Stereoselective Synthesis of 4-Piperidone and 4-Aminotetrahydropyridine Derivatives by the Imino Diels-Alder Reaction of 2-Amino-1,3-butadienes

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2-Amino-4-(alkoxymethyl)-1,3-butadienes react smoothly with nonactivated aldimines derived from aromatic aldehydes in the presence of $ZnCl_2$ as Lewis acid giving rise, with good yields and very high stereoselectivity, to substituted 4-aminotetrahydropyridines which upon hydrolysis yield 4-piperidone derivatives. Moreover, the stereochemistry of the cyclization process depends on the nature of the N-substituent of the imine.

Among six-membered azaheterocycles, 4-piperidones are important synthetic intermediates, particularly in the preparation of alkaloids and medicinal agents.[1] The presence of a keto functionality facilitates the introduction of other substituents on to the piperidine ring.[2]

The most widely-used methods for the synthesis of 4-piperidones are the Dieckmann cyclization of aminodicarboxylate esters and the condensation of carbonyl compounds with ammonia by a Mannich reaction.[3] One general problem associated with these methods is their ability to control stereochemistry when substituted 4-piperidones are the desired products. As a consequence, a stereoselective method for the preparation of substituted 4-piperidones would be an advance in the area of heterocyclic synthesis.

By comparison with the formation of six-membered carbocycles, we think that one of the most direct and stereoselective routes to piperidine derivatives might be the imino Diels-Alder reaction.[4] In spite of this, and because of the low reactivity of readily accessible simple imines, this strategy has scarcely been explored. Most of the reported cases have been limited to the use of imines carrying electron-withdrawing substituents such as acyl, tosyl, and triflate groups. However, Danishefsky et al.[5] have demonstrated that, by using a Lewis acid ($ZnCl_2$) catalyst, imines react smoothly with electron-rich dienes (e.g., Danishefsky's diene). Since that report, a few examples of reactions between electron-rich dienes and simple imines have appeared in the literature.[6] The cyclization reactions probably involve an intermediate immonium salt which reacts highly regio- and stereoselectively with the activated diene and usually is highly dependent on the reaction conditions.[7]

In a preliminary report,[8] we described the first cycloaddition reaction between imines derived from aromatic aldehydes and a 2-amino-1,3-butadiene in the presence of $ZnCl_2$. As an extension of our earlier work, we set out to investigate the scope and generality of this process. In this paper, we report the $ZnCl_2$-catalyzed reactions of some arylimines with 2-amino-1,3-butadienes[9] that results in a highly stereoselective method for the synthesis of substituted 2-aryl-4-piperidones and 2-aryl-4-aminotetrahydropyridines.

Results and Discussion

2-Morpholinobutadienes **1** react with imines derived from aromatic aldehydes **2** in the presence of $ZnCl_2$ (molar ratio 1:1.5:1.5) to lead to 4-morpholinotetrahydropyridines **3** or **4** in high yield in a totally stereoselective manner (Scheme I). The stereochemistry of the resulting cycloadducts is dependent on the nature of the imine used. Thus, when the imine is derived from aromatic amines (R^1 = Ar), only trans diastereoisomer **3** is observed in the crude reaction mixture after washing with a saturated solution of $NaHCO_3$. On the other hand, when imine **2** is derived from a silylamine (R^1 = Me_3Si), the sense of diastereoselectivity is reversed as only the cis 2,4-disubstituted piperidones **4** were produced after extractive isolation with saturated $NaHCO_3$. The relative stereochemistry of adducts **3** has been determined by comparing their ^1H and ^{13}C NMR data with **3a**, whose structure has been determined by a single-crystal X-ray analysis.[8] The structures for the corresponding hydrolyzed derivatives **5** and **6** have also been assigned by ^1H and ^{13}C NMR

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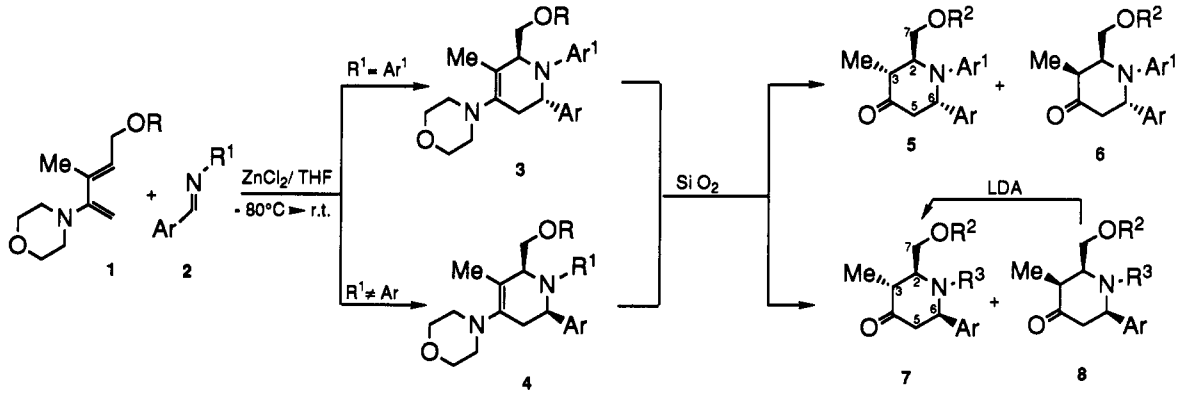
Scheme I



R^1=$SiMe_3$, R^3=H
R= $SiMe_3$, R^2= $SiMe_3$ or H

Table I. Reaction of 2-Morpholinobuta-1,3-dienes 1 with Imines 2 Promoted by $ZnCl_2$

					molar ratio,[c] %				
compds 5, 6, 7, 8	Ar	Ar^1	R^2	R^3	5	6	7	8	yield,[d] %
a	Ph	Ph	Me		71	29			88
b	2-furyl	4-$MeOC_6H_4$	Me		76	21			79
c	Ph	4-$MeOC_6H_4$	$SiMe_3$		11	89			87
d[a,b]	Ph		H	H			78	22	79
e[a,b]	2-furyl		H	H			71	29	71
f[b]	2-thienyl		Me	H			64	36	80
g[b]	3-pyridyl		Me	H			59	41	62
h	Ph		$SiMe_3$	Bn			61	39	85
i[b]	2-furyl		Bn	H			72	28	73
j	Ph		Me	Bu			>95		65
k[b]	2-BrPh		Me	H			>95		71

[a] R = $SiMe_3$. [b] R^1 = $SiMe_3$. [c] Deduced from the integrated ^{1}H-NMR spectra of the reaction mixture of epimers. [d] Yield of the reaction mixture of epimers.

spectroscopy. The structures of **4** were inferred from the hydrolyzed compounds **7**.

Hydrolysis of **3** and **4** was accomplished by passing them through a short SiO_2 column, giving rise to a mixture of C_3 epimers of 6-aryl-4-piperidones **5**, **6** and **7**, **8**, respectively, in good yield (Scheme I, Table I). The major diastereoisomers are conveniently isolated by flash chromatography. On the other hand, the mixture of **7** and **8** can be converted exclusively to epimer **7** by treating the mixture with LDA. A similar epimerization process does not take place for the mixture of **5** and **6** by treatment either with acidic or basic solutions.

