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Benzyl Cation Initiated Intramolecular Cyclizations. Synthesis of 1-Azabicyclo[3.2.1]octene Derivatives

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Abstract. Benzyl cation inititiated intramolecular cyclization reactions with conjugated C–C double bonds were performed providing rac. *endo-exo* isomers of 1-azabicyclo[3.2.1]octenes (**2** and **3**). Formation of the *endo* isomer **2** is favoured. Compounds **2** possess dopamine uptake inhibitory effect with an additional selective MAO-B enzyme inhibitory potential. The remarkable *in vitro* effects do not correspond to *in vivo* antidepressant activity.

Some considerations suggest that antidepressant agents with dual mode of action upon MAO enzyme and monoamine [*e.g.* dopamine (DA), norepinephrine (NE) or serotonine (5-HT)] uptake would be advantageous [1]. Excellent DA and 5-HT re-uptake inhibitory effect was noticed earlier at some hexahydropyrrolo[2,1-*a*]isoquinoline derivatives [2], and later we have found DA uptake inhibitory effect with some 1-azabicyclo-[3.3.1]nonadiene derivatives as well [3], containing a bridgehead nitrogen atom and two aryl rings. This prompted us to synthesize new types of azabicyclic compounds with a bridgehead nitrogen atom and a combination of 6 + 5 membered rings, bearing two phenyl substituents in relative proximity to each other to fit more or less to the requirements of the monoamine uptake inhibitory pharmacophore model [4].

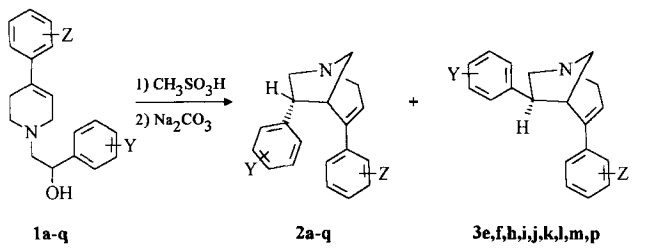
An additional MAO enzyme inhibitory effect was hoped to arise from the incorporation of structural elements, known to be substrate of the enzyme, into the new molecules. As such the 4-phenyl-1,2,5,6-tetrahydropyridine moiety [5] seemed to be appropriate. Especially, because during our earlier work several cyclization reactions were elaborated with 1-substituted 4-phenyl-1,2,5,6-tetrahydropyridine derivatives where bond formation took place between variously generated heteroatom-stabilized carbenium ions, formed in the substituent of the nitrogen atom and the conjugated carbon-carbon double bond of the tetrahydropyridine ring, preserving latter the moiety in the resulting 1-azabicyclic structures [3,6–9]. Moreover we have shown that the benzyl cation may be suitable for similar cyclization reaction as well, providing diaryl and alkoxy-carbonyl substituted 1-azabicyclo[3.3.1]nonene isomers [10]. This was of interest because benzyl cations are widely used for cyclization reactions [11], but mostly aromatic rings and less frequently isolated C–C double bonds have been used as internal nucleophilic terminator [12]. Based on our earlier success with benzyl cation initiated cyclization we attempted the same method for the synthesis of the desired diaryl substituted 1-azabicyclo[3.2.1]octene compounds.

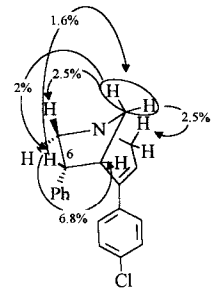
When benzylic alcohols **1a–q** were treated with methanesulfonic acid ring closure occured and rac. *endo-exo* isomers of 1-azabicyclo[3.2.1]octenes (**2** and **3** respectively) formed in moderate yield (Scheme 1).

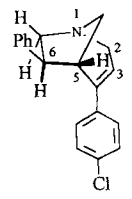
In all cases the rac. *endo* isomer **2** formed as the overwhelming product and isolation of the *exo* isomers **3** was performed only in cases indicated in the scheme. No cyclization reaction could be performed with compounds bearing a strong electron withdrawing group in the benzyl moiety (*i.e.* Y=NO_2 or NH_2 in protonated form) although super acidic conditions were not tried. However acetylation of the amino group as in **1k** made the ring closure possible.

