Conformational Analysis and Structural Elucidation of Spirocyclic Oxaziridines Using NMR, Crystallography, and Molecular Modeling

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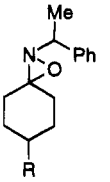
The ^{1}H NMR spectra of spirocyclic oxaziridines derived from substituted cyclohexanones and benzylamines were studied. Depending on substitution and on stereochemistry, these compounds often exhibit a substantial upfield shift of the cyclohexyl methylene or methine protons with a 1,3-diaxial relationship to the oxaziridine N-substituent. This effect is ascribed to a conformation that places an aromatic group over the plane of the cyclohexane ring. This conformation has also been found in the solid state by X-ray crystallography and is supported by molecular mechanics calculations. The use of the effect in assigning stereochemistry to this series of compounds is discussed.

N-Alkyl oxaziridines[1] are useful intermediates for the synthesis of amides and lactams[2] and have been used more recently to prepare chiral pyrrolidines and aziridines via nitrogen-centered radicals.[3] The potential of oxaziridines as enzyme inhibitors has also been recognized.[4] In each case, the stereochemistry and conformation of the oxaziridine and its substituents are critical.[5] Previous work in this laboratory uncovered an interesting NMR observation arising from certain spirocyclic oxaziridines that subsequently proved useful in gleaning stereochemical and conformational information in those systems.[6] Since the NMR-active sectors in spirocyclic oxaziridines like **1** are separated by a quaternary carbon and a stereogenic[1b] nitrogen atom, such information is unavailable from coupling constants and can rarely be obtained from NOE measurements. Moreover, only one other NMR method for determining whether the nitrogen or oxygen of the oxaziridine occupies an pseduoaxial or -equatorial position on the cyclohexyl ring had been previously published.[7,8]



This full account describes the NMR behavior of spirocyclic oxaziridines derived from substituted benzylamines and cyclohexanones and its consequences vis à vis the determination of oxaziridine conformation and stereochemistry. In particular, we introduce a new method for determining the relative orientation of the CN_{oxaz} or CO_{oxaz} bonds on a chairlike C_6 ring. This analysis has been carried out in the context of available X-ray crystallographic data and includes a molecular modeling study.

Results and Discussion

Oxaziridines Derived from α-Methylbenzylamine. In a study designed to exploit spirocyclic oxaziridines for asymmetric ring-expansion reactions, we were faced with the problem of determining the structure of the major oxaziridine obtained from a series of 4-alkylcyclohex-

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(1) Reviews: (a) Schmitz, E. *Adv. Heterocycl. Chem.* **1963**, *2*, 83–130. (b) Davis, F. A.; Jenkins, R. H., Jr. In *Asymmetric Synthesis*; Morrison, J. D., Scott, J. W., Eds.; Academic: Orlando, 1984; Vol. 4, pp 313-353. (c) Haddadin, M. J.; Freeman, J. P., In *Small Ring Heterocycles*; Hassner, A., Ed.; John Wiley & Sons: New York, 1985; Vol. 42, part 3, pp 283–350. (d) Davis, F. A.; Sheppard, A. C. *Tetrahedron* **1989**, *45*, 5703–5742.

(2) For some examples, see: (a) Schmitz, E.; Murawski, D. *Chem. Ber.* **1965**, *98*, 2525–2529. (b) Fischer, M. *Tetrahedron Lett.* **1969**, 2281–2284. (c) Parello, J.; Rivière, M.; Desherces, E.; Lattes, A. *C. R. Hebd. Seances Acad. Sci., Ser. C.* **1971**, *275*, 1097–1100. (d) Black, D. S. C.; Watson, K. G. *Aus. J. Chem.* **1973**, *26*, 2505–2513. (e) Oliveros-Desherces, E.; Rivière, M.; Parello, J.; Lattes, A. *Tetrahedron Lett.* **1975**, 851–854. (f) Schmitz, E.; Streigler, H.; Heyne, H.-U.; Hilgetag, K.-P.; Dilcher, H.; Lorenz, R. *J. Prakt. Chem.* **1977**, *319*, 274–280. (g) Oliveros, E.; Rivière, M.; Lattes, A. *Nouv. J. Chim.* **1979**, *3*, 739–753. (h) Oliveros, E.; Rivière, M.; Malrieu, J. P.; Teichteil, C. *J. Am. Chem. Soc.* **1979**, *101*, 318–322. (i) Langlois, Y.; Pouilhès, A.; Génin, D.; Andriamialisoa, R. Z.; Langlois, N. *Tetrahedron* **1983**, *39*, 3755–3761. (j) Kuehne, M. E.; Parsons, W. H. *Tetrahedron* **1983**, *39*, 3763–3765. (k) Edge, G. J.; Imam, S. H.; Marples, B. A. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2319–2325. (l) Johnson, G. P.; Marples, B. A. *Tetrahedron Lett.* **1984**, *25*, 3359–3362. (m) Duhamel, P.; Bénard, D.; Plaquevent, J.-C. *Tetrahedron Lett.* **1985**, *26*, 6065–6066. (n) Johnson, G. P.; Marples, B. A. *Tetrahedron Lett.* **1985**, *26*, 4115–4118. (o) Duhamel, P.; Goument, B.; Plaquevent, J.-C. *Tetrahedron Lett.* **1987**, *28*, 2595–2596. (p) Suda, K.; Umehara, T.; Hino, F. *Chem. Pharm. Bull.* **1990**, *38*, 839–841. (q) Aubé, J.; Wang, Y.; Ghosh, S.; Langhans, K. L. *Synth. Commun.* **1991**, *21*, 693–701. (r) Suda, K.; Sashima, M.; Izutsu, M.; Hino, F. *J. Chem. Soc., Chem. Commun.* **1994**, 949–950. (s) Aubé, J.; Ghosh, S.; Tanol, M. *J. Am. Chem. Soc.* **1994**, *116*, 9009–9018. (t) Heathcock, C. H.; Joe, D. *J. Org. Chem.* **1995**, *60*, 1131–1142.

(3) Aubé, J.; Peng, X.; Wang, Y.; Takusagawa, F. *J. Am. Chem. Soc.* **1992**, *114*, 5466–5467.

(4) Marchand-Brynbaert; Bounkhala-Khrouz, Z.; Vanlierde, H.; Ghosez, L. *Heterocycles* **1990**, *30*, 971–982.

(5) (a) Lattes, A.; Oliveros, E.; Rivière, M.; Belzecki, C.; Mostowicz, D.; Abramskj, W.; Piccinni-Leopardi, C.; Germain, G.; Van Meerssche, M. *J. Am. Chem. Soc.* **1982**, *104*, 3929–3934. (b) Aubé, J.; Burgett, P. M.; Wang, Y. *Tetrahedron Lett.* **1988**, *29*, 151–154. (c) Aubé, J. *Tetrahedron Lett.* **1988**, *29*, 4509–4512. (d) Aubé, J.; Wang, Y.; Hammond, M.; Tanol, M.; Takusagawa, F.; Vander Velde, D. *J. Am. Chem. Soc.* **1990**, *112*, 4879–4891. (e) Aubé, J.; Hammond, M. *Tetrahedron Lett.* **1990**, *31*, 2963–2966. (f) Aubé, J.; Hammond, M.; Gherardini, E.; Takusagawa, F. *J. Org. Chem.* **1991**, *56*, 499–508. Correction: *Idem. Ibid. J. Org. Chem.* **1991**, *56*, 4086. (g) Kitagawa, O.; Vander Velde, D.; Dutta, D.; Morton, M.; Takusagawa, F.; Aubé, J. *J. Am. Chem. Soc.* **1995**, *117*, 5169–5178.

