The Pyrido[1,2-*a*]azepine System, Part 4[+]

8-Phenyl-10,10a-dihydropyrido[1,2-*a*]azepines by 1,7-Electrocyclization of Conjugated Pyridinium Ylides—Rationalization of the Periselectivity

Karsten Marx and Wolfgang Eberbach*[a]

Abstract: Base treatment of the pyridinium bromides **11a–e** gives rise to the formation of the dihydropyridoazepines **14a–e** as the only monomolecular products. The reaction takes place by initial deprotonation to the ylides **12**, which undergo 8π-electrocyclization affording the seven-membered-ring systems; no products of a dipolar 6π-cyclization were detected. On the basis of quantum mechanical calculations a rationalization of the periselectivity of the electrocyclization process is given.

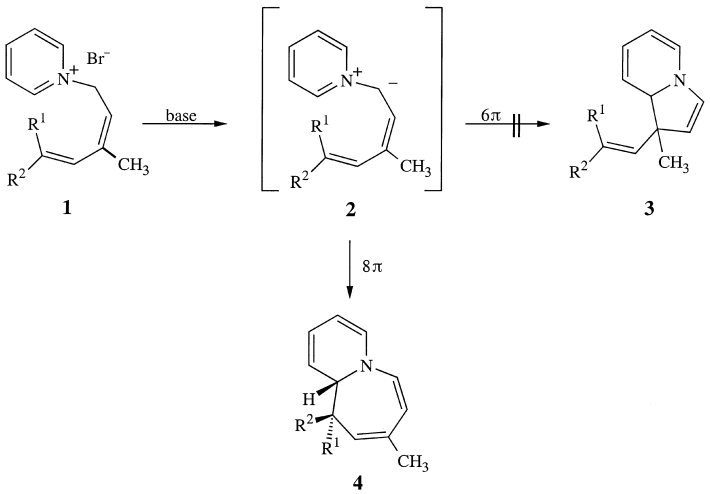
Keywords: azepines · cyclizations · heterocycles · pericyclic reactions · periselectivity

Introduction

In the last four decades the use of 1,3-dipoles has made available a multitude of mono- and polycyclic hetero systems. Besides the extremely powerful dipolar cycloaddition methodology[2] that has been applied to almost every kind of dipole species, dipolar cyclizations have become increasingly important as a synthetic alternative, especially when performed on 6π sytems which give rise to the formation of five-membered heterocycles.[3] In addition 8π-ring-closing reactions that afford seven-membered rings are now well documented.[4]

For the synthesis of azepine derivatives, the ring closure of butadienyl-substituted azomethine ylides would be appropriate. Until now only a few examples of this type have been described,[5] and some of the dipoles have only been postulated as intermediates in multistep rearrangements.[6,7] However, a special kind of this type of dipole has been found particularly valuable, namely the corresponding α-pyridinium ylides, which can be easily generated by base treatment of the corresponding pyridinium salts.[8]

Recently we have disclosed initial results regarding the 1,7-electrocyclization of pyridinium ylides of type **2** with differently substituted pentadienyl units leading to 8-methyl-10,10a-dihydropyrido[1,2-*a*]azepines (**4**).[1] As clearly shown by the stereochemistry of the respective stereogenic centers, the 8π-ring-closing reaction of the extended dipoles takes place by a conrotatory process, in accordance with orbital symmetry considerations.[9] Furthermore, the electrocyclization reactions are not only stereoselective but also periselective, that is, there were no indications of the competitive formation of products resulting from a 6π process (see Scheme 1).



Scheme 1. Reaction scheme for the formation of **4** by an 8π-ring-closing reaction.

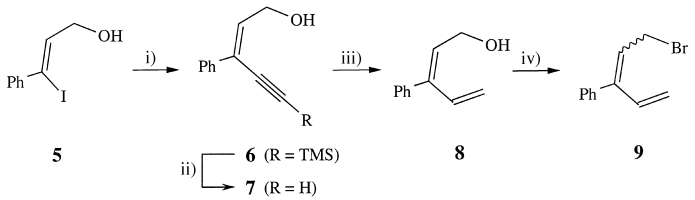
It was the aim of this work to i) investigate new cyclization reactions of some phenylbutadienyl pyridinium ylides bearing substituents at the heterocyclic ring (see compound **12** later), and ii) perform calculations regarding the competition between 6π- and 8π-cyclization processes.

[a] Prof. Dr. W. Eberbach, Dr. K. Marx
Institut für Organische Chemie und Biochemie
der Universität Freiburg i.Br., Albertstr. 21
79104 Freiburg (Germany)
Fax: (+49) 761-203-6085
E-mail: eberbach@organik.chemie.uni-freiburg.de

[+] For Part 3, see reference [1].

Results and Discussion[10]

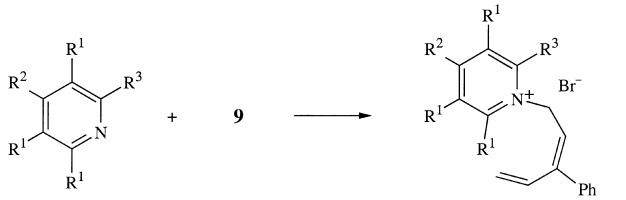
For the preparation of the ylide precursors, various commercially available pyridine derivatives were quarternized with 1-bromo-3-phenylpentadiene (**9**), which was obtained from the known iodopropene **5**[11] by a sequence of reactions. These included coupling with trimethylsilylacetylene[12] under Sonogashira conditions (→**6**),[13] hydrodesilylation with potassium carbonate in methanol, hydrogenation of **7** with activated zinc according to the procedure of Boland et al.,[14] and finally bromination of the pentadienol **8** to give **9** (Scheme 2).



Scheme 2. i) TMS–≡, $PdCl_2(PPh_3)_2$, NEt_3, CuI, 84%; ii) K_2CO_3, MeOH, 61%; iii) Zn (Cu, Ag), $MeOH/H_2O$, rfx, 50%; iv) PBr_3, $-78\,^{\circ}C$, 61%.

Unfortunately, the final step was unavoidably accompanied by partial isomerization of the internal C=C bond. Among the various bromination reagents, tribromophoshpane gave the best results for the required (*E*)-**9** with an average *E*/*Z* ratio of 5:1 with 75% overall yield. (It must be mentioned that the designation *E* is related to the *trans* configuration of the CH_2Br group with respect to the phenyl group; consequently, it is *syn*-arranged to the terminal alkene function). Very pure tribromophosphane must be used and the reaction must be performed below $-65\,^{\circ}C$ to obtain this mixture. Due to the instability of the bromo compound, the mixture for the alkylation step was used immediately after flash chromatography.

