

Synthetic Aspects of an Asymmetric Nitrogen-Insertion Process: Preparation of Chiral, Non-Racemic Caprolactams and Valerolactams. Total Synthesis of (-)-Alloyohimbane[†]

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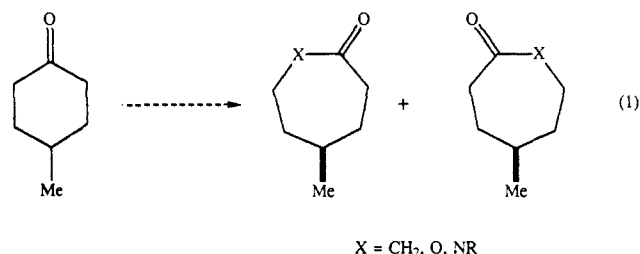
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Abstract: The conversion of a series of prochiral ketones to the corresponding ring-expanded lactams is described. The key step is a stereoelectronically controlled photochemical rearrangement reaction that is carried out on axially dissymmetric oxaziridines derived from the ketone substrates. The stereochemically enriched oxaziridine substrates are prepared by a strategy that utilizes a combination of intraannular and extraannular stereochemical control features. A model for the asymmetric induction imparted by the chiral substituent on nitrogen has been described, and the effect of using various achiral and chiral amines (including double diastereoselectivity) has been assessed. The intrinsic stereoselectivity of the photochemical oxaziridine to lactam rearrangement reaction has been determined for several oxaziridines, including several derived from *meso* five-membered-ring ketones. The direction of stereoselectivity for the rearrangement reaction in all cases examined was found to depend only on the axial chirality of the substrate oxaziridine and not on stereochemical or conformational factors. The stereoselectivity of the reaction was unambiguously demonstrated for the first time in cyclopentanone derivatives. Finally, an overall scheme for the practical preparation of a series of chiral caprolactams in enantiomerically homogeneous form is described, resulting in overall selectivities ranging from 54:46 to 88:12. This methodology was applied to the synthesis of a key intermediate in benzomorphinan synthesis and to the total synthesis of (-)-alloyohimbane.

The development of methodology to provide molecules in enantiomerically enriched form is a continuing challenge in chemical synthesis. Recently, approaches that utilize the stereochemical differentiation of enantiotopic or diastereotopic groups have received increased attention.¹ Most of these methods have featured the use of enzymatic catalysis, as exemplified by a selective hydrolysis of a prochiral diester.² However, an increasing number of reports of nonbiochemical means to achieve group selectivity have appeared, including approaches based on stereoselective ketalization³ and lactonization⁴ reactions, annulation approaches,⁵ and asymmetric hydroboration⁶ and epoxidation⁷ processes. This interest is largely due to (1) the desire to apply the concept of group selectivity to reactions that are not generally susceptible to enzymatic catalysis, (2) the greater structural diversity of substrate substitution patterns that can often be used in nonenzymatic processes, and (3) the increased potential for the stereospecific preparation of either enantiomer of a target compound from a single achiral starting material.

A powerful strategy in complex organic synthesis is the ring-expansion reaction of an *n*-membered cyclic ketone, which results in the formation of a cyclic compound of *n* + 1 ring size to which an additional oxygen,⁸ nitrogen,⁹ or carbon¹⁰ atom has been added. These reactions can be viewed as the formal insertion of a group into a carbon-carbon single bond. When a prochiral ketone such as 4-methylcyclohexanone is employed in such a reaction, the potential of carrying out asymmetric ring-expansion chemistry arises. While a number of nonenzymatic approaches can effect the differentiation of two enantiotopic carbonyl groups within a prochiral molecule,¹¹ significantly less work directed toward the stereoselective elaboration of a single prochiral ketone has been reported. The latter methods allow the formal differentiation of two enantiotopic methylene groups. Some important developments in this area have included asymmetric deprotonation¹² and olefination reactions¹³ of 4-alkylcyclohexanones. Enzymatic Baeyer-Villiger reactions have recently been demonstrated to proceed with high enantioselectivity on similar substrates.¹⁴

An asymmetric nitrogen insertion process mediated by nonbiological means is an attractive goal because it satisfies all the criteria outlined above. In this paper, we describe our efforts to



develop such a process, using the stereospecific rearrangements of axially dissymmetric oxaziridines as the key step.^{15,16}

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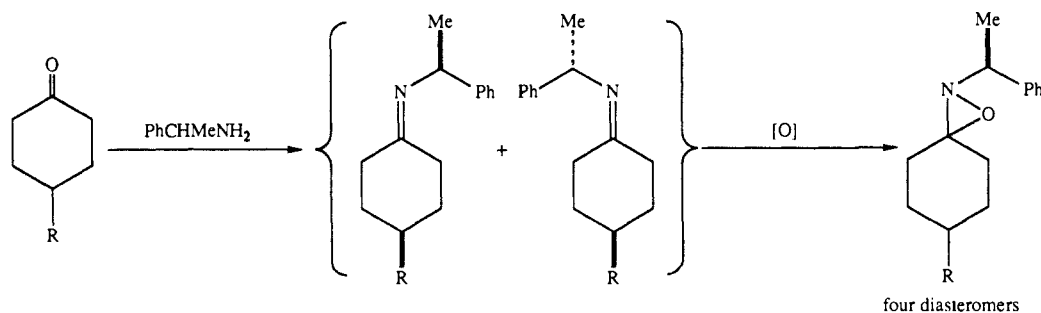
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[†] Dedicated to the memory of Professor Mathias Mertes.

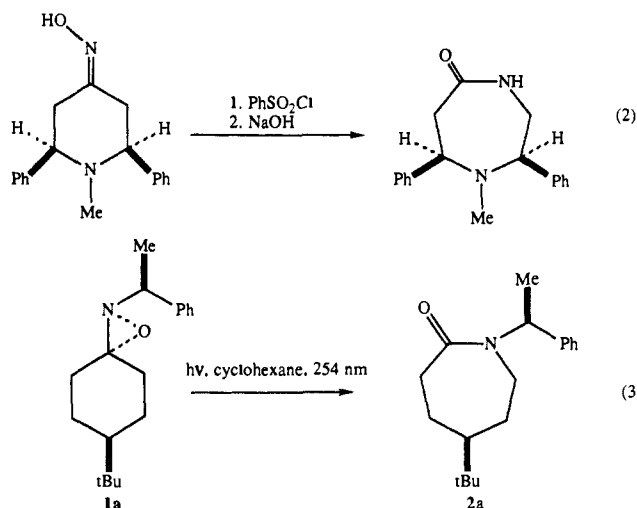
[‡] Department of Chemistry.

Scheme 1



In the Beckmann rearrangement of oximes, the regiochemistry is usually determined by the stereochemistry of the oxime.⁹ In order to effect a stereospecific insertion reaction of the type exemplified in eq 1, an oxime containing an element of axial dissymmetry must be prepared and subsequently undergo a stereoselective rearrangement reaction. While a single example of the resolution and subsequent migration of such an oxime has been reported (eq 2),²⁰ the stereospecific synthesis of optically pure oximes is not straightforward, and the stereospecificity of the Beckmann reaction is not completely reliable.⁹ In 1982, however, the reaction in eq 3 was reported by Lattes and co-workers.¹⁵ As part of this group's long-standing interest in mechanistic oxaziridine photochemistry,²¹ oxaziridine **1a** was shown to afford lactam **2a** as the major product upon photolysis. It was thus demonstrated that the carbon substituent *anti* to the lone pair on the oxaziridine nitrogen preferentially underwent migration to a formally electron-deficient nitrogen atom. Since both starting

oxaziridine and product lactams were purified by recrystallization prior to structural analysis, however, the actual diastereoselectivity obtained in the preparation of both compounds was unclear.



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(16) We are utilizing the term "axially dissymmetric" because we feel that it is most intuitively descriptive of the stereochemical feature important in the present reaction. Thus, although the spirocyclic oxaziridines discussed in this paper contain four stereogenic centers,¹⁷ the major product of the ring-expansion reaction does not depend on any particular such center but is a cumulative effect depending on the relative orientation of three of these centers (i.e., a "stereogenic triad"¹⁸). In the present examples, this is conveniently visualized by considering an "extended tetrahedron"¹⁹ that is roughly defined by the two substituents at C-6 of the spirocyclic oxaziridine (usually alkyl and hydrogen) and the two substituents at the N-2 atom (α -methylbenzyl and lone pair). If two isomers share the same sense of absolute chirality (*R* or *S*) along the "chiral axis" defined by such a tetrahedron, they will undergo rearrangement so as to preferentially afford the same lactam stereoisomer.

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We felt that this reaction offered a fine opportunity for the development of a general asymmetric nitrogen insertion reaction. The requisite axial stereochemical control element was present in the form of a spirocyclic ring system, and one of the valences of nitrogen was available for the incorporation of a chiral directing group into the substrate. The photochemical experiments suggested that the element of axial chirality present in the substrate could be translated into a stereochemical control feature. Finally, the high inversion barrier of the oxaziridine nitrogen (ca. 33 kcal/mol)²² typical in *N*-alkyl oxaziridines allowed for "storage" of nitrogen atom stereogenicity until photochemical activation. There were, however, several important questions that needed to be addressed at the outset of our study:

(1) What level of stereocontrol is obtainable in the synthesis of axially dissymmetric oxaziridines?

(2) What structural features of the starting ketones are needed to obtain suitable stereoselectivity in the oxidation reaction?

(3) What are the actual levels of diastereoselection obtained in the ring-expansion reaction of isomerically homogeneous oxaziridines?

(4) How do structural variations in the oxaziridines (substitution, stereochemistry, conformational considerations) affect the selectivities in the rearrangement step?

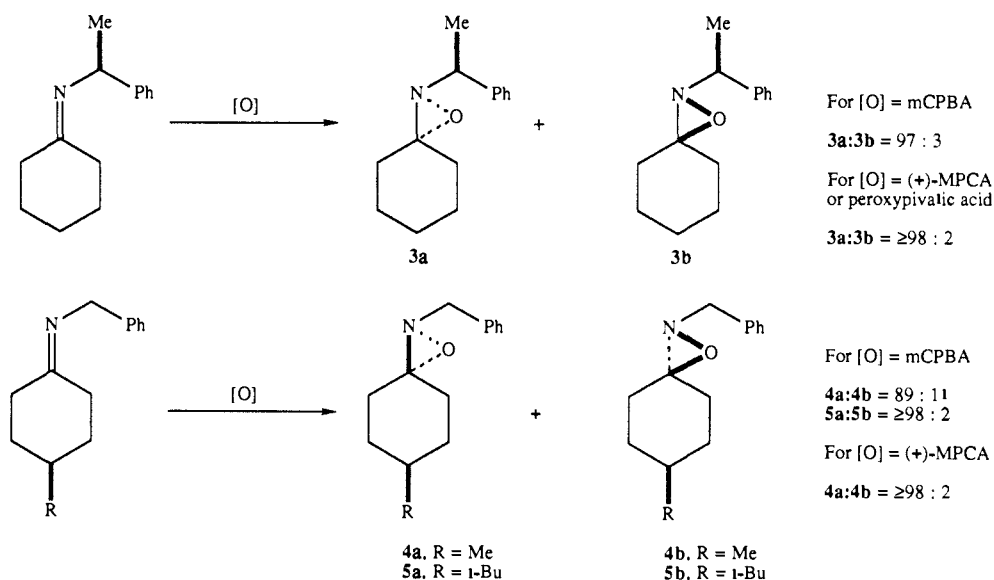
(5) Could the product lactams be processed into synthetically useful compounds?

Herein we report the results of our investigations aimed at the resolution of these points and the development of a serviceable asymmetric nitrogen insertion reaction.²³ Additionally, syntheses

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Scheme II



of optically active precursors to the benzomorphan analgesics and the optically active ($\geq 98\%$ ee) ring skeleton of the reserpine and alloxyhimbane alkaloid families will be described.

Results and Discussion

Preparation of Axially Dissymmetric Oxaziridines. The success of the overall asymmetric nitrogen insertion process depends on the selectivities inherent in both the synthesis of the axially dissymmetric oxaziridines and the subsequent photorearrangement step. We first focussed our efforts on the first step by determining the product distributions of oxaziridines obtained from a series of cyclic substrates. Selected examples were more closely examined to elucidate the control features necessary for a general route to axially dissymmetric oxaziridines.

A series of prochiral cyclohexanones was converted into the corresponding oxaziridines in the standard manner (Scheme I). Thus, a solution of the ketone and α -methylbenzylamine (α MBA, 1.2–1.5 equiv) in dry toluene was refluxed for several hours using an apparatus equipped with a Dean-Stark trap. The crude toluene solutions of imine were added dropwise to a suspension of the oxidizing agent in toluene kept at -78°C . The addition reactions were generally complete within 15 min (TLC analysis) and were quenched at low temperature by the addition of sodium thiosulfate. Standard aqueous workup afforded the oxaziridines, which were readily purified by silica gel chromatography.

The intermediate imines were rarely isolated, but the crude mixture of imines derived from 4-*tert*-butylcyclohexanone was examined by ^1H NMR spectroscopy and determined to consist of a very nearly equimolar mixture of diastereoisomers. However, the oxaziridine ratios are independent of the composition of this initial imine mixture.²⁴ The well-known lack of stereospecificity may be due to a two-step, Baeyer–Villiger-type mechanism in which the peracid adds to the imine, thus forming a tetrahedral intermediate that affords oxaziridine by nucleophilic attack of the nitrogen on the electron-deficient oxygen atom with the expulsion of the acid leaving group. Alternatively, rapid acid-catalyzed equilibration of the imines coupled to a kinetically controlled oxidation reaction has been suggested.²⁵

Regardless of mechanism, the overall establishment of axial dissymmetry in the spirocyclic oxaziridines ultimately depends

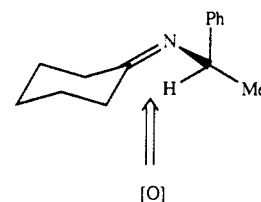


Figure 1. Proposed direction of attack of oxidizing agent.

on a synergism between two diastereofacially selective processes which results in the overall control of the relative configuration between the N_2 stereocenter with those at C_3 and C_6 . While a detailed view of the interaction of the two chemical processes involved depends on the mechanism of the oxidation reaction, it is instructive to consider the stereochemical consequences of each separately. Thus, the overall stereoselectivity was expected to roughly correspond to the additive effects of the chiral substituent on nitrogen (extraannular stereocontrol) and the prochiral C-4 substituent of the starting prochiral ketone (intraannular stereocontrol) since both could be correlated through a common stereocenter (C_3 of the product oxaziridines).