(6) Aubé, J.; Wang, Y. *Tetrahedron Lett.* **1988**, *29*, 6407–6408.

(7) Oliveros, E.; Rivière, M.; Lattes, A. *Org. Magn. Reson.* **1976**, *8*, 601–606.

(8) Other useful NMR methods for oxaziridine structure determination include: (a) Jordan, G. J.; Crist, D. R. *Org. Magn. Reson.* **1977**, *9*, 322–324. (b) Pirkle, W. H.; Rinaldi, P. L. *J. Org. Chem.* **1978**, *43*, 4475–4480. (c) Oliveros, E.; Rivière, M.; Lattes, A. *J. Heterocycl. Chem.* **1980**, *17*, 107–112. See also reference 1b.

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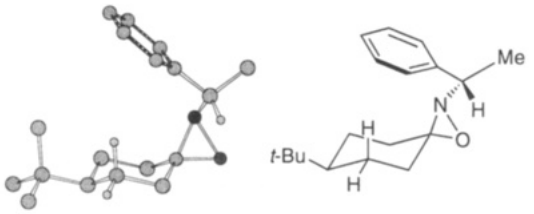
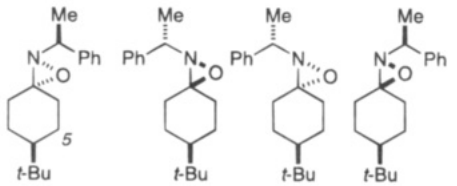


Figure 1. Ball-and-stick depiction of **1a** as determined by X-ray crystallography.[5a] Extraneous hydrogen atoms are removed for clarity.

anones and α-methylbenzylamine (α-MBA).[5b] These oxaziridines were synthesized by peracid oxidation of the corresponding imine. Four possible relative configurations **1a**–**d**, in which the amine stereocenter is arbitrarily depicted in the *S* absolute configuration, are shown below.



Although previous work had established the stereostructure of **1a** using X-ray crystallography,[5a] we wished to confirm that the same predominant isomer was obtained from analogous reactions. Examination of the NMR spectra of the purified isomers revealed that a cyclohexyl methylene proton appeared at δ 0.22 in compound **1a**; however, this signal was not cited in the initial report of **1a**.[5a] The signal, which appeared as an apparent doublet of quartets resulting from one small (axial–equatorial) and three large and coincidentally equivalent couplings (two axial–axial and one geminal), was assigned to the C-5 (axial) proton based on the published X-ray structure of **1a** (Figure 1). In this structure, the side-chain phenyl group is poised over the cyclohexane ring such that the proton bearing a 1,3-diaxial relationship to the oxaziridine nitrogen is in the shielding cone of the aromatic group.

A close examination of spectra obtained from the other isomers showed no such upfield signal; instead, the corresponding proton was presumably buried among the other methylene signals in these isomers (≥1.12 ppm). Assignments of these isomers were made by thermal correlations (pairs **1a**/**1c** and **1b**/**1d** could be equilibrated by forcing nitrogen inversion in refluxing toluene) and by stereoselectivity arguments (previous work had established the preference for oxaziridines to form with *unlike* vs *like* stereochemistry[9] and from equatorial vs axial peracid addition[7,8c]).[5b]

These observations are consistent with the hypothesis that this oxaziridine preferentially populates a conformation wherein the benzylic hydrogen atom occupies an "inside" position relative to the oxaziridine ring (Figure 2). This position should be the most sterically demanding

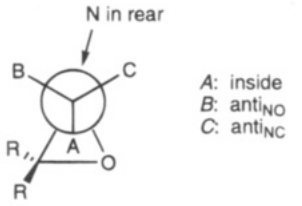


Figure 2. Proposed nomenclature for oxaziridine N-substituent conformations.

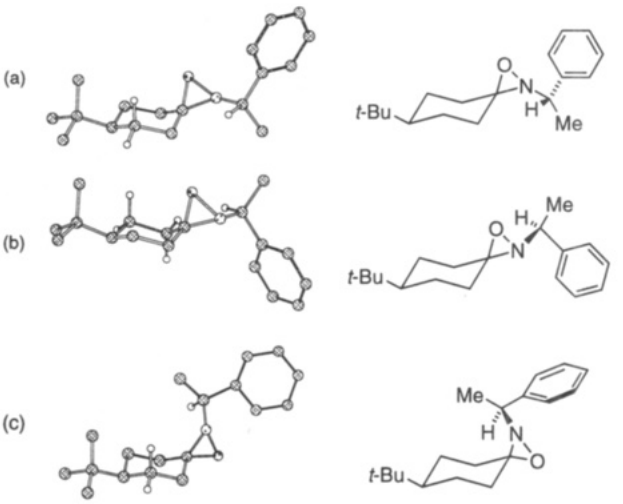


Figure 3. Proposed conformations for (a) oxaziridine **1b**, (b) oxaziridine **1c**, and (c) oxaziridine **1d**, each assuming that the benzylic hydrogen atom occupies the "inside" position relative to the oxaziridine ring. The ball-and-stick depictions do not represent crystal structures.

because of its proximity to the cis alkyl group at C-3 (oxaziridine numbering). Thus, compounds **1b** and **1d**, in which the oxaziridine nitrogen is equatorial, adopt a conformation in which the phenyl group is extended away from the six-membered ring (Figure 3; see also some examples derived from X-ray analyses in a later section of this paper). In this case, the only proton able to "feel" the anisotropic effect of the phenyl group would be the equatorial proton adjacent to the spiro center. Obviously, the only other isomer eligible for an upfield chemical shift effect at a nonadjacent proton is the *l,trans* oxaziridine **1c**. In this case, a conformation wherein the benzylic hydrogen is "inside" also swings the phenyl group away from the cyclohexyl group (Figure 3). Of course, one presumes that these systems are all in rapid equilibrium on the NMR time scale and that the proposed conformations are observed due to their high population relative to other possibilities.

The hypotheses derived from this analysis proved useful in structure determination in a number of structurally related compounds. Figure 4 shows oxaziridines derived from α-MBA and the chemical shift ascribed to the proton explicitly drawn in each compound. Each proton shown appears at higher field relative to all other methylene protons in the molecule shown. Note the slight downfield shifts experienced due to adjacent phenyl substitution in compound **3**. For compounds **2**–**4**, which were obtained as isomeric mixtures with the compound shown predominating, the signal noted in parentheses correctly integrated as belonging to the major diastereomer, and no other signal appeared in a similar region of the NMR (compounds **6**–**9** were isolated in pure form and are best compared with each other). These observa-

(9) (a) Belzecki, C.; Mostowicz, C. *J. Org. Chem.* **1975**, *40*, 3878–3880. (b) Bucciarelli, M.; Forni, A.; Moretti, I.; Torre, G. *J. Chem. Soc., Perkin Trans. 2* **1977**, 1339–1346. (c) Mostowicz, D.; Belzecki, C. *J. Org. Chem.* **1977**, *42*, 3917–3921. (d) Forni, A.; Garuti, G.; Moretti, I.; Torre, G.; Andreetti, G. D.; Bocelli, G.; Sgarabotto, P. *J. Chem. Soc., Perkin Trans. 2* **1978**, 401–405.