The stereoselectivity of this cyclization reaction arises most probably from the more favourable steric relationships between the two phenyl groups in transition states leading to isomers **2** than **3**, as could be concluded from studies with Dreiding models, where the intramolecular approaching possibilities of a planar benzyl cation and the conjugated C–C double bond were investigated.

Structure elucidation of compounds **2** and **3** was carried out by ^{1}H NMR measurements basing on the couplings of the geminal proton adjacent to the 6-phenyl group as well as ^{1}H NMR-NOE experiments. *E.g.* with **2e** the signal of 6-H (δ = 3.85 ppm) has a *ddd* coupling with J_1=10.0 Hz, J_2=6.7 Hz, and J_3=5.8 Hz and NOEs were found, as indicated in Scheme 1. These support the *endo* position of the unsubstituted phenyl ring. The corresponding 6-H signal of the isomeric *exo* compound **3e** at δ=3.26 ppm showed a simpler coupling pattern (dd, J_1=8.1 Hz, J_2=5.2 Hz) because of an approx. 90° dihedral angle between the protons on carbons 6 and 5,

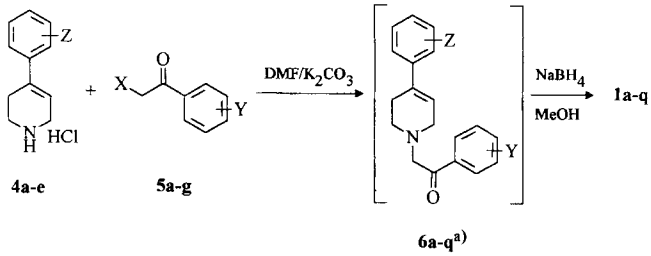






1,2,3	Z	Y	1,2,3	Z	Y
a	H	H	j	4-Cl	4-OCH_3
b	H	4-Cl	k	4-Cl	4-NH-$COCH_3$
c	H	4-Br	l	3-Cl	H
d	H	4-OCH_3	m	3-Cl	4-Cl
e	4-Cl	H	n	4-OCH_3	H
f	4-Cl	4-Cl	o	4-F	4-Br
g	4-Cl	4-Br	p	4-F	H
h	4-Cl	4-F	q	4-F	4-F
i	4-Cl	4-CH_3			

Scheme 1



4	a	b	c	d	e
Z	H	4-Cl	3-Cl	4-F	4-OCH_3

5	a	b	c	d	e	f	g
Y	H	4-Cl	4-Br	4-F	4-CH_3	4-OCH_3	4-NH-$COCH_3$
X	Br	Br	Br	Br	Br	Br	Cl

[a)] For the meanings of **a**–**q** see Scheme 1

Scheme 2

as shown in Scheme 1. Other compounds of the ring closure reactions were ranged into the structure series **2** or **3** according to their comparable ^1H NMR spectroscopic data as found for **2e** and **3e**. Compounds **2** and **3** were isolated as oils and a 1:1 fumarate salt was prepared from each.

The starting benzylic alcohols **1a**–**q** were prepared by sodium borohydride reduction of the corresponding crude

Table 1 1-(2'-Hydroxy-2'-phenyl)ethyl-4-phenyl-1,2,5,6-tetrahydropyridin Derivatives (**1a**–**q**)

