An Improved and Stereoselective Route to All-*cis*-2,6-Disubstituted 4-Hydroxypiperidines from Accessible 4-Substituted 4-*N*-Benzylaminobut-1-enes

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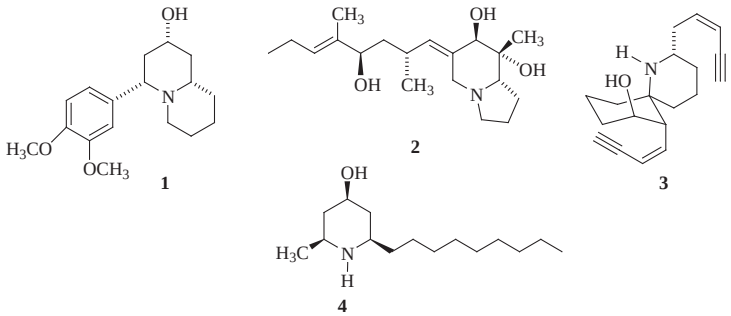
Abstract: The reaction between allylmagnesium bromide and imines **5a**–**l** leads to the corresponding 4-substituted 4-*N*-benzylaminobut-1-enes **6a**–**l**, which were oxidized in a regioselective manner to the alkenylnitrones **7a**–**l**. The intramolecular 1,3-dipolar cycloaddition of these nitrones gave 2-spiroannulated or 2-substituted 6-*exo*-phenyl-1-aza-7-oxabicyclo[2.2.1]heptanes **8a**–**j**. Reductive cleavage of the N–O bond of the obtained bicycles afforded the diverse substituted 4-hydroxypiperidines **9a**–**h** in good yields. This stereoselective approach allowed the preparation of all-*cis*-4-hydroxy-6-phenyl-2-nonylpiperidine (**9i**), a close analogue of dendrobatid frog alkaloid 241D.

Key words: homoallylamines, nitrones, stereoselective intramolecular 1,3-dipolar cycloadditions, 1-aza-7-oxabicyclo[2.2.1]heptanes, 4-hydroxypiperidines, 4-hydroxy-2-spiropiperidines

Substituted piperidines play an important role in heterocyclic chemistry from the chemical, biological and medicinal points of view. The piperidine ring system occurs in many alkaloids of both the plant and animal kingdom.[1,2] During the last 20–30 years, considerable effort has been directed towards the study, isolation and total synthesis of quinolizidines, indolizidines and piperidines such as *epi*-lasubine II (**1**),[3] allopumiliotoxin 323B (**2**), and histrionicotoxin 283A (**3**).[4,5] The structures **1** and **2** contain a substituted 4-hydroxypiperidine nucleus and the latter possesses a remarkable spiropiperidinecyclohexanol system. Moreover, relatively simple monocyclic 4-hydroxypiperidines such as piperidine 214D (**4**) (*cis*,*cis*-4-hydroxy-2-methyl-6-nonylpiperidine) has been discovered[6] and synthesized[7–9] (Figure). Special interest has been generated by those hydroxypiperidines which display important physiological properties such as cardiotonic,[4] tranquilizing (haloperidol analogues), and analgesic (promedol derivatives) activities.[10]

Despite the development of general methods for the synthesis of the above heterocycles, there are few examples where the accessible substituted 4-aminobut-1-enes (homoallylic amines) serve as starting materials to synthesize diverse 2,6-disubstituted 4-hydroxypipepiridines, including 2-spiropiperidine ring. Hoffman and coworkers[11] disclosed that the conversion of *N*-(homoallyl)-hydroxylamines to the *N*-(3-alkenyl)nitrones followed by intramolecular cycloaddition reaction afforded the 1-aza-7-oxabicyclo[2.2.1]heptanes,[12] principal precursors of 2,6-disubstituted 4-hydroxypiperidines. This methodology allowed the synthesis of alkaloid **1**.[13] It is also noteworthy that this nitrone strategy was developed for the preparation of all-*cis*-2,3,6-trisubstituted piperidines, which in turn were used in the total synthesis of carpamic acid.[14]

As part of our research program on the use of 4-*N*-aryl(benzyl)aminobut-1-enes (homo-allylamines) in the synthesis of diverse heterocycles of biological interest,[15–21] we decided to investigate the scope of the nitrone-



