcd for $C_{15}H_{16}FN_2O_3$ (M + H) 291.1140, found 291.1147. Anal. Calcd for $C_{15}H_{15}FN_2O_3$: C, 62.06; H, 5.21; N, 9.65. Found: C, 61.86; H, 4.99; N, 9.34.

Synthesis of 1-Hydroxy-3-isobutyl-5-*Z*-*m*-fluorobenzylidene-3*H*-pyrazine-2,6-dione (1e). MOM ether **23e** (60 mg) was deprotected with TFA and crystallized from acetone−hexane to provide the *N*-hydroxy compound **1e** (35 mg, 67.2%) as yellow needles: mp 133−137 °C; ^{1}H NMR ($CDCl_3$) δ 1.05 (6H, d, J = 6.9 Hz), 2.30 (1H, nonet, J = 6.9 Hz), 2.78 (2H, d, J = 7.2 Hz), 7.21 (1H, ddt, J = 8.4, 2.7, 1.2 Hz), 7.43 (1H, dt, J = 8.1, 6.0 Hz), 7.77 (1H, d, J = 7.8 Hz), 7.82 (1H, s), 8.18 (1H, dt, J = 10.5, 2.2, 2.0 Hz); HRESI−FTMS calcd for $C_{15}H_{16}FN_2O_3$ (M + H) 291.1140, found 291.1144. Anal. Calcd for $C_{15}H_{15}FN_2O_3 \cdot 0.10\ H_2O$: C, 61.68; H, 5.24; N, 9.59. Found: C, 61.46; H, 4.84; N, 9.56.

Synthesis of 1-Hydroxy-3-isobutyl-5-*Z*-*o*-fluorobenzylidene-3*H*-pyrazine-2,6-dione (1f). MOM ether **23f** (20 mg) was similarly deprotected with TFA and crystallized from acetone−hexane to furnish the *N*-hydroxy compound **1f** (10 mg, 57.6%) as yellow needles: mp 126−130 °C; ^{1}H NMR ($CDCl_3$) δ 1.04 (6H, d, J = 6.6 Hz), 2.30 (1H, nonet, J = 6.9 Hz), 2.79 (2H, d, J = 7.2 Hz), 7.16 (1H, ddd, J = 9.5, 8.4, 1.2 Hz), 7.25 (1H, t, J = 5.1 Hz), 7.50 (1H, m), 8.24 (1H, s), 8.78 (1H, dt, J = 7.8, 1.8 Hz); HRESI−FTMS calcd for $C_{15}H_{16}FN_2O_3$ (M + H) 291.1140, found 291.1146.

Synthesis of 1-Hydroxy-3-benzyl-5-*Z*-*p*-methoxybenzylidene-3*H*-pyrazine-2,6-dione (2a). Deprotection of the MOM group from MOM ether **23h** (60 mg) with TFA followed by preparative HPLC on a Zorbax RX C-8 (22 × 250 mm) column and elution with 50% aqueous CH_3CN at a flow rate of 10 mL/min gave 15 mg (25%) of pure product **2a** as a yellow powder: mp 150−152 °C; ^{1}H NMR ($CDCl_3$) δ 3.89 (3H, s), 4.12 (2H, s), 6.83 (2H, d, J = 9.3 Hz), 7.36 (5H, m), 7.81 (1H, s), 7.95 (2H, d, J = 9.0 Hz); HRESI−FTMS calcd for $C_{19}H_{17}N_2O_4$ (M + H) 337.1183, found 337.1189.

Synthesis of 1-Hydroxy-3-benzyl-5-*Z*-*p*-fluorobenzylidene-3*H*-pyrazine-2,6-dione (2b) and 1-Hydroxy-3-*p*-fluorobenzyl-5-*Z*-benzylidene-3*H*-pyrazine-2,6-dione (3). Deprotection of the MOM ether **23i** (50 mg) under the conditions described above gave two isomeric products **2b** and **3**. After completion of the reaction, the products were purified by reversed-phase HPLC on a Zorbax RX C-8 (45% aqueous CH_3CN containing 0.1% TFA at a flow rate of 1 mL/min). The fractions were quickly lyophilized to give 4 mg of product **3** (t_R = 13.7 min) and 4 mg of product **2a** (t_R = 14.7 min) as amorphous solids. **2a**: mp 138−142 °C; ^{1}H NMR ($CDCl_3$) δ 4.23 (2H, s), 6.98 (2H, t, J = 8.8 Hz), 7.32−7.40 (5 Hz, m), 7.79 (1H, s), 7.93 (2H, dd, J = 8.8, 5.6 Hz); CIMS m/z 325 [M + H]; HRESI−FTMS calcd for $C_{18}H_{14}FN_2O_3$ (M + H) 325.0983 found 325.0991. **3**: mp 125−129 °C; ^{1}H NMR ($CDCl_3$) δ 4.20 (2H, s), 7.07 (2H, t, J = 8.8 Hz), 7.31 (2H, dd, J = 8.4, 5.2 Hz), 7.36 (2H, t, J = 7.6 Hz), 7.48 (1H, dd, J = 7.6, 1.2 Hz), 7.86 (1H, s), 7.94 (2H, dd, J = 7.6, 1.2 Hz); CIMS m/z 325 [M + H]; HRESI−FTMS calcd for $C_{18}H_{14}FN_2O_3$ (M + H) 325.0983 found 325.0988.