No.	Yield (%)	*m.p.* (°C)	Molecular formula (Mol. mass)	Mikroanalyses Calcd./Found C	H	N
1a	67	99–100	$C_{19}H_{21}NO$	81.67	7.58	5.01
			(279,4)	81.66	7.28	5.02
1b	78	158–159	$C_{19}H_{20}ClNO$	72.71	6.42	4.46
			(313.8)	72.06	6.37	4.05
1c	69	155–157	$C_{19}H_{20}BrNO$	63.69	5.63	3.91
			(358.3)	63.51	5.17	3.54
1d	56	118–120	$C_{20}H_{23}NO_2$	77.64	7.49	4.53
			(309.4)	77.41	7.15	4.17
1e	65	128–129	$C_{19}H_{20}ClNO$	72.71	6.42	4.46
			(313.8)	72.08	6.41	4.81
1f	61	148–150	$C_{19}H_{19}Cl_2NO$	65.52	5.50	4.02
			(348.3)	65.50	5.37	4.00
1g	67	154–156	$C_{19}H_{19}BrClNO$	58.11	4.88	3.57
			(392.7)	58.30	4.68	3.60
1h	77	146–148	$C_{19}H_{19}ClFNO$	68.77	5.77	4.22
			(331.8)	68.49	5.61	4.03
1i	51	125–127	$C_{20}H_{22}ClNO$	73.27	6.76	4.27
			(327.8)	73.50	6.76	4.45
1j	53	138–139	$C_{20}H_{22}ClNO_2$	69.86	6.45	4.07
			(343.8)	70.02	6.50	4.11
1k	77	198–199	$C_{21}H_{23}ClN_2O_2$	68.01	6.25	7.56
			(370.9)	67.92	6.25	7.29
1l	81	113–114	$C_{19}H_{20}ClNO$	72.71	6.42	4.46
			(313.8)	72.27	6.52	4.66
1m	64	130–131	$C_{19}H_{19}Cl_2NO$	65.52	5.50	4.02
			(348.3)	65.09	5.17	4.11
1n	49	126–128	$C_{20}H_{23}NO_2$	77.64	7.49	4.53
			(309.4)	77.98	7.46	4.53
1o	63	167–169	$C_{19}H_{19}BrFNO$	60.64	5.09	3.72
			(376.3)	60.37	4.75	3.48
1p	59	117–118	$C_{19}H_{20}FNO$	76.74	6.80	4.71
			(297.4)	76.25	6.70	4.86
1q	57	150–151	$C_{19}H_{19}F_2NO$	72.37	6.07	4.44
			(315.3)	71.95	5.77	4.11

Table 2 4,6-Diaryl-1-azabicyclo[3.2.1]oct-3-ene Derivatives (**2** and **3**)

No.	React. time (h) Yield [a)] (%)	*m.p.* (°C) [b)] (solvent)	Molecular formula [b)] (Mol. mass) $\cdot C_4H_4O_4$	Microanalyses [b)] Calcd./Found C	H	N
2a	5 [c)]	243–245	$C_{19}H_{19}N$	73.19	6.14	3.71
	33		(377,4)	73.41	6.50	3.86
2b	20	238–240	$C_{19}H_{18}ClN$	67.07	5.38	3.17
	25		(411.9)	66.85	5.22	3.04
2c	5	232–235	$C_{19}H_{18}BrN$	60.53	4.86	3.07
	43		(456.3)	59.99	4.86	3.12
2d	18	220–222	$C_{20}H_{21}NO$	70.74	6.18	3.44
	63		(407.7)	70.74	6.13	3.53
2e	3	222–225	$C_{19}H_{18}ClN$	67.07	5.38	3.17
	60		(411.9)	66.84	5.32	3.43
3e	3	191–195	$C_{19}H_{18}ClN$	67.07	5.38	3.17
	17		(411.9)	67.01	5.33	3.11
2f	12	206–210	$C_{19}H_{17}Cl_2N$	61.90	4.74	3.14
	58		(446.3)	61.84	4.73	3.30
3f	12	230–232	$C_{19}H_{17}Cl_2N$	61.90	4.74	3.14
	15		(446.3)	62.31	4.70	3.29
2g	1.5 [d)]	218–222	$C_{19}H_{17}BrClN$	56.29	4.31	2.85
	30		(490.8)	56.45	4.16	2.80
2h	20	217–220	$C_{19}H_{17}ClFN$	64.26	4.92	3.26
	28		(429.9)	64.04	5.06	3.31
3h	20	215–216	$C_{19}H_{17}ClFN$	64.26	4.92	3.26
	12		(429.9)	63.98	4.67	3.18
2i	3	229–231	$C_{20}H_{20}ClN$	67.68	5.68	3.29
	40		(425.9)	67.63	5.70	3.70
3i	3	228–230	$C_{20}H_{20}ClN$	67.68	5.63	3.29
	15		(425.9)	67.31	5.37	3.10

Table 2 (continued)

