DOI: 10.1002/ejoc.200700913

1,6-Electrocyclization of 1-Azatriene Derivatives

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Keywords: 1-Azatrienes / (*E*)→(*Z*) isomerization / Electrocylization / Activation parameters / 6,7-Dihydro-4*H*-benzo[*a*]-quinolizines

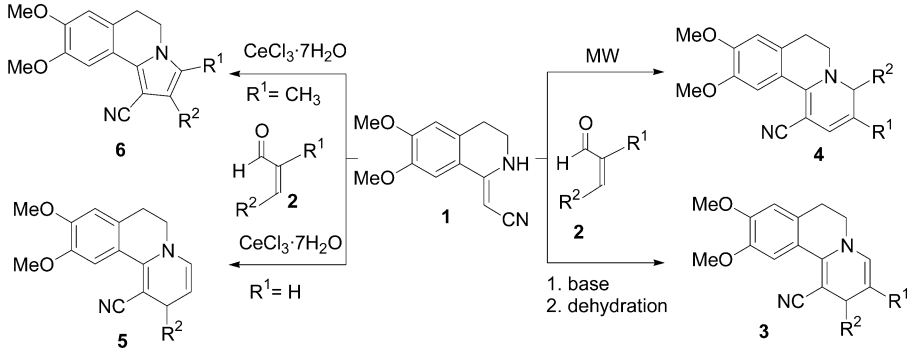
1-Cyanomethylene-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolinium mesylate (**10**) readily reacted with α,β-unsaturated aldehydes to afford 1-azatrienes **12a**–**h**, which could be cyclized to give 6,7-dihydro-4*H*-benzo[*a*]quinolizines **14a**–**h**. The reaction mechanisms were investigated by computational methods.

Introduction

Polycyclic N-heterocycles containing 1,2-fused tetrahydroisoquinoline moieties constitute the basic structural frameworks of various naturally occurring alkaloids and biologically active drugs.[1] Although several methods for the preparation of these heterocycles are known,[2] due to their great significance the development of new and efficient synthetic routes to this class of compounds might be of strong relevance.

Push-pull enamines, especially β-enaminonitriles, have proved in a number of cases to be valuable starting materials in the synthesis of various N-heterocycles.[3] We have previously reported that the readily accessible 1-cyanomethylene-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**1**) underwent base-catalyzed Michael reactions with various α,β-unsaturated carbonyl compounds **2**, followed by spontaneous cyclization to furnish different 6,7-dihydro-2*H*-benzo[*a*]quinolizine derivatives **3**.[4]

Surprisingly, the microwave-mediated transformation of the same starting compounds afforded 6,7-dihydro-4*H*-benzo[*a*]quinolizines **4**, with reversed regioselectivity.[5] Furthermore, in the presence of cerium(III) chloride the enaminonitrile **1** reacted with α,β-unsaturated aldehydes **2** to yield benzo[*a*]quinolizines **5**, while with α-alkyl-substituted unsaturated aldehydes (**2**, $R^1 = CH_3$), pyrrolo[2,1-*a*]isoquinolines **6** were obtained (Scheme 1).[6] In view of these interesting results, here we discuss the scope and the mechanism of the microwave-activated cyclisations of **1** and α,β-unsaturated aldehydes.



Scheme 1. Reactions of **1** with aldehydes.

Computational Methods

The B3LYP/6-31G(d)[7] and MP2/6-31G(d)//B3LYP/6-31G(d) levels of theory were used in this work, with $9 \times 5 = 45$ structures being optimized at the B3LYP/6-31G(d) level of theory in vacuo and in solvent (CH_2Cl_2), by use of the default PCM method (IEF-PCM, integral equation

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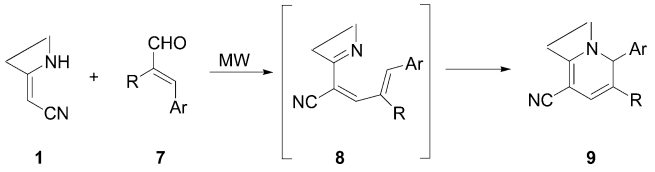
formalism polarizable continuum medium; PCM in brief) (Table 3) and the Gaussian 03 program.[8] The enthalpies and Gibbs free energies were calculated at 298.14 K.

Results and Discussion

As we suggested earlier, in the microwave-promoted reactions the nucleophilic addition takes place on the $C^{1'}$ carbon atom of enaminonitrile **1**, and the formed adduct **8** is transformed into 6,7-dihydro-4*H*-benzo[*a*]quinolizine **9** in a subsequent ring-closure reaction (Scheme 2).[5]



Scheme 2. Proposed mechanism of the microwave-activated ring-closure reaction.

Synthesis

In order to obtain the intermediate **8**, the mesylate salt of **1** (**10**) was prepared and used in the microwave-mediated reaction with α,β-unsaturated aldehydes **11a**–**h** (Scheme 3). In these solvent-free Knoevenagel-type condensations, protonated 1-azatrienes **12a**–**h** were obtained. The (*E*,*E*) configurations of the double bonds were determined by NMR (J-HMBC, J-INEPT)[9,10] methods.

Despite the fairly short microwave irradiation times applied (1 min), considerable decomposition of the azatrienes was observed. Higher yields were achieved, and the purification procedure was simple, when the reactions were carried out in acetic acid at room temperature (Table 1). Because of their low stabilities, compounds **12a**–**h** were stored at low temperature (–4 °C).

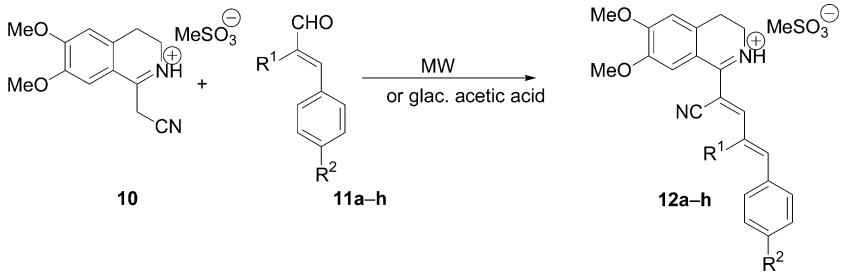
Table 1. Formation of the azatrienes in acetic acid.

Product	R^1	R^2	Time [h]	Yield [%]
12a	H	H	2	92
12b	CH_3	H	6	87
12c	H	NO_2	2	82
12d	CH_3	NO_2	7	65
12e	H	OMe	3	76
12f	CH_3	OMe	9	67
12g	H	NMe_2	2	89
12h	CH_3	NMe_2	8	71

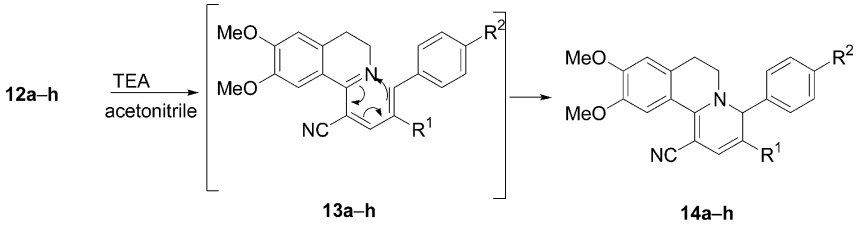
With addition of TEA in excess to the MeCN solutions of azatrienes **12b**, **12d**, **12f**, and **12h** ($R^1 = CH_3$), the cyclization took place at room temp. to give 6,7-dihydro-4*H*-benzo[*a*]quinolizines **14b**, **14d**, **14f**, and **14h**, while azatrienes **12a**, **12c**, **12e**, and **12g** (R^1 = H) could be cyclized only in MeCN at reflux (Scheme 4, Table 2). Noteworthy about the cyclizations of the azatrienes are the mild reaction conditions under which the ring-closure reaction occurs. In contrast, the electrocyclization of all-carbon triene analogues requires high temperatures (typically >130 °C).[11]

Table 2. Ring-closure reaction of 1-azatriene derivatives.