The relative configuration of the asymmetric centers of piperidones **7** was deduced by ^{1}H NMR analysis. Large three-bond coupling constants between H_2 and H_3 and H_5 and H_6 unequivocally shows that all the substituents are in equatorial positions (typically for **7d**, H_6 appears as a dd at 3.42 ppm, J_{H5a-H6} = 9.2 Hz and J_{H5b-H6} = 5.8 Hz, and H_2 appears as a ddd at 2.62 ppm J_{H2-H3} = 10.4 Hz, J_{H2-H7a} = 2.7 Hz, J_{H2-H7b} = 5.9 Hz).

The trans relationship of the substituents at C_2 and C_6 for piperidones **5** and **6** was assigned by single-crystal X-ray analysis of the intermediate tetrahydropyridine **3a**. The arrangement of the methyl group was determined by NOE experiments (stationary phase) performed using **5a** as a model (Figure 1). Thus, saturation of one of the hydrogens of the methylene group (H_{7a}) produces a positive NOE in H_{7b} and H_6 which points to an axial disposition of the methoxymethyl group and an equatorial arrangement of the aromatic ring. Moreover, when the signal of the methyl group is saturated, positive NOEs are observed for H_{5b}, H_2, and H_3, and there is no positive NOE for the methylenic

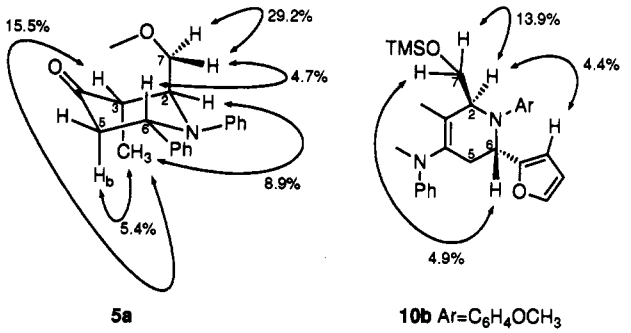


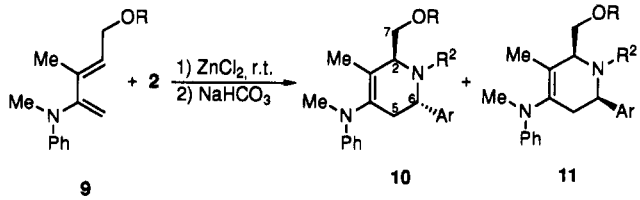
Figure 1. Some selected NOEs for **5a** and **10b**.

hydrogens at C_7, indicating a trans relationship between $-CH_3$ and $-CH_2OCH_3$. The stereochemistry for the other 4-piperidones **5** and **6** can be easily deduced by comparison of the coupling constants with those from **5a** and **6a**.

4-(*N*-methylbenzeneamino)-6-aryltetrahydropyridines can be easily obtained in this reaction, when 2-(*N*-methylbenzeneamino)-1,3-butadienes are used in place of 2-morpholino-1,3-butadienes. Therefore, when 2-(*N*-methylbenzeneamino)-1,3-butadienes **9** react with imines **2** under the same reaction conditions as above, 4-(arylamino)tetrahydropyridines **10** and **11** are obtained in a very high yield and with good to excellent stereoselectivity (Scheme II, Table II) after extraction with a saturated solution of $NaHCO_3$. Due to the more stable enamine function derived from aromatic amines, compounds **10** and **11** can be easily separated by flash chromatography without hydrolysis occurring.

The structures of tetrahydropyridines **10** were deter-

Scheme II



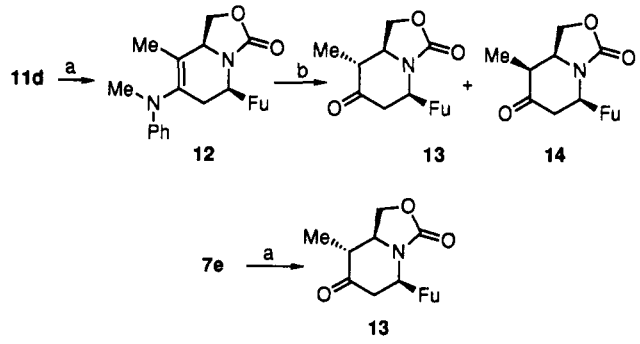
R^1 = $SiMe_3$, R^2=H

Table II. Reaction of 2-(*N*-Methylbenzeneamino)buta-1,3-dienes 9 with Imines 2 Promoted by $ZnCl_2$

compds 10, 11	R	R^2	Ar	molar ratio,[b] % 10	11	yield,[c] %
a	$SiMe_3$	4-$MeOC_6H_4$	Ph	>95		91
b	$SiMe_3$	4-$MeOC_6H_4$	2-furyl	90	10	81
c[a]	$SiMe_3$	H	Ph		>95	78
d[a]	$SiMe_3$	H	2-furyl	12	88	89
e[a]	Me	H	2-thienyl	15	85	80

[a] R^1 = $SiMe_3$. [b] Deduced from the integrated ^{1}H-NMR spectra of the reaction mixture of epimers. [c] Yield of the reaction mixture of epimers.

Scheme III[a]



[a] (a) Triphosgene/NEt_3, THF; (b) HCl (3 N).

mined by the analysis of their ^{1}H NMR spectra and NOE experiments performed on cycloaddition product **10b** (Figure 1). Saturation of the signal of the hydrogens of the methylene group at C_7, which appears as a multiplet, produces positive NOE effects at H_2 and H_6. Moreover, when the signal of H_2 is saturated, a positive NOE is observed for the signal of the higher field hydrogen of the furan ring. These observations indicate the trans relationship of the substituents at C_2 and C_6. The structures of tetrahydropyridines **11** were further deduced from their hydrolysis products.

The hydrolysis of **10** and **11** to the corresponding 4-piperidones **5**, **6** or **7**, **8** is more difficult than for **3** or **4**, and harsher reaction conditions are required. Unfortunately, this leads to a complex reaction mixture containing compounds resulting from a retro-Michael process. This problem can be overcome when R^2 = H (derived from silylimines) by making the corresponding cyclic carbamates.

Thus, treatment of **11d** with triphosgene and triethylamine furnished the bicyclic carbamate **12**, which can be hydrolyzed with 3 N HCl at room temperature to produce in quantitative yield a 70:30 mixture of the epimeric carbonyl derivatives **13** and **14** (Scheme III). These ketones were easily separated by flash chromatography. Bicyclic compound **13** was also prepared from 4-piperidone **7e** by treatment with triphosgene and triethylamine. This

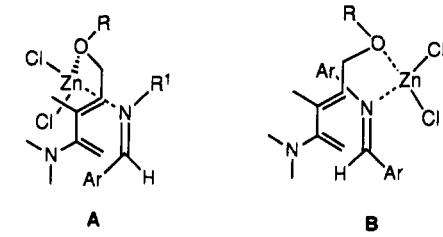


Figure 2.

confirms the structure for the 4-tetrahydropyridine **11**, where the substituents on C_2 and C_6 have a cis relationship.