No.	React. time (h) Yield [a] (%)	*m.p.* (°C) [b] (solvent)	Molecular formula [b] (Mol. mass) ·$C_4H_4O_4$	Microanalyses [b] Calcd./Found C	H	N
2j	3	195–198	$C_{20}H_{20}ClNO$	65.23	5.47	3.17
	38		(441.9)	65.41	5.60	3.14
3j	3	202–204	$C_{20}H_{20}ClNO$	65.23	5.47	3.17
	10		(441.9)	64.85	5.11	3.05
2k	20	220–221	$C_{21}H_{21}ClN_2O$	64.04	5.37	5.97
	36		(468.9)	64.19	5.91	5.80
3k	20	252–254	$C_{21}H_{21}ClN_2O$	64.04	5.37	5.97
	8		(468.9)	63.71	5.02	5.63
2l	48	212–215	$C_{19}H_{18}ClN$·	67.07	5.38	3.17
	37		(411.9)	66.95	5.35	3.28
3l	48	176–178	$C_{19}H_{18}ClN$	67.07	5.38	3.17
	9		(411.9)	66.82	5.17	3.02
2m	24	234–236	$C_{19}H_{17}Cl_2N$	61.90	4.74	3.14
	49		(446.3)	62.03	4.60	3.21
3m	24	185–186	$C_{19}H_{17}Cl_2N$	61.90	4.74	3.14
	16		(446.3)	61.76	4.50	2.98
2n	1.5	197–200	$C_{20}H_{21}NO$	70.74	6.18	3.44
	21		(407.4)	70.72	6.20	3.39
2o	20	225–229	$C_{19}H_{17}BrFN$	58.24	4.46	2.95
	26		(474.3)	58.02	4.49	3.01
2p	20	228–231	$C_{19}H_{18}FN$	69.87	5.61	3.54
	48		(395.4)	70.06	5.55	3.48
3p	20	169–170	$C_{19}H_{18}FN$	69.87	5.61	3.54
	13		(395.4)	69.92	5.41	3.29
2q	20	226–228	$C_{19}H_{17}F_2N$	66.82	5.12	3.39
	44		(413.4)	67.02	5.12	3.40

[a] Isolated yield of the base; [b] Refers to the (*E*)-2-Butanedioate (1:1) salt; [c] At reflux temperature in conc. HCl; [d] 80 °C

ketones **6a–q**, which resulted in a smooth alkylation procedure from known 4-phenyl-1,2,5,6-tetrahydropyridine derivatives (**4a–e**) with phenacyl halogenids **5a–g** as shown in Scheme 2.

Biological screening of the bicyclic compounds revealed that with rac. compounds **2** a relatively significant DA uptake inhibitory potential (IC_{50} values for the most active compounds **2e,f,g,h,i,m** are in the range of 0.15–1.23 μM) was combined with a selective MAO-B enzyme inhibitory effect (IC_{50} values of the same compounds were found between 2.6–4.1 μM) with negligible MAO-A enzyme inhibitory effect. Compound **2f** showed a remarkable 5-HT uptake inhibitory potential (IC_{50} = 0.8 μM). Unfortunately the favourable *in vitro* results of the compounds investigated were not linked with remarkable antidepressant activity in the *in vivo* models, therefore no efforts were made towards the pure enantiomers.

Experimental

Melting points: Boëtius hot-stage microscope, uncorrected values. – ^{1}H NMR ($CDCl_3$, internal standard TMS, T = 298 K): Bruker AC 250. Other solvents are indicated. Column chromatography: silica gel, Kieselgel 60, Merck.

Synthesis of the (±)-1-(2'-Hydroxy-2'-phenyl)ethyl-4-phenyl-1,2,5,6-tetrahydropyridine Derivatives (1a–q) (General Procedure)

The suspension of 20.0 mmol of the appropriate 4-phenyl-1,2,5,6-tetrahydropyridine **4** as hydrochloride salt, 3.04 g