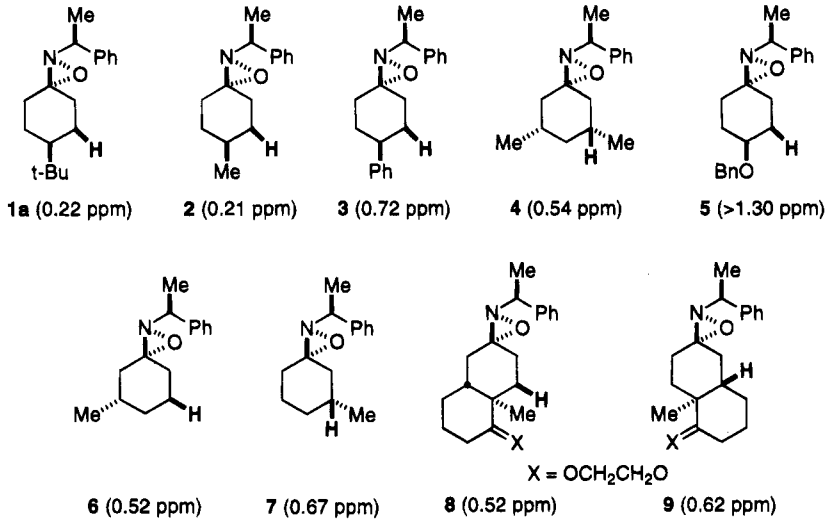
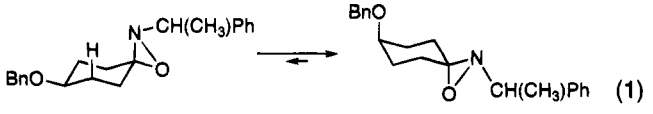


Figure 4. Chemical shifts for hydrogens shown in bold in various oxaziridines obtained at 300 MHz (except for **1a**, which was obtained at 500 MHz).[5d] All compounds are shown in the same antipodal series (i.e., as derived from (*S*)-α-MBA) for clarity; see original references for syntheses and actual absolute configurations (**1a** and **2-5**,[5d] **6/7**,[5f] and **8/9**.[5e]).

tions are consistant with each compound adopting the preferred conformations set forth in Figures 2 and 3.

No isomer of the benzyloxy-substituted **5** gives rise to an upfield methylene hydrogen signal. In analogy to **1-4**, only the *unlike* isomer with the N_{oxaz} cis to the benzyloxy group (shown in Figure 4) might be expected to do so. However, the ability of the 4-benzyloxy group to control the six-membered ring conformation should be greatly attenuated relative to oxaziridines bearing instead alkyl or aryl substituents on the six-membered ring (A-values:[10] OPh, 0.65 kcal/mol; Me, 1.74 kcal/mol). We hypothesize that CN_{equat} conformations win out over CN_{axial} ones, and therefore no upfield effect is observed (eq 1). An equatorial CN bond is preferred in oxaziridines derived from cyclohexanone itself.[8c]



(1)

Oxaziridines Derived from Other Amines. To assess the generality of this effect, a series of oxaziridines derived from achiral derivatives of benzylamine (benzylamine and diphenylmethylamine) and two positional isomers of α-methylnaphthylamine were prepared. The former series was designed to both provide further evidence for the conformational arguments advanced above and because of our need to determine whether various imines derived from chiral ketones underwent axial or equatorial attack by peracid. In such cases, twice as many imine stereoisomers would be formed with α-methylbenzylamine as with an achiral amine, greatly complicating product analysis. The replacement of the phenyl substituent on the side chain with a naphthyl group was originally inspired by our curiosity whether the anisotropic effect would be enhanced by "adding electrons" to the aromatic system. The compounds utilized in this part of the study were all prepared by reacting the appropriate ketone with its amine partner in benzene or toluene kept at reflux, followed by oxidation with *m*-CPBA. Yields ranged from 76–96% (both steps) for reactions carried out on scales ranging from 2.8–11.2 mmol (compound **18** was an exception, being obtained in 67% yield from 0.6 mmol of 4-phenylcyclohexanone). In every example, precedent and the results cited below lead us to believe that the major isomer obtained was that depicted, i.e., resulting from equatorial attack of oxidant and formation of *unlike* oxaziridine (where relevant). The chemical shifts listed in Table 1 can all be ascribed to this major isomer by integration.

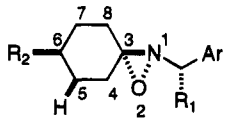
NMR examination of *N*-benzyl and *N*-diphenylmethyl oxaziridines are constant throughout each series. The upfield shift attributed to the C-5 proton is absent in the former series but present in each example of the latter. 2-D NMR experiments of **14** were carried out to further confirm the assignment of the NMR spectra. The signal of the methylene carbon syn to the nitrogen substituent is generally found ca. 7–10 ppm upfield from the anti carbon.[8a] Thus, C-4 and C-8 were assigned to δ 27.4 and δ 36.7, respectively. In the COSY spectrum of **14**, four cross-peaks from the signal at δ 0.18 were observed (δ 1.01, δ 1.45, δ 1.95, and δ 2.02). A HETCOR experiment confirmed that the signal at δ 1.01 could be attributed to the C-6 methine and that the two protons on C-4 occurred at δ 1.95 and δ 2.02, respectively. HETCOR also confirmed that two protons (δ 0.18 and δ 1.45) were connected to the same carbon (δ 24.9). These results show that the axial C-5 proton should be assigned to δ 0.18. Note that the two protons attached to the same carbon differ in chemical shift by 1.28 ppm.

Again, the results are most consistent with a picture whereby the most populous conformer(s) have a benzylic proton occupying the "inside" position of the oxaziridine. For an *N*-benzyl oxaziridine, two such conformations are possible, one of which places the phenyl group over the six-membered ring and one that does not (Figure 5a). Since both conformers place the smallest benzylic substituent in presumably the least sterically demanding position, they are likely populated to a similar extent. The C-5 axial proton does not experience any particular shielding and does not stand out in the time-averaged NMR spectra in this series.

On the other hand, only a single benzylic H "inside" conformation is possible for the diphenylmethylamine-

(10) Eliel, E. L.; Wilen, S. H.; Mander, L. N., In *Stereochemistry of Organic Compounds*; John Wiley & Sons: New York, 1994, pp 696–697 and references cited.

Table 1. NMR Results from Oxaziridines Derived from Various Amines



entry	comp	Ar	R_1	R_2	H-5 δ (ppm)[a]
1	10	Ph	H	Me	>0.90[b]
2	11	Ph	H	*t*-Bu	>0.90[b]
3	12	Ph	H	Ph	>0.90[b]
4	13	Ph	Ph	Me	0.17
5	14	Ph	Ph	*t*-Bu	0.18
6	15	Ph	Ph	Ph	0.66
7	16	Ph	Ph	OCH_2Ph	>1.30[b,c]
8	17	1-naphthyl	Me	Me	−0.32
9	18	1-naphthyl	Me	Ph	0.12
10	19	2-naphthyl	Me	Me	0.24
11	20	2-naphthyl	Me	Ph	0.54

[a] Chemical shifts refer to the major stereoisomer (assigned as depicted) and were obtained at 300 MHz. [b] No methine protons were observed at fields higher than the value noted. [c] Prepared as a mixture of isomers.

