Design, Synthesis, and *in Vitro* Evaluation of Cyclic Nitrones as Free Radical Traps for the Treatment of Stroke

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Analogs of the cyclic nitrone free radical trap **1** (3,3-dimethyl-3,4-dihydroisoquinoline *N*-oxide, a cyclic analog of phenyl-*tert*-butylnitrone (PBN)) were prepared in which (1) the fused phenyl ring was replaced with a naphthalene ring, an electron rich heterocycle, or a dimethylphenol, (2) the nitrone-containing ring comprised five, six, or seven atoms, and (3) the *gem*-dimethyl group was replaced with spirocyclic groups. The most active antioxidant, which bears a dimethylphenol fused to a 7-membered ring nitrone (compound **6h**), inhibited lipid peroxidation *in vitro* with an IC_{50} of 22 μM, a 75-fold improvement over that of **1**. The previously observed correlation between lipophilicity and activity vs lipid peroxidation *in vitro* has been further substantiated and refined by this study. Moreover, certain classes of compounds (namely, dimethylphenols **6g,h** and furan **6j**) have now been found which are considerably more active *in vitro* than expected on the basis of their log k'_w values.

Introduction

There are numerous disease states, including stroke, in which radical-induced oxidative tissue damage is prevalent.[1] For example, the occurrence of lipid peroxidation[2,3] with a concomitant decrease in the lipid soluble α-tocopherol has been reported[4] following cerebral ischemia/reperfusion injury. In order to minimize this type of damage, various classes of radical traps, or antioxidants, are being developed. Among these are nitrones, typified by phenyl-*tert*-butylnitrone (PBN, Figure 1), which can react with short-lived oxygen- or carbon-centered radicals at the nitrone double bond. The result is a relatively stable nitroxide radical which cannot propagate destructive radical chain reactions and has a sufficient lifetime to diffuse from the site at which it is generated, thereby preventing concentrated, debilitating tissue damage. Indeed, PBN has shown intriguing activity as a neuroprotectant in certain animal models, and free radical trapping has been proposed as the mechanism of action in these studies.[5]

We have recently reported the design and synthesis of cyclic analogs of PBN,[6] the simplest of these being compound **1** (Figure 1). The original premise for the synthesis of **1** and related analogs was that cyclic compounds should be more reactive toward radicals both electronically, by virtue of increased planarity resulting in better orbital overlap between the nitrone double bond and the aromatic ring, and sterically, because of restricted rotation. However, subsequent molecular modeling studies[7] suggested that, in their lowest energy conformations, PBN was actually more nearly planar than **1**. The X-ray crystal structures[8] show that in both molecules, at least in the solid state, the phenyl ring and the nitrone double bond form a dihedral angle of about 14°. Hence, there is no evidence to sustain the original argument with respect to planarity and orbital overlap. On the other hand, both the modeling and the

Figure 1.

X-ray crystal structures suggest that the nitrone double bond in **1** is sterically more accessible than that in PBN. Moreover, high-level HOMO/LUMO calculations[7] for the two molecules show that **1** has a higher energy HOMO orbital and a lower energy LUMO orbital than those for PBN. Thus, **1** should be more reactive toward both electrophilic, oxygen-centered radicals (which occur mainly through SOMO-HOMO interactions) and toward nucleophilic, carbon-centered radicals (which occur mainly through SOMO−LUMO interactions).[9] In fact, when tested for its ability to inhibit radical-induced lipid peroxidation or to trap hydroxyl radicals *in vitro*, **1** was substantially more potent than PBN.[7] Also, **1** possesses outstanding solubility characteristics, being highly soluble both in water and in nonpolar organic solvents.

Although possessing these favorable properties, **1** still suffers from low potency (the IC_{50} in an *in vitro* lipid peroxidation assay is 1.67 mM), and side effects (sedation at doses greater than 100 mg/kg, and an iv LD_{50} of 320 mg/kg). The overall result is an unacceptable therapeutic index. In this study we describe our efforts to improve the therapeutic index by increasing potency. The following paper in this issue addresses the issue of side effects.

Previous studies from our labs[6,7,10] focused mainly on placing various substituents on the aromatic ring, and to a lesser extent on expanding the nitrone-containing ring and replacing the *gem*-dimethyl moiety with spirocyclic groups. Herein we describe the synthesis and evaluation of compounds in which (1) the fused phenyl ring is replaced with more extended aromatic systems or electron rich heterocycles, (2) a second antioxidant functionality (*o*,*o*′-dimethylphenol) is added, (3) the nitrone-containing ring is contracted, and (4) the nitrone-containing ring is expanded and/or the *gem*-

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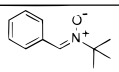
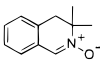
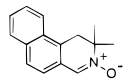
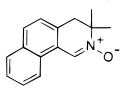
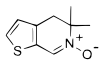
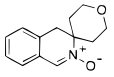
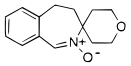
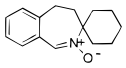
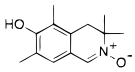
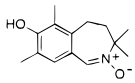
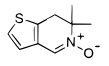
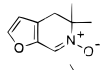
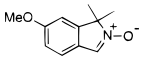
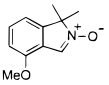
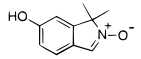
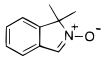
Table 1. *In Vitro* Activity and log k'_w Values for PBN and Cyclic Nitrones

Structure	Compd	Inhib. of Liposomal Perox. - IC_{50} (μM)[a] Measured	Predicted[b]	log k'_w[c]
	PBN	14,300		-
	1	1,670	750	1.90
	6a	100	220	2.67
	6b	69	210	2.69
	6c	1,720	1,500	1.47
	6d	1,240	1,120	1.65
	6e	310	660	1.98
	6f	730	130	2.99
	6g	66	70	1.82
	6h	22	30	2.29
	6i	1,590	1,280	1.57
	6j	1,070	2,490	1.16
	6k	910	950	1.75
	6l	1,090	660	1.98
	6m	810	460	0.68
	6n	1,360	1,200	1.61

[a] See ref 22. [b] Calculated from eq 1. [c] These values represent single determinations. The r^2 values for linear regression analyses of the raw chromatographic data were >0.999 in each case. See ref 21.

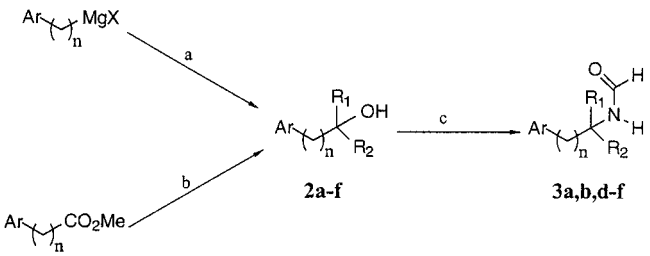
dimethyl group is replaced by a spirotetrahydropyran or a spirocyclohexyl moiety.

Chemistry

Compounds **6a**−**f** (Table 1) were prepared by the previously described route,[6] as summarized in Schemes 1 and 2. This involved preparation and reaction of tertiary alcohols **2** with NaCN under Ritter[11] conditions to give formamides **3**. Cyclization of the formamides by a method developed by Larsen and co-workers at Merck[12] afforded tricyclic intermediates **4**. These could be hydrolyzed or, preferrably in some cases, pyrolyzed[6b] to give the desired imines. The imines were converted into the requisite nitrones most efficiently by preliminary reduction ($NaBH_4$) to the corresponding amines, followed by tungstate-catalyzed H_2O_2 oxidation.[13]

Synthesis of the *o*,*o*′-dimethylphenol analogs **6g**,**h** followed the same general route, but additional steps were required to obtain the Ritter reaction substrates,

Scheme 1[a,b]



[a] Reagents: (a) tetrahydropyran-4-one or cyclohexanone, (b) MeMgBr, (c) NaCN, H_2SO_4. [b] Letter designations correspond to structures given in Table 1.