Table 3 Characteristic Spectroscopic Data of Compounds **2** and **3**

No.	^{1}H NMR data (of the bases)
2a	6-$H_{quasi\ equ}$: 3.86 (ddd, J_1 = 9.6 Hz, J_2 = J_3 = 6.4 Hz, 1H); 3-$H_{olefinic}$: 5.80 (dd, J_1 = J_2 = 2.6 Hz, 1H), aromatic protons: 6.78 (m, 2H), 6.95–7.25, (m, 8H).
2b	6-$H_{quasi\ equ}$: 3.82 (ddd, J_1 = 9.6 Hz, J_2 = J_3 = 6.0 Hz, 1H); 3-$H_{olefinic}$: 5.83 (br. s, 1H); aromatic protons: 6.80 (m, 2H), 7.00–7.20 (m, H).
2c	3.82 (ddd, J_1 = 9.7 Hz, J_2 = J_3 = 6.3 Hz, 1H); 3-$H_{olefinic}$: 5.87 (dd, J_1 = J_2 = 2.6 Hz, 1H); aromatic protons: 6.81 (m, 2H), 7.05–7.12 (m, 5H), 7.22 (d, J = 8.4 Hz, 2H).
2d	OCH_3: 3.65 (3H); 6-$H_{quasi\ equ}$: 3.75 (ddd, J_1 = 9.5 Hz, J_2 = J_3 = 6.4 Hz, 1H); 3-$H_{olefinic}$: 5.77 (br. s, 1H); aromatic protons: 6.57 (d, J = 7.9 Hz, 2H), 6.70–6.80 (m, 2H), 6.95–7.05 (m, 3H), 7.10 (d, J = 7.9 Hz, 2H).
2e	5-H: 3.01 (d, J = 5.8 Hz, 1H); 7-$H_{quasi\ ax}$: 3.02 (dd, J_1 = 13.3 Hz, J_2 = 6.7 Hz, 1H); 8-H: 3.16 (br. s, 2H); 7-$H_{quasi\ equ}$: 3.6 (dd, J_1 = 13.3 Hz, J_2 = 10.0 Hz, 1H); 2-H_{ax}: 3.46 (dd, J_1 = 19.8 Hz, J_2 = 3.3 Hz, 1H); 6-$H_{quasi\ equ}$: 3.85 (ddd, J_1 = 10.0 Hz, J_2 = 6.7 Hz, J_3 = 5.8 Hz, 1H); 2-H_{equ}: 4.01 (dd, J_1 = 19.8 Hz, J_2 = 2.5 Hz, 1H); 3-$H_{olefinic}$: 5.85 (br. s, 1H), aromatic protons: 6.67 (d, J = 8.7 Hz, 2H), 7.03 (d, J = 8.7 Hz, 2H), 7.05–7.15 (m, 3H), 7.16–7.25 (m, 2H).
3e	(in benzene-d_6) 5-H: 2.65 (d, J = 3.2 Hz, 1H); 8-H: 2.82 (dt, J_1 = 11.2 Hz, J_2 =J_3 = 1.3 Hz, 1H) and 3.05 (dd, J_1 = 11.2 Hz, J_2 = 3.2 Hz, 1H); 7-H: 3.16-3.20 (m, 2H); 6-$H_{quasi\ ax}$: 3.26 (dd, J_1 = 8.1 Hz, J_2 = 5.2 Hz, 1H); 2-H: 3.70 (dd, J_1 = 19.2 Hz, J_2 = 2.6 Hz, 1H) and 2.97 (dt, J_1 = 19.2 Hz, J_2 = J_3 = 1.5 Hz, 1H); 2'-$H_{chlorophenyl}$: 6.95 (d, J = 8.9 Hz, 2H); 3'-$H_{chlorophenyl}$: 7.05 (d, J = 8.9 Hz, 2H).
2f	6-$H_{quasi\ equ}$: 3.82 (ddd, J_1 = 9.6 Hz, J_2 = J_3 = 6.4 Hz, 1H); 3-$H_{olefinic}$: 5.85 (dd, J_1 = J_2 = 2.6 Hz, 1H); aromatic protons: 6.75 (d, J = 8.5 Hz, 2H), 7.05–7.20 (m, 6H).