Figure

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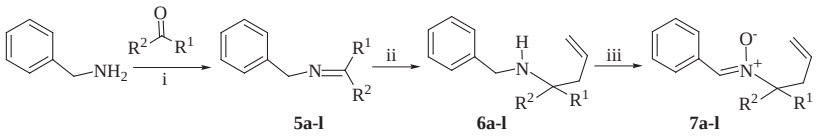
based methodology to the synthesis of dendrobate alkaloid analogues. Here, we propose another approach to the key starting material, alkenyl nitrones by using the catalytic oxidation reaction of 4-substituted 4-*N*-benzylaminobut-1-enes preformed from ket(ald)imines and allylmagnesium bromide. Moreover, we chose to examine the possibility of nitrone synthesis from amines, to determine the size of the ring or the influence of the C-4-substituent on the oxidation reaction of 4-*N*-benzylaminobut-1-enes. Additionally we studied the stereoselectivity of intramolecular dipolar cycloaddition of these nitrones and to test the compatibility of different substituents (aryl, pyridyl, furyl, alkyl) with this strategy. This paper describes a simple, stereoselective approach for the preparation of the 2,6-disubstituted 4-hydroxypiperidines, including the all-*cis*-2-spiro-4-hydroxy-6-phenylpiperidine as well as the all-*cis*-4-hydroxy-6-phenyl-2-nonylpiperidine, close analogues of dendrobate alkaloid 241D, from accessible and cheap ald- and ketimines.

Our synthetic strategy contains two parts: i) effective preparation of diverse alkenylnitrones from 4-aryl(hetaryl, alkyl)-4-*N*-benzylaminobut-1-enes and 1-allyl-1-*N*-benzylaminocycloalkanes starting from simple imines (Scheme 1); ii) stereoselective synthesis of structurally different 2,6-disubstituted (2,2,6-trisubstituted) 4-hydroxypiperidines via the reductive cleavage of the N–O bond of the 2-(spiro)substituted 6-phenyl-1-aza-7-oxabicyclo[2.2.1]heptanes prepared by the intramolecular 1,3 dipolar cycloaddition reaction of alkenylnitrones (Scheme 2).

The required imines **5a**–**l** were prepared according to literature procedure[15,18] and were used in subsequent synthesis without further purification. The nucleophilic addition of organometallic compounds to the C=N bond of the imines is one of the key methods for preparing various amines.[22] This reaction between allylmagnesium bromide and imines **5a**–**l** in diethyl ether leads to the corresponding 4-substituted 4-*N*-benzylaminobut-1-enes **6a**–**l** in 61–85% overall yields, except aminobutene **6a**, which was obtained in 40% yield. The addition of allylmagnesium bromide to *N*-pyridinylidenbenzylamines **5i**–**k** in diethyl ether was ineffective, but the use of THF resulted in the desired products in good yields. The key intermediate nitrones in our research were prepared by oxidation of the aminobutenes **6a**–**l** with 50% H_2O_2[22] in the presence of a catalytic amount of Na_2WO_4[23,24] in a mixture of acetone–water (9:1) at room temperature (Scheme 1).

It was established that the oxidation of 4-substituted 4-*N*-aminobutenes **5f**–**l** proceeds more easily than that of their 4,4-disubstituted analogues **5a**–**e**, and that the size of cycloalkane fragment in compounds **5a**–**d** did not play considerable influence on the reaction rate. The alkenyl nitrones **7a**–**l** were obtained in 42–87% yields as stable compounds which could be purified by fractional crystallisation or by alumina column chromatography (Table 1).

In the ^{1}H NMR spectra of compounds **6a**–**l** the characteristic signals of allyl moiety were observed in the region 2.07–2.56 (3-CH_2) and 4.96–5.94 ppm (CH_2=CH) with coupling constants $^2J_{1Hcis,2H}$ = 9–11, $^2J_{1Htrans,2H}$ = 16–17.6, $^2J_{1H,1H}$ = 1.0–2.1 Hz. At the same time the ^{1}H NMR data of all synthesized nitrones **7a**–**l** indicate the conservation of the characteristic signals of allyl fragment which proves that an allyl fragment is intact during the oxidation reaction. The signal of the aldiminic proton (HC=N) of all nitrones appears at the region 7.26–7.66 ppm as singlet, easily identified among the aromatic protons. It was found that these mild conditions guarantee a high regioselectivity; oxidation reaction occurs at the less steric bulky benzyl CH_2N group in the case of aminobutenes **6f**–**l** (Tables 2, 3).



