Intramolecular Hetero-Diels–Alder Reaction of N-Arylimines. Applications to the Synthesis of Octahydroacridine Derivatives

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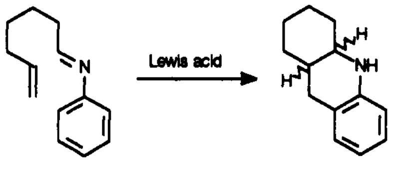
A new intramolecular Lewis acid catalyzed hetero-Diels–Alder reaction of N-arylimines **5** with nonactivated olefins tethered to the 2-azadiene system was developed in order to prepare 1,2,3,4,4a,9,9a,10-octahydroacridine derivatives **6**. Both reactivity and cis/trans selectivity of **6** were mainly dependent on the substitution pattern in the 3-position of the cyclization precursor **5**. The type of Lewis acid plays only a minor role in determination of the cis/trans ratio. The synthetic utility of this new cyclization was increased by performing it as a one-pot reaction (**3** + **4** → **6**). Both absolute configuration and preferred conformation were assigned by detailed NMR studies.

Introduction

The Lewis acid-catalyzed hetero-Diels–Alder reaction of N–arylimines, which were used as 2-azadienes, was studied almost 30 years by Povarov and co-workers.[1] However, until now only those reactions with electron-rich dienophiles such as dihydrofurans,[2] enol ethers,[1,3] enamines,[4] and ketenes[5] were investigated. In a more recent approach by Grieco[6] and Mellor,[7] N-arylimines derived from formaldehyde reacted with electron-rich dienophiles to give polycylic ring systems. In this article we report a new intramolecular type of hetero-Diels–Alder reaction of N-arylimines **1** with nonactivated olefins tethered to the diene system, which results in the formation of 1,2,3,4,4a,9,9a,10-octahydroacridines **2** (eq 1), a class of pharmacological interesting compounds.[8-10]



(1)

1 **2**

Several syntheses of the octahydroacridine skeleton have previously been reported, e.g., such as catalytic hydrogenation of acridine,[11] intramolecular Beckmann rearrangement of oxime sulfonates,[12] amino-Claisen rearrangement of geranyl aniline,[13] condensation of aniline with anthranilic acid followed by chlorination and reduction,[9] and acid-catalyzed condensation of aniline with isophorone.[14] However, the above-mentioned syntheses are only of limited synthetic value, especially because of the lack of stereochemical control of the ring fusion. An intramolecular Diels–Alder reaction of **1** should give rise to the desired ring system **2** in a stereocontrolled manner.[15]

Results and Discussion

As shown in Scheme I and Table I, treatment of N-arylimines **5** in CH_2Cl_2 with catalytic amounts of $SnCl_4$ (0.1 equiv) for several hours at −78 °C (method A) followed by basic hydrolysis resulted in the formation of octahydroacridines **6** in high yields. In the case of the 3-dimethyl-substituted N-arylimines **5a**,**b** the corresponding cyclization products were formed with extremely high trans selectivity (trans/cis = 99:1). We found that the cyclization also can be carried out as a one-pot reaction by successive addition of the Lewis acid and the aldehyde **3** to a precooled solution (−78 °C) of the amine **4** in CH_2Cl_2 (method B).[16] As shown in Table I the yields and cis/trans ratios of the one-pot reaction are quite similar to the cyclization of isolated imines **5**. Concerning the stereochemistry of the ring fusion, the substituents R^1 and R^2 in the 3-position of **5** have a significant influence on the cis/trans ratio.

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[15] For recently published stereocontrolled synthesis of the basic tetrahydroquinoline system by Diels–Alder reaction of azaxylylenes with electron-poor dienophiles, which is, however, limited to a specific substitution pattern of the aromatic ring and the dienophile, see: Wojciechowski, K. *Synlett* **1991**, 571–572.

[16] In order to obtain a clean one-pot reaction, the aldehyde **3** was added very slowly (over 1 h) to the reaction mixture; otherwise, a substantial amount of 3-substituted 6-(2-isopropenyl)cyclohexanol, i.e, the product of an intramolecular Lewis acid-catalyzed ene reaction of **3**, was isolated.

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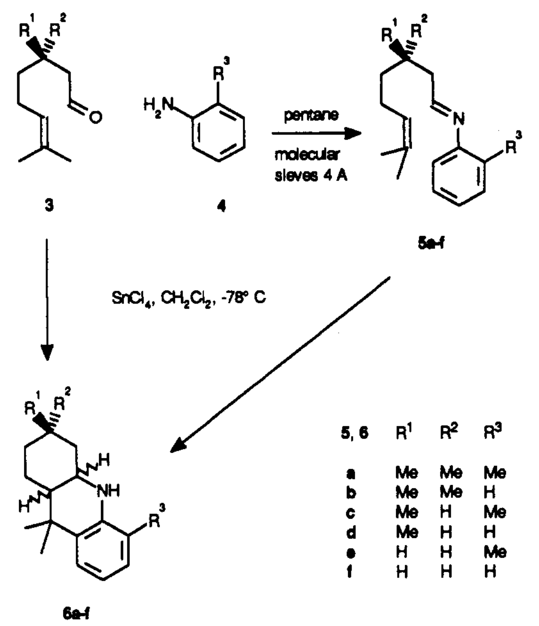
Scheme I



5, 6	R¹	R²	R³
a	Me	Me	Me
b	Me	Me	H
c	Me	H	Me
d	Me	H	H
e	H	H	Me
f	H	H	H

Table I. Preparation of Octahydroacridines 6[a,b]

imine	R¹	R²	R³	method	reactn time (h)	product	yield (%)	products 6 (%) cis	products 6 (%) trans
5a	Me	Me	Me	A	24	**6a**	91	1	99
5a	Me	Me	Me	B	27	**6a**	86	1	99
5b	Me	Me	H	A	21	**6b**	86	1	99
5b	Me	Me	H	B	27	**6b**	72	0	100
5c	Me	H	Me	B	46	**6c**	84	42	56[c]
5d	Me	H	H	B	46	**6d**	84	31	67[d]
5e	H	H	Me	A	109	**6e**	35	64	36
5e	H	H	Me	B	19	**6e**	64	57	43
5f	H	H	H	A	109	**6f**		39	60
5f	H	H	H	B	12	**6f**	62	41	57

[a] Cyclization of isolated imines **5** (method A) or one-pot reaction of aldehyde **3** and amine **4** (method B) with 0.1 equiv of $SnCl_4$ in CH_2Cl_2 at −78 °C. [b] Cis/trans ratios were determined by capillary GC. [c] Two additional diastereomers (0.3% and 1.5%, relative to *cis*/*trans*-**6c**) were also detected. [d] Two additional diastereomers (0.3% and 1.7%, relative to *cis*/*trans*-**6d**) were also detected.

