Reverse Cope Elimination Reactions. 2. Application to Synthesis[1]

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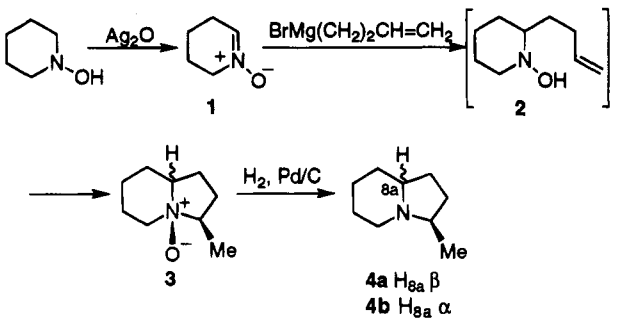
Intramolecular addition of *N,N*-disubstituted hydroxylamines to unactivated olefins was used to prepare an indolizine, a pyrrolo[2,1-*a*]isoquinoline, a 1,8-diazaspiro[4.5]decane, a cyclopenta[*b*]-pyrrole, and an isoindoline. A pyrrolizine and a 1-azabicyclo[2.2.1] heptane were synthesized from acyclic precursors by two consecutive reverse Cope elimination reactions.

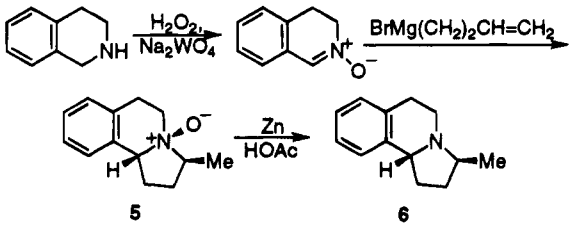
The first paper[1] in this series dealt with the mechanism and scope of the intramolecular addition of disubstituted hydroxylamines to unactivated olefins to give pyrrolidine and piperidine *N*-oxides. Here, we illustrate the potential in synthesis of this novel reaction. *N*-Oxides are of interest in their own right and as substrates in a variety of reactions.[3] We were particularly interested in preparing bicylic systems containing nitrogen at the ring junction because these are not accessible by the closely related cyclization of monosubstituted hydroxylamines to cyclic hydroxylamines.[4]

Results and Discussion

Addition of 3-butenylmagnesium bromide to nitrone **1**, prepared by dehydrogenation of 1-piperidinol, gave *N*-oxides **3** by cyclization of the intermediate hydroxylamine **2**. Reduction of the *N*-oxides gave a mixture of *cis*- and *trans*-3-methyloctahydroindolizine (**4a,b**) in a ratio of 85:15 in 42% yield from 1-piperidinol. The structural assignments were made by NOESY and agree with those in the literature.[5a] In addition, the ^{13}C NMR of isomer **4a** is different from that reported [5b] for isomer **4b**. Since the reverse Cope elimination is reversible,[1] the isomer ratio reflects the relative stabilities of the two isomeric *N*-oxides **3**.



In a variation of this approach, 1,2,3,4-tetrahydroisoquinoline was oxidized directly[6] to 3,4-dihydroisoquinoline 2-oxide, which on treatment with 3-butenylmagnesium bromide gave a single isomer of the hexahydropyrrolo[2,1-*a*]isoquinoline *N*-oxide **5**. Reduction of the latter gave the amine **6** in 27% overall yield from 1,2,3,4-tetrahydroisoquinoline. The stereochemical assignment was again made by NOESY.



Bicyclic systems may also be synthesized by two consecutive reverse Cope elimination reactions. Thus, 1,8-nonadien-5-one[7] was converted into the oxime which on reduction with sodium cyanoborohydride at pH 4[8] gave a mixture of the two epimeric *N*-oxides **8a,b** still containing ca. 30% of the hydroxylamines **7a,b**. The amount of the latter was reduced to 10% by allowing a chloroform solution to stand at room temperature for 2 days. Reduction of the *N*-oxides **8a,b** with hexachlorodisilane[9] gave a 55:45 mixture of the indolizines **9a** and **9b**[10] in 41% yield from 1,8-nonadien-5-one oxime (Scheme 1). Reverse Cope elimination reaction of hydroxylamine **7a** may lead to either *N*-oxide **8a** or **8b**, whereas cyclization of hydroxylamine **7b** in principle may give *N*-oxide **8b** and the third isomer which has both methyl groups on the concave side of the pyrrolizidine ring system. The latter isomer, however, is very strained and is not observed. When the two epimeric *N*-oxides **8a,b** were catalytically reduced in acetic acid at room temperature, a mixture consisting of 48% of **9a**, 12% of **9b**, and 40% of the secondary amine **10** was obtained. The latter was isolated by conversion into the urea **11**. *N*-Oxide **8b** thus