The stereochemical results of this process are consistent with a diene–imine–Lewis acid complex, such as that shown in Figure 2 (A and B). Assuming that the transition state of this reaction is asynchronic, an important charge separation could be expected. In this situation, electrostatic effects can play a significant role in determining the relative orientation of the diene and the dienophile in the transition state.

From the stereochemistry of the products, we postulate that when the imine is derived from silylamines (Figure 2, **A**) the endo preference for the phenyl ring could be explained on the basis of the endo selectivity typical of the Diels–Alder reactions. On the other hand, when the imine is derived from aromatic amines and aldehydes (Figure 2, **B**) the endo preference of the phenyl ring attached to the imine nitrogen can be attributed to a greater electrostatic interaction beween this ring and the diene moiety, in which a partial positive charge is developed in the transition state.

In conclusion, 6-aryl-4-aminotetrahydropyridine and 6-aryl-4-piperidone derivatives can be easily prepared in a stereoselective way from a [4 + 2] cycloaddition between 4-(alkoxymethyl)-2-amino-1,3-butadienes (prepared from the commercial 3-methyl-2-buten-4-yn-1-ol) and imines derived from aromatic aldehydes. Moreover, the stereoselectivity of the reaction is very high and strongly dependent on the nature of the imine.

Experimental Section

Materials. All reactions were run under Ar or N_2 atmosphere. THF was dried and distilled upon standard procedures before use. Commercial $ZnCl_2$ 1 M etheral solution was purchased from Aldrich Chemical Co. Solvents used in the extractions were distilled prior to use. All other reagents were of the best commercial grade available. Column chromatography was carried out on silica gel 60 (230–400 mesh). All melting points are uncorrected. NMR spectra were recorded at 300 or 200 MHz for ^{1}H and 75 or 50.3 MHz ^{13}C in $CDCl_3$, with tetramethylsilane as an internal standard, and chemical shift values are given in δ (ppm). Mass spectra were obtained by EI (70 eV). IR spectra are given in cm^{-1}.

N-silylimines were prepared according to the method described by Colvin et al.[10] *N*-aryl- and *N*-alkylaldimines were prepared by refluxing in benzene a mixture of the corresponding imine and aldehyde in the presence of a catalytic amount of *p*-toluenesulfonic acid in a system equipped with a Dean-Stark trap.

Preparation of (2*S,6*S**)-2-(Methoxymethyl)-3-methyl-4-morpholino-1,2-diphenyl-1,2,5,6-tetrahydropyridine (3a).**[8] To an ice-cooled solution of *N*-benzylideneaniline (3.26 g, 20 mmol) and $ZnCl_2$ (2.73 g, 20 mmol) in anhydrous THF (60 mL) was slowly added (20 min), under nitrogen, a THF solution (5 mL) of (*E*)-*N*-(4-methoxy-2-methyl-1-methylene-2-butenyl)morpholine (1.96 g, 10 mmol). The mixture was allowed to warm to

(10) Colvin, E. W.; McGarry, D.; Nugent, M. J. *Tetrahedron* **1988**, *44*, 4157.

rt and stirred overnight, the resulting mixture was hydrolyzed with $NaHCO_3$ solution (50 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were ashed with saturated aqueous $NaHCO_3$ (2 × 20 mL) and brine (15 mL), dried over Na_2SO_4, and evaporated under reduced pressure. The excess of *N*-benzylidenaniline was removed by stirring with hexane, and **3a** was recrystallized from ethanol, yield 1.95 g (52%), mp 148–151 °C/ethanol: ^1H NMR ($CDCl_3$, 200 MHz) δ 1.95 (d, 3H, J = 3.2 Hz), 2.12 (t, 4H, J = 8.9, 5.3 Hz), 2.55 (dd, 1H, J = 14.8, 3.2 Hz), 2.73 (m, 1H), 3.38 (s, 3H), 3.51 (m, 5H), 3.76 (dd, 1H, J = 8.9, 3.0 Hz), 4.38 (dd, 1H, J = 7.4, 3.0 Hz), 5.02 (dd, 1H, J = 6.0, 3.2), 6.63 (m, 3H), 7.10 (m, 7H); ^{13}C NMR ($CDCl_3$, 20 MHz) δ 15.4 (q), 29.0 (t), 47.7 (t, 56.6 (d), 57.6 (d), 57.8 (q), 65.6 (t), 73.7 (t), 111.7 (d), 114.7 (d), 124.9 (d), 125.0 (d), 125.1 (s), 126.4 (d), 127.3 (d), 136.9 (s), 142.3 (s), 144.8 (s); MS (m/z) 379 $(M + 1)^+$.

General Procedure for the Synthesis of 4-Piperidones 5–7. To a solution of an imine (10 mmol) in 40 mL of dry THF at rt were added 10 mL of a solution of $ZnCl_2$ in ether. The mixture was stirred for 10 min at room temperature, and then a solution of 2-morpholino diene (5 mmol) in 10 mL of dry THF was added dropwise. The reaction mixture was stirred at rt for 10 h before being diluted with saturated aqueous $NaHCO_3$. The layers wee separated, and the aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (2 × 20 mL) and brine (15 mL), dried over Na_2SO_4, and evaporated. The crude was dissolved in 3 mL of a mixture of ethyl acetate/CH_2Cl_2 (1:4) and filtered through a short chromatographic column (SiO_2, 35–80 mesh) using mixtures of ethyl acetate and CH_2Cl_2 as eluent. The fractions were combined and evaporated, affording an oil which was a mixture of aldehyde, imine, and 4-piperidones which were separated on a chromatographic column.

By this procedure were prepared the following compounds:

(2*S,3*R**,6*S**)- and (2*S**,3*S**,6*S**)-2-(Methoxymethyl)-3-methyl-1,6-diphenyl-4-piperidone (5a and 6a).** The reaction was performed as described in the General Procedure using (*E*)-*N*-(4-methoxy-2-methyl-1-methylene-2-butenyl)morpholine (980 mg, 5 mmol) and benzilideneaniline (1.86 g, 10 mmol) to yield 1.35 g (88%) as a mixture of epimers. Flash chromatography (SiO_2, hexane/ethyl acetate (10:1)) gives **5a**: 950 mg (62%); R_f = 0.22 (SiO_2, hexane/ethyl acetate (10:1)); ^1H NMR δ 1.63 (d, 3H, J = 6.5 Hz), 2.63 (m, 2H), 2.70 (qd, 1H, J = 6.5, 5.98 Hz), 3.21 (s, 3H), 3.31 (dd, 1H, J = 3.4, 9.9 Hz), 3.54 (dd, 1H, J = 5.1, 9.9 Hz), 3.67 (m, 1H), 4.92 (dd, 1 H, J = 7.6, 6.0 Hz), 6.7–7.3 (m, 10H); ^{13}C NMR δ 210.3 (s), 150.1 (s), 143.8 (s), 129.1 (d), 128.9 (d), 127.2 (d), 125.3 (d), 125.2 (d), 123.0 (d), 72.9 (t), 68.4 (d), 60.0 (q), 59.8 (d), 47.1 (t), 47.0 (d), 18.2 (q). Anal. Calcd for $C_{20}H_{23}NO_2$: C, 77.63; H, 7.49; N, 4.53. Found: C, 77.46; H, 7.54; N, 4.86. **6a**: 400 mg (26%); R_f = 0.33 (SiO_2, hexane/ethyl acetate (10:1)); ^1H NMR δ 1.09 (d, 3H, J = 7 Hz), 2.75 (dd, 1H, J = 18.2, 4.8 Hz), 2.8–3.0 (m, 2H), 3.32 (s, 3H), 3.61 (dd, 1H, J = 9.4, 5.4 Hz), 3.72 (dd, 1H, J = 9.4, 4.6 Hz), 4.03 (m, 1H), 4.92 (dd, 1H, J = 12.4, 4.8 Hz), 6.6–7.3 (m, 10H); ^{13}C NMR δ 209.4 (s), 149.6 (s), 143.5 (s), 128.4 (d), 128.1 (d), 126.6 (d), 125.6 (d), 118.9 (d), 117.2 (d), 74.8 (t), 64.1 (d), 58.8 (q), 57.2 (d), 47.5 (t), 45.1 (d), 10.8 (q). Anal. Calcd for $C_{20}H_{23}NO_2$: C, 77.63; H, 7.49; N, 4.53. Found: C, 77.39; H, 7.50; N, 4.79.

(2*S,3*R**,6*S**)-6-(2-Furyl)-2-(methoxymethyl)-3-methyl-*N*-(*p*-methoxyphenyl)-4-piperidone (5b).** (*E*)-*N*-(4-Methoxy-2-methyl-1-methylene-2-butenyl)morpholine (980 mg, 5 mmol) was treated with *N*-(*p*-methoxyphenyl)-2-furaldimine (2.16 g, 10 mmol) to yield 1.29 g (79%) as a mixture of epimers. Flash chromatography (SiO_2, hexane/ethyl acetate (10:1)) gives **5b**: 850 mg (52%); R_f = 0.21 (SiO_2, hexane/ethyl acetate (10:1)); ^1H NMR δ 1.25 (d, 3H, J = 7.0 Hz), 2.71 (dd, 1H, J = 4.6, 14.6 Hz), 2.87 (quint, 1H, J = 7.0, 7.0 Hz), 3.02 (dd, 1H, J = 6.0, 14.6 Hz), 3.34 (s, 3H), 3.35–3.45 (m, 3H), 3.71 (s, 3H), 4.78 (dd, 1H, J = 4.6, 6.0 Hz), 5.83 (d, 1H, J = 3.1 Hz), 6.18 (dd, J = 3.1, 1.9 Hz), 6.6–6.9 (m, 4H), 7.25 (d, 1H, J = 1.9 Hz); ^{13}C NMR δ 210.1 (s), 156.2 (s), 153.9 (s), 141.5 (d), 126.9 (d), 114.0 (s), 113.5 (d), 109.7 (d), 107.9 (d), 71.3 (t), 63.7 (d), 58.9 (q), 57.9 (q), 55.1 (d), 45.7 (t), 44.4 (d), 13.2 (q). Anal. Calcd for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25. Found: C, 69.19; H, 7.15; N, 4.42.

(2*S,3*S**,6*S**)-*N*-(*p*-Methoxyphenyl)-3-methyl-6-phenyl-2-[[(trimethylsilyl)oxy]methyl]-4-piperidone (6c).** (*E*)-*N*-[2-Methyl-1-methylene-4-[(trimethylsilyl)oxy]-2-butenyl]morpholine (1.27 g, 5 mmol) was treated with *N*-(*p*-methoxyphenyl)benzaldimine (2.16 g, 10 mmol) to yield 1.73 g (87%) as a mixture of epimers. Flash chromatography (SiO_2, hexane/ethyl acetate (8:1)) gives **6c**: 1.45 g (73%); R_f = 0.47 (SiO_2, hexane/ethyl acetate (6:1)); IR (film) 2955, 1721, 1510, 1246, 1040, 843, 700 cm^{-1}; ^1H NMR δ 0.2 (s, 9H), 1.12 (d, 3H, J = 6.7 Hz), 2.49 (dd, 1H, J = 3.8, 17.5 Hz), 2.8–3.0 (m, 2H), 3.56 (s, 3H), 3.6–3.9 (m, 3H), 4.67 (dd, 1H, J = 3.8, 11.9 Hz), 6.7–7.3 (m, 9H); ^{13}C NMR δ 209.7 (s), 153.7 (s), 143.9 (s), 143.6 (s), 128.2 (d), 126.5 (d), 126.3 (d), 121.1 (d), 113.5 (d), 66.7 (d), 63.7 (t), 59.2 (q), 54.9 (d), 47.9 (t), 44.2 (d), 10.9 (q), –1.1 (q) ppm; MS (m/z) 397 (M^+) (6), 294 (100), 222 (14), 131 (62). Anal. Calcd for $C_{23}H_{31}NO_3Si$: C, 69.48; H, 7.86; N, 3.52. Found: C, 69.64; H, 7.62; N, 3.43.

Epimerization of the Mixture of 4-Piperidones 7 and 8. To a solution of the epimeric 4-piperidones **7** and **8** in 15 mL of dry THF and cooled to 0 °C was added a solution of LDA (2 equiv) in dry THF (5 mL/equiv). The reaction mixture was stirred at room temperature for 4 h and quenched with water (2 × 10 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, and evaporated to afford the 4-piperidone that was purified through a chromatographic column.

By this procedure were prepared the following compounds:

(2*S,3*R**,6*R**)-2-(Hydroxymethyl)-3-methyl-6-phenyl-4-piperidone (7d).** (*E*)-*N*-(2-Methyl-1-methylene-4-[(trimethylsilyl)oxy]-2-butenyl)morpholine (1.27 g, 5 mmol) was treated with *N*-(trimethylsilyl)benzaldimine (4 mL, 10 mmol) to yield 860 mg (79%) after flash chromatography (SiO_2, ethyl acetate/dichloromethane (2:1)): R_f = 0.46 (SiO_2, ethyl acetate/dichloromethane (2:1)); IR (KBr) 3391, 2936, 1709, 1443, 1078, 897, 754 cm^{-1}; ^1H NMR δ 1.05 (d, 3H, J = 6.54 Hz), 2.7–2.4 (m, 3H+ $H_{alcohol}$ + H_{amine}), 2.79 (ddd, 1H, J = 2.70, 5.98, 10.05 Hz), 3.67 (dd, 1H, J = 5.98, 11.11 Hz), 3.82 (dd, 1H, J = 2.70, 11.11 Hz), 3.97 (dd, 1H, J = 5.80, 9.20 Hz), 7.2–7.4 (m, 5H); ^{13}C NMR δ 209.7 (s), 142.2 (s), 128.7 (d), 127.9 (d), 126.4 (d), 64.2 (t), 63.7 (d), 60.8 (d), 49.9 (t), 46.2 (d), 9.6 (q); MS (m/z) 219 (M^+) (<1), 188 (100), 131 (72). Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.81; N, 6.39. Found: C, 71.10; H, 7.94; N, 6.12.