Table II. Cyclization of N-Arylimines 5a ($R^1 = R^2 = R^3 =$ Me) and 5c ($R^1 = R^3 =$ Me, $R^2 =$ H) With 0.1 equiv of $SnCl_4$ in Different Solvents[a]

entry	imine	solvent	temp (°C)	time (h)	imine (%)	products 6a,c (%) cis	trans	minor diast of 6c[b]	
1	**5a**	CH_2Cl_2	−78	1	3	1	94		
2	**5a**	toluene	−78	1	0.6	2	97		
3	**5a**	pentane	−78	1	26	3	68		
4		↓	−78	18.5	1	1	97		
5	**5a**	ether	−78	3	69	1	24		
6		↓	−78	18.5	52	1	42		
7	**5a**	THF	−78	18.5	88		4		
8		↓	rt	22		1	97		
9	**5c**	CH_2Cl_2	−78	1		47	51	0.4	2
10	**5c**	toluene	−78	1	23	14	60		2
11		↓	−78	20		8	89		1
12	**5c**	pentane	−78	3	80	4	14	1	0.3
13		↓	rt	103	1	26	71		

[a] Yields of the products and recovered imine were determined by capillary GLC using *n*-octadecane as internal standard. [b] The configuration of these two minor diastereomers was not determined.

Table III. Cyclization of N-Arylimines 5a,c with Different Lewis Acids (0.1 equiv) in CH_2Cl_2[a]

imine	Lewis acid	temp (°C)	time (h)	imine (%)	products 6a,c (%) cis	trans	minor diast of 6c[b]	
5a	$ZnCl_2$	rt	14	5	3	91		
5a	$TiCl_4$	−78	17	1	1	98		
5a	$FeCl_3$	−78	1	1	3	94		
5a	$BF_3{\cdot}OEt_2$	−78	15	1	1	98		
5a	$AlCl_3$	rt	8.5		1	97		
5a	Et_2AlCl	−78	15	5	1	93		
5a	$EtAlCl_2$	−78	15	0.2	1	96		
5a	CF_3CO_2H	−78	25	2	0.4	97		
5a	*p*-TsOH	rt	8.5		1	98		
5a	PPA	rt	20.5		3	96		
5c	$ZnCl_2$	rt	14	1	39	58		2
5c	$TiCl_4$	−78	17	31	15	52		2
5c	$FeCl_3$	−78	1	2	47	49		2
5c	$BF_3{\cdot}OEt_2$	−78	1	1	22	73	0.3	3
5c	$AlCl_3$	−78	18	0.2	39	58		1
5c	Et_2AlCl	−78	18		45	53		0.1
5c	$EtAlCl_2$	−78	18		43	54		1
5c	CF_3CO_2H	−78	18	1	20	77		2
5c	*p*-TsOH	rt	1	0.5	11	76	6	3

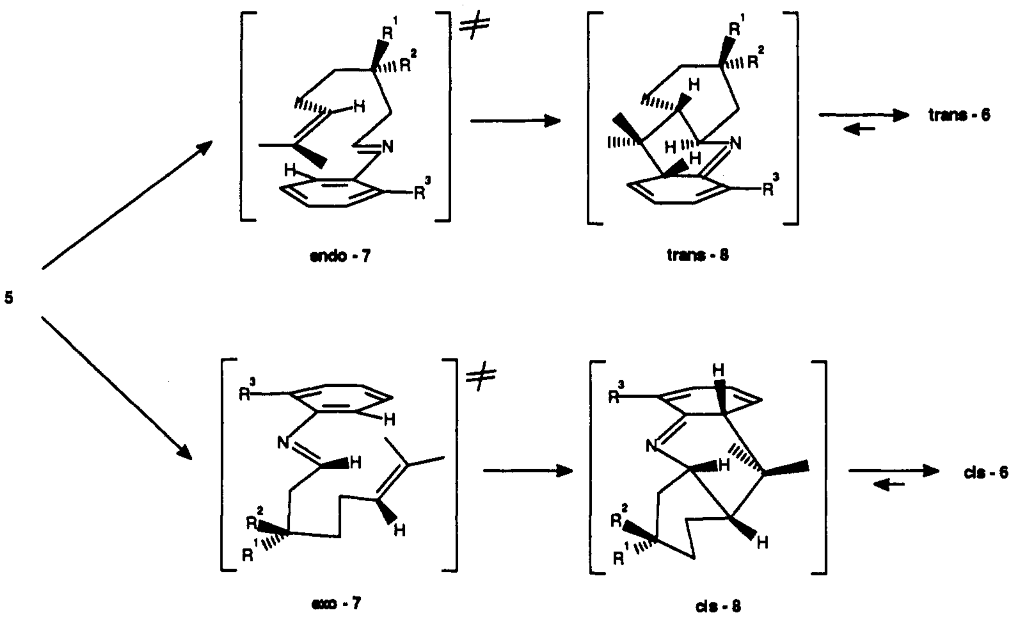
[a] For determination of yields and product ratios see Table II, footnote a. [b] See Table II, footnote b.

Steric bulk at C-3 favors formation of the trans product. While the *gem*-dimethyl-substituted derivative **5a** yielded almost exclusively the trans product **6a** (99% via method B), the amount of the cis isomer increased in the case of **6c** (42%, method B) and **6e** (57%, method B). In the case of imines **5c,d**, which were derived from optically pure (*R*)-citronellal, two minor cyclization products were also detected; however, their total amount was usually below 5%. The similarity of the GC–mass spectra of these minor products as compared to those of the major products suggests that they are diastereomers of *cis*/*trans*-**6c,d**.