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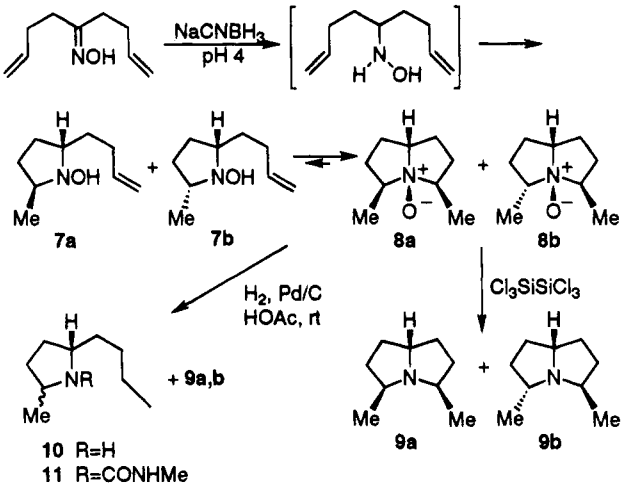
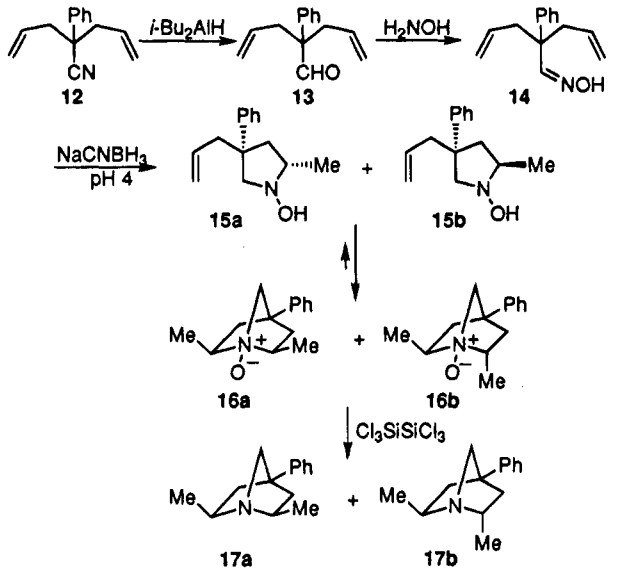
Scheme 1



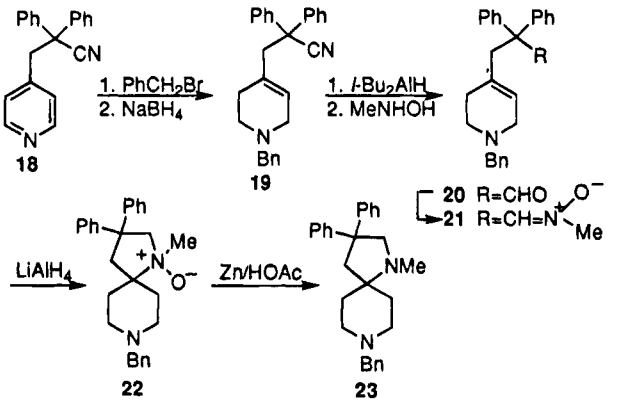
Scheme 2



reverts more readily under these conditions to its precursor than *N*-oxide **8a**. Since a variety of derivatives of 1,8-nonadien-5-one, 1,9-decadien-5-one, and 1,10-undecadien-6-one are accessible by alkylation of the dianion of acetoacetic ester,[7b] the route outlined in Scheme 1 provides a potential access to pyrrolizine, indolizine, and quinolizine alkaloids.[11]

A modification of this approach was used to synthesize the 1-azabicyclo[2.2.1]heptane derivatives **17** from 2-phenyl-2-(2-propenyl)-4-pentenenitrile (**12**) via the corresponding aldehyde **13** and oxime **14** (Scheme 2). Reduction of the latter gave the hydroxylamines **15** in quantitative yield; the ratio of isomers **15a** and **15b** was 60:40. Heating a solution of this mixture in chloroform to reflux for 72 h (or keeping it at 25 °C for 34 days) gave an eqilibrium mixture consisting of 17% of hydroxylamine **15b** and 83% of a 1:1 mixture of *N*-oxides **16a** and **16b**. The structure assignment of hydroxylamines **15** rests on their cyclization behavior: **15a** cyclized more rapidly, and an initial excess of *N*-oxide **16a** over **16b** (ratio 83:17 after 6 h, 54% cyclization) was observed. Only hydroxylamine

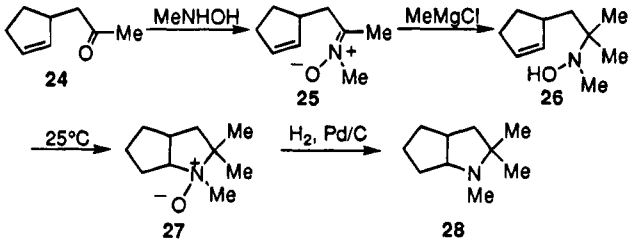
Scheme 3



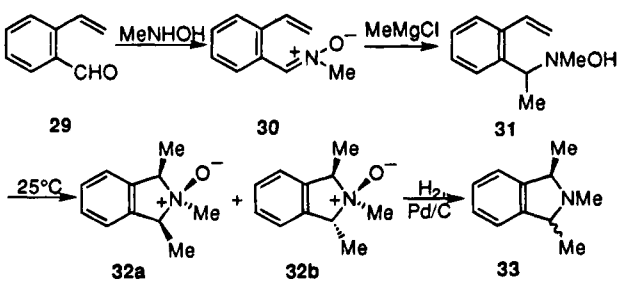
15a can cyclize to *N*-oxide **16a**. As in the example of Scheme 1, the third isomer, having both methyl groups *endo*, was not formed because this configuration involves severe crowding. The success of this reaction was somewhat surprising since the *N*-oxides **16** intuitively seem thermodynamically less stable than the precursor hydroxylamines **15**. Reduction of the mixture of *N*-oxides **16** with hexachlorodisilane gave a 1:1 mixture of the amines **17a** and **17b** in 58% yield from oxime **14**.