3f	6-$H_{quasi\ ax}$: 3.54 (dd, J_1 = 8.5 Hz, J_2 = 4.9 Hz, 1H), 3-$H_{olefinic}$: 5.82 (dd, J_1 = J_2 = 2.5 Hz, 1H); aromatic protons: 7.15 (d, J = 8.5 Hz, 2H), 7.20–7.40 (m, 6H).
2g	6-$H_{quasi\ equ}$: 3.80 (ddd, J_1 = 9.7 Hz, J_2 = J_3 = 6.2 Hz); 3-$H_{olefinic}$: 5.87 (br. s, 1H); aromatic protons: 6.72 (d, J = 8.6 Hz, 2H), 7.00–7.10 (m, 4H), 7.22 (d, J = 8.6 Hz, 2H).
2h	6-$H_{quasi\ equ}$: 3.84 (ddd, J_1 = 9.7 Hz, J_2 = J_3 = 6.3 Hz); 3-$H_{olefinic}$: (dd, J_1 = J_2 = 2.4 Hz); aromatic protons: 6.73 (d, J = 8.6 Hz, 2H), 6.82 (dd, J_1 = J_2 = 8.7 Hz, 2H), 7.02 (d, J = 8.6 Hz, 2H), 7.16 (dd, J_1 = 8.7 Hz, J_2 = 5.2 Hz, 2H).
3h	6-$H_{quasi\ ax}$: 3.53 (dd, J_1 = 8.3 Hz, J_2 = 5.0 Hz, 1H); 3-$H_{olefinic}$: 5.75 (dd, J_1 = J_2 = 2.2 Hz, 1H); aromatic protons: 7.03 (dd, J_1 = J_2 = 8.7 Hz, 2H), 7.18 (dd, J_1 = 8.7 Hz, J_2 = 5.3 Hz, 2H), 7.27 (br. s, 4H).
2i	CH_3: 2.40 (s, 3H); 6-$H_{quasi\ equ}$: 3.90 (ddd, J = 9.8 Hz, J_2 = 6.8 Hz, J_3 = 5.5 Hz, 1H); 3-$H_{olefinic}$: 5.85 (br. s, 1H).
3i	CH_3: 2.33 (s, 3H); 6-$H_{quasi\ ax}$: 3.55 (dd, J_1 = 8.3 Hz, J_2 = 5.1 Hz, 1H); aromatic protons: 7.10 (br. s, 4H), 7.25 (br. s, 4H).
2j	CH_3O-Ph: 3.8 (s, 3H); 6-$H_{quasi\ equ}$: 3.82 (ddd, J_1 = 10.0 Hz, J_2 = 6.6 Hz, J_3 = 5.6 Hz, 1H); 3-$H_{olefinic}$: 5.85 (br. s, 1H).
3j	6-$H_{quasi\ ax}$: 3.52 (dd, J_1 = 8.2 Hz, J_2 = 5.2 Hz, 1H); CH_3O-Ph: 3.80 (s, 3H); 3-$H_{olefinic}$: 5.76 (br. s, 1H); aromatic protons: 6.82 (d, J = 8.6 Hz, 2H), 7.16 (d, J = 8.6 Hz, 2H), 7.28 (br. s, 4H).
2k	CH_3: 2.10 (s, 3H); 6-$H_{quasi\ equ}$: 3.82 (ddd, J_1 = 9.8 Hz, J_2 = J_3 = 6.8 Hz, 1H); 3-$H_{olefinic}$: 6.85 (dd, J_1 = J_2 = 2.0 Hz); aromatic protons: 6.74 (d, J = 8.8 Hz, 2H), 7.00 (d, J = 8.8 Hz, 2H), 7.15 (d, J = 8.3 Hz, 2H), 7.27 (8.30 Hz, 2H); NH: 7.67 (br. s, 1H).
3k	CH_3–CO–NH-: 2.19 (s, 3H); 6-$H_{quasi\ ax}$: 3.53 (dd, J_1 = 8.3 Hz, J_2 = 5.2 Hz, 1H); 3-$H_{olefinic}$: 5.77 (br. s, 1H); -NH-: 7.25-7.45 (br, 1H); aromatic protons: 7.17 (d, J = 8.4 Hz, 2H), 7.28 (br. s, 4H), 7.46 (d, J = 8.4 Hz, 2H).