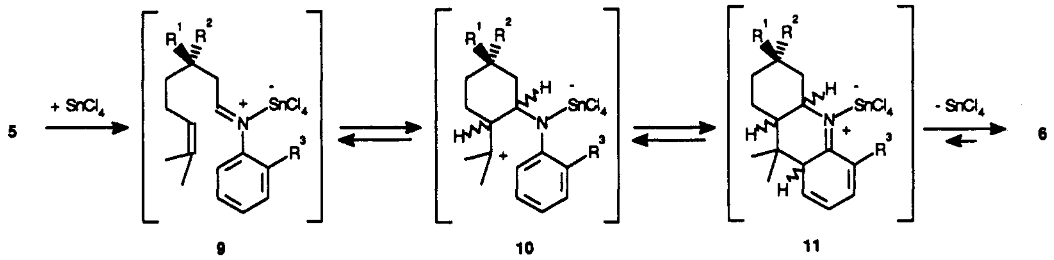
We studied the cyclization using different solvents and Lewis acids with N-arylimines **5a,c** as test substrates. Table II shows that the cyclization reaction can be done both in nonpolar and polar, noncoordinating solvents. Donor solvents like ether or THF which decrease the acidity of the Lewis acid by complexation are not useful. While the arylimine **5a** shows almost the same reactivity and selectivity (entries 1, 2, and 4) in either CH_2Cl_2, toluene, or pentane, the reactivity of **5c** decreases in the order toluene > CH_2Cl_2 > pentane (entries 9, 10, and 12), whereas the selectivity order for **5c** is toluene > pentane > CH_2Cl_2.

The formation of the octahydroacridine **6** can be catalyzed by a broad range of Lewis or Brönsted acids. As shown in Table III, the acid catalysts differ mainly in their reactivity. Strong Lewis acids like $TiCl_4$, $BF_3{\cdot}OEt_2$, $EtAlCl_2$, Et_2AlCl, $FeCl_3$, and CF_3CO_2H gave complete conversion of the imines **5a,c** within 20 h even at −78 °C, while $ZnCl_2$, *p*-TsOH, or PPA required room temperature. However, the selectivity was found to be more dependent on the substrate structure than on the type of Lewis acid used. In the case of **5a** best results were achieved with BF_3OEt_2 (trans:cis = 98:1), $TiCl_4$ (trans:cis = 98:1) or CF_3CO_2H (trans:cis = 97:0.4). Even the less selective catalysts like $ZnCl_2$ and $FeCl_3$ gave trans/cis ratios of 91:3 and 94:3, respectively. When **5c** was used for the cyclization, $ZnCl_2$, $FeCl_3$, $AlCl_3$, $EtAlCl_2$, and Et_2AlCl yielded trans/cis ratios close to 50:50 together with 1–2% of the two minor diastereomers. On the other hand, with $BF_3{\cdot}OEt_2$ or CF_3CO_2H trans/cis ratios were increased to 77:20. The above-mentioned strong dependence of reactivity and selectivity on the substrate and the only minor influence of the acidic catalyst is somewhat unexpected because it is known from other Lewis acid catalyzed reactions of imines that they are significantly controlled by the type of Lewis acid.[17,18]

Scheme II



Scheme III



To explain the stereochemical outcome of the cyclization, either a concerted [4 + 2]-cycloaddition (Scheme II) or a multistep reaction via ionic intermediates (Scheme III) could be proposed.[19] We favor the cycloaddition mechanism because it explains both the formation of the trans product 6 via the endocyclic transition state *endo*-7 and the formation of the cis product via the exocyclic transition state *exo*-7. Due to the steric congestion (H-1/H-5) in *exo*-7, the endo transition state should be much more favored, especially when the rotational freedom of the C4-tether is decreased, e.g., by introducing a *gem*-dimethyl group at C-3. On the other hand, removal of substituents from the C4-tether should increase the amount of cis product 6, because *exo*-7 is more easily accessible than in the previous case, thus decreasing the energy difference between *endo*- and *exo*-7. However, a stepwise mechanism could not be completely ruled out, in which the terminal cyclohexane ring is built up first by a nucleophilic attack at the iminium ion 9, followed by an electrophilic aromatic substitution initiated by the tertiary carbeniumion 10. Finally, a tautomerization of the resulting cyclohexadienylimine 11 should give the product 6. However, we have no NMR-spectroscopic evidence (at −78 °C) for such a cyclohexadienylimine 8 or 11. Probably, the tautomerization is faster than the NMR time scale. When we studied the selectivity as a function of both reaction time and conversion, we found that the relative amount of the trans product is increasing with increasing reaction time and conversion (see, for example, Table II, entries 3, 4 and 10, 11). However, the isolated products 6 could not be epimerized by treatment with $SnCl_4$ (1.2 equiv) either at room temperature or −78 °C.

Determination of the Absolute Configuration and Preferred Conformation of *cis*/*trans*-6c. The structure of the trans product 6c (diagram) could be completely assigned by first-order interpretation of the 360-MHz 1D-^{1}H-NMR spectrum together with spin decoupling experiments. The large vicinal coupling $J_{4a,9a}$ = 10.5 Hz was taken as a strong evidence for the trans ring fusion. By using the known (*R*)-configuration of C-3 as a stereochemical anchor, the vicinal coupling data of *trans*-6c were analyzed in terms of dihedral angles from the Karplus relationship, and thus the *trans*-decalin configuration **B** with an equatorial methyl group at C-3 was proposed. In structure **B** H-4ax should give the following couplings (values of dihedral angles are given in parentheses): $J_{4ax,4a}$ ~ 11 Hz (180°), $J_{4ax,3}$ ~ 11 Hz (180°), which were indeed observed (see Experimental Section for details). The other coupling data of *trans*-6c were in complete agreement with this assignment. On the contrary, the other diastereomeric *trans*-decalin configuration of 6c (with an axial methyl group at C-3) should have the following couplings for H-4ax: $J_{4ax,4a}$ ~ 11 Hz (180°), $J_{4ax,3}$ ~ 3–4 Hz (60°). The same analysis was not possible for the cis isomer 6c due to overlapping multiplets of H-2eq, H-4-eq, H-1eq and H-9a, H-1ax, H-4ax, respectively. Therefore, NOESY spectra were recorded from both *trans*-6c and *cis*-6c. NOE enhancements between NH and the aromatic methyl group

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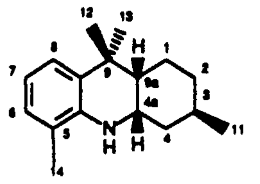
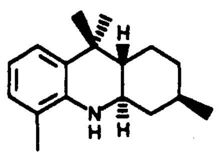
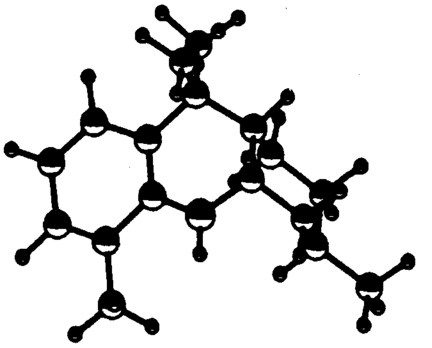
[19] The reviewers are gratefully acknowledged for their helpful discussions and suggestions, especially concerning the mechanism of the cyclization.