The spiro compound **22** was obtained as shown in Scheme 3. The intermediate hydroxylamine had to be heated in chloroform to reflux for 18 h to effect cyclization. The hydroxylamine lacking the two phenyl groups failed to undergo the reverse Cope elimination reaction.

5-*Exo* cyclization to give a fused product is illustrated in the preparation of the cyclopenta[*b*]pyrrole derivative **28** in 51% overall yield from ketone **24**.



Addition of methylmagnesium chloride to nitrone **30** gave a 9:1 mixture of *N*-oxides **32a** and **32b** which was reduced to the isoindolines **33**. Both *N*-oxides **32** and isolindolines **33** were unstable and decomposed rapidly on exposure to air.



In summary, we have demonstrated that the reverse Cope elimination reaction may be used to prepare a variety five- and six-membered nitrogen-containing heterocycles.[12]

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(12) For the application of the reverse Cope elimination reaction to the synthesis of 1,2,5-oxadiazinanes see: Gravestock, M. B.; Knight, D. W.; Thornton, S. R. *J. Chem. Soc., Chem. Commun.* **1993**, 169.

Experimental Section

General. ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra were determined in $CDCl_3$ unless otherwise specified. Melting points were measured in unsealed capillary tubes and are uncorrected. Mass spectra were obtained by chemical ionization (NH_3 or CH_4) or by electron ionization.

Materials. Starting materials were obtained from Janssen Chimica or Aldrich Chemical Co. The THF used was EM Science anhydrous grade (stored over 4A sieves). $MgSO_4$ was used throughout for drying solutions in organic solvents.

3-Methyloctahydroindolizine 4-Oxide (3). A mixture of 4.00 g (39.6 mmol) of 1-hydroxypiperidine, 16 g (70 mmol) of silver oxide, and 40 mL of CH_2Cl_2 was stirred for 30 min, keeping the temperature at 20–25 °C. $MgSO_4$ (3 g) was added, the mixture was filtered, the solids were washed twice with CH_2Cl_2, and the combined filtrates and washings were concentrated at rt. The residual nitrone **1** was immediately dissolved in 10 mL of THF, and the solution was added at 0 °C to a Grignard reagent prepared from 8.23 g (70 mmol) of 4-bromo-1-butene and 1.51 g (62 mmol) of Mg in 40 mL of Et_2O. The mixture was stirred at rt for 3 h, 80 mL of 20% NH_4Cl was added, and the aqueous phase was extracted several times with CH_2Cl_2. Removal of the solvents from the dried organic phases at room temperature left 4.75 g of the crude title compound which was reduced without purification. The ^1H NMR showed the absence of the unsaturated hydroxylamine **2**.

***cis*- and *trans*-3-Methyloctahydroindolizine (4a,b).** The crude *N*-oxide obtained above (4.75 g) was shaken with 2.1 g of 10% Pd/C and 20 mL of HOAc at 52 psi initial H_2 pressure for 16 h. The filtered mixture was treated with 7 mL of concd HCl and concentrated to dryness. The residue was made basic with 50% NaOH and extracted with Et_2O. Spinning-band distillation gave 2.30 g (42%) of the title compounds in four fractions, bp 80–82 °C (30 mm). The two earlier fractions contained all of the *trans* isomer **4b**; the summed ratio **4a/4b** in the four fractions was 85:15. ^1H NMR of **4a**: δ 3.3 (m, 1 H, H-3), 2.9 (d/t, J = 9/2 Hz, 1 H, H-5), 2.4–2.5 (m, 2 H, H-8a, H-5), 2.3 (m, 1 H, H-2), 1.9 (m, 1 H, H-1), 1.7–1.8 (m, 2 H, H-7, H-8), 1.5–1.6 (m, 2 H, H-6), 1.1–1.4 (m, 4 H, H-1, H-2, H-7, H-8), 0.9 (d, J = 6 Hz, 3 H). There was an NOE interaction between H-8a and the methyl group but none between H-8a and H-3. ^{13}C NMR of **4a**: δ 15.6, 24.2, 24.4, 30.0, 30.2, 31.1, 46.9, 55.2, 58.3. HRMS: calcd for $C_9H_{18}N$ [$(M + H)^+$] 140.1439, found 140.1429. The picrate of **4a** had mp 211–214 °C (dec, 90% EtOH) (lit.[5a] mp 197–205 °C). Anal. Calcd for $C_{15}H_{20}N_4O_4$: C, 48.91; H, 5.47; N, 15.21. Found: C, 48.67; H, 5.48; N, 15.04. The ^1H NMR of isomer **4b** had the Me group at δ 1.1.

1,2,3,5,6,10b-Hexahydro-3-methylpyrrolo[2,1-*a*]isoquinoline 4-Oxide (5). To a mixture of 3.5 g (28 mmol) of freshly distilled 1,2,3,4-tetrahydroisoquinoline, 0.34 g (1.0 mmol) of Na_2WO_4 dihydrate, and 40 mL of MeOH was added at 3–5 °C during 30 min 9 g of 30% H_2O_2 in 40 mL of MeOH. The mixture was stirred at rt for 3 h, treated with 50 mL of 20% NH_4OH, and extracted with CH_2Cl_2. Removal of the solvent at rt gave 2.58 g of 3,4-dihydroisoqunioline 2-oxide of ca. 80% purity. It was immediately dissolved in 8 mL of THF, and the solution was added below 10 °C to a Grignard reagent prepared from 5.03 g (37 mmol) of 4-bromobutene and 0.90 g (39 mmol) of Mg in 20 mL of Et_2O. The mixture was stirred at rt for 4 h, and the product was isolated as described above to give 3.08 g of the crude title compound of ca. 90% purity as a single isomer. ^1H NMR: δ 7.2–7.3 (m, 3 H), 7.1 (d, J = 7 Hz, 1 H), 4.8 (d/d, J = 8/4 Hz, 1 H), 3.6–3.7 (m, 2 H), 3.5 (m, 1 H), 3.2–3.3 (m, 2 H), 2.8–3.0 (m, 2 H), 2.2 (m, 1 H), 1.9–2.1 (m, 2 H), 1.4 (d, J = 6 Hz, 3 H). The product was reduced without purification.