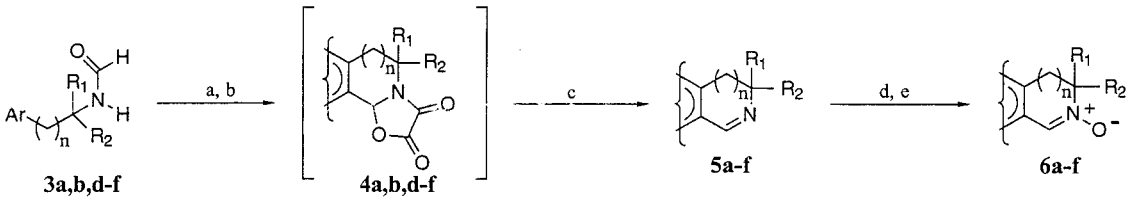
11g,**h** (Scheme 3). Carboxylic esters **7g**,**h**[14] were treated with MeMgBr and brominated in the 4-position to furnish tertiary alcohols **8g**,**h**. A double Mannich reaction with pyrrolidine and formaldehyde then provided **9g**,**h**. Numerous attempts to hydrogenolyze the bromine and both pyrrolidines in one step were unsuccessful, the more hindered C−N bond being inert to a wide variety of conditions.[15] Resubmission of a chromatographically purified, debrominated monopyrrolidine (not shown) to several hydrogenation conditions also failed to give **11g**. Finally, we found that the amino groups could be displaced by thiols[16] under harsh conditions (with concomitant debromination) to afford **10g**,**h**. These were readily desulfurized upon treatment with RaNi to give **11g**,**h**.

The Ritter reaction of **11g**,**h** with NaCN gave the cyclized imines **5g**,**h** directly *via* capture of the nitrilium ion intermediate by the electron rich phenol. This reaction was observed in the synthesis of thiophene **6c** as well. The yields were low with the thiophene and **11h** due to competing reactions of the tertiary cation intermediates, but **11g** gave imine **5g** in *ca*. 50% yield. Conversion of the imines into the corresponding nitrones could be carried out as described above ($NaBH_4$ reduction; H_2O_2/Na_2WO_4 oxidation), but because of the high water solubility of these compounds, it was preferrable to perform the reduction step by catalytic hydrogenation (RaNi).

Compounds **6i**−**n** were not accessible by the above route. For example, in an attempted synthesis of thiophene **6i**, the Ritter reaction gave neither the cyclized imine nor the formamide because of intermolecular reactions of the tertiary cation. Likewise, a 5-membered ring could not be formed by cyclization of the requisite formamide as described above. In order to avoid these problems, isocyanates were chosen as cyclization substrates since this functional group could be generated under milder conditions *via* the Curtius rearrangement.

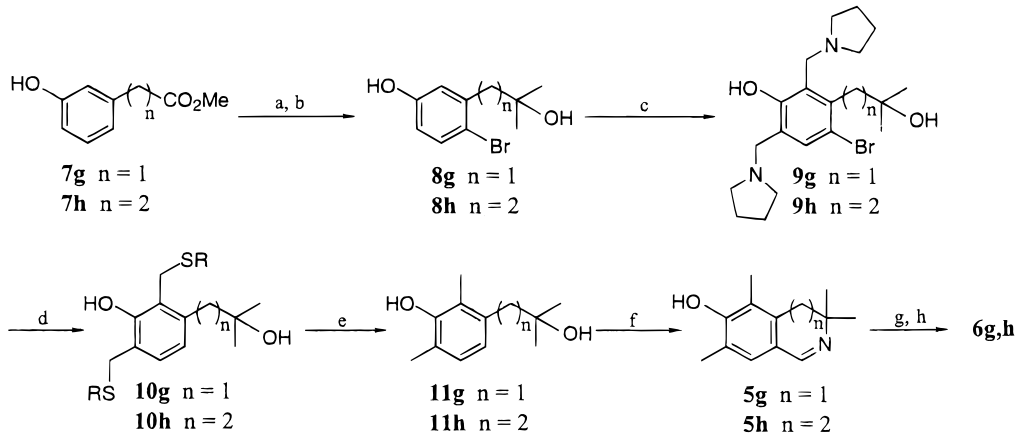
The Curtius rearrangement substrates (carboxylic acids **12**) were readily prepared as shown in Scheme 4. The isocyanates (**13**) formed smoothly upon treatment of the acids with diphenyl phosphorazidate. For the heterocycles, anhydrous H_3PO_4[17] or $BF_3{\cdot}Et_2O$ proved to be the best cyclization catalysts, whereas only $FeCl_3$ allowed formation of the isoindolones (i.e., **14k**, Scheme 5) to occur in reasonable yield.[18] In the latter case, an activating substituent (OMe) appropriately placed on the aromatic ring was also required. This resulted in the formation of regioisomers and necessitated removal of the activator[19] (Scheme 5) in order to obtain the unsubstituted analog **6n** for direct comparison to

Scheme 2[a,b]



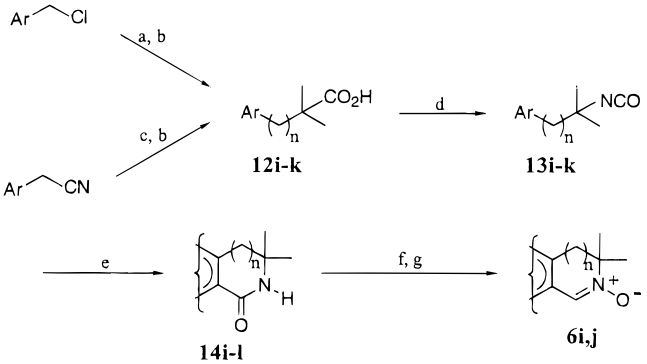
[a] Reagents: (a) $(COCl)_2$; (b) $FeCl_3$; (c) H_2SO_4/EtOH, Δ or Δ; (d) $NaBH_4$; (e) H_2O_2, cat. Na_2WO_4. [b] Letter designations correspond to structures given in Table 1.

Scheme 3[a]



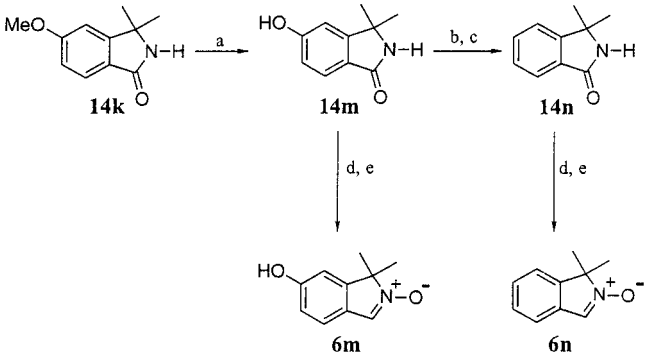
[a] Reagents: (a) MeMgBr; (b) NBS; (c) 37% aqueous HCHO, pyrrolidine, Δ; (d) RSH, 180 °C, no solvent; (e) RaNi, EtOH, Δ; (f) NaCN, H_2SO_4; (g) $NaBH_4$, or H_2/RaNi; (h) H_2O_2, cat. Na_2WO_4.

Scheme 4[a,b]



[a] Reagents: (a) ethyl isobutyrate, $LiN(TMS)_2$; (b) KOH; (c) MeI, NaH; (d) DPPA, Et_3N, Δ; (e) anhydrous H_3PO_4, or $BF_3{\cdot}Et_2O$, or $FeCl_3$; (f) BH_3/THF, Δ; (g) H_2O_2, cat. Na_2WO_4. [b] Letter designations correspond to structures given in Table 1.

Scheme 5[a]



[a] Reagents: (a) BBr_3, (b) 5-chloro-1-phenyl-1*H*-tetrazole, K_2CO_3, (c) H_2, Pd/C, (d) BH_3/THF, Δ, (e) H_2O_2, cat. Na_2WO_4.

1. Compounds **6k**−**m** were also prepared and submitted for testing (see Table 1 for structures and Scheme 5 and Experimental Section for synthesis).