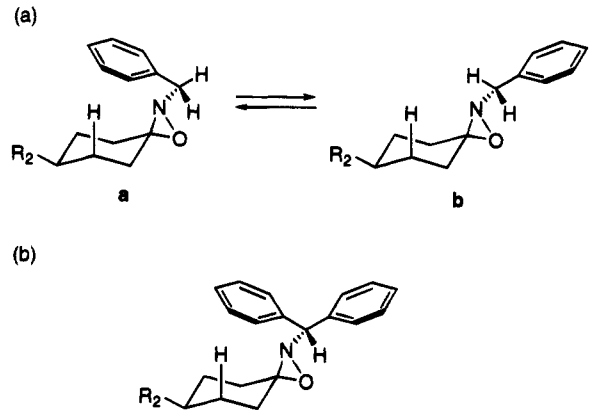


Figure 5. Proposed conformations of oxaziridines derived from 4-substituted cyclohexanones and (a) benzylamine and (b) diphenylmethylamine.

derived oxaziridines (Figure 5b). Here, dramatic shielding of the C-5 axial proton is expected and, in fact, observed (Table 1, entries 4–6). The sole exception is again due to an equatorial/axial conformational dichotomy in the case of the oxaziridine derived from 4-(benzyloxy)cyclohexanone (Table 1, entry 7). This oxaziridine was prepared as a very difficult to separate mixture of isomers, neither of which gave a methine signal upfield of 1.30 ppm: see Experimental Section and cf. eq 1).

These observations suggest a simple method for determining whether an oxaziridine substantially populates a conformation with an axial nitrogen substituent in solution. One could first compare the chemistry of oxaziridines derived from any given amine, benzylamine, and finally, diphenylmethylamine. If similar isomer ratios and spectroscopic properties are obtained throughout the series, with exception of a substantial upfield shift of the C-5 proton in the compound derived from diphenylmethylamine, chances are that the oxaziridine has a pseudoaxial nitrogen atom (or alternatively, arose from equatorial attack of oxidant). Note the comparisons in Table 1 of the following pairs of entries: 1/4, 2/5, and 3/6. In the absence of this phenomenon, alternative conformations should be considered (and unfortunately, other means to address the structural issues must be attempted).

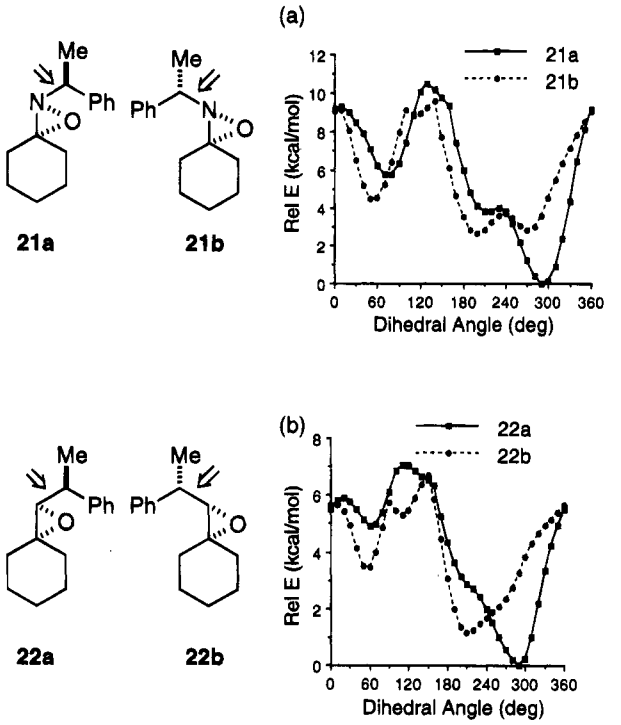


Figure 6. Compounds used for molecular modeling calculations and relative energies obtained by driving the dihedral angle noted. (a) Results for oxaziridines **21a** (*unlike*) and **21b** (*like*); the C–N bond was constrained into the pseudoaxial position. (b) Results obtained from the analogous epoxides **22a** and **22b**; the C_{spiro}–$C_{epoxide}$ bond was constrained into the pseudoaxial position.

Oxaziridines were prepared using α-(1′-naphthyl)-ethylamine and α-(2′-naphthyl)ethylamine (Table 1, entries 8–11) to determine whether other aromatic groups exert a similar effect. The oxaziridines were prepared using similar techniques as described above. The oxaziridines bearing a 1-naphthyl substituent experienced much greater upfield shifts relative to their α-methylbenzylamine counterparts ($-\Delta\delta = 0.44-0.59$). However, switching the aromatic functionality to its 2′-naphthyl isomer caused the chemical shifts to return to values close to those from the simple phenyl series. These results effectively rule out explanations based on the number of the aromatic electrons. It is more likely that the aromatic unit in the 1-naphthyl oxaziridines can more closely approach the C-5 axial proton than in the C-2′-connected isomers.

Molecular Modeling. To gain further insight into this system, we performed molecular mechanics calculations on oxaziridines conceptually derived from cyclohexanone itself and α-methylbenzylamine, namely the *unlike* and *like* isomers **21a** and **21b**, respectively (Figure 6). The calculations were carried out using the MM2* force field implemented by Macromodel version 4.5; default parameters were used. The models were built from cyclohexane, and the oxaziridine was constrained with the C_{spiro}–N_{oxaz} bond in the axial orientation. Since we were primarily interested in the rotational behavior of the N–$C_{benzylic}$ bond, calculations were carried out by driving the dihedral angle C_{oxaz}–N_{oxaz}–$C_{benzylic}$–C_{ipso} (defined here as ϕ) with 10° increments. A plot of this dihedral angle versus relative energy is given in Figure 6a.

Two clear mimina were found at $\phi = 290°$ and 70°, plus a much shallower dip at $\phi = 210°$. The former two

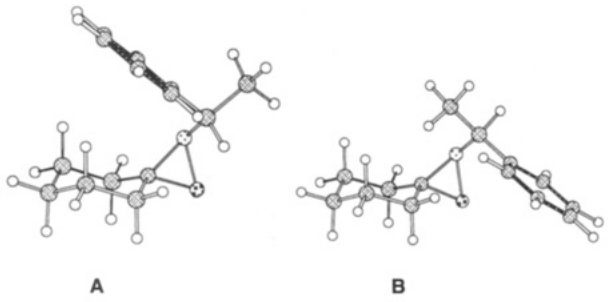


Figure 7. Low energy conformations of **21a** obtained from Macromodel (MM2*). Structure **A** is the global minimum with respect to the $N_{oxaz}-C_{benzylic}$ bond.

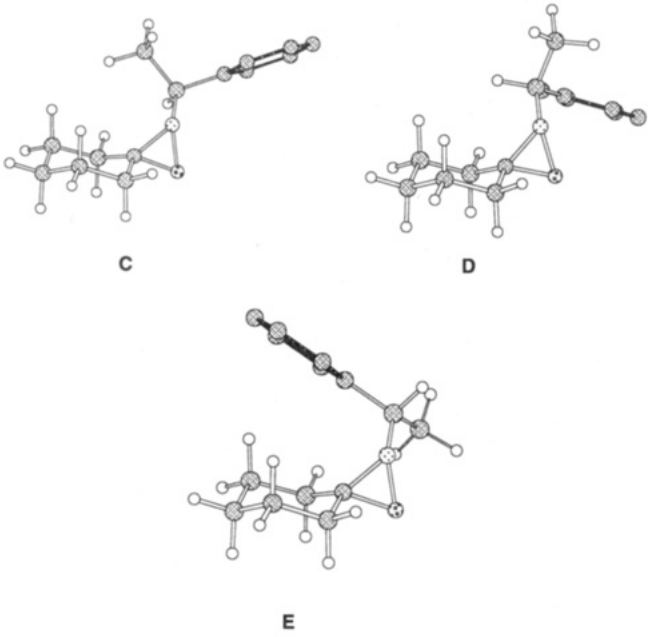


Figure 8. Low energy conformations of **21b** obtained from Macromodel (MM2*). Structure **D** is the global minimum with respect to the $N_{oxaz}-C_{benzylic}$ bond. Aromatic hydrogens have been removed for clarity.

mimina were further optimized to afford the structures shown in Figure 7. Structure **A** is the global minimum structure for this molecule, having a final ϕ value of 293°, i.e., with the benzylic proton taking up the "inside" position. Structure **B** (ϕ = 74.7°) puts the phenyl group "inside" and the hydrogen atom anti to the C−N bond; this structure lies about 5.7 kcal/mol higher than the minimum. Although the energy differences are almost certainly numerically exaggerated, they are qualitatively in line with the predictions put forth earlier in this paper for the preferred conformations of these oxaziridines.