Table 3 (continued)

No.	^{1}H NMR data (of the bases)
2l	6-$H_{quasi\ equ}$: 3.95 (m); 3-$H_{olefinic}$: 5.85 (br. s, 1H).
3l	6-$H_{quasi\ ax}$: 3.83 (dd, J_1 = 8.1 Hz, J_2 = 5.4 Hz, 1H); 3-$H_{olefinic}$: 5.85 (dd, J_1 = J_2 = 2.6 Hz); aromatic protons: 7.30–7.60 (m, 9H).
2m	6-$H_{quasi\ equ}$: 3.82 (ddd, J_1 = 9.5 Hz, J_2 = J_3 = 6.3 Hz, 1H); 3-$H_{olefinic}$: 5.85 (br. s, 1H); aromatic protons: 6.65 (m, 1H); 6.75 (br. s, 1H), 6.93–7.15 (m, 8H).
3m	6-$H_{quasi\ ax}$: 3.52 (dd, J_1 = 8.3 Hz, J_2 = 4.9 Hz, 1H); 5.76 (br. s, 1H); aromatic protons: 7.13–7.35 (m, 8H).
2n	7-$H_{quasi\ ax}$: 3.04 (dd, J_1 = 12.7 Hz, J_2 = 8.0 Hz, 1H); 5-H: 3.10 (dd, J_1 = 6.0 Hz, J_2 = 2.0 Hz, 1H); 8-H: 3.19 (d, J = 10.8 Hz, 1H) and 3.27 (dd, J_1 = 10.8 Hz, J_2 = 2.5 Hz, 1H); 2-H: 3.52 (dd, J_1 = 19.8 Hz, J_2 = 3.0 Hz); $C\underline{H}_3$O-Ph: 3.70 (s, 3H); 7-$H_{quasi\ equ}$: 3.7 (overlap ping); 6-$H_{quasi\ equ}$: 3.87 (ddd, J_1 = 9.1 Hz, J_2 = J_3 = 6.7 Hz, 1H); 2-H: 4.08 (dd, J_1 = 19.8 Hz, J_2 = 2.5 Hz, 1H); 3-$H_{olefinic}$: 5.85 (br. s, 1H); aromatic protons: 6.58 (d, J = 8.5 Hz, 2H), 6.70 (d, J = 8.5 Hz, 2H), 6.96–7.30 (m, 5H).
2o	6-$H_{quasi\ equ}$: 3.82 (ddd, J_1 = 9.8 Hz, J_2 = J_3 = 6.4 Hz, 1H); 3- $H_{olefinic}$: 5.80 (dd, J_1 = J_2 = 2.6 Hz, 1H); aromatic protons: 6.75 (m, 4H), 7.05 (d, J = 8.3 Hz, 2H), 7.22 (d, J = 8.3 Hz, 2H).
2p	6-$H_{quasi\ equ}$: 3.95 (ddd, J_1 = 9.8 Hz, J_2 = J_3 = 5.8 Hz, 1H); 3-$H_{olefinic}$: 5.85 (br. s, 1H); aromatic protons: 7.80 (m, 4H), 7.00–7.20 (m, 5H).
3p	6-$H_{quasi\ ax}$: 3.58 (dd, J_1 = 8.2 Hz, J_2 = 5.3 Hz, 1H); 3-$H_{olefinic}$: 5.74 (br. s, 1H); aromatic protons: 7.05 (dd, J_1 = J_2 = 8.7 Hz, 2H), 7.20–7.45 (m, 7H).
2q	6-$H_{quasi\ equ}$: 3.82 (ddd, J_1 = 9.8 Hz, J_2 = J_3 = 6.2 Hz, 1H); 3-$H_{olefinic}$: 5.80 (br. s, 1H); aromatic protons: 6.63-6.85 (m, 6H), 7.15 (dd, J_1 = 8.6 Hz, J_2 = 5.5 Hz, 2H).

(22.0 mmol) of K_2CO_3 and 22.0 mmol of the corresponding phenacyl bromide (or chloride) derivative **5** in DMF (60 ml) was stirred for 1.5–3 h at 40 °C. When the reaction was finished water was added to the reaction mixture and the resulting precipitate was filtered and washed with water. This crude intermediate **6** was dried until a constant weight was reached, then it was dissolved in methanol (300 ml). The solution was stirred and chilled with ice water and 10 equivalents of sodium borohydride were added gradually. Stirring was maintained at room temperature for 2–3 h, and the solution was then poured into water. The precipitated product was filtered and recrystallized from ethanol. Yields, *m.p.*-s and analytical data are collected in Table 1.

Synthesis of the (±)-4,6-Diaryl-1-azabicyclo[3.2.1]oct-3-ene Derivatives (2 and 3) (General Procedure)

Benzylic alcohols **1b–q** were added at room temperature to a 10 fold excess of methanesulfonic acid. Stirring was maintained for 3–48 hours (only the ring closure reaction of **1a** was performed in hydrochloric acid at *b.p.*). The reaction mixture was than diluted with water to 4 times of its original volume and made alkaline with Na_2CO_3. After extraction with ethyl acetate the extract was washed with brine, dried and evaporated. The remaining oil was chromatographed with the eluent chloroform–methanol (4:1). From the pure isomers fumarate salts were prepared in ethanol with the equivalent amount of fumaric acid. Reaction time, yields, *m.p.*-s and analytical data are collected in Table 2., spectroscopic data are shown in Table 3.

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