1,2,3,5,6,10b-Hexahydro-3-methylpyrrolo[2,1-*a*]isoqhinoline (6). Zinc dust (9 g) was added over a period of 2 h to a stirred mixture of 1.80 g of *N*-oxide **5** and 12 mL of HOAc, and stirring was continued for 18 h. CH_2Cl_2 (50 mL) was added, the mixture was filtered, and the filtrates were made basic with 50% NaOH. Short-path distillation at 90–120 °C bath temperature (0.001 mm) gave 0.95 g of the title compound of 90% purity (27% from tetrahydroisoquinoline). ^1H NMR: δ 7.0–7.2 (m, 4 H), 4.4 (t, J = 7 Hz, 1 H), 2.8–3.2 (m, 4 H), 2.6 (d/t, J = 16/4 Hz, 1 H), 2.4 (m, 1 H), 2.0 (m, 1 H), 1.8 (m, 1 H), 1.5 (m, 1 H), 1.2 (d, J = 6 Hz, 3 H). Irradiation of the Me signal caused a 2.7% NOE enhancement of the δ 4.4 t. ^{13}C NMR: δ 19.2, 24.5, 32.0, 32.6, 43.8, 55.4, 60.1, 125.4, 126.1, 126.4, 128.3, 134.6, 140.3. HRMS: calcd for $C_{13}H_{17}N$ 187.1361, found 187.1361. The base did not form a crystalline hydrochloride or fumarate and decomposed slowly at rt.

1,8-Nonadien-5-one Oxime. A mixture of 2.51 g (18.2 mmol) of 1,8-nonadien-5-one,[7] 3.51 g (50 mmol) of hydroxylamine hydrochloride, 4.4 g (54 mmol) of NaOAc, and 6 mL of EtOH was stirred at rt for 2 h, 20 mL of 10% Na_2CO_3 was added, the mixture was extracted with CH_2Cl_2 and the dried extracts were concentrated to give 2.71 g (97%) of the title compound which was used without purification. ^1H NMR: δ 8.0 (br, 1 H), 5.8–6.0 (m, 2 H), 5.0–5.1 (m, 4 H), 2.5 (t, J = 7 Hz, 2 H), 2.3 (m, 6 H),

***cis*- and *trans*-3,5-Dimethylhexahydropyrrolizine (9a,b).** A mixture of 2.69 g (17.6 mmol) of 1,8-nonadien-5-one oxime, 3.8 g (62 mmol) of $Na(CN)BH_3$, 20 drops of 0.01% methyl orange in EtOH, and 20 mL of MeOH was cooled to 10 °C, and a mixture of 16 mL of concd HCl and 84 mL of MeOH was added at a rate to keep the indicator pink. The cooling bath was removed after 30 min, and stirring and HCl addition were continued for 2.5 h. Concentrated HCl (10 mL) was added (**CAUTION**; HCN), and the mixture was concentrated to dryness. The residue was made basic with NH_4OH and extracted with $CHCl_3$. The solution was allowed to stand at rt for 2 d at which time ca. 10% of uncyclized hydroxylamines **7** remained. The solvent was removed at rt to give 3.02 g of the *N*-oxides **8a,b** which were reduced immediately. They were dissolved in 12 mL of dry $CHCl_3$, and 4 mL of $(Cl_3Si)_2$[9] was added slowly, keeping the temperature below 5 °C. After 5 h at rt, 50 mL of 15% NaOH was added and the aqueous phase was extracted twice with $CHCl_3$. Concentrated HCl (3 mL) was added, and the mixture was concentrated to dryness, taken up in water, and washed three times with Et_2O. The aqueous phase was made basic with NaOH and extracted with ether. Short-path distillation gave 1.00 g (41% from 1,8-nonadien-5-one oxime) of a 55:45 mixture of the *cis* and *trans* isomers **9a,b**,[10] boiling at a bath temperature of 60–90 °C (30 mm). HRMS: calcd for $C_9H_{18}N$ [$(M + H)^+$] 140.1439, found 140.1441. ^1H NMR of **9a:** δ 3.6 (m, 1 H), 2.8 (m, 2 H), 2.0 (m, 4 H), 1.4–1.6 (m, 4 H), 1.1 (d, J = 6 Hz, 6 H). ^1H NMR of **9b:** δ 3.2 (m, 1 H); 3.0 (m, 1 H), 1.2 (d, J= 6 Hz, 3 H), 1.1 ((d, J= 6 Hz, 3 H), among others. ^{13}C NMR: δ 16.6, 21.8, 23.1, 31.3, 32.0, 32.2, 35.0, 34.3, 52.5, 57.5, 61.3, 65.1, 66.1; the predicted number of signals is 14 (5 for **9a** and 9 for **9b**); two signals must have close chemical shifts. When the mixture of the *N*-oxides **8a,b** (0.75 g) was reduced with H_2 and Pd/C in HOAc at rt for 20 h, 0.69 g of a mixture consisting of 48% of **9a**, 12% of **9b**, and 40% of 2-methyl-4-butylpyrrolidine (**10**) was obtained. It was dissolved in 2 mL of Et_2O, treated with 1 mL of freshly distilled MeNCO, and allowed to stand at rt for 5 h. Removal of the solvent and MeNCO and partitioning of the residue into neutral and basic fractions gave 0.24 g of the urea **11** and 0.36 g of a mixture of 80% **9a** and 20% **9b.** Urea **11** was more than 80% a single isomer: ^1H NMR: δ 4.1 (br, 1 H), 3.8 (m, 1 H), 3.7 (m, 1 H), 2.8 (2s or d, J = 6 Hz, 3 H), 1.6–2.0 (m, 6 H), 1.2–1.4 (m+d, J = 7 Hz, 6 H), 0.9 (t, J =7 Hz, 3 H). LRMS: calcd for $C_{11}H_{23}N_2O$ [$(M + H)^+$] 199, found 199.