Product	R^1	R^2	Time [h]	Temp.	Yield [%]
14a	H	H	2	reflux	85
14b	CH_3	H	4	room temp.	82
14c	H	NO_2	5	reflux	75
14d	CH_3	NO_2	8	room temp.	72
14e	H	OMe	3	reflux	69
14f	CH_3	OMe	2	room temp.	65
14g	H	$N(Me)_2$	1	reflux	89
14h	CH_3	$N(Me)_2$	1	room temp.	82



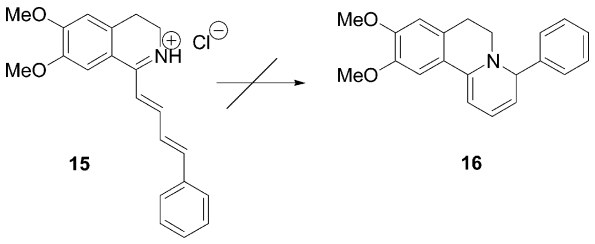
Scheme 3. Preparation of 1-azatrienes.



Scheme 4. 1,6-Electrocyclisation of 1-azatriene derivatives **12a**–**h**.

In addition to the effect of the methyl group in the $C^{3'}$ positions of azatrienes **12b**, **12d**, **12f**, and **12h**, the reaction rates were also affected by the substituents at the *para* positions of the phenyl rings. For the cyclization of **12d**, with the electron-withdrawing nitro group, the reaction time was longer than for the unsubstituted compound **12b**. In contrast, the electron-donating substituents in **12f** and **12h** shortened the reaction times. Similar tendencies could be ascertained for the compounds **12a**, **12c**, and **12g** (R^1 = H) in acetonitrile at reflux, but in the case of azatriene **12e** the presumed accelerating effect was not observed (Table 2).

For 6π-electrocyclization to be able to take place, the azatrienes must possess the appropriate geometry. Consequently, the first step of the process must be an (*E*)→(*Z*) isomerization, in which the electron-withdrawing CN group plays a crucial role. To confirm this assumption we attempted to cyclize the 1-azatriene derivative **15** (Scheme 5), prepared by known methods.[12]



Scheme 5. Attempted cyclization of **15**.

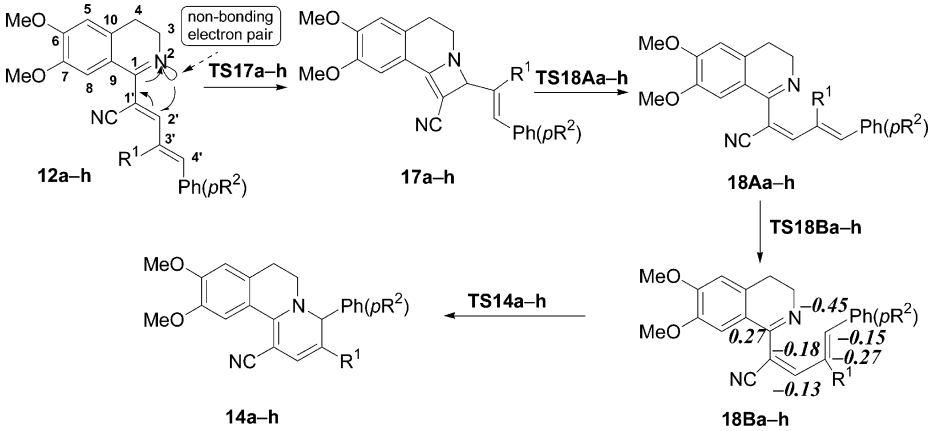
This compound, with no CN group in the $C^{1'}$ position, failed to undergo ring-closure reaction to **16** in the presence of TEA, even on heating at reflux in xylene for 24 h.

Mechanism of the Cyclization of 1-Azatrienes

Since the NMR spectroscopic data unambiguously showed (*E*,*E*) configurations of the double bonds in compounds **12a**–**h**, the first step of the reaction must be an (*E*)→(*Z*) isomerization (Scheme 6 and Figure 1).

In our computations, no direct saddle point could be found for the (*E*)→(*Z*) isomerization step of **12**, leading to **18**, and all optimizations led to dihydroazete intermediates **17a**–**h**. Each overall process, involving an intermediate (**17a**–**h**) and two TSs (**TS17a**–**h** and **TS18Aa**–**h**), requires an activation energy (**TS18A**; $\Delta G^{\ddagger}$ = 165–174 kJ mol^{-1}; Table 3) significantly lower than that of the all-carbon hexatriene analogue **19** ($\Delta G^{\ddagger}$ = 225 kJ mol^{-1}; Figure 2). The relatively low energy differences between compounds **12** and compounds **17** (57–83 kJ mol^{-1}; Figure 3), and consequently the formation of **17a**–**h**, can be explained by the low ring-strain enthalpies (46.0–48.6 kJ mol^{-1} for **17a**), calculated from the isodesmic reaction enthalpies (see Supporting Information). Furthermore, the computations reveal that the process is promoted by a nucleophilic intramolecular attack of the nitrogen atom on the electron-poor $C^{2'}$ atom, favoring a nucleophilic cyclisation process in which, beside the π-electrons of the two double bonds (N^2=C^1 and $C^{1'}$=$C^{2'}$), the nonbonding electron pair of the N atom is also involved (Scheme 6). In order to check the results of the B3LYP/6-31G(d) method, a more reliable MP2/6-31G(d)//B3LYP/6-31G(d) level of theory[13,14] was also utilized for the reaction sequence **12a** → **14a**. The energies calculated in this way are close to the values obtained by the DFT method [B3LYP/6-31G(d)], and only the $\Delta G^{\ddagger}$ values of TSs in the isomerization steps (**TS17a**, **TS18Aa**, **TS18Ba**) proved to be significantly higher, by roughly 10 kJ mol^{-1}. For this reason, the B3LYP/6-31G(d) level of theory was applied for other derivatives.

The calculated Nucleus-Independent Chemical Shift (NICS) values,[15] measures of the aromaticity forming in the transition state, are –5.6 and –4.6 ppm for **TS17a** and **TS18Aa**, respectively, indicating a moderate aromatization during the ring-closure and ring-opening reactions. The NICS value for the TS of butadiene → cyclobutene is –12.3 ppm.[16] The participation of the nonbonding electron pair of the N atom may be confirmed by the HOMOs of **TS17a** and **TS18Aa**. In both cases, the nonbonding electron pair of the N atom is strongly involved in the HOMOs of the transition states (Figure 4).



Scheme 6. Proposed mechanism for the transformations of **12a**–**h** into **14a**–**h**. The italic numbers in **18Ba**–**h** indicate the atomic natural bond orbital (NBO) charges of atoms in **18Ba**.