Treatment of the pyridine derivatives **10a–e** with the 5:1 mixture of (*E*/*Z*)-**9** at room temperature resulted in the formation of the pyridinium salts **11a–e** (Scheme 3) as

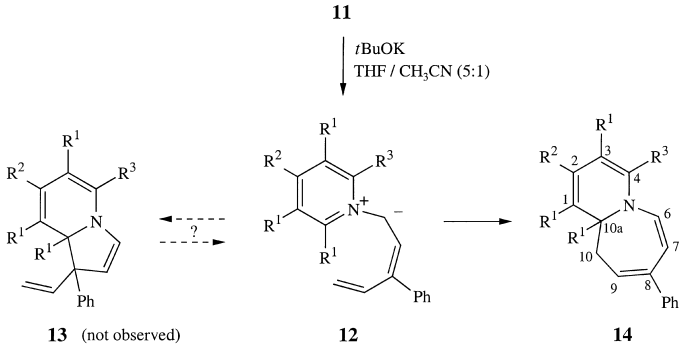


	a	b	c	d	e
R^1	H	D	H	H	H
R^2	H	D	$C(CH_3)_3$	CH_3	H
R^3	H	D	H	H	CH_3

Scheme 3. Reaction scheme for the formation of **11**.

viscous yellow or brown oils (81–97%). As expected, an *E*/*Z* ratio of 5:1 was obtained. As *Z* derivatives do not undergo electrocyclizations, or any other detectable monomolecular reactions under the reaction conditions, only the *E* structures are shown in the reaction schemes. The yields of the subsequently described cyclization reactions are therefore based on the amount of *E* starting material.

On addition of one equivalent of potassium *tert*-butoxide to the suspension of the pyridinium salts **11a–e** in boiling THF/CH_3CN (ca. 5:1) the solution immediately became dark red, an indication of the in situ formation of the corresponding immonium ylides **12** (Scheme 4). After heating under reflux



Scheme 4. Reaction scheme for the formation of **14**.

for 2–4 h, chromatographic purification afforded the dihydropyridoazepines **14a–e** as viscous oils, the yields ranging from 71 to 86%. The bicyclic aza compounds **14** are relatively unstable and tend to undergo decomposition reactions during the workup procedure and on longer standing. Therefore, as shown by ^1H NMR analysis of the raw mixtures, the actual amount of cyclization products is even higher than indicated.

The structural assignments of the pyridoazepines **14** are in full agreement with the spectroscopic data collected for the analogous compounds described previously.[1] As in the case of the 8-methyl derivative of **14** ($R^1–R^3 = H$, Me instead of Ph), the compounds **14a–e** have some conformational mobility (Figure 1). On the basis of the optimized structures,

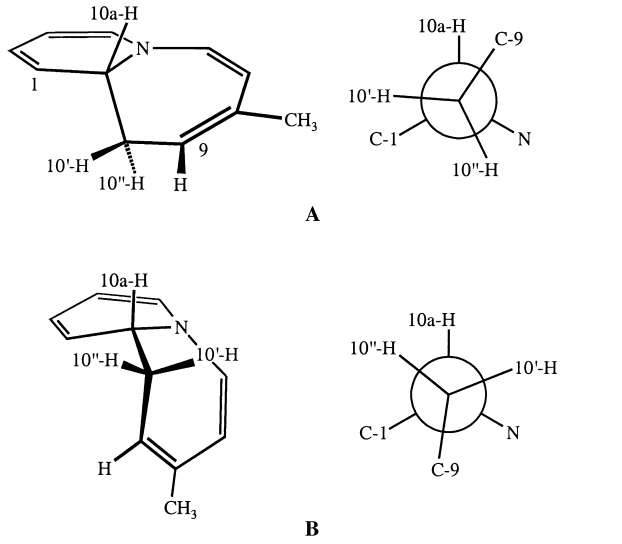


Figure 1. Low-energy conformations of the dihydropyridoazepine system.

the relevant dihedral angles were measured and used to calculate the coupling constants between the protons 10a-H/10′-H, 10a-H/10″-H, 9-H/10′-H, and 9-H/10″-H, respectively. From a comparison of the calculated values with the experimental ones, a predominance of conformation **A** is clearly indicated (see Table 1).

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Table 1. Dihedral angles [°] and coupling constants [Hz] of the conformations **A** and **B** of **14a,c–e** (theoretical results by PM3 calculations).

			calculated dihedral angles [°] and coupling constants [Hz]			
			10a-H/10′-H	10a-H/10″-H	9-H/10′-H	9-H/10″-H
14a	**A**	ϕ_{calcd}	89.4	−154.5	0.94	−114.8
		$^3J_{calcd}$	0.3	7.5	8.2	1.4
	B	ϕ_{calcd}	−62.3	53.0	122.8	7.2
		$^3J_{calcd}$	1.6	2.8	2.5	8.1
	Exp.	$^3J_{obs}$	–	4.8	9.1	4.3
14c	**A**	ϕ_{calcd}	89.3	−154.6	1.2	−114.5
		$^3J_{calcd}$	0.3	7.5	8.2	1.4
	B	ϕ_{calcd}	−62.8	52.6	122.5	6.8
		$^3J_{calcd}$	1.5	2.9	2.5	8.1
	Exp.	$^3J_{obs}$	–	5.7	9.1	4.1
14d	**A**	ϕ_{calcd}	89.4	−154.4	1.2	−114.6
		$^3J_{calcd}$	0.3	7.4	8.2	1.4
	B	ϕ_{calcd}	−62.7	52.6	122.6	6.9
		$^3J_{calcd}$	1.5	2.9	2.5	8.1
	Exp.	$^3J_{obs}$	–	5.0	9.2	4.3
14e	**A**	ϕ_{calcd}	90.8	−153.2	5.5	−110.1
		$^3J_{calcd}$	0.3	7.3	8.1	0.8
	B	ϕ_{calcd}	−65.7	49.5	118.9	3.4
		$^3J_{calcd}$	1.2	3.3	1.9	8.2
	Exp.	$^3J_{obs}$	–	5.8	9.0	3.5

In addition, geometric optimization at the PM3 level[15] revealed two local energy minima (see **A** and **B**) with that for structure **A** being about 3–4 kcal mol^{-1} more stable [$\Delta\Delta H_f^0 = \Delta H_f^0(\mathbf{A}) - \Delta H_f^0(\mathbf{B}) = -3.89$ (**14a**), −3.96 (**14c**), −3.86 (**14d**), and −2.83 kcal mol^{-1} (**14e**)].

On the basis of careful analytical investigations of the crude materials, the annulated dihydroazepine derivatives **14**, formed by 1,7-dipolar electrocyclization, were the only monomolecular reaction products after base treatment of **11**. In particular, there was no indication of competing 1,5-cyclization reactions of the ylide intermediates **12**, which would be expected to lead to indolizines of type **13** (Scheme 4). Evidently, either the latter reaction mode does not take place, or there is an equilibrium between **12** and **13**. As there are no indications of the reversibility of the 8π-cyclization process, the pyridoazepines **14** would be the only reaction products in either case.

There are other examples of related extended dipoles that also show a high preference for the eight-electron process which leads to seven-membered-ring products. A common qualitative explanation of this observation refers to the particular helical geometry of such delocalized systems, which are perfectly arranged for a conrotatory bonding of the π termini.[1, 4, 9, 16] In order to gain a better insight into the preference for the higher order pathway, quantum mechanical calculations (PM3) were performed on both reaction pathways (Scheme 5, R = CH_3 or Ph).