Results and Discussion

Several approaches toward increasing the potency of the cyclic nitrones (relative to **1**) were taken in this study. The electronic effects of increasing the degree of conjugation of the nitrone double bond (naphthalenes **6a**,**b**), or placing a heteroatom in conjugation with it (heterocycles **6c**,**i**,**j**), were expected to afford more reactive compounds. The dimethylphenol analogs (**6g**,**h**)[20a] were obviously members of the well-known class of antioxidants based on α-tocopherol,[20b−d] which are generally substantially more potent than **1** in the lipid peroxidation assay. Compounds in which the nitrone is contained within a 5-membered ring (e.g. **6n**), were predicted to be somewhat more sterically accessible than **1**, although HOMO/LUMO energy calculations[7] suggest that these compounds should be less reactive toward radicals than **1** (but more reactive than PBN), from a frontier molecular orbital standpoint. Finally, we had observed in previous studies[6,7,10] a general trend that *in vitro* activity against lipid peroxidation was correlated with lipophilicity. Accordingly, some spirocyclic and ring-expanded analogs (**6d**−**f**) were targeted.

The cyclic nitrones prepared (**6a**−**n**) are listed in Table 1, along with their IC_{50} values for inhibition of lipid peroxidation *in vitro*. In addition, the relative lipophilicity of the compounds was determined by a well-established chromatographic technique (log k'_w values).[21] Compound **1** and PBN are also included for comparison. The *in vitro* assay procedure involved measuring the ability of the test compounds to inhibit oxidation of soybean phosphatidylcholine liposomes.[22] A mixture of Fe^{2+}/Fe^{3+} was used to initiate peroxidation, as this system produces an as yet uncharacterized, weak oxidant which reacts solely with polyunsaturated fatty

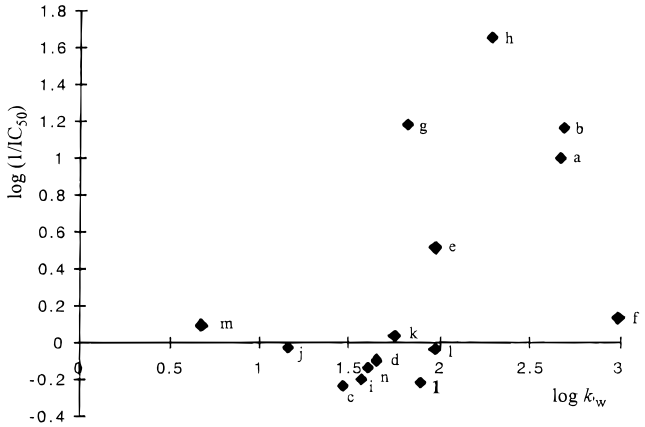


Figure 2. Plot of log(1/IC_{50}) vs log k'_w for **1** and **6a**−**n**. IC_{50} values in mM units were used. log k'_w values were measured as described in ref 21. Points labeled a−n correspond to compounds **6a**−**n**.

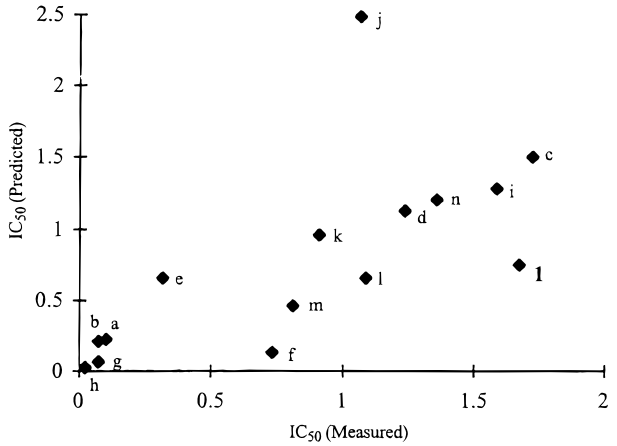


Figure 3. Plot of measured vs predicted IC_{50} values for 1 and **6a**−**n**. Predicted values were calculated with eq 1. See text. Points labeled a−n correspond to compounds **6a**−**n**.

acids.[23] Thus, measurement of nitrone trapping of lipid-derived oxygen- or carbon-centered radicals is not subject to the interference of initiating radicals.

In general, the more lipophilic compounds are more active *in vitro*, as expected based on previous results. A plot of log(1/IC_{50}) vs log k'_w (Figure 2) shows the trend, but fails to give a statistically valid quantitative structure−activity relationship. The major outliers in the plot seem to be spirocyclohexyl derivative **6f** and the phenolic compounds **6g,h,m**. Compound **6f** is the most lipophilic member of the series, and it is possible that micelle formation, which impairs incorporation into the liposomes, is confounding the data. The phenolic compounds **6g**,**h**,**m** (points g, h, and m in Figure 2) are well-behaved among themselves, showing a steady increase in potency as the log k'_w increases from 0.68 for **6m** to 2.29 for **6h**. We believe the relationship between the three phenolic compounds and the remaining, nonphenolic analogs reflects the expected increase in potency resulting from the presence of a second antioxidant moiety. If separate lines were drawn to fit these two sets of points (excluding point f), one can see that the lines would have approximately the same slope, but the line for the phenols would be offset by about 1 log unit in the direction of greater activity. Thus, while log k'_w alone gives a poor correlation with activity, if we add an indicator variable for the presence ($D = 1$) or absence ($D = 0$) of a phenol, the statistically significant eq 1 is obtained[24] which correlates the antioxidant activity of this series with lipophilicity. The predicted IC_{50} values shown in Table 1 were calculated with this equation.

$$\log(1/IC_{50}) = 0.701\ (\pm 0.076)\log k'_w + 1.06\ (\pm 0.054)D - 1.20\ (\pm 0.013) \quad (1)$$

$n = 15$, $r^2 = 0.729$, $r = 0.854$, $q^2 = 0.502$,
standard error of estimate = 0.350,
standard error of prediction cross-validated = 0.474.

A plot of the measured vs calculated IC_{50} values gives a different perspective on the data set (Figure 3). The major outlier in this plot is furan **6j**, which seems to be much more potent than anticipated from lipophilicity measurements. This effect was suspected from analysis of the plot in Figure 2, but is more dramatically evident here.

The data described above show that increased lipophilicity, the presence of a phenol, and the incorporation of an electron rich heterocycle (furan, but not thiophene) can each have an appreciable beneficial effect on the antioxidant activity. The remaining parameters investigated in this study, the degree of conjugation of the nitrone (naphthalenes **6a** and **6b**), and the size of the nitrone-containing ring (five, six, or seven atoms) seem to have relatively little effect on the radical-trapping ability of the compounds. The naphthalenes are quite potent, but in both plots (Figures 2 and 3) these compounds show no significant deviation from the expected values based on log k'_w. Thus, the added aromatic ring apparently contributes nothing beyond lipophilicity to these molecules.

In order to assess the effect of the ring size we can compare three pairs of compounds in which ring size is the only difference. With spirotetrahydropyrans **6d** (IC_{50} = 1240 μM, log k'_w = 1.65) and **6e** (IC_{50} = 310 μM, log k'_w = 1.98), the increase in potency on going from a 6-membered ring to a 7-membered ring is essentially in line with the increase in lipophilicity. Likewise, the data for phenols **6g** (IC_{50} = 66 μM, log k'_w = 1.82) and **6h** (IC_{50} = 22 μM, log k'_w = 2.29) support the contention that there is little or no difference (beyond lipophilicity) between 6- and 7-membered rings. On the other hand, the 5-membered ring nitrone **6n** (IC_{50} = 1360 μM, log k'_w = 1.61) is perhaps slightly more active than its 6-membered ring counterpart **1** (IC_{50} = 1670 μM, log k'_w = 1.90) despite being more polar, suggesting that a 5-membered ring nitrone might be inherently more reactive toward free radicals. However, the ring size clearly has no dramatic impact on the activity of the nitrones.

