then 7 mL of water was added. The solution was diluted with 30 mL of diethyl ether and transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with additional Et_2O (2 × 100 mL). The combined extracts were dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was sublimed at 70 °C (1 × 10^{-3} mmHg) to give **24** as a white solid in 57% yield (0.5 g, 3.1 mmol): mp 195–198 °C. Spectroscopic data were in agreement with literature.[19] IR (Nujol, cm^{-1}): 2918, 2600, 1336, 1252, 1139, 1055, 1002, 933, 838, 784, 726. ^1H NMR ($(CD_3)_2CO$): 3.45 (s, 1 H), 1.74 (s, 3 H). ^{13}C NMR ($(CD_3)_2CO$): 71.6, 56.9, 26.2. ^{11}B NMR (acetone): −2.68 (d, 1 B), −9.20 (d, 1 B), −9.94 (d, 4 B), −12.45 (d, 2 B), −15.81 (d, 2 B).

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Registry No. 1, 16872-09-6; 2, 135457-04-4; 3, 138490-21-8; 4, 135481-15-1; 5, 135457-07-7; 6, 138490-22-9; 7, 138490-23-0; 8, 138490-24-1; 9, 138490-25-2; 10, 138490-26-3; 11, 138490-27-4; 12, 138490-28-5; 13, 23835-38-3; 14, 17526-10-2; 15, 93784-70-4; 16, 138490-29-6; 17, 30619-60-4; 18, 17522-80-4; 19, 23835-93-0; 20, 19610-34-5; 21, 51999-28-1; 22, 138490-30-9; 23, 138490-31-0; 24, 17378-55-1; *tert*-butyldimethylsilyl chloride, 18162-48-6; α,α′-dibromo-*o*-xylene, 91-13-4; 1-bromobutane, 109-65-9; benzyl bromide, 100-39-0; 1,3-dibromopropane, 109-64-8; 2-benzyl-1,3-bis(*p*-toluenesulfonyloxy)propane, 86103-46-0; allyl bromide, 106-95-6; 4-bromo-1-butene, 5162-44-7; trimethylene oxide, 503-30-0; methyl chloroformate, 79-22-1.

Regiospecific Synthesis of the Aminoimidazoquinoxaline (IQx) Mutagens from Cooked Foods

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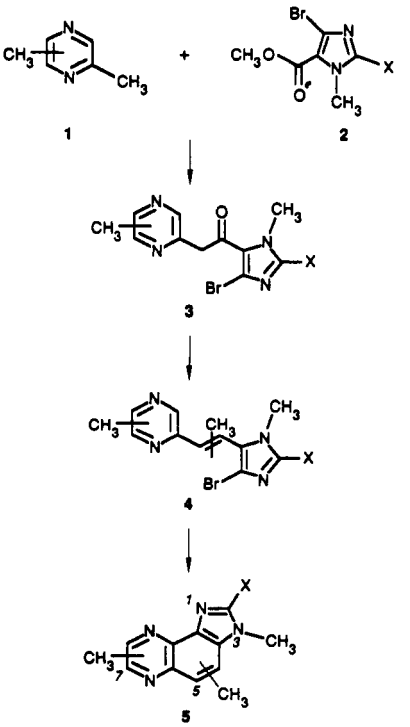
A versatile regiospecific synthesis has been developed to prepare the six dimethyl- and trimethyl-substituted 2-aminoimidazoquinoxaline (IQx) regioisomers **35**, **36**, **37**, **38**, **39**, and **40** for complete and unambiguous characterization. The key reaction step in the synthetic sequence for these angular tricycles is a photodehydrohalogenative cyclization of suitably substituted pyrazinylimidazolylethylene intermediates derived from common pyrazine and fully functionalized imidazole precursors. The reaction sequence developed allows for versatility in the substitution pattern as well as total regioisomeric control for the synthesis of all possible methyl and polymethyl analogues of IQx. Comparison of the physical properties among the isomeric di- and trimethyl-IQx's has established the value of unambiguous regiospecific synthesis for structural assignments in this food mutagen series.

Among the mutagens and potential carcinogens formed when protein-containing foods are cooked at high temperatures,[1] the dimethyl- and trimethyl-2-aminoimidazo-[4,5-*f*]quinoxalines (the IQx's) are among the most potent.[2] The isolation from cooked food, assignment of structure, and synthesis have been reported for a number of these dimethyl- and trimethyl-2-amino-IQx's.[3,4,5] Most of the synthetic methods encounter regioisomer problems at one or more stages or are restricted to a single substitution pattern.[6,7] Furthermore, since the various cooked food

Scheme I. Synthetic Plan



(1) (a) Vuolo, L. L.; Schuessler, G. J. *Environ. Mutagen* **1985**, *7*, 577. (b) Hargraves, W. A.; Pariza, M. W. *J. Environ. Sci. Health* **1984**, *62*, 1. (c) Hatch, F. T.; Felton, J. S.; Stuermer, D. H.; Bjeldanes, L. F. *Chemical Mutagens*, 9; deSerres, F. J., Ed.; Plenum: New York, 1984; Chapter 4, p 111.

(2) (a) Hashimoto, Y.; Shudo, K.; Okamoto, T. *Acc. Chem. Res.* **1984**, *17*, 403. (b) Sugimura, T. *Science* **1986**, *233*, 312.

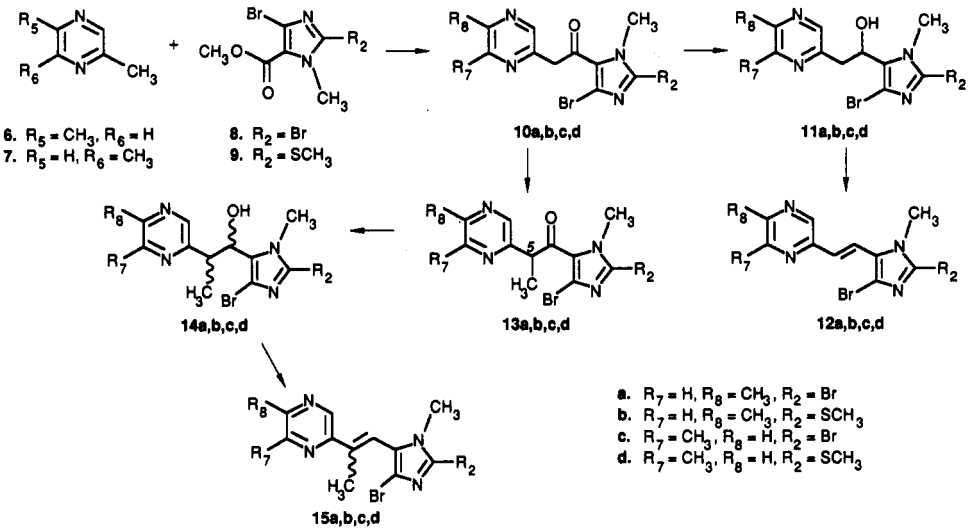
(3) (a) Kasai, H.; Yamaizumi, Z.; Shiomi, T.; Yokoyama, S.; Miyazawa, T.; Wakabayashi, K.; Nagao, M.; Sugimura, T.; Nishimura, S. *Chem. Lett.* **1981**, 485. (b) Takahashi, M.; Wakabayashi, K.; Nagao, M.; Yamaizumi, Z.; Sato, S.; Kinae, N.; Tomita, I.; Sugimura, T. *Carcinogenesis* **1985**, *6*, 1537. (c) Hayatsu, H.; Matsui, Y.; Ohara, Y.; Oka, T.; Hayatsu, T. *Gann* **1983**, *74*, 472. (d) Hargraves, W. A.; Pariza, M. W. *Cancer Res.* **1983**, *43*, 1467. (e) Kato, T.; Kikugawa, K.; Hayatsu, H. *J. Agric. Food Chem.* **1986**, *34*, 810. (f) Kikugawa, K.; Kato, T. *Mutation Res.* **1987**, *179*, 5. (g) Becher, G.; Knize, M. G.; Nes, I. F.; Felton, J. S. *Carcinogenesis* **1988**, *9*, 247.

(4) (a) Negishi, C.; Wakabayashi, K.; Tsuda, M.; Sato, S.; Sugimura, T.; Saitô, H.; Maeda, M.; Jägerstad, M. *Mutation Res.* **1984**, *140*, 55. (b) Jägerstad, M.; Olsson, K.; Grivas, S.; Negishi, C.; Wakabayashi, K.; Tsuda, M.; Sato, S.; Sugimura, T. *Mutation Res.* **1984**, *126*, 239. (c) Felton, J. S.; Knize, M. G.; Wood, C.; Wuebbles, B. J.; Healy, S. K.; Stuermer, D. H.; Bjeldanes, L. F.; Kimble, B. J.; Hatch, F. T. *Carcinogenesis* **1984**, *5*, 95.

(5) (a) Kasai, H.; Shiomi, T.; Sugimura, T.; Nishimura, S. *Chem. Lett.* **1981**, 675. (b) Grivas, S.; Olsson, K. *Acta Chem. Scand.* **1985**, *B39*, 31. (c) Grivas, S. *Acta Chem. Scand.* **1986**, *B40*, 404.

0022-3263/92/1957-1390$03.00/0

Scheme II. Synthesis of Pyrazinylmethyl Imidazolyl Ketones and Substituted Ethylenes[14]



mutagens show very small differences in chemical and physical properties,[8,9] unambiguous synthesis could be determinant for structural assignments.

These considerations delineated our synthetic strategy. We sought a process that would totally avoid any regioisomer problems and also would be sufficiently flexible to target the reported mutagens as well as related isomers. Driven by these objectives, we turned to the versatile photocyclization of 1,2-diarylethylenes for the synthesis of angular triaryl ring systems.[10] The overwhelming number of examples lead to substituted phenanthrenes. Final aromatization has been achieved by oxidative or catalytic[11] removal of hydrogen or by dehydrobromination with base.

While the application of this method to heterocycles is much more limited, a few examples exist to indicate its potential. Thus a styrylimidazole has been successfully photocyclized to an imidazonaphthalene,[12] and a successful photocyclization of styrylpyrazine to diazaphenanthrene has been reported.[13] In both of these examples, final aromatization was carried out by oxidative elimination of hydrogen from the dihydro intermediate. Alternatively, a hydrogen atom could be replaced with a bromine at one of the cyclization positions and the photochemical cyclization conducted in the presence of base to provide the final aromatized tricycle via dehydrobromination. Thus with both "half" reactions having precedent, what remained to be demonstrated was the photocyclization of an imidazole–pyrazine ethylene precursor to yield imidazoquinoxalines.

The general synthetic plan is outlined in Scheme I. Starting with the appropriate dimethylpyrazine **1**, its carbanion would be condensed with *N*-methylimidazole bromo ester **2**. The group X at C-2 of this imidazole would be an easily displaced group for ultimate introduction of the 2-amino substituent. Formation of the pyrazinylmethyl ketone **3** would be followed by reduction and dehydration to the ethylene **4**. Alternatively, the latter sequence would be preceded by methylation at either the methylene or carbonyl carbon to give the methyl-substituted ethylene **4**. Photocyclization followed by dehydrobrominative aromatization would then give imidazoquinoxalines **5**, to be followed by displacement at C-2 to introduce the 2-amino substituent.

To include the various mutagens isolated and their regioisomers, we targeted the synthesis of six 2-aminoimidazoquinoxalines: 3,7-dimethyl, 3,8-dimethyl, 3,4,7-trimethyl, 3,4,8-trimethyl, 3,5,7-trimethyl, and 3,5,8-trimethyl.[14] Although this report is confined to the synthesis of these six compounds, clearly the method can be easily extended to other analogues all proceeding through common intermediates in this relatively simple and comprehensive process.

We shall consider the synthesis by first describing the preparation of the imidazolylpyrazinylethylenes and their photocyclization followed by introduction of the 2-amino function. Since our synthesis was designed to provide, among other virtues, unambiguous structure proof, it was required that each component be regioisomerically pure and each reaction be regiospecific.

The Pyrazines and Imidazoles. Both 2,5- and 2,6-dimethylpyrazine are commercially available,[15] but the purity of each had to be questioned.[16] By ^1H NMR analysis, commercial 2,5-dimethylpyrazine (2,5-DMP) was shown to contain 8–19% of its 2,6-dimethyl regioisomer,

(6) (a) Nyhammar, T.; Grivas, S. *Acta Chem. Scand.* **1986**, *B40*, 583. (b) Grivas, S. *Acta Chem. Scand.* **1985**, *B39*, 213. (c) Knapp, S.; Ziv, J.; Rosen, J. D. *Tetrahedron* **1989**, *45*, 1293.

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(9) Nyhammar, T.; Grivas, S.; Olsson, K.; Jägerstad, M. *Mutation Res.* **1986**, *174*, 5.

(10) Mallory, F. B.; Mallory, C. W. *Organic Reactions*; Wiley: New York, 1984; Vol. 30, p 1.

(11) Rawal, V. H.; Jones, R. J.; Cava, M. P. *Tetrahedron Lett.* **1985**, *26*, 2423.

(12) Lindgren, G.; Stensiö, K. E.; Wahlberg, K. *J. Heterocycl. Chem.* **1980**, *17*, 679.

(13) Perkampus, H. H.; Bluhm, T. *Tetrahedron* **1972**, *28*, 2099.

(14) The nomenclature of these compounds is somewhat confused by the initial assignment of IQx (imidazoquinoxaline) as the name for a compound having an amino group at C-2 and a methyl group at N-3. Thus Me-IQx has been used as the abbreviation for a compound with an amino and two methyl groups, although the designator implies only one methyl group. To avoid this ambiguity, throughout this article IQx refers to the unaminated and unmethylated ring system, and all substituents, including methyl groups, are specifically numbered. Furthermore, for compounds containing both the pyrazine and imidazole moieties in the schemes, tables, and narrative, the IQx numbering system is used to designate the positions of substituents, reflecting the regioisomer relationship between the precursor ethylene and its product IQx. Fully systematic names are given in the Experimental Section.

(15) Our material was variously obtained from Alpharetta Aromatics, Fluka, Chemical Dynamics, and Aldrich.

(16) (a) Cheesman, G. W. H.; Werstiuk, E. S. G. *Adv. Heterocycl. Chem.* **1972**, *14*, 99–209. (b) Langdon, W. K.; Levis, W. W., Jr.; Jackson, D. R.; Cenker, M.; Baxter, G. E. *Ind. Eng. Chem. Prod. Res. Develop.* **1964**, *3*, 8.

depending on lot and supplier; commercial 2,6-dimethylpyrazine (2,6-DMP) appeared to be pure by ^{1}H NMR integration. Since the detection limit achievable by quantitative ^{1}H NMR analysis is not sufficient for our needs, an alternative method to assess regiochemical purity was necessary, and a base-line separation of the two regioisomers was achieved by capillary GC.[17] Specific analytical conditions based on GC/MS then established that our commercial 2,6-DMP was >99% regiochemically pure.

For purification of the 2,5-DMP isomer, attempts to use its *N*-oxide[18] or di-*N*-oxide gave satisfactory results. A better method, however, was to use the HCl salt, conveniently prepared by treating 2,5-DMP with HCl gas in an ether solution. Recrystallization of the HCl salt from 2-propanol/ether, conversion back to the free pyrazine with base, and distillation afforded 2,5-DMP with >99.9% regiochemical purity.

Regiochemically pure imidazoles **8** and **9** were prepared from sarcosine or diaminomaleonitrile as described previously,[19] but the diaminomaleonitrile process required modification for large-scale preparations. To avoid the quite insoluble monosodium salt in the isolation of the diacid, hydrolysis of the 4,5-dicyanoimidazole was done with KOH. Initial precipitation gave the monopotassium salt which could be converted completely to diacid by re-solution, acidification, and treatment with ammonia.

Preparation of the 1-Imidazolyl-2-pyrazinylethylenes. Synthesis of the substituted ethylenes began with a condensation between the pyrazinylmethyl anions of 2,5-DMP (**6**) and 2,6-DMP (**7**) and the methyl imidazolecarboxylates **8** and **9** to form ketones **10** (Scheme II). The pyrazinylmethyl anions are unstable,[16a,20,21] and considerable experimentation was required to develop satisfactory and reproducible condensation conditions.

To generate the anion of 2,5-DMP, the pyrazine was added dropwise to LDA in THF at −78 °C. This deep red solution of the anion was rapidly added to a cold solution of ester **8** or **9** dropwise, being careful not to have excess anion in the condensation vessel. The deep red color of the anion is a convenient indicator, and at the appearance of a permanent red color, the reaction was quenched. Excess anion was prepared, and in the case of dibromo ester **8**, longer addition times and limited excess anion were necessary to prevent debromination. With these precautions, 80% yields of ketones **10a,b** were reproducibly realized.

For the synthesis of the 7-methyl-IQx regioisomers, condensations with the anion of 2,6-DMP (**7**) were required, and these were more difficult to effect. Under the condition used for the preparation of **10a,b**, much lower yields (<40%) of **10c,d** were obtained, primarily due to the instability of the anion solutions. This problem was overcome by carrying out the condensation under higher dilution and adding the anion solution more rapidly (5–10 min) to the ester. By quenching the reactions after the appearance of the first persistent red color due to unreacted anion, 51–55% yields of ketones **10c,d** were realized along with 30–45% of recovered esters.

To prepare the ethylenes without additional substituents on the double bond, these ketones were reduced to the corresponding alcohols **11a–d** with sodium borohydride, and the latter were dehydrated by refluxing in toluene in the presence of methanesulfonic acid. The yields from ketone **10** to olefin **12** varied from 75 to 91%, and the olefins were all trans as shown in Scheme II.

The next group of intermediates needed were those with methyl groups on either carbon of the double bond. For those compounds in which the methyl group would ultimately appear at C-5 of the IQx's, we planned to alkylate the α-methylene group of ketones **10**. This was readily accomplished by enolate formation with KHMDS or NaH followed by alkylation with methyl iodide, yielding methylated ketones **13** in 69–85% yields along with small amounts of dialkylated ketone. Reduction with sodium borohydride yielded the diastereomeric alcohols **14**, and these were dehydrated similarly to the unmethylated analogues **11**. The overall yields from ketones **13** to trisubstituted ethylenes **15** were about 70% and the olefins were obtained as mixtures of *E* and *Z* isomers, with the *E* isomers predominating.

Those analogues in which the methyl group would ultimately appear at C-4 of the IQx's proved much more difficult to prepare. We were unable to convert ketone **10** to a tertiary methylcarbinol, as originally planned. Methyllithium and methyl Grignard led only to enolate formation and recovery of ketone. Use of the less basic cesium[22] or titanium[23] reagents also failed, as did the cuprate reagent. Attempts at converting the carbonyl to a methylene group also were unsuccessful. The Wittig reagent and an equilibrating Wittig reaction[24] gave only recovered ketone, and use of the zinc reagent, $CH_2(ZnBr)_2$,[25] afforded a number of unidentified products.

Faced with these failures we completely changed our synthetic strategy. We projected bringing in this methyl group with the imidazole residue as a methyl ketone. The pyrazine portion was then to be attached via an aldol condensation with the pyrazinylmethyl anion as shown in Scheme III.

This plan required the preparation of the imidazolyl methyl ketones **20** and **21**, which was to proceed by decarboxylation of β-keto esters **18** and **19**, themselves to be prepared by Claisen condensation of *tert*-butyl acetate with imidazole esters **8** and **9**. Yields for this overall process were poor, the major product of the initial condensation being tertiary alcohol **16/17** rather than anticipated β-keto ester **18/19**. Apparently enolate formation from β-keto ester **18/19** was insufficient to prevent condensation with a second acetate anion, and this was independent of the order of addition. Tertiary alcohol **16/17** is not a total loss, however, since refluxing in trifluoroacetic acid led to the desired methyl ketone **20/21** by reverse Claisen, followed by *tert*-butyl ester cleavage and decarboxylation. Since the cause of this unexpected dicondensation product was the apparent failure of the initial

(17) Separation of 2,5-DMP from 2,6-DMP was achieved using an HP 5890A gas chromatograph equipped with a mass selective detector and a DB-wax column under the following sets of conditions: (a) oven temp, 50 °C; ramp, 2.0 °C/min; oven max, temp, inj. temp, det. temp, 240 °C; gas flow through column, 0.56 mL/min; t_R for 2,5-DMP = 30.01 min; t_R for 2,6-DMP = 30.41 min; (b) oven temp, 75 °C; ramp, 2.0 °C/min; oven max. temp, inj. temp, det. temp, 240 °C; gas flow through column, 2.0 mL/min; t_R for 2,5-DMP = 8.74 min; t_R for 2,6-DMP = 8.91 min.