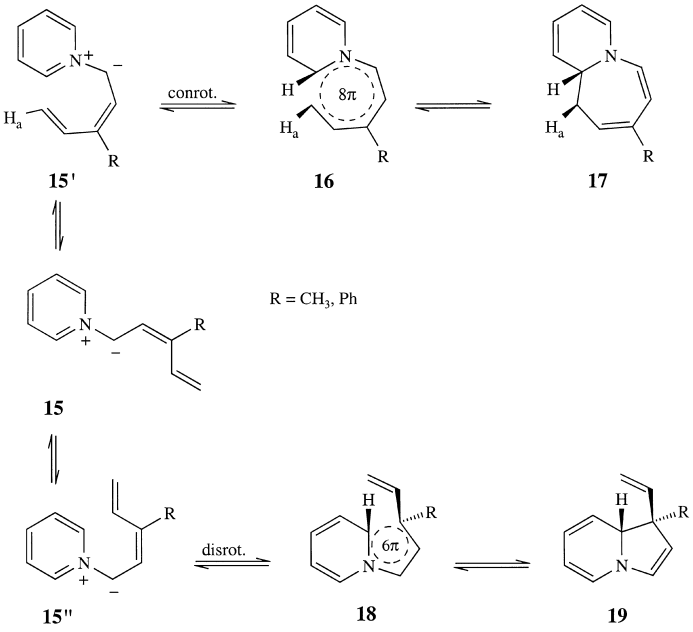
Firstly, a comparison of the relative stability of the two cyclization products (see Figure 1) indicated that system **17** is more stable than **19** by approximately 10 kcal mol^{-1} (Table 2).

When estimating the activation parameters, the most stable conformation of the ylide intermediate **15** was used as a reference structure, because only small amounts of energy should be required to produce the conformations **15′** and **15″**; in other words, these small energy changes are regarded as an incremental part of the activation energy for each pathway. The transition structures **16** and **18** were calculated by using the LST (linear synchronous transit) protocol (see Table 3 and Figure 2).[17]

A direct comparison of the activation parameters $\Delta G^{\neq}$ of the 1,7- and 1,5-cyclization reactions (see Table 3) reveals that the 8π process is favored by approximately 20 kcal mol^{-1} when compared with the 6π-ring-closing reaction.

A schematic representation of the two competing pathways is given in Figure 2.

Until now only very few results of estimations of dipolar cyclizations have been published. The only calculations on the 8π-ring-closing process of conjugated azomethine ylide systems have been performed by Noguchi et al.,[7] who, on the basis of the results with *N*-allyl compounds of type **20**, were able to discard the direct transformation to **21** by an ene reaction in favor of a two-step sequence that included a hydrogen shift followed by a 1,7-dipolar electrocyclization (see Scheme 6).



Scheme 5. 6π- and 8π-cyclization pathways of the conjugated pyridinium ylides **15**.

Table 2. Relative energies of the cyclization products **17** and **19**.

R	$\Delta H^\circ(\mathbf{17}) - \Delta H^\circ(\mathbf{19})$ [kcal mol^{-1}]	$\Delta S^\circ(\mathbf{17}) - \Delta S^\circ(\mathbf{19})$ [cal mol^{-1} K^{-1}]	$\Delta G^\circ(\mathbf{17}) - \Delta G^\circ(\mathbf{19})$ [kcal mol^{-1}]
CH_3	−9.20	−0.41	−9.08
C_6H_5	−12.60	−2.50	−11.31

Table 3. Activation parameters of the 1,5- and 1,7-cyclization processes.

R	15 → 17			15 → 19			
	$\Delta H^{\neq}$	$\Delta S^{\neq}$	$\Delta G^{\neq}$	$\Delta H^{\neq}$	$\Delta G^{\neq}$	$\Delta S^{\neq}$	$\Delta\Delta G^{\neq}$
CH_3	19.28	−5.84	21.02	39.22	−5.32	40.81	−19.79
C_6H_5	17.96	−10.88	21.20	38.81	−6.92	40.87	−19.67

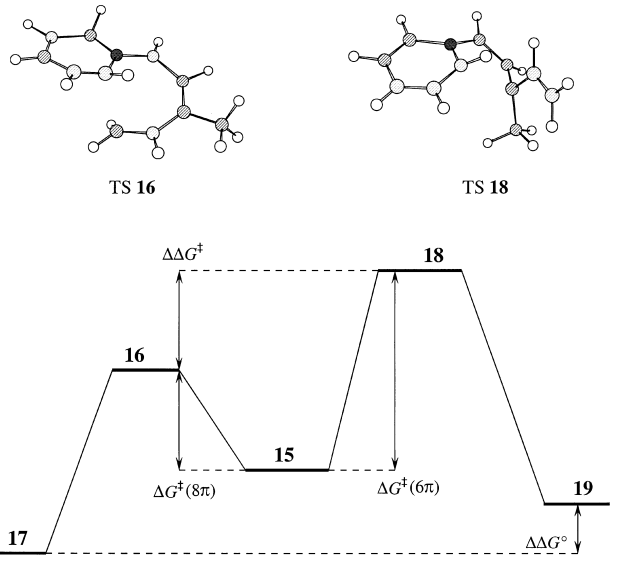
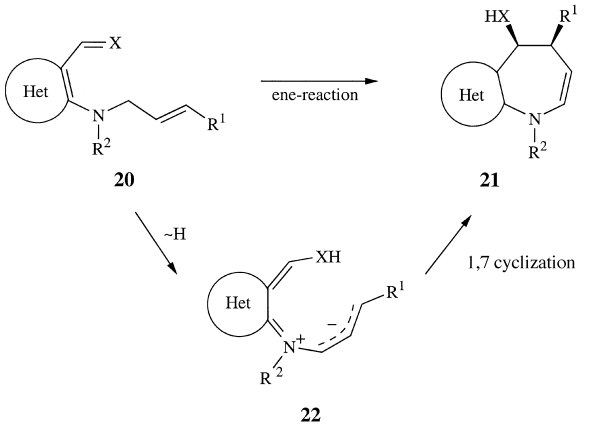


Figure 2. Transition state structures and energy values of the 6π- and 8π-dipolar cyclization processes of **15**.



Scheme 6. Reaction pathway for the formation of **21**.

Conclusion

The results of the electrocyclization reactions of the conjugated pyridinium ylides **12a–e** strengthen earlier observations with related systems; again only the products of a 1,7-ring-closing reaction are observed, namely the pyridoazepine derivatives **14a–e**. There was no indication of a competing 1,5-cyclization reaction mode, which would lead to compounds of type **13**. An explanation of this preference between two, a priori, possible processes, which has been generally attributed to favorable stereoelectronic factors and especially to the helical geometry of such delocalized systems being particularly adopted for a conrotatory 8π-cyclization,[9, 16, 18] comes from theoretical considerations. As a result of our calculations we conclude that the eight-electron 1,7-electrocyclization is clearly favored over the six-electron process by both thermodynamic and kinetic factors. The significant differences of these values ($\Delta\Delta G^{\circ} \approx 10$ kcal mol^{-1} and $\Delta\Delta G^{\neq} \approx 20$ kcal mol^{-1}) provide a good rationale for the high periselectivity experimentally observed in the cyclization behavior of butadienyl pyridinium ylides.