Starting compounds			R^1	R^2	Starting Compounds			R^1	R^2
Imine	Amine	Nitrone			Imine	Amine	Nitrone		
5a	**6a**	**7a**	$(CH_2)_4$		**5g**	**6g**	**7g**	4-$CH_3OC_6H_4$	H
5b	**6b**	**7b**	$(CH_2)_5$		**5h**	**6h**	**7h**	α-furyl	H
5c	**6c**	**7c**	$(CH_2)_6$		**5i**	**6i**	**7i**	α-pyridyl	H
5d	**6d**	**7d**	$(CH_2)_7$		**5j**	**6j**	**7j**	β-pyridyl	H
5e	**6e**	**7e**	$(CH_2)_6CH_3$	CH_3	**5k**	**6k**	**7k**	γ-pyridyl	H
5f	**6f**	**7f**	C_6H_5	H	**5l**	**6l**	**7l**	$(CH_2)_8CH_3$	H

Scheme 1 *Reagents and Conditions*: i) benzene, reflux, 6–10 h; ii) CH_2=$CHCH_2MgBr/Et_2O$ (THF for **5i–k**), r.t., 2 h; aq sat. NH_4Cl solution; iii) $Na_2WO_4 \cdot 2H_2O$, 50% H_2O_2, acetone–H_2O, r.t., 2–4 d.

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Table 1 4-Substituted 4-*N*-Benzylaminobut-1-enes **6a–l** and *N*-Benzylidene-*N*-butenylamino-*N*-oxides **7a–l**

Product[a]	Molecula Mass *m*/*z*		Bp (°C)/ Torr or Mp (°C)[b]	R_f (Silufol UV_{254})	IR (cm^{-1})				Yield (%)
	Found M^+	Calcd			$\nu_{C=C}$	ν_{NH}	$\nu_{N\rightarrow O}$	$\nu_{C=N}$	
6a	215	215	115–118/2.0	0.48[c]	1645	3327	–	–	40
6b	229	229	120–125/2.0	0.50[c]	1640	3330	–	–	78
6c	202[d]	243	121–126/1.5	0.48[c]	1642	3335	–	–	70
6d	216[d]	257	148–150/1.0	0.80[e]	1638	3330	–	–	65
6e	232[d]	273	oil[f]	0.96[e]	1639	3335	–	–	61
6f	237	237	124–130/1.5	0.39[c]	1640	3333	–	–	84
6g	267	267	165–172/1.5	0.50[g]	1643	3331	–	–	83
6h	227	227	115–118/1.5	0.45[c]	1645	3330	–	–	82
6i	238	238	oil[f]	0.86[h]	1642	3326	–	–	64
6j	197[d]	238	168–170/5.0	0.81[h]	1640	3308	–	–	82
6k	238	238	152–154/1.5	0.44[c]	1632	3290	–	–	82
6l	246[d]	287	oil[f]	0.95[e]	1640	3325	–	–	85
7a	229	229	40–43	0.30[g]	1636	–	1156, 954	1576, 1560	65
7b	243	243	36–38	0.38[c]	1643	–	1140	1577, 1562	70
7c	257	257	oil[f]	0.21[c]	1638	–	1150, 935	1560	75
7d	271	271	oil[f]	0.32[g]	1640	–	1122, 921	1557	55
7e	287	287	oil[f]	0.36[e]	1641	–	1127, 919	1559	61
7f	251	251	127.5–130.0	0.36[g]	1644	–	1152, 941	1591, 1576	81
7g	281	281	81.5–83.0	0.18[g]	1643	–	1153, 935	1587, 1615	66
7h	241	241	90.5–91.5	0.21[g]	1644	–	1155, 930	1579, 1565	42
7i	252	252	129–130	0.37[h]	1644	–	1138, 917	1586, 1577	87
7j	252	252	130–132	0.33[h]	1639	–	1115, 923	1583	76
7k	252	252	103–104	0.44[h]	1645	–	1150	1598	45
7l	301	301	oil[f]	0.27[g]	1643	–	1126, 919	1563	75

[a] All compounds showed satisfactory elemental analysis: C ±0.21, H ±0.25, N ±0.25.
[b] Recrystallisation from hexane–Et_2O.
[c] EtOAc–hexane, 1:10.
[d] $[M - CH_2{=}CHCH_2]^+$.
[e] Heptane.
[f] Purification by Al_2O_3 (EtOAc–hexane, 1:40).
[g] EtOAc–hexane, 1:5.
[h] Acetone.