A similar study was carried out on the stereoisomeric *like* oxaziridine **21b** (Figures 6a and 8). In this case, three clear minima were found and were further minimized to afford structures **C**−**E**. Structures **C** (ϕ = 199.2°) and **D** (ϕ = 271.2°) differed in energy by only 0.2 kcal/mol favoring **C** (the global minimum in this case). Although **C** has the benzylic hydrogen in the "inside" position, neither **C** nor **D** places the aromatic group over the cyclohexyl ring. Conformer **E** does, but is disfavored according to these calculations by 1.5−1.7 kcal/mol. Overall, these calculations support our supposition that the *like* isomer should not show an upfield C-5 proton even when the oxaziridine C−N bond is pseudoaxial. Interestingly, the global minima for **21a** and **21b** differ

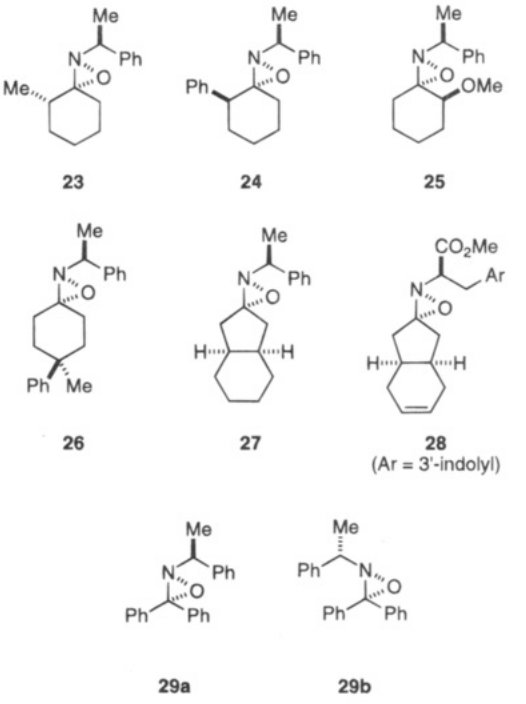


Figure 9. Structures of oxaziridines cited in Table 2. References: **23**−**25**,[5f] **26** and **27**,[5d] **28**,[2s] and **29**.[9b] All compounds are drawn in the same absolute configuration with respect to the oxaziridine for clarity; see original papers for actual absolute configurations prepared.

substantially in energy according to this model (ca. 2.7 kcal/mol). A comparable energy difference encountered en route from imine to oxaziridine may well explain the preference of *unlike* vs *like* oxaziridine formation;[9] however, such a study would require high-quality modeling well beyond the scope of this paper.

Since the MM2* force field was not parameterized for oxaziridines, we sought reassurance that the results from the molecular modeling study were qualitatively relevant. First, the nitrogen atom was replaced with a carbon, resulting in the corresponding epoxides **22a** and **22b**; fully parameterized in the MM2* force field, these structures were subjected to a similar exercise (Figure 6b). Comparison of the results obtained by driving the benzylic dihedral angle (ϕ defined here as $C_{spiro}-C_{epoxide}-C_{benzylic}-C_{ipso}$, see structures in Figure 6) showed that the epoxides were subject to similar conformational restraints in both isomers, although energy differences were smaller.

Survey of Crystallographic Conformations. In addition, the bond lengths and angles, as well as the torsion angle about the $N_{oxaz}-C_{benzylic}$ bond were compared to the values obtained from X-ray crystallographic studies of a total of nine previously reported oxaziridines: compounds **1a** (Figure 1) and **23**−**29** (Figure 9). Only oxaziridines **1a** and **23** crystallized in conformations with an axial C−N substituent (although the latter adopted the alternative chairlike conformation in solution[5d]), with **24**−**26** having an axial spiro oxygen atom. The point, of course, does not pertain to either the five-membered ring oxaziridines or to the two stereoisomers obtained from benzophenone.

The crystal structures show that the various oxaziridines are quite similar throughout the three types of compounds represented (Table 2). Despite the fact that Macromodel is not parameterized for oxaziridines, it came remarkably close to reproducing the values from

Table 2. Comparison of Selected Bond Lengths, Bond Angles, and Dihedral Angles of Oxaziridines Minimized by MM2* (Macromodel) and X-ray Crystallographic Structures[a]

	A	C	1a	23	24	25	26	27	28	29a	29b
					Bond Lengths, Å						
O1–C3	1.483	1.485	1.428	1.417	1.425	1.421	1.424	1.419	1.418	1.433	1.419
O1–N2	1.528	1.528	1.535	1.502	1.511	1.528	1.522	1.525	1.517	1.544	1.519
N2–C3	1.477	1.478	1.456	1.418	1.442	1.432	1.444	1.457	1.439	1.473	1.464
N2–C′	1.444	1.445	1.453	1.485	1.490	1.467	1.469	1.486	1.456	1.485	1.475
C3–C_{syn}	1.525	1.527	1.529	1.512	1.495	1.510	1.507	1.489	1.514	1.515	1.491
C3–C_{anti}	1.525	1.527	1.521	1.519	1.520	1.495	1.502	1.509	1.518	1.504	1.506
					Bond Angles (deg)						
O1–N2-C3	59.0	59.2	57.0	58.0	57.6	57.3	57.3	56.8	57.3	56.7	56.8
O1–C3–N2	62.2	62.1	64.3	64.0	63.6	64.8	64.1	64.1	64.1	64.2	63.6
N2–O1–C3	58.2	58.7	58.7	58.0	58.8	57.9	58.6	59.2	58.6	59.2	59.7
O1–C3–C_{syn}	110.3	109.5	116.4	117.2	115.0	115.7	115.8	120.2	116.7	115.3	115.2
O1–C3–C_{anti}	110.2	108.7	115.2	114.1	113.3	114.6	118.8	118.2	116.9	114.1	113.1
N2–C3–C_{syn}	124.0	124.6	125.4	124.4	126.3	123.5	124.5	124.4	127.0	120.0	122.2
N2–C3–C_{anti}	116.5	116.7	111.0	113.0	114.8	115.7	113.2	116.8	117.4	114.4	112.7
C3–N2–C′	119.8	122.0	118.2	119.4	119.4	119.6	118.7	116.6	117.1	116.9	118.3
					Dihedral Angles (deg)						
C_{syn}–C_3–N_2–C′	7.2	5.1	12	10.9	6.3	10.0	5.5	12.8	9.4	12.8	9.2
C_3–N_2–C′–C_{ipso} (ϕ)	293.1	199.2	266	266.6	258.5	274.4	248.0	267.4	246.6[b]	259.2	218.5