Experimental Section

General: IR: Perkin–Elmer 257 Infracord; ^{1}H NMR: Bruker WM250 (250 MHz) and WM400 (400 MHz); ^{13}C NMR: Bruker WM400 (100 MHz), $CDCl_3$ as solvent and TMS as internal standard, signals marked by an asterisk are not clearly separated; MS: Finnigan MAT44S (70 eV) with Datasystem MAT SS200; elemental analyses: Perkin–Elmer Elemental Analyzer 240; flash chromatography was performed on SiO_2 (Silica 32–36, ICN Biomedicals) or Al_2O_3 (Alumina N, Biomedicals); TLC: SiO_2 60 F-254, 0.2 mm (Merck), Al_2O_3 60F-254, neutral type E, 0.2 mm (Merck).

(*Z*)-3-Phenyl-5-(trimethylsilyl)-pent-2-en-4-in-1-ol (6): Bis(triphenylphosphane)palladium(II) chloride (0.48 g, 0.65 mmol) and CuI (41 mg, 0.026 mmol) were added to a stirred solution of **5**[11] (6.720 g, 25.84 mmol) and trimethylsilyl ethyne (3.81 g, 38.76 mmol) in dry NEt_3 (130 mL) at room temperature under argon. After stirring for 2 h the mixture was filtered through a small Al_2O_3 column (neutral, activity III) and the solution was concentrated in vacuo. The dark brown, viscous residue was purified by flash chromatography (SiO_2, cyclohexane/ethyl acetate 7:1) and gave 4.99 g (84%) of **6** as brown-yellow liquid. $R_f = 0.65$ (cyclohexane/ethyl acetate 1:1); IR (CCl_4): $\tilde{\nu} = 3614$ (br, OH), 2959 (br), 2148, 1496, 1451, 1377 (br), 1252, 1018, 862, 694 cm^{-1}; ^{1}H NMR (250 MHz): $\delta = 7.64–7.56$ (m, 2H; *o*-phenyl), 7.40–7.24 (m, 3H; *p*-phenyl, *m*-phenyl), 6.57 (t, $^3J_{2,1} = 6.4$ Hz, 1H; 2-H), 4.58 (d, $^3J_{1,2} = 6.4$ Hz, 2H; 1-H), 1.84 (br s, 1H; OH), 0.26 (s, 9H; $Si(CH_3)_3$); ^{13}C NMR: $\delta = 137.0$ (C-2), 136.6 (C-3), 128.5 (C-1′), 128.3 (C-3′), 126.2 (C-4′), 125.0 (C-2′), 102.7 (C-5), 101.0 (C-4), 62.1 (C-1), 0.02 ($Si(CH_3)_3$); MS (70 eV, EI): *m*/*z* (%): 230 (15) $[M]^+$, 229 (7), 216 (7), 215 (27) $[M - CH_3]^+$, 198 (5), 197 (13), 185 (10), 157 (9), 155 (7), 141 (91), 140 (21), 131 (6), 128 (9), 115 (15), 105 (80), 104 (6), 99 (12), 77 (35), 74 (13), 73 (100) $[C_3H_9Si]^+$, 51 (17).

(*Z*)-3-Phenylpent-2-en-4-in-1-ol (7): Potassium carbonate (294 mg, 2.13 mmol) was added to the solution of **6** (4.90 g, 21.3 mmol) in methanol (220 mL) at room temperature. After stirring for 50 min, the mixture was concentrated to about 10 mL and then diluted with diethyl ether (100 mL). The solution was washed three times with saturated sodium chloride solution, dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography of the residue (SiO_2, cyclohexane/ethyl acetate 7:1) gave 2.05 g (61%) of **7** as a yellow liquid. $R_f = 0.61$ (cyclohexane/ethyl acetate 1:1); IR (CCl_4): $\tilde{\nu} =$ 3605 (br, OH), 3205, 3060 (br), 2095 (C4C), 1660, 1485, 1448, 1238, 1037, 695, 649 cm^{-1}; ^{1}H NMR (250 MHz): $\delta = 7.65–7.58$ (m, 2H; *o*-Ph), 7.40–7.27 (m, 3H; *p*-Ph, *m*-Ph), 6.63 (t, $^3J_{2,1} = 6.4$ Hz, 1H; 2-H), 4.59 (d, $^3J_{1,2} = 6.4$ Hz, 2H; 1-H), 3.41 (s, 1H; 5-H), 1.85 (br s, 1H; OH); ^{13}C NMR: $\delta = 137.3$ (C-2), 128.6 (C-3), 128.4 (C-1′), 126.2 (C-3′), 125.6 (C-4′), 124.0 (C-2′), 84.8 (C-4), 79.8 (C-5), 61.9 (C-1); MS (70 eV, CI, *iso*-butane): *m*/*z* (%): 197 (9), 175 (19), 173 (6), 161 (5), 159 (10), 158 (5) $[M]^+$, 157 (28), 147 (9), 146 (9), 145 (64), 141 (100) $[M - OH]^+$, 140 (8), 137 (8), 131 (24), 117 (13).

(2*E*)-3-Phenyl-2,4-pentadien-1-ol (8): Compound **7** (2.00 g, 12.64 mmol) was added to a suspension of activated zinc (freshly prepared from 10 g of Zn powder) in methanol/water (1:1, 50 mL), and the mixture was heated to reflux under argon until completion of the reaction (^{1}H NMR, ca. 18 h). After filtration over Celite the residue was washed with methanol (50 mL) and diethyl ether (50 mL). The organic solvents were then removed in vacuo, and the aqueous solution was extracted with diethyl ether (4 × 50 mL). The combined organic phase was dried ($MgSO_4$) and concentrated. Purification of the residue by flash chromatography (SiO_2, cyclohexane/ethyl acetate 5:1) gave 997 mg (6.32 mmol, 50%) of **8** as a yellow viscous liquid. $R_f = 0.44$ (cyclohexane/ethyl acetate 1:1); IR (CCl_4): $\tilde{\nu} = 3625$ (br, OH), 3055 (br), 1676 (br), 1493, 1445, 1373 (br), 1264, 1030 (br), 942,

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700 cm^{-1}; ^1H NMR (250 MHz): $\delta = 7.39-7.26$ (m, 5H; Ph-H), 6.78 (dd, $^3J_{4,5cis} = 10.7$ Hz, $^3J_{4,5trans} = 17.4$ Hz, 1H; 4-H), 5.79 (t, $^3J_{2,1} = 6.7$ Hz, 1H; 2-H), 5.36 (d, $^3J_{5cis,4} = 10.7$ Hz, 1H; 5-H_{cis}), 5.14 (d, $^3J_{5trans,4} = 17.4$ Hz, 1H; 5-H_{trans}), 4.46 (d, $^3J_{1,2} = 6.7$ Hz, 2H; 1-H), 1.50 (br s, 1H; OH); HRMS calcd for $C_{11}H_{12}O$: 160.0888; found 160.0886.