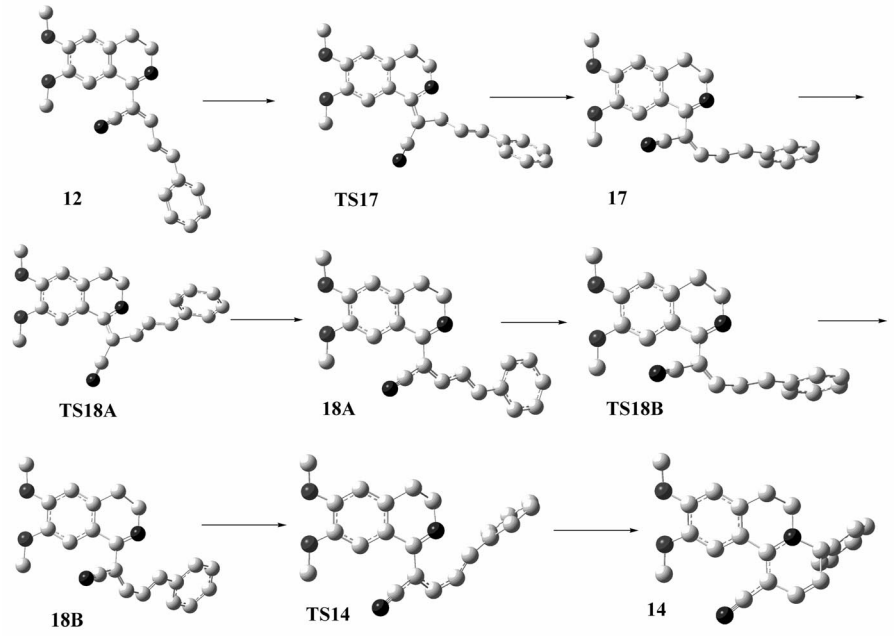


Figure 1. Ball-and-stick representation of the reaction sequence **12a** → **17a** → **18Aa** → **18Ba** → **14a** (hydrogen atoms are ignored).

Table 3. Δ*G* values [kJ mol^{-1}] for compounds and transition states involved in the mechanism.

						(*E*)→(*Z*) isomerization step		Conformational step		Ring-closure step	
	R^1	R^2	**12**	**TS17**	**17**	**TS18A**	**18A**	**TS18B**	**18B**	**TS14**	**14**
12a	H	H	0.00	147.75	80.63	173.78	8.37	46.83	31.63	102.61	–10.67
12a[a]	H	H	0.00	161.04	95.31	186.66	9.78	38.64	29.55	96.57	–40.98
12b	Me	H	0.00	132.56	61.67	165.47	11.57	26.51	17.74	89.29	–46.70
12c	H	NO_2	0.00	150.01	77.30	173.62	7.13	45.20	31.06	103.61	7.13
12g	H	NMe_2	0.00	142.10	84.14	172.68	4.35	54.95	30.15	95.63	–6.26
19	H	H	0.00	186.46	117.65	210.82	9.13	43.358	32.01	115.80	7.98

[a] Computed at the MP2/6-31G(d)//B3LYP/6-31G(d) level of theory.

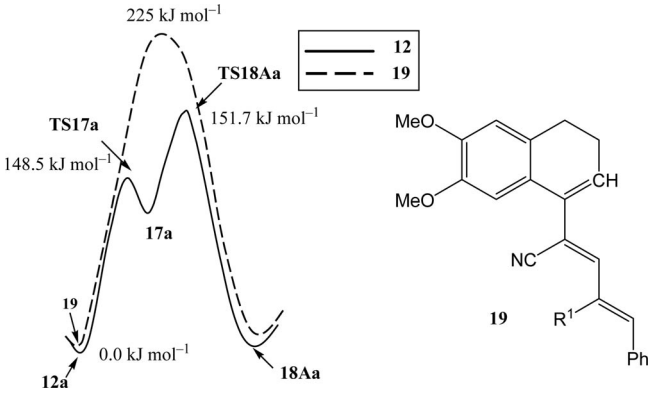


Figure 2. Gibbs free energy [kJ mol^{-1}] diagram for the isomerization of **12** and hypothetical C^2 analogue **19**.

In order to obtain more evidence for the nitrogen participation, the 3D potential surface was computed at the HF/3-21G level of theory (Figure 5). The absence of a first-order saddle point between **12** and **18A** in the 3D cross-section unambiguously shows that the 1,2-dihydroazete structures **17a**–**h** should be involved as intermediates in the isomerization process. The intermediates **17** can readily undergo ring-opening reaction to give **18A** with a (*Z*,*E*) configuration.

Besides the synthetic verification, computational results showed unequivocally that the electron-withdrawing CN group significantly influences the reaction rates of all steps.[17] As the natural bond orbital (NBO) charges (**18B** in Scheme 6) indicate, the CN group lowers the electron density at the $C^{2'}$ and $C^{4'}$ atoms, promoting the nucleophilic attack of the N^2 atom and decreasing all activation parameters (Figure 3, Table 3).

To achieve the optimal molecular geometry, a rotation takes place around the $C^{2'}$–$C^{3'}$ single bond, with a low energy barrier (Figure 2, Table 3). The subsequent cyclization of the 1-azatrienes **18Ba**–**h** seems to be a classical 6π-electrocyclic mechanism. However, the calculated NICS value[18] for **TS14a** is only –5.1 ppm. This value is significantly lower than the similarly calculated NICS value in the ring-closure reaction of cyclohexatriene [–14.5 ppm at B3LYP/6-31G(d)], which may be considered a pure electrocyclization. From these data, one may conclude that the

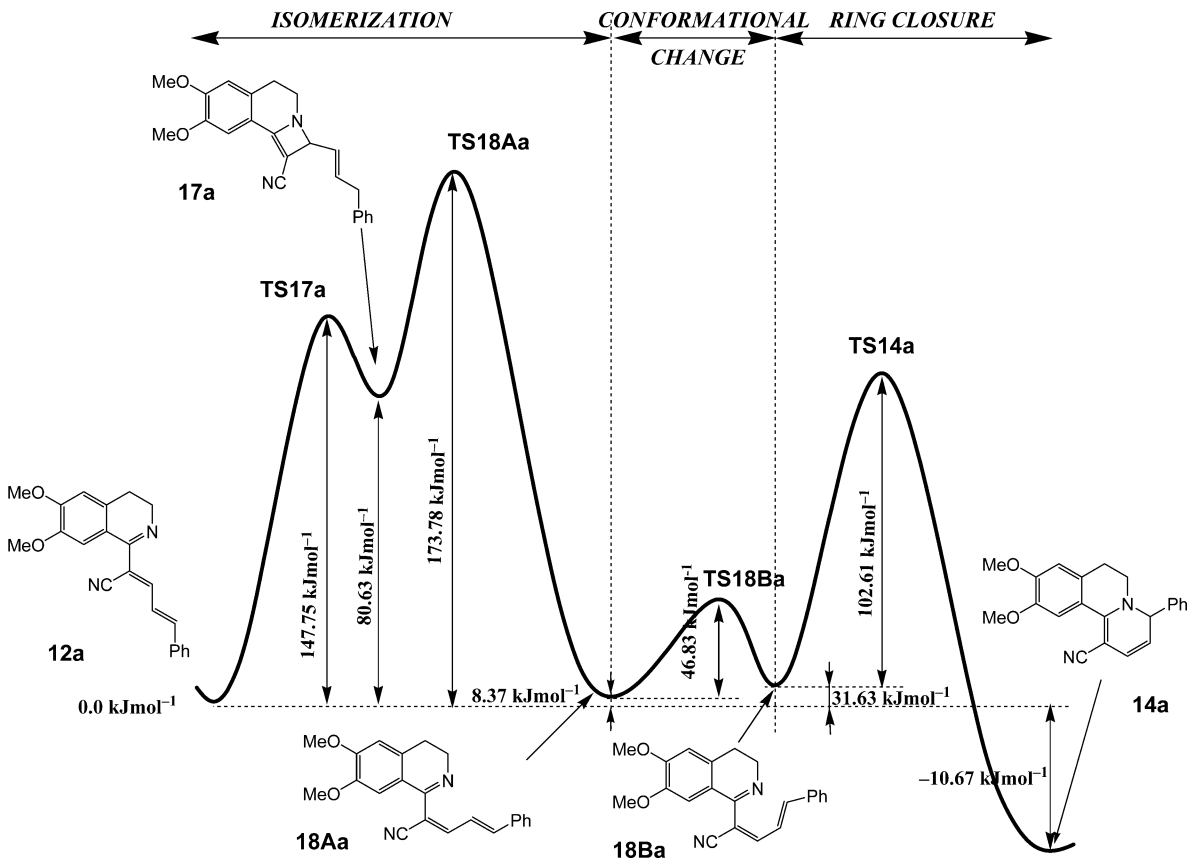


Figure 3. Computed Gibbs free energy [kJ mol^{-1}] diagram for the mechanism of the transformation **12a** → **14a**.