We believe that the lipophilicity correlation is to some extent inherent in the assay, i.e. compounds having greater residence time in the lipid phase should be more effective at protecting the lipid from peroxidation.[25] Therefore, the most interesting compounds are those for which *in vitro* potency exceeds that expected on the basis of log k'_w values, indicating inherently superior radical trapping ability. Of the compounds reported here, only the phenolic compounds **6g**,**h**,**m** and furan **6j** seem to fit this description. The effect of the phenol, however, does not seem to be additive as hoped; simple phenolic compounds, such as vitamin E and probucol, lacking a nitrone moiety yield IC_{50} values of about 10

μM in this assay.[10,22] Hence, the activity of the phenol moiety may actually be diminished as a consequence of being in conjugation with the nitrone functionality, a situation which was prompted by consideration of synthetic accessibility.

Conclusion

The significant new findings of this study can be summarized as follows: (a) new chemistry was developed in order to prepare some compounds inaccessible by the previously reported route, (b) the relative lipophilicities (log k'_w) of the compounds were *measured* (rather than calculated) by a rapid, convenient, and reliable method, (c) two different classes of compounds were found to be significantly more active than expected on the basis of their lipophilicity, and, most importantly, (d) an equation was derived from the data which allows us for the first time to find such compounds. This latter point represents a significant departure from, and extension of, our previous studies.

More specifically, the results described above demonstrate that relatively simple modifications of the nitrone radical trap PBN can yield large increases in potency in an *in vitro* assay measuring inhibition of lipid peroxidation. Incorporation of the nitrone unit within a ring, as shown also in previous studies,[6,7,10] gives a *ca*. 10-fold improvement of the IC_{50}, presumably as a result of favorable changes in the HOMO and LUMO energy levels, and greater steric accessibility of the nitrone double bond. Other desirable structural features revealed by this work include the presence of a phenolic hydroxyl, a furan ring in place of the fused phenyl ring, and log k'_w values of *ca*. 2.0−2.5. The scatter in the data evident in Figures 2 and 3 is believed to result from the smaller contributions of electronic or steric effects to the activity of the compounds. Compound **6h**, which combines several of the best features noted above (cyclic nitrone, phenolic hydroxyl, log k'_w of 2.29), is the most potent nitrone we have synthesized to date. With an IC_{50} of 22 μM, this compound is 650-fold more potent than PBN in the *in vitro* lipid peroxidation assay.

Having learned how to maximize *in vitro* radical trapping activity, we are now focusing attention on optimizing the physicochemical properties of the cyclic nitrones so as to obtain potent compounds with good solubility and brain penetration and minimal side effects (see the following paper in this issue).

Experimental Section

General Methods. Except where noted otherwise, reagents and starting materials were obtained from common commercial sources and used as received. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl immediately prior to use. Other reaction solvents, and all chromatographic, recrystallization, and workup solvents, were spectroscopic grade and used as received. Reactions were carried out under an atmosphere of dry N_2 in oven-dried flasks when required.

Thin layer chromatography (TLC) was performed on glass-backed, silica gel 60F-254 plates (EM Science). Spots were visualized by one or more of the following methods: UV light, I_2 vapor, or staining with phosphomolybdic acid, $Ce(SO_4)_2$, or $KMnO_4$.[26] Gas chromatography (GC) was performed on a Hewlett-Packard 5890 Series II gas chromatograph equipped with a Hewlett-Packard 3392A integrator. Separations were carried out on a 15 m × 0.32 mm i.d. fused silica capillary column (DB-5, 0.25 mm film) from J & W Scientific. Flash chromatography (FC) was carried out using EM Science silica gel 60 (40−63 μm) according to the literature procedure.[27]

Melting points were determined on a Thomas-Hoover Unimelt capillary melting point apparatus and are uncorrected. IR spectra were recorded on a Mattson Galaxy Series 5020 infrared spectrophotometer with samples prepared as indicated and are reported in wavenumbers (cm^{-1}). ^1H NMR and ^{13}C NMR spectra were recorded on Varian Unity (300 or 400 MHz) or Gemini (300 MHz) spectrometers with chemical shifts (δ) reported in ppm relative to tetramethylsilane (0.00 ppm) and chloroform-*d* (77.0 ppm), respectively. Mass spectra were obtained on a Finnigan MAT Model TSQ 700 mass spectrometer system using electron impact or chemical ionization with the molecular ion designated as M^+ or $(M + H)^+$ given in parentheses. Combustion analyses were obtained with a Perkin-Elmer Model 2400 elemental analyzer.

Biochemical Methods. Preparation of the liposomes and analysis of oxidation products were carried out essentially as described by Thomas.[22] Compound **1** was included as an internal standard during testing of new compounds. If the value obtained for **1** varied by more than 15% from the value given in Table 1, the experiment was excluded.

Determination of log k'_w Values.[21] Compounds were dissolved in MeOH at 0.5 mg/mL, injected onto a Zorbax Rx-C18 column (15 cm × 4.6 mm i.d.; 5 μm) from MAC-MOD Analytical, Inc., and eluted with various percentages of MeOH (32−62%, three concentrations/compound) in pH 7.4 phosphate buffer. The flow rate was 1 mL/min, the column temperature was 30 °C, and the UV detector wavelength was $\lambda = 230$ nm. log k values were calculated by using the equation: $\log k = \log((t - t_0)/t_0)$, where t is the retention time of the compound of interest and t_0 is the elution time of MeOH, which is not retained on the column. Linear regression analysis ($r^2 > 0.999$) was performed on the three data points for each compound and the resulting line extrapolated to 100% aqueous to give the log k'_w values listed in Table 1.

General Procedure for Oxidation of Amines to Nitrones (Procedure A). The amine (1 equiv) was dissolved in MeOH and treated sequentially with Na_2WO_4 (0.1 equiv) and 30% H_2O_2 (3 equiv). The resulting mixture was stirred at room temperature until TLC analysis indicated complete reaction (*ca*. 4 h). The reaction mixture was poured into brine containing $Na_2S_2O_3$ (to destroy excess peroxide) and extracted several times with EtOAc (until aqueous phase showed little or no product by TLC). The organic phase was dried (Na_2SO_4), filtered, and evaporated. The crude product was purified as indicated.

General Procedure for Hydrolysis of Esters or Nitriles (Procedure B). The ester or nitrile (1 equiv) was added to a solution of KOH (2.5 equiv) in 10% aqueous MeOH, and the resulting mixture was heated at reflux until TLC showed the absence of starting material. The mixture was cooled and most of the MeOH evaporated. The residue was diluted with water and extracted with Et_2O (2×, discarded). The aqueous phase was acidified by adding dilute HCl and extracted with EtOAc (3×). The organic phase was washed with brine, dried ($MgSO_4$), filtered, and evaporated. The crude product was used without further purification.

General Procedure for the Curtius Rearrangement (Procedure C). To a solution of the carboxylic acid (1 equiv) in toluene at 0 °C were added Et_3N (0.95 equiv) and diphenyl phosphorazidate (0.95 equiv). The mixture was stirred at 0 °C for 30 min and then heated at reflux for 3 h. The mixture was cooled, washed with cold $NaHCO_3$ solution (2×) and brine (2×), then dried ($MgSO_4$), filtered, and evaporated. The crude product was used without purification.

General Procedure for Reduction of Lactams (Procedure D). The lactam (1 equiv) was carefully (gas evolution) added to BH_3·THF solution (1 M in THF, 2.5 equiv). After gas evolution subsided, the mixture was heated at reflux overnight. The reaction mixture was cooled, treated cautiously with MeOH (*ca*. 50% by volume, gas evolution) and 1 M NaOH solution, and heated at reflux for 7 h. The resulting mixture was cooled and extracted with EtOAc (2×). The organic phase was extracted with 1 M HCl (2×), and the aqueous phase was neutralized by adding $NaHCO_3$. The product was extracted

into EtOAc (2×), and the organic phase was washed with brine, dried ($MgSO_4$), filtered, and evaporated. The amines were used without further purification.