2-Phenyl-2-(2-propenyl)-4-pentenenitrile (12). To a mixture of 11.7 g (0.1 mol) of phenylacetonitrile, 1.0 g (2 mmol) of hexadecyltribuylphosphonium bromide, and 30 mL of 50% NaOH was added slowly below 50 °C 28 g (0.23 mol) of allyl bromide, and stirring was continued for 24 h. Extraction with toluene and short-path distillation of the crude product at 110 °C bath temperature (1.8 mm) gave 19.69 g (100%) of the title compound. ^1H NMR: δ 7.2–7.4 (m, 5 H), 5.6–5.8 (m, 2 H), 5.1–5.2 (m, 4 H), 2.6 (d, J = 7 Hz, 4 H).

2-Phenyl-2-(2-propenyl)-4-pentenecarboxaldehyde (13). To 80 mL of THF was added below −50 °C 90 mL (0.135 mole) of 1.5 M *i*-Bu_2AlH in toluene followed by 13.0 g (0.067 mol) of nitrile **12** in 20 mL of THF. The bath was removed, the

mixture was stirred for 3.5 h, 15 mL of EtOH followed by 130 mL of 10% HCl were added below −40 °C, and the mixture was warmed to −10 °C and extracted with toluene. Spinning-band distillation gave 10.74 g (81%) of the title compound, bp 75 °C (10 mm), n^{25}_D 1.5300. ^{1}H NMR: δ 9.5 (s, 1 H), 7.2−7.4 (m, 5 H), 5.5−5.6 (m, 2 H), 5.0−5.1 (m, 4 H), 2.7 (d, J = 7 Hz, 4 H). Anal. Calcd for $C_{14}H_{16}O$: C, 83.96; H, 8.05. Found: C, 84.13; H, 8.15.

2-Phenyl-2-(2-propenyl)-4-pentenecarboxaldehyde Oxime (14). A mixture of 4.10 g (20.3 mmol) of aldehyde **13**, 4.07 g (58 mmol) of hydroxylamine hydrochloride, 4.29 g (38 mmol) of NaOAc, and 12 mL of EtOH was stirred at rt for 4 h, and 30 mL of 10% Na_2CO_3 was added. Extraction with CH_2Cl_2 and short-path distillation of the crude product at 100−160 °C (0.01 mm) gave 4.30 g (98%) of the title compound. ^{1}H NMR: δ 7.8 (broadened s, 1 H), 7.5 (s, 1 H), 7.2−7.4 (m, 5 H), 5.5−57 (m, 2 H), 5.0−5.1 (m, 4 H), 2.7 (d, J = 7 Hz, 4 H).

2-*exo*-6-*exo*- and 2-*exo*-6-*endo* 2,6-Dimethyl-4-phenyl-1-azabicyclo[2.2.1]heptane 1-Oxides (16a,b). Oxime **14** (4.30 g, 20 mmol) was reduced as described for the preparation of **8a,b** to give 4.47 g (103%) of a mixture consisting of 40% hydroxylamine **15a** and 60% **15b**. ^{1}H NMR: δ 7.2−7.4 (m, 5 H), 5.3−57 (m, 1 H), 4.9−5.1 (m, 2 H), 3.6 + 3.8 (2 d, J = 9 Hz, ratio 40:60, 1 H), 1.6−3.2 (m, 6 H), 1.2 and 1.3 (2 d, J = 7 Hz, ratio 60:40, 3 H). A solution of 3.66 g of this mixture in 100 mL of $CHCl_3$ was heated under reflux for 72 h after which the composition remained constant. The percent cyclization and the ratios of **15a/15b** and **16a/16b** were as follows: after 6 h, 54%, 25:75 and 83:17; after 24 h, 75%, 0:100 and 64:34; after 42 h, 84%, 0:100 and 56:44; after 72 h, 84%, 0:100 and 50:50. The same equilibrium mixture was obtained when a $CHCl_3$ solution of hydroxylamines **15a,b** was allowed to stand ar rt for 34 d. In the ^{1}H NMR, **16a** had a 2H s at δ 3.4 (bridge CH_2) and a 6 H d at δ 1.5 (Me); **16b** had two 3 H d at δ 1.4 and 1.6.