In other work, treatment of the α -methylbenzyl-substituted imine derived from cyclohexanone with *m*-chloroperoxybenzoic acid (mCPBA) gave oxaziridines **3a,b** in a ratio of 97:3 (Scheme II).^{25c} In our hands, when this reaction was performed with bulky peracids prepared from pivalic acid²⁶ or (+)-camphoric anhydride ((+)-MPCA)²⁷ the sole formation of **3a** was observed (^1H and ^{13}C NMR).²⁸ In similar systems, the major isomer has been determined^{15,25d,29} to result from attack on αS imines to afford product with *R* stereochemistry at the oxaziridine nitrogen (i.e. the *unlike* product³⁰). A useful mnemonic device results from the placement of the hydrogen atom in the plane of the $\text{C}=\text{N}$ double bond, with attack of oxidizing agent taking place from the face opposite the larger phenyl group (Figure 1). A similar picture was drawn for the oxidation of an acyclic *N*-(α -methylbenzyl)-imine,²⁹ and it seems more reasonable than an alternative proposal that placed the phenyl group in the imine plane.^{25d} Parenthetically, closely related reactive conformations have been proposed for other asymmetric reactions that involve *N*-(α -methylbenzyl) substituents.³¹ For a concerted process, this picture suffices to explain

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Scheme III

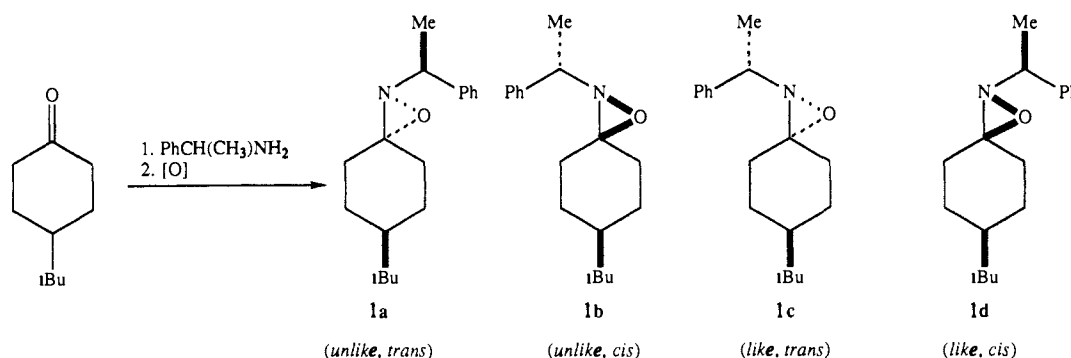
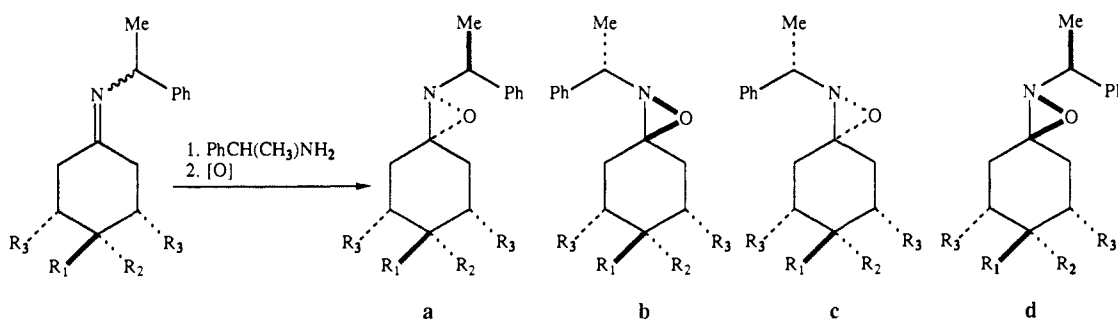


Table I. Preparation of Axially Dissymmetric Oxaziridines



entry	R_1	R_2	R_3	amine ^a	peracid ^b	product ^a	yield (%) ^c	isomer ratio ^d			
								a	b	c	d
1	CH_3	H	H	(±)	mCPBA	(±)-6	75	60	23	10	7
2				R	(+)-MPCA	αR -6	89	80	8	8	4
3				S	(+)-MPCA	αS -6	72	83	8	6	4
4	CH_3CH_2	H	H	(±)	mCPBA	(±)-7	83	63	28	6	3
5				R	(+)-MPCA	αR -7	83	79	9	7	5
6	$(\text{CH}_3)_3\text{C}$	H	H	(±)	mCPBA	(±)-1	85	74	19	4	3
7				R	(+)-MPCA	αR -1	83	85	10	4	1
8	C_6H_5	H	H	(±)	mCPBA	(±)-8	90	73	20	5	2
9				R	(+)-MPCA	αR -8	87	83	12	3	2
10	$\text{C}_6\text{H}_5\text{CH}_2\text{O}$	H	H	(±)	mCPBA	(±)-9	75	58	30	6	6
11				R	(+)-MPCA	αR -9	70	62	22	10	6
12	$\text{CH}_3\text{CH}_2\text{O}_2\text{C}$	H	H	(±)	mCPBA	(±)-10	97	60 ^{e,f}	40 ^{e,f}		
13				R	(+)-MPCA	αR -10	94	65 ^{e,f}	35 ^{e,f}		
14	CH_3	C_6H_5	H	(±)	mCPBA	(±)-11	82	59 ^e	27	14	
15				R	(+)-MPCA	αR -11	76	74 ^e	26		
16	H	H	CH_3	(±)	mCPBA	(±)-12	94	82	9	6	3
17				R	(+)-MPCA	αR -12	92	91	2	4	3

^aThe enantiomer of α MBA used in the condensation reactions. In the drawing, all structures are depicted with the αS configuration. ^bmCPBA: *m*-chloroperoxybenzoic acid. (+)-MPCA: (+)-monoperoxyxycamphoric acid. ^cYield is based on starting ketone and refers to chromatographically purified material. ^dRatios are determined by HPLC analysis of the crude reaction mixtures, except where noted. ^eApproximate ratios as determined by ^{13}C NMR spectroscopy (peak heights). ^fStereostructure of minor compound not verified.

the stereoselectivity of the reaction. For a stepwise mechanism, however, it becomes necessary to add the provisos that N–O bond formation be faster than N–C₃ bond rotation (oxaziridine numbering) and that imine interconversion be faster than the oxidation process. While both conditions have been elsewhere proposed as characteristics of the oxidation of *N*-alkyl-substituted imines,^{25d,32} it is plausible that the stereoselectivity arises due to the minimization of nonbonded interactions in the ring-closure portion of the two-stage mechanism. The results of experiments designed to sort out these possibilities will be reported in due course.

Meanwhile, with respect to the C₄ substituent of the starting ketone, a competition exists between axial and equatorial addition; in most cases, equatorial attack is known to be preferred (Scheme

II).^{33,34} In control experiments with mCPBA, we found the equatorial (*trans*)/axial (*cis*) ratios to range between 89:11 for *N*-benzyl-4-methylcyclohexanone imine and $\geq 98:\leq 2$ for *N*-benzyl-4-*tert*-butylcyclohexanone imine, affording compounds 4a,b and 5a,b respectively (^{13}C NMR analysis). As before, these ratios increased such that only one oxaziridine could be detected when either imine was oxidized by (+)-MPCA or peroxypivalic acid.

The overall effect of combining these two senses of stereochemical control was assessed by examination of the product mixture derived from utilization of the general protocol on 4-*tert*-butylcyclohexanone (Scheme III). The four possible products shown are depicted as isomers a–d, and they result from the four possible permutations of *u* vs *l* product formation (extraannular stereocontrol) and equatorial (*trans*) vs axial (*cis*) attack (intraannular stereocontrol) (cf. Schemes II and III). The stereo-

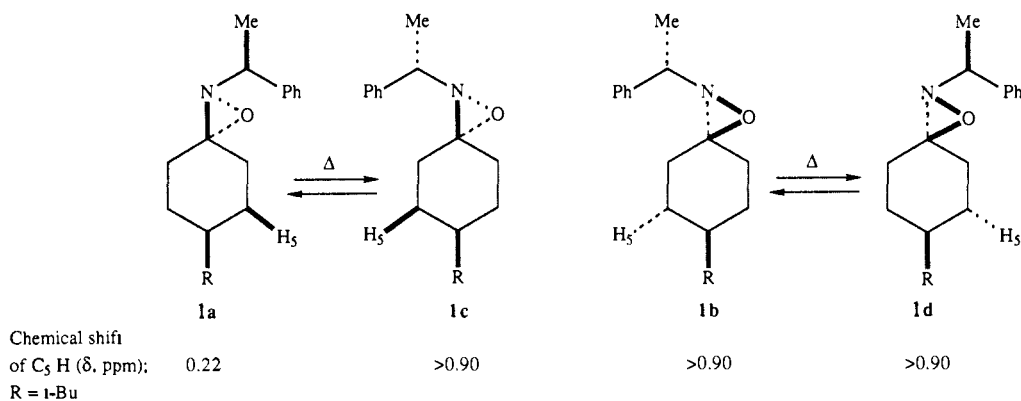
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Scheme IV



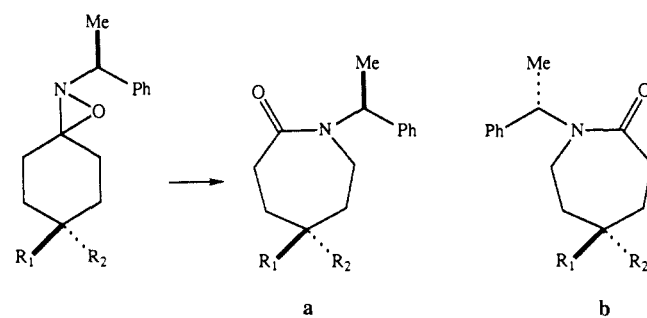
chemical structure of the major product **1a** (*u,trans*) was previously determined through X-ray crystallographic analysis.¹⁵ The next two most prevalent isomers should be those that result from a combination of a preferred *u* product formation and a disfavored axial attack (*u,cis*) and the alternative (*l,trans*) combination. Reflux of **1a** in dilute toluene solution results in equilibration at the nitrogen stereocenter^{29,35} and affords a mixture consisting of compounds **1a** and **1c** exclusively, which means the latter must have (*l,trans*) stereochemistry (Scheme IV). In a similar manner, **1b** and **1d** could be cleanly equilibrated at toluene reflux. The latter material is assigned as the (*l,cis*) isomer because it results from two disfavored processes.

The results of a survey of the selectivities obtained in syntheses of a series of oxaziridines derived from substituted cyclohexanones are collected in Table I. The stereoisomeric oxaziridines obtained from 4-monosubstituted cyclohexanones and 3,5-dimethylcyclohexanone are assigned by analogy with the 4-*tert*-butyl system. These assignments are supported by the observation of the C₅ proton at unusually high field in the major oxaziridine stereoisomers of oxaziridines **1**, **6–8**, **10**, and **12** (i.e. stereostructures **a**, Scheme IV). This signal is absent in each of the other stereoisomers.³⁶ The thermal correlations between isomers **a** \leftrightarrow **c** and **b** \leftrightarrow **d** were also carried out for the 4-methylcyclohexanone and 4-methyl-4-phenylcyclohexanone series (compounds **6** and **11**) as described above. In addition, the stereochemical structure of **11b** was also settled with X-ray crystallography (see supplementary material). Isomers **b–d** of the remaining compounds are assigned by analogy with the above arguments, taking into account that a greater drop in *cis/trans* selectivity is expected for compounds bearing smaller cyclohexyl substituents (relative to *u/l* selectivity, which should remain fairly invariant).

The application of this reaction to a group-selective insertion process requires both high *trans/cis* and *u/l* ratios, since both pairs of diastereomers **a/d** and **b/c** have the same sense of axial chirality. Thus, since **d** only contributes to the product mixture in a minor way, either an erosion in *trans/cis* selectivity (yielding **b**) or *u/l* selectivity (affording **c**) will result in a drop in the overall level of axial dissymmetry. The best results are obtained with (+)-MPCA as oxidant, which gives rise to products that contains as much as 85–90% of the major *u,trans* stereoisomer.

It is interesting that although slightly different results are obtained with the different chiral combinations of (*R*)- or (*S*)- α MBA and the (+)-MPCA oxidizing agent, there are apparently no large effects arising from considerations of double diastereoselectivity.³⁷ This contrasts with results reported for an *N*-(α -methylbenzyl) aldimine,³⁸ implying that the chiral interactions observed in that example arose from interactions between the oxaziridine *C* substituent and the incoming reagent, rather than the *N* substituent. In the present case, the practical outcome is

Table II. Intrinsic Stereoselectivity of Rearrangement



entry	oxaziridine ^a	product	isomer ratio ^b	
			a	b
1	1a	2	93	7
2	1b	2	11	89
3	1c	2	5	95
4	1d	2	96	4
5	8a	13	90	10
6	11a	14	88	12
7	11b	14	10	90

^aSee Table I for oxaziridine structures. ^bDetermined by HPLC analysis of the crude reaction mixtures. Yields not determined; however, when compared, HPLC traces were similar to those observed in the preparative scale experiments (Table III).

that both enantiomeric oxaziridines can be obtained with good de's with use of a single, readily available oxidizing agent.

Intrinsic Selectivity of Photochemical Rearrangement. In several examples, we have been able to purify the intermediate oxaziridines by recrystallization or using HPLC. This allowed us to examine the stereoselectivity inherent in the photochemical rearrangement reaction. Although the stereochemistry of the major product obtained from one such reaction had already been established,¹⁵ the product ratio—a critical value with respect to synthetic work—was not reported. In addition, we felt it advisable to ensure that this stereocontrol was general, and not an anomaly due to the particular stereoisomeric structure of the oxaziridine (stereochemical type **a**) employed. Thus, a number of oxaziridines differing in substitution type and stereochemical fine structure were examined. These results are collected in Table II.

The major oxaziridine derived from 4-*tert*-butylcyclohexanone (**1a**) has been previously reported to afford (*S*)-5-*tert*-butylcaprolactam **2a** (see eq 3). HPLC analysis of the crude lactam mixture after photolysis (Rayonet merry-go-round reaction chamber, 2 h, 30 °C) indicated the formation of two isomeric lactams in a 93:7 ratio. The expected dependence of stereoselectivity on the sense of axial dissymmetry was observed for all of the isomers investigated; thus, **1a** and **1d** each afforded **2a** as the major lactam, whereas **1b** and **1c** gave rise to the isomeric **2b**. In addition, the level of stereoselectivity was approximately the same for either process. Similar results were obtained with **8a**, **11a**, and **11b**.

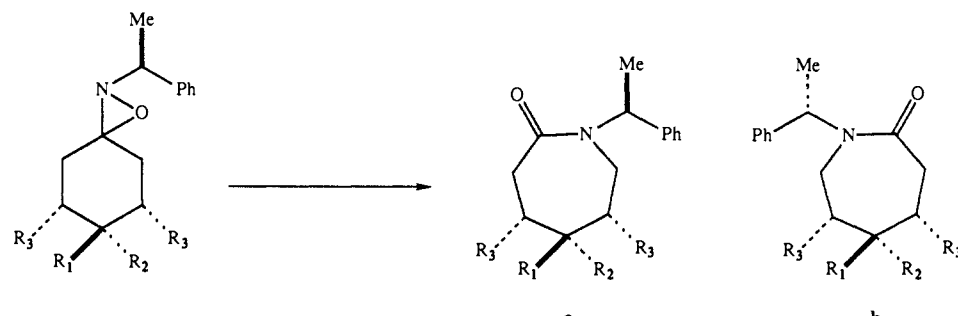
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Table III. Rearrangement of Oxaziridine Mixtures



entry	oxaziridine			product	yield (%) ^c	isomer ratio ^d	
	compd ^a	preparation method ^b	photolysis solvent (time, h)			a	b
1	6	A	C ₆ H ₁₂ (4)	15	77	74	26
2		B	C ₆ H ₁₂ (3)		61	84	16
3	7	A	CH ₂ Cl ₂ (7)	16	76	79	21
4		B	CH ₂ Cl ₂ (7)		71	84	16
6	1	A	C ₆ H ₁₂ (6)	2	69	80	20
7		B	C ₆ H ₁₂ (6)		70	88	12
8	8	A	C ₆ H ₁₂ (2.5)	13	55	80	20
9		B	CH ₂ Cl ₂ (2)		87	88	12
10	9	A	CH ₂ Cl ₂ (5)	17	74	59	41
11		B	C ₆ H ₁₂ (6)		45	59	41
12	10	A	CH ₂ Cl ₂ (2.5)	18	67	54	46
13		B	CH ₃ CN (9.5)		80	63	37
14	11	A	CH ₂ Cl ₂ (2)	14	79	62	38
15		B	CH ₃ CN (8)		89	70	30
16	12	A	CH ₂ Cl ₂ (4)	19	78	84	16
17		B	C ₆ H ₁₂ (6)		45	84	16

^a See Table I for structure of oxaziridines and lactams. ^b The oxaziridines used were prepared as follows: A, the starting ketone was condensed with (±)-αMBA and oxidized with mCPBA; B, the starting ketone was condensed with (*R*)-αMBA and oxidized with (+)-MPCA. In all cases, the oxaziridine was purified with column chromatography (silica gel) before photolysis. ^c Yields are based on oxaziridines purified by column chromatography. ^d Determined by HPLC analysis of the crude reaction mixtures.