4-Bromo-3-(2-hydroxy-2-methylpropyl)phenol (8g). MeMgBr solution (3 M in Et_2O, 150 mL, 450 mmol) was diluted with 150 mL of THF and cooled to −78 °C. The ester **7g**[14] (14.5 g, 87.3 mmol) was dissolved in THF and added dropwise over 15 min (vigorous gas evolution). Vigorous mechanical stirring was required to prevent solidification of the reaction mixture. The cooling bath was removed after the addition was complete, and the reaction mixture was allowed to stir overnight. Excess MeMgBr was quenched by adding saturated NH_4Cl solution, and the resulting mixture was poured into 0.5 M HCl and extracted with EtOAc (2×). The organic phase was washed with brine, dried (Na_2SO_4), filtered, and evaporated. The resulting crude product was dissolved in warm CH_2Cl_2 and diluted with hexane to produce a white, crystalline solid: mp 91−94 °C (12.3 g, 85%); ^{1}H NMR ($CDCl_3$) 7.14 (t, 1, J = 7.7), 6.80−6.68 (m, 3), 2.70 (s, 2), 1.23 (s, 6); ^{13}C NMR ($CDCl_3$) 155.9, 139.0, 129.4, 122.6, 117.3, 113.8, 71.5, 49.4, 29.0; MS (EI, 70 eV) m/z 166 (M^+), 152, 151, 133, 115, 108 (base peak), 107, 90, 79, 77. Anal. ($C_{10}H_{14}O_2$) C, H.

This material (12.3 g, 74.2 mmol) was dissolved in DMF and cooled to 0 °C. Solid *N*-bromosuccinimide (14.77 g, 83.0 mmol) was added in small portions (the yellow color was allowed to dissipate between additions) over 1.5 h. After the addition was complete, stirring at 0 °C was continued for 30 min. The mixture was then poured into water and extracted with EtOAc (3×). The organic phase was washed with water (1×) and brine (1×), dried ($MgSO_4$), filtered, and evaporated. The residue was dissolved in EtOAc/CH_2Cl_2 and diluted with hexane to afford **8g** as white crystals, mp 139−141 °C (12.7 g, 70%). Concentration of the mother liquor gave two more crops (1.2 and 1.0 g) of crystals, bringing the total to 14.9 g (82%): ^{1}H NMR (acetone-d_6, 2.05 ppm) 8.43 (s, 1), 7.34 (d, 1, J = 8.7), 7.01 (d, 1, J = 2.7), 6.64 (dd, 1, J = 8.7, 2.8), 2.89 (s, 2), 1.21 (s, 6); ^{13}C NMR (acetone-d_6, 20.83 ppm) 147.9, 131.0, 124.6, 111.3, 107.1, 106.2, 62.4, 39.6, 20.8; MS (EI, 70 eV) m/z 246/244 (M^+), 231/229, 201, 188/186, 163, 150, 131, 108, 107, 91, 77, 63, 59 (base peak). Anal. ($C_{10}H_{13}BrO_2$) C, H.

4-Bromo-3-(2-hydroxy-2-methylpropyl)-2,6-bis(pyrrolidin-1-ylmethyl)phenol (9g). The bromophenol **8g** from the previous step (5.7 g, 23.3 mmol) and pyrrolidine (4.8 mL, 58.2 mmol) were placed in a flask with a reflux condenser. Aqueous formaldehyde (37%, 4.7 mL, 58.2 mmol) was added to the mixture, causing a vigorous exothermic reaction. The yellow mixture was stirred and heated at *ca.* 85 °C for 6 h, with an additional 2 equiv of pyrrolidine and formaldehyde being added after 3 h. The reaction mixture was cooled, poured into water, and extracted with EtOAc (3×). The organic phase was washed with brine, dried (Na_2SO_4), filtered, and evaporated. The residue was taken up in CH_2Cl_2 and diluted with hexane to afford **9g** as white crystals, mp 111−113 °C. Two more crops of crystals were obtained upon concentration of the mother liquor. The total yield of **9g** was therefore 8.0 g (83%): ^{1}H NMR ($CDCl_3$) 8.50 (br s, 1), 7.19 (s, 1), 3.75 (v br s, 8), 3.16 (v br s, 2), 2.62 (v br s, 8), 1.84 (br s, 4), 1.78 (br s, 4), 1.38 (v br s, 6); ^{13}C NMR ($CDCl_3$) 156.3, 139.2, 131.0, 125.8, 121.8, 115.8, 68.7, 58.1, 53.3, 52.3, 49.1, 46.8, 34−28 (v br, *gem*-dimethyl), 23.7, 23.2; MS (CI/CH_4, 70 eV) m/z 413/411 ($M + H)^+$, 397/395, 395/393, 370/368, 342/340 (base peak), 324/322, 290, 283, 262, 211, 183, 145, 100. Anal. ($C_{20}H_{31}BrN_2O_2$) C, H, N.

3-(2-Hydroxy-2-methylpropyl)-2,6-bis[[(4-methoxybenzyl)sulfanyl]methyl]phenol (10g). The bis(pyrrolidine) compound **9g** (5.00 g, 12.17 mmol) and 4-methoxybenzyl mercaptan (11.24 g, 73.0 mmol) were combined in a flask equipped with a reflux condenser. The mixture was stirred and heated at 180 °C (sand bath in a heating mantle) for 3 h, then cooled, diluted with CH_2Cl_2, and applied to a pad of silica gel. The nonpolar impurites were eluted with CH_2Cl_2, and then the crude product was eluted with 10:1 CH_2Cl_2/iPrOH. The material was further purified by FC (4:1, CH_2Cl_2/CH_3CN) to give **10g** as a pale yellow oil (4.60 g, 76%): ^{1}H NMR ($CDCl_3$) 7.26 (d, 2, J = 8.5), 7.18 (d, 2, J = 8.6), 7.00−6.80 (m, 6), 6.71 (d, 1, J = 7.8), 3.85 (s, 2), 3.80 (s, 3), 3.79 (s, 3), 3.72 (s, 2), 3.66 (s, 2), 3.59 (s, 2), 2.68 (s, 2), 1.53 (s, 1), 1.15 (s, 6); ^{13}C NMR ($CDCl_3$) 158.7, 154.1, 137.3, 130.0, 129.5, 128.9, 124.5, 123.8, 121.7, 114.2, 113.9, 113.9, 71.0, 55.2, 55.2, 45.3, 36.2, 34.9, 31.8, 29.5, 27.7; MS (CI/CH_4, 70 eV) m/z 499 ($M + H)^+$, 481, 427, 389, 346, 327, 287, 237, 207, 175, 155, 122, 121 (base peak), 109, 91.

3-(2-Hydroxy-2-methylpropyl)-2,6-dimethylphenol (11g). Raney nickel (RaNi, *ca.* 20 g) was washed five times with water and twice with anhydrous EtOH. A slurry of this catalyst in EtOH was then added to a solution of bis(sulfide) **10g** (3.01 g, 6.04 mmol) in EtOH (30 mL). The resulting mixture was heated at vigorous reflux for 2 h and then cooled. The supernatant was decanted, and the catalyst was washed successively with MeOH and EtOAc (2×). The decanted organic layers were combined and evaporated. The residue was purified by FC (10:1 CH_2Cl_2/iPrOH) to give **11g** as a pale yellow oil (0.98 g, 84%): ^{1}H NMR ($CDCl_3$) 6.94 (d, 1, J = 7.7), 6.72 (d, 1, J = 7.7), 2.81 (s, 2), 2.24 (s, 6), 1.24 (s, 6); ^{13}C NMR ($CDCl_3$) 152.4, 135.1, 127.4, 123.4, 122.9, 121.0, 71.6, 45.7, 29.4, 15.9, 12.8; MS (CI/CH_4, 70 eV) m/z 195 ($M + H)^+$, 177 (base peak), 175, 149, 136, 91, 79.