Synthesis of 1-Hydroxy-3-isobutyl-5-*p*-fluorobenzylpiperazine-2,6-dione (28). To a solution of imine **23d** (6.6 mg) in EtOAc (1 mL) and methanol (0.2 mL) was added 10% Pd/C (5 mg), and the mixture was evacuated and flushed with hydrogen. The evacuation and flush cycle was repeated three times and was finally connected to a balloon filled with hydrogen. The starting material was consumed within 20 min (HPLC, Zorbax RX C-8, 50% aqueous CH_3CN, 1 mL per min) and a single product was formed. Catalyst was removed by filtration and solvents were evaporated under reduced pressure to give a gum, which was triturated with methylene chloride−hexane to give a colorless solid (6.1 mg) of **28**: mp 104−108 °C; ^{1}H NMR ($CDCl_3$) δ 0.86 (3H, d, J = 6.3 Hz), 0.91 (3H, d, J = 6.6 Hz), 1.46 (1H, ddd, J = 14.1, 9.0, 5.1 Hz), 1.74 (1H, m), 1.96 (1H, ddd, J = 13.5, 9.3, 2.6 Hz), 3.15 (1H, dd, J = 14.4, 7.5 Hz), 3.36 (1H, dd, J = 14.4, 4.2 Hz), 3.57 (1H, dd, J = 9.0, 3.6 Hz), 3.82 (1H, dd, J = 7.2, 4.5 Hz), 7.02 (2H, t, J = 8.7 Hz), 7.23 (2H, dd, J = 8.7, 5.7 Hz), ^{13}C NMR ($CDCl_3$) δ 21.4, 23.1, 24.6, 35.4, 39.3, 57.3, 59.7, 115.8 (d, J = 25.3 Hz), 131.1 (d, J = 10 Hz), 131.6 (d, J = 3.5 Hz), 162.1 (d, J = 294.3 Hz), 167.5, 169.0; ESIMS m/z 295 [M + H], 589 (2M + H]; HRESI−FTMS calcd for $C_{15}H_{20}FN_2O_3$ (M + H) 295.1452 found 295.1455.

Synthesis of 3*S*-Isobutyl-4-*p*-methoxybenzyl-5*S*-[(*p*-fluorophenyl)-1*R*-hydroxymethyl]piperazine-2,6-dione (30). To a cooled (0 °C) solution of **18d** (600 mg) in a mixture of methanol (8 mL) and water (1.5 mL) were added concentrated sulfuric acid (0.3 mL) and concentrated hydrochloric acid (0.3 mL), and the solution was stirred at room temperature for 96 h. The progress of the reaction was monitored on an analytical HPLC using a Zorbax RX C-8 column and 50% aqueous CH_3CN containing 0.1% TFA. After the formation of *N*-hydroxy compound was maximized, a small aliquot was extracted with EtOAc, washed with water, dried over Na_2SO_4, and chromatographed over a Zorbax RX C-8 HPLC column. Elution with a 40−50% aqueous CH_3CN (0.1% TFA) gradient at a flow rate of 10 mL per min eluted **29** between 42 and 43 min which upon lyophilization gave pure **29** as a amorphous powder: mp 66−70 °C; ^{1}H NMR ($CDCl_3$) δ 0.47 (3H, d, J = 6.0 Hz), 0.85 (3H, d, J = 6.3 Hz), 1.50 (2H, m), 1.75 (1H, m), 3.20 (1H, d, J = 12.9 Hz), 3.64 (1H, dd, J = 10.2, 4.5 Hz), 3.70 (3H, s), 3.86 (1H, d, J = 12.9 Hz), 4.10 (1H, d, J = 7.5 Hz), 5.28 (1H, d, J = 7.8 Hz), 6.65 (2H, d, J = 8.7 Hz), 6.72 (2H, d, J = 8.7 Hz), 7.10 (2H, t, J = 8.7 Hz), 7.33 (2H, dd, J = 8.7, 5.4 Hz); ESIMS m/z 431 [M + H], 861 [2M + H]; HRESI−FTMS calcd for $C_{23}H_{28}FN_2O_5$ (M + H) 431.1977, found 431.1977.