The latter two results bear special mention. Most of the oxaziridines give ¹H and ¹³C NMR spectra which indicate that the six-membered ring exists primarily as a single stable chairlike conformation on the NMR time scale. However, oxaziridines **11a** and **11b** are each undergoing fast conformational equilibration on the NMR time scale as determined by ¹³C NMR spectroscopy. Thus, whereas the methyl substituent of 4-methyl-4-phenylcyclohexane normally appears at about 24 ppm for the axial conformer and about 10 ppm downfield in the equatorial conformation,³⁹ the 500-MHz NMR spectra of two purified oxaziridines derived from 4-methyl-4-phenylcyclohexanone each show a resonance at about 30 ppm. Upon cooling, the signal at δ 30.2 in **11a** broadens and disappears; finally, at -70 °C, new resonances assignable to axial and equatorial methyl groups begin to appear in the spectrum. These observations are best explained by the presence of rapidly interconverting chair conformers present at room temperature. Thus, the high intrinsic selectivities observed for rearrangement of **11a** and **11b** show that a conformationally fixed substrate is not a prerequisite to obtain high stereoselectivity in the rearrangement reaction.

On the basis of these results, it appears that the limiting selectivity in the photochemical rearrangement is ≥80% de. Of course, the ease of separation of the lactam stereoisomers with column chromatography greatly mitigates this limitation, as will be demonstrated below.

Overall Ketone-to-Lactam Conversions. From the viewpoint of preparative organic chemistry, the most attractive option is the direct throughput of material from the prochiral ketone substrates to optically active lactams, with a minimum of purification of intermediates. Considering the relative difficulty of obtaining diastereomerically pure oxaziridines, we have undertaken the conversion of the crude oxaziridine mixtures to the corresponding lactams. Thus, unseparated oxaziridines are purified by filtration

through silica gel and subjected to photolysis as outlined above. The product lactams are easily separated by simple flash chromatography ($\Delta R_f \sim 0.1$), readily affording diastereomerically pure lactams in good overall yield (Table III). The assignments of the major lactams obtained in each of these reactions are made in analogy to the known **2a**.¹⁵ For lactams **2**, **13**, **15**, **16**, and **19**, the assignments are supported by the observation that each of the minor lactam isomers shows an upfield resonance (ca. 0.5–0.9 ppm) in the ¹H NMR spectra that is absent in the spectra of the corresponding major isomers. This is ascribed to the different conformational behaviors of the *N*-phenylethyl substituent for the two sets of compounds. As shown in the table, the best results are generally achieved with (+)-MPCA as the oxidant. The ratios were obtained by HPLC measurements of the crude reaction mixtures.⁴⁰

It is clear that the present method shows promise for the synthesis of this versatile class of synthetic intermediates. Singly substituted 5-alkyl lactams can be synthesized with a de of ≥68% with this methodology, with bulky cases being somewhat better. Even those compounds that are obtained with somewhat lesser ratios due to conformational mobility in the precursor imines can be obtained diastereomerically pure in respectable yield due to the ready separation of the lactams. The fact that some of these ratios are very close to those obtained with diastereomerically pure oxaziridines suggests that further improvement of the results must await further development of the photochemical rearrangement step of the sequence. While such work is underway in this laboratory, the method as reported stands as a very general and simple way to procure quantities of these useful intermediates in enantiomerically pure form.

(40) In our original communication,^{23a} the ratios of lactams resulting from rearrangement of oxaziridines prepared with mCPBA were based on isolation of diastereomerically purified lactams, which were somewhat higher than those found by the HPLC method.

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Scheme V

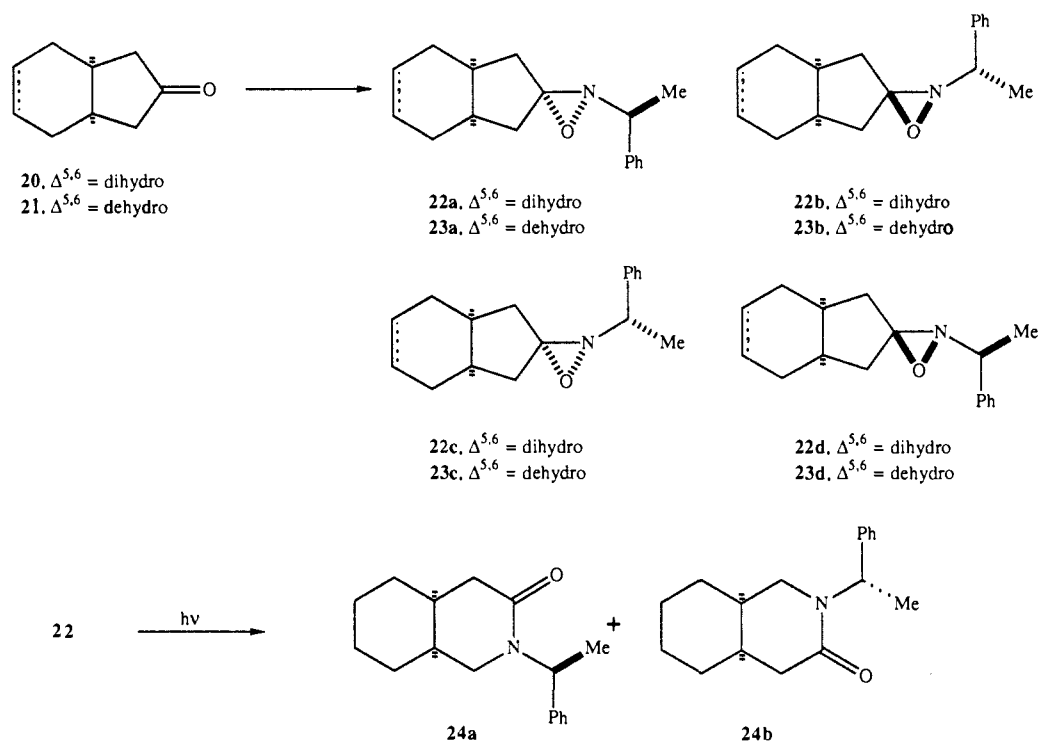


Table IV. Formation of Axially Dissymmetric Oxaziridines from Bicyclic Ketones

entry	ketone ^a	amine ^b	peracid ^c	product	yield (%) ^d	isomer ratio ^e							
						a	b ^f	c ^f	d				
1	20	(±)	mCPBA	22	83	62	18	15	5				
2		R	(+)-MPCA							71	19	8	2
3		S	(+)-MPCA							65	19	13	3
4	21	(±)	mCPBA	23	96	64	13	22	1				
5		R	(+)-MPCA							90	68	16	4

^aSee Scheme V for ketone and oxaziridine structures. ^bThe enantiomeric form of α MBA used in the condensation reactions. ^cmCPBA: *m*-chloroperoxybenzoic acid. (+)-MPCA: (+)-monoperoxycamphoric acid. ^dYield is based on starting ketone and refers to chromatographically purified material. ^eRatios are determined by HPLC analysis of the crude reaction mixtures. ^fThese assignments may be reversed.

Extension to Prochiral Cyclopentanone Substrates.^{23b} Symmetry considerations require that prochiral cyclopentanones bear multiple substituents suitably placed on the five-membered ring. Meso compounds bearing *cis* disubstitution on either carbons 2/5 or 3/4 meet this criterion. Since neither oxaziridines derived from such ketones nor their subsequent rearrangement chemistry had been previously investigated, ketones **20** and **21** were examined in this regard. Our eventual goal is the development of an asymmetric synthetic approach to the alkaloids of the reserpine and yohimbine classes and some of their synthetic congeners.⁴¹⁻⁴³ Our initial results are depicted in Scheme V and Table IV.

Treatment of **20** and **21** afforded mixtures of isomeric oxaziridines in overall yields of 80–96%, in the ratios shown. As before, the overall stereoselectivity of this reaction arises from

two separate diastereofacial processes. As before, the *u* product is expected to predominate, although control experiments show a slightly diminished diastereofacial selectivity in the reactions of cyclopentanone-derived imines relative to the six-membered-ring analogues.^{25c} In addition, selectivity is expected to arise from the propensity of bicyclic systems to suffer attack from the *exo* (i.e. convex) face. The major oxaziridine product could be isolated by fractional crystallization from the reaction mixture of ketone **20**. An X-ray crystallographic study of this material confirmed the relative stereochemistry to be that depicted in structure **22a** (supplementary material). A modest improvement in the proportion of the major product could be realized through the use of (+)-MPCA as oxidant. Overall, similar results were obtained with the unsaturated ketone **21**; notably, it proves possible to carry out the oxidation reaction in the presence of an alkene moiety elsewhere in the molecule.

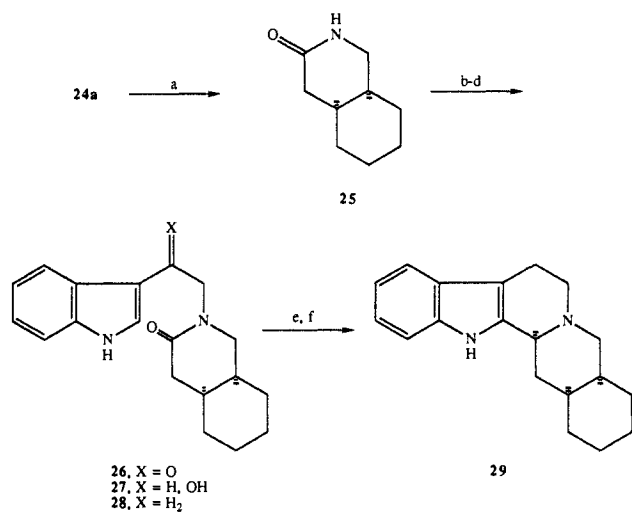
Photolysis of homogeneous **22a** afforded an 85:15 mixture of isomeric lactams (HPLC), which is only slightly less than the observed intrinsic selectivities in the cyclohexyl cases. The structure of the major lactam obtained through this procedure was proved to be **24a** by its eventual conversion to (–)-alloyohimbane (see below). These experiments unambiguously demonstrate for the first time the applicability of the Lattes stereoelectronic proposal¹⁵ to oxaziridines containing a 5-membered carbocyclic ring. Preparatively, photolysis of the crude mixture of **22a–d** gave **24a** and **24b** in a ratio of ca. 2.1:1 (45–55% combined yield).

The conversion of the key chiral lactam **24a** to (–)-alloyohimbane was carried out in a straightforward manner (Scheme VI). Compound **24a** was converted to the N-unsubstituted lactam **25**

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(42) Approaches to alkaloid synthesis utilizing oxaziridines: (a) Langlois, Y.; Pouilhès, A.; Génin, D.; Andriamialisoa, R. Z.; Langlois, N. *Tetrahedron* **1983**, *39*, 3755–3761. (b) Kuehne, M. E.; Parsons, W. H. *Tetrahedron* **1983**, *39*, 3763–3765.

(43) Recent asymmetric synthetic approaches to *cis*-fused yohimbinoïd alkaloids: (a) Danishefsky, S.; Langer, M. E.; Vogel, C. *Tetrahedron Lett.* **1985**, *26*, 5983–5986. (b) Isobe, M.; Fukami, N.; Goto, T. *Chem. Lett.* **1985**, 71–74. (c) Isobe, M.; Fukami, N.; Nishikawa, T.; Goto, T. *Heterocycles* **1987**, *25*, 521–532. (d) Meyers, A. I.; Miller, D. B.; White, F. H. *J. Am. Chem. Soc.* **1988**, *110*, 4778–4787.

Scheme VI^a

^a Reagents: (a) Na/NH₃. (b) NaH, THF; then 3-chloroacetylindole. (c) NaBH₄, EtOH. (d) 1 atm of H₂, Pd/C, EtOH, 0.01 equiv of HClO₄. (e) POCl₃, benzene reflux. (f) NaBH₄, MeOH.

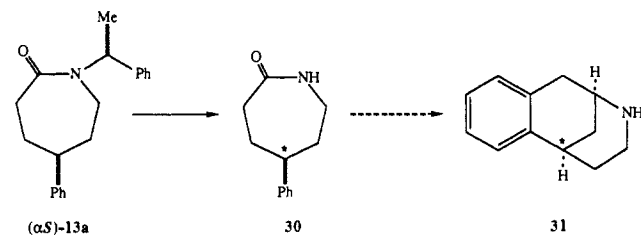
([α]_D = -30.9° (c = 1.02, MeOH)) by brief exposure to sodium in liquid ammonia in 77–92% yield based on recovered starting material. Alkylation was achieved through the generation of the sodium salt of **25** by the action of sodium hydride in dimethylformamide followed by the rapid addition of 3-chloroacetylindole (48–53%).⁴⁴ Deoxygenation was carried out by using the protocol of Fujii;⁴⁵ treatment with sodium borohydride in ethanol (24 h, room temperature) followed by hydrogenolysis (Pd/C, EtOH, 0.01 molar equiv of HClO₄, 1 h) afforded **28** in 45% overall yield. The final Bischler–Napieralski cyclization was performed in the standard manner (POCl₃, benzene, reflux; NaBH₄, methanol, 59% for two steps). In this way was obtained (-)-alloyohimbane **29**, the physical and spectral properties of which, including optical rotation, were in complete agreement with literature^{46,47} values.

Continuing work in our laboratories is designed to determine structural types and oxidation conditions that would be more favorable for the realization of higher ratios in these reactions. In addition, the development of means to secure more versatile and efficient routes to these indole alkaloids is in progress.

Conversion to N-Unsubstituted Lactams. Synthesis of a Key Chiral Intermediate for Benzomorphan Synthesis. The removal of the chiral alkyl substituent on nitrogen is essential for realization of an overall enantiotopic group selective insertion process. In order to demonstrate the synthetic viability of this chemistry, we chose to prepare N-unsubstituted lactam **30**, which has been reported as a key intermediate for the synthesis of the benzomorphan family of synthetic analgesics.⁴⁸ This synthesis, reported by Mitsuhashi in 1969,⁴⁹ utilized a standard Beckmann rearrangement sequence from 4-phenylcyclohexanone and yielded racemic material only. To date, members of this medicinally important class of compounds have only been the subject of a single nonracemic synthesis, reported by Meyers, utilizing an elegant application of chiral formamidine-stabilized anion technology.⁵⁰

The commercially available 4-phenylcyclohexanone was processed as outlined above to the optically active and diastereomerically pure lactam **13a** in 70–75% overall yield after purification. Dissolving metal reduction afforded the benzomorphan

Scheme VII



intermediate **30** in 75% yield. No products resulting from overreduction of the 4-phenyl substituent were observed. Compound **30** has previously been converted (in racemic form) to the ring skeleton of the benzomorphan analgesics **31**.

The following lactams were submitted to the dissolving metal reduction conditions and resulted in the formation of optically active N-unsubstituted lactams in the yields noted in parentheses: **2a** (76%), **14a** (82%), **19a** (94%), **15a** (78%), and **16a** (81%). In addition, double “deprotection” of 5-benzyloxy lactam **17** could be accomplished to afford 5-hydroxycaprolactam in 39% unoptimized yield.

Summary

A general route to the synthesis of optically active lactams with use of an asymmetric nitrogen insertion sequence has been presented. In the course of this work, a protocol for the synthesis of axially dissymmetric oxaziridines has been developed, and the generality of stereoelectronically controlled rearrangements of such oxaziridines has been established. The chemistry has already proven useful for the synthesis of an intermediate in benzomorphan synthesis and in the total syntheses of indole alkaloids, as exemplified by the preparation of (-)-alloyohimbane. The further application of this process to synthetic problems is a matter of continuing concern in this laboratory, as are the questions of mechanism that have been raised by this fascinating reaction.