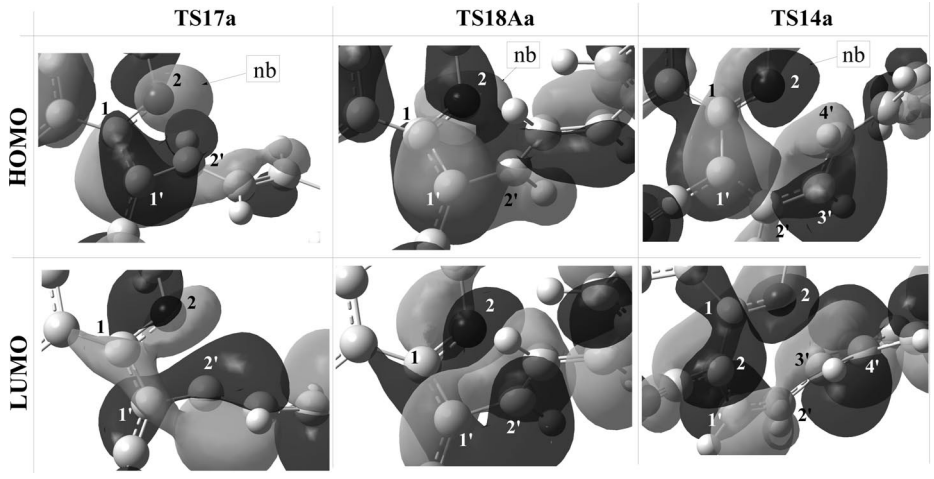
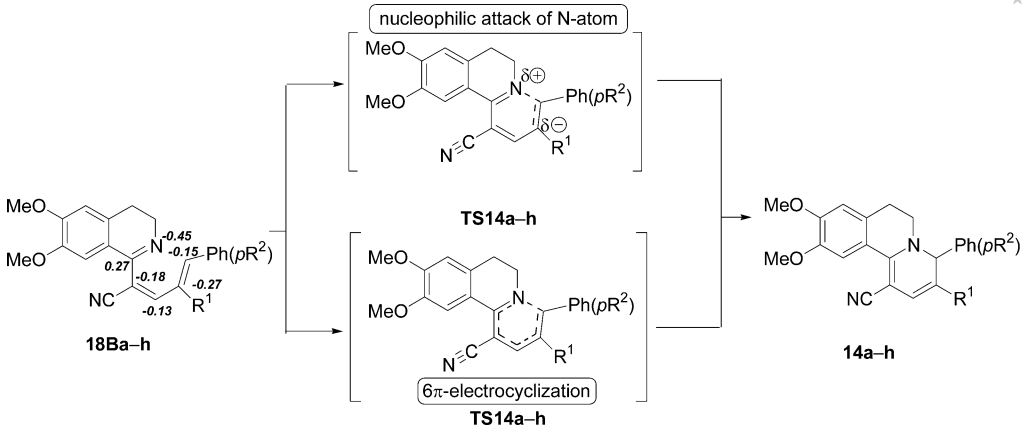


Figure 4. Schematic representation of the HOMO and LUMO atomic orbitals of **TS17a**, **18Aa**, and **TS14a** (nb refers to the nonbonding electron pair of the N atom).

cyclization step takes place with a mixed mechanism, composed of a nucleophilic attack of the N^1 atom on the electron-poor $C^{4'}$ atom (see NBO charges of **18B** in Scheme 6), and a 6π-electrocyclization process (Scheme 7). The strong involvement of the nonbonding electron pair of the N atom in the HOMO and not in the LUMO of **TS14**, where the LUMO is instead dominated by the $C^1{=}N^2$ double bond, may support its participation in the reaction (Figure 4). Because the position of the N atom is fixed by the tetrahydroisoquinoline ring, the $C^{1'}{-}C^1{=}N^2{-}C^3$ torsion angle does not change (ca. 3°) during the reaction, in contrast with the significant rotation of the $C^2{-}C^3{=}C^4{-}C^{Ph}$ torsion angle (ca. 35°; Figure 1). Consequently, the process can not be regarded either as a disrotatory or a conrotatory mechanism.



Scheme 7. Schematic representation of the proposed mixed mechanism for the ring-closure step, involving a nucleophilic attack of the N atom and a 6π-electrocyclisation.

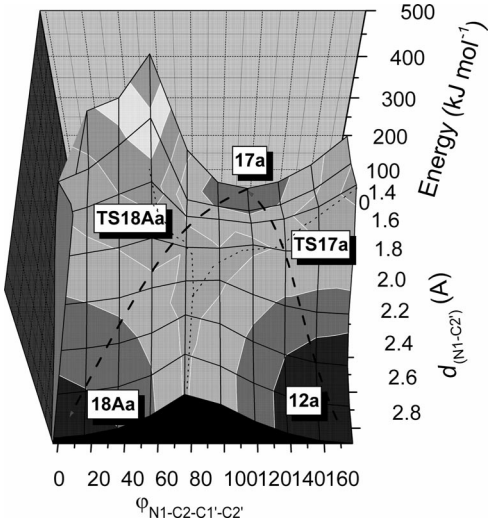


Figure 5. Computed 3D PES for **12a** → **17a** → **18Aa**.

Since the direction of the rotation of the torsion angle C^2–C^3=C^4–C^{Ph} is not specified, the reaction is therefore not stereoselective.

The computational studies also showed considerable substituent effects in the cyclization sequence. The presence of an Me group in the $C^{3'}$ position ($R^1 = CH_3$, **12b**) decreases the activation parameters of all the steps by ca. 10–20 kJ mol^{-1}, increasing the overall reaction rate significantly. Moreover, it decreases the energy difference between **12b** and **18Ab** as well as between **18Ab** and **18Bb**. Finally, it is noteworthy that the Me substitution also lowers the energy content of the product **14b**. From these data, we may conclude that the electron donor character dominates the overall effect of the Me group, and because of its relatively large distance from the reaction center the steric hindrance is less significant. The energy differences between the Me-substituted and unsubstituted rotamers, **18Ab** and **18Bb**; **18Aa** and **18Ba** respectively, however, can undoubtedly be explained by the steric effect of the Me group (Table 3).

The *para* substituents on the phenyl group modify all activation parameters of the reaction sequence (Table 3). The electron-donating NMe_2 group (**12g**) decreases, while the electron-withdrawing NO_2 group (**12c**) increases the activation parameters of the ring-closure reaction.

Conclusions

A new method has been developed for the synthesis of 1-azatrienes **12a**–**h**, which could be isolated and cyclized to 6,7-dihydro-4*H*-benzo[*a*]quinolizines **14a**–**h**. We have suggested that the presence of the electron-withdrawing CN group plays an important role in the 6π-aza electrocyclization. We found that the rate of cyclization is influenced mainly by the presence of a methyl group in the $C^{3'}$ position and the substituents at the *para* position in the phenyl ring, in accordance with the computational results. The activation parameters of the cyclization were calculated, and we have proposed a mechanism for the formation of 6,7-dihydro-4*H*-benzo[*a*]quinolizines.