[a] Definitions: C_{syn} is the carbon attached to C-3 of the oxaziridine and syn to the N_{oxaz} substituent; C_{anti} is the other carbon attached to C-3. C′ is the carbon attached to N-2 of the oxaziridine. All compounds are assumed to be in the same enantiomeric series—that containing (*S*)-α-methylbenzylamine or its equivalent—for ease of comparison; see original papers for actual absolute stereostructures (Figure 9). [b] For compound **28**, the C-2 carbon of the indolylethyl substituent takes the C_{ipso} position in this measurement.

the crystal structures. The most notable differences occurred in the bond angles, with the computer-generated structures systematically overestimating the O1–C3 distances by about 0.06 Å and the N2–C3 distances by a smaller amount. In addition, the N2–C′ (benzylic) distances were slightly longer in the MM2* structures than in the X-ray data. Bond angles were within 2° for the most part. Overall, these agreements combined with the similar energy curves obtained from oxaziridines **21** and epoxide analogues **22** lend credence to the modeling results vis à vis the N_{oxaz}–C′ (benzylic) torsion angles.

Referring back to Figure 2, we wish to further define the "inside" position as being bounded by conformations wherein the $C_{benzylic}$–substituent bond (A in Figure 2) eclipses the N–O or N–C bonds of the oxaziridine. This corresponds to dihedral angles ϕ of 240–300° for *unlike* oxaziridine stereoisomers (e.g., **21a**, **23–27**, and **29a**) and ϕ = 180–240° for *like* oxaziridines (e.g., **21b** and **29b**). As Table 2 shows, all of the oxaziridines examined fall nicely into these categories, although the calculated values fall decidedly on the low end of the scales as opposed to the crystallographically determined structures. There is a paucity of information on oxaziridines not bearing an α-methylbenzyl substituent, but **28** does serve as one example. It is comforting that the trend seems to apply to oxaziridines derived from substituted cyclopentanones and at least two acyclic examples, as well.

Summary. Overall, the tendency of chiral oxaziridines to exhibit a conformation with the C–H bond on the "inside" seems to be general as seen through crystallography and the NMR and theoretical methods examined herein. These features may be relevant to various aspects of oxaziridine chemistry, such as their rearrangement chemistry. For the moment, the utility of the C-5 upfield proton effect in determining the structures of spirocyclic oxaziridines is worthy of mention.

Experimental Section

Methods and Materials. HPLC was carried out isocratically using a UV detector set on 254 nm; CN bonded (4.6 × 250 mm) or silica gel (7.8 × 300 mm) columns were used. Unless otherwise noted, starting materials were obtained from commercial suppliers and used without further purification. 4-(Benzyloxy)cyclohexanone[11] and 1-(2′-naphthyl)ethylamine[12] were prepared according to literature procedures. Commercially available *m*-CPBA (Aldrich, 57–86%) was purified by extraction with phosphonate buffer.[13]

General Procedure for Synthesis of Oxaziridines. A solution of ketone (1.0 equiv) and amine (1.2–1.5 equiv) in toluene was refluxed for 5–7 h in a round-bottomed flask which was equipped with a condenser connected via a Dean–Stark trap. After cooling to room temperature, the crude toluene solution of imine was transferred via a cannula or an addition funnel dropwise under nitrogen atmosphere to a round-bottomed flask which contained a suspension of *m*-CPBA (1.2–1.5 equiv) in dichloromethane at −78 °C. The oxidation reaction was usually completed within 20 min (TLC analysis, 5–25% EtOAc/hex) and quenched with saturated aqueous $Na_2S_2O_3$ at −78 °C. The resulting mixture was allowed to warm to room temperature and poured into a separatory funnel to be partitioned between saturated $Na_2S_2O_3$ and Et_2O. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine and dried over Na_2SO_4. Flash column chromatography with 230–400 mesh silica gel and the indicated solvent system afforded the product.

***trans*-2-Benzyl-6-methyl-1-oxa-2-azaspiro[2.5]octane (10) and isomer.** 4-Methylcyclohexanone (1.251 g, 11.2 mmol) was reacted with benzylamine (1.560 g, 14.6 mmol) followed by *m*-CPBA (2.343 g, 13.4 mmol). Column chromatography (10% EtOAc/hex) afforded the title compound (mixture of isomers) as an oil (2.470 g, 96%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (d, *J* = 6.2 Hz, 3 H), 0.99–1.09 (m, 1 H), 1.25 (m, 1 H), 1.47 (m, 1 H), 1.54 (m, 1 H), 1.76–1.84 (m, 3 H), 1.93–1.99 (m, 2 H), 3.96 (AB q, *J* = 14.4 Hz, Δν = 14.8 Hz, 2 H), 7.22–7.41 (m, 5 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 21.0, 26.6, 31.0, 32.7, 35.4, 57.7, 84.9, 127.4, 128.5, 137.1; IR ($CDCl_3$) 3032, 2919, 1495 cm^{-1}; MS (FAB) *m*/*e* 218 (M^+ + 1), 202 (100), 106, 91; HRMS (FAB) calcd for $C_{14}H_{20}NO$ (M^+ + H) 218.1545, found 218.1538. ***cis*-10** (diagnostic peaks only): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 56.9, 84.5.

***trans*-2-Benzyl-6-*tert*-butyl-1-oxa-2-azaspiro[2.5]-octane (11).** 4-*tert*-Butylcyclohexanone (800 mg, 5.07 mmol)

(11) Jones, E. R. H.; Sondheimer, F. *J. Chem. Soc.* **1949**, 615–618.
(12) Blicke, F. F.; Maxwell, C. E. *J. Am. Chem. Soc.* **1939**, *61*, 1780–1782.
(13) Bortolini, O.; Campestrini, S.; Di Furia, F.; Modena, G. *J. Org. Chem.* **1987**, *52*, 5093–5095.

was reacted with benzylamine (830 mg, 7.58 mmol) followed by *m*-CPBA (1.308 g, 7.58 mmol). Flash column chromatography (8% EtOAc/hex) afforded the title compound as a pale yellow solid (1.190 g, 89%). An analytically pure sample was prepared by recrystallization from hexane-dichloromethane: mp 57.5–59 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.81 (s, 9 H), 0.86–1.48 (m, 4 H), 1.82–1.92 (m, 3 H), 1.96–2.06 (m, 2 H), 3.98 (AB q, J = 14.2 Hz, $\Delta\nu$ = 22.2 Hz, 2 H), 7.24–7.43 (m, 5 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 25.6, 25.7, 27.3, 27.4, 27.5, 30.2, 32.2, 36.4, 46.8, 57.9, 85.2, 125.4, 127.3, 128.39, 128.43, 136.7; IR (CCl_4) 3020, 2950, 1485 cm^{-1}; MS (CI) m/e 260 (M^+ + 1), 106 (100); HRMS (FAB) calcd for $C_{17}H_{26}NO$ (M^+ + H): 260.2014, found 260.1993. Anal. Calcd for $C_{17}H_{25}NO$: C, 78.72; H, 9.71; N, 5.40. Found: C, 78.90; H, 10.00; N, 5.38.