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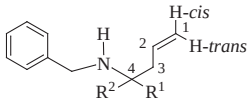
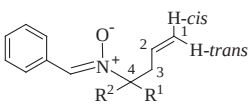
Table 2 ^{1}H NMR Spectra [($CDCl_3$/TMS), δ, *J* (Hz)] of 4-*N*-Benzylaminobut-1-enes **6a–l** and *N*-Benzylidene-*N*-butenylamino-*N*-oxides **7a–l**



6a-l



7a-l

Product	1-H_{cis}	1-H_{trans}	2-H	3-H_A,H_B	4-H
6a	5.14 (dd, $J_{1,1}$ = 2.0, $J_{1\text{-H}cis,2}$ = 10.3)	5.16 (m, $J_{1\text{-H}trans,2}$ = 17.6)	5.92 (ddt, $J_{2,3A}$ = $J_{2,3B}$ = 7.2)	2.37 (d)	–
6b	5.18 ($J_{1,1}$ = 1.4, $J_{1\text{-H}cis,2}$ = 9.3)	5.10 (m, $J_{1\text{-H}trans,2}$ = 17.8)	5.92 (m, $J_{2,3A}$ = $J_{2,3B}$ = 7.4)	2.28 (d)	–
6c	5.15 (m, $J_{1,1}$ = 1.0, $J_{1\text{-H}cis,2}$ = 9.1)	5.16 (m, $J_{1\text{-H}trans,2}$ = 16.6)	5.94 (m, $J_{2,3A}$ = $J_{2,3B}$ = 7.5)	2.30 (d)	–
6d	5.09 (dd, $J_{1,1}$ = 1.5, $J_{1\text{-H}cis,2}$ = 10.2)	5.10 (m, $J_{1\text{-H}trans,2}$ = 17.2)	5.88 (m, $J_{2,3A}$ = $J_{2,3B}$ = 7.2)	2.22 (d)	–
6e	5.08 (m, $J_{1,1}$ = 1.0, $J_{1\text{-H}cis,2}$ = 11.1)	5.11 (m, $J_{1\text{-H}trans,2}$ = 17.5)	5.85 (m, $J_{2,3A}$ = $J_{2,3B}$ = 7.4)	~2.21 (m, $J_{3A,3B}$ = 13.6)	–
6f	5.18 (dd, $J_{1,1}$ = 1.5, $J_{1\text{-H}cis,2}$ = 10.0)	5.22 (ddt, $J_{1\text{-H}trans,2}$ = 16.9, $J_{1\text{-H}trans,3}$ = 1.5)	5.84 (m, $J_{2,3A}$ = 8.1, $J_{2,3B}$ = 6.5)	~2.56 (m, $J_{3A,4}$ = 5.8, $J_{3B,4}$ = 7.9)	3.84 (dd)
6g	5.16 (m, $J_{1,1}$ = 1.5, $J_{1\text{-H}cis,2}$ = 10.4)	5.20 (ddt, $J_{1\text{-H}trans,2}$ = 17.3, $J_{1\text{-H}trans,3}$ = 1.5)	5.82 (m, $J_{2,3A}$ = 7.7, $J_{2,3B}$ = 6.4)	~2.52 (m, $J_{3A,4}$ = $J_{3B,4}$ = 6.9)	3.77 (t)
6h	4.99 (dd, $J_{1,1}$ = 2.1, $J_{1\text{-H}cis,2}$ = 10.1)	5.05 (dd, $J_{1\text{-H}trans,2}$ = 17.2)	5.69 (ddt, $J_{2,3A}$ = $J_{2,3B}$ = 7.0)	2.49 (t, $J_{3A,4}$ = $J_{3B,4}$ = 7.0)	3.74 (t)
6i	4.82 (dd)	4.76 (dd)	5.50 (m)	2.40–2.15 (m)	3.56 (t)
6j	5.06 (dd, $J_{1,1}$ = 1.5 $J_{1\text{-H}cis,2}$ = 10.9)	5.04 (dd, $J_{1\text{-H}trans,2}$ = 16.1)	5.67 (m)	2.40 (t, $J_{3A,4}$ = $J_{3B,4}$ = 7.0)	3.72 (t)