(18) (a) Klein, B.; Berkowitz, J. *J. Am. Chem. Soc.* **1959**, *81*, 5160. (b) Ohta, A.; Imazeki, A.; Itoigawa, Y.; Yamada, H.; Suga, C.; Takagai, C.; Sano, H.; Wantabe, T. *J. Heterocycl. Chem.* **1983**, *20*, 311.

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(20) (a) Houminer, Y. *J. Org. Chem.* **1980**, *45*, 999. (b) Bassfield, R. L.; Houminer, Y. *J. Org. Chem.* **1983**, *48*, 2130. (c) Rizzi, G. P. *J. Org. Chem.* **1968**, *33*, 1333. (d) Rizzi, G. P. *J. Org. Chem.* **1974**, *39*, 3598.

(21) Previous examples of pyrazinylmethyl alkylations are: (a) Wheeler, J. W.; Avery, J.; Olubajo, O.; Shamim, M. T.; Storm, C. B.; Duffield, R. M. *Tetrahedron* **1982**, *38*, 1939. (b) Beumel, O. F.; Smith, W. N.; Rybalka, B. *Synthesis* **1974**, 43.

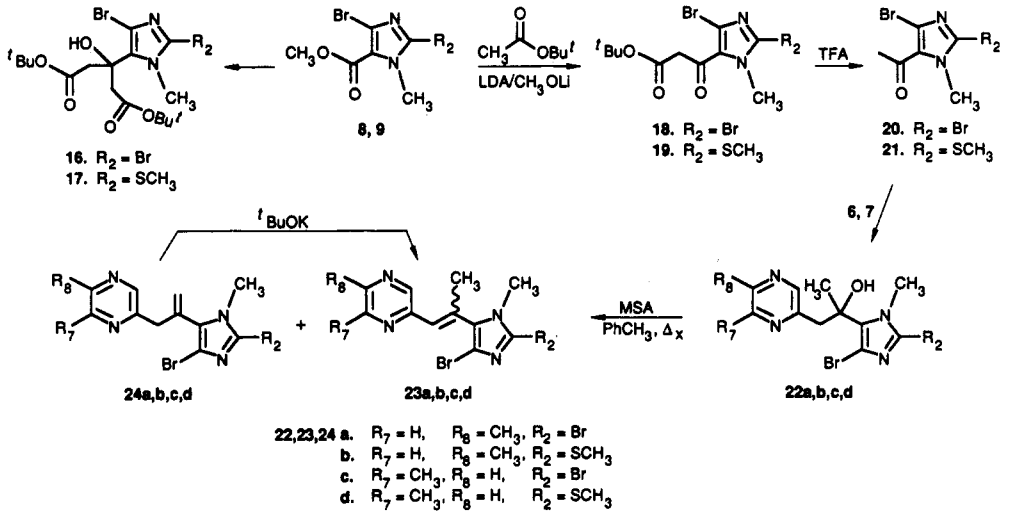
(22) Imamoto, T.; Kusomoto, T.; Tawarayama, Y.; Sugiura, Y.; Mita, T.; Hatanaka, Y.; Yokoyama, M. *J. Org. Chem.* **1984**, *49*, 3904.

(23) Reetz, M. T.; Kyung, S. H.; Hullmann, M. *Tetrahedron* **1986**, *42*, 2931.

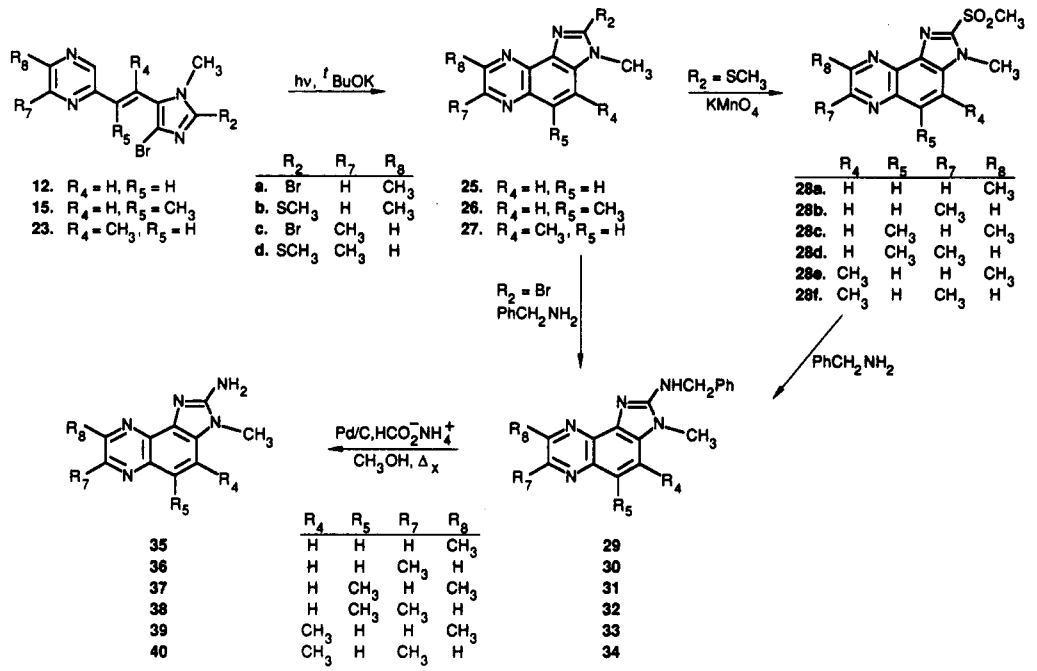
(24) Conia, J.-M.; Limaset, J.-C. *Bull. Soc. Chim. Fr.* **1967**, 1936.

(25) Takai, K.; Hotta, Y.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1978**, 2417.

Scheme III. Synthesis of (4-Methylpyrazinyl)imidazolylethylenes[14]



Scheme IV. Photocyclization to IQx's and Introduction of the 2-Amino Substituent



β-keto ester to enolize, 200 mol % of lithium methoxide was added to the imidazole ester prior to the addition of *tert*-butyl acetate anion. Under these conditions, diadduct formation was completely suppressed, and the sequence to methyl ketone **20/21** proceeded in excellent yield.

Condensation of the methyl imidazolyl ketones **20/21** with the anions of 2,5-DMP (**6**) and 2,6-DMP (**7**), patterned after the reactions with the corresponding esters, was uneventful and led to the tertiary alcohols **22a–d** which were dehydrated to the olefins as previously described. The product mix, however, was more complex and consisted of the *E* and *Z* isomers plus small amounts (3–10%) of the exo isomers **24**. Treatment with potassium *tert*-butoxide internalized the double bond, and this could be effected on the isolated exo isomer or on the product mixture, thus converting the dehydration product solely to (*E*/*Z*)-**23**.

Photocyclization to the IQx's. For the photocyclization to the IQx's, we initially considered the oxidative procedure in which the trans dihydro intermediate is oxidatively aromatized, usually with oxygen and catalytic iodine,[10] since both a styrylimidazole[12] and a styrylpyrazine[13] have been successfully oxidatively cyclized. Furthermore, the intermediate ethylenes needed for oxidative cyclization would require one less bromo substituent, and hence would be more easily prepared. Preliminary experiments, however, quickly established that oxidative cyclization was inapplicable to our system. Yields were poor and irreproducible. Therefore, all of our intermediates were designed with a 4-bromo substituent on the imidazole moiety in order to apply the dehydrobrominative aromatization.

Initial efforts at dehydrobrominative photochemistry centered around the (dibromoimidazolyl)pyrazinylethylene intermediates (Scheme IV) and were successful on a small scale. For example, dehydrohalogenative photocyclization of **15a** afforded a 95% yield of the 2-bromo tricycle **26a** after irradiation for 15 min through a Pyrex sleeve, while the corresponding unsubstituted ethylenes **12a** and **12c** were photoeliminatively cyclized to their respective bromotricycles **25a** and **25c** in 55% and 50% yields, respectively, after irradiation for 50 min.

However, these reactions became problematic and irreproducible upon scale-up. Photocleavage of the C-2 car-

bon–bromide bond was a major problem. In some instances, the corresponding 2-phenyl-IQx derivative was the reaction product plus polymeric material. To avoid such products, benzene was eliminated as a cosolvent. When it was replaced with mesitylene, the corresponding 2-mesityl tricycle was isolated. Photolysis of ethylene **23** in pyridine/*t*-BuOH gave a promising 63% yield (83% overall) of tricycle **27c** when ethylene **23c** was used; however, this solvent system has not been examined with other ethylenes.

The labile C-2 bromine also proved sensitive to isolation procedures. When methanol was included in the isolation, 2-methoxy-IQx derivatives were observed as the sole reaction product in 30–70% yields, although the corresponding 2-bromo tricycles **25a** and **26a** were observed (by TLC) initially. Limited solubility of the (dibromoimidazolyl)pyrazinylethylenes was another problem encountered with increased scale. THF appeared to be a good cosolvent for increased solubility; furthermore, THF is transparent at the irradiation wavelengths. Unfortunately, prolonged irradiation was required for both stilbenes **12c** and **12a** in THF, and the yields of the corresponding 2-bromo tricycle never exceeded 25%.

While the inherent reactivity of the 2-bromo substituent was advantageous for subsequent transformations (i.e., methoxide, azide, amine displacements), its lability under photolysis conditions led to abandoning the use of (2-bromoimidazolyl)pyrazinylethylenes as intermediates for the IQx compounds. Although the dehydrobrominative photochemical cyclization reactions involving (2-bromoimidazolyl)pyrazinylethylenes had limitations, small amounts of each tricycle were prepared and carried on to their respective 2-(*N*-benzylamino)-IQx derivatives (Scheme IV).

Cyclization efforts then turned to the 2-(methylthio)-substituted derivatives. Dehydrobrominative photochemical cyclization of the 2-methylthio derivatives afforded angular tricycles **25–27b,d** in yields ranging up to 87% on a preparative scale, with the success of the reaction being highly dependent on the methyl substitution pattern. The experimental parameters which varied were dilution, reaction scale, solvent composition, base concentration, *E*/*Z* ratio of the starting ethylenes, filters, irradiation time, and lamp variables. From these experiments, a number of generalizations can be made. The methyl substitution pattern of the imidazolylpyrazinylethylene derivative was clearly the most important factor in the photochemical cyclization reaction. Yields followed the sequence: 3,5,8 > 3,5,7 > 3,4,7 > 3,4,8 > 3,8 > 3,7 in decreasing order of yield. Reactions involving the *Z* isomer consistently gave higher yields of tricycle than did those with the *E* isomer. For example, when an *E*/*Z* mixture (~1/1) of **15d** was subjected to photolysis, 71–87% yields of tricycle **26d** were obtained. Use of only the *E* isomer resulted in 32–49% yields of **26d**. An efficient *E* → *Z* photoisomerization procedure for ethylenes **23b,d** was developed, which resulted in the in situ generation of the *Z* isomer. Thus, the best procedure was indirect irradiation of the solution for 2 min followed by photolysis.

Concentration and reaction scale were important variables. In general, the more dilute the reaction mixture and the smaller the scale, the higher the yield of tricycle. Routinely, photochemical experiments with the 3,4,7-, 3,5,8-, and 3,5,7-substituted ethylenes could be carried out on a 200–400-mg scale, while experiments involving the 3,4,8-, 3,8-, and 3,7-substituted ethylenes could not be scaled up beyond 100 mg without significant losses. These examples pertaining to the photochemical cyclization of **12d** are representative of this trend.

Table I. UV Absorption Maxima of Pyrazinylimidazolylethylenes 12, 15, and 23

compd	substitution	stereochem	solvent	λ_{max}, nm
12b	2-CH_3S-3,8-Me_2	*E*	C_6H_6	374
12c	2-Br-3,7-Me_2	*E*	CH_3CN	348
12c	2-Br-3,7-Me_2	*Z*	CH_3CN	300
12d	2-CH_3S-3,7-Me_2	*E*	CH_3OH	365
12d	2-CH_3S-3,7-Me_2	*Z*	CH_3OH	270
15b	2-CH_3S-3,5,8-Me_3	*E*	CH_3CN	335
15b	2-CH_3S-3,5,8-Me_3	*Z*	CH_3CN	276
15c	2-Br-3,5,7-Me_3	*E*	CH_3CN	324
15c	2-Br-3,5,7-Me_3	*Z*	CH_3CN	276
15d	2-CH_3S-3,5,7-Me_3	*E*	CH_3OH	322
15d	2-CH_3S-3,5,7-Me_3	*Z*	CH_3OH	264
23b	2-CH_3S-3,4,8-Me_3	*E*	CH_3OH	323
23b	2-CH_3S-3,4,8-Me_3	*Z*	CH_3OH	255
23c	2-Br-3,4,7-Me_3	*E*	CH_3CN	315
23c	2-Br-3,4,7-Me_3	*Z*	CH_3CN	276
23d	2-CH_3S-3,4,7-Me_3	*E*	CH_3OH	319
23d	2-CH_3S-3,4,7-Me_3	*Z*	CH_3OH	240

Table II. UV Absorption Maxima of 2-Bromo- and 2-(Methylthio)dimethyl- and -trimethylimidazo[4,5-*f*]quinoxaline

compd	substitution	solvent	λ_{max}, nm
25b	2-CH_3S-3,8-Me_2	CH_3OH	275
25c	2-Br-3,7-Me_2	CH_3CN	265
25d	2-CH_3S-3,7-Me_2	CH_3OH	272
26b	2-CH_3S-3,5,8-Me_3	CH_3CN/CH_3OH[a]	279
26d	2-CH_3S-3,5,7-Me_3	CH_3OH	279
27b	2-CH_3S-3,4,8-Me_3	CH_3OH	276
27d	2-CH_3S-3,4,7-Me_3	CH_3OH	276

[a] The same absorption was found in either solvent.

Base concentration and solvent composition had little effect on the yield. However, irradiation time and lamp variables proved to be extremely important and were the most difficult to control. Experiments involving imidazolylpyrazinylethylene **12b** are representative. In early experiments the reaction time was recorded from the moment the lamp transformer was turned on. This procedure was not cognizant of lamp warm-up, which could take from 1–2 min, and gave irreproducible results. To better control this variable, subsequent experiments were done with a 5-min lamp warm-up period before the hot lamp was transferred to the reaction photochamber. The yield of tricycle **25b** improved using this protocol.

The use of filters also was investigated. Certain filters necessitated an increase in irradiation time, effectively blocking the high-energy UV light from reaching the reaction medium. With the (*Z*)-(2-(methylthio)-imidazolyl)pyrazinylethylenes having their $\pi \rightarrow \pi^*$ transitions at a wavelength <300 nm (Tables I and II), the cis-S_0 → cis-S_1 transition is effectively blocked, allowing other pathways to occur leading to starting material decomposition. Prolonged irradiation also was detrimental to yield. However, unlike their 2-bromo-IQx counterparts, product stability studies of the 2-(methylthio)-IQx derivatives established their stability in such experiments.

Amination. Attempts at Amination of 2-Hydridoimidazoquinoxalines. Our first attempts at converting IQx analogues into the corresponding 2-amino derivatives were centered on functionalizing of the 2-unsubstituted tricycle **26a** (R_2 = H). Based on precedent that 2-halogen functionality can readily be displaced by amine nucleophiles, we sought to introduce a bromine at the 2-position of tricycle **26a** (R_2 = H). However, treatment with molecular bromine (in the light or dark), cyanogen bromide, or NBS led to complex mixtures. Amination and nitration of tricycle **26a** (R_2 = H) was also investigated. All attempts[26] at introduction of nitro functionality into the

2-position either led to recovered starting material or many products. Amination, using freshly prepared sodium amide[27] or hydroxylamine-*O*-sulfonic acid,[28] also failed, as did introduction of the 2-amino functionality via an intermediate anion.

Amination of the 2-Bromo-IQx Derivatives. Attention then focused on replacement of the 2-bromo substituent of the 2-bromo-IQx's. Although liquid ammonia under pressure at 80–130 °C afforded only recovered 2-bromo tricycle, hydrazine led to successful displacement. 2-Bromo-IQx **26a** with refluxing aqueous hydrazine gave the 2-hydrazino-3,5,8-Me_3-IQx derivative in yields greater than 50%; the remaining material was the corresponding 2-hydrido-IQx. On the assumption that the source of the 2-hydrido tricycle resulted from reductive debromination by diimide formed in the reaction mixture, an *N,N*-dialkylhydrazine was used in an attempt to avoid this complication. Treatment of the 2-bromo tricycle **26a** with refluxing *N,N*-dimethylhydrazine afforded a 40/60 mixture of two hydrazino derivatives in excellent yield, one resulting from displacement at the NH_2 moiety, the other resulting from attack at the *N,N*-dimethyl nitrogen followed by loss of methyl bromide. It was then found that neat benzylamine at 150 °C cleanly displaced the 2-bromo substituent to afford 2-(benzylamino)-3,5,7-Me_3-IQx **32** in a 90% yield. The other 2-bromo-IQx regioisomers reacted in an analogous manner.

Animation of the 2-(Methylthio)-IQx Derivatives. Faced with numerous failures to displace the methylthio functionality,[29,30] these attempts were abandoned. An alternative was to convert the methylthio group into a better leaving group, either a sulfoxide or sulfone derivative, and the latter was pursued. To prepare the sulfones, sulfur oxidation by $HOAc/H_2O_2$ or MCPBA had to be avoided due to the parallel formation of pyrazine *N*-oxides.[18] Although potassium permanganate also will oxidize heterocyclic nitrogen, it appeared more selective for sulfur. Oxidation of methylthio tricycle **26b** with aqueous $KMnO_4$ in glacial acetic acid at room temperature afforded a 79% yield of sulfone **28c** after low-pressure liquid chromatography (LPLC). Some *N*-oxide formation occurred, but the sulfones could be obtained analytically pure by sublimation; all six sulfones **28** were obtained in this manner. The sulfonyl moiety was then readily displaced with neat benzylamine at 145–150 °C, affording 86–99% yields of the 2-(*N*-benzylamino)-IQx derivatives after purification by LPLC.[31]

Use of the *N*-benzyl intermediate is quite advantageous since it allows for thorough purification at a derivative stage, thus minimizing exposure to the mutagen. The combination of column chromatography and reverse-phase preparative HPLC was particularly effective in providing analytically pure *N*-benzyl tricycles. Once pure, the *N*-benzyl tricycles could then be deprotected by hydrogenolysis. Thus, the benzyl group serves a dual purpose: it allows for the introduction of the amine functionality in a protected and readily purified form and affords a simple method for generating the aminoimidazoquinoxaline mutagen under controlled conditions in pure form.