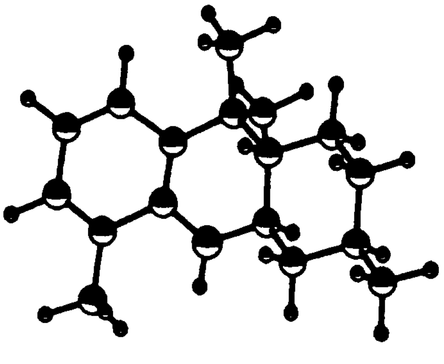
cis-6c



trans-6c



A



B

(H-14) and between NH and H-4eq were observed in both spectra. The NOE between NH and H-4a was smaller in *trans*-**6c** compared to *cis*-**6c**; however, effects due to saturation transfer from trace amounts of residual water may obscure possible enhancements. The trans decalin configuration **B** for *trans*-**6c** was confirmed by diagnostic NOE's between H-4a/H-13, i.e., the methyl group below the ring system, and H-1eq/H-12, i.e., the corresponding methyl group above the ring system. For the cis isomer we propose the structure *cis*-**6c** and a *cis*-decalin conformation **A** and assign the singlets at 0.98 and 0.93 ppm to the methyl groups below (H-13) and above (H-12) the ring system, respectively. Two strong NOE's were observed, i.e., H-4a/H-12 and H-4a/H-9a, and smaller NOE's between H-4a/H-4eq and H-4a/H-4ax. However, the expected cross peak between protons H-12/H-9a, which are located on the same side of the ring, could not be detected due to the overlap of multiplets and cross peaks close to the diagonal. In order to check the stereochemical assignment of the cis isomer, a ^{13}C,^{1}H shift correlated 2D-NMR spectrum with polarization transfer via the ^{1}J couplings was recorded and cross sections, i.e., ^{1}H-NMR subspectra along individual carbon resonance portions were taken. Besides confirmation of ^{1}H and ^{13}C shift assignments, some of the multiplets could be interpreted as first-order spectra, e.g., H-9a, H-4eq, H-4ax, and H-1ax. Especially the coupling constants of H-4ax (ddd at 0.75 ppm, $^{2}J_{4ax,4eq} = -13.0$ Hz, $^{3}J_{4ax,3} = 13.0$ Hz, $^{3}J_{4a,4ax} = 4.0$ Hz) were taken as evidence for the *cis*-decalin structure **A** for *cis*-**6c**.[20]

Conclusion

The Lewis acid-mediated cyclization of *N*-arylimines described herein allows easy and convenient access to octahydroacridines. Especially the one-pot procedure, which does not require the isolation of the moisture- and oxygen-sensitive imines, seems to be useful for the preparation of octahydroacridines with a variety of substituents on the ring system, just by choosing suitable aldehyde and aniline derivatives. The selectivity of the ring fusion can be adjusted to some extent by the choice of Lewis acid and solvent. It was shown that the absolute stereochemistry and preferred conformation of tricyclic ring systems with one known stereocenter can be elucidated by NMR techniques.

Experimental Section

All reactions were carried out under an argon atmosphere using standard Schlenk techniques. Solvents were dried and deoxygenated by standard procedures. Analytical TLC was performed on precoated SiO_2 254 F plates (0.25-mm thickness) and visualized with a solution of phosphomolybdic acid in EtOH (5%, v/v). Flash chromatography was carried out with silica gel 60 (230–400 mesh). Melting points were measured on a capillary melting point apparatus and are uncorrected. IR spectra were recorded on an FT-IR spectrometer. Optical rotations were measured in 1-dm cells (1 mL capacity) at ambient temperature. Mass spectra were obtained at an ionization potential of 70 eV. For GC analysis a HP5 fused silica capillary column (0.32-mm i.d., length 25 m) was used. 7-Methyl-6-octenal and 3,3,7-trimethyl-6-octenal were prepared according to literature procedues;[21] (*R*)-(+)-citronellal was commercially available.

General Procedure for the Preparation of N-Arylimines 5. To a solution of aniline or toluidine (1.00 mmol) in pentane (10 mL) was added aldehyde **3** (1.00 mmol) and 4-Å molecular sieves, and the mixture was stirred overnight at room temperature. After filtration via Celite the solvent was removed, and the crude products were used without further purification.

***N*-(3,3,7-Trimethyl-6-octenylidene)-*o*-toluidine (5a)**: 255 mg (quant.) of a colorless oil; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.86 (t, $J = 5.7$ Hz, 1 H, HC=N), 7.24–7.08 (m, 3 H, H-4′, H-5′, H-6′), 6.78–6.74 (m, 1 H, H-3′), 5.19 (m, 1 H, H-6), 2.46 (d, $J = 5.7$ Hz, 2 H, H-2), 2.34 [s, 3 H, (C-2′)CH_3], 2.20–2.09 (m, 2 H, H-5), 1.76 (d, $J = 1.0$ Hz, 3 H, H-9), 1.69 (s, 3 H, H-8), 1.48–1.35 (m, 2 H, H-4), 1.06 [s, 6 H, (C-3)Me_2]; ^{13}C-NMR (50 MHz, $CDCl_3$) δ 164.5, 151.9, 131.0, 130.3, 129.9, 126.5, 124.6, 118.3, 48.1, 42.6, 33.8, 29.7, 27.3, 25.6, 22.7, 17.7, 17.5; IR (film) 1653, 1457, 745 cm^{-1}; MS (EI) *m/z* 257 (M, 23). 242 (26), 174 (35), 158 (33), 133 (35), 118 (54), 107 (40), 95 (42), 91 (37), 84 (41), 69 (82), 55 (100); HRMS calcd for $C_{18}H_{27}N$ 257.2143, found 257.2137.

***N*-(3,3,7-Trimethyl-6-octenylidene)aniline (5b)**: 247 mg (quant.) of a colorless oil; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.90 (t, $J = 5.7$ Hz, 1 H, HC=N), 7.32 ("t", $J = 7.1$ Hz, 2 H, H-2′, H-6′), 7.17 ("d", $J = 7.3$ Hz, 1 H, H-4′), 7.01 ("t", $J = 7.1$ Hz, 2 H, H-3′, H-5′), 5.12 (m, 1 H, H-6), 2.39 (d, $J = 5.7$ Hz, 2 H, H-2), 2.12–1.98 (m, 2 H, H-5), 1.69 (d, $J = 1.0$ Hz, 3 H, H-9), 1.62 (s, 3 H, H-8), 1.40–1.21 (m, 2 H, H-4), 1.06 [s, 6 H, (C-3)Me_2]; ^{13}C-NMR (50 MHz, $CDCl_3$) δ 164.4, 152.4, 131.1, 129.9, 128.9, 125.3, 124.6, 120.5, 48.1, 42.6, 33.9, 29.6, 27.3, 25.6, 22.7, 17.5; IR (film) 1653, 1451, 694 cm^{-1}; MS (EI) *m/z* 243 (M, 26), 228 (65), 160 (90), 147 (77), 118 (100), 104 (50), 91 (50), 77 (89), 69 (74), 55 (85); HRMS calcd for $C_{17}H_{25}N$ 243.1987, found 243.1983.