6k	5.06 (dd, $J_{1,1}$ = 1.5, $J_{1\text{-H}cis,2}$ = 11.0)	5.04 (dd, $J_{1\text{-H}trans,2}$ = 16.2)	5.68 (m)	2.50–2.25 (m, $J_{3A,4}$ = 6.1, $J_{3B,4}$ = 7.6)	3.69 (dd)
6l	4.96 (dd, $J_{1,1}$ = 1.4, $J_{1\text{-H}cis,2}$ = 10.1)	4.98 (dd, $J_{1\text{-H}trans,2}$ = 17.4)	5.70 (m, $J_{2,3A}$ = 7.4, $J_{2,3B}$ = 6.7)	2.17–2.07 (m, $J_{3A,4}$ = 5.7, $J_{3B,4}$ = 6.2)	2.54 (dd)
7a	5.07 (dd, $J_{1,1}$ = 2.1, $J_{1\text{-H}cis,2}$ = 10.2)	5.11 (dd, $J_{1\text{-H}trans,2}$ = 17.1)	5.71 (ddt, $J_{2,3A}$ = $J_{2,3B}$ = 7.0)	2.66 (d)	–
7b	5.06 (d, $J_{1\text{-H}cis,2}$ = 10.0)	5.08 (d, $J_{1\text{-H}trans,2}$ = 17.0)	5.66 (m, $J_{2,3A}$ = $J_{2,3B}$ = 7.6)	2.59 (d)	–
7c	5.07 (dd, $J_{1,1}$ = 2.4, $J_{1\text{-H}cis,2}$ = 10.1)	5.08 (dd, $J_{1\text{-H}trans,2}$ = 17.1)	5.63 (ddt, $J_{2,3A}$ = $J_{2,3B}$ = 7.0)	2.60 (d)	–
7d	5.02 (dd, $J_{1,1}$ = 2.1, $J_{1\text{-H}cis,2}$ = 10.1)	5.09 (dd, $J_{1\text{-H}trans,2}$ = 17.2)	5.60 (ddt, $J_{2,3A}$ = $J_{2,3B}$ = 7.3)	2.58 (d)	–
7e	5.09 (dd, $J_{1,1}$ = 1.0, $J_{1\text{-H}cis,2}$ = 11.2)	5.12 (dd, $J_{1\text{-H}trans,2}$ = 18.0)	5.67 (m, $J_{2,3A}$ = 6.4, $J_{2,3B}$ = 8.4)	2.88 (dd), 2.38 (dd), $J_{3A,3B}$ = 13.8	–
7f	5.10 (ddt, $J_{1,1}$ = 1.5, $J_{1\text{-H}cis,2}$ = 10.4)	5.23 (ddt, $J_{1\text{-H}trans,2}$ = 17.1, $J_{1\text{-H}trans,3}$ = 0.5)	5.80 (ddt, $J_{2,3A}$ = $J_{2,3B}$ = 6.8)	3.35 (m), 2.78 (m), $J_{3A,3B}$ = 13.8, $J_{3A,4}$ = 5.8, $J_{3B,4}$ = 9.2	4.97 (dd)
7g	5.06 (dd, $J_{1,1}$ = 1.2, $J_{1\text{-H}cis,2}$ = 10.1)	5.17 (dd, $J_{1\text{-H}trans,2}$ = 17.1)	5.75 (ddt, $J_{2,3A}$ = $J_{2,3B}$ = 7.0)	3.29 (ddd), 2.74(ddd), $J_{3A,3B}$ = 14.4, $J_{3A,4}$ = 8.5, $J_{3B,4}$ = 6.1	4.88 (dd)

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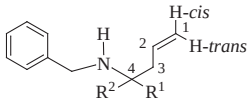
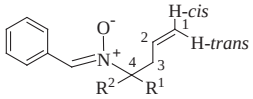
Table 2 ^{1}H NMR Spectra [($CDCl_3$/TMS), δ, *J* (Hz)] of 4-*N*-Benzylaminobut-1-enes **6a–l** and *N*-Benzylidene-*N*-butenylamino-*N*-oxides **7a–l** (continued)