Experimental Section

General: All melting points were measured with a Büchi SMP-20 melting point apparatus and are uncorrected. NMR spectra were recorded with a Bruker DRX 250 spectrometer (^{1}H: 250 MHz; ^{13}C: 62.5 MHz). The HPLC-MS analyses were performed with a PE API 2000 apparatus. IR spectra were recorded with a Perkin–Elmer series 1600 FT/IR spectrometer. Column chromatography was conducted with Merck Kieselgel 60 (0.063–0.100 mm). Solvents were dried and freshly distilled according to the common practice.

General Procedure for the Microwave-Assisted Synthesis of 1-Azatrienes 12a and 12b: 1-Cyanomethyl-6,7-dimethoxy-3,4-dihydroisoquinolinium mesylate (**10**, 500 mg, 1.54 mmol) was mixed with the α,β-unsaturated aldehyde (**11a**, **11b**, 3.08 mmol), and the mixture was irradiated in an open vessel in a Synthewave S402 (Prolabo) monomode, focused MW (2.45 GHz) reactor with continuous rotation for 1 min. During the irradiation, the temperature of the reaction mixture (measured by infrared thermometry) increased linearly, and reached 95 °C after 1 min. The oily material was then cooled, and the product was crystallized from diisopropyl ether. The crude product was purified by flash chromatography (silica gel, EtOAc). Yield: 45% (**12a**), 35% (**12b**).

General Procedure for the Synthesis of 1-Azatrienes in Acetic Acid (12a–h): The α,β-unsaturated aldehyde (**11a**–**h**, 3.0 mmol) was added to a solution of 1-cyanomethyl-6,7-dimethoxy-3,4-dihydroisoquinolinium mesylate (**10**, 670 mg, 2 mmol) in glacial acetic acid (6 mL). The reaction mixture was stirred at room temperature for 2–9 h. The solution was then poured into diisopropyl ether (30 mL). The formed precipitate was filtered off and washed with diethyl ether.

1-(1-Cyano-4-phenylbuta-1,3-dienyl)-6,7-dimethoxy-3,4-dihydroisoquinolinium Mesylate (12a): Orange crystals, yield: 810 mg (1.84 mmol, 92%). M.p. 75–76 °C (decomp.). ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 2.84 (s, 3 H, *Me*SO_3), 3.09 (t, J = 8.0 Hz, 2 H, 4-H), 3.86 (t, J = 8.0 Hz, 2 H, 3-H), 4.03 (s, 3 H, O*Me*), 4.05 (s, 3 H, O*Me*), 6.88 (s, 1 H, 5-H), 7.27 (s, 1 H, 8-H), 7.42–7.55 (m, 5 H, *Ph*), 7.71 (dd, J_1 = 15.2, J_2 = 11.5 Hz, 1 H, 3′-H), 7.93 (d, J = 15.2 Hz, 1 H, 4′-H), 8.78 (d, J = 11.5 Hz, 1 H, 2′-H) ppm. ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 26.1 (C-4), 39.8 (*Me*SO_3), 41.7 (C-3), 56.8 (O*Me*), 57.2 (O*Me*), 101.0 (C-1′), 111.7 (C-5), 113.0 (C-8), 115.4 (*C*N), 116.5 (C-9), 123.8 (C-3′), 129.6 (*Ph*), 129.8 (*Ph*), 132.6 (*Ph*), 135.0 (*Ph*), 135.8 (C-10), 148.9 (C-7), 155.0 (C-4′), 157.5 (C-6), 161.1 (C-2′), 165.9 (C-1) ppm.

1-(1-Cyano-3-methyl-4-phenylbuta-1,3-dienyl)-6,7-dimethoxy-3,4-dihydroisoquinolinium Mesylate (12b): Yellow crystals, yield: 790 mg (1.74 mmol, 87%). M.p. 132 °C (decomp.). ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 2.48 (s, 3 H, *Me*), 2.84 (s, 3 H, *Me*SO_3), 3.19 (t, J = 7.9 Hz, 2 H, 4-H), 3.88 (t, J = 7.9 Hz, 2 H, 3-H), 3.90 (s, 3 H, O*Me*), 3.94 (s, 3 H, O*Me*), 6.85 (s, 1 H, 5-H), 7.28 (s, 1 H, 8-H), 7.71–7.95 (m, 5 H, *Ph*), 8.16 (s, 1 H, 2′-H), 8.17 (s, 1 H, 4′-H) ppm. ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 21.6 (*Me*), 25.4 (C-4), 39.8 (*Me*SO_3), 49.0 (C-3), 56.2 (O*Me*), 56.2 (O*Me*), 106.1 (C-1′), 110.8 (C-5), 113.3 (C-8), 116.3 (*C*N), 117.1 (C-9), 126.1 (C-3′), 129.1 (*Ph*), 129.3 (*Ph*), 131.7 (*Ph*), 133.7 (C-10), 134.1 (*Ph*), 147.5 (C-7), 152.7 (C-4′), 154.1 (C-6), 158.7 (C-2′), 159.1 (C-1) ppm.

1-[1-Cyano-4-(4-nitrophenyl)buta-1,3-dienyl]-6,7-dimethoxy-3,4-dihydroisoquinolinium Mesylate (12c): Yellow crystals, yield: 796 mg (1.64 mmol, 82%). M.p. 93–95 °C (decomp.). ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 2.82 (s, 3 H, *Me*SO_3), 3.11 (t, J = 7.4 Hz, 2 H, 4-H), 3.98 (t, J = 7.4 Hz, 2 H, 3-H), 4.05 (s, 3 H, O*Me*), 4.09 (s, 3 H, O*Me*), 6.90 (s, 1 H, 5-H), 7.43 (s, 1 H, 8-H), 7.52 (dd, J_1 = 14.9, J_2 = 11.2 Hz, 1 H, 3′-H), 7.85 (d, J = 8.4 Hz, 2 H, $C_6H_4NO_2$), 7.99 (d, J = 14.9 Hz, 1 H, 4′-H), 8.28 (d, J = 8.4 Hz, 2 H, $C_6H_4NO_2$), 8.78 (d, J = 11.2 Hz, 1 H, 2′-H) ppm. ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 25.4 (C-4), 39.1 (*Me*SO_3), 41.3 (C-3), 56.2 (O*Me*), 56.6 (O*Me*), 103.1 (C-1′), 111.0 (C-5), 112.4 (C-8), 114.2 (*C*N), 115.7 (C-9), 124.0 (C-3′), 126.3 ($C_6H_4NO_2$), 129.4 ($C_6H_4NO_2$), 135.2 (C-10), 140.2 ($C_6H_4NO_2$), 148.6 ($C_6H_4NO_2$), 148.8 (C-7), 150.0 (C-4′), 157.4 (C-6), 159.2 (C-2′), 165.1 (C-1) ppm.

1-[1-Cyano-3-methyl-4-(4-nitrophenyl)buta-1,3-dienyl]-6,7-dimethoxy-3,4-dihydroisoquinolinium Mesylate (12d): Yellow crystals, yield: 650 mg (1.30 mmol, 65%). M.p. 143–144 °C (decomp.). ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 2.52 (s, 3 H, *Me*), 2.79 (s, 3 H, *Me*SO_3), 3.11 (t, J = 7.6 Hz, 2 H, 4-H), 3.90 (t, J = 7.6 Hz, 2 H, 3-H), 4.02 (s, 3 H, O*Me*), 4.04 (s, 3 H, O*Me*), 6.90 (s, 1 H, 5-H), 7.39 (s, 1 H, 8-H), 7.65 (d, J = 8.4 Hz, 2 H, $C_6H_4NO_2$), 7.85 (s, 1 H, 4′-H), 8.26 (d, J = 8.4 Hz, 2 H, $C_6H_4NO_2$), 8.41 (s, 1 H, 2′-H) ppm. ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 21.6 (*Me*), 25.5 (C-4), 39.5 (*Me*SO_3), 41.3 (C-3), 56.2 (O*Me*), 56.5 (O*Me*), 102.1 (C-1′), 111.2 (C-5), 112.4 (C-8), 114.0 (*C*N), 115.6 (C-9), 125.9 (C-3′), 126.0 ($C_6H_4NO_2$), 130.0 ($C_6H_4NO_2$), 135.2 (C-10), 140.2 ($C_6H_4NO_2$), 148.5 ($C_6H_4NO_2$), 147.8 (C-7), 149.8 (C-4′), 157.3 (C-6), 159.1 (C-2′), 165.4 (C-1) ppm.