Experimental Section

General Methods. ¹H and ¹³C NMR spectra were recorded on either a Varian XL-300 (300 and 75.4 MHz, respectively) or a Bruker AM-500 (500 and 125.7 MHz) instrument at ambient temperature unless noted. Chemical shifts are given in parts per million downfield from tetramethylsilane with either TMS or residual CHCl₃ as an internal reference. The following abbreviations are used to indicate signal multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Infrared spectra were recorded on a Perkin-Elmer 1420 spectrometer. Mass spectra were taken on a Varian MAT CH5 instrument. Optical rotations were measured on a Perkin-Elmer 241 polarimeter; concentrations are reported in g/100 mL. Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Flash chromatography was carried out as described by Still.⁵¹ HPLC was carried out on a Waters 590 isocratic pump equipped with a Waters 481 UV detector set on 254 nm. Chromatography was carried out on CN bonded (4.6 × 250 mm) and silica gel (7.8 × 300 mm) columns purchased from Alltech Associates. Elemental analyses were performed in-house or by Midwest Microlab (Indianapolis, Indiana).

Materials. Except where noted, all starting materials were purchased from either Aldrich or Fluka Chemical Comp. and used as received. The following compounds were prepared by using literature procedures: peroxyvalic acid,²⁶ (+)-MPCA,²⁷ *cis*-3,5-dimethylcyclohexanone,⁵² 4-(phenylmethoxy)cyclohexanone,⁵³ 4-methyl-4-phenylcyclohexanone,⁵⁴ *cis*-1,3,4,7-tetrahydroindan-2(2*H*)-one,⁵⁵ and *cis*-hexahydroindan-2(2*H*)-one.⁵⁶

General Procedure for Synthesis of Oxaziridines. A solution of ketone (1.0 equiv) and 1-phenylethylamine (1.2–1.5 equiv) in toluene was refluxed for 5–7 h in a round-bottomed flask that was equipped with a condenser connected via a Dean-Stark trap. The crude toluene solutions of imine were then cooled to room temperature and added through an addition funnel dropwise under nitrogen to a round-bottomed flask that

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(56) Deprés, J.-P.; Greene, A. E. *J. Org. Chem.* **1980**, *45*, 2036–2037.

contained a suspension of *m*-chloroperoxybenzoic acid (mCPBA, 1.2 equiv) or (+)-monoperoxycamphoric acid ((+)-MPCA, 2.0 equiv) in toluene kept at $-78\text{ }^{\circ}\text{C}$ (dry ice/acetone bath). The oxidation reaction was usually completed within 20 min (TLC analysis) and quenched with saturated $\text{Na}_2\text{S}_2\text{O}_4$ at $-78\text{ }^{\circ}\text{C}$. The reaction solution was then poured into a separatory funnel and partitioned between saturated $\text{Na}_2\text{S}_2\text{O}_4$ and diethyl ether. The organic layer was washed with saturated NaHCO_3 and brine and dried with Na_2SO_4 . The product was isolated by concentration followed by column chromatography (ethyl acetate/hexane 1:9). HPLC analyses were carried out with CN-bonded normal phase columns (flow rate 0.5 mL/min).

[2S*(R*),3(trans)]-6-(1,1-Dimethylethyl)-2-(1'-phenylethyl)-1-oxa-2-azaspiro[2.5]octane ([2S*(R*),3(trans)]-1, 1a) and Isomers. Thermal Equilibration of Oxaziridines. According to the general procedure, 4-*tert*-butylcyclohexanone (0.269 g, 1.74 mmol) was reacted with (\pm)-1-phenylethylamine (0.318 g, 2.61 mmol) followed by mCPBA (0.435 g, 2.04 mmol). Column chromatography afforded the title compound¹⁵ (mixture of isomers) as an oil (0.405 g, 85%). IR (neat) 2955, 2852, 1450, 1390, 1360, 700 cm^{-1} . Recrystallization from methanol gave a sample of **1a** as colorless crystals. **1a**: mp 96–97 $^{\circ}\text{C}$; ^1H NMR (CDCl_3 , 500 MHz) δ 0.22 (apparent qd, $J = 11.7, 4.5$ Hz, 1 H, C_5 axial H), 0.58 (s, 9 H, $\text{C}(\text{CH}_3)_3$), 0.95 (m, 2 H), 1.43 (dq, $J = 12.4, 1.5$ Hz, 1 H), 1.48 (m, 1 H), 1.58 (d, $J = 6.4$ Hz, 3 H, $\text{NCH}(\text{CH}_3)\text{Ph}$), 1.85 (complex, 4 H), 3.59 (q, $J = 6.4$ Hz, 1 H, $\text{NCH}(\text{CH}_3)\text{Ph}$), 7.31 (complex, 5 H, aromatics); ^{13}C NMR (CDCl_3 , 125.8 MHz) δ 23.8, 25.1, 25.3, 27.2, 27.3, 32.0, 36.7, 46.4, 62.7, 85.9, 127.0, 127.5, 128.6, 141.7. **[2S*(R*),3(cis)]-1 (1b)**: **1b** was isolated from the mother liquor of the recrystallization of **1a** by preparative HPLC (0.4% 2-propanol/hexane, retention time 11.4 min). **1b**: ^1H NMR (CDCl_3 , 500 MHz) δ 0.85 (s, 9 H, $\text{C}(\text{CH}_3)_3$), 1.12 (m, 1 H, C_6 methine), 1.33 (m, 2 H), 1.42 (m, 1 H), 1.57 (d, $J = 6.4$ Hz, 3 H, $\text{NCH}(\text{CH}_3)\text{Ph}$), 1.58 (obscured m, 1 H), 1.78 (m, 2 H), 1.94 (m, 2 H), 3.74 (q, $J = 6.4$ Hz, 1 H, $\text{NCH}(\text{CH}_3)\text{Ph}$), 7.38 (m, 5 H, aromatics); ^{13}C NMR (CDCl_3 , 125.8 MHz) δ 23.0, 24.6, 25.6, 27.5, 28.3, 32.4, 36.0, 47.2, 61.5, 85.5, 126.9, 127.5, 128.6, 141.2. Oxaziridine **1a** was refluxed in toluene overnight to afford a mixture of **1a** and **1c** from which **1c** was isolated by concentration followed by HPLC (retention time 16.6 min). **[2R*(R*),3(trans)]-1 (1c)**: ^1H NMR (CDCl_3 , 500 MHz) δ 0.92 (s, 9 H, $\text{C}(\text{CH}_3)_3$), 1.24 (dt, $J = 12, 3$ Hz, 1 H, C_6 methine), 1.35 (m, 2 H), 1.47 (d, $J = 6.7$ Hz, 3 H, $\text{NCH}(\text{CH}_3)\text{Ph}$), 1.55 (dq, $J = 12, 3$ Hz, 1 H), 1.83–2.14 (complex, 5 H), 3.65 (q, $J = 6.7$ Hz, 1 H, $\text{NCH}(\text{CH}_3)\text{Ph}$), 7.39 (br m, 5 H, aromatics); ^{13}C NMR (CDCl_3 , 125.8 MHz) δ 20.3, 25.6, 26.1, 27.1, 27.6, 32.4, 36.6, 46.9, 61.1, 86.3, 126.9, 127.2, 128.4, 143.1. Oxaziridine **1b** was refluxed in toluene overnight to afford a mixture of **1b** and **1d** from which **1d** could be partially purified by concentration followed by HPLC (retention time 13.6 min). **[2R*(R*),3(cis)]-1 (1d)**: ^1H NMR (CDCl_3 , 500 MHz) δ 0.89 (s, 9 H, $\text{C}(\text{CH}_3)_3$), 1.18 (m, 1 H), 1.37 (d, $J = 6.8$ Hz, 3 H, $\text{NCH}(\text{CH}_3)\text{Ph}$), 1.28–1.45 (complex, 2 H), 1.48 (m, 1 H), 1.85 (m, 1 H), 1.93–2.08 (complex, 4 H), 3.83 (q, $J = 6.8$ Hz, 1 H, $\text{NCH}(\text{CH}_3)\text{Ph}$), 7.41 (br m, 5 H, aromatics); ^{13}C NMR (CDCl_3 , 125.8 MHz) δ 19.2, 24.7, 25.6, 27.6, 27.8, 32.4, 36.4, 47.5, 60.8, 85.6, 125.7, 127.7, 128.4, 140.7.

[2S*(R*),3(trans)]-6-Methyl-2-(1'-phenylethyl)-1-oxa-2-azaspiro[2.5]octane ([2S*(R*),3(trans)]-6 (6a) and Isomers. According to the general procedure, 4-methylcyclohexanone (0.252 g, 2.25 mmol) was reacted with (\pm)- α MBA (0.411 g, 3.38 mmol) followed by mCPBA (0.575 g, 2.70 mmol). Column chromatography afforded the title compound (mixture of isomers) as an oil (0.391 g, 75% yield). HPLC (0.2% 2-propanol/hexane) retention times: **6a** 7.1 min, **6b** 6.9 min, **6c** 10.0 min, **6d** 7.8 min. IR (neat) 2940, 2910, 2850, 1600, 1490, 1445, 1390, 755, 730, 700 cm^{-1} . **6a**: ^1H NMR (CDCl_3 , 300 MHz) δ 0.21 (m, 1 H, C_5 axial H), 0.62 (d, $J = 6.2$ Hz, 3 H, C_6 methyl), 1.56 (d, $J = 6.3$ Hz, 3 H, $\text{NCH}(\text{CH}_3)\text{Ph}$), 1.21–2.04 (complex, 8 H), 3.59 (q, $J = 6.3$ Hz, 1 H, $\text{NCH}(\text{CH}_3)\text{Ph}$), 7.32 (br, m, 5 H, aromatics); ^{13}C NMR (CDCl_3 , 75.4 MHz) δ 21.2, 23.8, 26.8, 30.9, 32.5, 32.7, 36.1, 62.6, 85.6, 126.9, 127.0, 127.5, 128.5, 141.7; MS, m/e 231(M^+), 105 (100); HRMS calcd for $\text{C}_{15}\text{H}_{21}\text{NO}$ 231.1622, found 213.1623. **[2S*(R*),3(cis)]-6 (6b)**: ^1H NMR (CDCl_3 , 300 MHz) δ 3.66 (q, $J = 6.3$ Hz, 1 H, $\text{NCH}(\text{CH}_3)\text{Ph}$); ^{13}C NMR (CDCl_3 , 75.4 MHz) δ 61.4 (benzylic C). **[2R*(R*),3(trans)]-6 (6c)**: ^1H NMR (CDCl_3 , 300 MHz) δ 3.73 (q, $J = 6.3$ Hz, 1 H, $\text{NCH}(\text{CH}_3)\text{Ph}$); ^{13}C NMR (CDCl_3 , 75.4 MHz) δ 61.0 (benzylic C). Anal. Calcd for $\text{C}_{15}\text{H}_{21}\text{NO}$: C, 77.88; H, 9.15; N, 6.05. Found: C, 77.67; H, 8.95; N, 5.99.

[2S*(R*),3(trans)]-6-Ethyl-2-(1'-phenylethyl)-1-oxa-2-azaspiro[2.5]octane ([2S*(R*),3(trans)]-7 (7a) and Isomers. According to the general procedure, 4-ethylcyclohexanone (0.112 g, 0.89 mmol) was reacted with (\pm)- α MBA (0.163 g, 1.34 mmol) followed by mCPBA (0.220 g, 1.08 mmol). Column chromatography afforded the title compound (mixture of isomers) as an oil (0.181 g, 83% yield). HPLC retention times (0.4% 2-propanol/hexane): **7a** 12.9 min, **7b** 12.3 min, **7c** 18.3 min, **7d** 15.1 min. IR (neat) 2960, 2910, 1600, 1490, 1450, 750, 700 cm^{-1} .

7a: ^1H NMR (CDCl_3 , 300 MHz) δ 0.19 (m, 1 H, C_5 axial H), 0.69 (t, $J = 7.3$ Hz, 3 H, CH_2CH_3), 0.82–2.05 (complex, 8 H), 1.41 (m, 2 H), 1.56 (d, $J = 6.4$ Hz, 3 H, $\text{NCH}(\text{CH}_3)\text{Ph}$), 3.60 (q, $J = 6.4$ Hz, 1 H, $\text{NCH}(\text{CH}_3)\text{Ph}$), 7.31 (br m, 5 H, aromatics); ^{13}C NMR (CDCl_3 , 75.4 MHz) δ 11.5, 24.0, 27.1, 28.7, 30.3, 30.4, 36.4, 37.8, 62.8, 86.2, 127.1, 127.2, 127.8, 128.6, 128.8, 142.0; MS, m/e 245 (M^+), 105 (100); HRMS calcd for $\text{C}_{16}\text{H}_{23}\text{NO}$ 245.1780, found 245.1781. **[2S*(R*),3(cis)]-7 (7b)**: ^1H NMR (CDCl_3 , 300 MHz) δ 3.63 (q, $J = 6.4$ Hz, $\text{NCH}(\text{CH}_3)\text{Ph}$); ^{13}C NMR (CDCl_3 , 75.4 MHz) δ 62.0 (benzylic C). **[2R*(R*),3(trans)]-7 (7c)**: ^1H NMR (CDCl_3 , 300 MHz) δ 3.75 (q, $J = 6.4$ Hz, $\text{NCH}(\text{CH}_3)\text{Ph}$); ^{13}C NMR (CDCl_3 , 75.4 MHz) δ 61.6 (benzylic C). Anal. Calcd for $\text{C}_{16}\text{H}_{23}\text{NO}$: C, 78.32; H, 9.45; N, 5.71. Found: C, 78.22; H, 9.33; N, 5.62.

[2S*(R*),3(trans)]-6-Phenyl-2-(1'-phenylethyl)-1-oxa-2-azaspiro[2.5]octane ([2S*(R*),3(trans)]-8 (8a) and Isomers. According to the general procedure, 4-phenylcyclohexanone (0.169 g, 0.97 mmol) was reacted with (\pm)- α MBA (0.177 g, 1.46 mmol) followed by mCPBA (0.237 g, 1.16 mmol). Column chromatography afforded the title compound (mixture of isomers) as an oil (0.256 g, 90% yield). HPLC retention times (0.4% 2-propanol/hexane): **8a** 16.6 min, **8b** 15.7 min, **8c** 25.7 min, **8d** 22.0 min. IR (neat) 2990, 2960, 1600, 1490, 1450, 1390, 1170, 700 cm^{-1} . Recrystallization from methanol gave a sample of **8a** as colorless crystals. **8a**: mp 110–111 $^{\circ}\text{C}$; ^1H NMR (CDCl_3 , 300 MHz) δ 0.72 (apparent qd, $J = 12.7, 4.6$ Hz, 1 H, C_5 axial H), 1.38–1.60 (complex, 2 H), 1.61 (d, $J = 6.3$ Hz, 3 H, $\text{NCH}(\text{CH}_3)\text{Ph}$), 1.64 (m, 1 H), 1.83 (m, 1 H), 1.92–2.13 (complex, 3 H), 2.50 (tt, $J = 12.2, 3.3$ Hz, 1 H), 3.66 (q, $J = 6.3$ Hz, 1 H, $\text{NCH}(\text{CH}_3)\text{Ph}$), 6.75 (d, $J = 7.2$ Hz, 2 H, aromatics), 7.17 (br m, 3 H, aromatics), 7.37 (br m, 5 H, aromatics); ^{13}C NMR (CDCl_3 , 75.4 MHz) δ 23.9, 27.5, 31.8, 32.5, 36.8, 43.0, 63.0, 85.4, 126.2, 126.6, 127.2, 127.7, 128.3, 128.9, 141.9, 145.9; MS, m/e 293 (M^+), 105 (100); HRMS calcd for $\text{C}_{20}\text{H}_{23}\text{NO}$ 293.1780, found 293.1779. The other three isomers were separated by preparative HPLC (0.4% 2-propanol/hexane). **[2S*(R*),3(cis)]-8 (8b)**: ^1H NMR (CDCl_3 , 300 MHz) δ 1.51 (dq, $J = 12, 4$ Hz, 1 H), 1.60 (d, $J = 6.3$ Hz, 3 H, $\text{NCH}(\text{CH}_3)\text{Ph}$), 1.70–2.10 (complex, 7 H), 2.56 (tt, $J = 11.2, 3.4$ Hz, 1 H), 3.78 (q, $J = 6.3$ Hz, 1 H, $\text{NCH}(\text{CH}_3)\text{Ph}$), 7.26 (br m, 10 H, aromatics); ^{13}C NMR (CDCl_3 , 75.4 MHz) δ 23.1, 28.3, 31.2, 32.4, 36.0, 43.3, 61.6, 85.0, 126.3, 126.8, 127.0, 127.7, 128.5, 128.7, 141.2, 145.9. **[2R*(R*),3(trans)]-8 (8c)**: ^1H NMR (CDCl_3 , 300 MHz) δ 1.55 (d, $J = 6.9$ Hz, 3 H, $\text{NCH}(\text{CH}_3)\text{Ph}$), 1.59–1.66 (complex, 2 H), 1.80–1.88 (complex, 2 H), 2.01–2.22 (br m, 4 H), 2.78 (tt, $J = 12.1, 3.5$ Hz, 1 H), 3.70 (q, 1 H, $J = 6.9$ Hz, $\text{NCH}(\text{CH}_3)\text{Ph}$), 7.32 (br m, 10 H, aromatics); ^{13}C NMR (CDCl_3 , 75.4 MHz) δ 20.5, 27.1, 31.9, 33.1, 36.6, 42.9, 61.3, 85.8, 126.5, 126.8, 127.0, 127.2, 127.4, 128.3, 128.5, 128.6, 143.1, 145.5. **[2R*(R*),3(cis)]-8 (8d)**: ^1H NMR (CDCl_3 , 300 MHz) δ 1.40 (d, $J = 6.9$ Hz, 3 H, $\text{NCH}(\text{CH}_3)\text{Ph}$), 1.58–2.25 (complex, 8 H), 2.72 (tt, $J = 11.9, 3.1$ Hz, 1 H), 3.77 (q, $J = 6.9$ Hz, 1 H, $\text{NCH}(\text{CH}_3)\text{Ph}$), 7.31 (br m, 10 H, aromatics); ^{13}C NMR (CDCl_3 , 75.4 MHz) δ 19.4, 27.8, 31.3, 32.2, 36.3, 43.6, 60.9, 85.0, 126.3, 126.8, 126.9, 127.4, 128.5, 128.6, 142.8, 145.8. Anal. Calcd for $\text{C}_{20}\text{H}_{23}\text{NO}$: C, 81.87; H, 7.90; N, 4.71. Found: C, 82.00; H, 7.80; N, 5.00.