3,3,5,7-Tetramethyl-3,4-dihydroisoquinolin-6-ol (12g). Powdered NaCN (3.79 g, 77.3 mmol) was placed in a flask cooled in an ice bath. A mixture of concentrated H_2SO_4 in an equal volume of HOAc (70 mL total) was prepared, cooled to room temperature, and then added to the NaCN through a dropping funnel (CAUTION! HCN generated). The mixture was stirred vigorously during the addition. Tertiary alcohol **11g** (12.5 g, 64.4 mmol) in 30 mL of HOAc was added *via* pipet to the acid/cyanide mixture (at room temperature) over a 2.5 h period, and the resulting red reaction mixture was stirred overnight at room temperature. Because of the high water solubility of the product, the aqueous phase was saturated with NaCl and extracted six times with EtOAc to obtain an acceptable recovery of material. The organic phase was dried (Na_2SO_4), filtered, and concentrated. The residue was filtered through silica gel with 10:1 CH_2Cl_2/MeOH, and the appropriate fractions were combined and diluted with hexane to produce **5g** as yellow crystals, mp 220−234 °C (dec.). A lower R_f product was also isolated. This material displayed the same type of TLC behavior (blue fluorescence) and a ^{1}H NMR spectrum very similar to that of **5g**, and is thought to be a symmetrical, macrocyclic dimer.[28] Upon being left to stand in solution, this byproduct was slowly converted into **5g**, which then precipitated. The solid was collected, and two more crops of the yellow crystals were subsequently obtained from the mother liquor, for a total yield of 6.8 g (52%): ^{1}H NMR (CD_3OD, 3.30 ppm) 7.76 (s, 1), 7.10 (s, 1), 4.93 (s, 1), 2.82 (s, 2), 2.10 (s, 3), 2.07 (s, 3), 1.33 (s, 6); ^{13}C NMR (CD_3OD, 49.05 ppm) 158.2, 136.2, 134.9, 127.6, 126.9, 54.3, 38.2, 27.3, 17.0, 11.4; MS (CI/CH_4, 70 eV) m/z 204 [$(M + H)^+$, base peak], 188, 177, 122.

3,3,5,7-Tetramethyl-3,4-dihydroisoquinolin-6-ol *N*-Oxide (6g). Imine **5g** (1.00 g, 4.93 mmol) was hydrogenated (50 psi of H_2) over RaNi (spatula scoop, washed three times with water and three times with EtOH) in EtOH (20 mL) for 2 h at room temperature. Filtration of the reaction mixture through filter aid and evaporation of the solvent gave the amine as a light yellow solid which was used without further purification: yield 0.90 g (89%); ^{1}H NMR ($CDCl_3$) 6.68 (s, 1), 3.95 (s, 2), 3.62 (br s, 2), 2.45 (s, 2), 2.21 (s, 3), 2.08 (s, 3), 1.20 (s, 6); ^{13}C NMR ($CDCl_3$) 150.4, 131.4, 125.9, 125.1, 122.2, 121.2, 48.9, 43.9, 39.0, 27.9, 16.0, 11.0. The amine from above (0.90 g, 4.39 mmol) was oxidized according to general procedure A. The nitrone **6g** was obtained (0.66 g, 69%) as light yellow crystals: mp 225−240 °C; ^{1}H NMR ($CDCl_3$) 7.60 (s, 1), 6.80 (s, 1), 2.97 (s, 2), 2.23 (s, 3), 2.17 (s, 3), 1.44 (s, 6); ^{13}C NMR (DMSO-d_6, 39.43 ppm) 154.1, 130.8, 127.3, 124.7, 122.7, 122.4, 120.4, 64.9, 38.1, 24.4, 16.5, 11.6; MS (EI, 70 eV) m/z 219 (M^+, base peak), 202, 187, 172, 160, 115, 91, 77. Anal. ($C_{13}H_{17}NO_2$) C, H, N.

3-Thiophene-2-yl-2,2-dimethylpropionic Acid (12i). To a solution of $LiN(TMS)_2$ (1 M solution in THF, 122 mL, 122 mmol) cooled at −78 °C was added ethyl isobutyrate (10.9 mL, 81.7 mmol). Stirring was continued at −78 °C for 1 h and then 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU, 3 mL) was added, followed by 2-(chloromethyl)thiophene (10.8

g, 81.7 mmol).[29] The cooling bath was removed, and the reaction mixture was stirred overnight. The reaction mixture was poured into cold 1 M HCl and extracted with EtOAc (3×). The organic phase was washed with water and brine, then dried ($MgSO_4$), filtered, and evaporated. The residue was purified by FC (CH_2Cl_2) to give the product as a yellow liquid (16.4 g, 95%): ^{1}H NMR ($CDCl_3$) 7.15−7.10 (m, 1), 6.95−6.90 (m, 1), 6.77 (d, 1, J = 3.6), 4.15 (t, 2, J = 7.0), 3.07 (s, 2), 1.26 (t, 3, J = 7.0), 1.21 (s, 6); ^{13}C NMR ($CDCl_3$) 177.0, 139.8, 126.7, 126.4, 123.9, 60.6, 43.7, 40.3, 25.1, 14.2; MS (CI/CH_4, 70 eV) m/z 213 [$(M + H)^+$, base peak], 193, 179, 167, 140, 139, 125, 98, 97. The ester from above (16.4 g, 77.2 mmol) was hydrolyzed according to general procedure B to give **12i** as a milky liquid (11.0 g, 77%): ^{1}H NMR ($CDCl_3$) 7.15 (d, 1, J = 5.1), 6.95−6.90 (m, 1), 6.83 (d, 1, J = 3.4), 3.10 (s, 2), 1.26 (s, 6); ^{13}C NMR ($CDCl_3$) 184.0, 139.4, 127.1, 126.7, 124.2, 43.6, 39.9, 24.7; MS (EI, 70 eV) m/z 184 (M^+), 139, 123, 97 (base peak), 77.

6,6-Dimethyl-6,7-dihydro-5*H*-thieno[3,2-*c*]pyridin-4-one (14i). Carboxylic acid **12i** from the previous reaction (11.0 g, 60.0 mmol) was subjected to the Curtius rearrangement according to general procedure C to give the isocyanate **13i** as a pale yellow liquid (9.94 g, 92%): ^{1}H NMR ($CDCl_3$) 7.22 (d, 1, J = 5.1), 6.99 (m, 1), 6.89 (d, 1, J = 3.5), 3.00 (s, 2), 1.38 (s, 6); ^{13}C NMR ($CDCl_3$) 138.2, 127.6, 126.7, 124.8, 58.1, 43.8, 29.9; IR ($CHCl_3$) 2982, 2259, 1265, 1167, 704; MS (EI, 70 eV) m/z 181 (M^+), 149, 138, 127, 123, 99, 97 (base peak), 84, 77, 71. To a mixture of 1,2-dichloroethane (DCE, 60 mL) and anhydrous H_3PO_4 (35 mL, prepared from 85% H_3PO_4 and P_2O_5) was added a solution of isocyanate **13i** (5.12 g, 28.3 mmol) in DCE (20 mL). The resulting mixture was stirred vigorously at room temperature for 2 h and then at reflux for 4 h. The reaction mixture was allowed to cool and separate into two layers. The upper, organic layer was decanted, diluted with EtOAc and Na_2CO_3 solution, and extracted with EtOAc (2×). The organic extract was washed with brine (2×) and dried ($MgSO_4$), filtered, and evaporated. The residue was purified by FC (6:4 CH_2Cl_2/CH_3CN) to give a yellow solid (2.10 g, 41%): mp 153−154 °C; ^{1}H NMR ($CDCl_3$) 7.43 (d, 1, J = 5.2), 7.10 (d, 1, J = 5.2), 6.82 (s, 1), 2.99 (s, 2), 1.38 (s, 6); ^{13}C NMR ($CDCl_3$) 162.6, 145.0, 130.9, 125.7, 123.0, 54.0, 37.3, 29.1; MS (EI, 70 eV) m/z 181 (M^+), 166, 151, 148, 125, 124 (base peak), 96, 83, 70. Anal. ($C_9H_{11}NOS$) C, H, N.