1-{1-Cyano-4-[4-(dimethylamino)phenyl]buta-1,3-dienyl}-6,7-dimethoxy-3,4-dihydroisoquinolinium Mesylate (12g): Dark blue crystals, yield: 860 mg (1.78 mmol, 89%). M.p. 132 °C (decomp.). ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 2.84 (s, 3 H, *Me*SO_3), 3.02 (t, J = 7.5 Hz, 2 H, 4-H), 3.16 (s, 6 H, H-NMe_2), 3.92 (t, J = 7.5 Hz, 2 H, H-3), 3.98 (s, 3 H, O*Me*), 4.02 (s, 3 H, O*Me*), 6.70 (d, J = 9.3 Hz, 2 H, $C_6H_4NMe_2$), 6.84 (s, 1 H, 5-H), 7.29 (dd, J_1 = 14.4, J_2 = 11.6 Hz, 1 H, 3′-H), 7.60 (s, 1 H, H-8), 7.67 (d, J = 9.3 Hz, 2 H, $C_6H_4NMe_2$), 7.95 (d, J = 14.4 Hz, 1 H, 4′-H), 8.75 (d, J = 11.6 Hz, 1 H, 2′-H) ppm. ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 26.1 (C-4), 39.2 (*Me*SO_3), 40.1 (C-3), 40.5 (N*Me*$_2$), 56.1 (O*Me*), 56.3 (O*Me*), 93.1 (C-1′), 110.7 (C-5), 112.1 (C-8), 112.7 (*C*N), 116.7 (C-9), 119.0 ($C_6H_4NMe_2$), 123.2 (C-3′), 125.0 ($C_6H_4NMe_2$), 133.1 (C-10), 134.6 ($C_6H_4NMe_2$), 148.0 ($C_6H_4NMe_2$), 153.5 (C-7), 155.7 (C-4′), 157.9 (C-6), 160.7 (C-2′), 165.6 (C-1) ppm.

1-{1-Cyano-4-[4-(dimethylamino)phenyl]-3-methylbuta-1,3-dienyl}-6,7-dimethoxy-3,4-dihydroisoquinolinium Mesylate (12h): Dark red crystals, yield: 706 mg (1.42 mmol, 71%). M.p. 130 °C (decomp.). ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 2.33 (s, 3 H, *CH*$_3$), 2.58 (s, 3 H, *Me*SO_3), 3.08 (s, 6 H, *NMe*$_2$), 3.88 (t, J = 6.3 Hz, 2 H, 4-H), 3.97 (s, 3 H, O*Me*), 4.00 (s, 3 H, O*Me*), 4.48 (t, J = 6.3 Hz, 2 H, 3-H), 6.87 (s, 1 H, 5-H), 7.26 (d, J = 8.7 Hz, 2 H, $C_6H_4NMe_2$), 7.26 (s, 1 H, 8-H), 7.45 (d, J = 8.7 Hz, 2 H, $C_6H_4NMe_2$), 7.97 (s, 1 H, 4′-H), 8.47 (s, 1 H, 2′-H) ppm. ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 20.1 (*Me*), 26.7 (C-4), 39.0 (*Me*SO_3), 40.3 (*NMe*$_2$), 52.6 (C-3), 56.2 (O*Me*), 56.3 (O*Me*), 107.8 (C-1′), 109.9 (C-5), 111.7 (C-8), 112.7 (*C*N), 115.8 (C-9), 117.3 ($C_6H_4NMe_2$), 117.5 (C-3′), 129.8 ($C_6H_4NMe_2$), 131.9 (C-10), 136.1 ($C_6H_4NMe_2$), 148.3 ($C_6H_4NMe_2$), 149.3 (C-7), 150.1 (C-4′), 151.1 (C-6), 153.9 (C-2′), 159.6 (C-1) ppm.

1-[1-Cyano-4-(4-methoxyphenyl)buta-1,3-dienyl]-6,7-dimethoxy-3,4-dihydroisoquinolinium Mesylate (12e): Wine-red crystals, yield: 750 mg (1.52 mmol, 76%). M.p. 91 °C (decomp.). ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 2.83 (s, 3 H, *Me*SO_3), 3.06 (t, J = 7.7 Hz, 2 H, 4-H), 3.89 (s, 3 H, O*Me*), 3.98 (s, 3 H, O*Me*), 4.04 (s, 3 H, O*Me*), 4.12 (t, J = 7.7 Hz, 2 H, 3-H), 6.87 (s, 1 H, 5-H), 6.96 (d, J = 8.7 Hz, 2 H, C_6H_4OMe), 7.35 (dd, J_1 = 14.8, J_2 = 11.4 Hz, 1 H, 3′-H), 7.51 (s, 1 H, 8-H), 7.69 (d, J = 8.7 Hz, 2 H, C_6H_4OMe), 7.93 (d, J = 14. 8 Hz, 1 H, 4′-H), 8.74 (d, J = 11. 4 Hz, 1 H, 2′-H) ppm. ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 26.1 (C-4), 39.0 (*Me*SO_3), 42.2 (C-3), 55.9 (O*Me*), 56.4 (O*Me*), 56.9 (O*Me*), 99.1 (C-1′), 110.9 (C-5), 113.7 (C-8), 114.0 (C_6H_4OMe), 117.5 (*C*N), 119.8 (C-9), 124.6 (C_6H_4OMe), 127.0 (C_6H_4OMe), 131.2 (C-3′), 132.2 (C-10), 147.8 (C-7), 148.0 (C-4′), 152.5 (C-6), 160.1 (C-2′), 163.0 (C_6H_4OMe), 166.0 (C-1) ppm.

1-[1-Cyano-4-(4-methoxyphenyl)-3-methylbuta-1,3-dienyl]-6,7-dimethoxy-3,4-dihydroisoquinolinium Mesylate (12f): Red crystals, yield: 650 mg (1.34 mmol, 67%). M.p. 91 °C (decomp.). ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 2.44 (s, 3 H, *CH*$_3$), 2.80 (s, 3 H, *Me*SO_3), 3.05 (t, J = 7.6 Hz, 2 H, 4-H), 3.90 (s, 3 H, O*Me*), 3.98 (s, 3 H, O*Me*), 4.07 (s, 3 H, O*Me*), 4.15 (t, J = 7.6 Hz, 2 H, 3-H), 6.91 (s, 1 H, 5-H), 6.95 (d, J = 8.7 Hz, 2 H, C_6H_4OMe), 7.51 (s, 1 H, 8-H), 7.70 (d, J = 8.7 Hz, 2 H, C_6H_4OMe), 7.92 (s, 1 H, 4′-H), 8.43 (s, 1 H, 2′-H) ppm. ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 20.2 (*Me*), 26.2 (C-4), 39.0 (*Me*SO_3), 42.2 (C-3), 55.9 (O*Me*), 56.3 (O*Me*), 56.8 (O*Me*), 104.1 (C-1′), 110.9 (C-5), 113.0 (C-8), 114.0 (C_6H_4OMe), 115.5 (*C*N), 120.2 (C-9), 124.6 (C_6H_4OMe), 127.0 (C_6H_4OMe), 128.4 (C-3′), 132.9 (C-10), 149.0 (C-7), 150.2 (C-4′), 152.5 (C-6), 162.5 (C-2′), 164.0 (C_6H_4OMe), 166.1 (C-1) ppm.