***N*-(*R*)-(3,7-Trimethyl-6-octenylidene)-*o*-toluidine (5c)**: 230 mg (quant.) of a colorless oil; $[\alpha]^{20}_{D}$ +4.6° (*c* 1.00; $CHCl_3$); ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.75 (t, $J = 5.5$ Hz, 1 H, HC=N), 7.19–7.06 (m, 3 H, H-4′, H-5′, H-6′), 6.72 (dd, $J = 6.3$, 1.9 Hz, 1

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[20] The stereochemical assignment of the other cyclization products **6a,b,d–f** was deduced from the known configuration of *cis/trans*-**6c** because the corresponding cis and trans isomers showed similar couplings and chemical shifts for H-4a.

[21] Sakane, S.; Maruoka, K.; Yamamoto, H. *Tetrahedron* **1986**, *42*, 2203–2209.

H, H-3′), 5.14 (m, 1 H, H-6), 2.57–2.33 (m, 2 H, H-2), 2.29 [s, 3 H, (C-2′)CH_3], 2.26–1.85 (m, 3 H, H-5, H-3), 1.71 (s, 3 H, H-8), 1.64 (s, 3 H, H-9), 1.63–1.23 (m, 2 H, H-4), 1.05 [d, J = 6.6 Hz, 3 H, (C-3)CH_3]; ^{13}C-NMR (50 MHz, $CDCl_3$) δ 165.4, 151.8, 131.4, 130.3, 129.9, 126.6, 124.9, 124.4, 118.3, 43.6, 36.9, 30.6, 25.6, 25.4, 19.7, 17.7, 17.6; IR (film) 1654, 1487, 1457, 747 cm^{-1}; MS (EI) *m/z* 229 (M, 28), 214 (27), 172 (26), 147 (94), 146 (100), 119 (89), 117 (88), 93 (41), 85 (37), 77 (91), 69 (64); HRMS calcd for $C_{16}H_{23}N$ 229.1830, found 229.1836.

***N*-(*R*)-(3,7-Trimethyl-6-octenylidene)aniline (5d)**: 240 mg (quant.) of a colorless oil; $[\alpha]^{20}_D$ +11.1° (*c* 1.00; $CHCl_3$); ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.83 (t, J = 5.5 Hz, 1 H, HC=N), 7.36–7.28 (m, 2 H, H-3′), 7.19–7.12 (m, 1 H, H-4′), 7.04–7.00 (m, 2 H, H-2′), 5.12 (m, 1 H, H-6), 2.44 ("t", J = 5.4 Hz, 1 H, H-2a), 2.33 (dd, J = 7.7, 5.6 Hz, 1 H, H-2b), 2.11–1.91 (m, 3 H, H-3, H-5), 1.69 (s, 3 H, H-8), 1.62 (s, 3 H, H-9), 1.62–120 (m, 2 H, H-4), 1.02 [d, J = 7.7 Hz, 3 H, (C-3)CH_3]; ^{13}C-NMR (50 MHz, $CDCl_3$) δ 165.9, 152.3, 131.3, 128.8, 125.2, 124.3, 120.4, 43.6, 36.9, 30.6, 25.6, 24.5, 19.6, 17.8; IR (film) 1654, 1596, 1486, 755, 695 cm^{-1}; MS (EI) *m/z* 243 (M, 12), 228 (16), 214 (16), 160 (65), 146 (23), 118 (100), 107 (49), 91 (64), 77 (22), 69 (28), 65 (41), 57 (25); HRMS calcd for $C_{17}H_{25}N$ 243.1987, found 243.1995.

***N*-(7-Methyl-6-octenylidene)-*o*-toluidine (5e)**: 230 mg (quant.) of a colorless oil; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.76 (t, J = 5.7 Hz, 1 H, HC=N), 7.21–7.06 (m, 3 H, H-4′, H-5′, H-6′), 6.77–6.52 (m, 1 H, H-3′), 5.15 (m, 1 H, H-6), 2.55–2.45 (m, 2 H, H-2), 2.29 [s, 3 H, (C-2′)CH_3], 2.18–1.98 (m, 4 H, H-3, H-5), 1.73 (s, 3 H, H-8), 1.65 (s, 3 H, H-9), 1.57–1.31 (m, 2 H, H-4); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 165.7, 131.0, 130.2, 129.9, 126.5, 124.9, 124.3, 118.2, 36.4, 29.6, 29.4, 27.7, 25.6, (2 × CH_3), 17.6; IR (film) 1655, 1456, 746 cm^{-1}; MS (EI) *m/z* 229 (M, 16), 214 (19), 161 (27), 146 (33), 118 (72), 107 (39), 91 (42), 83 (58), 69 (78), 57 (100); HRMS calcd for $C_{16}H_{23}N$ 229.1830, found 229.1827.

***N*-(7-Methyl-6-octenylidene)aniline (5f)**: 212 mg (quant.) of a colorless oil; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.87 (t, J = 5.0 Hz, 1 H, HC=N), 7.36–6.50 (m, 5 H, H-2′, H-3′, H-4′, H-5′, H-6′), 5.12 (m, 1 H, H-6), 2.70–2.51 (m, 1 H, H-2a), 2.10–1.98 (m, 5 H, H-3, H-5, H-2b), 1.71 (s, 3 H, H-8), 1.61 (s, 3 H, H-9), 1.80–1.20 (m, 2 H, H-4); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 166.4, 132.0, 131.0, 126.6, 124.3, 118.2, 36.5, 29.8, 29.3, 27.8, 25.7 (2 × CH_3); IR (film) 1653, 1601, 1501, 1487, 747, 693 cm^{-1}; MS (EI) *m/z* (M, 25), 200 (35), 185 (28), 147 (44), 132 (39), 105 (48), 95 (50), 84 (49), 69 (57), 57 (100), 55 (96); HRMS calcd for $C_{15}N_{21}N$ 215.1674, found 215.1679.