(2*S,3*R**,6*R**)-2-(Hydroxymethyl)-6-(2-furyl)-3-methyl-4-piperidone (7e).** (*E*)-*N*-(2-Methyl-1-methylene-4-[(trimethylsilyl)oxy]-2-butenyl)morpholine (1.27 g, 5 mmol) was treated with *N*-(trimethylsilyl)-2-furfuraldimine (1.3 mL, 10 mmol) to yield 740 mg (71%) after flash chromatography (SiO_2, ethyl acetate/dichloromethane (2:1)): R_f = 0.14 (SiO_2, ethyl acetate/hexane (2:1)); ^1H NMR δ 1.02 (d, 1H, J = 6.70 Hz), 2.2 (m, 1H + NH + OH), 2.5 (m, 2H), 2.75 (ddd, 1H, J = 2.64, 5.94, 10.20 Hz), 3.65 (dd, 1H, J = 5.94, 12.30 Hz), 3.78 (dd, 1H, J = 2.64, 12.30 Hz), 3.92 (dd, 1H, J = 5.75, 9.25 Hz), 6.40 (d, 1H), 6.61 (dd, 1H), 7.41 (d, 1H); ^{13}C NMR δ 209.5 (s), 153.7 (s), 142.9 (d), 111.4 (d), 106.3 (d), 64.0 (t), 63.5 (d), 54.5 (d), 46.9 (t), 46.2 (d), 9.8 (q). Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.22; N, 6.69. Found: C, 63.31; H, 7.12; N, 6.84.

(2*S,3*R**,6*R**)-2-(Methoxymethyl)-3-methyl-6-(2-thienyl)-4-piperidone (7f).** (*E*)-*N*-(4-Methoxy-2-methyl-1-methylene-2-butenyl)morpholine (980 mg, 5 mmol) was treated with *N*-(trimethylsilyl)-2-thiophenealdimine (3 mL, 10 mmol) to yield 950 mg (80%) after flash chromatography (SiO_2, ethyl acetate/hexane (1:2)): R_f = 0.15 (SiO_2, ethyl acetate/hexane (1:2)); ^1H NMR δ 0.98 (d, 3H, J = 7.02 Hz), 2.35 (m, 1H), 2.6–2.8 (m, 3H), 3.31 (s, 3H), 3.34 (dd, 1H, J = 5.85, 12.02 Hz), 3.62 (dd, 1H, J = 3.02, 12.02 Hz), 4.22 (dd, 1H, J = 4.51, 10.30 Hz), 6.8–7.0 (m, 2H), 7.3 (m, 1H); ^{13}C NMR δ 208.8 (s), 146.2 (s), 126.5 (d), 124.5 (d), 123.5 (d), 74.2 (t), 61.9 (d), 59.1 (q), 56.3 (d), 50.9 (t), 46.8 (d), 9.6 (q). Anal. Calcd for $C_{12}H_{17}NO_2S$: C, 60.22; H, 7.16; N, 5.85. Found: C, 59.98; H, 7.32; N, 5.94.

(2*S,3*R**,6*R**)-2-(Methoxymethyl)-3-methyl-6-(3-pyridyl)-4-piperidone (7g).** (*E*)-*N*-(4-Methoxy-2-methyl-1-methylene-2-butenyl)morpholine (980 mg, 5 mmol) was treated with *N*-(trimethylsilyl)-3-pyridinealdimine (1.3 mL, 10 mmol) to yield 720 mg (62%) after flash chromatography (SiO_2, ethyl acetate/methanol (10:1)): R_f = 0.14 (SiO_2, ethyl acetate/methanol (10:1)); ^1H NMR δ 0.97 (d, 3H, J = 6.85 Hz), 2.4–2.6 (m, 2H), 2.82 (m, 1H), 3.25–3.35 (m, 1H), 3.32 (s, 3H), 3.47 (m, 1H), 3.60 (dd, 1H, J = 2.86, 11.20 Hz), 3.87 (dd, 1H, J = 5.17, 9.70 Hz), 7.25 (m,

2H), 7.75 (m, 1H), 8.45 (m, 2H); ^{13}C NMR δ 208.6 (s), 149.0 (d), 148.2 (d), 138.5 (s), 134.2 (d), 123.5 (d), 74.4 (t), 62.0 (d), 59.0 (q), 58.4 (d), 49.7 (t), 46.8 (d), 9.4 (q). Anal. Calcd for $C_{13}H_{18}N_2O_2$: C, 66.64; H, 7.74; N, 11.95. Found: C, 66.81; H, 7.45; N, 11.82.

(2*S,3*R**,6*R**)-*N*-Benzyl-3-methyl-6-phenyl-2-[[(trimethylsilyl)oxy]methyl]-4-piperidone (7h).** (*E*)-*N*-(2-Methyl-1-methylene-4-[(trimethylsilyl)oxy]-2-butenyl)morpholine (1.27 g 5 mmol) was treated with *N*-benzylbenzaldimine (1.95 g, 10 mmol) to yield 1.60 g (85%) after flash chromatography (SiO_2, hexane/ether (4:1)): ^{1}H NMR δ 0.2 (s, 9H), 1.05 (d, 3H, *J* = 6.4 Hz), 2.41 (dd, 1H, *J* = 3.3, 18 Hz), 2.80 (m, 1H), 2.88 (dd, *J* = 12.4, 18 Hz), 3.11 (ddd, 1H, *J* = 3.0, 3.2, 3.4 Hz), 3.19 (dd, 1H, *J* = 3.0, 11.11 Hz), 3.44 (m, 2H), 3.83 (d, $1H_{benz}$, *J* = 3.4 Hz), 4.09 (dd, 1H, *J* = 3.2, 12.4 Hz), 7.1–7.6 (m, 10H); ^{13}C NMR δ 210.7 (s), 144.5 (s), 139.3 (s), 129.1 (d), 128.9 (d), 128.6 (d), 128.0 (d), 127.4 (d), 127.3 (d), 64.1 (t), 63.1 (d), 62.0 (d), 59.3 (t), 48.1 (t), 41.7 (d), 11.0 (q), −1.0 (q). Anal. Calcd for $C_{23}H_{31}NO_2Si$: C, 72.39; H, 8.19; N, 3.67. Found: C, 72.52; H, 8.02; N, 3.85.