6,6-Dimethyl-6,7-dihydrothieno[3,2-*c*]pyridine *N*-Oxide (6i). Lactam **14i** (2.76 g, 15.2 mmol) was reduced according to general procedure D to give a dark liquid (1.82 g, 71%): ^{1}H NMR ($CDCl_3$) 7.07 (d, 1, J = 5.1), 6.75 (d, 1, J = 5.1), 3.93 (s, 2), 2.66 (s, 2), 1.64 (br s, 1), 1.21 (s, 6). The crude amine (1.82 g, 10.9 mmol) was oxidized according to general procedure A to give the nitrone **6i** as a yellow solid (660 mg, 33%, mp 130−131 °C) after recrystallization from 4:1 hexane/CH_2Cl_2: ^{1}H NMR ($CDCl_3$) 7.72 (s, 1), 7.17 (d, 1, J = 5.1), 6.89 (d, 1, J = 5.1), 3.15 (s, 2), 1.50 (s, 6); ^{13}C NMR ($CDCl_3$) 131.2, 130.3, 128.6, 124.7, 123.5, 67.9, 37.41, 25.0; MS (EI, 70 eV) m/z 181 (M^+, base peak), 166, 149, 138, 134, 110, 96, 91, 77. Anal. ($C_9H_{11}NOS$) C, H, N.

2-(3-Methoxyphenyl)-2-methylpropionic Acid (12k). To an ice cold slurry of NaH (17.69 g, 60% dispersion in mineral oil, 440 mmol) in THF (500 mL) was added a solution of 3-methoxyphenylacetonitrile (25.0 g, 170 mmol) in THF (25 mL) over 30 min. The mixture was stirred for 30 min and then a solution of CH_3I (55.5 g, 390 mmol) in THF (25 mL) was added over 30 min. The reaction mixture was allowed to reach room temperature, and stirring was continued until GC analysis indicated complete reaction (25 min). The reaction mixture was poured into cold water/EtOAc, the layers were separated, and the aqueous phase was extracted again with EtOAc. The organic phase was washed with brine, dried ($MgSO_4$), filtered, and evaporated to give the dimethylated nitrile[30] as a dark liquid, 31.0 g (104%), which was used without purification: ^{1}H NMR ($CDCl_3$) 7.31 (t, 1, J = 8.1), 7.05−7.00 (m, 2), 6.90−6.85 (m, 1), 3.83 (s, 3), 1.72 (s, 6). The crude nitrile (23.12 g, 132.1 mmol) was hydrolyzed according to general procedure B to afford the carboxylic acid **12k** as a pale yellow solid (20.76 g, 81%): mp 46−47 °C; ^{1}H NMR ($CDCl_3$) 7.24 (t, 1, J = 8.0), 7.00−6.95 (m, 2), 6.85−6.80 (m, 1), 3.81 (s, 3), 1.58 (s, 6); ^{13}C NMR ($CDCl_3$) 182.9, 159.6, 145.4, 129.4, 118.3, 112.4, 111.7, 55.2, 46.2, 26.1; MS (CI/CH_4, 70 eV) m/z 195 $(M + H)^+$, 194, 177, 150, 149 (base peak), 137, 121, 109.

1-(1-Isocyanato-1-methylethyl)-3-methoxybenzene (13k). Carboxylic acid **12k** (23.12 g, 132.1 mmol) was submitted to the Curtius rearrangement according to general procedure C to give isocyanate **13k** as a yellow liquid. The crude product (16.84 g, 96%) was used in the next step without purification: ^{1}H NMR ($CDCl_3$) 7.26 (t, 1, J = 8.2), 7.00 (m, 2), 6.85−6.80 (m, 1), 3.80 (s, 3), 1.69 (s, 6); ^{13}C NMR ($CDCl_3$) 159.6, 147.6, 129.5, 116.7, 112.0, 111.1, 60.7, 55.3, 33.0.

5-Methoxy-3,3-dimethyl-2,3-dihydroisoindol-1-one (14k) and 7-Methoxy-3,3-dimethyl-2,3-dihydroisoindol-1-one (14l). To an ice cold slurry of $FeCl_3$ (35.69 g, 220 mmol) in dry DCE (800 mL) was added a solution of isocyanate **13k** (19.12 g, 100.0 mmol) in the same solvent (100 mL) over 45 min. After completion of the addition, GC analysis of an aliquot indicated complete reaction. Water (600 mL) was added, and the resulting mixture was stirred vigorously. The layers were separated, and the organic phase was washed with 1 M tartaric acid solution (2 × 1 L) and once with brine. The solution was dried ($MgSO_4$), filtered, and evaporated to a dark liquid. This was purified by FC (1:4 hexane/EtOAc, then EtOAc) to provide the 5-methoxyisoindolone **14k** as a pale yellow solid, mp 146−147 °C, 7.38 g (39%), and the regioisomeric 7-methoxyisoindolone **14l** as a yellow solid, mp 155−158 °C, 2.85 g (15%). For **14k**: ^{1}H NMR ($CDCl_3$) 7.74 (d, 1, J = 8.5), 7.00−6.95 (m, 1), 6.85 (d, 1, J = 2.2), 3.89 (s, 3), 1.54 (s, 6); ^{13}C NMR ($CDCl_3$) 169.6, 163.2, 155.4, 125.3, 123.1, 114.2, 105.9, 58.6, 55.6, 27.8; MS (EI, 70 eV) m/z 191 (M^+), 176 (base peak), 161, 133, 118, 88, 77.

For **14l**: ^{1}H NMR ($CDCl_3$) 7.51 (t, 1, J = 8.0), 6.95 (d, 1, J = 8.0), 6.88 (d, 1, J = 8.0), 6.28 (br s, 1), 3.98 (s, 3), 1.51 (s, 6); ^{13}C NMR ($CDCl_3$) 168.6, 157.6, 156.1, 133.8, 131.4, 112.9, 109.9, 57.9, 55.9, 27.9; MS (EI, 70 eV) m/z 191 (M^+), 176 (base peak), 162, 158, 133, 118, 103, 89.

6-Methoxy-1,1-dimethyl-1*H*-isoindole *N*-Oxide (6k). Lactam **14k** from the previous reaction (170 mg, 0.889 mmol) was reduced according to general procedure D to furnish the corresponding amine as a colorless liquid which was not purified or characterized. The crude material (177 mg, 0.889 mmol, maximum) was oxidized according to general procedure A. The nitrone **6k** was obtained as beige crystals (54 mg, 28%, mp 119−122 °C) after FC (97:3 CH_2Cl_2/iPrOH): ^{1}H NMR ($CDCl_3$) 7.61 (s, 1), 7.29 (d, 1, J = 8.4), 6.90−6.85 (m, 1), 6.84 (d, 1, J = 2.3), 3.86 (s, 3), 1.56 (s, 6); ^{13}C NMR ($CDCl_3$) 160.1, 147.6, 131.4, 124.9, 121.2, 113.5, 107.9, 55.6, 24.5; MS (EI, 70 eV) m/z 191 (M^+, base peak), 176, 158, 145, 131, 115, 103, 91, 89, 77. Anal. ($C_{11}H_{13}NO_2$) C, H, N.

5-Hydroxy-3,3-dimethyl-2,3-dihydroisoindol-1-one (14m). A 1 M solution of BBr_3 in CH_2Cl_2 (88.0 mL, 88.0 mmol) was dissolved in CH_2Cl_2. A solution of lactam **14k** (7.65 g, 40.0 mmol) in CH_2Cl_2 (50 mL) was added to the BBr_3 solution dropwise over 10 min. The resulting mixture was stirred at room temperature overnight. The reaction mixture was poured into water and extracted with EtOAc (3×). The organic phase was dried ($MgSO_4$), filtered, and evaporated, leaving the product **14m** as a white solid (4.03 g, 57%), mp 231−233 °C, which required no purification: ^{1}H NMR (DMSO-d_6, 2.50 ppm) 8.18 (s, 1), 7.28 (d, 1, J = 8.5), 6.75 (d, 1, J = 1.6), 6.67 (dd, 1, J = 8.5, 1.6), 1.25 (s, 6); ^{13}C NMR ($CDCl_3$ + DMSO-d_6) 169.3, 161.1, 155.4, 124.7, 121.5, 115.4, 107.3, 58.0, 27.5; MS (EI, 70 eV) m/z 177 (M^+), 163, 162 (base peak).