Hydrogenolysis of the 2-(*N*-Benzylamino)-IQx Analogues. Hydrogenolysis of 2-(*N*-benzylamino)-3,5,7-Me_3-IQx **32** using 10% Pd/C or Pearlman's $(Pd(OH)_2/C)$ in methanol at 1 atm of hydrogen at room temperature resulted in many products including the corresponding tetrahydropyrazine; the pyrazine ring had been reduced preferentially to hydrogenolysis of the benzyl group.[32]

Catalytic transfer hydrogenolysis has been used successfully for N-debenzylation,[34] mostly with amino acid and peptide derivatives[35] or simple amines. Applications to *N*-benzyl-protected heterocycles have been limited or generally unsuccessful;[35d,36] however, a number of recent examples using ammonium formate as the catalytic transfer hydrogenation agent, including application to the debenzylation of *N*-benzyl-protected heterocycles, were encouraging.[37,38]

When 2-*N*-benzylamino tricycle was treated with an equal weight of 10% Pd/C and 1000 mol % anhydrous ammonium formate in refluxing methanol, the reaction proceeded to completion after 2 days and 2-amino-3,5,7-Me_3-IQx **38** was isolated in 96% yield along with 2% of unreacted **32**. The use of large excesses of ammonium formate under similar conditions was detrimental and led to some overreduction (presumably the debenzylated tetrahydropyrazine). Efforts to enhance the rate of the debenzylation using the trifluoroacetate salt of **32** had no effect, and the use of sonication[39] led only to recovered starting material after 8 h. With an acceptable method of preparing the IQx mutagens in pure form, the remaining five isomers were deprotected using similar conditions. The purity of the *N*-benzylamino tricycle is critical to the success of the hydrogenolysis reaction, as traces of impurities poison the catalyst, rendering it ineffective.

After the debenzylations of all six (*N*-benzylamino)-IQx analogues were completed, we turned our attention to final purification of the mutagens. In the isolation of the two "natural" isomers from cooked beef, purification involved reverse-phase HPLC using methanol/aqueous buffered solvent systems.[3a] We chose to avoid such solvent systems

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Table III. Melting Point and UV Absorption Data for Dimethyl- and Trimethyl-2-aminoimidazo[4,5-f]quinoxalines[a]

compd	substitution	mp, °C	λ_{max}, nm	ϵ
35	3,8-Me_2[b]	279–282[e] (295–300)	211 (214)	28460 (24300)
			274 (274)	35200 (41100)
			341 (340)	3920 (3900)
36	3,7-Me_2[b]	250–255[e] (330–340)	217 (214)	32970 (29000)
			274 (274)	38110 (42000)
			343 (337)	6450 (4000)
37	3,5,8-Me_3[c]	>300 (>300)	214 (215)	25420 (4.4)[f]
			275 (276)	36950 (4.6)
			335 (343)	2510 (3.5)
38	3,5,7-Me_3	>340	210	35290
			275	40770
			340	4090
39	3,4,8-Me_3[d]	>300 (>300)	218 (220)	22400 (4.4)[f]
			274 (275)	25320 (4.6)[f]
			342 (347)	3590 (3.7)[f]
40	3,4,7-Me_3[d]	>300 (>300)	217	29260
			274	32900
			344	5640

[a] Literature values are reported in parentheses; UV absorptions were recorded in MeOH. [b] Literature mp is in ref 5b; UV in ref 3a and 5a. [c] Literature mp is in ref 6a; UV in ref 9. [d] Literature mp is in ref 6b; UV in ref 9. [e] Taken in sealed, evacuated glass capillary; sample partially sublimed. [f] Literature values for 37 and 39 were reported as log ϵ.

since extraction would be required following HPLC to desalt the product. Initial purification of the IQx mutagens involved simple column chromatography. Elution with ethyl acetate removed any unreacted starting material, and further elution with 10–25% MeOH/ethyl acetate (depending on the isomer) afforded the mutagen. The dimethyl isomers, 3,7 and 3,8-Me_2, **35** and **36**, are more polar than the trimethyl isomers and require 25% MeOH/ethyl acetate to wash them from the column. Thus these isomers generally contained more contaminants from the silica gel which were removed by repeated trituration of the residue with hot $CHCl_3$ followed by filtration and evaporation. A final sublimation at 240–270 °C (0.1 Torr) gave the analytically pure materials.

Characterization of the Synthetic IQx's and Comparison to the Mutagens Isolated from Cooked Food. With the regiospecific synthesis of all six IQx's completed, we turned to the full characterization of each by mp, IR, UV, ^1H NMR, and LRMS. The melting points agree with the reported values but are of little value for characterization purposes (Table III). The UV absorption data of the two 2-amino-Me_2-IQx's are very similar and differ somewhat from the reported extinction coefficients. Likewise, the UV data of the four isomeric 2-amino-Me_3-IQx's are very similar (Table III). Thus UV spectroscopy cannot be used as a method for distinguishing the IQx mutagens.

The mass spectral data of the four isomeric 2-amino-Me_3-IQx's also are very similar, differing only in relative intensity. The same is true for the mass spectra of the 3,8- and 3,7-dimethyl compounds **35** and **36**. Thus, mass spectrometry cannot be used as a characterization method for the IQx mutagens. The infrared spectrum of each IQx compound was recorded, involving the use of FTIR in most instances. Small differences in the fingerprint region were observed among the various isomers. However, these small differences in this complex region are of limited value for structural and identification purposes.

This leaves NMR as the only method available to differentiate among the various IQx isomers. Fortunately, although the ^1H NMR absorptions of the various isomers are similar, there are enough differences for unambiguous characterization of the various regioisomers. The ^1H NMR spectra of the four isomeric 2-amino-Me_3-IQx's and the two isomeric 2-amino-Me_2-IQx's were recorded in MeOH-d_4, DMSO-d_6, and $CDCl_3$, and the results are given in Table IV.

In comparing the ^1H NMR spectra of the two Me_2-IQx isomers, it is immediately obvious that they are quite similar. The same is true of the four isomeric Me_3-IQx isomers. There are, however, some differences in the ^1H NMR spectra which allow for unambiguous characterization of the mutagens. In general, when similar isomers are compared (i.e., 3,4,8 vs 3,4,7) the 8-H resonance is observed

Table IV. ^1H NMR Spectral Data for the Dimethyl- and Trimethyl-2-aminoimidazo[4,5-f]quinoxalines

			δ values[a]									
compd	substitution	solvent[b]	8-CH_3	7-CH_3	8-H	7-H	5-H	4-H	5-CH_3	4-CH_3	3-CH_3	2-NH_2
35	3,8-Me_2	$CDCl_3$	2.82	–	–	8.68	7.78	7.56	–	–	3.72	4.68
							7.76	7.54				
35	3,8-Me_2	MeOH	2.77	–	–	8.63	7.73	7.65	–	–	3.70	absent[c]
							7.71	7.64				
35	3,8-Me_2	DMSO	2.75	–	–	8.82	7.93	7.84	–	–	3.71	absent
							7.91	7.82				
36	3,7-Me_2	$CDCl_3$	–	2.78	8.78	–	7.74	7.61	–	–	3.72	4.90
							7.72	7.59				
36	3,7-Me_2	MeOH	–	2.73	8.76	–	7.78	7.63	–	–	3.71	absent
							7.76	7.62				
36	3,7-Me_2	DMSO	–	2.69	8.83	–	7.92	7.70	–	–	3.70	absent
							7.90	7.67				
37	3,5,8-Me_3	$CDCl_3$	2.81	–	–	8.69	–	7.38	2.83	–	3.68	4.57
37	3,5,8-Me_3	MeOH	2.75	–	–	8.63	–	7.52	2.74	–	3.65	absent
37	3,5,8-Me_3	DMSO	2.70	–	–	8.78	–	7.71	2.73	–	3.65	2.98
38	3,5,7-Me_3	$CDCl_3$	–	2.79	8.74	–	–	7.44	2.84	–	3.69	4.61
38	3,5,7-Me_3	MeOH	–	2.75	8.73	–	–	7.67	2.84	–	3.70	absent
38	3,5,7-Me_3	DMSO	–	2.71	8.83	–	–	7.83	2.74	–	3.67	absent
39	3,4,8-Me_3	$CDCl_3$	2.79	–	–	8.63	7.45	–	–	2.84	3.91	4.56
39	3,4,8-Me_3	MeOH	2.74	–	–	8.57	7.34	–	–	2.84	3.90	absent
39	3,4,8-Me_3	DMSO	2.83	–	–	8.73	7.52	–	–	2.70	3.88	absent
40	3,4,7-Me_3	$CDCl_3$	–	2.75	8.69	–	7.41	–	–	2.84	3.91	4.65
40	3,4,7-Me_3	MeOH	–	2.70	8.68	–	7.30	–	–	2.84	3.88	absent
40	3,4,7-Me_3	DMSO	–	2.70	8.83	–	7.60	–	–	2.85	3.90	absent

[a] δ Values are given as the chemical shift (ppm) relative to internal TMS for $CDCl_3$ or the deuterated solvent septets at 2.49 ppm for CD_3OD and 3.35 ppm for DMSO-d_6). [b] All solvents are deuterated: MeOH-d_4, DMSO-d_6. [c] The NH resonance was not observed due to exchange with the solvent.

Table V. Comparison of the ^{1}H NMR Spectral Data in $CDCl_3$ Reported for IQx Mutagens Isolated from Beef with Synthetic Compounds

	δ values[a]					
source	8- or 7-CH_3	8- or 7-H	5-H	4-H	5- or 4-CH_3	3-CH_3
isolated from cooked beef						
3,8-Me_2[b]	2.82	8.67	7.77 (d)	7.54 (d)	–	3.71
3,4,8-Me_3[c]	2.79	8.63	7.46	–	2.83	3.92
synthetic[d]						
35, 3,8-Me_2	2.82	8.68	7.78, 7.76	7.56, 7.54	–	3.72
36, 3,7-Me_2	2.78	8.78	7.74, 7.72	7.61, 7.59	–	3.72
37, 3,5,8-Me_3	2.81	8.69	–	7.38	2.8	3.68
38, 3,5,7-Me_3	2.80	8.72	–	7.66	2.75	3.70
39, 3,4,8-Me_3	2.79	8.63	7.45	–	2.84	3.91
40, 3,4,7-Me_3	2.75	8.69	7.41	–	2.84	3.91

[a] Values are reported in ppm relative to internal TMS. [b] Reported in ref 3a. [c] Reported in ref 6b. [d] All synthetic compounds are those prepared in this work.

slightly downfield (0.05–0.10 ppm) from the corresponding 7-H resonance in $CDCl_3$ and MeOH-d_4. In DMSO-d_6 this effect varies. Similarly, the 8-CH_3 resonance is observed slightly downfield from the corresponding 7-CH_3 resonance, although the effect can be minimal (0.06–0.00 ppm). Thus 2-amino-3,8-Me_2-IQx can be differentiated from the isomeric 2-amino-3,7-Me_2-IQx on the basis of the 7-H and 8-CH_3 resonances of the former, which are observed at 8.68 and 2.82 ppm ($CDCl_3$), respectively, while the corresponding 8-H and 7-CH_3 resonances of the 3,7-isomer appear at 8.78 and 2.78 ppm, respectively.

The pyrazine methyl resonances (8-CH_3 and 7-CH_3) can be differentiated from the 5- and 4-CH_3 substituent in the following manner. In the 500-MHz ^{1}H NMR spectra of the various Me_3-IQx isomers, the 8-CH_3, 7-CH_3, and 5-CH_3 resonances appear as singlets, with the 5- and 4-CH_3 resonances being of lower intensity. Sometimes when the instrument is at optimal shim, some splitting of the 5- and 4-CH_3 methyl resonances is observed. However, when a squared sine bell apodization with zero filling is used instead of exponential multiplication prior to Fourier transform, the 5-CH_3 and 4-CH_3 resonances become well-defined doublets with a coupling constant of 1.0 Hz, while the pyrazine methyl resonances remain singlets. Furthermore, when squared sine bell apodization and zero filling is used, the 5-H or 4-H resonances become quartets while the pyrazine-H resonances remain singlets, allowing for unambiguous identification of the 5-H and 4-H resonances as well.

The 5-CH_3 and 4-CH_3 substituents can be distinguished from one another on the basis of the chemical shift observed for the N-CH_3 resonance. In the Me_3-IQx isomers, the 5-methyl substituent results in a resonance for the *N*-CH_3 group at 3.65–3.70 ppm (all solvents) whereas the 4-CH_3 substituent shifts the *N*-CH_3 resonance to 3.88–3.91 ppm, a 0.3 ppm downfield shift. Thus the 3,5,8- and 3,5,7-Me_3-IQx's can be differentiated based on the downfield chemical shift observed for the 8-H resonance vs the 7-H resonance. The 3,5,8/3,5,7-isomers can be distinguished from the 3,4,8/3,4,7-isomers based on the 0.3 ppm downfield shift observed for the *N*-CH_3 resonance whenever a 4-methyl substituent is present. Finally, 3,4,8- and 3,4,7-Me_3-IQx can be identified by the appearance of the 8-proton resonance downfield to that of the 7-proton.

With unambiguous characterization of the six IQx isomers completed, our attention was focused on the complementary identification of the "natural" isomers. It has been reported that 2-amino-3,8-Me_2-IQx (8-Me-IQx)[3a] (**35**) and 2-amino-3,4,8-Me_3-IQx (4,8-Me_2-IQx)[3a,9] (**39**) are the natural cooked food mutagens. The ^{1}H NMR data for each are presented in Table V along with the NMR data recorded in $CDCl_3$ for each of the IQx isomers which we have prepared. From these data it is clear that the ^{1}H NMR spectra are quite similar. However, after unambiguous synthesis of each isomer, the small differences in chemical shift discussed earlier allow definitive identification of the natural cooked food mutagens. Without this reliance on regiospecific synthesis, however, the differences in chemical shifts among the various isomers are too small to permit rigorous assignment of structures to the regioisomers. Prior to this report, syntheses of the IQx mutagens admitted some ambiguities that precluded unequivocal identification.

The reported NMR data for the natural 2-amino-3,8-Me_2-IQx agrees with the NMR data obtained for our synthetic 2-amino-3,8-Me_2-IQx **35**. Thus, the structure of the natural isomer now can be definitively assigned. Identification of the 2-amino-Me_3-IQx mutagen is more difficult. The NMR data reported for the natural homologue agree with that obtained for our synthetic 2-amino-3,4,8-Me_3-IQx **39**. The isomeric 3,5,8- and 3,5,7-trimethyl structures can be ruled out on the basis of the large chemical shift difference observed for the *N*-3-CH_3 resonances. However, it should be noted that the ^{1}H NMR data for the isomeric 3,4,7-trimethyl isomer are very similar to that observed for the 3,4,8-regioisomer. Previous attempts to rule out the 3,4,7 regioisomer have been flawed for two reasons: (1) it was obtained as a byproduct of an ambiguous synthesis, and (2) its ^{1}H NMR spectrum was reported in DMSO-d_6, and not in $CDCl_3$. No previously reported data eliminate the 3,4,7-regioisomer, yet it is the isomer for which the NMR data most closely match the 3,4,8-isomer.

The ^{1}H NMR spectrum of the synthetic IQx's were recorded on a 500-MHz instrument. While the 3,4,7- and 3,4,8-isomers have chemical shifts differing by only ≤0.06 ppm, this difference is significant enough to distinguish between the two isomers when their spectra are recorded at high-field. Furthermore, the 500-MHz HMR spectrum of a mixture of 3,4,8- and 3,4,7-trimethyl isomers show distinct signals for the 8- and 7-CH_3's, 8- and 7-H's and 5-H's. Thus the assignment of the remaining natural food mutagen as the 3,4,8-isomer now can be made with certainty. Without the support of an unambiguous synthesis of each isomer of the trimethyl series, it would not have been possible to confidently distinguish between the 3,4,8- and 3,4,7-regioisomers.

Conclusion

We have presented an unambiguous regiospecific synthesis of all six possible 2-amino-Me_2-IQx and -trimethyl-IQx's **35**, **36**, **37**, **38**, **39**, and **40**. Each is prepared

from the common intermediate, imidazole ester **2**. The key step in our synthetic methodology involves the dehydrobrominative photochemical cyclization of imidazolylpyrazinylethylene derivatives which, prior to this account, has been an unexplored area. Such ethylene derivatives photocyclize to the desired tricyclic imidazoquinoxaline precursor in yields ranging from 25 to 90% depending on the methyl substitution pattern of the ethylene derivatives. The 3,5,8-, 3,5,7-, 3,4,8-, and 3,4,7-trimethyl isomers were prepared in overall yields of 24, 11, 2.4, and 6.4%, respectively, from the functionalized imidazole **9** (30, 31, 57, and 23%, respectively, allowing for recovered starting materials). The 3,8- and 3,7-dimethyl isomers were prepared in overall yields of 12% (15) and 5.4% (14), respectively from **9**. Additionally, the synthetic process can obviously be extended to other analogues without introducing structural ambiguities.

Experimental Section

General Methods. Tetrahydrofuran was dried by storage over KOH, distilled first from CaH_2 and then from potassium and benzophenone prior to use; methanol was distilled from Mg; 2-propanol was distilled from Na; toluene, benzene, diisopropylamine, benzylamine, bromoform, and hexanes were distilled from CaH_2; methyl iodide, *tert*-butyl acetate,[40,41] 2,5-DMP, and 2,6-DMP were distilled from CaH_2 and stored under nitrogen. Purity of dibromoimidazole ester **8** and 4-bromo-2-(methylthio)imidazole ester **9** was established by GC-mass spectrometry.[19] Commercial 2,6-DMP was determined to be >99% free of its regioisomer by GC–MS. Commercial 2,5-DMP was purified by preparing its HCl salt followed by recrystallization three times from 2-propanol/ether (9/1) and then treatment with aqueous sodium hydroxide and distillation; >99% pure by GC/MS. Organic layers from aqueous extractions were dried over anhydrous $MgSO_4$ unless otherwise indicated and concentrated on a Berkeley rotary evaporator using water aspirator vacuum. Low-pressure liquid chromatography (LPLC) was carried out by applying air pressure to columns packed with EM Reagents silica gel 60 (0.040–0.063-mm particle size, 230–400 mesh). Column chromatography was carried out on EM Science Kieselgel 60 (0.063–0.200 mm, 60–200 mesh). For HPLC purification of the IQx's, detection was at 278 nm unless otherwise noted. ^1H and ^{13}C NMR spectra were recorded at 500 and 125 MHz, chemical shifts are reported in ppm downfield from internal $(CH_3)_4Si$ (TMS) in $CDCl_3$, and coupling constants, J, are reported in hertz. For coupling constants of <1.1 Hz, squared sine bell apodization with zero filling was used for resolution enhancement. In such cases ^1H NMR data are reported according to the following example: 7.45 [d(q), 1 H, J = 1.0, 5-H], where d represents the multiplicity of the 5-H resonance under normal ^1H NMR conditions, and (q) represents the multiplicity of the resonance when resolution enhancement was used. Chemical shifts for ^{13}C NMR are reported in ppm relative to TMS (0 ppm), DMSO-d_6 (39.0 ppm), CD_3OD (49.0 ppm), or $CDCl_3$ (77.0 ppm) as noted. In cases where DEPT experiments were carried out during ^{13}C NMR experiments, the carbon multiplicities are listed as (0) quaternary, (1) methine, (2) methylene, (3) methyl. UV spectra were taken in CH_3CN unless otherwise noted. All melting points were determined with a Buchi melting point apparatus and are uncorrected.

1-Methyl-4,5-imidazoledicarboxylic Acid. To a 3-L, three-neck Morton flask equipped with a mechanical stirrer was added 6 M KOH (1500 mL). With cooling (ice bath) 1-methyl-4,5-dicyanoimidazole[19] (1.51 mol, 200 g) was introduced in 5 portions. After the addition was completed, the contents of the flask were refluxed for 9 h, the hot reaction mixture was adjusted to pH 2.0 with 6 M HCl, and the product was allowed to crystallize overnight at 0 °C. The crude diacid was recrystallized in two equal portions. Half of the crude diacid was suspended in water (200 mL), the pH was adjusted to 5.5 with 3% aqueous ammonia, and the resulting solution was then readjusted to pH 2.0 with 1.0 M HCl and was brought to near boiling to redissolve any precipitate. Crystallization overnight at 0 °C followed by sequential washing with cold dilute HCl (pH 2.0) and acetone afforded 105 g of the diacid as brown plates: combined yield of 215 g (85%); mp 259–260 °C (lit.[19] mp 259–260 °C). Anal. Calcd for $C_6H_6N_2O_4$: C, 42.4; H, 3.6; N, 16.5. Found: C, 42.4; H, 3.6; N, 16.6; K, <0.0007.