(2*S,3*R**,6*R**)-2-[(Benzyloxy)methyl]-6-(2-furyl)-3-methyl-4-piperidone (7i).** (*E*)-*N*-[4-(Benzyloxy)-2-methyl-1-methylene-2-butenyl]morpholine (1.36 g, 5 mmol) was treated with *N*-(trimethylsilyl)furaldimine (1.35 mL, 10 mmol) to yield 1.10 g (73%) after flash chromatography (SiO_2, hexane/ethyl acetate (3:1)): R_f = 0.27 (SiO_2, hexane/ethyl acetate (3:1)); IR (film) 3337, 2930, 1732, 1244, 1113 cm^{-1}; ^{1}H NMR δ 0.96 (d, 3H, *J* = 7.04 Hz), 2.4–2.9 (m, 3H + NH), 3.45 (m, 2H), 3.67 (dd, 1H, *J* = 3.42, 13.06 Hz), 4.02 (dd, 1H, *J* = 2.95, 9.47 Hz), 4.45 (m, 2H), 6.11 (d, 1H), 6.34 (dd, 1H), 7.1–7.4 (m, 6H); ^{13}C NMR δ 208.9 (s), 154.3 (s), 142.0 (d), 137.5 (s), 128.4 (d), 128.3 (d), 127.7 (d), 110.1 (d), 105.6 (d), 73.4 (t), 71.5 (t), 61.7 (d), 53.9 (d), 47.0 (d), 46.5 (t), 9.6 (q); MS (*m*/*z*) 289 (M$^+$) (<1), 287 (27), 244 (100), 241 (100). Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.21; H, 7.07; N, 4.68. Found: C, 72.37; H, 7.30; N, 4.56.

(2*S,3*R**,6*R**)-*N*-Butyl-6-phenyl-2-(methoxymethyl)-3-methyl-4-piperidone (7j).** (*E*)-*N*-(4-Methoxy-2-methyl-1-methylene-2-butenyl)morpholine (980 mg, 5 mmol) was treated with *N*-butylbenzaldimine (1.60 g 10 mmol) to yield 940 mg (65%) after flash chromatography (SiO_2, hexane/ethyl acetate (7:1)): R_f = 0.73 (SiO_2, hexane/ethyl acetate (7:1)); IR (film) 2932, 1719, 1194, 1113, 758, 702 cm^{-1}; ^{1}H NMR δ 0.65 (t, 3H, *J* = 7.31 Hz), 1.03 (d, 3H, *J* = 6.70 Hz), 1.1–1.4 (m, 6H), 2.2–2.5 (m, 3H), 2.60 (m, 1H), 2.75 (m, 1H), 3.05 (m, 1H), 3.24 (s 3H), 3.25 (m, 1H), 3.41 (dd, 1H, *J* = 3.50, 12.4 Hz), 3.95 (dd, 1H, *J* = 3.17, 9.21 Hz), 7.25 (m, 5H); ^{13}C NMR δ 211.2 (s), 143.9 (s), 128.3 (d), 127.1 (d), 127.0 (d), 75.4 (d), 61.5 (t), 61.2 (d), 58.9 (q), 53.8 (d), 47.8 (t), 42.7 (t), 28.4 (t), 19.9 (t), 13.7 (q), 10.9 (q). Anal. Calcd for $C_{18}H_{27}NO_2$: C, 74.70; H, 9.40; N, 4.84. Found: C, 74.93; H, 9.67; N, 4.52.

(2*S,3*R**,6*R**)-6-(2-Bromophenyl)-2-(methoxymethyl)-3-methyl-4-piperidone (7k).** (*E*)-*N*-(4-Methoxy-2-methyl-1-methylene-2-butenyl)morpholine (980 mg, 5 mmol) was treated with *N*-(trimethylsilyl)-2-bromobenzaldimine (2.45 g, 10 mmol) to yield 1.10 g (71%) after flash chromatography (SiO_2, hexane/ethyl acetate (5:1)): R_f = 0.38 (SiO_2, hexane/ethyl acetae (3:1)); ^{1}H NMR δ 0.99 (d, 3H, *J* = 6.85 Hz), 2.2–2.5 (m, 2H + NH), 2.59 (dd, 1H, *J* = 2.58, 13.33 Hz), 2.71 (ddd, 1H, *J* = 2.58, 8.60, 10.74 Hz), 3.32 (s, 3H), 3.39 (dd, 1H, *J* = 8.60, 9.00 Hz), 3.52 (dd, 1H, *J* = 2.58, 9.00 Hz), 4.28 (dd, 1H, *J* = 2.58, 11.61 Hz), 7.04 (dd, 1H), 7.26 (dd, 1H), 7.32 (d, 1H), 7.52 (d, 1H); ^{13}C NMR δ 208.7 (s), 141.1 (s), 132.7 (d), 128.9 (d), 127.8 (d), 127.5 (d), 122.8 (s), 74.6 (t), 61.6 (q), 58.9 (d), 58.8 (d), 48.0 (d), 46.7 (t), 9.5 (q). Anal. Calcd for $C_{14}H_{18}NO_2Br$: C, 53.86; H, 5.81; N, 4.48. Found: C, 53.92; H, 5.95; N, 4.63.

General Procedure for the Synthesis of Tetrahydropyridines 10 and 11. To a solution of an imine (7.5 mmol) in 40 mL of dry THF at rt was added 7.5 mL of a solution of $ZnCl_2$ in ether. The mixture was cooled to −40 °C and stirred for 10 min. Then a solution of 2-amino diene (5 mmol) in 10 mL of dry THF was added dropwise. The reaction mixture was maintained at −40 °C for 1 h, stirred for 10 h, allowing the mixture to warm to room temperature, and quenched by the addition of saturated aqueous $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (2 × 20 mL) and brine (15 mL), dried over Na_2SO_4, and evaporated. The crude was a mixture of 4-tetrahydropyridine and an excess of imine and aldehyde that were separated through a chromatographic column.

By this procedure were prepared the following compounds:

(2*S,6*S**)-1-(*p*-Methoxyphenyl)-4-(*N*-methylbenzeneamino)-3-methyl-6-phenyl-2-[[(trimethylsilyl)oxy]methyl]-1,2,5,6-tetrahydropyridine (10a).** (*E*)-*N*-[2-Methyl-1-methylene-4-[(trimethylsilyl)oxy]-2-butenyl]-*N*-methylaniline (1.37 g, 5 mmol) was treated with *N*-(*p*-methoxyphenyl)benzaldimine (1.58 g, 7.5 mmol) to yield 2.21 g (91%) as a mixture of epimers. Flash chromatography (SiO_2, hexane/ethyl acetate (8:1)) gives **10a** 2.05 g (85%): R_f = 0.53 (SiO_2, hexane/ethyl acetate (8:1)); IR (film) 2932, 1580, 1512, 1503, 1244, 1040, 829, 752, 698 cm^{-1}; ^{1}H NMR δ −0.5 (s, 9H), 1.61 (s broad, 3H), 2.09 (dd, 1H, *J* = 4.3, 15.9 Hz), 2.34 (s, 3H), 2.79 (m, 1H), 3.53 (s, 3H), 3.75 (m, 2H), 4.11 (dd, 1H, *J* = 4.7, 4.7 Hz), 4.95 (dd, 1H, *J* = 4.6, 4.6 Hz), 6.5–7.1 (m, 14 H); ^{13}C NMR δ 151.7 (s), 147.4 (s), 144.0 (s), 141.0 (s), 134.8 (s), 130.4 (s), 128.9 (d), 127.9 (d), 127.0 (d), 126.3 (d), 116.9 (d), 116.3 (d), 114.2 (d), 112.5 (d), 63.0 (t), 62.8 (d), 57.3 (q), 55.3 (q), 35.1 (t), 34.8 (d), 17.0 (q). Anal. Calcd for $C_{30}H_{38}N_2O_2Si$: C, 74.03; H, 7.87; N, 5.76. Found: C, 74.42; H, 7.56; N, 5.69.