***trans*-2-Benzyl-6-phenyl-1-oxa-2-azaspiro[2.5]octane (12) and Isomer.** 4-Phenylcyclohexanone (1.080 g, 6.2 mmol) was reacted with benzylamine (0.861 g, 8.1 mmol), and the crude imine solution was oxidized with *m*-CPBA (0.594 g, 7.4 mmol). Column chromatography (10% EtOAc/hex) afforded the title compound (mixture of isomers) as a solid (1.520 g, 87%): mp 112–113 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.62 (apparent qd, J = 11.9, 3.3 Hz, 1 H), 1.69 (m, 1 H), 1.89 (m, 1 H), 2.09–2.38 (m, 5 H), 2.81 (tt, J = 12.1, 3.5 Hz, 1H), 4.12 (AB q, J = 14.2 Hz, $\Delta\nu$ = 20.6 Hz, 2 H), 7.21–7.62 (m, 10 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 27.2, 32.06, 32.14, 36.2, 42.8, 57.9, 84.7, 126.4, 126.8, 127.7, 128.57, 128.68, 128.75, 136.9, 145.7; IR ($CDCl_3$) 3030, 2936, 1494, 1451 cm^{-1}. Anal. Calcd for $C_{19}H_{21}NO$: C, 81.68; H, 7.58; N, 5.01. Found: C, 81.77; H, 7.60; N, 5.12. ***cis*-12** (diagnostic peaks only): ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 84.6.

***trans*-2-(Diphenylmethyl)-6-methyl-1-oxa-2-azaspiro-[2.5]octane (13).** 4-Methylcyclohexanone (562 mg, 5.01 mmol) was reacted with diphenylmethylamine (1.390 g, 7.58 mmol) followed by *m*-CPBA (1.309 g, 7.58 mmol). Flash column chromatography (5% EtOAc/hex) afforded the title compound as a white solid (1.108 g, 75%). An analytically pure sample was prepared by recrystallization from hexane–dichloromethane: mp 84–86 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.17 (m, 1 H), 0.66 (d, J = 4.7 Hz, 3 H), 0.88–1.98 (m, 8 H), 4.64 (s, 1 H), 7.18–7.36 (m, 6 H), 7.44–7.51 (m, 4 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 21.3, 26.9, 30.9, 32.3, 32.6, 36.0, 70.4, 85.7, 127.1, 127.3, 127.67, 127.71, 128.4, 128.7, 140.1, 142.2; IR (CCl_4) 3020, 2920, 1485, 1395 cm^{-1}; MS (CI) m/e 294 (M^+ + 1), 167 (100); HRMS (FAB) calcd for $C_{20}H_{24}NO$ (M^+ + H): 294.1858, found 294.1872. Anal. Calcd for $C_{20}H_{23}NO$: C, 81.87; H, 7.90; N, 4.77. Found: C, 82.00; H, 8.20; N, 4.68.

***trans*-6-*tert*-Butyl-2-(diphenylmethyl)-1-oxa-2-azaspiro-[2.5]octane (14).** 4-*tert*-Butylcyclohexanone (781 mg, 5.07 mmol) was reacted with diphenylmethylamine (1.388 g, 7.58 mmol) followed by *m*-CPBA (1.309 g, 7.58 mmol). Flash column chromatography (3% EtOAc/hex) afforded the title compound as a white solid (1.634 g, 96%). An analytically pure sample was prepared by recrystallization from hexane–dichloromethane: mp 125–126.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.18 (apparent qd, J = 12.8, 4.3 Hz, 1 H), 0.61 (s, 9 H), 0.82–2.07 (m, 8 H), 4.63 (s, 1 H), 7.17–7.34 (m, 6 H), 7.45–7.51 (m, 4 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 24.9, 25.3, 27.3, 27.4, 32.0, 36.7, 46.4, 70.5, 85.8, 127.1, 127.3, 127.6, 127.7, 128.4, 128.7, 140.0, 142.1; IR (CCl_4) 3020, 2950, 1485 cm^{-1}; MS (CI) m/e 336 (M^+ + 1), 167 (100); HRMS (FAB) calcd for $C_{23}H_{30}NO$ (M^+ + H): 336.2327, found 336.2304. Anal. Calcd for $C_{23}H_{29}NO$: C, 82.34; H, 8.71; N, 4.18. Found: C, 82.27; H, 8.60; N, 4.20.

***trans*-2-(Diphenylmethyl)-6-phenyl-1-oxa-2-azaspiro-[2.5]octane (15).** 4-Phenylcyclohexanone (889 mg, 5.10 mmol) was reacted with diphenylmethylamine (1.390 g, 7.59 mmol) followed by *m*-CPBA (1.309 g, 7.58 mmol). Flash column chromatography (5–10% EtOAc/hex) afforded the title compound as a white solid (1.371 g, 76%). An analytically pure sample was prepared by recrystallization from hexane-dichloromethane: mp 140–142 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.66 (m, 1 H), 1.41–2.52 (m, 8 H), 4.68 (s, 1 H), 6.78 (d, J = 7.1 Hz, 2 H), 7.10–7.39 (m, 9 H), 7.50–7.55 (m, 4 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 27.4, 31.5, 32.3, 36.6, 42.8, 70.5, 85.2, 126.0, 126.5, 127.1, 127.2, 127.7, 127.8, 128.2, 128.4, 128.8, 140.1, 142.0, 145.6; IR (CCl_4) 3020, 2920, 1485 cm^{-1}; MS (CI) m/e 356 (M^+ + 1), 167 (100); HRMS (FAB) calcd for $C_{25}H_{26}NO$ (M^+ + H): 356.2014, found 356.2019. Anal. Calcd for $C_{25}H_{25}NO$: C, 84.47; H, 7.09; N, 3.94. Found: C, 84.41; H, 7.20; N, 3.91.

6-(Benzyloxy)-2-(diphenylmethyl)-1-oxa-2-azaspiro-[2.5]octane (16). 4-(Benzyloxy)cyclohexanone (377 mg, 1.84 mmol) was reacted with diphenylmethylamine (507 mg, 2.77 mmol) followed by *m*-CPBA (478 mg, 2.77 mmol). Flash column chromatography (2% EtOAc/hex) afforded the title compound as a mixture of two diastereomers (603 mg, 85%). The less polar isomer was partially isolated as a white solid by preparative HPLC on a 30 × 300 mm μPorasil column (Waters) with 0.5% 2-propanol/hexane (retention time 24.0 min). **Isomer 1**: mp 99–101 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38 (m, 1 H), 1.60–1.97 (m, 6 H), 2.21 (m, 1 H), 3.39 (m, 1 H), 4.49 (AB q, J = 11.9 Hz, $\Delta\nu$ = 9.9 Hz, 2 H), 4.70 (s, 1 H), 7.21–7.49 (m, 15 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 24.0, 28.4, 29.1, 32.1, 69.7, 70.0, 73.1, 84.9, 127.0, 127.2, 127.3, 127.4, 127.6, 128.2, 128.2, 128.6, 138.5, 139.8, 141.9; IR (neat) 3020, 2920, 1485 cm^{-1}; MS (FAB) m/e 386 (M^+ + 1), 167 (100). Anal. Calcd for $C_{26}H_{27}NO_2$: C, 81.01; H, 7.06; N, 3.63. Found: C, 80.70; H, 7.01; N, 3.89. **Isomer 2** (diagnostic peaks only): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.54 (m, 1 H), 2.05 (m, 1 H), 3.54 (m, 1 H), 4.40 (AB q, J = 12.2 Hz, $\Delta\nu$ = 8.1 Hz, 2 H), 4.73 (s, 1 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 23.5, 28.1, 28.8, 31.6, 69.6, 69.7, 72.8, 85.4, 127.11, 127.43, 128.62, 139.5, 142.0.