General Procedure for the Synthesis of 6,7-Dihydro-4*H*-benzo[*a*]-quinolizines: TEA (2 mmol) was added to a solution of a 1-azatriene (**12a**–**h**, 1 mmol) in acetonitrile (10 mL). The solution

was stirred at room temp. or at reflux temperature (**12b**,**d**,**f**,**h** and **12a**,**c**,**e**,**g**, respectively) for the required time (1–8 h). The solvent was removed under reduced pressure, and the residue was dissolved in CH_2Cl_2 (10 mL). The CH_2Cl_2 solution was washed with water (2 × 10 mL), dried (Na_2SO_4), and then concentrated under reduced pressure to give the crude product, which was purified by column chromatography on silica gel with hexane/EtOAc as eluent.

9,10-Dimethoxy-4-phenyl-6,7-dihydro-4*H*-benzo[*a*]quinolizine-1-carbonitrile (14a): Yellow crystals, yield: 292 mg (0.85 mmol, 85%). M.p. 175 °C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 2.68 (m, 1 H, 7-H), 2.88 (m, 1 H, 7-H), 3.08 (m, 1 H, 6-H), 3.22 (m, 1 H, 6-H), 3.89 (s, 3 H, O*Me*), 3.98 (s, 3 H, O*Me*), 5.19 (d, *J* = 4.9 Hz, 1 H, 4-H), 5.27 (dd, *J* = 4.9, *J* = 9.8 Hz, 1 H, 3-H), 6.15 (d, *J* = 9.8 Hz, 1 H, 2-H), 6.62 (s, 1 H, 8-H), 7.31–7.38 (m, 5 H, *Ph*), 7.94 (s, 1 H, 11-H) ppm. ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 29.3 (C-7), 47.1 (C-6), 56.0 (O*Me*), 56.3 (O*Me*), 66.1 (C-4), 73.3 (C-1), 110.0 (C-8) 111.0 (C-11), 114.5 (C-3), 121.0 (C-12), 123.0 (C-2), 124.1 (*C*N), 126.5 (*Ph*), 128.5 (*Ph*), 129.0 (*Ph*), 129.6 (C-13), 142.0 (*Ph*), 147.3 (C-10), 150.7 (C-9), 150.9 (C-14) ppm. $C_{22}H_{20}N_2O_2$ (344.41): calcd. C 76.72, H 5.85, N 8.13; found C 76.40, H 5.51, N 8.03.

9,10-Dimethoxy-3-methyl-4-phenyl-6,7-dihydro-4*H*-benzo[*a*]quinolizine-1-carbonitrile (14b): Yellow crystals, yield: 294 mg (0.82 mmol, 82%). M.p. 176 °C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.42 (s, 3 H, *Me*), 2.69 (m, 1 H, 7-H), 2.83 (m, 1 H, 7-H), 2.98 (m, 1 H, 6-H), 3.20 (m, 1 H, 6-H), 3.83 (s, 3 H, *OMe*), 3.89 (s, 3 H, *OMe*), 4.67 (s, 1 H, 4-H), 5.75 (s, 1 H, 2-H), 6.40 (s, 1 H, 8-H), 7.11–7.16 (m, 5 H, *Ph*), 7.73 (s, 1 H, 11-H) ppm. ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 20.3 (*Me*), 29.7 (C-7), 47.4 (C-6), 56.3 (*OMe*), 56.6 (*OMe*), 70.7 (C-4), 73.9 (C-1), 110.3 (C-8), 111.2 (C-11), 119.2 (C-12), 121.4 (C-2), 123.6 (*C*N), 124.7 (*Ph*), 127.5 (*Ph*), 129.0 (*Ph*), 129.2 (C-13), 129.7 (C-3), 140.7 (*Ph*), 147.6 (C-10), 149.0 (C-9), 150.7 (C-14) ppm. $C_{23}H_{22}N_2O_2$ (358.43): calcd. C 77.07, H 6.19, N 7.82; found C 76.99, H 6.34, N 7.71.

9,10-Dimethoxy-4-(4-nitrophenyl)-6,7-dihydro-4*H*-benzo[*a*]quinolizine-1-carbonitrile (14c): Yellow crystals, yield: 292 mg (0.75 mmol, 75%). M.p. 197 °C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 2.68 (m, 1 H, 7-H), 2.88 (m, 1 H, 7-H), 3.08 (m, 1 H, 6-H), 3.22 (m, 1 H, 6-H), 3.89 (s, 3 H, O*Me*), 3.98 (s, 3 H, O*Me*), 5.16 (d, *J* = 5.0 Hz, 1 H, 4-H), 5.25 (dd, *J* = 5.0, *J* = 9.3 Hz, 1 H, 3-H), 6.11 (d, *J* = 9.3 Hz, 1 H, 2-H), 6.57 (s, 1 H, 8-H), 7.45 (d, *J* = 8.7 Hz, 2 H, $C_6H_4NO_2$), 7.83 (s, 1 H, 11-H), 8.13 (d, *J* = 8.7 Hz, 2 H, $C_6H_4NO_2$) ppm. ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 28.2 (C-7), 46.6 (C-6), 55.0 (O*Me*), 55.3 (O*Me*), 64.2 (C-4), 73.0 (C-1), 109.0 (C-8), 109.8 (C-11), 112.1 (C-3), 122.3 (C-12), 123.1 (C-2), 123.2 (*C*N), 123.4 ($C_6H_4NO_2$), 126.2 ($C_6H_4NO_2$), 127.5 ($C_6H_4NO_2$), 128.4 (C-13), 146.4 ($C_6H_4NO_2$), 146.9 (C-10), 147.1 (C-9), 149.9 (C-14) ppm. $C_{22}H_{19}N_3O_4$ (389.40): calcd. C 67.86, H 4.92, N 10.79; found C 67.65, H 4.86, N 10.88.

9,10-Dimethoxy-3-methyl-4-(4-nitrophenyl)-6,7-dihydro-4*H*-benzo[*a*]quinolizine-1-carbonitrile (14d): Yellow crystals, yield: 290 mg (0.72 mmol, 72%). M.p. 160 °C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.57 (s, 3 H, *Me*), 2.63 (m, 1 H, 7-H), 2.81 (m, 1 H, 7-H), 2.99 (m, 1 H, 6-H), 3.17 (m, 1 H, 6-H), 3.81 (s, 3 H, O*Me*), 3.89 (s, 3 H, O*Me*), 4.93 (s, 1 H, 4-H), 5.92 (s, 1 H, 2-H), 6.54 (s, 1 H, 8-H), 7.47 (d, *J* = 8.5 Hz, 2 H, $C_6H_4NO_2$), 7.84 (s, 1 H, 11-H), 8.13 (d, *J* = 8.5 Hz, 2 H, $C_6H_4NO_2$) ppm. ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 20.3 (*Me*), 29.6 (C-7), 47.7 (C-6), 56.4 (O*Me*), 56.6 (O*Me*), 70.0 (C-4), 74.6 (C-1), 108.9 (C-8) 110.4 (C-11), 111.1 (C-3), 120.4 (C-12), 120.9 (C-2), 122.4 (*C*N), 124.0 ($C_6H_4NO_2$), 124.6 ($C_6H_4NO_2$), 128.2 ($C_6H_4NO_2$), 129.5 (C-13), 147.1 ($C_6H_4NO_2$), 147.8 (C-10), 148.9 (C-9), 151.0 (C-14) ppm. $C_{23}H_{21}N_3O_4$ (403.43): calcd. C 68.47, H 5.25, N 10.42; found C 68.59, H 5.19, N 10.40.