Procedure A. Reactions of 2,6-Dimethylpyrazine (7) and Imidazole Ester 9. 2-(6-Methyl-2-pyrazinyl)-1-(1-methyl-2-(methylthio)-4-bromo-5-imidazolyl)ethan-1-one (10d). To diisopropylamine (250 mol %, 28.3 mmol, 2.86 g, 3.97 mL) in THF (142 mL), chilled to −5 °C, was slowly added butyllithium (250 mol %, 1.59 M in hexanes, 28.3 mmol, 17.8 mL). The solution was stirred at −5 to 0 °C for 0.5 h, and then cooled to −78 °C as a cold solution (−78 °C) of 2,6-DMP (7) in THF (250 mol %, 28.3 mmol, 3.06 g, in 142 mL of THF) was added in a steady stream of drops via a Teflon cannula, maintaining the temperature of the reaction at −78 °C. To a separate flask was added ester **9** (100 mol %, 11.3 mmol, 3.00 g) in THF (126 mL, 0.09 M), and the resulting solution was chilled to −15 °C. The solution of the pyrazinylmethyl anion (held at −78 °C) was added dropwise to the solution of ester via a Teflon cannula over a 30-min period, maintaining reaction temperature between −15 and −19 °C. Addition was continued until a deep red color persisted in the reaction mixture. The reaction was immediately quenched with 1 M H_3PO_4/MeOH (5 mL) and evaporated to dryness. Phosphate buffer (pH 8.0, 1 M H_3PO_4/K_2HPO_4) was added to pH 7.0, the product was extracted into chloroform (5 × 150 mL), and the combined organic extracts were dried, filtered, and evaporated to leave an orange brown oil which solidified upon standing. Purification by LPLC (25% EtOAc/hexanes) afforded (a) recovered **9** (40%), (b) an intermediate fraction (TLC, R_f 0.47 in 50% EtOAc/hexanes), and (c), with 50% EtOAc/hexanes, ketone **10d**, 2.13 g, 55% yield: mp 116–117 °C; ^1H NMR δ 8.27 (s, 1 H, pyrH), 8.26 (s, 1 H, pyrH), 4.56 (s, 2 H, CH_2), 3.68 (s, 3 H, NCH_3), 2.60 (s, 3 H, pyrCH_3), 2.46 (SCH_3); ^{13}C NMR δ 185.69, 153.30, 151.82, 149.47, 142.66 (pyrCH), 142.65 (pyrCH), 129.58, 124.46, 47.49 (CH_2), 34.46 (NCH_3), 21.37 (pyrCH), 14.42 (SCH_3); IR (KBr) 1640 (C=O), 1338, 1247 cm^{-1}. Anal. Calcd for $C_{12}H_{13}N_4OS$: C, 42.3; H, 3.8; N, 16.4. Found: C, 42.6; H, 3.9; N, 16.8.

Procedure B. Alkylation of 2-(Methylthio)imidazolyl Pyrazinyl Ketones. 2-(6-Methyl-2-pyrazinyl)-1-(1-methyl-2-(methylthio)-4-bromo-5-imidazolyl)propan-1-one (13d). To ketone **10d** (5.39 mmol, 1.84 g) and THF (95 mL), cooled to −78 °C, was added KHMDS (1.85 M in THF, 150 mol %, 8.08 mmol, 4.37 mL) dropwise such that the internal temperature remained below −70 °C. The contents were stirred for 30 min at −78 °C, methyl iodide (150 mol %, 8.08 mmol, 1.15 g) was added, the reaction mixture was stirred for 36 h, while it gradually came to rt, and then 1 M H_3PO_4/MeOH (10 mL) was added. After evaporation, the residue was taken up in 1 M KH_2PO_4/K_2HPO_4 pH 8 buffer to pH 6.5 (about 300 mL) and extracted with ethyl acetate (3 × 200 mL) followed by chloroform (3 × 200 mL). The combined extracts were dried and evaporated to afford crude ketone as a red-brown oil. Purification by LPLC (25% EtOAc/hexanes and then 50% EtOAc/hexanes) gave 1.32 g, 69% yield, of ketone **13d**: TLC (EtOAc) R_f 0.68; mp 106–107 °C; ^1H NMR δ 8.34 (s, 1 H, pyrH), 8.22 (s, 1 H, pyrH), 5.12 (q, 1 H, CH), 3.66 (s, 3 H, NCH_3), 2.57 (s, 3 H, 7-CH_3), 2.41 (s, 3 H, SCH_3), 1.50 (d, 3 H, 5-CH_3); ^{13}C NMR δ 189.5 (C=O), 154.67, 152.83, 150.99, 142.23 (pyrCH), 140.89 (pyrCH), 129.68, 122.66, 48.23 (CH), 34.17 (NCH_3), 21.29 (7-CH_3), 16.97 (5-CH_3), 14.34 (SCH_3); IR (KBr) 3190, 2982, 2930, 1675 (C=O) cm^{-1}. Anal. Calcd for $C_{13}H_{15}N_4OSBr$: C, 43.9; H, 4.3; N, 15.8. Found: C, 43.8; H, 4.3; N, 15.7. Further elution with 50% EtOAc/hexanes provided 0.23 g (12%) of recovered ketone **10d**: R_f (EtOAc) 0.63. Dimethylated ketone also was isolated in a 3% yield: TLC (EtOAc) R_f 0.72; ^1H NMR 8.41 (s, 1 H, pyrH), 8.29 (s, 1 H, pyrH), 3.72 (s, 3 H, NCH_3), 2.63 (s, 3 H, 7-CH_3), 2.45 (s, 3 H, SCH_3), 1.73 (s, 6 H, 5-CH_3's); ^{13}C NMR δ 194.48 (C=O), 158.93, 152.42, 149.77, 141.67 (pyrCH), 139.04 (pyrCH), 130.60, 119.42, 52.94 (0), 34.57 (NCH_3), 26.44 (5-CH_3's), 21.41 (7-CH_3), 14.66 (SCH_3).

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Procedure C. Reduction of 2-(Methylthio)imidazolyl Pyrazinyl Ketones. 2-(6-Methyl-2-pyrazinyl)-1-(1-methyl-2-(methylthio)-4-bromo-5-imidazolyl)propan-1-ol (14d). To ketone **13d** (3.55 mmol, 1.26 g) in ethanol (125 mL), cooled to 0 °C, was added $NaBH_4$ (100 mol %, 3.55 mmol, 134 mg), and the reaction mixture was stirred overnight while gradually coming to rt. After the addition of acetone and evaporation to dryness, the residue was dissolved in $NaCl/H_2O$ (150 mL) and extracted with chloroform (3 × 150 mL). The combined chloroform layers were dried, filtered, and evaporated to afford 1.30 g, 100% yield, of alcohols **14d** as an orange-brown solid: mp 128–140 °C. Major diastereomer: ^1H NMR δ 8.33 (s, 1 H, pyrH), 8.30 (s, 1 H, pyrH), 5.15 (q, 1 H, C*H*OH), 3.73 (NCH_3), 3.47–3.37 (dq, 1 H, C*H*CH_2), 2.57 (s, 3 H, 7-CH_3), 2.47 (s, 3 H, SCH_3), 1.13 (d, 3 H, J = 7.11, 5-CH_3); ^{13}C NMR δ 157.53, 152.78, 144.57, 140.06, 140.94, 129.69, 115.07, 69.35 (CHOH), 43.73 (CH), 32.28 (NCH_3), 21.42 (7-CH_3), 17.01 (5-CH_3), 15.47 (SCH_3). Minor diastereomer: ^1H NMR δ 8.19 (s, 1 H, pyrH), 8.12 (s, 1 H, pyrH), 5.09 (q, 1 H, C*H*OH), 3.70 (NCH_3), 3.47–3.37 (dq, 1 H, C*H*CH_2), 2.56 (s, 3 H, 7-CH_3), 2.46 (s, 3 H, SCH_3), 1.49 (d, 3 H, J = 7.11, 5-CH_3); ^{13}C NMR δ 156.74, 152.69, 143.86, 142.19, 140.13, 130.10, 113.71, 69.59 (CHOH), 44.09 (CH), 32.39 (NCH_3), 21.28 (7-CH_3), 17.10 (5-CH_3), 15.47 (SCH_3).

Procedure D. Dehydration of 2-(Methylthio)imidazolyl Pyrazinyl Alcohols to Imidazolylpyrazinylethylenes. 2-(6-Methyl-2-pyrazinyl)-1-(1-methyl-2-(methylthio)-4-bromo-5-imidazolyl)prop-1-ene (15d). To diastereomeric alcohols **14d** (5.54 mmol, 2.04 g) in gently refluxing toluene was added methanesulfonic acid (MSA, 0.77 mmol, 74 mg, 13 mol %), and refluxing was continued for 20 min (Dean–Stark trap). After cooling, water (150 mL) was added, and the reaction mixture was made alkaline by addition of solid K_2CO_3, the pH of the aqueous layer was adjusted to pH 7.0 with 85% H_3PO_4, and the toluene layer was separated. The aqueous layer was extracted with chloroform (3 × 100 mL), and the combined organic layers were dried, filtered, and evaporated to give the crude product as an orange-brown solid. Purification by LPLC (25%, then 50% EtOAc/hexanes) afforded ethylenes **15d**, 1.31 g, 70% yield, and further chromatography allowed separation of the *E* and *Z* isomers. *E* isomer: TLC (50% EtOAc/hexanes) R_f 0.48; mp 96–97 °C; ^1H NMR δ 8.61 (s, 1 H, pyrH), 8.37 (s, 1 H, pyrH), 7.15 (d(q), 1 H, J = 1.29, vinylH) 3.50 (s, 3 H, NCH_3), 2.65 (s, 3 H, pyrCH_3), 2.56 (s, 3 H SCH_3), 2.25 (s(d), 3 H, J = 1.29, 5-CH_3); ^{13}C NMR δ 152.30, 151.17, 143.89, 142.84 (1, pyrCH), 138.39, 138.11 (1, pyrCH), 128.54, 115.71 (vinyl CH), 114.89 (0, vinylC), 31.58 (NCH_3), 21.37 (pyrCH_3), 16.87 (5-CH_3), 15.40 (SCH_3); UV λ_{max}, nm (ϵ) 264 (19 330), 332; UV (MeOH) 263, 322. *Z* isomer: TLC (50% EtOAc/hexanes) R_f 0.37; ^1H NMR δ 8.24 (s, 1 H, pyrH), 8.07 (s, 1 H, pyrH), 6.30 (q, 1 H, J = 1.60, vinylH), 3.26 (s, 3 H, NCH_3), 2.57 (s, 3 H, pyrCH_3), 2.51 (s, 3 H, SCH_3), 2.35 (d, 3 H, J = 1.60, 5-CH_3); ^{13}C NMR δ 153.17, 153.01, 143.47, 142.37 (pyrCH), 141.43, 140.76 (pyrCH), 127.67, 115.63 (vinylCH), 114.56 (0, vinylC), 31.83 (NCH_3), 22.97 (pyrCH_3), 21.52 (5-CH_3), 15.76 (SCH_3). Anal. Calcd for $C_{13}H_{15}N_4BrS$: C, 46.0; H, 4.5; N, 16.5. Found: C, 46.0; H, 4.6; N, 16.2.

Procedure E. Photochemical Cyclization of (2-(Methylthio)imidazolyl)pyrazinylethylenes. 2-(Methylthio)-3,5,7-trimethylimidazo[4,5-*f*]quinoxaline (26d). In a 340-mL quartz photochamber fitted with a magnetic stirring bar and nitrogen atmosphere were placed ethylene **15d** (0.88 mmol, 300 mg, mixtures of isomers), anhyd benzene (240 mL), and potassium *tert*-butoxide in *tert*-butyl alcohol (2000 mol %, 0.088 M, 100 mL). Nitrogen was bubbled through the solution for 30 min. In a separate quartz water-cooled jacket was placed a 450-W Hanovia lamp. The lamp was turned on and after 4 min was transferred to the quartz photochamber containing the reaction mixture which was irradiated for 7 min with continued nitrogen bubbling. Following the addition of 85% H_3PO_4 (0.8 g) and evaporation, the residue was suspended in a pH 8.0 1 M KH_2PO_4/K_2HPO_4 buffer (200 mL), and the pH of the resulting solution was adjusted to 7.0 with 85% H_3PO_4. Brine (200 mL) was added, and the aqueous layer was extracted with chloroform (5 × 100 mL). The combined chloroform phase was dried, filtered, and evaporated to give the crude tricycle. Purification by LPLC (50% EtOAc/hexanes) gave **26d**, 163.1 mg, 71.4% yield, as a yellow solid: TLC (EtOAc) R_f 0.52, (50% EtOAc/hexanes) R_f 0.21, (anisaldehyde stain); mp 211–213 °C dec; ^1H NMR δ 8.79 (s, 1 H, 8-H), 7.46 (s, 1 H, 4-H), 3.74 (s, 3 H, NCH_3), 2.92 (s, 3 H, SCH_3), 2.81 (s, 3 H, 5-CH_3), 2.78 (s, 3 H, 7-CH_3); ^{13}C NMR δ 151.43, 150.23, 144.36 (1, C8), 138.44, 136.86, 134.85, 133.80, 130.74, 112.58 (1, C4), 30.13 (NCH_3), 22.53 (7-CH_3), 17.98 (5-CH_3), 14.88 (SCH_3); IR (KBr) 3000, 2920, 1602, 1401, 1345, 1308, 1247, 1205, 1120, 1010, 984, 926 cm^{-1}; UV (MeOH) λ_{max}, nm (ϵ) 279 (52 480), 217. The analytical sample was sublimed at 100 °C (0.08 Torr). Anal. Calcd for $C_{13}H_{14}N_4S$: C, 60.4; H, 5.5; N, 21.7. Found: C, 60.0; H, 5.5; N, 21.3. Isomerized ethylene (*Z*)-**15d** was recovered: 25.7 mg (8.5%); TLC (EtOAc) R_f 0.67.

Procedure F. Oxidation of 2-(Methylthio)imidazoquinoxalines to Sulfones. 2-(Methylsulfonyl)-3,5,7-trimethylimidazo[4,5-*f*]quinoxaline (28d). 2-Methylthio tricycle **26d** (0.77 mmol, 200 mg) was dissolved in glacial acetic acid (20 mL), and aqueous $KMnO_4$ (0.1 M, 145 mol %, 1.12 mmol, 11.2 mL) was added dropwise at rt over a 15-min period then stirred for an additional hour at rt. Sodium sulfite was added until the mixture changed from dark brown to light yellow; it was diluted with water (200 mL), adjusted to pH 6.5 with sodium carbonate, adding water as necessary to keep the solution homogeneous, and extracted with chloroform (4 × 100 mL). Washing the combined organic layers with brine (100 mL), drying, and evaporating gave crude sulfone, 230 mg. LPLC (50% EtOAc/hexanes) gave 199 mg, 89% yield, of **28d** as a white solid: TLC (EtOAc) R_f 0.47; mp 226.5–227.5 °C dec; ^1H NMR δ 8.85 (s, 1 H, 8-H), 7.60 (d, 1 H, 4-H), 4.22 (s, 3 H, SO_2CH_3), 3.71 (s, 3 H, NCH_3), 2.86 (s, 3 H, 5-CH_3), 2.82 (s, 3 H, 7-CH_3); ^{13}C NMR δ 151.81, 147.32, 145.06 (C8), 140.02, 136.25, 135.32, 134.60, 134.47, 112.96 (C4), 42.46 (SO_2CH_3), 31.85 (NCH_3), 22.52 (7-CH_3), 18.38 (5-CH_3); IR (KBr) 3022, 3000, 2920, 1611, 1511, 1463, 1372, 1310 (asym SO_2), 1250, 1200, 1143 (sym SO_2) cm^{-1}. The analytical sample of sulfone **28d** was recrystallized from isooctane/$CHCl_3$ then sublimed (135 °C, 0.25 Torr). Anal. Calcd for $C_{13}H_{14}N_4O_2S$: C, 53.8; H, 4.9; N, 19.3. Found: C, 54.0; H, 5.0; N, 18.9.

Procedure G. Preparation of 2-(*N*-Benzylamino)-imidazoquinoxalines from 2-Methylsulfonyl Derivatives. 2-(*N*-Benzylamino)-3,5,7-trimethylimidazo[4,5-*f*]quinoxaline (32). Methylsulfonyl tricycle **28d** (0.34 mmol, 100 mg), dissolved in benzylamine (25 mL), was heated at 140–150 °C under a nitrogen atmosphere for 7 days. After cooling, the excess benzylamine was removed by rotary evaporation followed by Kugelrohr distillation (50 °C, 0.4 Torr). The oily yellow residue was purified by LPLC (50%, then 75% EtOAc/hexanes) to afford 94 mg, 86% yield, of **32** as a bright yellow solid: mp 252–254 °C (from CH_3CN); TLC (EtOAc) R_f 0.35; ^1H NMR ($CDCl_3$) δ 8.70 (s, 1 H, 8-H), 7.5–7.15 (m, 6 H, PhH, 4-H), 4.84 (d, 2 H, J = 4.0, CH_2), 4.5 (br s, 1 H, NH), 3.59 (s, 3 H, NCH_3), 2.83 (s, 3 H, 5-CH_3), 2.76 (s, 3 H, 7-CH_3); ^{13}C NMR ($CDCl_3$) δ 154.61, 148.80, 140.28, (C8), 136.90, 134.90, 132.68, 132.45, 128.17, 127.22, 126.60, 125.55, 113.00, 112.96; ^1H NMR (DMSO-d_6) δ 8.86 (s, 1 H, 8-H), 7.69 (q, 1 H, J = 1.0, 4-H), 7.42 (dd, 2 H, ortho H's), 7.32 (t, 2 H, meta H's), 7.23 (t, 1 H, para H), 4.68 (d, 2 H, J = 5.76, CH_2), 3.67 (s, 3 H, NCH_3), 2.71 (d, 3 H, J = 1.0, 5-CH_3), 2.67 (s, 3 H, 7-CH_3), 2.51 (br s, 2 H, NH_2); ^{13}C NMR (DMSO-d_6) δ 154.61, 148.81, 140.28 (C8), 136.90, 134.90, 132.68, 132.45, 128.17, 127.22, 126.66, 125.55, 113.00, 112.96; IR (KBr) 3300 (NH), 3115, 2978, 2960, 2886, 1612, 1594, 1560, 1515, 1472, 1392, 1351, 1302, 1246, 1221, 1189 cm^{-1}; UV (MeOH) λ_{max}, nm (ϵ) 279 (36 860), 215 (18 090); LRMS (EI) 317 (100, M^+), 302 (8), 240 (12, Ph), 226 (97, CH_2Ph), 199 (37, CH_2Ph, HCN), 172 (7), 158 (6), 91 (31, CH_2Ph). Anal. Calcd for $C_{19}H_{19}N_5$: C, 71.9; H, 6.0; N, 22.1. Found: C, 71.9; H, 6.0; N, 22.0. An additional 6% of **32** was obtained from the mother liquors along with 2 mg (2%) of methylthio tricycle **26d** which resulted from incomplete oxidation during the previous step.