(2*S,6*S**)-6-(2-Furyl)-1-(*p*-methoxyphenyl)-4-(*N*-methylbenzeneamino)-3-methyl-2-[[(trimethylsilyl)oxy)]methyl]-1,2,5,6-tetrahydropyridine (10b).** (*E*)-*N*-[2-Methyl-1-methylene-4-[(trimethylsilyl)oxy]-2-butenyl]-*N*-methylaniline (1.37 g, 5 mmol) was treated with *N*-(*p*-methoxyphenyl)-2-furaldimine (1.50 g 7.5 mmol) to yield 1.93 g (81%) as a mixture of epimers. Flash chromatography (SiO_2, hexane/ethyl acetate (7:1)) gives **10b**: 1.44 g (61%); R_f = 0.51 (SiO_2, hexane/ethyl acetate (7:1)); ^{1}H NMR δ −0.6 (s, 9H), 1.60 (s broad, 3H), 2.31 (dd, 1H, *J* = 5.6, 16.3 Hz), 2.51 (m, 1H, *J* = 4.7, 16.3 Hz), 2.60 (s, 3H), 3.55 (s, 3H), 3.72 (s broad, 2H), 3.88 (s broad, 1H), 4.98 (dd. 1H, *J* = 5.6, 4.7 Hz), 5.72 (d, 1H), 6.08 (dd, 1H), 6.5–7.1 (m, 9H), 7.19 (d, 1H); ^{13}C NMR δ 155.2 (s), 153.3 (s), 147.4 (s), 141.4 (s), 140.7 (d), 135.2 (s), 129.8 (s), 128.9 (d), 120.1 (d), 116.2 (d), 113.7 (d), 112.2 (d), 109.9 (d), 107.1 (d), 63.1 (t), 62.5 (d), 55.2 (q), 53.3 (d), 35.6 (q), 29.5 (t), 15.9 (q), −0.6 (q). Anal. Calcd for $C_{28}H_{36}N_2O_3Si$: C, 70.55; H, 7.61; N, 5.87. Found: C, 70.64; H, 7.81; N, 5.37.

(2*R,6*S**)-6-Phenyl-4-(*N*-methylbenzeneamino)-3-methyl-2-[[(trimethylsilyl)oxy]methyl]-1,2,5,6-tetrahydropyridine (11c).** (*E*)-*N*-[2-Methyl-1-methylene-4-[(trimethylsilyl)-oxy]-2-butenyl]-*N*-methylaniline (1.37 g, 5 mmol) was treated with *N*-(trimethylsilyl)-2-benzaldimine (1.35 mL, 7.5 mmol) to yield 1.48 g (78%) as a mixture of epimers. Flash chromatography (SiO_2, hexane/ethyl acetate (5:1)) gives **11c**: 1.37 g (72%); R_f = 0.42 (SiO_2, hexane/ethyl acetate (5:1)); ^{1}H NMR δ −0.2 (s), 1.46 (s broad, 3H), 2.12 (m, 1H), 2.42 (m, 1H), 2.85 (s, 3H), 3.3–3.6 (m, 2H + NH), 3.72 (m, 1H), 4.00 (dd, 1H, *J* = 3.81, 11.1 Hz), 6.5–7.5 (10 H); ^{13}C NMR δ 157.0 (s), 147.1 (s), 143.9 (s), 137.3 (d), 129.2 (s), 129.0 (d), 126.8 (d), 125.8 (d), 113.9 (d), 111.9 (d), 64.3 (t), 60.2 (d), 57.3 (d), 36.1 (q), 34.3 (t), 13.2 (q), −0.6 (q). Anal. Calcd for $C_{23}H_{32}N_2OSi$: C, 72.58; H, 8.48; N, 7.36. Found: C, 72.36; H, 8.44; N, 7.59.

(2*R,6*S**)-6-(2-Furyl)-4-(*N*-methylbenzeneamino)-3-methyl-2-[[(trimethylsilyl)oxy]methyl]-1,2,5,6-tetrahydropyridine (11d).** (*E*)-*N*-[2-Methyl-1-methylene-4-[(trimethylsilyl)-oxy]-2-butenyl]-*N*-methylaniline (1.37 g, 5 mmol) was treated with *N*-(trimethylsilyl)-2-furaldimine (1.35 mL, 7.5 mmol) to yield 1.65 g (89%) as a mixture of epimers. Flash chromatography (SiO_2, hexane/ethyl acetate (5:1)) gives **11d**: 1.25 g (68%); R_f = 0.38 (SiO_2, hexane/ethyl acetate (5:1)); IR (film) 2915, 1599, 1501, 1348, 1252, 1101, 872, 843, 748 cm^{-1}; ^{1}H NMR δ −0.2 (s), 1.42 (s broad, 3H), 2.1–2.4 (m, 2H + NH), 2.81 (s, 3H), 3.45 (m, 1H), 3.60 (dd, 1H, *J* = 5.1, 9.5 Hz), 3.63 (dd, 1H, *J* = 2.9, 9.5 Hz), 3.91 (dd, 1H, *J* = 6.7, 8.0 Hz), 6.02 (d, 1H), 6.18 (dd, 1H), 6.5–7.2 (m, 5H), 7.26 (dd, 1H); ^{13}C NMR δ 156.1 (s), 146.9 (s), 141.3 (d), 136.5 (s), 129.8 (s), 128.8 (d), 116.0 (d), 113.8 (d), 111.8 (d), 104.7 (d), 63.3 (t), 59.6 (d), 50.7 (d), 35.9 (q), 30.2 (t), 13.2 (q), −0.8 (q); MS (*m*/*z*) 370 (M$^+$) (4), 323 (10), 267 (100). Anal. Calcd for $C_{21}H_{30}N_2O_2Si$: C, 68.06; H, 8.16; N, 7.56. Found: C, 67.89; H, 8.12; N, 7.78.