[2S*(R*),3(trans)]-6-(Phenylmethoxy)-2-(1'-phenylethyl)-1-oxa-2-azaspiro[2.5]octane ([2S*(R*),3(trans)]-9 (9a) and Isomers. According to the general procedure, 4-(phenylmethoxy)cyclohexanone (0.194 g, 0.95 mmol) was reacted with (\pm)- α MBA (0.365 g, 1.43 mmol) followed by mCPBA (0.250 g, 1.20 mmol). Column chromatography afforded the title compound (mixture of isomers) as an oil (0.228 g, 74% yield). HPLC retention times (0.4% 2-propanol/hexane): **9a** 11.7 min, **9b** 11.2 min, **9c** 14.4 min, **9d** 12.5 min. IR (neat) 3010, 2960, 2920, 2850, 1600, 1490, 1450, 1400, 1100, 1080, 1060, 750, 730, 700 cm^{-1} . **9a**: ^1H NMR (CDCl_3 , 300 MHz) δ 1.22–2.20 (complex, 8 H), 1.56 (d, $J = 6.3$ Hz, 3 H, $\text{NCH}(\text{CH}_3)\text{Ph}$), 3.36 (m, 1 H, $-\text{CH}(\text{OCH}_2\text{Ph})-$), 3.64 (m, 1 H, $\text{NCH}(\text{CH}_3)\text{Ph}$), 4.47 (AB q, $J = 12.6$ Hz, $\Delta\nu = 23.9$ Hz, 2 H, OCH_2Ph), 7.31 (m, 10 H, aromatics); ^{13}C NMR (CDCl_3 , 75.4 MHz) δ 23.7, 24.2, 28.8, 29.5, 32.5, 62.8, 70.1, 73.5, 85.2, 127.1, 127.2, 127.6, 127.7, 127.9, 128.6, 128.9, 129.0, 129.1, 139.0, 141.7; MS, m/e 323 (M^+), 105 (100); HRMS calcd for $\text{C}_{21}\text{H}_{25}\text{NO}_2$ 323.1884, found 323.1898. **[2S*(R*),3(cis)]-9 (9b)**: ^1H NMR (CDCl_3 , 300 MHz) δ 3.56 (m, 1 H, $-\text{CH}(\text{OCH}_2\text{Ph})-$), 3.69 (m, 1 H, $\text{NCH}(\text{CH}_3)\text{Ph}$), 4.43 (distorted AB q, 2 H, OCH_2Ph); ^{13}C NMR (CDCl_3 , 75.4 MHz) δ 62.2 (benzylic C). Anal. Calcd for $\text{C}_{21}\text{H}_{25}\text{NO}_2$: C, 77.99; H, 7.79; N, 4.33. Found: C, 78.09; H, 7.95; N, 4.38.

[2S*(R*),3(trans)]-6-Carbethoxy-2-(1'-phenylethyl)-1-oxa-2-azaspiro[2.5]octane ([2S*(R*),3(trans)]-10 (10a) and Isomers. According to the general procedure, ethyl 4-oxocyclohexanecarboxylate (0.232 g, 1.37 mmol) was reacted with (\pm)- α MBA (0.250 g, 2.06 mmol) followed by mCPBA (0.318 g, 1.64 mmol). Column chromatography afforded the title compound (mixture of isomers) as an oil (0.385 g, 97% yield). The isomer ratio was 60:40 by the average intensities of the ^{13}C NMR signals. IR (neat) 2960, 2920, 1728, 1445, 1190, 1165, 700 cm^{-1} ; ^1H NMR

(CDCl₃, 300 MHz) δ 1.01 (m, 1 H) 1.15 (t, $J = 7.0$ Hz, 3 H, CO₂CH₂CH₃), 1.57 (d, $J = 6.3$ Hz, 3 H, NCH(CH₃)Ph), 1.48–2.06 (complex, 7 H), 2.31 (m, 1 H, –CH(CO₂Et)–), 3.63 (q, $J = 6.3$ Hz, 1 H, NCH(CH₃)Ph), 4.01 (q, $J = 7.0$ Hz, 2 H, CO₂CH₂CH₃), 7.35 (m, 5 H, aromatics); ¹³C NMR (CDCl₃, 75.4 MHz) δ 14.1, 23.6, 26.0, 26.6, 35.0, 41.0, 60.2, 62.5, 84.6, 126.8, 126.9, 127.6, 127.7, 128.7, 128.8, 141.2, 174.2; MS, *m/e* 289 (M⁺), 105 (100); HRMS calcd for C₁₇H₂₃NO₃, 289.1677, found 289.1678. [**2S***(R*),3(*cis*)]-10 (**10b**): ¹H NMR (CDCl₃, 300 MHz) δ 1.03 (t, $J = 7.0$ Hz, 3 H, CO₂CH₂CH₃), 3.71 (q, $J = 6.3$ Hz, 1 H, NCH(CH₃)Ph), 4.12 (q, $J = 7.0$ Hz, 3 H, CO₂CH₂CH₃); ¹³C NMR (CDCl₃, 75.4 MHz) δ 14.2, 23.2, 26.3, 26.6, 34.6, 41.4, 60.4, 61.8, 84.6, 141.2, 174.6. Anal. Calcd for C₁₇H₂₃NO₃: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.51; H, 7.89; N, 5.00.

[**2S***(R*),3(*cis*)]-6-Methyl-6-phenyl-2-(1'-phenylethyl)-1-oxa-2-azaspiro[2.5]octane ([**2S***(R*),3(*cis*)]-11 (**11a**)) and Isomers. Thermal Equilibration of Oxaziridines. According to the general procedure, 4-methyl-4-phenylcyclohexanone (0.204 g, 1.09 mmol) was reacted with (\pm)-1-phenylethylamine (0.207 g, 1.70 mmol) followed by mCPBA (0.277 g, 1.30 mmol). Column chromatography afforded the title compound (mixture of isomers) as an oil (0.273 g, 82%). IR (neat) 3080, 3060, 3020, 1600, 1490, 1450, 1400, 1370, 750, 700 cm⁻¹. The major isomer (**11a**) was isolated by HPLC (2.5% ethyl acetate/hexane, silica column, retention time 13.9 min). ¹H NMR (CDCl₃, 500 MHz) δ 0.97 (s, 3 H, C₆ methyl), 1.04 (m, 1 H), 1.50–1.59 (complex, 2 H), 1.58 (d, $J = 6.4$ Hz, 3 H, NCH(CH₃)Ph), 1.65 (m, 1 H), 1.81 (m, 1 H), 1.89 (m, 1 H), 2.04 (m, 1 H), 2.19 (m, 1 H), 3.66 (q, $J = 6.4$ Hz, 1 H, NCH(CH₃)Ph), 7.34 (br m, 10 H, aromatics); ¹³C NMR (CDCl₃, 75.4 MHz) δ 23.6, 24.2, 29.7, 30.3, 32.8, 35.4, 37.3, 62.4, 85.7, 125.7, 125.8, 127.0, 127.7, 128.6, 128.8, 141.7, 147.4. [**2S***(R*),3(*trans*)]-11 (**11b**): Recrystallization from pentane afforded **11b** as a white crystalline powder: mp 102–103 °C; HPLC retention time 15.4 min (2.5% ethyl acetate/hexane, silica column); ¹H NMR (CDCl₃, 500 MHz) δ 1.25 (s, 3 H, C₆ methyl), 1.57 (d, $J = 6.4$ Hz, 3 H, NCH(CH₃)Ph), 1.59–1.76 (complex, 5 H), 1.96 (m, 2 H), 2.08 (m, 1 H), 3.70 (q, $J = 6.4$ Hz, 1 H, NCH(CH₃)Ph), 7.30 (br m, 10 H, aromatics); ¹³C NMR (CDCl₃, 75.4 MHz) δ 23.4, 24.5, 29.8, 32.8, 35.7, 35.9, 37.6, 61.8, 86.1, 125.7, 125.8, 127.1, 127.7, 128.4, 128.8, 141.3, 147.3; MS, *m/e* 307 (M⁺), 105 (100); HRMS calcd for C₂₁H₂₅NO 307.1935, found 307.1945. [**2R***(R*),3(*cis*)]-11 (**11c**): Oxaziridine **11a** was refluxed in toluene overnight to afford a mixture of **11a** and **11c** from which **11c** could be isolated by concentration followed by preparative HPLC (2.5% ethyl acetate/hexane, silica column, retention time 15.8 min). ¹H NMR (CDCl₃, 500 MHz) δ 1.34 (s, 3 H, C₆ methyl), 1.48 (d, $J = 6.4$ Hz, 3 H, NCH(CH₃)Ph), 1.62 (m, 1 H), 1.82–2.03 (complex, 4 H), 2.15–2.32 (complex, 3 H), 3.73 (q, $J = 6.4$ Hz, 1 H, NCH(CH₃)Ph), 7.38 (br m, 10 H, aromatics). ¹³C NMR (CDCl₃, 125.8 MHz) δ 19.9, 23.9, 28.2, 32.6, 35.4, 36.1, 37.2, 61.0, 85.6, 125.5, 125.9, 126.9, 127.3, 128.5, 128.5, 142.9, 148.1. [**2R***(R*),3(*trans*)]-11 (**11d**): Oxaziridine **11b** was refluxed in toluene overnight to afford a mixture of **11b** and **11d** from which **11d** could be isolated by concentration followed by preparative HPLC (2.5% ethyl acetate/hexane, silica column, retention time 13.3 min). ¹H NMR (CDCl₃, 500 MHz) δ 1.24 (s, 3 H, C₆ methyl), 1.27 (d, $J = 6.8$ Hz, 3 H, NCH(CH₃)Ph), 1.46 (m, 1 H), 1.80–2.02 (complex, 5 H), 2.36 (m, 1 H), 2.52 (m, 1 H), 3.69 (q, $J = 6.8$ Hz, 1 H, NCH(CH₃)Ph), 7.38 (m, 10 H, aromatics); ¹³C NMR (CDCl₃, 75.4 MHz) δ 19.5, 24.5, 33.0, 34.9, 35.9, 38.3, 61.0, 85.9, 126.0, 126.0, 127.0, 127.4, 128.6, 128.8, 143.0, 146.5. Anal. Calcd for C₂₁H₂₅NO: C, 82.04; H, 8.20; N, 4.56. Found: C, 81.92; H, 8.14; N, 4.51.

[**2R***(S*),3 α ,5 α ,7 α]-5,7-Dimethyl-2-(1'-phenylethyl)-1-oxa-2-azaspiro[2.5]octane ([**2R***(S*),3 α ,5 α ,7 α]-12 (**12a**)) and Isomers. According to the general procedure, *cis*-3,5-dimethylcyclohexanone (0.249 g, 1.97 mmol) was reacted with (\pm)- α MBA (0.243 g, 2.00 mmol) followed by mCPBA (0.430 g, 2.01 mmol). Column chromatography afforded the title compound (mixture of isomers) as an oil (0.456 g, 94% yield). HPLC retention times (0.3% 2-propanol/hexane): **12a** 15.4 min, **12b** 15.0 min, **12c** 20.2 min, **12d** 18.2 min. IR (CDCl₃) 2940, 2910, 1450, 1370, 900, 730, 650 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 0.54 (m, 1 H, C₅ axial H), 0.74 (d, $J = 5.6$ Hz, 3 H, –CH(CH₃)–), 0.84 (d, $J = 5.6$ Hz, 3 H, –CH(CH₃)–), 1.36–1.51 (complex, 5 H), 1.57 (d, $J = 6.3$ Hz, 3 H, NCH(CH₃)Ph), 1.84 (m, 2 H), 3.61 (q, $J = 6.3$ Hz, 1 H, NCH(CH₃)Ph), 7.30 (m, 5 H, aromatics); ¹³C NMR (CDCl₃, 75.4 MHz) δ 22.0, 22.0, 23.8, 30.6, 30.8, 35.4, 42.6, 44.6, 63.0, 85.7, 126.9, 127.6, 128.6, 141.6; MS, *m/e* 245 (M⁺), 105 (100). Anal. Calcd for C₁₆H₂₃NO: C, 78.32; H, 9.45; N, 5.71. Found: C, 78.10; H, 9.37; N, 5.74. [**2R***(S*),3 β ,5 α ,7 α]-12 (**12b**): ¹³C NMR (CDCl₃, 75.4 MHz) δ 62.8 (benzylic C). [**2S***(S*),3 α ,5 α ,7 α]-12 (**12c**): ¹³C NMR (CDCl₃, 75.4 MHz) δ 62.0 (benzylic C). [**2S***(S*),3 β ,5 α ,7 α]-12 (**12d**): ¹³C NMR (CDCl₃, 75.4 MHz) δ 61.2 (benzylic C).

[**2R***(S*),2 α ,3 α ,7 α]-2'-(1-Phenylethyl)octahydrospiro[2H-indene-2,3'-oxaziridine] ([**2R***(S*),2 α ,3 α ,7 α]-22 (**22a**)) and Isomers. Ac-

ording to the general procedure, *cis*-octahydroindan-2-one (0.303 g, 2.19 mmol) was reacted with (\pm)- α MBA (0.399 g, 3.29 mmol) followed by mCPBA (0.567 g, 2.65 mmol). Column chromatography afforded the title compound (mixture of isomers) as an oil (0.472 g, 83% yield). HPLC retention times (0.4% 2-propanol/hexane): **22a** 11.4 min, **22b** 11.0 min, **22c** 15.3 min, **22d** 12.5 min. Recrystallization from 2-propanol/ether gave a sample of major isomer (**22a**): mp 71–73 °C; IR (CCl₄) 2920, 2840, 1450, 1370, 700 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 0.71 (m, 1 H), 1.12–1.52 (complex, 7 H), 1.58 (d, $J = 5.4$ Hz, 3 H, NCH(CH₃)Ph), 1.82–2.32 (complex, 6 H), 3.33 (q, $J = 5.4$ Hz, 1 H, NCH(CH₃)Ph), 7.38 (br m, 5 H, aromatics); ¹³C NMR (CDCl₃, 75.4 MHz) δ 21.4, 23.4, 23.5, 26.8, 26.9, 30.5, 36.4, 37.0, 40.1, 65.5, 92.8, 127.6, 128.4, 128.6, 128.7, 141.1; MS, *m/e* 257 (M⁺), 105 (100). Anal. Calcd for C₁₇H₂₃NO: C, 79.33; H, 9.01; N, 5.44. Found: C, 79.53; H, 9.03; N, 5.43. [**2R***(S*),2 β ,3 α ,7 α]-22 (**22b**): ¹³C NMR (CDCl₃, 75.4 MHz) δ 64.9 (benzylic C). [**2S***(S*),2 α ,3 α ,7 α]-22 (**22c**): ¹³C NMR (CDCl₃, 75.4 MHz) δ 64.4 (benzylic C). [**2S***(S*),2 β ,3 α ,7 α]-22 (**22d**): ¹³C NMR (CDCl₃, 75.4 MHz) δ 66.4 (benzylic C).