Procedure H. Debenzylation of 2-(*N*-Benzylamino)-imidazoquinoxalines: 2-Amino-3,5,7-trimethylimidazo[4,5-*f*]quinoxaline (38). To a refluxing suspension of *N*-benzylamino tricycle **32** (43.9 mg, 0.138 mmol) and 10% Pd/C (44 mg) in anhyd methanol (5 mL) under a nitrogen atmosphere was added anhyd ammonium formate (26 mg, 300 mol %). Reflux was continued for 7 days. The mixture was cooled, the catalyst was removed by filtration through a Celite bed (3 × 1 cm) supported on a 5.0-μm millipore filter and washed with methanol (200 mL), and the filtrate was evaporated. Column chromatography (EtOAc) of the residue gave 6.5 mg, 15% yield, of unreacted *N*-benzylamino compound **32**. Further elution with 25% MeOH/EtOAc afforded

38, 25.2 mg, 81% yield, as a bright yellow solid: TLC (25% MeOH/EtOAc) R_f 0.14. The solid residue was triturated repeatedly with $CHCl_3$, the combined triturates were filtered and then evaporated, and the residue was dissolved in 0.6 M HCl (20 mL) and washed with $CHCl_3$ (3 × 20 mL). The separated aqueous layer was basified to pH 10 with concd aqueous NH_3, saturated with NaCl, and extracted with $CHCl_3$ (3 × 20 mL). The combined $CHCl_3$ extracts were dried, filtered, and evaporated to afford 22.1 mg, 70.6% yield, of **38** as a bright yellow solid: mp >340 °C after sublimation (270 °C, 0.3 Torr); ^{1}H NMR ($CDCl_3$) δ 8.74 (s, 1 H, 8-H), 7.44 (q, 1 H, J = 1.0, 4-H), 4.61 (br s, 2 H, NH_2), 3.69 (s, 3 H, NCH_3), 2.84 (d, 3 H, J = 1.0, 5-CH_3), 2.79 (s, 3 H, 7-CH_3); ^{1}H NMR (CD_3OD) δ 8.73 (s, 1 H, 8-H), 7.67 (d(q), 1 H, J = 1.0, 4-H), 3.70 (s, 3 H, NCH_3), 2.84 (s, 3 H, J = 1.0, NCH_3), 2.75 (s, 3 H, 7-CH_3); ^{1}H NMR (DMSO-d_6) δ 8.83 (s, 1 H, 8-H), 7.83 (d(q), 1 H, J = 1.0, 4-H), 3.67 (s, 3 H, NCH_3), 2.74 (s(d), 3 H, J = 1.0, 5-CH_3), 2.71 (s, 3 H, 7-CH_3); IR (KBr) 3380 (br), 3115 (br), 2920, 1627, 1543, 1460, 1339, 1241, 1192, 1114 cm^{-1}; LRMS (EI) 228 (39), 227 (100, M^+), 226 (93), 212 (32), 199 (32), 185 (12), 159 (10), 158 (11), 117 (9), 114 (14), 90 (7); UV (MeOH) λ_{max}, nm (ε) 340 (4090), 275 (40770), 210 (35290); HRMS (EI) calcd for $C_{12}H_{13}N_5$ 227.1173, found 227.1181.

2-(5-Methyl-2-pyrazinyl)-1-(4-bromo-1-methyl-2-(methylthio)-5-imidazolyl)ethan-1-one (10b) was prepared from 2,5-DMP (**6**, 35.4 mmol, 3.82 g) in 40 mL of THF and ester **9** (14.1 mmol, 3.75 g) in THF (70 mL) in accordance to procedure A. The crude orange brown solid product (5.22 g), after purification by LPLC (column pretreated with 1% triethylamine in 50% EtOAc/Hex) and elution with 50% EtOAc/hexanes, afforded ketone **10b**, 3.88 g, 80% yield, as a light yellow solid: mp 121 °C (from isooctane–minimal $CHCl_3$); TLC (EtOAc) R_f 0.48, (50% EtOAc/hexanes) R_f 0.31; ^{1}H NMR (200 MHz) δ 8.43 (s, 2 H pyrH), 4.54 (s, 2 H, CH_2), 3.77 (s, 3 H, NCH_3), 2.70 (s, 3 H, pyrCH_3), 2.56 (s, 3 H, SCH_3); ^{13}C NMR (50 MHz) δ 185.47 (C=O), 151.43, 146.99, 144.25, 143.46, 129.30, 124.15, 46.85, 34.26, 20.83, 14.24; IR (KBr) 2935, 1643 (C=O) cm^{-1}. Anal. Calcd for $C_{12}H_{13}N_4BrOS$: C, 42.2; H, 3.8; N, 16.4. Found: C, 42.4; H, 3.8; N, 16.4.

2-(5-Methyl-2-pyrazinyl)-1-(4-bromo-1-methyl-2-(methylthio)-5-imidazolyl)propan-1-one (13b). According to procedure B, a solution of ketone **10b** (10.5 mmol, 3.58 g) in THF (175 mL) was treated sequentially with KHMDS (0.5 M in toluene, 150 mol %, 15.7 mmol, 31.4 mL) and methyl iodide (120 mol %, 12.5 mmol, 1.78 g). A second portion of methyl iodide (912 mg) was introduced after 6 h, and the reaction mixture was stirred for an additional 24-h period, followed by a third portion of methyl iodide (912 mg) and stirring for an additional 24 h. Isolation and LPLC (25%, then 50% EtOAc/hexanes) gave 3.15 g, 85% yield, of ketone **13b** as a yellow oil: TLC (50% EtOAc/hexanes) R_f 0.56; ^{1}H NMR (200 MHz) δ 8.36 (s, 1 H, pyrH), 8.17 (s, 1 H, pyrH), 5.04 (q, 1 H, J = 7.0, CH), 3.57 (s, 3 H, NCH_3), 2.46 (s, 3 H, pyrCH_3), 2.34 (s, 3 H, SCH_3), 1.41 (d, 3 H, J = 7.0, 5-CH_3); ^{13}C NMR (50 MHz) δ 189.05 (C=O), 151.00, 151.97, 143.92, 143.59, 48.16, 34.77 (NCH_3), 21.41 (pyrCH_3), 17.55 (5-CH_3), 14.85 (SCH_3); IR (neat) 1655 cm^{-1} (C=O). Also isolated was 0.12 g (3.4%) of unreacted ketone **10b** and 0.11 g (3%) of the dialkylated ketone: TLC (50% EtOAc/hexanes) R_f 0.64; ^{1}H NMR (200 MHz) δ 8.64 (s, 1 H, pyrH), 8.42 (s, 1 H, pyrH), 3.86 (s, 3 H, NCH_3), 2.76 (s, 3 H, pyrCH_3), 2.67 (s, 3 H, SCH_3), 1.86 (s 6 H, 5-CH_3's).

2-(5-Methyl-2-pyrazinyl)-1-(4-bromo-1-methyl-2-(methylthio)-5-imidazolyl)prop-1-ene (15b). Reaction of ketone **13b** (5.85 mmol, 2.08 g) with $NaBH_4$ (100 mol %, 5.85 mmol, 221 mg) in ethanol according to procedure C afforded the crude diastereomeric alcohols **2-(5-methyl-2-pyrazinyl)-1-(4-bromo-1-methyl-2-(methylthio)-5-imidazolyl)propan-1-ol (14b)**, 2.0 g, 96% yield, which were treated with MSA (4.6 mmol, 79 mol %, 444 mg) in toluene according to procedure D. LPLC (25%, then 50% EtOAc/hexanes) afforded 1.34 g (70% from ketone **13b**) of olefin **15b** as a mixture of E and Z isomers, melting at 102–112 °C, separated by further chromatography. E isomer: TLC (EtOAc) R_f 0.64; mp 94.5–96.5 °C; ^{1}H NMR δ 8.69 (s, 1 H, pyrH), 8.44 (s, 1 H, pyrH), 7.09 (s, 1 H, vinylH), 3.50 (s, 3 H, NCH_3), 2.65 (s, 3 H, 5-CH_3), 2.60 (s, 3 H, pyrCH_3), 2.25 (s, 3 H, SCH_3); ^{13}C NMR δ 152.52 (0), 149.81 (0, pyrC), 144.18 (0, pyrC), 143.31 (1, pyrCH), 140.44 (1, pyrCH), 138.63 (0, vinyl C), 128.76 (0), 115.35 (1, vinylCH), 115.22 (0), 31.79 (NCH_3), 21.23 (pyrCH_3), 16.96 (5-CH_3), 15.67 (SCH_3); IR (KBr) 1621, 1570, 1445, 1435, 1403, 1304, 1219, 1159 cm^{-1}; UV λ_{max} 335 nm. Z isomer: TLC (EtOAc) R_f 0.58; ^{1}H NMR (250 MHz) δ 8.53 (s, 1 H, pyrH), 8.41 (s, 1 H, pyrH), 6.29 (s, 1 H, vinylH), 3.30 (s, 3 H, NCH_3), 2.61 (s, 3 H, pyrCH_3), 2.53 (s, 3 H, 5-CH_3), 2.35 (s, 3 H, SCH_3); UV λ_{max} 276 nm. Anal. Calcd for $C_{13}H_{15}N_4BrS$: C, 46.0; H, 4.5; N, 16.5. Found: C, 46.1; H, 4.4; N, 16.2.

2-(Methylthio)-3,5,8-trimethylimidazo[4,5-*f*]quinoxaline (26b). Following procedure E, mixed ethylene isomers **15b** (0.74 mmol, 250 mg) were photolyzed in benzene (125 mL) and *tert*-butoxide in *tert*-butyl alcohol (2500 mol %, 0.15 M, 125 mL). LPLC (50% EtOAc/hexanes) afforded tricycle **26b**, 160 mg, 83.7% yield, as a yellow solid: TLC (1/49.5/49.5 Et_3N/EtOAc/hexanes) R_f 0.35, (EtOAc) R_f 0.49; mp 141–143 °C dec; ^{1}H NMR δ 8.72 (s, 1 H, 7-H), 7.43 (s, 1 H, 4-H), 3.74 (s, 3 H, NCH_3), 2.93 (s, 3 H, 8-CH_3), 2.86 (s, 3 H, 5-CH_3), 2.79 (s, 3 H, SCH_3); ^{13}C NMR δ 152.67 (0), 151.11 (0), 142.14 (1, C7), 136.98 (0), 136.04 (0), 135.38 (0), 134.83 (0), 131.00 (0), 111.53 (0, C4), 30.01 (3, NCH_3), 22.37 (3, 8-CH_3), 17.97 (3, 5-CH_3), 14.76 (3, SCH_3); UV λ_{max} 279 nm; IR (KBr) 1420, 1347, 1298, 1200 cm^{-1}. A sample of tricycle **26b** was sublimed (106 °C, 0.15 Torr). Anal. Calcd for $C_{13}H_{14}N_4S$: C, 60.4; H, 5.5; N, 21.7. Found: C, 60.3; H, 5.5; N, 21.3.

2-(Methylsulfonyl)-3,5,8-trimethylimidazo[4,5-*f*]quinoxaline (28b). Treatment of 2-methylthio tricycle **26b** (0.38 mmol, 100 mg) with $KMnO_4$ (0.1 M, 129 mol %, 5 mL) according to procedure F gave, following LPLC (50% EtOAc/hexanes), 89.1 mg, 79.3% yield, of sulfone **28b** as a white solid: TLC (EtOAc) R_f 0.54; mp 233–234 °C dec; ^{1}H NMR δ 8.75 (s, 1 H, 7-H), 7.51 (s, 1 H, 4-H), 4.16 (s, 3 H, SO_2CH_3), 3.65 (s, 3 H, NCH_3), 2.83 (s, 3 H, 8-CH_3), 2.81 (s, 3 H, 5-CH_3); ^{13}C NMR δ 153.97, 147.35, 143.59 (C7), 138.70, 136.75, 136.57, 135.40, 112.11 (C4), 42.50 (SO_2CH_3), 31.91 (NCH_3), 22.55 (8-CH_3), 18.50 (5-CH_3); UV λ_{max} 272, 235, 230 nm; IR (KBr) 1305 cm^{-1} (asym SO_2), 1140 cm^{-1} (sym SO_2). The analytical sample was sublimed (130 °C, 0.8 Torr). Anal. Calcd for $C_{13}H_{14}N_4O_2S$: C, 53.8; H, 4.9; N, 19.3. Found: C, 53.9; H, 5.0; N, 18.7.

2-(*N*-Benzylamino)-3,5,8-trimethylimidazo[4,5-*f*]quinoxaline (31). Reaction of sulfone **28c** (0.34 mmol, 100 mg) with benzylamine (23 mL) at 145–150 °C for 51 h according to procedure G followed by LPLC (50% EtOAc/hexanes, then EtOAc) gave 100 mg, 91% yield, of **31**: TLC (EtOAc) R_f 0.39; mp 219–220 °C (from CH_3CN); ^{1}H NMR δ 8.62 (s, 1 H, 7-H), 7.35 (s, 1 H, 4-H), 7.30–7.24 (m, 5 H, PhH), 4.80–4.70 (3 H, overlapping broad NH singlet and CH_2 singlet at 4.75), 3.62 (s, 3 H, NCH_3), 2.83 (s, 3 H, 8-CH_3), 2.70 (s, 3 H, 5-CH_3); ^{13}C NMR δ 153.83, 152.13, 141.80 (C7), 138.57, 136.80, 134.47, 134.34, 133.15, 128.43, 128.24 (1, 2 carbons, Ph), 128.05 (1, 2 carbons, Ph), 127.40 (1, Ph), 111.31 (C4), 47.82 (CH_2), 28.64 (NCH_3), 22.35 (8-CH_3), 18.00 (5-CH_3); IR (KBr) 3350 (br, NH), 3012, 2960, 2920, 1558 (s) cm^{-1}; UV λ_{max}, nm (ε) 279 (53600), 216. Anal. Calcd for $C_{19}H_{19}N_5$: C, 71.9; H, 6.0; N, 22.1. Found: C, 71.8; H, 6.1; N, 22.4.

2-Amino-3,5,8-trimethylimidazo[4,5-*f*]quinoxaline (37). Debenzylation of 2-*N*-benzylamino tricycle **31** (35 mg, 0.11 mmol) using 10% Pd/C (35 mg) and ammonium formate (800 mol%, 55 mg) in refluxing methanol (10 mL) for 5 days according to procedure H afforded 5.9 mg (17%) of unreacted **31** and 20.7 mg, 83% yield, of **37**: mp >300 °C (lit.[6a] mp >300 °C); ^{1}H NMR ($CDCl_3$) δ 8.68 (s, 1 H, 7-H), 7.38 (d(q), 1 H, J = 1.0, 4-H), 4.56 (s, 2 H, NH_2), 3.68 (s, 3 H, NCH_3), 2.84 [s(d), 3 H, J = 1.0, 5-CH_3], 2.82 (s, 3 H, 8-CH_3), ^{1}H NMR (CD_3OD) δ 8.62 (s, 1 H, 7-H), 7.51 (d(q), 1 H, J = 1.0, 4-H), 3.65 (s, 3 H, NCH_3), 2.75 (s, 3 H, 8-CH_3), 2.74 [d(d), 3 H, J = 1.0, 5-CH_3]; ^{13}C NMR (CD_3OD) δ 155.92, 153.57, 143.00, 137.75, 134.74, 134.07, 133.86, 129.61, 29.21, (NCH_3), 22.20 (8-CH_3), 18.00 (5-CH_3); UV (MeOH) λ_{max}, nm (ε) 335 (2510), 275 (36950), 214 (25420); LRMS (EI) 227 (100, M^+), 226 (71), 212 (11, CH_3), 199 (19.5), 185 (11), 129 (10), 158 (10), 117 (8), 114 (3), 90 (6.5); FTIR (KBr) 3500–2800 br (NH_2), 3080, 2914, 1634, 1556, 1544, 1485, 1418, 1377, 1295, 1190, 1126, 1040, 998, 853, 826 cm^{-1}; HRMS (EI) calcd for $C_{12}H_{13}N_5$ 227.1173, found 227.1167. Anal. Calcd for $C_{12}H_{13}N_5$: C, 63.4; H, 5.8; N, 30.8. Found: C, 63.4, H, 5.6; N, 30.4.

2-(6-Methyl-2-pyrazinyl)-1-(4-bromo-1-methyl-2-(methylthio)-5-imidazolyl)ethan-1-ol (11d). A solution of ketone **10d** (5.30 mmol, 1.81 g) in ethanol (180 mL) and THF (60 mL) was treated with $NaBH_4$ according to procedure C to give alcohol **11d**, 1.85 g, 100% yield: mp 125–126 °C ($CHCl_3$/hexanes); ^{1}H NMR (200 MHz) δ 8.30 (s, 1 H, pyrH), 8.24 (s, 1 H, pyrH), 5.27 (m, 2

H, CH, OH), 3.76 (s, 3 H, NCH_3), 3.5–3.35 (m, 1 H, CH_AH_B), 3.2–3.05 (m, 1 H, CH_AH_B), 2.55 (s, 3 H, 7-CH_3), 2.53 (s, 3 H, SCH_3); IR (KBr) 3235 (br, OH), 3005, 1533 cm^{-1}. Anal. Calcd for $C_{12}H_{15}N_4OSBr$: C, 42.0; H, 4.4; N, 16.3. Found: C, 42.2; H, 4.5; N, 16.3.

2-(6-Methyl-2-pyrazinyl)-1-(4-bromo-1-methyl-2-(methylthio)-5-imidazolyl)ethene [(*E*)-12d]. Dehydration of alcohol **11d** (1.03 g, 2.93 mmol) using MSA (100 μL) in refluxing toluene (150 mL) according to procedure D gave (*E*)-**12d** following LPLC (50% EtOAc/hexanes): 870 mg, 91.3% yield; TLC (EtOAc) R_f 0.57; mp 126–126.5 °C; ^1H NMR δ 8.36 (s, 1 H, pyrH), 8.28 (s, 1 H, pyrH), 7.54 (d, 1 H, J_{AB} = 16.1, 5-H), 7.30 (d, 1 H, J_{AB} = 16.1, 4-H), 3.68 (s, 3 H, NCH_3), 2.65 (s, 3 H, pyrCH_3), 2.58 (s, 3 H, SCH_3); ^{13}C NMR δ 153.34, 149.47, 145.57, 142.65 (pyrCH), 140.77 (pyrCH), 128.13, 123.80 (vinyl C), 118.75 (vinyl C), 117.27, 32.01 (NCH_3), 21.66 (7-CH_3), 15.54 (SCH_3); IR (KBr) 3100 (olefinic CH), 1632 (C=C), 1510, 1460, 1233, cm^{-1}; UV λ_{max}, nm (ϵ) 365 (14600). Anal. Calcd for $C_{11}H_{13}N_4SBr$: C, 44.3; H, 4.0; N, 17.2. Found: C, 44.5; H, 4.1; N, 17.2.

3,7-Dimethyl-2-(methylthio)imidazo[4,5-*f*]quinoxaline (25d). A solution of ethylene **12d** (0.31 mmol, 100 mg) in benzene (100 mL) and *tert*-butoxide/*tert*-butyl alcohol (2280 mol %, 0.1 M, 70 mL) was irradiated for 5 min according to procedure E. Isolation and purification of the crude residue by LPLC (50% EtOAc/hexanes) afforded 2-methylthio tricycle **25d**, 19.6 mg, 26% yield: TLC (EtOAc) R_f 0.27; ^1H NMR δ 8.83 (s, 1 H, 8-H), 7.80 (d, 1 H, J = 8.73, 5-H), 7.66 (d, 1 H, J = 8.73, 4-H), 3.79 (s, 3 H, NCH_3), 2.94 (s, 3 H, SCH_3), 2.79 (s, 3 H, 7-CH_3); ^{13}C NMR δ 152.89, 151.45, 144.95 (C8), 139.23, 138.36, 135.31, 133.67, 122.39 (C5), 113.01 (C4), 30.29 (NCH_3), 22.39 (7-CH_3), 14.83 (SCH_3); UV (MeOH) λ_{max}, nm (ϵ) 334, 275 (60960). The analytical sample was purified by preparative TLC (EtOAc, 1000 μ) and then sublimed (91 °C, 0.1 Torr). Anal. Calcd for $C_{12}H_{12}N_4S$: C, 59.0; H, 5.0; N, 22.9. Found: C, 58.7; H, 5.0; N, 22.8.

3,7-Dimethyl-2-(methylsulfonyl)imidazo[4,5-*f*]quinoxaline (28b). Treatment of 2-methylthio tricycle **25d** (0.18 mmol, 43.9 mg) with aqueous $KMnO_4$ (145 mol %, 0.26 mmol, 0.1 M, 2.6 mL) in HOAc (4 mL) according to procedure F for 1 h gave 36.7 mg, 73.8% yield, of sulfone **28b** following purification by LPLC (50% EtOAc/hexanes, then EtOAC): TLC (EtOAc) R_f 0.51; mp 235–237 °C dec. The analytical sample was sublimed (160 °C, 0.09 Torr). Anal. Calcd for $C_{12}H_{12}N_4O_2S$: C, 52.2; H, 4.4; N, 20.4. Found: C, 52.2; H, 4.4; N, 20.1.