2-*exo*-6-*exo*- and 2-*exo*-6-*endo*-2,6-Dimethyl-4-phenyl-1-azabicyclo[2.2.1]heptane (17a,b). The $CHCl_3$ solution from the above experiment was concentrated to ca. 15 mL, and 3 mL of $Cl_3SiSiCl_3$ were added slowly below 0 °C. After 3 h at rt, 50 mL of 15% NaOH were added below 0 °C, the mixture was stirred at rt 3 h, and the aqueous phase was extracted with $CHCl_3$. The solvent was removed from the dried extracts, the residue was dissolved in 15 mL of Et_2O, and 2.4 g of freshly distilled MeNCO was added. The solvent and excess reagent were removed after 3 h at rt, and the residue was partitioned into basic and neutral fractions. Short-path distillation of the former at 80−100 °C (0.07 mm) gave 1.90 g (58% from oxime **14**) of a 1:1 mixture of the title compounds. HRMS: calcd for $C_{14}H_{20}N$ [(M + H)$^+$] 202.1596, found 202.1587. Anal. Calcd for $C_{14}H_{19}N$: C, 83.53; H, 9.51; N, 6.96. Found: C, 83.13; H, 9.53; N, 6.76. ^{13}C NMR: δ 17.5, 22.8, 22.8, 44.6, 45.6, 47.5, 50.7, 54.8, 55.6, 56.3, 59.7, 61.3, 62.1, 126.0, 126.0, 126.5, 126.7, 128.2 (double intensity), 142.5, 143.1. ^{1}H NMR of **17a**: δ 7.1−7.4 (m, 5 H), 2.9 (m, 2 H), 2.7 (s, 2 H), 1.8 (m, 2 H), 1.4 (m, 2 H), 1.2 (d, J = 7 Hz, 6 H). ^{1}H NMR of **17b**: δ 7.1−7.4 (m, 5 H), δ 3.2−3.4 (m, 2 H), 2.7 and 2.0 (presumably 2 d, obscured by **17a**, 2 H), 2.0 (t/d, J = 10/3 Hz, 1 H), 1.8 (m, 1 H), 1.4 (m, 1 H), 1.2 (d, J = 7 Hz, 3 H), 1.1 (d, J = 7 Hz, 3 H), 1.0 (m, 1 H).

α,α-Diphenyl-4-pyridinepropanenitrile (18). 4-(Chloromethyl)pyridine hydrochloride (7.5 g, 45.7 mmol) was added to a mixture of 9.5 g (49.2 mmol) of diphenylacetonitrile, 25 mL of 50% NaOH solution, 25 mL of toluene, and 1.0 g (2 mmol) of hexadecyltributylphosphonium bromide, and the mixture was stirred without cooling for 4 h. Toluene (100 mL) and 100 mL of ice−water were added, a small amount of CH_2Cl_2 was added to dissolve some solids, the layers were separated, and the aqueous layer was extracted with 2 × 25 mL of toluene. Removal of the solvent form the dried extracts and crystallization from 10 mL of EtOAc gave 9.06 g (70%) of the title compound, mp 119−120 °C. ^{1}H NMR: δ 8.4 (d, J = 6 Hz, 2 H), 7.3 (m, 10 H), 6.8 (d, J = 6 Hz, 2 H), 3.6 (s, 2 H). Anal. Calcd for $C_{20}H_{16}N_2$: C, 84.48; H, 5.67; N, 9.85. Found: C, 84.19; H, 5.56; N, 9.59.

1-(Phenylmethyl)-α,α-diphenyl-1,2,5,6-tetrahydro-4-pyridinepropanenitrile (19). A mixture of 5.31 g (18.7 mmol) of nitrile **18** and 15 mL of 2-propanol was heated under reflux until the solids dissolved, the solution was allowed to cool to ca. 60 °C, 5 mL (7.2 g, 5.84 mmol) of benzyl bromide was added, and the mixture was heated under reflux for 10 min. The mixture was cooled with ice, and the solids were collected by filtration, washed once with 2-propanol, and dried to give 7.81 g (92%) of the quaternary pyridinium salt. A mixture of 13.0 g (28.6 mmol) of the finely powdered salt and 70 mL of EtOH was cooled to 0 °C, and 5.0 g (151 mmol) of sodium borohydride was added over 30 min. The mixture was stirred in an ice bath for 30 min, 10 mL of H_2O was added, and stirring was continued for 30 min. The reaction was quenched by addition (< 0 °C) of 100 mL of 15% NaOH, and the product was extracted into 100 and 3 × 20 mL of CH_2Cl_2. Removal of the solvent from the dried solution gave 10.92 g (100%) of essentially pure title compound which was used directly: ^{1}H NMR δ 7.2−7.4 (m, 15 H), 5.5 (narrow t, 1 H); 3.5 (s, 2 H), 3.0 (s, 2 H), 2.5 (narrow t, 2 H), 2.4 (t, J = 5 Hz, 2 H), 1.7 (m, 2 H). The unstable base may be stored as the hydrochloride, mp 241−242 °C (EtOH). Anal. Calcd for $C_{27}H_{27}ClN_2$: C, 78.18; H, 6.56; N, 6.75. Found: C, 77.75; H, 6.46; N, 6.53.