5-Bromo-3-phenyl-1,3-pentadiene (9): A solution of phosphorus tribromide (1.86 g, 6.87 mmol) in dry diethyl ether (6 mL, $T < -60\,^\circ C$) was added dropwise to a stirred solution of **8** (2.20 g, 13.74 mmol) under N_2 at $-78\,^\circ C$. Stirring was continued until complete conversion (TLC, ca. 3 h). The mixture was warmed to $-10\,^\circ C$, hydrolyzed with ice/water (30 mL), and extracted with diethyl ether. After washing with saturated aqueous sodium bicarbonate (4×20 mL) and sodium chloride solutions (3×20 mL), the combined organic phases were dried ($MgSO_4$) and concentrated. Purification of the residue by flash chromatography (Al_2O_3, neutral, activity II; cyclohexane/ethyl acetate 7:1) gave 1.87 g (61%) of **9** as a yellow, slightly lachrymatory liquid, which on standing underwent polymerization. According to the ^1H NMR analysis, a mixture of (*E*)- and (*Z*)-**9** was obtained in a 5:1 ratio (this varied from 2:1 to 10:1 for different runs). IR (CCl_4) of the isomeric mixture: $\tilde{\nu} = 3060$ (br), 1495, 1445, 1200, 985, 928, 700 cm^{-1}. Due to instability, the bromide was used without further purification for the alkylation reactions.

General procedure for the quarternization of the *N*-heteroaromatic compounds 11: A solution (ca. 1 mol L^{-1}) of the pyridines **10a–e** and 1 equivalent of **9** (isomer mixture) in acetonitrile was stirred at room temperature for the given period. After addition of diethyl ether, precipitation of a viscous oil or a solid takes place. Isolation was accomplished either by filtration and washing of the amorphic/solid residue with diethyl ether (in case of solids) or by a repeated solvation–separation procedure (in case of oils) with acetonitrile and diethyl ether as dissolving and separating agents, respectively. The pyridinium salts **11** obtained by this method were characterized by ^1H NMR analysis and used directly for the cyclization reactions.

1-(3-Phenyl-2,4-pentadienyl)pyridinium bromide (11a): By using the general procedure, the reaction of **9** (444 mg, 1.99 mmol, $E/Z = 5:1$) and pyridine **10a** (157 mg, 1.99 mmol) in 4 mL of acetonitrile afforded after 2 d 520 mg (1.72 mmol, 86%) of 1-(3-phenyl-2,4-pentadienyl)pyridinium bromide (**11a**) ($E/Z = 5:1$) as a brown oil. ^1H NMR (250 MHz, [D_6]DMSO) (*Z*)-**11a**: $\delta = 8.92$ (m, $^3J_{2,3} = 5.5$ Hz, 2H; 2-H), 8.65 (m, 1H; 4-H), 8.20 (m, 2H; 3-H), 7.5–7.21 (m, 5H; Ph-H), 6.71 (dd, $^3J_{4',5'cis} = 10.7$ Hz, $^3J_{4',5'trans} = 17.4$ Hz, 1H; 4′-H), 6.16 (t, $^3J_{2',1'} = 7.1$ Hz, 1H; 2′-H), 5.30 (d, $^3J_{5'cis,4'} = 10.7$ Hz, 1H; 5′-H_{cis}), 5.18 (d, $^3J_{1',2'} = 7.1$ Hz, 2H; 1′-H), 4.81 (d, $^3J_{5'trans,4'} = 17.4$ Hz, 1H; 5′-H_{trans}); (*E*)-**11a**: $\delta = 9.16$ (m, $^3J_{2,3} = 5.5$ Hz, 2H; 2-H), 8.65 (m_c, 1H; 4-H), 8.20 (m_c, 2H; 3-H), 7.54–7.21 (m, 5H; Ph-H), 7.15 (dd, $^3J_{4',5'cis} = 10.7$ Hz, $^3J_{4',5'trans} = 17.4$ Hz, 1H; 4′-H), 5.95 (t, $^3J_{2',1'} = 7.1$ Hz, 1H; 2′-H), 5.66 (d, $^3J_{1',2'} = 7.1$ Hz, 2H; 1′-H), 5.57 (d, $^3J_{5'cis,4'} = 10.7$ Hz, 1H; 5′-H_{cis}), 5.22 (d, $^3J_{5'trans,4'} = 17.4$ Hz, 1H; 5′-H_{trans}).

2,3,4,5,6-Pentadeutero-1-(3-phenyl-2,4-pentadienyl) pyridinium bromide (11b): Following the general procedure, **9** (441 mg, 1.98 mmol, $E/Z = 7:1$) was treated with pentadeuteropyridine (**10b**) (166 mg, 1.98 mmol). After 2 d 493 mg (81%) of **11b** ($E/Z = 7:1$) was isolated as a hygroscopic and sticky beige wax. ^1H NMR (250 MHz, [D_6]DMSO) (*Z*)-**11b**: $\delta = 7.5-7.22$ (m, 5H; Ph-H), 6.71 (dd, $^3J_{4',5'cis} = 10.8$ Hz, $^3J_{4',5'trans} = 17.1$ Hz, 1H; 4′-H), 6.16 (t, $^3J_{2',1'} = 6.9$ Hz, 1H; 2′-H), 5.30 (d, $^3J_{5'cis,4'} = 10.8$ Hz, 1H; 5′-H_{cis}), 5.19 (d, $^3J_{1',2'} = 6.9$ Hz, 2H; 1′-H), 4.81 (d, $^3J_{5'trans,4'} = 17.1$ Hz, 1H; 5′-H_{trans}); (*E*)-**11b**: $\delta = 7.54-7.22$ (m, 5H; Ph-H), 7.16 (dd, $^3J_{4',5'cis} = 11.0$ Hz, $^3J_{4',5'trans} = 17.3$ Hz, 1H; 4′-H), 5.95 (t, $^3J_{2',1'} = 7.0$ Hz, 1H; 2′-H), 5.67 (d, $^3J_{1',2'} = 7.3$ Hz, 2H; 1′-H), 5.57 (d, $^3J_{5'cis,4'} = 11.0$ Hz, 1H; 5′-H_{cis}), 5.22 (d, $^3J_{5'trans,4'} = 17.3$ Hz, 1H; 5′-H_{trans}).