6-Hydroxy-1,1-dimethyl-1*H*-isoindole *N*-Oxide (6m). Lactam **14m** (1.42 g, 8.01 mmol) was reduced according to general procedure D except that the HCl extract was simply evaporated to furnish the amine hydrochloride salt. Residual water was removed by repeatedly dissolving the residue in acetonitrile and evaporating the mixture. A white solid (1.6 g, 100%) was obtained which was not purified further: ^{1}H NMR ($CDCl_3$ + DMSO-d_6) 8.98 (vbr s, 2), 6.95 (d, 1, J = 9.0), 6.59 (d, 1, J = 9.0), 6.55 (s, 1), 4.02 (s, 2), 1.32 (s, 6); ^{13}C NMR (DMSO-d6, 39.43 ppm) 157.0, 143.4, 122.2, 121.2, 111.6, 106.4, 66.5, 45.6, 24.3. The amine hydrochloride from above (615 mg, 3.08 mmol) was oxidized according to general procedure A

except that 1.0 equiv of NaOH was added to generate the free amine *in situ*. The nitrone **6m** was obtained as a white solid (60 mg, 11%, mp 225−230 °C) after FC (EtOAc): ^{1}H NMR (DMSO-d_6, 2.50 ppm) 9.48 (s, 1), 7.70 (s, 1), 7.20 (d, 1, J = 8.0), 6.82 (d, 1, J = 2.2), 6.80−6.75 (m, 1), 1.50 (s, 6); ^{13}C NMR (DMSO-d_6, 39.43 ppm) 157.5, 147.2, 130.0, 121.0, 115.0, 109.1, 76.0, 24.1; MS (EI, 70 eV) m/z 177 [(M^+), base peak], 162, 144, 131, 115, 91, 89, 77. Anal. ($C_{10}H_{11}NO_2$) H, N; C: calcd, 67.78; found, 67.09.

3,3-Dimethylisoindol-1-one (14n). A solution of lactam **14m** (1.77 g, 10.0 mmol) and 5-chloro-1-phenyl-1*H*-tetrazole (2.17 g, 12.0 mmol) in DMF (50 mL) was treated with solid K_2CO_3 (2.07 g, 15.0 mmol). The mixture was stirred overnight at room temperature, then poured into water, and extracted with EtOAc (2×). The organic phase was washed with water (3×) and brine (2×), then dried ($MgSO_4$), filtered, and evaporated. The residue was crystallized from CH_2Cl_2 to give the intermediate tetrazolyl ether as a white solid (3.10 g, 97% yield): mp 202−204 °C; ^{1}H NMR ($CDCl_3$) 7.90 (d, 1, J = 8.3), 7.80 (m, 2), 7.60−7.55 (m, 4), 7.50−7.45 (m, 1), 6.78 (s, 1), 1.59 (s, 6); ^{13}C NMR ($CDCl_3$) 168.5, 158.8, 156.2, 155.3, 132.8, 129.8, 128.8, 125.8, 122.3, 119.4, 112.1, 59.1, 53.4, 27.6; MS (EI, 70 eV) m/z 321 (M^+), 306, 293, 278, 261, 250, 236, 222, 208, 187, 176, 161 (base peak), 145, 133, 117, 103, 91, 77. The product from above (3.10 g, 9.65 mmol) was dissolved in EtOH (80 mL) and hydrogenated over 5% Pd/C (400 mg) at 50 psi of H_2 on a Parr shaker overnight at room temperature. The catalyst was filtered off and the solvent evaporated. The residue was purified by FC (Et_2O) to furnish **14n** as a white solid (1.03 g, 66%): mp 159−160 °C; ^{1}H NMR ($CDCl_3$) 7.83 (d, 1, J = 7.6), 7.57 (t, 1, J = 7.6), 7.45−7.40 (m, 2), 1.57 (s, 6); ^{13}C NMR ($CDCl_3$) 169.9, 153.2, 132.0, 130.7, 127.9, 123.8, 120.8, 59.1, 27.7; MS (EI, 70 eV) m/z 161 (M^+), 146 (base peak), 128, 103, 91, 77.

1,1-Dimethyl-1*H*-isoindole *N*-Oxide (6n). Lactam **14n** (1.42 g, 8.01 mmol) was reduced according to general procedure D, except that the HCl extract was simply evaporated to furnish the amine hydrochloride salt. Residual water was removed by repeatedly dissolving the residue in acetonitrile and evaporating the mixture. A white solid (918 mg, 100%) was obtained which was not purified further: ^{1}H NMR ($CDCl_3$ + DMSO-d_6) 10.30 (br s, 2), 7.40−7.35 (m, 3), 7.25−7.20 (m, 1), 4.55 (s, 2), 1.76 (s, 6); ^{13}C NMR ($CDCl_3$ + DMSO-d_6) 132.0, 128.1, 127.9, 122.3, 120.3, 110.4, 61.0, 46.8, 25.5. The amine hydrochloride from above (918 mg, 5.00 mmol) was oxidized according to general procedure A except that 1.0 equiv of NaOH was added to generate the free amine *in situ*. The nitrone **6n** was obtained as a white solid (113 mg, 14%, mp 64−65 °C) after FC (8:2 CH_2Cl_2/CH_3CN): ^{1}H NMR ($CDCl_3$) 7.66 (s, 1), 7.36 (m, 3), 7.27 (m, 1), 1.57 (s, 6); ^{13}C NMR ($CDCl_3$) 145.4, 132.3, 131.5, 128.4, 127.5, 120.7, 120.1, 77.6, 24.5; MS (CI/CH_4, 70 eV) m/z 162 [($M + H)^+$, base peak], 144, 128. Anal. ($C_{10}H_{11}NO$) C, H, N.

4-Methoxy-1,1-dimethyl-1*H*-isoindole *N*-Oxide (6l). Lactam **14l** (1.19 g, 6.22 mmol) was reduced according to general procedure D, except that the HCl extract was simply evaporated to furnish the amine hydrochloride salt. Residual water was removed by repeatedly dissolving the residue in acetonitrile and evaporating the mixture. A white solid (1.33 g, 100%) was obtained which was not purified further: ^{1}H NMR ($CDCl_3$ + DMSO-d_6) 10.26 (br s, 2), 7.35 (t, 1, J = 7.7), 6.85−6.75 (m, 2), 4.47 (br s, 2), 3.86 (s, 3), 1.74 (s, 6); ^{13}C NMR ($CDCl_3$ + DMSO-d_6) 143.6, 129.5, 125.0, 118.9, 111.6, 108.9, 67.4, 53.9, 44.2, 24.2. The amine hydrochloride from above (1.33 g, 6.21 mmol) was oxidized according to general procedure A except that 1.0 equiv of NaOH was added to generate the free amine *in situ*. The nitrone **6l** was obtained (190 mg, 16%) as a pale yellow solid, mp 149−152 °C, after FC (EtOAc, the 9:1 CH_2Cl_2/MeOH) and crystallization from CH_2Cl_2/hexane: ^{1}H NMR ($CDCl_3$ + CD_3OD) 7.74 (s, 1), 7.35−7.25 (m, 1), 6.88 (d, 1, J = 8.9), 6.84 (d, 1, J = 8.9), 3.90 (s, 3), 1.55 (s, 6); ^{13}C NMR ($CDCl_3$ + CD_3OD) 152.1, 147.2, 129.3, 129.1, 113.3, 110.2, 77.8, 55.5, 24.5; MS (EI, 70 eV) m/z 191 [(M^+), base peak], 176, 158, 134, 131, 128, 115, 91, 77. Anal. ($C_{11}H_{13}NO_2$) C, H, N.

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Supporting Information Available: Full experimental details and spectral data for compounds **2a−f**, **3a,b,d−f**, **5a−f,h**, **6a−f,h,j**, **7g**, **7−11h**, and **12−14j** (18 pages). Ordering information is given on any current masthead page.

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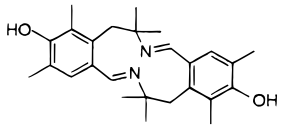

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