[**2R***(S*),2 α ,3 α ,7 α]-2'-(1-Phenylethyl)-1,3,3a,4,7,7a-hexahydrospiro[2H-indene-2,3'-oxaziridine] ([**2R***(S*),2 α ,3 α ,7 α]-23 (**23a**)) and Isomers. According to the general procedure, *cis*-3a,4,7,7a-tetrahydroindan-2-one (0.324 g, 2.38 mmol) was reacted with (\pm)- α MBA (0.389 g, 3.20 mmol) followed by mCPBA (0.618 g, 2.88 mmol). Column chromatography afforded the title compound (mixture of isomers) as an oil (0.586 g, 96%). HPLC retention times (0.4% 2-isopropanol/hexane): **23a** 13.4 min, **23b** 12.8 min, **23c** 18.2 min, **23d** 17.5 min. IR (neat) 3020, 2960, 2920, 1450, 1370, 750, 660 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 1.15 (m, 1 H), 1.57 (d, $J = 6.3$ Hz, 3 H, NCH(CH₃)Ph), 1.60–2.35 (complex, 9 H), 3.33 (q, $J = 6.3$ Hz, 1 H, NCH(CH₃)Ph), 5.39 (m, 2 H, vinyl H), 7.31 (m, 5 H, aromatics); ¹³C NMR (CDCl₃, 75.4 MHz) δ 23.3, 25.8, 25.9, 32.5, 32.8, 34.3, 40.8, 65.3, 92.6, 123.9, 124.9, 126.7, 127.2, 127.6, 128.7, 128.8, 141.0; MS, *m/e* 255 (M⁺), 105 (100); HRMS calcd for C₁₇H₂₁NO 255.1623, found 255.1638. [**2R***(S*),2 β ,3 α ,7 α]-23 (**23b**): ¹³C NMR (CDCl₃, 75.4 MHz) δ 64.9 (benzylic C). [**2S***(S*),2 α ,3 α ,7 α]-23 (**23c**): ¹³C NMR (CDCl₃, 75.4 MHz) δ 64.1 (benzylic C).

General Procedure for Photochemical Rearrangement. The substrate oxaziridine was dissolved in the noted solvent (0.05–0.10 M) in a quartz tube. The solution was degassed with nitrogen for 20 min and then photolyzed in a Rayonet RPR-100 chamber reactor (room temperature, 2537 Å). The solution was concentrated and products purified by column chromatography (1:4 ethyl acetate/hexane). For starting materials, solvents, times, and yields of these reactions, see Table III.

Hexahydro-5-methyl-1-(1-phenylethyl)-2H-azepin-2-one (15). [**R***(R*),**R***(R*)]-15 (**15a**): IR (neat) 2940, 2920, 1630, 1470, 1440, 1410, 1195, 1180, 700 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 0.93 (d, $J = 6.7$ Hz, 3 H, –CH(CH₃)–), 1.00–1.95 (complex, 5 H), 1.49 (d, $J = 6.8$ Hz, 3 H, NCH(CH₃)Ph), 2.59 (m, 2 H, –C(O)CH₂–), 3.01 (m, 2 H, –N(R)CH₂–), 6.04 (q, $J = 6.8$ Hz, 1 H, NCH(CH₃)Ph), 7.29 (m, 5 H, aromatics); ¹³C NMR (CDCl₃, 75.4 MHz) δ 16.2, 22.5, 31.4, 36.1, 36.2, 37.7, 42.7, 50.4, 126.9, 126.9, 128.1, 128.2, 140.9, 175.2; [α]_D = +125.9° (*c* = 1.30, MeOH). Anal. Calcd for C₁₅H₂₀N: C, 77.88; H, 9.15; N, 6.06. Found: C, 77.49; H, 9.10; N, 6.20. [**R***(R*),**S***(S*)]-15 (**15b**): IR (neat) 2940, 2920, 1630, 1470, 1450, 1410, 1195, 1180, 700 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 0.51 (m, 1 H, C₆ axial H), 0.80 (d, $J = 6.5$ Hz, 3 H, –CH(CH₃)–), 1.25 (m, 1 H), 1.41 (m, 1 H), 1.43 (d, $J = 7.1$ Hz, 3 H, NCH(CH₃)Ph), 1.79 (m, 2 H), 2.51 (ddd, $J = 14.3, 11.8, 2.1$ Hz, 1 H, –C(O)CH₂–), 2.64 (ddd, $J = 14.3, 7.8, 2.2$, 1 H, –C(O)CH₂–), 3.11 (m, 2 H, –N(R)CH₂–), 6.04 (q, $J = 7.1$ Hz, 1 H, NCH(CH₃)Ph), 7.30 (m, 5 H, aromatics); ¹³C NMR (CDCl₃, 75.4 MHz) δ 15.6, 22.3, 31.2, 35.8, 36.3, 36.5, 42.0, 50.6, 127.3, 127.8, 128.2, 140.6, 175.3; [α]_D = +140.9° (*c* = 0.97, MeOH).

Hexahydro-5-ethyl-1-(1-phenylethyl)-2H-azepin-2-one (16). [**R***(R*),**R***(R*)]-16 (**16a**): IR (CDCl₃) 2960, 2920, 1620, 1480, 1445, 1420, 1260, 700 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 0.86 (t, $J = 7.4$ Hz, 3 H, CH₂CH₃), 1.02 (m, 1 H), 1.24 (complex, 4 H), 1.47 (d, $J = 7.5$ Hz, 3 H, NCH(CH₃)Ph), 1.92 (m, 2 H), 2.51 (m, 2 H, –C(O)CH₂–), 2.99 (m, 2 H, –N(R)CH₂–), 6.03 (q, $J = 7.5$ Hz, 1 H, NCH(CH₃)Ph), 7.26 (m, 5 H, aromatics); ¹³C NMR (CDCl₃, 75.4 MHz) δ 11.3, 16.4, 29.3, 29.7, 35.6, 36.3, 42.9, 43.0, 50.6, 127.1, 128.4, 141.1, 175.5; [α]_D = +111.5° (*c* = 1.80, MeOH). Anal. Calcd for C₁₆H₂₃NO: C, 78.32; H, 9.45; N, 5.71. Found: C, 77.95; H, 9.54; N, 5.96. [**R***(R*),**S***(S*)]-16 (**16b**): IR (CDCl₃) 2960, 2920, 1620, 1471, 1449, 1420, 700 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 0.50 (m, 1 H, C₆ axial H), 0.77 (t, $J = 7.3$ Hz, 3 H, CH₂CH₃), 1.04–1.18 (complex, 5 H), 1.46 (d, $J = 6.7$ Hz, 3 H, NCH(CH₃)Ph), 2.85 (m, 1 H), 2.49 (ddd, $J = 13.2, 11.0, 1.3$, 1 H, –C(O)CH₂–), 2.65 (ddd, $J = 13.2, 7.6, 1.3$, 1 H, –C(O)CH₂–), 3.01 (m, 2 H, –N(R)CH₂–), 6.03 (q, $J = 6.7$ Hz, 1 H, NCH(CH₃)Ph), 7.26 (m, 5 H, aromatics); ¹³C NMR (CDCl₃, 75.4 MHz) δ 11.3, 15.6, 28.9, 29.2,

34.3, 36.3, 42.0, 42.5, 50.6, 127.3, 127.8, 128.3, 140.7, 175.5; $[\alpha]_D = +126.9^\circ$ ($c = 1.30$, MeOH).

Hexahydro-5-phenyl-1-(1-phenylethyl)-2H-azepin-2-one (13). [*S*-(*R**,*R**)]-13 (13a): IR (CDCl₃) 2920, 1620, 1445, 691 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 1.57 (d, $J = 7.4$ Hz, 3 H, NCH(CH₃)Ph), 1.75–2.18 (m, 4 H), 2.75 (m, 3 H), 3.14 (m, 2 H), 6.12 (q, $J = 7.4$ Hz, 1 H, NCH(CH₃)Ph), 7.28 (m, 10 H, aromatics); ¹³C NMR (CDCl₃, 75.4 MHz) δ 16.8, 31.1, 37.0, 37.8, 43.4, 48.6, 51.0, 126.8, 126.9, 127.4, 127.5, 128.7, 128.9, 129.0, 141.3, 146.3, 175.4; $[\alpha]_D = -63.1^\circ$ ($c = 1.12$, MeOH). Anal. Calcd for C₂₀H₂₃NO: C, 81.87; H, 7.90; N, 4.78. Found: C, 82.00; H, 7.80; N, 5.00. [*S*-(*R**,*S**)]-13 (13b): IR (CCl₄) 2930, 1640, 1470, 1450, 1410, 700 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 0.85 (m, 1 H, C₆ axial H), 1.48 (d, $J = 7.7$ Hz, 3 H, NCH(CH₃)Ph), 1.50–1.82 (m, 2 H), 2.01 (m, 1 H), 2.71 (m, 3 H), 3.25 (m, 2 H), 6.13 (q, $J = 7.7$ Hz, 1 H, NCH(CH₃)Ph), 7.30 (m, 10 H, aromatics); ¹³C NMR (CDCl₃) δ 15.8, 30.9, 36.2, 37.2, 42.6, 48.2, 51.0, 126.6, 126.8, 127.8, 128.1, 128.4, 128.5, 128.6, 128.7, 140.8, 146.3, 175.3; $[\alpha]_D = -133.5^\circ$ ($c = 0.93$, MeOH).

Hexahydro-5-(phenylmethoxy)-1-(1-phenylethyl)-2H-azepin-2-one (17). [*R*-(*R**,*R**)]-17 (17a): IR (neat) 2992, 2940, 1620, 1490, 1478, 1450, 1420, 1170, 1070, 700 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 1.50 (d, $J = 6.7$ Hz, 3 H, NCH(CH₃)Ph), 1.64 (m, 2 H), 1.91 (m, 2 H), 2.29 (m, 1 H), 2.84 (m, 1 H), 2.96 (m, 1 H), 3.37 (m, 1 H), 3.61 (m, 1 H, -CH(OCH₂Ph)-), 4.48 (AB q, $J = 11.6$ Hz, $\Delta\nu = 13.1$ Hz, 2 H, OCH₂Ph), 6.05 (q, $J = 6.7$ Hz, 1 H, NCH(CH₃)Ph), 7.30 (m, 10 H, aromatics); ¹³C NMR (CDCl₃, 75.4 MHz) δ 16.5, 28.3, 31.3, 34.3, 38.1, 50.9, 70.2, 127.5, 127.6, 127.7, 128.6, 128.7, 138.7, 141.0, 175.6; $[\alpha]_D = +73.4^\circ$ ($c = 1.00$, MeOH). Anal. Calcd for C₂₁H₂₅NO: C, 77.98; H, 7.79; N, 4.33. Found: C, 78.38; H, 7.90; N, 4.25. [*R*-(*R**,*S**)]-17 (17b): ¹H NMR (CDCl₃, 300 MHz) δ 1.48 (d, $J = 6.6$ Hz, 3 H, NCH(CH₃)Ph), 1.55 (m, 1 H), 1.80 (m, 1 H), 1.91 (m, 2 H), 2.41 (m, 1 H), 2.89 (m, 2 H), 3.39 (m, 1 H), 3.53 (m, 1 H, -CH(OCH₂Ph)-), 4.49 (AB q, $J = 12.0$ Hz, $\Delta\nu = 13.7$ Hz, 2 H, OCH₂Ph), 6.60 (q, $J = 6.6$ Hz, 1 H, NCH(CH₃)Ph), 7.30 (m, 10 H, aromatics); ¹³C NMR (CDCl₃, 75.4 MHz) δ 10.5, 22.9, 26.1, 28.7, 32.8, 45.4, 64.7, 121.9, 122.0, 122.1, 122.1, 122.3, 123.1, 133.2, 135.5, 169.9; $[\alpha]_D = +86.8^\circ$ ($c = 1.10$, MeOH).

5-Carboethoxy-(1-phenylethyl)-2H-azepin-2-one (18). [*R*-(*R**,*R**)]-18 (18a): IR (neat) 2967, 2940, 2920, 1729, 1640, 1470, 1440, 1420, 1190, 1160, 700 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 1.26 (t, $J = 7.5$ Hz, 3 H, COOCH₂CH₃), 1.48 (d, $J = 6.7$ Hz, 3 H, NCH(CH₃)Ph), 1.68 (m, 1 H), 1.87 (m, 2 H), 2.06 (m, 1 H), 2.53 (complex, 2 H), 2.75 (ddd, $J = 14.4, 9.0, 1.7$, 1 H, -C(O)CH₂-), 3.10 (ddd, $J = 15.6, 9.2, 1.8$, 1 H, -N(R)CH₂-), 3.23 (ddd, $J = 15.6, 7.8, 1.8$, 1 H, -N(R)CH₂-), 4.13 (q, $J = 7.5$ Hz, 2 H, CO₂CH₂CH₃), 6.04 (q, $J = 6.7$ Hz, 1 H, NCH(CH₃)Ph), 7.29 (m, 5 H, aromatics); ¹³C NMR (CDCl₃) δ 14.2, 16.3, 25.7, 31.6, 35.4, 41.6, 45.8, 50.7, 60.7, 126.2, 127.3, 127.3, 128.5, 128.7, 140.8, 174.4, 174.6; $[\alpha]_D = +81.3^\circ$ ($c = 1.30$, MeOH); MS, m/e 289 (M⁺), 105 (100); HRMS calcd for C₁₇H₂₃NO 289.1678, found 289.1680. [*R*-(*R**,*S**)]-18 (18b): ¹H NMR (CDCl₃, 500 MHz) δ 1.22 (t, $J = 7.5$ Hz, 3 H, CO₂CH₂CH₃), 1.27 (m, 1 H), 1.48 (d, $J = 7.1$ Hz, 3 H, NCH(CH₃)Ph), 1.69 (m, 1 H), 1.93 (m, 1 H), 2.05 (m, 1 H), 2.44–2.62 (complex, 2 H), 2.73 (dd, $J = 14.5, 8.3$ Hz, 1 H, -C(O)CH₂-), 3.02 (dd, $J = 15.6, 9.8$ Hz, 1 H, -N(R)CH₂-), 3.17 (dd, $J = 15.6, 7.3$, 1 H, -N(R)CH₂-), 4.12 (m, 2 H, CO₂CH₂CH₃), 6.04 (q, $J = 7.1$, 1 H, NCH(CH₃)Ph), 7.42 (m, 5 H, aromatics); ¹³C NMR (CDCl₃, 75.4 MHz) δ 14.1, 15.9, 25.3, 30.9, 35.3, 41.2, 45.1, 50.8, 60.6, 127.3, 127.5, 127.6, 128.5, 128.7, 140.4, 174.3, 174.7; $[\alpha]_D = +98.0^\circ$ ($c = 1.00$, MeOH).