[2*S(*R**),3(*trans*)]-6-Methyl-2-(1-(1′-naphthyl)ethyl)-1-oxa-2-azaspiro[2.5]octane (17) and Isomers.** 4-Methylcyclohexanone (0.313 g, 2.8 mmol) was reacted with 1-(1′-naphthyl)ethylamine (0.633 g, 3.7 mmol), and the crude imine solution oxidized with *m*-CPBA (0.271 g, 3.4 mmol). Column chromatography (10% EtOAc/hex) afforded the title compound (mixture of isomers) as an oil (0.677 g, 86%). **Compound 17.** Crystallization at ca. −20 °C in Et_2O afforded the major isomer as colorless crystals: mp 99–101 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ -0.32 (apparent qd, J = 11.7, 5.4 Hz, 1 H), 0.49 (d, J = 6.5 Hz, 3 H), 0.89–2.14 (m, 8 H), 1.74 (d, J = 6.4 Hz, 3 H), 4.34 (q, J = 6.4 Hz, 1 H), 7.44–8.18 (m, 7 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 21.1, 23.1, 26.7, 30.8, 31.9, 32.6, 36.0, 58.2, 85.6, 122.9, 124.2, 125.5, 126.1, 127.6, 128.9, 130.0, 133.7, 138.5; IR (CCl_4) 3054, 2926, 1451 cm^{-1}; MS(EI) m/e 281 (M^+), 265, 208, 155 (100), 127. Anal. Calcd for $C_{19}H_{23}NO$: C, 81.10 H, 8.24; N, 4.98. Found: C, 80.91; H, 8.22; N, 5.01. **2*R**(*S**),3-(*cis*)-17** (diagnostic peaks only): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.44 (q, J = 6.5 Hz, 1 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 58.7, 85.3. **2*R**(*R**),3(*trans*)-17** (diagnostic peaks only): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.57 (q, J = 6.7 Hz, 1 H).

[2*S(*R**),3(*trans*)]-2-(1-(1′-Naphthyl)ethyl)-6-phenyl-1-oxa-2-azaspiro[2.5]octane (18) and Isomer.** 4-Phenylcyclohexanone (0.097 g, 0.6 mmol) was reacted with 1-(1′-naphthyl)ethylamine (0.154 g, 0.9 mmol), and the crude imine solution was oxidized with *m*-CPBA (0.057 g, 0.7 mmol). Column chromatography afforded (10% EtOAc/hex) the title compound (mixture of isomers) as a solid (0.128 g, 67%): mp 106–108 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.12 (apparent qd, J = 12.3, 5.3 Hz, 1 H), 0.93 (m, 1 H), 1.21 (m, 1 H), 1.52 (m, 1 H), 1.65 (m, 1 H), 1.78 (d, J = 6.4 Hz, 3 H), 1.79–1.99 (m, 3 H), 2.38 (m, 1 H), 4.38 (q, J = 6.4 Hz, 1 H), 6.45 (m, 1 H), 7.04–8.20 (m, 11 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 23.1, 27.3, 31.2, 32.4, 36.6, 42.8, 58.3, 85.3, 125.5, 125.6, 125.7, 125.9, 126.3, 126.4, 126.6, 127.8, 128.0, 128.3, 129.0, 133.9, 138.6, 145.5; IR (CCl_4) 3050, 2920, 1450 cm^{-1}; MS m/e 343 (M^+), 327, 244, 223, 208, 155 (100), 127, 91; HRMS calcd for $C_{24}H_{25}NO$ 343.1936, found 343.1936. Anal. Calcd for $C_{24}H_{25}NO$: C, 83.93; H, 7.34; N, 4.08. Found: C, 84.07; H, 7.13; N, 4.10. **2*R**(*S**),3(*cis*)-18** (diagnostic peaks only): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.49 (q, J = 6.4 Hz, 1 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 84.8.

[2*S(*R**),3(*trans*)]-6-Methyl-2-(1-(2′-naphthyl)ethyl)-1-oxa-2-azaspiro[2.5]octane (19) and Isomer.** 4-Methylcyclohexanone (0.407 g, 3.6 mmol) was reacted with 1-(2′-naphthyl)ethylamine (0.823 g, 4.8 mmol), and the crude imine solution was oxidized with *m*-CPBA (0.353 g, 4.4 mmol). Column chromatography (10% EtOAc/hex) afforded the title compound (mixture of isomers) as an oil (0.921 g, 90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.24 (m, 1 H), 0.50 (d, J = 6.4 Hz, 3 H), 0.89–1.01 (m, 2 H), 1.31–1.94 (m, 6 H), 1.66 (d, J = 6.4

Hz, 3 H), 3.80 (q, J = 6.4 Hz, 1 H), 7.44–7.68 (m, 3 H), 7.78–7.89 (m, 4 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 21.0, 23.8, 26.7, 30.8, 32.4, 32.6, 35.9, 62.3, 85.7, 124.9, 125.6, 125.7, 126.0, 127.6 (2 signals), 128.2, 132.7, 133.3, 139.2; IR (CCl_4) 3080, 2921, 1451 cm^{-1}; MS (EI) m/e 281 (M^+), 169, 155 (100), 127; HRMS calcd for $C_{19}H_{23}NO$ 281.1780, found 281.1789. **2*R***(S*),3(*cis*)-19** (diagnostic peaks only): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.91 (q, J = 6.4 Hz, 1 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 85.3.

[2S*(*R),3(*trans*)]-2-(1-(2′-Naphthyl)ethyl)-6-phenyl-1-oxa-2-azaspiro[2.5]octane (20).** 4-Phenylcyclohexanone (1.001 g, 5.7 mmol) was reacted with 1-(2′-naphthyl)ethylamine (1.000 g, 5.8 mmol), and the crude imine solution was oxidized with m-CPBA (1.202 g, 6.9 mmol). Column chromatography (10% EtOAc/hex) afforded the title compound (mixture of isomers) as a solid (1.800 g, 91%): mp 107–109 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.56 (apparent qd, J = 12.5, 5.2 Hz, 1 H), 1.41 (qd, J = 2.3, 12.6 Hz, 1 H), 1.49–1.62 (m, 2 H), 1.71 (d, J = 6.4 Hz, 3 H), 1.80 (m, 1 H), 1.91–2.11 (m, 3 H), 2.39 (tt, J = 3.7, 12.5 Hz, 1 H), 3.83 (q, J = 6.4 Hz, 1 H), 6.34 (d, J = 6.9 Hz, 2 H), 6.86 (t, J = 7.4 Hz, 2 H), 6.89 (m, 1 H), 7.54 (m, 3 H), 7.87 (m, 3 H), 7.97 (s, 1 H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 23.8, 27.3, 31.5, 32.6, 36.6, 42.7, 62.8, 85.3, 125.2, 125.8, 126.0, 126.3, 126.6, 127.7, 127.8, 127.9, 128.0, 128.5, 132.8, 133.4, 139.4, 145.4; IR ($CDCl_3$) 3060, 2934, 1451 cm^{-1}. Anal. Calcd for $C_{24}H_{25}NO$: C, 83.93; H, 7.34; N, 4.08. Found: C, 84.07; H, 7.37; N, 4.23. **2S*(*R**),3(*cis*)-20** (diagnostic peaks only): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.89 (q, J = 7.1 Hz, 1 H).

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