4-*tert*-Butyl-1-(3-phenyl-2,4-pentadienyl)pyridinium bromide (11c): By using the general procedure, the reaction of **9** (284 mg, 1.27 mmol, $E/Z = 2:1$) and 4-*tert*-butyl pyridine (**10c**) (172 mg, 1.27 mmol) gave after 2 d 371 mg (82%) of **11c** ($E/Z = 2:1$) as a yellow hygroscopic solid which deliquesces within a few minutes to a yellow oil. ^1H NMR (250 MHz) (*Z*)-**11c**: $\delta = 9.12$ (pd, $^3J_{2,3} = 7.0$ Hz, 2H; 2-H), 7.93 (pd, $^3J_{3,2} = 7.0$ Hz, 2H; 3-H), 7.45–7.13 (m, 5H; Ph-H), 6.62 (dd, $^3J_{4',5'cis} = 11.0$ Hz, $^3J_{4',5'trans} = 17.3$ Hz, 1H; 4′-H), 6.16 (t, $^3J_{2',1'} = 7.6$ Hz, 1H; 2′-H), 5.46 (d, $^3J_{1',2'} = 7.6$ Hz, 2H; 1′-H), 5.32 (d, $^3J_{5'cis,4'} = 11.0$ Hz, 1H; 5′-H_{cis}), 4.92 (d, $^3J_{5'trans,4'} = 17.3$ Hz, 1H; 5′-H_{trans}), 1.38 (s, 9H; $C(CH_3)_3$); (*E*)-**11c**: $\delta = 9.48$ (pd, $^3J_{2,3} = 7.2$ Hz, 2H; 2/6-H), 8.00 (m, $^3J_{3,2} = 7.2$ Hz, 2H; 3/5-H), 7.45–7.13 (m, 5H; Ph-*H*), 7.20 (dd, $^3J_{4',5'cis} = 11.3$ Hz, $^3J_{4',5'trans} = 18.0$ Hz, 1H; 4′-H), 5.99 (d, $^3J_{1',2'} = 7.6$ Hz, 2H; 1′-H), 5.84 (t, $^3J_{2',1'} = 7.6$ Hz, 1H; 2′-H), 5.60 (d, $^3J_{5'cis,4'} = 11.3$ Hz, 1H; 5′-H_{cis}), 5.30 (d, $^3J_{5'trans,4'} = 18.0$ Hz, 1H; 5′-H_{trans}), 1.38 (s, 9H; $C(CH_3)_3$).

4-Methyl-1-(3-phenyl-2,4-pentadienyl)pyridinium bromide (11d): By using the general procedure, the reaction of **9** (597 mg, 2.68 mmol, $E/Z = 4:1$) and γ-picoline (**10d**) (250 mg, 2.68 mmol) gave after 2 d 818 mg (97%) of **11d** ($E/Z = 4:1$) as a yellow, very viscous oil. ^1H NMR (250 MHz) (*Z*)-**11d**: $\delta = 8.97$ (pd, $^3J_{2,3} = 6.7$ Hz, 2H; 2/6-H), 7.78 (pd, $^3J_{3,2} = 6.7$ Hz, 2H; 3/5-H), 7.4–7.13 (m, 5H; Ph-H), 6.62 (dd, $^3J_{4',5'cis} = 10.7$ Hz, $^3J_{4',5'trans} = 17.2$ Hz, 1H; 4′-H), 6.15 (t, $^3J_{2',1'} = 7.4$ Hz, 1H; 2′-H), 5.44 (d, $^3J_{1',2'} = 7.4$ Hz, 2H; 1′-H), 5.33 (d, $^3J_{5'cis,4'} = 10.7$ Hz, 1H; 5′-H_{cis}), 4.92 (d, 5′-H_{trans}, $^3J_{5'trans,4'} = 17.2$ Hz, 1H), 2.29 (s, 3H; CH_3), (*E*)-**11d**: $\delta = 9.29$ (pd, $^3J_{2,3} = 6.6$ Hz, 2H; 2/6-H), 7.83 (pd, $^3J_{3,2} = 6.6$ Hz, 2H; 3/5-H), 7.75–7.26 (m, 5H; Ph-H), 7.14 (dd, $^3J_{4',5'cis} = 11.0$ Hz, $^3J_{4',5'trans} = 17.0$ Hz, 1H; 4′-H), 5.96 (d, $^3J_{1',2'} = 7.4$ Hz, 2H; 1′-H), 5.82 (t, $^3J_{2',1'} = 7.4$ Hz, 1H; 2′-H), 5.61 (d, $^3J_{5'cis,4'} = 11.0$ Hz, 1H; 5′-H_{cis}), 5.32 (d, $^3J_{5'trans,4'} = 17.0$ Hz, 1H; 5′-H_{trans}), 2.29 (s, 3H; CH_3).

2-Methyl-1-(3-phenyl-2,4-pentadienyl)pyridinium bromide (11e): By using the general procedure, **9** (597 mg, 2.68 mmol, $E/Z = 3:1$) and α-picoline (**10e**) (250 mg, 2.68 mmol) afforded after 2d 720 mg (85%) of **11e** ($E/Z = 3:1$) as a yellow viscous oil. ^1H NMR (250 MHz) (*Z*)-**11e**: $\delta = 9.44$ (m, $^3J_{6,5} = 6.0$ Hz, 1H; 6-H), 8.41–8.29 (m, 1H; 4-H), 7.80–7.78 (m, 2H; 3-H, 5-H), 7.4–7.24 (m, 5H; Ph-H), 6.56 (dd, $^3J_{4',5'cis} = 11.0$ Hz, $^3J_{4',5'trans} = 17.1$ Hz, 1H; 4′-H), 5.96 (t, $^3J_{2',1'} = 6.9$ Hz, 1H; 2′-H), 5.45 (d, $^3J_{1',2'} = 6.9$ Hz, 2H; 1′-H), 5.23 (d, $^3J_{5'cis,4'} = 11.0$ Hz, 1H; 5′-H_{cis}), 4.94 (d, $^3J_{5'trans,4'} = 17.1$ Hz, 1H; 5′-H_{trans}), 2.60 (s, 3H; CH_3); (*E*)-**11e**: $\delta = 9.66$ (m, $^3J_{6,5} = 6.0$ Hz, 1H; 6-H), 8.4–8.29 (m, 1H; 4-H), 7.80–7.78 (m, 2H; 3-H, 5-H), 7.47–7.24 (m, 5H; Ph-*H*), 7.07 (dd, $^3J_{4',5'cis} = 11.1$ Hz, $^3J_{4',5'trans} = 17.1$ Hz, 1H; 4′-H), 5.94 (d, $^3J_{1',2'} = 7.0$ Hz, 2H; 1′-H), 5.60 (t, $^3J_{2',1'} = 7.0$ Hz, 1H; 2′-H), 5.61 (d, $^3J_{5'cis,4'} = 11.1$ Hz, 1H; 5′-H_{cis}), 5.34 (d, $^3J_{5'trans,4'} = 17.1$ Hz, 1H; 5′-H_{trans}), 3.02 (s, 3H; CH_3).

General procedure for the transformation of the pyridinium salts 11a–e into the dihydropyridoazepines 14a–e: Dry THF (20 mL) was added to a solution of the pyridinium bromides **11** (1.5–2.5 mmol) in acetonitrile (3–5 mL and, if necessary, 1 mL of dry ethanol). The resulting suspension was heated to reflux under argon and then treated (maintaining reflux) with 1.1 equivalents of potassium *tert*-butoxide. On addition of the base the color of the reaction mixture spontaneously changed to dark brown-violet. Refluxing was continued until completion of the reaction (TLC, 2–4 h). After cooling to room temperature, diethyl ether (50 mL) was added and the mixture was filtered and then washed with saturated aqueous sodium chloride solution (4×20 mL). The combined organic fractions were dried ($MgSO_4$), concentrated in vacuo, and then purified by flash chromatography. The stated yields of compounds **14** are related to the respective pentadienyl pyridinium salts with *E* configuration of the double bond at 2′-C. The dihydropyridoazepines **14** were relatively unstable compounds that tended to undergo decomposition reactions during workup and on longer standing; therefore, as shown by the ^1H NMR analysis of the raw mixtures, the amount of **14** formed during the deprotonation–cyclization process was usually higher than indicated.