2-(*N*-Benzylamino)-3,7-dimethylimidazo[4,5-*f*]quinoxaline (30). Methylsulfonyl tricycle **28b** (0.36 mmol, 100 mg) was treated as in procedure G to afford 100 mg (91%) of **30**: TLC (EtOAc) R_f 0.18; mp 160–171 °C. Reverse-phase HPLC (80/20, CH_3CN–H_2O, 3 mL/min flow rate) afforded 95 mg, 86% yield, of analytically pure **30**: mp 195.5–196.5 °C; ^1H NMR δ 8.65 (s, 1 H, 8-H), 7.67 (d, 1 H, J = 8.63, 5-H), 7.51 (d, 1 H, J = 8.63, 4-H), 7.42–7.2 (m, 5 H, PhH), 4.97 (bs, 1 H, NH), 4.78 (s, 2 H, CH_2), 3.60 (s, 3 H, NCH_3), 2.72 (s, 3 H, 7-CH_3); ^{13}C NMR δ 154.56, 150.62, 144.23 (C8), 138.85, 138.56, 136.86, 132.92, 132.76, 128.40 (PhCH, 2 carbons), 127.97 (PhCH, 2 carbons), 127.36 (*p*-PhCH), 119.45 (C5), 112.14 (C4), 47.62 (CH_2), 28.62 (NCH_3), 22.30 (7-CH_3); IR (KBr) 3385 (NH), 3035, 3000, 1561, 1462, 1350, 1298 cm^{-1}; UV (MeOH) λ_{max}, nm (ϵ) 339 (2870), 278 (72400), 215 (32610); LRMS (EI) 303 (M^+, 100), 302 (37), 288 (13, CH_3), 226 (20, Ph), 212 (91, CH_2Ph), 198 (19, C_7H_7N), 185 (56, CH_2Ph, HCN), 158 (14), 117 (15), 91 (76, CH_2Ph). Anal. Calcd for $C_{18}H_{17}N_5$: C, 71.3; H, 5.7; N, 23.1. Found: C, 71.4; H, 5.7; N, 23.1.

2-Amino-3,7-dimethylimidazo[4,5-*f*]quinoxaline (36). Debenzylation of the 2-*N*-benzylamino tricycle **30** (11.7 mg, 0.038 mmol) using 10% Pd/C (14 mg) and ammonium formate (1300 mol %, 32 mg) in refluxing methanol (20 mL) according to procedure H afforded 3.5 mg of unreacted **30** (30%) and 5.1 mg, 62.2% yield, of **36**: TLC (25% MeOH/EtOAc) R_f 0.10; mp >300 °C, 250–255 °C (sealed evacuated capillary, sublimed) (lit.[5b] mp 330–340 °C (sealed tube, dec)); ^1H NMR ($CDCl_3$) δ 8.78 (s, 1 H, 8-H), 7.73 (d, 1 H, J = 8.8, 5-H), 7.60 (d, 1 H, J = 8.8, 4-H), 4.90 (s, 2 H, NH_2), 3.72 (s, 3 H, NCH_3), 2.78 (s, 3 H, 7-CH_3); ^1H NMR (CD_3OD) δ 8.76 (s, 1 H, 8-H), 7.77 (d, 1 H, J = 8.8, 5-H), 7.62 (d, 1 H, J = 8.8, 4-H), 3.71 (s, 3 H, NCH_3), 2.73 (s, 3 H, 7-CH_3); ^1H NMR (DMSO-d_6) δ 8.83 (s, 1 H, 8-H), 7.91 (d, 1 H, J = 8.8, 5-H), 7.69 (d, 1 H, J = 8.8, 4-H), 3.70 (s, 3 H, NCH_3), 2.69 (s, 3 H, 7-CH_3); FTIR (KBr) 3300, 3152, 2961, 2926, 2852, 1561, 1551, 1468, 1452, 1349, 1289, 1249, 1179, 1130, cm^{-1}; UV λ_{max}, nm (ϵ) 343 (6450), 270 (38110), 217 (32970); LRMS (EI) 214 (28), 213 (M^+, 100), 198 (CH_3, 16), 185 (38), 171 (13), 159 (5), 145 (15), 144 (29), 130 (13), 117 (21), 116 (11), 103 (27); HRMS (EI) calcd for $C_{11}H_{11}N_5$ 213.1016, found 213.1019.

2-(5-Methyl-2-pyrazinyl)-1-(4-bromo-1-methyl-2-(methylthio)-5-imidazolyl)ethene (12b). Ketone **10b** (6.53 mmol, 2.23 g) was reduced with $NaBH_4$ (100 mol %, 248 mg) in a mixture of THF (100 mL) and 2-propanol (80 mL) according to procedure C. A second aliquot of $NaBH_4$ (100 mol %) was then added at 0 °C, and the reaction mixture was stirred an additional 8 h (0 °C to rt). Isolation and LPLC (50% EtOAc/hexanes) gave unreacted ketone **10b**, 0.47 g (21%); further elution with 2-propanol afforded alcohol **2-(5-methyl-2-pyrazinyl)-1-(4-bromo-1-methyl-2-(methylthio)-5-imidazolyl)ethan-1-ol (11b)**, 1.80 g, 79% yield: ^1H NMR (200 MHz) δ 8.28 (s, 2 H, pyrH's), 5.2 (dq, 1 H, CH), 3.75 (s, 3 H, NCH_3), 3.30 (m, 1 H, CH_AH_B), 3.10 (m, 1 H, CH_AH_B), 2.50 (s, 3 H, 8-CH_3), 2.48 (s, 3 H, SCH_3); ^{13}C NMR (50 MHz) δ 151.27 (0), 149.97 (0), 144.02 (0), 143.48 (1), 143.05 (1), 130.19 (0), 113.12 (0), 64.97 (CHOH), 40.13 (CH_2), 32.10 (NCH_3), 20.64 (8-CH_3), 15.48 (SCH_3). Treatment of alcohol **11b** (5.18 mmol, 1.78 g) with MSA (60 mol%, 3.1 mmol, 298 mg) in refluxing toluene according to procedure D afforded, after LPLC (50% EtOAc/hexanes, then EtOAc), 1.42 g, 84.5% yield, of ethylene **12b** after sublimation (102 °C, 0.2 Torr): TLC (EtOAc) R_f 0.43; mp 198–199 °C; ^1H NMR δ 8.44 (d, 1 H, J = 1.1, pyrH), 8.41 (s, 1 H, pyrH), 7.42 (ABq, 2 H, J_{trans} = 16.1, 4-H, 5-H), 3.67 (s, 3 H, NCH_3), 2.66 (s, 3 H, 8-CH_3), 2.57 (s, 3 H, SCH_3); ^{13}C NMR δ 152.05, 147.74, 145.41, 144.08 (pyrCH), 142.84 (pyrCH), 128.17, 123.73 (C5), 118.01 (C4), 116.98, 31.98 (NCH_3), 21.35 (8-CH_3), 15.63 (SCH_3); UV λ_{max} 374 nm. Anal. Calcd for $C_{12}H_{13}N_4BrS$: C, 44.3; H, 4.0; N, 17.2. Found: C, 44.6; H, 4.14; N, 17.2.

3,8-Dimethyl-2-(methylsulfonyl)imidazo[4,5-*f*]quinoxaline (28a). A solution of ethylene **12b** (0.31 mmol, 100 mg) in benzene (100 mL) and *tert*-butoxide/*tert*-butyl alcohol (2000 mol %, 0.088 M, 70 mL) was photolyzed according to procedure E for 10 min. Purification of the crude residue by LPLC (50% EtOAc/hexanes) yielded 67 mg, 68% yield, of **3,8-dimethyl-2-(methylthio)-imidazo[4,5-*f*]quinoxaline (25b)**: TLC (EtOAc) R_f 0.36; ^1H NMR δ 8.72 (s, 1 H, 7-H), 7.75 (ABq, 2 H, J = 8.9, 4-H, 5-H), 3.82 (s, 3 H, NCH_3), 2.95 (s, 3 H, 8-CH_3), 2.86 (s, 3 H, SCH_3); ^{13}C NMR δ 153.52, 152.77, 143.80 (1, C7), 138.09, 137.83, 136.05, 134.92, 123.21 (1, C5), 112.02 (1, C4), 30.40 (NCH_3), 22.68 (8-CH_3), 14.91 (SCH_3); IR ($CHCl_3$) 2998, 2940, 1557, 1510, 1450, 1423, 1350, 1305, 1138, 1094 cm^{-1}; UV λ_{max}, nm (ϵ) 326, 275 (55600), 215. Oxidation of 2-methylthio tricycle **25b** (0.325 mmol, 79.5 mg) with aqueous $KMnO_4$ (0.1 M, 145 mol %, 0.47 mmol, 4.7 mL) according to procedure F (rt, 45 min), yielded sulfone **28a**, 45.9 mg (51.1%): mp 222–223 °C dec; ^1H NMR δ 8.83 (s, 1 H, 7-H), 8.12–7.77 (ABq, 2 H, J = 9.1, 4 H, 5 H), 4.29 (s, 3 H, SO_2CH_3), 3.73 (s, 3 H, NCH_3), 2.91 (s, 3 H, 8-CH_3); ^{13}C NMR δ 154.63, 148.36, 145.00 (C7), 139.34, 136.81, 135.73, 135.44, 128.04 (C5), 112.95 (C4), 42.52 (SO_2CH_3), 32.16 (NCH_3), 22.79 (8-CH_3); IR (KBr) 1295 (SO_2), 1133 (SO_2) cm^{-1}; the analytical sample of sulfone **28a** was sublimed (0.09 Torr, 166 °C); HRMS (FAB) calcd for $C_{12}H_{12}N_4O_2S$ 276.0683, found 276.0679.

2-(*N*-Benzylamino)-3,8-dimethylimidazo[4,5-*f*]quinoxaline (29). Sulfone **28a** (16 mg, 0.06 mmol) was treated with benzylamine for 45 h according to procedure G, affording 16 mg, 88% yield, of *N*-benzylamino tricycle **29** after reverse-phase HPLC (80/20, CH_3CN/H_2O, 3.0 mL/min): mp 98–103 °C; ^1H NMR δ 8.63 (s, 1 H, 7-H), 7.76 (d, 1 H, J = 8.81, 5-H), 7.52 (d, 1 H, J = 8.81, 4-H), 7.37–7.25 (m, 5 H, PhH), 4.84 (d, 2 H, J = 5.09, CH_2), 4.70 (br t, 1 H, J = 5.09 NH), 3.65 (s, 3 H, NCH_3), 2.78 (s, 3 H, 8-CH_3); ^{13}C NMR δ 154.35, 152.74, 143.34 (C7), 138.52, 137.90, 136.19, 134.27, 133.55, 128.61 (1, Ph, 2 carbons), 128.16 (1, Ph, 2 carbons) 127.61 (1, Ph, 1 carbon), 120.65 (1, C5), 111.16 (1, C4), 47.93 (CH_2), 28.75 (NCH_3), 22.55 (8-CH_3); IR (KBr) 3270 (br NH), 3060, 3010, 1580, 1358, 1302, 1262, cm^{-1}; UV (MeOH) λmax nm (ϵ) 342 (3300), 278 (45640), 215 (30560); LRMS (EI) 303 (M^+, 100), 302 (31), 298 (12.6, CH_3), 226 (15.6, Ph), 212 (63, CH_2Ph), 198 (13.5, C_7H_7N), 185 (37, CH_2Ph, HCN), 158 (9), 117 (8), 91 (42.6, CH_2Ph); HRMS (EI) calcd for $C_{18}H_{17}N_5$ 303.1486, found 303.1490.

2-Amino-3,8-dimethylimidazo[4,5-*f*]quinoxaline (35). Debenzylation of *N*-benzylamino tricycle **29** (9.9 mg, 0.032 mmol)

using 10% Pd/C (11.2 mg) and ammonium formate (1150 mol %, 24 mg) in refluxing methanol (10 mL) for 4 days according to procedure H afforded 5.0 mg, 72% yield, of **35** after sublimation (240 °C, 0.05 Torr): mp 279–282 °C (sealed evacuated capillary, dec) [lit.[5b] mp 295–300 °C (sealed capillary, dec)]; ^{1}H NMR ($CDCl_3$) δ 8.68 (s, 1 H, 7-H), 7.77 (d, 1 H, J = 8.80, 5-H), 7.55 (d, 1 H, J = 8.80, 4-H), 4.68 (br s, 2 H, NH_2), 3.72 (s, 3 H, NCH_3), 2.82 (s, 3 H, 8-CH_3); ^{1}H NMR (CD_3OD) δ 8.63 (s, 1 H, 7-H), 7.72 (d, 1 H, J = 8.80, 5-H), 7.64 (d, 1 H, J = 8.80, 4-H), 3.70 (s, 3 H, NCH_3), 2.77 (s, 3 H, 8-CH_3); ^{1}H NMR (DMSO-d_6) δ 8.82 (s, 1 H, 7-H), 7.92 (d, 1 H, J = 8.80, 5-H), 7.83 (d, 1 H, J = 8.80, 4-H), 3.71 (s, 3 H, NCH_3), 2.75 (s, 3 H, 8-CH_3); FTIR (KBr) 3308 (br), 3186 (br), 2957, 2925, 2852, 1652, 1636, 1559, 1543, 1466, 1393, 1376, 1305, 1290 cm^{-1}; UV (MeOH) λmax nm (ε) 341 (3920), 274 (35 200), 211 (28 460); LRMS (EI) 214 (26), 213 (M^+, 100), 212 (84), 198 (14), 197 (13), 185 (14), 171 (22), 159 (15), 145 (52), 144 (37), 130 (15), 117 (25), 116 (14), 103 (31); HRMS (EI) calcd for $C_{11}N_{11}N_5$ 213.1016, found 213.1007.

***tert*-Butyl 3-Oxo-3-(4-bromo-1-methyl-2-(methylthio)-5-imidazolyl)propanoate (19).** To THF (100 mL) and diisopropylamine (300 mol %, 45.2 mmol, 6.3 mL) at 0 °C was slowly added *n*-butyllithium (1.58 M, 300 mol %, 28.6 mL), and the solution was stirred for 1 h at 0 °C. After further cooling to −78 °C, *tert*-butyl acetate (300 mol %, 45.2 mmol, 6.1 mL) was slowly introduced while maintaining the internal temperature between −78 and −70 °C, and then the reaction mixture was stirred for an additional 1 h at −78 °C.

To imidazole ester **9** (100 mol %, 4.0 g, 15.1 mmol) and THF (100 mL), cooled to 0 °C, was added 1 M LiOMe (200 mol %, in THF) via a Teflon cannula at 0 °C. THF (30 mL) was used to transfer this solution quantitatively. The reaction mixture was further cooled to −5 °C, and then the *tert*-butyl acetate anion solution was transferred dropwise (3 drops/s) over 30 min to the imidazole ester solution via a Teflon cannula, followed immediately by methanolic H_3PO_4 (2 M, 60 mmol). After evaporation to dryness, the residue was taken up in water (300 mL) and chloroform (300 mL), the organic layer was separated, the aqueous phase was adjusted to pH 7 and further extracted with chloroform (3 × 200 mL), and the combined chloroform layers were dried. Evaporation following filtration afforded crude β-keto ester, 6.3 g, which was purified by LPLC (10% EtOAc/hexanes) to give 5.19 g, 98.7% yield, of **19** after recrystallization from isooctane: mp 115–115.5 °C; ^{1}H NMR δ 3.90 (s, 2 H, CH_2), 3.73 (s, 3 H, NCH_3), 2.62 (s, 3 H, SCH_3), 1.42 (s, 9 H, *tert*-butyl); ^{13}C NMR δ 182.60 (C=O), 166.52 (C(=O)OR), 151.67 (C2), 129.66 (C5), 124.72 (C4), 81.93 (0, *tert*-butyl), 49.04 (CH_2), 34.52 (NCH_3), 27.92 (*tert*-butyl CH_3's), 14.49 (SCH_3): IR (KBr) 1730 (C=O(OR)), 1652 (C=O), 1495, 1464, 1398 (*tert*-butyl), 1374 (*tert*-butyl), 1253 (C-O), 1135 (C-O) cm^{-1}. Anal. Calcd for $C_{12}H_{17}N_2BrO_3S$: C, 41.3; H, 4.9; N, 8.0. Found: C, 41.3; H, 4.7; N, 7.7.

1-(4-Bromo-1-methyl-2-(methylthio)-5-imidazolyl)ethanone (21). Trifluoroacetic acid (TFA, 20 mL) and β-keto ester **19** (1.16 g, 3.32 mmol) were refluxed for 24 h. Cooling and evaporation left an oily residue which was suspended in water (150 mL), and the pH was adjusted to 7.2 using Na_2CO_3. The aqueous layer was extracted with chloroform (4 × 50 mL), and the combined chloroform layers were dried, filtered, and evaporated to give crude ketone (0.81 g) which was purified by LPLC (5%, then 10% EtOAc/hexanes). Ketone **21** was isolated in a 99% yield (0.81 g): mp 92–93 °C (from isooctane); TLC (10% EtOAc/hexanes) R_f 0.25; ^{1}H NMR δ 3.53 (s, 3 H, NCH_3), 2.46 (s, 3 H), 2.38 (s, 3 H); ^{13}C NMR δ 186.87 (C=O), 150.35 (C2), 129.60 (C5), 123.85 (C4), 34.02 (NCH_3), 29.93 (CH_3), 14.11 (SCH_3). Anal. Calcd for $C_7H_9N_2BrOS$: C, 33.7; H, 3.6; N, 11.2. Found: C, 33.6; H, 3.6; N, 11.0.

3-(6-Methyl-2-pyrazinyl)-2-(4-bromo-1-methyl-2-(methylthio)-5-imidazolyl)propan-2-ol (22d). A 0.09 M solution of 2,6-DMP anion was prepared according to procedure A and used immediately. In a separate flask were placed imidazole ketone **21** (100 mol %, 8.02 mmol, 2.00 g) and THF (89 mL); the resulting 0.09 M solution was chilled to −5 °C, and the pyrazinylmethyl anion solution (held at −78 °C) was added to the ester solution dropwise via a Teflon cannula over a 30-min period. The addition was carried out such that the internal reaction temperature was kept between −6 and −1 °C. After addition was complete, stirring was continued for an additional 15 min, 2 M H_3PO_4/MeOH (250 mol %) was added, and the mixture was evaporated. The residue was suspended in water (400 mL), the pH was adjusted to 7.5 by addition of K_2CO_3, the product was extracted into chloroform (3 × 150 mL), and the combined organic phase was dried, filtered, and evaporated. Purification of the residue by LPLC gave (a) 200 mg (10%) of unreacted ketone **21** (25% EtOAc/hexanes), (b) 2,6-DMP (50% EtOAc/hexanes), and (c) tertiary alcohol **22d** (75% EtOAc/hexanes), 2.48 g, 86.7% yield: mp 97–99.5 °C, TLC (25% EtOAc/hexanes) R_f 0.16; ^{1}H NMR δ 8.34 (s, 1 H, pyrH), 8.32 (s, 1 H, pyrH), 6.56 (s, 1 H, OH), 3.90 (d, 1 H, J = 15.5, CH_AH_B), 3.78 (s, 3 H, NCH_3), 3.17 (d, 1 H, J = 15.5, CH_AH_B), 2.52 (s, 3 H, 7-CH_3), 2.49 (s, 3 H, SCH_3), 1.65 (s, 3 H, 4-CH_3); ^{13}C NMR δ 152.99, 151.39, 143.84, 142.78 (pyrCH), 142.52 (pyrCH), 138.10, 110.85, 73.02, (0, C), 43.40 (CH_2), 34.71 (NCH_3), 29.33 (4-CH_3), 21.24 (7-CH_3), 15.43 (SCH_3). Anal. Calcd for $C_{13}H_{17}N_4BrOS$: C, 43.7; H, 4.8; N, 15.7. Found: C, 43.8; H, 4.7; N, 15.5.