1-(Phenylmethyl)-α,α-diphenyl-1,2,3,6-tetrahydro-4-pyridinepropanal (20). A solution of 7.64 g (20.2 mmol) of amine **19** in 40 mL of toluene was treated below −50 °C with 28 mL (42 mmol) of 1.5 M *i*-Bu_2AlH in toluene, and the mixture was stirred in a dry ice/acetone bath for 2 h. EtOH (20 mL) was added (←50 °C) followed by 30 mL of 10% HCl. The mixture was allowed to come to rt, made basic with 15% NaOH, and extracted with toluene to give 7.50 g (88%) of the title compound of ca. 90% purity. ^{1}H NMR: δ 9.8 (s, 1 H), 7.2−7.4 (m, 15 H), 5.2 (narrow m, 1 H), 3.4 (s, 2 H), 3.1 (s, 2 H), 2.8 (narrow m, 2 H), 2.2 (t, J = 5 Hz, 2 H), 1.5 (m, 2 H). The hydrochloride (95% EtOH) had mp 216−217 °C dec. Anal. Calcd for $C_{27}H_{28}ClNO$: C, 77.59; H, 6.75; N, 3.35. Found: C, 77.10: H, 6.76; N, 3.30.

***N*-[2,2-Diphenyl-3-[1,2,3,6-tetrahydro-1-(phenylmethyl)-4-pyridinyl]propylidene]methanamine *N*-Oxide (21).** A mixture of 4.93 g (12.9 mmol) of aldehyde **20**, 3.0 g (35.9 mmol) of *N*-methylhydroxylamine hydrochloride, 3.0 g of NaOAc, and 15 mL of EtOH was stirred at rt overnight. Addition of 30 mL of 10% Na_2CO_3 and extraction with CH_2Cl_2 gave 5.15 g (97%) of essentially pure title compound. ^{1}H NMR: δ 7.4 (s, 1 H), 7.1−7.3 (m, 15 H), 5.2 (narrow m, 1 H), 3.7 (s, 3 H), 3.5 (s, 2 H), 3.4 (s, 2 H), 2.8 (narrow m, 2 H), 2.3 (t, J = 5 Hz, 2 H), 1.6 (m, 2 H). An analytical sample (MeCN) had mp 170−171 °C. Anal. Calcd for $C_{28}H_{30}N_2O$: C, 81.91; H, 7.37; N, 6.82. Found: C, 81.64; H, 7.26; N, 6.83.

1-Methyl-3,3-diphenyl-8-(phenylmethyl)-1,8-diazaspiro-[4.5]decane (23). A solution of 1.52 g (3.70 mmol) of nitrone **21** in 15 mL of anhydrous THF was treated at −5 °C with 6 mL (6 mmol) of 1 M $LiALH_4$ in THF, and the mixture was stirred in an ice bath for 1 h. A solution of 1 mL of H_2O in 10 mL of THF was added below −5 °C, the mixture was allowed to come to room temperature, 2 g of $MgSO_4$ was added, and the mixture was filtered. The solids were washed repeatedly with CH_2Cl_2, and the combined filtrates were concentrated. The residual crude hydroxylamine was dissolved in 50 mL of $CHCl_3$, and the solution was heated under reflux for 18 h and left at room temperature for 18 d. Removal of the solvent gave the essentially pure *N*-oxide **22**. ^{1}H NMR: δ 7.1−7.4 (m, 15 H), 4.6 (d, J = 13 Hz, 1 H), 4.4 (d, J = 13 Hz, 1 H), 3.5 (AB q, J = 15 Hz, 2 H), 3.2 (s, 2 H), 3.1 (s, 3 H), 3.0 (m, 1 H), 2.9 (m, 1 H), 1.9−2.2 (m, 5 H), 1.4 (m, 1 H). The *N*-oxide was immediately dissolved in 12 mL of acetic acid, and zinc dust (5 g) was added in small portions over 2.5 h. The mixture was filtered after stirring another hour, and the solids were washed repeatedly with CH_2Cl_2. The cooled filtrates were made basic with 50% NaOH. Removal of the solvent from the dried solution gave 1.20 g (82% from nitrone **21**) of essentially pure title compound as an oil. ^{1}H NMR: δ 7.1−7.3 (m, 15 H); 3.5 (2s, 4 H), 2.8 (d, J = 11 Hz, split further, 2 H); 2.6 (s, 2 H), 2.4 (s, 3 H), 2.0 (t, J = 11 Hz, split further, 2 H),1.8 (t/d, J = 11/4 Hz, 2 H), 1.2 (d, J = 11 Hz, 2 H). ^{13}C NMR: δ 32.5, 34.0, 48.4, 51.7, 51.9, 61.3, 63.2, 65.8, 125.5, 126.9, 126.9, 128.0, 128.1, 129.1, 138.4, 149.5. HRMS: calcd for $C_{28}H_{32}N_2$ 396.2566,

found 396.2570. The difumarate had mp 204–206 °C dec, 90% *n*-PrOH). Anal. Calcd for $C_{36}H_{40}N_2O_8$: C, 68.77; H, 6.41; N, 4.46. Found: C, 69.37; H, 6.45; N, 4.55.

***N*-[1-(2-Cyclopenten-1-yl)ethylidene]methanamine *N*-Oxide (25).** A mixture of 10.02 g (81 mmol) of 1-(2-cyclopenten-1-yl)-2-propanone (**24**), 10.0 g (119 mmol) of *N*-methylhydroxylamine hydrochloride, 11.0 g (134 mmol) of NaOAc, and 25 mL of EtOH was stirred at room temperature for 17 h. Isolation as described for nitrone **21** gave 11.38 g of crude nitrone **25** as a mixture of two isomers. ^{1}H NMR: δ 5.4–5.8 (m, 2 H), 3.7 (2s, 3 H), 2.0–3.2 (m + 2s, 9 H), 1.4–1.6 (m, 1 H).