General Procedure for the Cyclization of N-Arylimines 5. (For temperatures and reaction times see Tables I–III.) Method A. To a solution of imine **5** (0.50 mmol) in CH_2Cl_2 (14 mL) was added a Lewis acid (0.05 mmol) over 30 min, and the mixture was stirred until GC showed no more conversion. NaOH (2 N, 50 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 100 mL). After the combined organic layers were washed with saturated NaCl (200 mL) and dried over $MgSO_4$, the crude products were purified by flash chromatography (100:1 hexanes–ethyl acetate).

Method B. To a precooled solution (−78 °C) aniline or *o*-toluidine (0.50 mmol) in CH_2Cl_2 (14 mL) was added a Lewis acid (0.05 mmol) over 30 min. Then aldehyde **3** (0.50 mmol) in CH_2Cl_2 (1 mL) was added slowly over 1 h and the reaction mixture was stirred until completion and worked up as described above.

3,3,5,9,9-Pentamethyloctahydroacridine (*trans*-6a): 111 mg (86%) of colorless crystals; mp 82 °C; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.18 (d, J = 7.7 Hz, 1 H, H-8), 6.86 (dd, J = 7.5, 0.7 Hz, 1 H, H-6), 6.58 (t, J = 7.5 Hz, 1 H, H-7), 3.43 (s, broad, 1 H, NH), 3.30 (ddd, J = 10.5, 10.4, 3.9 Hz, 1 H, H-4a), 2.12 (s, 3 H, H-15), 1.78–1.50 (m, 4 H, H-2eq, H-4eq, H-1eq, H-9a), 1.45–1.17 (m, 3 H, H-1ax, H-2ax, H-4ax), 1.32 (s, 3 H, H-13), 1.13 (s, 3 H, H-14), 1.04 (s, 6 H, H-11, H-12); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 140.7, 130.0, 127.5, 124.4, 120.1, 116.1, 47.5, 47.4, 47.3, 39.3, 34.9, 33.0, 31.0, 27.2, 26.9, 25.1, 20.9, 17.4; IR (film) 3407, 1598, 1478, 1362, 743 cm^{-1}; MS (EI) *m/z* 257 (M, 55), 242 (100), 158 (56), 91 (29), 69 (73), 55 (60); HRMS calcd for $C_{18}H_{27}N$ 257.2143, found 257.2131. Anal. Calcd for $C_{18}H_{27}N$: C, 83.98; H, 10.57; N, 5.45. Found: C, 83.62; H, 10.61; N, 5.40.

3,3,9,9-Tetramethyloctahydroacridine (*trans*-6b). 87 mg (72%) of colorless crystals; mp 69 °C; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.28 (d, J = 7.4 Hz, 1 H, H-8), 7.00 (t, J = 7.4 Hz, 1 H, H-6), 6.70 (t, J = 7.4 Hz, 1 H, H-7), 6.47 (d, J = 7.4 Hz, 1 H, H-5), 3.53 (s, broad, 1 H, NH), 3.27 (ddd, J = 10.5, 10.4, 4.1 Hz, 1 H, H-4a), 1.81–1.47 (m, 4 H, H-1eq, H-2eq, H-4eq, H-9a), 1.40 (s, 3 H, H-13), 1.40–1.27 (m, 3 H, H-1ax, H-2ax, H-4ax), 1.20 (s, 3 H, H-14), 1.04 (s, 6 H, H-11, H-12); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 143.1, 131.2, 126.5, 126.4, 116.8, 113.7, 47.8, 47.3, 47.1, 39.3, 34.8, 33.0, 30.9, 27.2, 26.7, 25.1, 20.9, 17.4; IR (film) 3394, 1605, 1582, 1498, 743 cm^{-1}; MS (EI) *m/z* 243 (M, 20), 228 (54), 158 (24), 149 (28), 69 (77), 55 (100); HRMS calcd for $C_{17}H_{25}N$ 243.1987, found 243.1983.