1-(6-Methyl-2-pyrazinyl)-2-(4-bromo-1-methyl-2-(methylthio)-5-imidazolyl)prop-1-ene (23d). Alcohol **22d** (3.08 mmol, 1.10 g) was treated with MSA (2.31 mmol, 222 mg) in refluxing toluene (200 mL) according to procedure D. Purification of the crude residue by LPLC (50% EtOAc/hexanes) afforded ethylene **23d**, 870 mg, 83.6% yield, as a 4/1, E/Z, mixture of isomers. E isomer: TLC (50% EtOAc/hexanes) R_f 0.37; ^{1}H NMR δ 8.37 (s, 1 H, pyrH), 8.29 (s, 1 H, pyrH), 6.56 (d(q), 1 H, J = 1.5, vinyl H), 3.55 (s, 3 H, NCH_3), 2.64 (s, 3 H, 7-CH_3), 2.60 (s, 3 H, SCH_3), 2.50 [s(d), 3 H, J = 1.5, 4-CH_3]; ^{13}C NMR δ 152.67, 152.63, 150.26, 142.45 (pyrCH), 141.57 (pyrCH), 134.40, 132.07, 129.29 (vinyl CH), 113.25 (0, vinyl), 32.24 (NCH_3), 21.49 (7-CH_3), 19.02 (4-CH_3), 15.58 (SCH_3); UV λmax 319 nm. Z isomer: TLC (50% EtOAc/hexanes) R_f 0.31; ^{1}H NMR δ 8.19 (s, 1 H, pyrH), 7.97 (s, 1 H, pyrH), 6.82 [d(q), 1 H, J = 1.64, vinyl H], 3.27 (s, 3 H, NCH_3), 2.61 (s, 3 H, 7-CH_3), 2.41 (s, 3 H, SCH_3), 2.23 (s(d), 3 H, J = 1.64, 4-CH_3); ^{13}C NMR δ 152.84, 149.32, 143.20, 141.99 (pyrCH), 140.72 (pyrCH), 131.14, 130.84 (vinyl CH), 130.66, 112.16 (0, vinyl), 31.52 (NCH_3), 24.77 (7-CH_3), 21.50 (4-CH_3), 15.99 (SCH_3); UV (MeOH) λmax 240 nm; IR ($CHCl_3$) 1530, 1450, 1423, 1413, 1382, 1160 cm^{-1}. A sample of **23d** containing predominantly the Z isomer (10/1 E/Z) had mp 81–91 °C. The analytical sample was further purified by preparative TLC (1-mm thick, 50% EtOAc/hexanes). Anal. Calcd for $C_{13}H_{15}N_4BrS$: C, 46.0; H, 4.5; N, 16.5. Found: C, 46.1; H, 4.5; N, 16.3. Further elution with ethyl acetate provided *exo*-stilbene **24d**, 40 mg (3.8%), as an orange-brown oil: TLC (50% EtOAc/hexanes) R_f 0.14.

2-(Methylthio)-3,4,7-trimethylimidazo[4,5-*f*]quinoxaline (27d). Method A. In a 1.1-L quartz photochamber a solution of ethylene **23d** (0.96 mmol, 325 mg, 4/1 E/Z in benzene (588 mL), *tert*-butoxide/*tert*-butyl alcohol (3150 mol %, 0.088 M, 343 mL), and *tert*-butyl alcohol (68 mL) was irradiated for 5 min according to procedure E. The crude residue, purified by LPLC (50% EtOAc/hexanes), gave 260 mg, 80% yield, of isomerized stilbene (Z)-**23d** as an orange oil: TLC (EtOAc) R_f 0.64. Further elution with 75% EtOAc/hexanes yielded tricycle **27d**, 22.7 mg (9.2%), as a yellow solid: TLC (EtOAc) R_f 0.21.

Method B. In a 340-mL quartz photochamber fitted with a magnetic stirring bar were placed ethylene **23d** (0.64 mmol, 219 mg, 4/1 E/Z ratio), benzene (194 mL), and *tert*-butoxide/*tert*-butyl alcohol (1830 mol %, 0.088 M, 134 mL), and nitrogen was bubbled through the solution for 30 min. In a separate quartz water-cooled jacket was placed a 450-W Hanovia lamp; it was turned on for 5 min and then transferred to the quartz photochamber containing the reaction mixture and placed inside the water-cooled jacket above the solution. The solution was irradiated for 2 min, the lamp was removed and after 5 min returned to the reaction photochamber, and the solution was irradiated for an additional 2.5 min. Addition of 2 M H_3PO_4/CH_3OH (2000 mol %) and evaporation left a residue that was suspended in water (400 mL), and the pH was adjusted to 7.0 with Na_2CO_3. Extraction with chloroform (200 mL), addition of brine (100 mL), and extraction with more chloroform (3 × 150 mL) gave a combined chloroform phase that was dried, filtered, and evaporated to give the crude product. Purification by LPLC (50% EtOAc/hexanes) gave unreacted ethylene (Z)-**23d**, 150.7 mg, 69% recovery, as an 8.4/1 ratio of Z/E isomers. Further elution with 75% EtOAc/hexanes afforded 29.5 mg, 17.7% yield, of tricycle **27d**: mp 178–180 °C; ^{1}H NMR δ 8.76 (s, 1 H, 8-H), 7.45 [d(q), 1 H, J = 1.0, 5-H], 3.96 (s, 3 H, NCH_3), 2.93 (s, 3 H, SCH_3), 2.81

(s(d), 3 H, J = 1.0, 4-CH_3), 2.76 (s, 3 H, 7-CH_3); ^{13}C NMR δ 153.31, 151.56, 144.24 (1, C8), 139.15, 138.64, 134.66, 133.02, 125.84, 123.31 (1, C5), 32.89 (NCH_3), 22.39 (7-CH_3), 19.65 (4-CH_3), 15.06 (SCH_3); UV (MeOH) λmax 276 nm; IR (KBr) 3010, 2925, 1512, 1430, 1407, 1355 1252 cm^{-1}. Anal. Calcd for $C_{13}H_{14}N_4S$: C, 60.4; H, 5.5; N, 21.7. Found: C, 60.4; H, 5.5; N, 21.5.

2-(Methylsulfonyl)-3,4,7-trimethylimidazo[4,5-*f*]quinoxaline (28f). 2-Methylthio tricycle **27d** (0.014 mmol, 29 mg) was converted to sulfone following procedure F. The crude product was purified by LPLC (75% EtOAc/hexanes), yielding 27.2 mg (82.4%) of sulfone **28f** after sublimation (120 °C, 0.02 Torr): mp 277–277.5 °C dec; TLC (EtOAc) R_f 0.22; ^1H NMR δ 8.81 (s, 1 H, 8-H), 7.70 (d(q), 1 H, J = 1.02, 5-H), 4.48 (s, 3 H, SO_2CH_3), 3.74 (s, 3 H, NCH_3), 2.92 [s(d), 3 H, J = 1.02, 4-CH_3), 2.80 (s, 3 H, 7-CH_3); ^{13}C NMR δ 153.08, 148.85, 144.96 (C8), 140.45, 136.21, 134.50, 134.46, 127.93 (C5), 127.06, 42.49, (SO_2CH_3), 34.23 (NCH_3), 22.43 (7-CH_3), 19.83 (4-CH_3); IR (KBr) 1320 (asym SO_2), 1157 (sym SO_2) cm^{-1}; HRMS (EI) calcd for $C_{13}H_{14}N_4O_2S$ 290.0839, found 290.0846.

2-(*N*-Benzylamino)-3,4,7-trimethylimidazo[4,5-*f*]quinoxaline (34). Treatment of sulfone **28f** (0.11 mmol, 32 mg) with benzylamine according to procedure G afforded, following purification by LPLC (50% EtOAc/hexanes, then 75% EtOAc/hexanes), 35 mg, 99.4% yield, of **34**, TLC (EtOAc) R_f 0.14. Further purification by reverse-phase HPLC (70/30, CH_3CN/H_2O, 3.0 mL/min) gave **34** of mp 242–244 °C after recrystallization from CH_3CN: ^1H NMR δ 8.61 (s, 1 H, 8-H), 7.6–7.2 (m, 6 H, PhH's, 4-H), 4.84 (d, 2 H, CH_2), 4.56 (br s, 1 H, NH), 3.80 (s, 3 H, NCH_3), 2.80 [s(d), 3 H, J = 1.02, 4-CH_3], 2.72 (s, 3 H, 7-CH_3); ^{13}C NMR δ 154.55, 150.95, 143.73, 138.84, 138.70, 136.95, 132.47, 131.78, 128.67 (Ph, 2 carbons), 128.22 (Ph, 2 carbons), 127.63 (Ph, 1 carbon), 125.03, 121.27 (C5), 48.08 (CH_2), 31.00 (NCH_3), 22.39 (7-CH_3), 19.60 (4-CH_3); IR (KBr) 3440 (br, NH), 3318, 1608, 1584 cm^{-1}; UV (MeOH) λmax, nm (ε) 344 (6400), 280 (47 550), 221 (32 960); LRMS (EI) 317 (M^+, 95), 302 (20, CH_3), 251 (15), 226 (100, CH_2Ph), 212 (15, C_7H_7N), 199 (63, CH_2Ph, HCN), 172 (9), 158 (8), 131 (11), 91 (56, CH_2Ph). Anal. Calcd for $C_{19}H_{19}N_5$: C, 71.9; H, 6.0; N, 22.0. Found: C, 71.6; H, 5.8; N, 21.6.

2-Amino-3,4,7-trimethylimidazo[4,5-*f*]quinoxaline (40). Debenzylation of **34** (7.0 mg, 0.022 mmol) according to procedure H gave 2.5 mg (36%) of unreacted **34** and 3.1 mg, 62% yield, of **40** after sublimation (170 °C, 0.05 Torr): mp >300 °C (lit.[6b] mp > 300 °C); TLC (25% MeOH/EtOAc) R_f 0.15; ^1H NMR ($CDCl_3$) δ 8.69 (s, 1 H, 8-H), 7.41 (s(q), 1 H, J = 1.0, 5-H), 4.65 (s, 2 H, NH_2), 3.91 (s, 3 H, NCH_3), 2.84 (s(d), 3 H, J = 1.0, 4-CH_3), 2.75 (s, 3 H, 7-CH_3); ^1H NMR (CD_3OD) δ 8.68 (s, 1 H, 8-H), 7.30 (s(q), 1 H, J = 1.0, 5-H), 3.88 (s, 3 H, NCH_3), 2.84 (s(d), 3 H, J = 1.0, 4-CH_3), 2.70 (s, 3 H, 7-CH_3); ^1H NMR (DMSO-d_6) δ 8.83 (s, 1 H, 8-H), 7.60 [s(q), 1 H, J = 1.0, 5-H], 3.90 (s, 3 H, NCH_3), 2.85 (s(d), 3 H, J = 1.0, 4-CH_3), 2.70 (s, 3 H, 7-CH_3); FTIR (KBr) 3317 (br), 3161 (br), 2960, 2916, 2849, 1696, 1674, 1638, 1562, 1513, 1384, 1360, 1258, 1184, 1130 cm^{-1}; UV (MeOH) λmax nm (ε) 344 (5640), 274 (32 900), 217 (29 260); LRMS (EI) 228 (23), 227 (100, M^+), 112 (19), 199 (21), 185 (8), 173 (4), 159 (11), 144 (4.5), 131 (6), 117 (7); HRMS (EI) calcd for $C_{12}H_{13}N_5$ 227.1173, found 227.1170.

1-(5-Methyl-2-pyrazinyl)-2-(4-bromo-1-methyl-2-(methylthio)-5-imidazolyl)propan-2-ol (22b). A solution of 2,5-DMP anion (200 mol %, 0.09 M) was prepared at −78 °C according to procedure A and used immediately. In a separate flask ketone **21** (100 mol %, 8.67 mmol, 2.16 g) in THF (96 mL) was chilled to −15 °C. The pyrazinylmethyl anion solution (held at −78 °C) was added to the ketone solution dropwise via a Teflon cannula over a 30-min period such that the internal reaction temperature was kept between −15 and −20 °C. Upon the first persistence of a deep red color, the reaction mixture was immediately quenched with 1 M H_3PO_4/MeOH (25 mL) and then evaporated. Brine (400 mL) was added, the pH was adjusted to 7.0 (by the addition of a pH 8 phosphate buffer), and the solution was extracted with chloroform (4 × 200 mL). The combined organic phase was dried, filtered, and evaporated, and the residue was purified by LPLC (10% EtOAc/hexanes), affording unreacted ketone **21**, 1.0 g (46%); further elution with 50% EtOAc/hexanes yielded 1.39 g (45%) of tertiary alcohol **22b** as an orange brown oil: ^1H NMR δ 8.41 (s, 1 H, pyrH), 8.23 (s, 1 H, pyrH), 3.86 (d, 1 H, J = 15.5, H_A), 3.78 (s, 3 H, NCH_3), 3.20 (d, 1 H, J = 15.5, H_B), 2.51 (s, 3 H, 8-CH_3), 1.65 (s, 3 H, 4-CH_3); ^{13}C NMR δ 151.68, 150.51, 144.45 (pyrCH), 143.71, 141.66 (pyrCH), 132.93, 110.59, 72.63 (0), 43.18 (CH_2), 34.53 (NCH_3), 29.09 (4-CH_3), 20.85 (8-CH_3), 15.26 (SCH_3).

1-(5-Methyl-2-pyrazinyl)-2-(4-bromo-1-methyl-2-(methylthio)-5-imidazolyl)prop-1-ene (23b). Alcohols **22b** (0.56 mmol, 200 mg) were dehydrated according to procedure D except that *p*-TsOH·H_2O (100 mol %, 0.62 mmol, 0.12 g) was used and the solution was refluxed for 10 min. Isolation as described gave a residue which was subjected to LPLC. Elution with 25% EtOAc/hexanes afforded ethylenes **23b**, 129 mg (68%), as a yellow-orange oil, and further elution with 50% and then 75% EtOAc/hexanes gave 20 mg (10%) of exo isomer **24b** and unreacted alcohol **22b** as a mixture. Separation of the *E* and *Z* isomers could be accomplished by further chromatography. *E* isomer: TLC (50% EtOAc/hexanes) R_f 0.38; ^1H NMR δ 8.50 (d, 1 H, J = 1.37, pyrH), 8.45 (d, 1 H, J = 1.37, pyrH), 6.56 (q, J = 1.70, 1 H, 5-H), 3.55 (s, 3 H, NCH_3), 2.64 (s, 3 H, 8-CH_3), 2.58 (s, 3 H, SCH_3), 2.45 (d, 3 H, J = 1.70, 4-CH_3); ^{13}C NMR δ 150.89, 148.20, 144.32 (pyrCH), 143.39, 143.20 (pyrCH), 134.27, 131.01, 129.02 (C5), 113.03 (C4), 32.13 (NCH_3), 21.02 (8-CH_3), 18.81 (4-CH_3), 15.46 (SCH_3); UV (MeOH) λmax 323 nm. *Z* isomer: TLC (50% EtOAc/hexanes) R_f 0.28; ^1H NMR δ 8.29 (d, 1 H, J = 1.70, pyrH), 8.02 (d, 1 H, J = 1.70, pyrH), 6.83 (q, 1 H, J = 1.62, 5-H), 3.27 (s, 3 H, NCH_3), 2.62 (s, 3 H, 8-CH_3), 2.49 (s, 3 H, SCH_3), 2.21 (d, 3 H, 4-CH_3); ^{13}C NMR δ 151.41, 147.64, 143.78 (pyrCH), 143.37, 142.68 (pyrCH), 130.96, (1, C5), 130.56, 130.04, 112.44 (0, C4), 31.51 (NCH_3), 24.72 (8-CH_3), 21.19 (4-CH_3), 15.93 (SCH_3); UV (MeOH) λmax 255 nm. Exo isomer **24b**: TLC (50% EtOAc/hexanes) R_f 0.15; ^1H NMR δ 8.27 (s, 2 H, pyrH's), 5.51 (s, 1 H, exo-H), 5.21 (s, 1 H, exo-H), 3.86 (s, 2 H, CH_2), 3.49 (s, 3 H, NCH_3), 2.52 (s, 3 H, 8-CH_3), 2.46 (s, 3 H, SCH_3). The analytical sample of (*E*)-**23b** was sublimed (72 °C, 0.02 Torr), mp 84–89 °C (11.4 1, *E*/*Z*). Anal. Calcd for $C_{13}H_{15}N_4BrS$: C, 46.0; H, 4.5; N, 16.5. Found: C, 45.9; H, 4.5; N, 16.2.

2-(Methylthio)-3,4,8-trimethylimidazo[4,5-*f*]quinoxaline (27b). From (*Z*)-23b. Irradiation of ethylene (*Z*)-**23b** (0.20 mmol, 69.0 mg) according to procedure E gave starting material, (*Z*)-**23b**, 16.0 mg (23%), (10/1 *Z*/*E* by ^1H NMR), and further elution with 75% EtOAc/hexanes yielded tricycle **27b**, 14.8 mg (28.2%), as a yellow solid.

From (*E*)-23b. Irradiation of ethylene (*E*)-**23b** (0.29 mmol, 101 mg, 25/1, *E*/*Z*) following procedure E and purification by LPLC (50% EtOAc/hexanes) gave recovered ethylene (*Z*)-**23b**, 49.3 mg (49.3%), as a 7.5/1 mixture of *Z*/*E* isomers. Further elution with 75% EtOAc/hexanes and sublimation (120 °C, 0.2 Torr) afforded **27b**, 11.6 mg, 15.1% yield: mp 204–206 °C dec; TLC (EtOAc) R_f 0.13; ^1H NMR δ 8.67 (s, 1 H, 7-H), 7.54 [d(q), 1 H, J = 1.02, 5-H], 4.04 (s, 3 H, NCH_3), 2.94 (s, 3 H, SCH_3), 2.87 (s(d), 3 H, J = 1.02, 4-CH_3), 2.84 (s, 3 H, 8-CH_3); ^{13}C NMR δ 153.07, 152.61, 143.83 (1, C7), 138.01, 137.93, 135.26, 134.09, 124.57 (0, C4), 123.91 (1, C5), 32.88 (NCH_3), 22.55 (8-CH_3), 19.47 (4-CH_3), 15.03 (SCH_3); IR (KBr) 2980, 2928, 1560, 1508, 1442, 1347, 1312, 1175, cm^{-1}; UV (MeOH) λmax 276 nm. Anal. Calcd for $C_{13}H_{14}N_4S$: C, 60.4; H, 5.5; N, 21.7. Found: C, 60.3; H, 5.5; N, 21.8.

Isomerization of Ethylene (*E*)-23b to (*Z*)-23b. In a 340-mL Pyrex photochamber fitted with a magnetic stirring bar and nitrogen atmosphere were placed ethylene (*E*)-**23b** (0.31 mmol, 107 mg, 11.4/1, *E*/*Z*) and benzene (330 mL). Nitrogen was bubbled into the solution for 30 min. In a separate quartz water-cooled jacket equipped with a uranium filter was placed a 450-W Hanovia lamp. The lamp was turned on, and the solution was irradiated for 7 min. Isolation by procedure E and purification by LPLC (50% EtOAc/hexanes) afforded ethylene (*Z*)-**23b**, 79.6 mg (74.1%), as an 18/1 mixture of *Z*/*E* isomers.