1,2,2-Trimethyloctahydrocyclopenta[*b*]pyrrole 1-Oxide (27). Crude nitrone **25** (8.31g, 54.3 mmol) in 25 mL of toluene was added at 0 °C to a mixture of 30 mL (90 mmol) of 3 M MeMgCl in THF and 150 mL of toluene. The cooling bath was removed, and the mixture was stirred for 4 h. Twenty percent NH_4Cl (100 mL) was added (<0 °C), and the mixture was extracted with CH_2Cl_2. The dried extracts were concentrated at 25 °C to give 9.44 g of a mixture containing *N*-oxide **27** and uncyclized hydroxylamine **26** in a ratio of 2:1. The mixture was dissolved in 50 mL of CH_2Cl_2, and the solution was allowed to stand at room temperature for 16 h. Removal of the solvent at 25 °C gave 9.40 g of the crude title compound as a semisolid. ^{1}H NMR: δ 4.0 (m, 1 H), 2.8 (s, 3 H), 2.6–2,7 (m, 2 H), 1.5 (s, 3 H), 1.4 (s, 3 H), among others. A small sample (0.40 g) was converted into the picrate (0.48 g, 48% from ketone **24**), mp 173–174 °C. Anal. Calcd for $C_{16}H_{22}N_4O_8$: C, 48.24; H, 5.57; N, 14.07. Found: C, 48.33; H, 5.52; N, 13.96.

1,2,2-Trimethyloctahydrocyclopenta[*b*]pyrrole (28). A mixture of 8.13 g (48.1 mmol) of crude **27**, 50 mL of HOAc, and 1.70 g of 10% Pd/C was agitated in a Parr shaker under 48 psi initial H_2 pressure for 70 min. The filtered solution was treated with 8 mL of concd HCl and concentrated. The residue was taken up in 50 mL of H_2O, and the solution was washed with ether. The aqueous phase was made basic with 50% NaOH and extracted with CH_2Cl_2. Distillation through a 20-cm spinning-band column gave 3.91 g (51% from ketone **24**) of the title compound, bp 78 °C (20 mm), n^{25}1.4612. ^{1}H NMR: δ 2.9 (m, 1 H), 2.5 (m, 1 H), 2.2 (s, 3 H), 1.8 (m, 1 H), 1.1–1.9 (m, 7 H), 1.1 (s, 3 H), 0.8 (s, 3 H). HRMS: calcd for $C_{10}H_{19}N$ 153.1518, found 153.1516. The fumarate of **28** was obtained by adding 2.16 g of fumaric acid to a hot solution of 2.86 g of the free base in 6 mL of *i*-PrOH, heating under reflux until all solids dissolved, and cooling. Yield: 4.80 g (95%). Mp: 140–141 °C. Anal. Calcd for $C_{14}H_{23}NO_4$: C, 62.43; H, 8.61; N, 5.20. Found: C, 62.55; H, 8.70; N, 5.14.

***N*-(2-Vinylbenzylidene)methanamine *N*-oxide (30)** was prepared in 91% yield from aldehyde **29** as described for the preparation of nitrone **21**. ^{1}H NMR: δ 9.1 (m, 1H), 7.6 (s, 1 H), 7.3–7.5 (m, 3H), 6.9 (d/d, J = 17/11 Hz, 1 H), 5.6 (d, J = 17 Hz, split further, 1 H), 5.4 (d, J =11 Hz, 1 H), 3.9 (s, 3 H).

1,2,3-Trimethyl-1,3-dihydroisoindole *N*-Oxide (32). To a solution of 2.10 g (13.0) mmol) of nitrone **30** in 9 mL of THF was added at −15 °C 5 mL (15.0 mmol) of 3 M MeMgCl in THF. The mixture was stirred in an ice bath for 1 h, and 20 mL of 20% NH_4Cl was added below 0 °C. Extraction with CH_2Cl_2 yielded 1.83 g (82%) of crude **15** as an unstable solid. ^{1}H NMR of **32a** (*ca.* 90%): δ 7.1–7.4 (m, 4 H), 4.6 (q, J = 7Hz, 2 H), 3.2 (s, 3 H), 1.8 (d, J = 7 Hz, 6 H). ^{1}H NMR of **32b** (*ca.* 10%): δ 4.8 (q, J = 7 Hz, 1 H), 4.5 (q, J = 7Hz, 1 H), 3.0 (s, 3 H), 1.7 (2 d, J = 7 Hz, 6 H) in addition to the aromatic H. The product turned dark rapidly on exposure to air.

1,2,3-Trimethyl-1,3-dihydroisoindole (33). Deoxygenation of *N*-oxides **32** (1.27 g) as described for the preparation of amine **28** gave 0.85 g (74%) of crude title compound. ^{1}H NMR for **33a**: δ 7.1–7.3 (m, 4 H), 3.6 (q, J = 7Hz, 2 H), 2.5 (s, 3 H), 1.4 (d, J = 7 Hz, 6 H). ^{1}H NMR for **33b**: δ 4.2 (q, J = 7 Hz, 2 H) and 1.3 (d, J = 7 Hz, 6 H), among others. High-resolution MS: calcd for $C_{11}H_{15}N$ 161.1204, found 161.1204. The product could not be purified since it decomposed on short-path distillation and turned black rapidly on exposure to air.

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Supporting Information Available: ^{1}H and/or ^{13}C NMR spectra of new compounds **5**, **6**, **9a,b**, **11**, **14**, **15a,b**, **17a,b**, **23**, **32a,b**, and **33a,b** for which elemental analyses were not obtained (13 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be obtained from the ACS; see any current masthead page for ordering information.

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