Hexahydro-5-methyl-5-phenyl-1-(1-phenylethyl)-2H-azepin-2-one (14). [*R*-(*R**,*S**)]-14 (14a): IR (CHCl₃) 3060, 3000, 2980, 2960, 2920, 1640, 1600, 1490, 1480, 1450, 1420, 700 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ 0.94 (m, 1 H), 1.10 (s, 3 H, C₅ methyl), 1.42 (d, $J = 7.3$ Hz, 3 H, -NCH(CH₃)Ph), 1.82 (m, 1 H), 2.10–2.40 (complex, 4 H), 3.01 (m, 2 H, -N(R)CH₂-), 6.04 (q, $J = 7.3$ Hz, 1 H, -NCH(CH₃)Ph), 7.28 (m, 10 H, aromatics); ¹³C NMR (CDCl₃, 75.4 MHz) δ 16.4, 32.0, 33.5, 34.5, 39.8, 40.6, 41.4, 50.6, 126.0, 126.3, 127.2, 127.3, 128.4, 128.8, 141.0, 175.3; $[\alpha]_D = +36.6^\circ$ ($c = 0.72$, MeOH); MS, m/e 307 (M⁺), 105 (100); HRMS calcd for C₂₁H₂₅NO 307.1935, found 307.1929. [*R*-(*R**,*R**)]-14 (14b): ¹H NMR (CDCl₃, 300 MHz) δ 0.95 (m, 1 H), 1.15 (s, 3 H, C₅ methyl), 1.42 (d, $J = 6.7$ Hz, 3 H, -NCH(CH₃)Ph), 1.76 (dd, $J = 14.8, 11.0$, 1 H), 2.04 (m, 1 H), 2.35 (m, 1 H), 2.59 (m, 2 H, -C(O)CH₂-), 3.09 (m, 2 H, -N(R)CH₂-), 6.04 (q, $J = 6.7$ Hz, 1 H, -NCH(CH₃)Ph), 7.30 (m, 10 H, aromatics); ¹³C NMR (CDCl₃, 75.4 MHz): δ 15.7, 29.6, 33.3, 34.3, 39.2, 39.9, 40.3, 50.5, 125.9, 127.2, 127.5, 128.1, 128.3, 128.5, 140.6, 175.1; $[\alpha]_D = +98.9^\circ$ ($c = 0.53$, MeOH).

Hexahydro-4,6-dimethyl-1-(1-phenylethyl)-2H-azepin-2-one (19). [*R*-(*R**,*R**,*S**)]-19 (19a): IR (CDCl₃) 2960, 2920, 1630, 1480, 1447, 1420, 910, 730, 700 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 0.80–1.10 (obscured m, 1 H), 0.86 (d, $J = 6.8$, 3 H, -CH(CH₃)-), 1.03 (d, 6.7 Hz,

3 H, -CH(CH₃)-, 1.49 (d, $J = 7.1$ Hz, 3 H, NCH(CH₃)Ph), 1.64 (m, 1 H), 1.87 (apparent br d, 2 H), 2.46 (m, 2 H, -C(O)CH₂-), 2.72 (br d, $J = 14.6$ Hz, 1 H, -N(R)CH₂-), 2.82 (br dd, $J = 14.6, 9.6$ Hz, 1 H, -N(R)CH₂-), 6.07 (q, $J = 7.1$ Hz, 1 H, NCH(CH₃)Ph), 7.30 (m, 5 H, aromatics); ¹³C NMR (CDCl₃, 75.4 MHz) δ 16.5, 20.7, 24.5, 30.1, 35.2, 45.1, 48.0, 50.2, 50.5, 127.0, 127.1, 127.8, 128.2, 128.3, 141.0, 174.1; $[\alpha]_D = +113.2^\circ$ ($c = 1.00$, MeOH). MS, m/e 245 (M⁺), 105 (100); HRMS calcd for C₁₆H₂₃NO 245.1780, found 245.1783. [*R*-(*R**,*S**,*S**)]-19 (19b): ¹H NMR (CDCl₃, 300 MHz) δ 0.48 (d, $J = 6.2$ Hz, 3 H, -CH(CH₃)-, 0.79 (m, 1 H), 1.00 (d, $J = 6.7$ Hz, 3 H, -CH(CH₃)-, 1.05 (obscured m, 1 H), 1.51 (d, $J = 7.0$ Hz, 3 H, NCH(CH₃)Ph), 1.60–2.25 (m, 2 H), 2.45 (m, 2 H, -C(O)CH₂-), 2.85 (m, 2 H, -N(R)CH₂-), 6.06 (q, $J = 6.8$ Hz, 1 H, -NCH(CH₃)Ph), 7.30 (m, 5 H, aromatics); ¹³C NMR (CDCl₃, 75.4 MHz) δ 15.5, 20.5, 24.5, 30.1, 33.9, 45.5, 47.9, 49.5, 50.6, 127.0, 127.2, 127.5, 127.9, 128.3, 128.4, 174.1; $[\alpha]_D = +147.4^\circ$ ($c = 0.61$, MeOH).

Decahydro-1-(1-phenylethyl)isoquinolin-3-one (24). [*S*-(*R**,*4aR**,*8aR**)]-24 (24a): mp 88 °C, $[\alpha]_D = -101.7^\circ$ ($c = 0.97$, MeOH); IR (CHCl₃) 2990, 2920, 2840, 1605, 1487, 1445, 700 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 1.31–1.81 (complex, 8 H), 1.48 (d, $J = 7.1$ Hz, 3 H, NCH(CH₃)Ph), 1.83 (m, 1 H), 2.09 (m, 1 H), 2.41 (dd, $J = 18.0, 6.1$ Hz, 1 H, -C(O)CH₂-), 2.52 (dd, $J = 18.0, 7.5$ Hz, 1 H, -C(O)CH₂-), 2.69 (dd, $J = 12.4, 5.1$ Hz, 1 H, -N(R)CH₂-), 3.12 (dd, $J = 12.0, 6.8$ Hz, 1 H, -N(R)CH₂-), 6.16 (q, $J = 7.1$ Hz, 1 H, NCH(CH₃)Ph), 7.30 (m, 5 H, aromatics); ¹³C NMR (CDCl₃, 75.4 MHz) δ 15.1, 22.7, 23.0, 26.4, 28.4, 32.2, 32.7, 35.5, 43.8, 49.5, 127.2, 127.2, 127.4, 128.4, 140.4, 169.1. Anal. Calcd for C₁₇H₂₃NO: C, 79.33; H, 9.01; N, 5.44. Found: C, 79.00; H, 9.30; N, 5.70. [*S*-(*R**,*4aS**,*8aS**)]-24 (24b): $[\alpha]_D = -106^\circ$ ($c = 2.07$, MeOH); ¹H NMR (CDCl₃, 300 MHz) δ 1.12 (m, 1 H), 1.42 (m, 7 H), 1.48 (d, $J = 7.3$ Hz, 3 H, NCH(CH₃)Ph), 1.85 (m, 1 H), 2.09 (m, 1 H), 2.45 (m, 2 H, -C(O)CH₂-), 2.67 (ddd, $J = 12.4, 4.8, 1.8$ Hz, 1 H, -N(R)CH₂-), 3.11 (dd, $J = 12.4, 5.4, 1.9$ Hz, 1 H, -N(R)CH₂-), 6.16 (q, $J = 7.3$ Hz, 1 H, NCH(CH₃)Ph), 7.28 (m, 5 H, aromatics); ¹³C NMR (CDCl₃, 75.4 MHz) δ 15.1, 21.6, 23.8, 25.6, 28.7, 31.9, 33.3, 34.4, 44.4, 49.5, 127.2, 127.4, 128.3, 128.4, 140.4, 169.2.

(4a*S*,8a*R*)-Decahydroisoquinolin-3-one (25). Liquid ammonia (20 mL) was condensed into a 100-mL two-necked flask to which 24a (0.504 g, 1.96 mmol) was added dissolved in a minimum of THF. Small pieces of sodium metal were added to the solution until it turned deep blue. The solution was stirred for 1 min and quenched with ammonium chloride. After the solvent evaporated, the residue was partitioned between CH₂Cl₂ and H₂O, the aqueous layer extracted with CH₂Cl₂, and the organic layers combined, washed with brine, and dried with Na₂SO₄. Filtration, concentration and column chromatography (2% MeOH/CHCl₃) gave 25 (0.277 g, 92% yield). Recrystallization from diethyl ether afforded an analytical sample as white crystalline powder, mp 61–62 °C; $[\alpha]_D = -30.9^\circ$ ($c = 1.02$, MeOH); ¹H NMR (CDCl₃) δ 1.31–1.67 (m, 8 H), 2.01 (m, 1 H), 2.12 (m, 1 H), 2.36 (m, 2 H), 3.32 (m, 2 H), 6.85 (br s, 1 H, NH); ¹³C NMR (CDCl₃, 75.4 MHz) δ 22.9, 23.6, 26.7, 28.9, 32.5, 34.6, 45.0, 172.8. Anal. Calcd for C₉H₁₅NO: C, 70.55; H, 9.87; N, 9.14. Found: C, 70.38; H, 10.25; N, 9.47.

(4a*S*,8a*R*)-3-(3'-Oxo-2'-decahydroisoquinolinyl)acetylindole (26). A 25-mL two-necked round-bottom flask equipped with a gas inlet tube, a septum cap, and a magnetic stirbar was charged with sodium hydride (ca. 42 mg, 0.87 mmol, 50% in mineral oil). The solid was washed three times with pentane to remove the mineral oil, and the solid residue was suspended in 2 mL of DMF. To this suspension was added at 0 °C lactam 25 (0.045 g, 0.29 mmol, dissolved in a minimum of dry DMF) via syringe, followed by 3-(chloroacetyl)indole⁴⁴ (0.095 g, 0.49 mmol), and the reaction was allowed to stir overnight, gradually warming up to room temperature. The mixture was quenched by addition of 1 mL of water and partitioned between water and CH₂Cl₂, and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were washed with water (3 × 5 mL) and dried with MgSO₄. Concentration followed by chromatography (2% MeOH/CHCl₃) afforded 26 (0.044 g, 48% yield) as an oil: ¹H NMR (CDCl₃, 300 MHz) δ 1.41 (complex, 8 H), 2.12 (m, 2 H), 2.45 (m, 2 H), 3.36 (m, 2 H), 4.34 (AB q, $J = 16.6$ Hz, $\Delta\nu = 28.2$ Hz, 2 H, -C(O)CH₂-), 7.12–8.22 (complex, 6 H, aromatics); ¹³C NMR (CDCl₃, 75.4 MHz) δ 22.7, 23.2, 26.8, 28.2, 32.8, 32.9, 35.5, 51.8, 53.6, 112.2, 114.8, 121.7, 122.4, 123.4, 125.4, 132.5, 136.6, 170.6, 189.2; MS, m/e 311 (M⁺ + 1), 310 (M⁺), 159, 144 (100), 116, 89, 67, 56; HRMS calcd for C₁₉H₂₂N₂O₂ 310.1681, found 310.1690.

(4a*S*,8a*R*)-3-(3'-Oxo-2'-decahydroisoquinolinyl)ethylindole (28). Sodium borohydride (0.038 g, 1.00 mmol) was added to a solution of ketone 26 (0.158 g, 0.51 mmol) dissolved in 2 mL of ethanol containing a drop of water at room temperature, and the reaction mixture was stirred at room temperature for 7.5 h. The reaction mixture was partitioned between ethyl acetate and 10% acetic acid solution, and the aqueous layer was extracted with ethyl acetate. The combined organic

layers were washed with sodium bicarbonate and brine and dried with MgSO_4 . Concentration gave a light yellow oil that was dissolved in 5 mL of ethanol, and 0.15 mL of a 0.0354 M solution of HClO_4 and a spatula of 10% Pd/C were added. The mixture was hydrogenated at room temperature and 1 atm of pressure for 14 h. The mixture was filtered, and the filtrate was washed with EtOH and concentrated. The residue was partitioned between ethyl acetate and saturated sodium bicarbonate, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine and dried with Na_2SO_4 . Concentration followed by chromatography (2% MeOH/ CHCl_3) afforded compound **28** (0.068 g, 45% yield): $^1\text{H NMR}$ (CDCl_3 , 300 MHz) δ 1.20–1.60 (complex, 8 H), 1.97 (m, 2 H), 2.38 (m, 2 H), 3.17 (complex, 4 H), 3.65 (m, 2 H), 7.11–8.20 (complex, 6 H, aromatics); $^{13}\text{C NMR}$ (CDCl_3 , 75.4 MHz) δ 23.0, 23.1, 26.5, 28.3, 32.5, 32.9, 33.0, 35.2, 48.1, 51.1, 111.2, 118.8, 119.3, 121.9, 122.0, 122.1, 127.6, 136.3, 169.2.

(-)-Alloyohimbane (**29**). Oxyphosphorous trichloride (0.024 g, 0.16 mmol) was added to a solution of lactam **28** (0.039 g, 0.13 mmol) dissolved in benzene (3 mL). The reaction mixture was refluxed overnight and then concentrated, and the residue was dissolved in ca. 1 mL of methanol. A spatula of sodium borohydride was added and the solution allowed to stir for ca. 10 min. Glacial acetic acid (5 drops) was added, the reaction mixture was partitioned between ethyl acetate and water, and the aqueous layer was reextracted with ethyl acetate. The combined organic layers were washed with NaHCO_3 and brine and dried with MgSO_4 . Concentration followed by chromatography (2% MeOH/ CH_2Cl_2) afforded (-)-alloyohimbane (**29**)^{46,47} (0.022 g, 59% yield). Recrystallization from diethyl ether/acetone gave off-white needles: mp 155–156 °C; $[\alpha]_D = -164^\circ$ ($c = 0.5$, pyridine) (lit.⁴⁷ mp 156 °C; $[\alpha]_D -166^\circ$ ($c = 0.5$, pyridine)); IR (neat) 3479, 2920, 2840, 2800, 2750 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3 , 500 MHz) δ 1.19–1.47 (complex, 4 H), 1.55–1.74 (complex, 5 H), 1.87–2.01 (complex, 5 H), 2.68 (m, 1 H), 2.77 (dd, $J = 11.2$, 1.7 Hz, 1 H), 2.87 (m, 2 H), 3.19 (m, 1 H), 7.01–7.69 (m, 6 H, aromatics); $^{13}\text{C NMR}$ (CDCl_3 , 125 MHz) δ 20.8, 21.8, 26.5, 26.6, 30.5, 31.6, 34.8, 36.7, 53.4, 60.5, 62.0, 108.2, 110.7, 118.1, 119.3, 121.2, 127.5, 135.6, 135.9.

General Procedure for Synthesis of Removal of *N*-Phenylethyl Substituents. Ammonia was condensed into a two-necked flask that contained the substrate dissolved in a minimum amount of THF or ether. Small pieces of sodium metal were added to the reaction mixture until a deep blue color persisted for 15 min, at which time it was quenched with solid ammonium chloride and partitioned between CH_2Cl_2 and H_2O . The reaction mixture was extracted with CH_2Cl_2 and dried with NaSO_4 . The product was purified by column chromatography with 2% MeOH/ CHCl_3 as eluent.

(*S*)-Hexahydro-5-phenyl-2*H*-azepin-2-one (**30**). According to the general procedure, α *S*-**13a** (0.136 g, 0.46 mmol) was reacted to afford **30** as colorless crystals (0.075 g, 85% yield): mp 194–196 °C; $[\alpha]_D = -45.3^\circ$ ($c = 0.73$ MeOH); $^1\text{H NMR}$ (CDCl_3 , 300 MHz) δ 1.67–1.94 (m, 2 H), 2.09 (m, 2 H), 2.50–2.82 (m, 3 H), 3.39 (m, 2 H), 6.99 (m, 1 H, -CONH-), 7.21 (m, 5 H, aromatics); $^{13}\text{C NMR}$ (CDCl_3 , 75.4 MHz) δ 30.6, 35.9, 37.4, 42.1, 48.8, 126.5, 126.7, 128.6, 146.4, 178.8. Anal. Calcd for $\text{C}_{12}\text{H}_{15}\text{NO}$: C, 76.16; H, 7.99; N, 7.40. Found: C, 76.50; H, 8.19; N, 7.21.