2-(Methylsulfonyl)-3,4,8-trimethylimidazo[4,5-*f*]quinoxaline (28e). 2-Methylthio tricycle **27b** (0.103 mmol, 26.7 mg) was oxidized to its sulfone according to procedure F. Purification by column chromatography (EtOAc) gave sulfone **28e**, 19.7 mg, 67% yield: mp 278–280 °C dec; ^1H NMR δ 8.77 (s, 1 H, 7-H), 7.76 (q, 1 H, J = 1.0 Hz, 5-H), 4.50 (s, 3 H, SO_2CH_3), 3.76 (s, 3 H, NCH_3), 2.92 (d, 3 H, J = 1.0, 4-CH_3), 2.87 (s, 3 H, 8-CH_3); ^{13}C NMR δ 153.73, 148.84, 145.05 (1, C7), 139.12, 135.79, 135.71, 135.19, 128.40 (1, C5), 125.86 (O, C4), 42.49 (SO_2CH_3), 34.29 (NCH_3), 22.70 (8-CH_3), 19.78 (4-CH_3); IR (KBr) 1300 (asym SO_2), 1146 (sym SO_2) cm^{-1}; HRMS (EI) calcd for $C_{13}H_{14}N_4O_2S$ 290.0839, found 290.0837.

2-(*N*-Benzylamino)-3,4,8-trimethylimidazo[4,5-*f*]quinoxaline (33) was prepared following procedure G from 2-methylsulfonyl tricycle **28e** (0.048 mmol, 14.0 mg) to give an oily residue that was purified by column chromatography (75% EtOAc/hexanes, then EtOAc), followed by reverse-phase HPLC (80/20 CH_3CN/H_2O, 3.0 mL/min, detection at 278 nm) yielding 14.4 mg (94%) of **33**: mp 200–203 °C; ^1H NMR δ 8.61 (s, 1 H, 7-H), 7.46 (d(q), 1 H, J = 1.05, 5-H), 7.45–7.27 (m, 5 H, PhH), 4.90 (d, 2 H, J = 5.0, CH_2), 4.3 (t, 1 H, J = 5.0, NH), 3.86 (s, 3 H, NCH_3), 2.84 [s(d), 3 H, J = 1.04, 4-CH_3], 2.81 (s, 3 H, 8-CH_3); ^{13}C NMR δ 154.39, 152.05, 143.50, 138.59, 137.72, 136.22, 133.60, 132.53, 128.74 (1, Ph, 2 carbons), 128.23 (1, Ph, 2 carbons), 127.74 (1, Ph, 1 carbon), 123.86 (0, C4), 122.12 (1, C5), 48.19 (CH_2), 31.09 (NCH_3), 22.56 (8-CH_3), 19.58 (4-CH_3); IR (KBr) 3130 (br, NH), 1560, 1310, 1110 cm^{-1}; UV (MeOH) λmax, nm (ϵ) 345 (5464), 279 (46 380), 221 (30 220); LRMS (EI) 317 (100, M^+), 302 (16, CH_3), 226 (77, CH_2Ph), 212 (17, C_7H_7N), 199 (35, CH_2Ph, HCN), 91 (CH_2Ph); HRMS (EI) calcd for $C_{19}H_{19}N_5$ 317.1643, found 317.1640.

2-Amino-3,4,8-trimethylimidazo[4,5-*f*]quinoxaline (39). Hydrogenolysis of *N*-benzylamino tricycle **33** (12.2 mg, 0.0384 mmol) followed procedure H to give 7.1 mg, 82% yield, of **39** after sublimation at 260 °C, 0.08 Torr: mp >300 °C (lit.[6b] mp >300 °C); ^1H NMR ($CDCl_3$) δ 8.63 (s, 1 H, 7-H), 7.45 (s(q), 1 H, J = 1.0, 5-H), 4.56 (s, 2 H, NH_2), 3.91 (s, 3 H, NCH_3), 2.84 (s(d), 3 H, J = 1.0, 4-CH_3), 2.79 (s, 3 H, 8-CH_3); ^1H NMR (CD_3OD) δ 8.57 (s, 1 H, 7-H), 7.34 (s(q), 1 H, J = 1.0, 5-H), 3.90 (s, 3 H, NCH_3), 2.84 (s(d), 3 H, J = 1.0, 4-CH_3), 2.74 (s, 3 H, 8-CH_3); ^1H NMR (DMSO-d_6) δ 8.73 (s, 1 H, 7-H), 7.52 (s(q), 1 H, J = 1.0, 5-H), 3.88 (s, 3 H, NCH_3), 2.83 (s, 3 H, 8-CH_3), 2.70 (s(d), 3 H, J = 1.0, 4-CH_3); FTIR (KBr) 3500–2800 (br, NH), 2955, 2929, 2925, 2857, 1635, 1558, 1384, 1309, 1122 cm^{-1}; UV (MeOH) λmax, nm (ϵ) 342 (3590), 274 (25 320), 218 (22 400); LRMS (EI) 228 (15), 227 (100, M^+), 212 (15), 199 (18), 185 (11), 173 (4), 159 (16.5), 144 (6.5), 131 (9), 117 (10.5); HRMS (EI) calcd for $C_{12}H_{13}N_5$ 227.1173, found 227.1166.

2-(6-Methyl-2-pyrazinyl)-1-(2,4-dibromo-1-methyl-5-imidazolyl)ethan-1-one (10c) was prepared according to procedure A from 2,6-DMP anion (0.83 M, 150 mol %) in THF and dibromo ester **8** (5 g, 16.8 mmol, 100 mol %) in THF (20 mL). Column chromatography (49.5/49.5/1, EtOAc/hexanes/triethylamine) afforded unreacted imidazole ester **8**, 1.5 g (33%), and ketone **10c** (3.2 g, 51%): ^1H NMR δ 8.38 (s, 1 H, pyrH), 8.32 (s, 1 H, pyrH), 4.55 (s, 2 H, CH_2), 3.88 (s, 3 H, NCH_3), 2.54 (s, 3 H, 7-CH_3). Anal. Calcd for $C_{11}H_{10}N_4OBr_2$: C, 35.3; H, 2.7; N, 15.0. Found: C, 35.4; H, 2.8; N, 14.9.

2-(6-Methyl-2-pyrazinyl)-1-(2,4-dibromo-1-methyl-5-imidazolyl)ethene (12c). Ketone **10c** (2.06 g, 5.51 mmol) was reduced following procedure C to give crude alcohol **11c**: TLC (EtOAc) R_f 0.2; ^1H NMR δ 8.33 (s, 1 H, pyrH), 8.24 (s, 1 H, pyrH), 5.28 (dd, 1 H, J_1 = 10.2, J_2 = 3.4 *H*COH), 3.76 (s, 3 H, NCH_3), 3.34 (dd, 1 H, J_{gem} = 15.3, J_1 = 10.2, CH_ACH_B) 3.02 (dd, 1 H, CH, J_{gem} = 15.3, J_2 = 3.4, CH_ACH_B), 2.80 (s, 3 H, 7-CH_3). This crude alcohol **11c**, dehydrated by procedure D, afforded 1.5 g, 75% yield, of pure (*E*)-**12c**, mp 142–144 °C: TLC (EtOAc) R_f 0.38; ^1H NMR δ 8.37 (s, 1 H, pyrH), 8.32 (s, 1 H, pyrH), 7.55 (d, 1 H, J = 16.1, vinylH), 7.37 (d, 1 H, J = 16.1, vinylH), 3.75 (s, 3 H, NCH_3), 2.59 (s, 3 H, 7-CH_3); ^{13}C NMR δ 153.59 (0), 148.99 (0), 143.29 (1), 141.11 (1), 129.67 (0), 125.90 (1), 118.47 (1), 116.80 (0), 33.68 (NCH_3), 21.74 (7-CH_3); UV λ_{max} 348 nm. Anal. Calcd for $C_{11}H_{10}N_4Br_2$: C, 36.9; H, 2.8; N, 15.6. Found: C, 37.0; H, 2.9; N, 15.5.

2-Bromo-3,5,7-trimethylimidazo[4,5-*f*]quinoxaline (26c) was prepared by procedure E from ethylene **15c** (105 mg, 0.28 mmol, 100 mol %). Column chromatography of the residue (EtOAc/1% TEA) afforded 33 mg (40%) of **26c**: TLC (EtOAc) R_f 0.32; ^1H NMR δ 8.81 (s, 1 H, 8-H), 7.53 (s, 1 H, 4-H), 3.89 (s, 3 H, NCH_3), 2.84 (s, 3 H, 7-CH_3), 2.80 (s, 3 H, 5-CH_3).

3,7-Dimethyl-2-(*N*-benzylamino)imidazo[4,5-*f*]quinoxaline (30) was prepared from 2-bromotricycle **25c** (60 mg) according to procedure G. LPLC of the residue ($CHCl_3$, then 10% MeOH/$CHCl_3$) gave *N*-benzylamino tricycle **30**, and reverse-phase HPLC (45/55, H_2O/CH_3CN, 1.96 mL/min) afforded analytically pure **30**, which agreed in all respects with the compound prepared from sulfone **28b**.

2-(6-Methyl-2-pyrazinyl)-1-(1-methyl-2,4-dibromo-5-imidazolyl)propan-1-one (13c) was prepared by methylation of ketone **10c** (1.78 g, 4.76 mmol) according to procedure B. Column chromatography (49.5/49.5/1, EtOAc/hexanes/TEA) afforded 1.36 g, 75% yield, of **13c** as a yellow-red oil: TLC (50% EtOAc/hexanes) R_f 0.27, (EtOAc) R_f 0.38; ^1H NMR δ 8.46 (s, 1 H, pyrH), 8.35 (s, 1 H, pyrH), 5.20 (q, 1 H, J = 7.0, CH), 3.89 (s, 3 H, NCH_3), 2.52 (s, 3 H, 7-CH_3), 1.61 (d, 3 H, J = 7.0, 5-CH_3). Anal. Calcd for $C_{12}H_{12}N_4OBr$: C, 37.1; H, 3.1; N, 14.4. Found: C, 37.2; H, 3.2; N, 14.3.

2-(6-Methyl-2-pyrazinyl)-1-(2,4-dibromo-1-methyl-5-imidazolyl)propan-1-ol (14c) resulted from reduction of ketone **13c** (1.7 g, 4.4 mmol) as described in procedure C. The diastereomeric alcohols were obtained in a 3/1 ratio. Major isomer: ^1H NMR (400 MHz) δ 8.31 (s, 1 H, pyrH), 8.25 (s, 1 H, pyrH), 5.20 (d, 1 H, J = 10.2, HOC*H*), 3.81 (s, 3 H, NCH_3), 3.39 (m, 1 H, H_3CCH), 2.54 (s, 3 H, 7-CH_3), 1.13 (d, 1 H, J = 7.1, $CHCH_3$); ^{13}C NMR (100 MHz) δ 157.13 (0), 152.77 (0), 141.76 (0), 140.79 (1), 131.63 (0), 120.28 (0), 114.25 (0), 68.96 (1), 42.69 (1), 33.94 (NCH_3), 21.26 (7-CH_3), 16.80 (5-CH_3). Minor isomer: ^1H NMR (400 MHz) δ 8.31 (s, 1 H, pyrH), 8.25 (s, 1 H, pyrH), 5.06 (d, 1 H, J = 9.0, HOC*H*), 3.81 (s, 3 H, NCH_3), 3.39 (m, 1 H, H_3CCH), 2.54 (s, 3 H, pyrCH_3), 1.13 (d, 1 H, J = 7.1, $HCCH_3$).

2-(6-Methyl-2-pyrazinyl)-1-(2,4-dibromo-1-methyl-5-imidazolyl)prop-1-ene (15c) was obtained from the diastereomeric alcohols **14c** (0.15 g, 3.85 mmol) as described in procedure D. Column chromatography of the residue (49.5/49.5/1 EtOAc/hexanes/TEA) afforded 0.95 g, 65% yield, of ethylene **15c** as a 1/1 *E*/*Z* mixture. *E* isomer: ^1H NMR δ 8.58 (s, 1 H, pyrH), 8.35 (s, 1 H, pyrH), 7.11 (q, 1 H, J = 1.36, 4-H), 3.53 (s, 3 H, NCH_3), 2.56 (s, 3 H, 7-CH_3), 2.21 (d, 3 H, J = 1.36, 5-CH_3); ^{13}C NMR δ 152.72 (0), 151.09 (0), 143.46 (1), 140.10 (1), 130.25 (0), 119.70 (0), 115.59 (1), 114.85 (0), 33.80 (NCH_3), 21.62 (7-CH_3), 16.85 (5-CH_3); UV λmax 324 nm. *Z* isomer: ^1H NMR δ 8.24 (s, 1 H, 7-H), 8.07 (s, 1 H, pyrH), 6.27 (q, 1 H, J = 1.84, 5-H), 3.33 (s, 3 H, NCH_3), 2.48 (s, 3 H, 7-CH_3), 2.53 (d, 3 H, J = 1.85, 5-CH_3); UV λmax 276 nm. Anal. Calcd for $C_{12}H_{12}N_4Br_2$: C, 38.7; H, 3.3; N, 15.1. Found: C, 38.4; H, 3.3; N, 14.7.

***tert*-Butyl 3-Oxo-3-(1-methyl-2,4-dibromo-5-imidazolyl)-propanoate (18).** To a solution of LDA in THF (40 mL), prepared from diisopropylamine (175 mol %, 12.7 mmol, 1.75 mL) and *n*-BuLi (1.5 M, 175 mol %, 12.7 mmol, 8.5 mL), cooled to −78 °C, was added *tert*-butyl acetate (175 mol %, 12.1 mmol, 1.71 mL) dropwise, and the mixture was stirred for an additional hour at −78 °C. In a separate flask were placed dibromo ester **8** (2.15 g, 7.24 mmol) and THF (40 mL), the solution was cooled to 0 °C, and then a 1 M solution of LiOMe (200 mol %, 14.5 mmol, 7.2 mL) in THF was introduced followed by the *tert*-butyl acetate anion solution, cannulated in at a rate of 2 drops/s. Following the 1.5-h cannulation period, 2 M H_3PO_4 (16 mL) was added, the mixture was evaporated, the residue was taken up in H_2O (100 mL), and the pH was adjusted to 7 with solid K_2CO_3. The aqueous solution was then extracted with ethyl acetate (3 × 100 mL), and the combined organic phase was washed with brine, dried, and evaporated to a red oil. Chromatography with 50% EtOAc/hexanes gave β-keto ester **18**, 63% yield: ^1H NMR (400 MHz) δ 3.98 (s, 2 H), 3.91 (s, 3 H), 1.47 (s, 9 H); ^{13}C NMR (100 MHz) δ 183.39 (C=O, ketone), 166.62 (C=O, *t*-Bu ester), 131.33 (0), 128.54 (0), 124.32 (0), 82.38 (*t*-Bu, O), 49.17 (CH_2), 36.62 (NCH_3), 27.98 (*t*-Bu CH_3). Anal. Calcd for $C_{11}H_{14}N_2Br_2O_3$: C, 34.6; H, 3.7; N, 7.3. Found: C, 34.2; H, 3.6; N, 7.3.

1-(1-Methyl-2,4-dibromo-5-imidazolyl)ethan-1-one (20). The crude oil obtained above was evaporated twice with toluene and dried overnight in vacuo. TFA (30 mL) was added, and the resulting solution was refluxed for 8 h. After evaporation, the residue was taken up in H_2O (50 mL), the pH was adjusted to 7 with solid K_2CO_3, and the solution was extracted with ethyl acetate (4 × 100 mL). The combined organic phase was washed with 1 M K_2CO_3 (2 × 50 mL), brine, and dried. Filtration and evaporation gave a reddish-brown solid which was sublimed (50 °C, 0.01 Torr), affording ketone **20**, 1.5 g, 74% yield: ^1H NMR (200 MHz) δ 3.84 (s, 1 H), 2.60 (s, 3 H); mp 111–112 °C. Anal. Calcd for $C_6H_6N_2Br_2O$: C, 25.6; H, 2.2; N, 9.9. Found: C, 25.8; H, 2.2; N, 9.8.

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Supplementary Material Available: Spectroscopic data and experimental procedures for the preparation of compounds **10a**, **11a**, **12a**, **13a**, **14a**, **15a**, **23c**, **25a**, **25c**, **26a**, **27c**, **29**, **31**, **32**, and **34** from their respective 2-bromo tricycles and ^1H and/or ^{13}C NMR spectra of compounds **13b**, **14d**, (*Z*)-**15d**, **22b**, (*Z*)-**23b**, **24b**, **25b**, **25c**, **28a–f**, and **29–40** (60 pages). Ordering information is given on any current masthead page.

Regiochemical Control of the Ring-Opening of 1,2-Epoxides by Means of Chelating Processes. 2.[1] Synthesis and Reactions of the *cis*- and *trans*-Oxides of 4-[(Benzyloxy)methyl]cyclohexene, 3-Cyclohexenemethanol, and Methyl 3-Cyclohexenecarboxylate

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The synthesis of the diastereoisomeric epoxides *cis*-**1b–d** and *trans*-**2b–d** and the products of their ring-opening by various nucleophiles are described. The results of the ring-openings of the *trans*-epoxides **2b–d** can be rationalized by combining stereoelectronic and conformational arguments. However, the regioselectivity of the ring-openings of the *cis*-epoxides **1b–d** can, in principle, be influenced by the chelation of a metal ion by the oxygen atom of the epoxy group and that of the substituent on the 4-position. The results of the reactions of the *cis*-epoxides **1b–d** indicate that, to some degree, chelation is indeed a factor. How important a factor it is is dependent both on the reaction conditions and on the concentration and nature of the metal ion. In the ring-openings of the *cis*-epoxides **1b** and **1d**, chelation seems to be a larger factor than it is in the ring-openings of *cis*-epoxide **1c**. However, in no case is chelation as large a factor as it was in the ring-openings of the *cis*-epoxide **1a**, which was studied earlier. On the other hand, the autocatalyzed methanolysis, under neutral conditions, of epoxy acid **1e**, followed by CH_2N_2 methylation of the crude product, afforded a mixture of the two regioisomeric hydroxy ethers in which the *C-2-type compound* predominates. This result suggests that intramolecular hydrogen bonding may determine the reactive conformation of **1e**.

Introduction

The ring-opening of oxiranes, when carried out under conditions of stereo- and regiochemical control, can be profitably utilized to synthesize complex molecules like organic natural products.

In an earlier study[1,2] aimed at developing methods whereby the regioselectivity of the ring-opening of epoxides by nucleophiles could be controlled by means of chelation by a metal ion, we found that *cis*-4-(benzyloxy)cyclohexene oxide (**1a**), under conditions favorable for the chelation of a metal ion by the oxygen atoms of the epoxy and benzyloxy groups, preferentially yielded *C-1-type compounds*.[3] In contrast, under conditions where such chelation was not possible, *C-2-type compounds*[3] were produced preferentially (Scheme I).[1,2] In an effort to further define the scope of this strategy for regiocontrol, we have evaluated reactions of cyclohexene oxides **1b–d** and **2b–d** with heteronucleophiles under several types of reaction conditions designed to probe for regioalternating selectivity.[1,2] Of additional interest was the possibility that epoxides **1b–d** and **2b–d** could be used in a stereoselective synthesis of the C_{23}–C_{34} cyclohexyl moiety of the potent immunosuppressive agent FK-506,[4] the subject of intense pharmaceutical interest.[5]

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(1) For the preceding paper in this series, see: Chini, M.; Crotti, P.; Flippin, L. A.; Macchia, F. *J. Org. Chem.* **1990**, *55*, 4265.
(2) Chini, M.; Crotti, P.; Flippin, L. A.; Macchia, F. *Tetrahedron Lett.* **1989**, *30*, 6563.
(3) The terms *C-1-* and *C-2-type compound* refer to the site at which the nucleophile attacks, i.e., at C-1 or C-2 of the oxirane ring of **1** and **2**. See the numbering scheme shown in Scheme I.
(4) (a) Tanaka, H.; Kuroda, A; Marusawa, H.; Hatanaka, H.; Kino, T.; Goto, T.; Hashimoto, M.; Taga, T. *J. Am. Chem. Soc.* **1987**, *109*, 5031 and references therein. (b) Kino, T.; Hatanaka, H.; Miyata, S.; Inamura, N.; Nishiyama, M.; Yajimina, T.; Goto, T.; Okuara, M.; Kohsaka, M.; Aoki, H.; Ochiai, T. *J. Antibiot.* **1987**, *40*, 1256.

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