8-Phenyl-10,10a-dihydropyrido[1,2-*a*]azepine (14a): By using the general procedure for the cyclization of pyridinium bromides, the reaction of **11a** (336 mg, 1.11 mmol, $E/Z = 5:1$) gave, after flash chromatography of the raw material (SiO_2, cyclohexane/ethyl acetate 2:1), 153 mg of **14a** (75%) as a dark red oil. $R_f = 0.69$ (cyclohexane/ethyl acetate 1:1); IR (CCl_4): $\tilde{\nu} = 3050$ (br) , 1630 (br), 1595 (C=C), 1573, 1490, 1259, 755, 700 cm^{-1}; ^1H NMR (400 MHz): $\delta = 7.39$ (m_c, 2H; *o*-Ph), 7.31 (m_c, 2H; *m*-Ph), 7.27–7.21 (m, 1H; *p*-Ph), 6.44 (d, $^3J_{6,7} = 9.6$ Hz, 1H; 6-H), 6.27 (d, $^3J_{4,3} = 7.4$ Hz, 1H; 4-H), 6.03 (dd, $^3J_{9,10'} = 9.1$ Hz, $^3J_{9,10''} = 4.3$ Hz, 1H; 9-H), 5.91 (dd, $^3J_{2,3} = 5.9$ Hz, $^3J_{2,1} = 9.6$ Hz, 1H; 2-H), 5.51 (dd, $^3J_{1,2} = 9.6$ Hz, $^3J_{1,10a} = 4.2$ Hz, 1H; 1-H), 5.31 (d, $^3J_{7,6} = 9.6$ Hz, 1H; 7-H), 4.87 (m_c, 1H; 3-H), 3.78 (m_c, 1H; 10a-H), 2.80 (dd, $^3J_{10',10''} = 16.6$ Hz, $^3J_{10',9} = 9.1$ Hz, 1H; 10′-H), 2.27 (ddd, $^3J_{10'',10'} = 16.6$ Hz, $^3J_{10'',10a} = 4.8$ Hz, $^3J_{10'',9} = 4.3$ Hz, 1H; 10″-H); ^{13}C NMR: $\delta = 144.5$ (C-8), 138.7 (C-1′), 133.9 (C-9), 131.3 (C-4), 128.2 (C-6), 128.1 (C-4′), 127.0 (C-2′), 126.7 (C-3′), 121. 9 (C-1), 120.4 (C-2), 103.6 (C-7), 96.5 (C-3), 59.7 (C-10a), 44.4 (C-10); MS (70 eV, EI): *m/z* (%): 222 (8), 221 (47) $[M]^+$, 143 (12), 142 (100) $[M-N]^+$ 141 (62), 115 (20), 110 (10), 80 (54) $[C_5H_6N]^+$; HRMS calcd for $C_{16}H_{15}N$: 221.1204; found 221.1197.

1,2,3,4,10a-Pentadeutero-8-phenyl-10,10a-dihydropyrido[1,2-*a*]azepine (14b): By using the general procedure, the reaction of **11b** (428 mg, 1.39 mmol, $E/Z = 7:1$) gave, after flash chromatography of the raw material (SiO_2, cyclohexane/ethyl acetate 2:1), 285 mg of the **14b** (86%) as a red-orange, very viscous liquid. $R_f = 0.68$ (cyclohexane/ethyl acetate 1:1); IR

(CCl_4): $\tilde{\nu}$ = 3050 (br), 1630 (br) (C=C), 1595 (br) (C=C), 1573, 1490, 1259, 755, 700 cm^{-1}; ^1H NMR (400 MHz): δ = 7.39 (m_c, 2H; *o*-Ph-H), 7.30 (m_c, 2H; *m*-Ph), 7.27–7.21 (m, 1H; *p*-Ph), 6.44 (d, $^3J_{6,7}$ = 9.6 Hz, 1H; 6-H), 6.04 (dd, $^3J_{9,10'}$ = 9.1 Hz, $^3J_{9,10a}$ = 4.0 Hz, 1H; 9-H), 5.31 (d, $^3J_{7,6}$ = 9.6 Hz, 1H; 7-H), 2.79 (dd, $^3J_{10',10''}$ = 16.6 Hz, $^3J_{10',9}$ = 9.1 Hz, 1H; 10′-H), 2.25 (dd, $^3J_{10'',10'}$ = 16.6 Hz, $^3J_{10'',9}$ = 4.0 Hz, 1H; 10″-H); ^{13}C NMR: δ = 144.6 (C-8), 138.7 (C-1′), 133.9 (C-9), 128.2 (C-6), 128.1 (C-4′), 127.0 (C-2′), 126.7 (C-3′), 103.6 (C-7), 44.3 (C-10); MS (70 eV, EI): *m*/*z* (%): 222 (8), 221 (47) $[M]^+$, 142 (100) $[M - C_5H_5N]^+$, 141 (62), 115 (20), 110 (10), 80 (54) $[C_5H_6N]^+$; HRMS calcd for $C_{16}H_{15}N$: 226.1534; found 221.1534.

2-*tert*-Butyl-8-phenyl-10,10a-dihydropyrido[1,2-*a*]azepine (14c): Following the general procedure, the reaction of **11c** (349 mg, 0.97 mmol, *E*/*Z* = 2:1) gave, after flash chromatography of the raw material (SiO_2, cyclohexane/ethyl acetate 3:1), 140 mg of **14c** (78%) as a brown wax. R_f = 0.72 (cyclohexane/ethyl acetate 1:1); IR (CCl_4): $\tilde{\nu}$ = 2965 cm^{-1} (br), 1660, 1630 (C=C), 1575 (br), 1273, 1090, 868, 697; ^1H NMR (400 MHz): δ = 7.40 (m, $^3J_{2',3'}$ = 8.0 Hz, 2H; 2′-H), 7.31 (m, $^3J_{3',2'}$ = 8.0 Hz, $^3J_{3',4'}$ = 8.0 Hz, 2H; 3′-H), 7.24 (pd, $^3J_{4',3'}$ = 8.0 Hz, 1H; 4′-H), 6.43 (d, $^3J_{6,7}$ = 9.5 Hz, 1H; 6-H), 6.27 (d, $^3J_{4,3}$ = 7.7 Hz, 1H; 4-H), 6.00 (dd, $^3J_{9,10'}$ = 9.0 Hz, $^3J_{9,10''}$ = 4.1 Hz, 1H; 9-H), 5.26 (d, $^3J_{1,10a}$ = 4.5 Hz, $^3J_{1,3}$ = 2.0 Hz, 1H; 1-H and d, $^3J_{7,6}$ = 9.5 Hz, 1H; 7-H), 4.96 (dd, $^3J_{3,4}$ = 7.7 Hz, $^3J_{3,1}$ = 2.0 Hz, 1-H, 3-H), 3.77 (dd, $^3J_{10a,10'}$ = 5.7 Hz, $^3J_{10a,1}$ = 4.5 Hz, 1H; 10a-H), 2.78 (dd, $^3J_{10',10''}$ = 16.4 Hz, $^3J_{10',9}$ = 9.1 Hz, 1H; 10′-H), 2.23 (ddd, $^3J_{10',10'}$ = 16.4 Hz, $^3J_{10'',10a}$ = 5.7 Hz, $^3J_{10'',9}$ = 4.1 Hz, 1H; 10″-H), 1.10 (s, 9H; $C(CH_3)_3$); ^{13}C NMR: δ = 144.6 (C-8), 140.7 (C-2), 138.7 (C-1′), 133.8 (C-1), 103.0 (C-7), 97.0 (C-3), 59.8 (C-10a), 44.5 (C-10), 33.6 ($C(CH_3)_3$), 29.0 ($C(CH_3)_3$); MS (70 eV, EI): *m*/*z* (%): 277 (8) $[M]^+$, 143 (12), 142 (90) $[M - (t\text{Bu-}C_5H_4N)]^+$, 141 (47), 136 (100) $[(CH_3)_3C{-}C_5H_4NH]^+$, 121 (18), 115 (17), 106 (5), 92 (8), 91 (5), 77 (7) $[C_6H_5]^+$, 65 (5), 57 (7) $[C_4H_9]^+$; HRMS calcd for $C_{20}H_{23}N$: 277.1830; found 277.1830.