(*R*)-Hexahydro-5-methyl-2*H*-azepin-2-one. According to the general procedure, α *R*-**15a** (1.372 g, 5.93 mmol) was reacted to obtain the title compound as a colorless oil (0.588 g, 78% yield):⁵⁷ $[\alpha]_D +18.0^\circ$ ($c = 1.40$ MeOH); IR (CCl_4) 3205, 2950, 2920, 2860, 1665, 1350 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3 , 300 MHz) δ 0.97 (d, $J = 6.6$ Hz, 3 H, - $\text{CH}(\text{CH}_3)$ -), 1.25 (m, 2 H), 1.64 (m, 1 H, - $\text{CH}(\text{CH}_3)$ -), 1.79 (m, 2 H), 2.41 (m, 2 H, - $\text{C}(\text{O})\text{CH}_2$ -), 3.22 (m, 2 H, - NHCH_2 -), 7.08 (m, 1 H, -CONH-); $^{13}\text{C NMR}$ (CDCl_3 , 75.4 MHz) δ 22.9, 31.1, 35.3, 36.7, 37.7, 41.4, 179.1; MS, m/e 127 (M^+), 110, 99, 91, 69, 55 (100).

(*R*)-Hexahydro-5-ethyl-2*H*-azepin-2-one. According to the general procedure, α *R*-**16a** (0.213 g, 0.86 mmol) was reacted to obtain the title compound as a colorless crystalline solid (0.100 g, 81% yield):⁵⁸ mp 61–62 °C; $[\alpha]_D = +14.3^\circ$ ($c = 0.46$ MeOH); IR (CCl_4) 3205, 2970, 2920, 2510, 1668, 1565 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3 , 300 MHz) δ 0.90 (t, $J = 7.5$ Hz, 3 H, CH_2CH_3), 1.21 (m, 2 H), 1.31 (q, $J = 7.5$ Hz, 2 H, CH_2CH_3), 1.44 (m, 1 H, - $\text{CH}(\text{C}_2\text{H}_5)$ -), 1.84 (m, 2 H), 2.45 (m, 2 H, - $\text{C}(\text{O})\text{CH}_2$ -), 3.22 (m, 2 H, - NHCH_2 -), 7.04 (m, 1 H, -CONH-); $^{13}\text{C NMR}$ (CDCl_3 , 75.4 MHz) δ 11.3, 28.8, 29.7, 35.3, 35.4, 41.7, 43.4, 179.2; MS, m/e 142 ($\text{M}^+ + 1$), 124, 83, 55, 41 (100).

(*R*)-Hexahydro-5-(1,1-dimethylethyl)-2*H*-azepin-2-one. According to the general procedure, α *R*-**2a** (0.146 g, 0.53 mmol) was reacted to obtain the title compound as a crystalline solid (0.068 g, 76% yield):⁵⁸ mp 151–152 °C; $[\alpha]_D = +14.7^\circ$ ($c = 0.50$ MeOH); IR (CCl_4) 3205,

2950, 2860, 1665, 1362, 1350 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3 , 300 MHz) δ 0.89 (s, 9 H, $\text{C}(\text{CH}_3)_3$), 1.25 (m, 3 H), 1.95 (m, 2 H), 2.46 (m, 2 H, - $\text{C}(\text{O})\text{CH}_2$ -), 3.22 (m, 2 H, - NHCH_2 -), 7.37 (m, 1 H, -CONH-); $^{13}\text{C NMR}$ (CDCl_3 , 75.4 MHz) δ 23.9, 27.6, 30.6, 33.2, 35.7, 42.1, 52.3, 179.4; MS, m/e 169 (M^+), 154, 141, 98, 84, 57 (100), 41.

(4*R*,6*S*)-Hexahydro-4,6-dimethyl-2*H*-azepin-2-one. According to the general procedure, α *R*-**19a** (0.227 g, 0.92 mmol) was reacted to obtain the title compound as a colorless crystalline solid (0.123 g, 94% yield):⁵⁸ mp 134–136 °C; $[\alpha]_D = -15.1^\circ$ ($c = 0.57$ MeOH); IR (CCl_4) 3201, 2950, 2910, 2900, 1665, 1450 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3 , 300 MHz) δ 0.90 (d, $J = 6.8$ Hz, 3 H, - $\text{CH}(\text{CH}_3)$ -), 1.02 (d, $J = 6.6$ Hz, 3 H, - $\text{CH}(\text{CH}_3)$ -), 1.71 (m, 1 H, - $\text{CH}(\text{CH}_3)$ -), 1.88 (m, 3 H), 2.25 (dq, $J = 13.5$, 1.7 Hz, 1 H, - $\text{C}(\text{O})\text{CH}_2$ -), 2.43 (dd, $J = 13.5$, 11.2 Hz, 1 H, - $\text{C}(\text{O})\text{CH}_2$ -), 3.01 (m, 2 H, - NHCH_2 -), 7.49 (m, 1 H, -CONH-); $^{13}\text{C NMR}$ (CDCl_3 , 75.4 MHz) δ 20.6, 24.6, 29.8, 35.0, 44.4, 48.5, 49.0, 178.0, MS, m/e 141 (M^+), 112, 97, 69 (100), 41.

(*S*)-Hexahydro-5-methyl-5-phenyl-2*H*-azepin-2-one. According to the general procedure, α *R*-**14a** (0.141 g, 0.46 mmol) was reacted to obtain the title compound as a colorless crystalline solid (0.0762 g, 82% yield): mp 134–135 °C; $[\alpha]_D = +24.6^\circ$ ($c = 0.79$ MeOH); IR (CCl_4) 3205, 2960, 2930, 1670, 1441, 700 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3 , 300 MHz) δ 1.25 (s, 3 H, C_5 methyl), 1.71 (m, 2 H), 2.38 (complex, 4 H), 3.18 (m, 2 H, - NHCH_2 -), 7.15 (m, 1 H, -CONH-), 7.33 (m, 5 H, aromatics); $^{13}\text{C NMR}$ (CDCl_3 , 75.4 MHz) δ 31.9, 32.4, 34.0, 38.5, 40.6, 41.2, 126.1, 126.1, 126.3, 128.7, 146.7, 179.0; MS, m/e 203 (M^+), 131, 117, 85 (100), 84; HRMS calcd for $\text{C}_{13}\text{H}_{17}\text{NO}$ 203.1310, found 203.1308.

(*R*)-Hexahydro-5-hydroxy-2*H*-azepin-2-one. According to the general procedure, α *R*-**17a** (0.218 g, 0.72 mmol) was reacted to obtain the title compound as a colorless crystalline solid (0.036 g, 39% yield):⁵⁹ mp 130–132 °C; $[\alpha]_D = +18.9^\circ$ ($c = 0.46$ MeOH); IR (CH_2Cl_2) 3600, 3410, 2900, 2970, 2930, 1660, 890, 725 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3 , 300 MHz) δ 1.62 (m, 3 H), 1.93 (m, 2 H), 2.31 (dd, $J = 14$, 12 Hz, 1 H, - $\text{CH}_2\text{C}(\text{O})$ -), 2.62 (dd, $J = 14$, 9.8 Hz, 1 H, - $\text{CH}_2\text{C}(\text{O})$ -), 3.09 (ddd, $J = 15$, 9, 1 Hz, 1 H, - NHCH_2 -), 3.34 (m, 1 H, - NHCH_2 -), 3.89 (m, 2 H, -NH- and OH); $^{13}\text{C NMR}$ ($\text{MeOH}-d_4$, 75.4 MHz) δ 32.6, 33.7, 39.6, 39.9, 72.8, 109.1; MS, m/e 130 ($\text{M}^+ + 1$), 129 (M^+), 101, 83, 72, 56 (100), 43. Anal. Calcd for $\text{C}_6\text{H}_{11}\text{NO}_2$: C, 55.79; H, 8.58; N, 10.84. Found: C, 55.75; H, 8.45; N, 10.70.

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Registry No. (\pm)-**19**, 116837-82-2; (\pm)-**16**, 126785-26-0; (\pm)-**1c**, 126785-27-1; (\pm)-**1d**, 126785-28-2; α *R*-**2a**, 126785-64-6; α *R*-**2b**, 126785-65-7; (\pm)-**6a**, 126785-29-3; (\pm)-**6b**, 126785-30-6; (\pm)-**6c**, 126785-31-7; (\pm)-**6d**, 126785-32-8; (\pm)-**7a**, 126785-33-9; (\pm)-**7b**, 126785-34-0; (\pm)-**7c**, 126785-35-1; (\pm)-**7d**, 126785-36-2; (\pm)-**8a**, 126785-37-3; (\pm)-**8b**, 126785-38-4; (\pm)-**8c**, 126785-39-5; (\pm)-**8d**, 126785-40-8; (\pm)-**9a**, 126785-41-9; (\pm)-**9b**, 126785-42-0; (\pm)-**9c**, 126786-61-6; (\pm)-**9d**, 126785-43-1; (\pm)-**10a**, 126694-32-4; (\pm)-**10b**, 126785-44-2; (\pm)-**11a**, 126785-45-3; (\pm)-**11b**, 126785-46-4; (\pm)-**11c**, 126785-47-5; (\pm)-**11d**, 126785-48-6; (\pm)-**12a**, 126785-49-7; (\pm)-**12b**, 126785-50-0; (\pm)-**12c**, 126785-51-1; (\pm)-**12d**, 126785-52-2; α *S*-**13a**, 116837-84-4; α *S*-**13b**, 126785-66-8; α *R*-**14a**, 126785-69-1; α *R*-**14b**, 126786-62-7; α *R*-**15a**, 126785-60-2; α *R*-**15b**, 126785-61-3; α *R*-**16a**, 126785-62-4; α *R*-**16b**, 126785-63-5; α *R*-**17a**, 126785-67-9; α *R*-**17b**, 126785-68-0; α *R*-**18a**, 126694-34-6; α *R*-**18b**, 126694-35-7; α *R*-**19a**, 126785-70-4; α *R*-**19b**, 126785-71-5; **20**, 5689-04-3; **21**, 25886-63-9; (\pm)-**22a**, 126785-53-3; (\pm)-**22b**, 126785-54-4; (\pm)-**22c**, 126785-55-5; (\pm)-**22d**, 126785-56-6; (\pm)-**23a**, 126694-33-5; (\pm)-**23b**, 126785-57-7; (\pm)-**23c**, 126785-58-8; (\pm)-**23d**, 126785-59-9; **24a**, 121696-08-0; **24b**, 121696-09-1; **25**, 121786-13-8; **26**, 121696-10-4; **28**, 121786-14-9; **29**, 483-26-1; **30**, 116750-05-1; (\pm)- α MBA, 618-36-0; 4-*tert*-butylcyclohexanone, 98-53-3; 4-methylcyclohexanone, 589-92-4; 4-ethylcyclohexanone, 5441-51-0; 4-phenylcyclohexanone, 4894-75-1; 4-(phenylmethoxy)cyclohexanone, 2987-06-6; ethyl 4-oxocyclohexanecarboxylate, 17159-79-4; 4-methyl-4-phenylcyclohexanone, 18932-33-7; *cis*-3,5-dimethylcyclohexanone, 7214-52-0; 3-(chloroacetyl)indole, 28755-03-5; (*R*)-hexahydro-5-methyl-2*H*-azepin-2-one, 126785-72-6; (*R*)-hexa-

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hydro-5-ethyl-2*H*-azepin-2-one, 126694-36-8; (*R*)-hexahydro-5-(1,1-dimethylethyl)-2*H*-azepin-2-one, 126872-02-4; (4*R*,6*S*)-hexahydro-4,6-dimethyl-2*H*-azepin-2-one, 126785-73-7; (*R*)-hexahydro-5-methyl-5-phenyl-2*H*-azepin-2-one, 126694-37-9; (*R*)-hexahydro-5-hydroxy-2*H*-azepin-2-one, 126694-38-0.

Supplementary Material Available: Experimental details of

crystal data, intensity measurements, and structure solution and refinement, tables of fractional coordinates and equivalent isotropic thermal parameters, anisotropic thermal parameters, bond distances, bond angles, and torsion angles, and PLUTO representations of **11b** and **23a** (26 pages). Ordering information is given on any current masthead page.

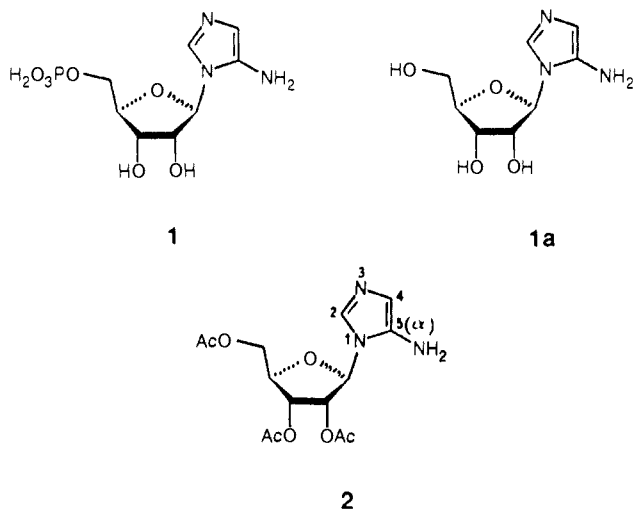
Nonenzymatic Synthesis and Properties of 5-Aminoimidazole Ribonucleotide (AIR). Synthesis of Specifically ¹⁵N-Labeled 5-Aminoimidazole Ribonucleoside (AIRs) Derivatives

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Abstract: The chemical synthesis of 5-aminoimidazole ribonucleoside (AIRs) and 5-aminoimidazole ribonucleotide (AIR) is described. The syntheses of specifically ¹⁵N-labeled derivatives of AIRs are also described. These provide, by ¹⁵N NMR determinations, unequivocal structure assignment of rearrangement products and of loci of protonation.

5-Amino-1-(β-D-ribofuranosyl)imidazole 5'-monophosphate, or 5-aminoimidazole ribonucleotide (AIR, **1**), is the precursor of the purine ribonucleotides *in vivo*¹ in both prokaryotic² and eukaryotic³ systems. It is also the biosynthetic precursor of the pyrimidine portion of thiamin (vitamin B₁) in certain prokaryotic organisms.⁴⁻⁷ Because of the pivotal role of AIR, it is a requisite for answering fundamental questions concerning these biosynthetic pathways, yet it has not been available in sufficient supply, well characterized,⁸ to facilitate the examination of all of the biochemical and physicochemical properties that one would desire to investigate. Its availability until the present has depended upon phosphorylation of an enzymatically prepared precursor.^{3,9-11} Moreover, the chemistry of AIR, the corresponding ribonucleoside (AIRs, **1a**), and related compounds¹² has been complicated by their often-mentioned lability during routine chromatographic purification procedures, concentration of solutions, or even dry storage at ambient temperature.^{3,6,13}



We have recently described a simple chemical (nonenzymatic) synthesis of 5-amino-1-(β-D-ribofuranosyl)imidazole (AIRs, **1a**).^{14a}

and further details are provided here. The compound 5-amino-1-(β-D-ribofuranosyl)imidazole-4-carboxamide (AICARs) was saponified in 6 M NaOH according to the method of Srivastava et al.^{15,16} to yield sodium 5-amino-1-(β-D-ribofuranosyl)imidazole-4-carboxylate (CAIRs, sodium salt). The strategy that permitted the isolation of pure AIRs was to release 5-amino-1-(β-D-ribofuranosyl)imidazole-4-carboxylic acid and effect its decarboxylation in a pH 4.8 aqueous NaOAc/HOAc buffer with N₂ bubbling through and *not* to use pH 7.0 conditions.

We were interested in extending the chemical synthesis of AIRs (**1a**) to 5-amino-1-(β-D-ribofuranosyl)imidazole 5'-phosphate (AIR, **1**)^{3,9-11} so as to make this compound readily available in pure form and well characterized.⁸ Compound **1a**, unprotected, was phosphorylated with pyrophosphoryl chloride in *m*-cresol¹⁷ at 0 °C under argon to give 5-amino-1-(β-D-ribofuranosyl)-

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