(2*R,6*S**)-4-(*N*-Methylbenzeneamino)-3-methyl-2-(methoxymethyl)-6-(2-thienyl)-1,2,5,6-tetrahydropyridine (11e).** (*E*)-*N*-(4-Methoxy-2-methyl-1-methylene-2-butenyl)-*N*-methylaniline (1.08 g, 5 mmol) was treated with *N*-(trimethylsilyl)-2-thiophenealdimine (1.35 mL, 7.5 mmol) to yield 1.31 g (80%) as a mixture of epimers. Flash chromatography (SiO_2, hexane/ethyl acetate (5:1)) gives **11e**: 1.02 g (62%); R_f = 0.40 (SiO_2, hexane/

ethyl acetate (4:1)); ^{1}H NMR δ 1.53 (s broad, 3H), 2.35 (m, 2H), 2.89 (s, 3H), 3.27 (s, 3H), 3.35 (dd, 1H, J = 7.3, 9.0 Hz), 3.59 (dd, 1H, J = 3.0, 9.0 Hz), 3.68 (m, 1 H), 4.16 (dd, 1H, J = 6.7, 6.9 Hz), 6.6–7.3 (m, 8H). ^{13}C δ 147.3 (s), 147.2 (s), 136.8 (s), 129.5 (s), 129.2 (d), 126.5 (d), 124.0 (d), 123.5 (d), 116.4 (d), 114.3 (d), 112.1 (d), 74.0 (t), 59.1 (d), 58.7 (q), 53.2 (d), 36.5 (q), 34.5 (t), 13.5 (q). Anal. Calcd for $C_{19}H_{24}N_2OS$: C, 69.47; H, 7.36; N, 8.52. Found: C, 69.72; H, 7.39; N, 8.45.

Carbonylation of Tetrahydropyridine (11d). Synthesis of (2*R,6*S**)-1-Aza-2-(2-furyl)-5-methyl-4-(*N*-methylbenzeneamino)-8-oxa-9-oxobicyclo[4.3.0]-4-nonene (12).** To a solution of tetrahydropyridine **11d** (2.5 mmol) in 25 mL of methanol was added 500 mg of K_2CO_3, and the mixture was stirred for 2 h. The solvents were evaporated, and the solid residue was dissolved in 30 mL of ether and washed with brine (15 mL) and water (15 mL). The organic layer was dried over Na_2SO_4 and evaporated. The residue was the tetrahydropyridine deprotected in the –OH, which was not purified. The residue was dissolved in 30 mL of ether, and 750 mg (2.5 mmol) of triphosgene was added. Over the solution cooled at 0 °C was slowly added a solution of triethylamine (2.5 mmol, 0.35 mL) in 5 mL of THF and the mixture stirred for 20 min. The reaction was quenched with 15 mL of H_2O, the layers were separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and evaporated. The crude was purified through a very short chromatographic column to give **12**, 760 mg (93%). Flash chromatography (SiO_2, hexane/ethyl acetate (4:1)), R_f = 0.15 (SiO_2, hexane/ethyl acetate (2:1)). Recrystallized from methanol: mp 145 °C; IR (film) 2980, 1728, 1597, 1499, 1246, 1154, 1047, 752, 698 cm^{-1}; ^{1}H δ 1.62 (s, 3H), 2.43 (m, 1H, ^2J = 16.8 Hz, ^3J = 3.7 Hz, ^5J = 2.1 Hz, ^5J = 1.5 Hz), 2.87 (m, 1H, ^2J = 16.8 Hz, ^3J = 10.0 Hz, ^5J = 2.9 Hz, ^5J = 1.4 Hz), 3.00 (s, 3H), 4.13 (dd, 1H, ^2J = 8.1 Hz, ^3J = 5.3 Hz), 4.45 (dd, 1H, ^2J = 8.1 Hz, ^3J = 8.1 Hz), 4.51 (m, 1H, ^3J = 8.1 Hz, ^3J = 5.3 Hz, ^5J = 2.9 Hz, ^5J = 2.1 Hz), 4.63 (dd, 1H, ^3J = 10.0 Hz, ^3J = 3.8 Hz), 6.23 (d, 1H), 6.35 (dd, 1H), 6.7–6.9 (m, 3H), 7.25 (m, 2H), 7.40 (d, 1H); ^{13}C NMR δ 156.7 (s), 152.0 (s), 146.6 (d), 142.0 (s), 135.2 (s), 129.1 (d), 126.9 (s), 117.2 (d), 112.4 (d), 110.3 (d), 106.6 (d), 66.9 (t), 53.5 (d), 46.3 (d), 36.1 (q), 27.1 (t), 12.7 (q). Anal. Calcd for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.21; N, 8.63. Found: C, 70.56; H, 6.24; N, 8.87.

(1*R,5*R**,6*S**)- and (1*R**,5*S**,6*S**)-1-Aza-2-(2-furyl)-5-methyl-8-oxa-4,9-dioxobicyclo[4.3.0]nonane (13 and 14).** Bicyclic compound **12** (750 mg, 2.3 mmol) was dissolved in 25 mL of THF, and 15 mL of 3 N HCl was added. The mixture was vigorously stirred for 1 h. The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 20 mL). The organic layers were combined, washed with aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and evaporated. The crude was a mixture 70:30 of epimers **13** and **14** that was separated by flash chromatography (SiO_2, hexane/ethyl acetate (1:2)) to yield **13**: 358 mg (66%); R_f = 0.44 (SiO_2, hexane/ethyl acetate (1:2)). Recrystallized from ethyl ether: mp 86 °C; IR (film) 2974, 2943, 1763, 1723, 1408, 1281, 1013, 752 cm^{-1}; ^{1}H NMR δ 1.04 (d, 3H, J = 6.8 Hz), 2.64 (dq, 1H, J = 10.4, 6.8 Hz), 2.85 (m, 2H), 3.93 (m, 2H), 4.45 (m, 1H), 4.96 (dd, 1H, J = 5.4, 5.4 Hz), 6.29 (m, 2H), 7.35 (m, 1H). ^{13}C NMR δ 205.9 (s), 155.1 (s), 150.9 (s), 141.9 (d), 109.8 (d), 107.5 (d), 66.9 (t), 56.9 (d), 47.6 (d), 47.1 (d), 42.0 (t), 9.5 (q); MS (m/z) = 235 (M^+). Anal. Calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.95. Found: C, 61.54; H, 5.49; N, 5.86. **14**: yield 150 mg (28%); R_f = 0.29 (SiO_2, hexane/ethyl acetate (1:2)); ^{1}H NMR ($CDCl_3$) δ 1.22 (d, 3H, J = 7.3 Hz), 2.66 (qd, 1H, J = 7.3, = 3.9 Hz), 2.9–3.1 (m, 2H), 4.11 (dd, 1H, J = 8.6, 9.0 Hz), 4.37 (dd, 1H, J = 8.6, 8.6 Hz), 4.57 (ddd, 1H, J = 9.0, 8.6, 3.9 Hz), 5.02 (dd, 1H, J = 6.7, 4.2 Hz), 6.42 (s, 2H), 7.41 (d, 1H). Anal. Calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.95. Found: C, 61.47; H, 5.38; N, 5.92.

Carbonylation of Piperidone 7e. Synthesis of 13. The procedure is identical to that described for the carbonylation of tetyrahydropyridine **11d**. Bicyclic compound **13** was purified by flash chromatography (SiO_2, hexane/ethyl acetate (1:2)), yield 99%.

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