9,10-Dimethoxy-4-(4-methoxyphenyl)-6,7-dihydro-4*H*-benzo[*a*]quinolizine-1-carbonitrile (14e): Yellow crystals, yield: 258 mg (0.69 mmol, 69%). M.p. 142 °C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 2.55 (m, 1 H, 7-H), 2.81 (m, 1 H, 7-H), 2.98 (m, 1 H, 6-H), 3.20 (m, 1 H, 6-H), 3.80 (s, 3 H, *OMe*), 3.82 (s, 3 H, O*Me*), 3.90 (s, 3 H, O*Me*), 4.99 (d, *J* = 4.8 Hz, 1 H, 4-H), 5.11 (dd, *J* = 4.8, *J* = 9.6 Hz, 1 H, 3-H), 6.00 (d, *J* = 9.6 Hz, 1 H, 2-H), 6.54 (s, 1 H, 8-H), 6.84 (d, *J* = 7.3 Hz, 2 H, C_6H_4OMe), 7.27 (d, *J* = 7.3 Hz, 2 H, C_6H_4OMe), 7.91 (s, 1 H, 11-H) ppm. ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 29.6 (C-7), 47.9 (C-6), 55.3 (O*Me*), 56.4 (O*Me*), 56.6 (O*Me*), 65.8 (C-4), 73.7 (C-1), 110.3 (C-8), 110.4 (C-3), 111.2 (C-11), 119.1 (C-12), 122.8 (C-2), 123.6 (*C*N), 124.7 (C_6H_4OMe), 128.6 (C_6H_4OMe), 129.7 (C_6H_4OMe), 132.9 (C-13), 147.5 (C-10), 148.8 (C-9), 150.6 (C-14), 160.1 (C_6H_4OMe) ppm. $C_{23}H_{22}N_2O_3$ (374.43): calcd. C 73.78, H 5.92, N 7.48; found C 73.57, H 6.03, N 7.55.

9,10-Dimethoxy-4-(4-methoxyphenyl)-3-methyl-6,7-dihydro-4*H*-benzo[*a*]quinolizine-1-carbonitrile (14f): Yellow crystals, yield: 252 mg (0.65 mmol, 65%). M.p. 127 °C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.60 (s, 3 H, *Me*), 2.59 (m, 1 H, 7-H), 2.82 (m, 1 H, 7-H), 3.00 (m, 1 H, 6-H), 3.20 (m, 1 H, 6-H), 3.76 (s, 3 H, *OMe*), 3.86 (s, 3 H, O*Me*), 3.95 (s, 3 H, O*Me*), 4.79 (s, 1 H, 4-H), 5.92 (s, 1 H, 2-H), 6.59 (s, 1 H, 8-H), 6.82 (d, *J* = 7.3 Hz, 2 H, C_6H_4OMe), 7.27 (d, *J* = 7.3 Hz, 2 H, C_6H_4OMe), 7.90 (s, 1 H, 11-H) ppm. ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 20.3 (*Me*), 29.7 (C-7), 47.2 (C-6), 55.6 (O*Me*), 56.3 (O*Me*), 56.6 (O*Me*), 70.0 (C-4), 73.8 (C-1), 110.3 (C-8), 111.2 (C-11), 114.5 (C-3), 119.1 (C-12), 121.5 (C-2), 123.7 (*C*N), 124.8 (C_6H_4OMe), 128.6 (C_6H_4OMe), 129.7 (C_6H_4OMe), 132.9 (C-13), 147.6 (C-10), 148.8 (C-9), 150.7 (C-14), 160.2 (C_6H_4OMe) ppm. $C_{24}H_{24}N_2O_3$ (388.46): calcd. C 74.21, H 6.23, N 7.21; found C 74.09, H 6.19, N 7.20.

4-[4-(Dimethylamino)phenyl]-9,10-dimethoxy-6,7-dihydro-4*H*-benzo-[*a*]quinolizine-1-carbonitrile (14g): Yield: 345 mg (0.89 mmol, 89%). M.p. 153 °C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 2.70 (m, 1 H, 7-H), 2.75 (m, 1 H, 7-H), 2.84 (s, 6 H, N*Me*$_2$) 2.97 (m, 1 H, 6-H), 3.09 (m, 1 H, 6-H), 3.78 (s, 3 H, O*Me*), 3.87 (s, 3 H, O*Me*), 4.95 (d, *J* = 4.8 Hz, 1 H, 4-H), 5.13 (dd, *J* = 4.8, *J* = 9.7 Hz, 1 H, 3-H), 6.02 (d, *J* = 9.7 Hz, 1 H, 2-H), 6.51 (s, 1 H, 8-H), 6.59 (d, *J* = 8.6 Hz, 2 H, $C_6H_4NMe_2$), 7.16 (d, *J* = 8.6 Hz, 2 H, $C_6H_4NMe_2$), 7.82 (s, 1 H, 11-H) ppm. ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 29.7 (C-7), 40.8 (*NMe*$_2$), 47.2 (C-6), 56.4 (O*Me*), 56.6 (O*Me*), 65.8 (C-4), 73.1 (C-1), 110.3 (C-8), 111.4 (C-11), 112.8 (*Ph*-NMe$_2$), 115.3 (C-12), 121.5 (C-2), 122.9 (*C*N), 124.9 (C-3), 128.0 ($C_6H_4NMe_2$), 128.1 ($C_6H_4NMe_2$), 130.1 (C-13), 147.5 (C-10), 150.9 (C-9), 151.0 ($C_6H_4NMe_2$), 151.0 (C-14) ppm. $C_{24}H_{25}N_3O_2$ (387.47): calcd. C 74.39, H 6.50, N 10.84; found C 74.30, H 6.60, N 10.82.

4-[4-(Dimethylamino)phenyl]-9,10-dimethoxy-3-methyl-6,7-dihydro-4*H*-benzo[*a*]quinolizine-1-carbonitrile (14h): Yield: 329 mg (0.82 mmol, 82%). M.p. 155 °C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.55 (s, 3 H, *Me*) 2.59 (m, 1 H, 7-H), 2.85 (s, 6 H, *NMe*$_2$), 2.95 (m, 1 H, 7-H), 3.10 (m, 1 H, 6-H), 3.63 (m, 1 H, 6-H), 3.86 (s, 3 H, O*Me*), 3.89 (s, 3 H, O*Me*), 4.67 (s, 1 H, 4-H), 5.86 (s, 1 H, 2-H), 6.52 (s, 1 H, 8-H), 6.59 (d, *J* = 8.5 Hz, 2 H, $C_6H_4NMe_2$), 7.16 (d, *J* = 8.5 Hz, 2 H, $C_6H_4NMe_2$), 7.84 (s, 1 H, 11-H) ppm. ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 20.4 (*Me*), 29.7 (C-7), 40.8 (*NMe*$_2$), 47.2 (C-6), 56.3 (OMe), 56.6 (O*Me*), 70.1 (C-4), 73.7 (C-1), 110.3 (C-8) 111.2 (C-11), 112.6 ($C_6H_4NMe_2$), 118.8 (C-12), 121.7 (C-2), 123.9 (*C*N), 125.0 (C-3), 128.4 ($C_6H_4NMe_2$), 128.6 ($C_6H_4NMe_2$), 129.7 (C-13), 147.6 (C-10), 149.7 (C-9), 150.6 ($C_6H_4NMe_2$), 150.6 (C-14) ppm. $C_{25}H_{27}N_3O_2$ (401.50): calcd. C 74.79, H 6.78, N 10.47; found C 74.83, H 6.77, N 10.55.

Supporting Information (see footnote on the first page of this article): Electronic total energies of all computed species, additional data for the ring-strain estimation for **17a**.

Acknowledgments

The authors are grateful to Dr. Sándor Boros for the NMR measurements and to Mrs. Vali Sz. Marjai for her technical help.

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Received: September 26, 2007
Published Online: January 3, 2008