(3*R*)-3,5,9,9-Tetramethyloctylhydroacridine (6c). Flash chromatography yielded 31 mg (26%) of a pale yellow oil as the first fraction (98% cis by GC), 8 mg (7%) of a pale yellow oil as the second fraction (35% cis, 61% trans by GC), and 43 mg (36%) of colorless crystals as the third fraction (99% trans by GC). ***cis*-6c**: $[\alpha]^{20}_D$ −43.0° (*c* 1.00; $CHCl_3$); ^{1}H-NMR (200 MHz, C_6D_6) δ 6.86 ("d", J = 7.5 Hz, 1 H, H-8), 6.67 ("ddq", J = 7.5, 1.6, 0.8 Hz, 1 H, H-6), 6.46 (t, J = 7.5 Hz, 1 H, H-7), 3.41 (dddd, $J_{4a,9a}$ = 4.8 Hz, $J_{4a,NH}$ = 4 Hz, $J_{4a,4ax}$ = 4 Hz, $J_{4a,4eq}$ = 4 Hz, 1 H, H-4a), 2.80 (s, broad, 1 H, NH), 1.63 (s, 3 H, H-14), 1.50–1.37 (m, 1 H, H-3), 1.32–1.22 (m, 1 H, H-2eq), 1.22 (dddd, $J_{4ax,4eq}$ = 13.0 Hz, $J_{4a,4eq}$ = 4 Hz, $J_{4eq,3}$ = 4 Hz, $J_{4eq,2eq}$ = 4 Hz, 1 H, H-4eq), 1.18 ("dd", $J_{1ax,1eq}$ = 13.0 Hz, $J_{9a,1eq}$ = 4.8 Hz, 1 H, H-1eq), 0.98 (s, 3 H, H-13), 0.93 (s, 3 H, H-12), 0.80 (ddd, $J_{9a,1ax}$ = 11.7 Hz, $J_{4a,9a}$ = 4.8 Hz, $J_{9a,1eq}$ = 4.8 Hz, 1 H, H-9a), 0.76 (dddd, $J_{1ax,1eq}$ = 13.0 Hz, $J_{1ax,2ax}$ = 13.0 Hz, $J_{9a,1ax}$ = 11.7 Hz, $J_{1ax,2eq}$ = 5.0 Hz, 1 H, H-1ax), 0.75 (ddd, $J_{4ax,4eq}$ = 13.0 Hz, $J_{4ax,3}$ = 13.0 Hz, $J_{4a,4ax}$ = 4 Hz, 1 H, H-4ax), 0.57 (d, J = 6.6 Hz, 3 H, H-11), 0.62–0.39 (m, 1 H, H-2ax); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 141.1 (C-10a), 128.1 (C-8), 128.0 (C-8a), 124.4 (C-6), 119.6 (C-5), 116.6 (C-7), 47.1 (C-4a), 44.7 (C-9a), 41.6 (C-4), 35.8 (C-9), 35.1 (C-2), 34.3 (C-12), 26.6 (C-13), 25.7 (C-3), 23.1 (C-1), 22.6 (C-11), 17.5 (C-14); IR (film) 3432, 1598, 1477, 1300, 740 cm^{-1}; HRMS calcd for $C_{17}H_{25}N$ 243.1987, found 243.1981. ***trans*-6c**: mp 68 °C; $[\alpha]^{20}_D$ +58.0° (*c* 1.00; $CHCl_3$); ^{1}H-NMR (200 MHz, C_6D_6) δ 6.63 (d, J = 7.6 Hz, 1 H, H-8), 6.39 ("ddq", J = 7.6, 1.6, 0.8 Hz, 1 H, H-6), 6.21 (t, J = 7.6 Hz, 1 H, H-7), 2.92 (s, broad, 1 H, NH), 2.70 (dddd, $J_{4a,4ax}$ = 10.7, $J_{4a,9a}$ = 10.5 Hz, $J_{4a,4eq}$ = 4.2 Hz, $J_{4a,NH}$ = 1.3 Hz, 1 H, H-4a), 1.70 (s, 3 H, H-14), 1.38 (dddd, $J_{1ax,1eq}$ = 13.0 Hz, $J_{1eq,9a}$ = 3.0 Hz, $J_{1eq,2eq}$ = 3.0 Hz, $J_{1eq,2ax}$ = 3.0 Hz, 1 H, H-1eq), 1.30 (ddddd, $J_{2ax,2eq}$ = 12.5 Hz, $J_{2eq,3}$ = 3.1 Hz, $J_{1eq,2eq}$ = 3.1 Hz, $J_{1ax,2eq}$ = 3.1 Hz, $J_{4eq,2eq}$ = 2.1 Hz, 1 H, H-2eq), 1.21 (dddd, $J_{4ax,4eq}$ = 12.0 Hz, $J_{4a,4eq}$ = 4.2 Hz, $J_{4eq,3}$ = 3.0 Hz, $J_{4eq,2eq}$ = 2.1 Hz, 1 H, H-4eq), 0.98 (s, 3 H, H-12), 1.02–0.93 (m, 1 H, H-3), 0.91 (ddd, $J_{1ax,9a}$ = 12.0 Hz, $J_{4a,9a}$ = 10.5 Hz, $J_{1eq,9a}$ = 3.0 Hz, 1 H, H-9a), 0.82 (s, 3 H, H-13), 0.68 (dddd, $J_{1ax,1eq}$ = 13.0 Hz, $J_{1ax,2ax}$ = 13.0 Hz, $J_{1ax,9a}$ = 12.0 Hz, $J_{1ax,2eq}$ = 3.1 Hz, 1 H, H-1ax), 0.58 (ddd, $J_{4ax,4eq}$ = 12.0 Hz, $J_{4ax,3}$ = 12.0 Hz, $J_{4a,4ax}$ = 10.7 Hz, 1 H, H-4ax), 0.57 (d, J = 6.5 Hz, 3 H, H-11), 0.49 (dddd, $J_{1ax,2ax}$ = 13.0 Hz, $J_{2ax,2eq}$ = 12.5 Hz, $J_{2ax,3}$ = 11.6 Hz, $J_{1eq,2ax}$ = 3.0 Hz, 1 H, H-2ax); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 141.3 (C-10a), 130.7 (C-8a), 128.3 (C-6), 124.8 (C-8), 120.1 (C-5), 116.8 (C-7), 50.8 (C-4a), 47.1 (C-9a), 43.7 (C-4), 35.3 (C-2), 35.0 (C-9), 31.1 (C-12), 27.3 (C-13), 27.0 (C-3), 25.0 (C-1), 22.4 (C-11), 17.5 (C-14); IR (film) 3434, 1598, 1478, 1305, 739 cm^{-1}; MS (EI) *m/z* 243 (M, 40), 228 (100), 172 (27), 158 (35), 146 (30), 97 (21), 57 (26); HRMS calcd for $C_{17}H_{25}N$ 243.1987, found 243.1990. Anal. Calcd for $C_{17}H_{25}N$: C, 83.89; H, 10.35; N, 5.76. Found: C, 83.66; H, 10.60; N, 5.93.

(3*R*)-3,9,9-Trimethyloctahydroacridine (6d). Flash chromatography yielded 28 mg (23%) of a yellow oil as the first fraction (95% cis by GC), 28 mg (23%) of a yellow oil as the second fraction (11% cis, 88% trans by GC), and 29 mg (24%) of a yellow oil as the third fraction (90% trans by GC). ***cis*-6d**: $[\alpha]^{20}_D$ −87.0° (*c* 1.00; $CHCl_3$); ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.17 (dd, J = 7.5, 1.5 Hz 1 H, H-8), 6.99 (ddd, J = 7.9, 7.5, 1.5 Hz, 1 H, H-6), 6.63 (dt, J = 7.5, 1.3 Hz, 1 H, H-7), 6.46 (dd, J = 7.9, 1.3 Hz, 1 H, H-5), 3.87 (m, J = 2.9 Hz, 1 H, H-4a), 3.60 (s, broad, 1 H, NH), 1.83–1.60 (m, 5 H, H-3, H-2eq, H-4eq, H-1eq, H-9a), 1.37 (s, 3 H, H-12), 1.27 (s, 3 H, H-13), 1.33–1.12 (m, 3 H, H-1ax, H-4ax, H-2ax), 0.94 (d, J = 6.3 Hz, 3 H, H-11); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 143.0, 128.2, 126.4, 126.1, 116.1, 112.8, 46.7, 44.5, 41.1, 35.5, 34.7, 34.1, 26.1, 25.4, 22.9, 22.2; IR (film) 3400, 1606, 1493, 1302, 742 cm^{-1}; HRMS calcd for $C_{16}H_{23}N$ 229.1830, found 229.1836. Anal. Calcd for $C_{16}H_{23}N$: C, 83.78; H, 10.11; N, 6.11. Found: C, 83.97; H, 10.17; N, 6.62. ***trans*-6d**: $[\alpha]^{20}_D$ +111.0° (*c* 1.00; $CHCl_3$); ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.31 (dd, J = 7.7, 1.5