Titanium trichloride (460 mg) was added, and the remainder of the reaction was stirred for an additional 16 h. Aqueous $NaHCO_3$ was added to the reaction mixture, and the product was extracted with EtOAc, which was washed with water, dried over Na_2SO_4, evaporated under reduced pressure, and chromatographed on a silica gel column and eluted with 30−

40% EtOAc in hexane to give pure **30** (150 mg) as an amorphous powder: mp 58−60 °C; ^{1}H NMR ($CDCl_3$) δ 0.43 (3H, d, J = 6.0 Hz), 0.83 (3H, d, J = 6.0 Hz), 1.42 (2H, m), 1.70 (1H, m), 3.18 (1H, d, J = 12.9 Hz), 3.40 (1H, dd, J = 10.8, 4.2 Hz), 3.76 (3H, s), 3.85 (1H, d, J = 12.9 Hz), 3.94 (1H, d, J = 8.1 Hz), 5.23 (1H, d, J = 8.1 Hz), 6.65 (2H, d, J = 9.0 Hz), 6.72 (2H, d, J = 8.7 Hz), 7.10 (2H, t, J = 8.7 Hz), 7.35 (2H, dd, J = 8.7, 5.4 Hz), 8.19 (1H, brs, NH); ^{13}C NMR ($CDCl_3$) δ 20.8, 23.2, 23.8, 37.0, 52.3, 55.3, 58.8, 62.5, 72.0, 113.9, 115.4 (d, J = 25.7 Hz), 127.8, 129.3 (d, J = 10 Hz), 130.2, 135.1 (d, J = 3.9 Hz), 159.3, 162.8 (d, J = 294.8 Hz), 173.1, 173.5; ESIMS m/z 415 [M + H], 829 [2M + H]; HRESI−FTMS calcd for $C_{23}H_{28}FN_2O_4$ (M + H) 415.2027, found 415.2024.

Synthesis of 3*S*-Benzyl-4-*p*-methoxybenzyl-5-*Z*-*p*-fluorobenzylidenepiperazine-2,6-dione (31). The elimination reaction was repeated on 150 mg of the substrate **30** using the conditions of aromatic series and a similar chromatography on silica gel employing 5−15% EtOAc in hexane gave elimination product **31** (90 mg, 63%) as a yellow solid: mp 50−55 °C; ^{1}H NMR ($CDCl_3$) δ 0.84 (3H, d, J = 6.6 Hz), 0.87 (3H, d, J = 6.6 Hz), 1.45 (1H, ddd, J = 14.1, 9.0, 5.4 Hz), 1.60 (1H, ddd, J = 13.8, 9.9, 5.4 Hz), 1.81 (1H, m), 3.64 (1H, dd, J = 9.6, 5.1 Hz), 3.78 (3H, s), 3.92 (2H, ABq, J = 13.5 Hz), 6.82 (2H, d, J = 9.0 Hz), 7.10 (2H, d, J = 8.7 Hz), 7.15 (2H, t, J = 8.7 Hz), 7.52 (1H, s), 8.00 (2H, dd, J = 8.7, 5.4 Hz); EIMS m/z 396 [M, 25%]; HRESI−FTMS calcd for $C_{23}H_{26}FN_2O_3$ (M + H) 397.1922, found 397.1919.

Synthesis of 3-Isobutyl-5-*Z*-*p*-fluorobenzylidene-3*H*-pyrazine-2,6-dione (32). DDQ oxidation of **31** (80 mg) using the conditions described earlier followed by workup and crystallization from acetone−hexane gave 20 mg of imine product **32** as yellow needles: mp 168−172 °C; ^{1}H NMR ($CDCl_3$) δ 1.05 (6H, d, J = 6.9 Hz), 2.27 (1H, m), 2.74 (2H, d, J = 6.9 Hz), 7.16 (2H, t, J = 8.7 Hz), 7.75 (1H, s), 8.22 (2H, dd, J = 8.7, 5.4 Hz); EIMS m/z 274 [M, 50%]; HRESI−FTMS calcd for $C_{15}H_{16}FN_2O_2$ (M + H) 275.1190, found 275.1180.

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Supporting Information Available: ^{1}H NMR spectra of compounds **1b**,**c**,**f**, **2a**, **3**, **17a**, **21a**, **23g**, **24**, **26**, **27**, and **29**−**32**. This material is available free of charge via the Internet at http://pubs.acs.org.

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