2-Methyl-8-phenyl-10,10a-dihydropyrido[1,2-*a*]azepine (14d): By using the general procedure, the reaction of **11d** (740 mg, 2.34 mmol, *E*/*Z* = 4:1) gave, after flash chromatography of the raw material (SiO_2, cyclohexane/ethyl acetate 3:1), 322 mg of **14d** (73%) as a dark red oil. R_f = 0.70 (cyclohexane/ethyl acetate 1:1); IR (CCl_4): $\tilde{\nu}$ = 3020, 2913 (br), 1667, 1630, 1520, 1488, 1440, 1259, 1157, 863, 695 cm^{-1}; ^1H NMR (250 MHz): δ = 7.44–7.19 (m, 5H; Ph-H), 6.44 (d, $^3J_{6,7}$ = 9.7 Hz, 1H; 6-H), 6.25 (d, $^3J_{4,3}$ = 7.5 Hz, 1H; 4-H), 6.00 (dd, $^3J_{9,10'}$ = 9.2 Hz, $^3J_{9,10''}$ = 4.3 Hz, 1H; 9-H), 5.28 (d, $^3J_{7,6}$ = 9.7 Hz, 1H; 7-H), 5.23 (m_c, $^3J_{1,10a}$ = 4.3 Hz, $^3J_{1,3}$ = 1.5 Hz, 1H; 1-H), 4.76 (m_c, $^3J_{3,4}$ = 7.5 Hz, $^3J_{3,1}$ = 1.5 Hz, 1H; 3-H), 3.75 (br ps, $^3J_{10a,10''}$ = 5.0 Hz, $^3J_{10a,1}$ = 4.3 Hz, 1H; 10a-H), 2.78 (dd, $^3J_{10',10''}$ = 16.5 Hz, $^3J_{10',9}$ = 9.2 Hz, 1H; 10′-H), 2.24 (ddd, $^3J_{10'',10'}$ = 16.5 Hz, $^3J_{10'',10a}$ = 5.0 Hz, $^3J_{10'',9}$ = 4.3 Hz, 1H; 10″-H), 1.78 (ps, 3H; CH_3); ^{13}C NMR (100.6 MHz): δ = 144.6 (C-8), 138.6 (C-2), 133.8 (C-1′), 131.0 (C-6), 128.4 (C-4), 128.2(C-2′), 127.7 (C-3′), 127.0 (C-4′), 126.6 (C-9), 117.3 (C-1), 103.3 (C-7), 100.0 (C-3), 59.8 (C-10a), 44.4 (C-10), 21.0 (CH_3); MS (70 eV, EI): *m*/*z* (%): 235 (22) $[M]^+$, 143 (10), 142 (78) $[M - (H_3C{-}C_5H_5N)]^+$, 141 (59), 118 (6), 115 (33), 94 (100) $[H_3C{-}C_5H_5NH]^+$, 89 (5), 77 (6) $[C_6H_5]^+$; HRMS calcd for $C_{17}H_{17}N$: 235.1361; found 235.1361.

4-Methyl-8-phenyl-10,10a-dihydropyrido[1,2-*a*]azepine (14e): By using the general procedure, the reaction of **11e** (720 mg, 2.23 mmol, *E*/*Z* = 3:1) gave, after flash chromatography of the raw material (SiO_2, cyclohexane/ethyl acetate 3:1), 268 mg of **14e** (71%) as a dark red oil. R_f = 0.70 (cyclohexane/ethyl acetate 1:1); IR (CCl_4): $\tilde{\nu}$ = 3020, 2895 (br), 1625, 1560, 1415, 1315, 700 cm^{-1}; ^1H NMR (400 MHz): δ = 7.43–7.37 (m, 2H; *o*-Ph), 7.35–7.28 (m, 2H; *m*-Ph), 7.27–7.21 (m, 1H; *p*-Ph), 6.72 (d, $^3J_{6,7}$ = 9.1 Hz, 1H; 6-H), 6.19 (dd, $^3J_{9,10'}$ = 9.0 Hz, $^3J_{9,10''}$ = 3.5 Hz, 1H; 9-H), 5.93 (dd, $^3J_{2,1}$ = 9.7 Hz, $^3J_{2,3}$ = 5.9 Hz, 1H; 2-H), 5.57 (dd, $^3J_{1,2}$ = 9.7 Hz, $^3J_{1,10a}$ = 5.1 Hz, 1H; 1-H), 5.48 (d, $^3J_{7,6}$ = 9.1 Hz, 1H; 7-H), 4.92 (d, $^3J_{3,2}$ = 5.9 Hz, 1H; 3-H), 3.46 (t, $^3J_{10a,10''}$ = 5.8 Hz, $^3J_{10a,1}$ = 5.1 Hz, br., 1H; 10a-H), 2.71 (dd, $^3J_{10',10''}$ = 17.5 Hz, $^3J_{10',9}$ = 9.0 Hz, 1H; 10′-H), 2.16 (ddd, $^3J_{10'',10'}$ = 17.5 Hz, $^3J_{10'',10a}$ = 5.8 Hz, $^3J_{10'',9}$ = 3.5 Hz, 1H; 10″-H), 2.02 (m, 3H; CH_3); ^{13}C NMR: δ = 145.4 (C-8), 138.1 (C-4), 136.5 (C-1′), 130.5 (C-6), 130.3 (C-2), 128.2 (C-2′), 127.1 (C-3′), 126.9 (C-4′), 126.5 (C-9), 120.7 (C-1), 105.9 (C-7), 97.2 (C-3), 59.2 (C-10a), 43.8 (C-10), 20.8 (CH_3); MS (70 eV, EI): *m*/*z* (%):235 (26) $[M]^+$, 143 (13), 142 (100) $[M - (H_3C{-}C_5H_5N)]^+$, 141 (66), 139 (5), 128 (12), 118 (14), 116 (5), 115 (34), 102 (5), 95 (7), 94 (65) $[H_3C{-}C_5H_5NH]^+$, 93 (7), 89 (6), 77 (8) $[C_6H_5]^+$; HRMS calcd for $C_{17}H_{17}N$: 235.1361; found 235.1361.

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