Hz 1 H, H-8), 7.04 (ddd, *J* = 7.9, 7.7, 1.5 Hz, 1 H, H-6), 6.72 ("ddd", *J* = 7.7, 1.3 Hz, 1 H, H-7), 6.51 ("dd", *J* = 7.9, 1.3 Hz, 1 H, H-5), 3.75 (s, broad, 1 H, NH), 3.15 (ddd, *J* = 10.5, 10.2, 4.0 Hz, 1 H, H-4a), 2.01–1.62 (m, 6 H, H-3, H-2eq, H-4eq, H-1, H-9a), 1.42 (s, 3 H, H-13), 1.21 (s, 3 H, H-12), 1.42–1.25 (m, 2 H, H-4ax, H-2ax), 1.05 (d, *J* = 6.5 Hz, 3 H, H-11); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 143.0, 131.1, 126.4 (2 × C), 116.7, 113.6, 50.5, 47.0, 43.3, 35.1, 34.8, 30.8, 27.0, 26.6, 24.6, 22.2; IR (film) 3397, 1606, 1498, 1318, 743 cm^{-1}; MS (EI) *m/z* 229 (M, 25), 214 (35), 187 (13), 172 (23), 158 (29), 97 (34), 55 (100); HRMS calcd for $C_{16}H_{23}N$ 229.1830, found 229.1827.

5,9,9-Trimethyloctahydroacridine (6e). Flash chromatography yielded 18 mg (16%) of a colorless oil as the first fraction (93% cis by GC) and 16 mg (14%) of a yellow oil as the second fraction (78% trans by GC). ***cis*-6e**: ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.05 (d, *J* = 7.4 Hz, 1 H, H-8), 6.89 ("d", *J* = 7.4 Hz, 1 H, H-6), 6.56 (t, *J* = 7.4 Hz, 1 H, H-7), 3.87 (m, *J* = 1.9 Hz, 1 H, H-4a), 3.34 (s, broad, 1 H, NH), 2.11 (s, 3 H, H-13), 1.67–1.10 (m, 7 H, H-3, H-2eq, H-4eq, H-1, H-9a), 1.33 (s, 3 H, H-12), 1.23 (s, 3 H, H-11), 1.33–1.12 (m, 2 H, H-4ax, H-2ax), 1.10–0.85 (m, 2 H, H-4eq, H-2eq); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 140.9, 127.6, 127.3, 124.0, 119.4, 115.5, 46.1, 44.5, 35.8, 33.9, 32.5, 26.3, 25.9, 22.8, 19.6, 17.5; IR (KBr) 3436, 1598, 1478, 1308, 740 cm^{-1}. Anal. Calcd for $C_{16}H_{23}N$: C, 83.78; H, 10.11; N, 6.11. Found: C, 83.69; H, 10.02; N, 6.03. ***trans*-6e**: ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.18 (d, *J* = 7.5 Hz, 1 H, H-8), 6.91 (dd, *J* = 7.5, 0.8 Hz, 1 H, H-6), 6.56 (t, *J* = 7.6 Hz, 1 H, H-7), 3.53 (s, broad, 1 H, NH), 3.10 (ddd, *J* = 10.3, 10.0, 4.2 Hz, 1 H, H-4a), 2.20–1.15 (m, 9 H, H-2, H-1, H-3, H-4, H-9a), 2.13 (s, 3 H, H-13), 1.36 (s, 3 H, H-11), 1.16 (s, 3 H, H-12); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 140.8, 130.5, 127.6, 124.3, 119.9, 116.0, 50.9, 47.1, 35.0, 27.9, 27.0, 26.6, 26.4, 25.0, 24.6, 17.4; IR (KBr) 3420, 1598, 1478, 1302, 739 cm^{-1}; MS (EI) *m/z* 229 (M, 14), 214 (25), 163 (16), 153 (18), 95 (39), 55 (100); HRMS calcd for $C_{16}H_{23}N$ 229.1830, found 229.1827.

9,9-Dimethyloctahydroacridine (6f). Flash chromatography yielded 8 mg (7%) of a yellow oil as the first fraction (98% cis by GC) and 57 mg (53%) of a yellow oil as the second fraction (75% trans by GC). ***cis*-6f**: ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.12 (dd, *J* = 7.5, 1.5 Hz, 1 H, H-8), 6.96 (ddd, *J* = 7.9, 7.5, 1.5 Hz, 1 H, H-6), 6.60 (dt, *J* = 7.4, 1.2 Hz, 1 H, H-7), 6.44 (dd, *J* = 7.9, 1.2 Hz, 1 H, H-5), 3.83 (m, *J* = 2.4 Hz, 1 H, H-4a), 3.53 (s, broad, 1 H, NH), 1.74–1.15 (m, 7 H, H-3, H-4eq, H-2eq, H-1, H-9a), 1.32 (s, 3 H, H-12), 1.21 (s, 3 H, H-11), 1.15–0.85 (m, 2 H, H-4ax, H-2ax); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 143.1, 128.1, 126.5, 126.1, 116.2, 112.9, 46.1, 44.7, 35.7, 34.0, 32.4, 26.0, 25.8, 22.7, 19.6; IR (film) 3400, 1606, 1493, 1303, 742 cm^{-1}; HRMS calcd for $C_{15}H_{21}N$ 215.1674, found 215.1674. ***trans*-6f**: ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.20–7.12 (m, 2 H, H-8, H-6), 6.67–6.51 (m, 2 H, H-7, H-5), 3.92 (s, broad, 1 H, NH), 3.15 (ddd, *J* = 10.5, 10.2, 4.0 Hz, 1 H, H-4a), 2.11–1.45 (m, 9 H, H-3, H-4, H-2, H-1, H-9a), 1.68 (s, 3 H, H-11), 1.45 (s, 3 H, H-12); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 143.3, 131.0, 126.4, 126.3, 116.7, 113.4, 50.8, 47.3, 35.7, 27.6, 25.6 (2 × C), 24.8, 24.7, 24.4; IR (film) 3397, 1606, 1498, 1319, 743 cm^{-1}; MS (EI) *m/z* 215 (M, 35), 200 (100), 182 (15), 157 (24), 97 (32), 91 (28), 55 (85); HRMS calcd for $C_{15}H_{21}N$ 215.1674, found 215.1671.

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Supplementary Material Available: Portions of the 360-MHz NOESY spectra of *trans*-**6c** and *cis*-**6c** and cross sections through selected ^{13}C chemical shifts of the 90.5-MHz, ^{13}C,^{1}H shift-correlated 2D-NMR of *cis*-**6c** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.