6a-l

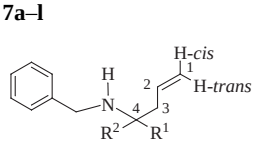


7a-l

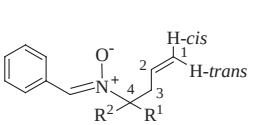
Product	1-H_{cis}	1-H_{trans}	2-H	3-H_A,H_B	4-H
7h[a]	5.11 (dd, $J_{1,1}$ = 1.5, $J_{1\text{-H}cis,2}$ = 10.2)	5.23 (dd, $J_{1\text{-H}trans,2}$ = 17.2)	5.79 (ddt, $J_{2,3A}$ = $J_{2,3B}$ = 6.8)	3.25 (ddd, $J_{3A,3B}$ = 14.0, $J_{3A,4}$ = $J_{3B,4}$ = 7.2)	5.05 (t)
7i	5.10 (d, $J_{1\text{-H}cis,2}$ = 10.3)	5.24 (dd, $J_{1\text{-H}trans,2}$ = 17.1, $J_{1\text{-H}trans,3}$ = 1.4)	5.82(m)	3.32 (ddd), 2.92 (ddd), $J_{3A,3B}$ = 13.0, $J_{3A,4}$ = 7.0, $J_{3B,4}$ = 5.6	5.15 (dd)
7j	5.01 (dd, $J_{1\text{-H}cis,2}$ = 9.2, $J_{1,1}$ = 1.5)	5.10 (dt, $J_{1\text{-H}trans,2}$ = 17.1, $J_{1\text{-H}trans,3}$ = 2.7)	5.70 (m)	3.22 (ddd), 2.64 (ddd), $J_{3A,3B}$ = 13.0, $J_{3A,4}$ = 6.8, $J_{3B,4}$ = 5.9	4.88 (dd)
7k	5.13 (ddt, $J_{1,1}$ = 1.5, $J_{1\text{-H}cis,2}$ = 10.1)	5.23 (ddd, $J_{1\text{-H}trans,2}$ = 17.1, $J_{1\text{-H}trans,3}$ = 1.5)	5.78 (m, $J_{2,3A}$ = $J_{2,3B}$ = 7.0)	3.31 (m), 2.73 (m), 3.35 (ddd), $J_{3A,3B}$ = 13.7, $J_{3A,4}$ = 9.5, $J_{3B,4}$ = 5.5	4.90 (dd)
7l	4.97 (dd, $J_{1,1}$ = 1.5, $J_{1\text{-H}cis,2}$ = 10.0)	5.06 (dddd, $J_{1\text{-H}trans,2}$ = 17.1)	5.67 (m, $J_{2,3A}$ = 6.5, $J_{2,3B}$ = 8.2)	2.70 (ddd), 2.27(ddd), $J_{3A,3B}$ = 14.5, $J_{3A,4}$ = 9.4, $J_{3B,4}$ = 4.7	3.70 (m)

[a] Internal reference: HMDS (hexamethyldisilane).

Table 3 ^{1}H NMR Spectra [$CDCl_3$/TMS, δ, *J* (Hz)] of 4-*N*-Benzylaminobut-1-enes **6a–l** and *N*-Benzylidene-*N*-butenylamino-*N*-oxides **7a–l**



6a-l



7a-l

Product	*N*–CH_AH_B (N=CH)	H_{arom}	Other Protons (R^1, R^2)
6a	3.71 (s)	7.39–7.19 (m)	1.80–1.48 (m)
6b	3.69 (s)	7.46–7.21 (m)	1.67–1.28 (m)
6c	3.71 (s)	7.21–7.07 (m)	1.76–1.40 (m)
6d	3.63 (s)	7.37–7.20 (m)	1.68–1.44 (m)
6e	3.59 (s)	7.39–7.19 (m)	1.55–1.10 [m, $(CH_2)_6$], 1.09 (s, 4-CH_3), 0.88 [t, CH_2CH_3, *J* (CH_3,CH_2) = 6.8]
6f	3.82 (d), 3.66 (d), *J* (H_A,H_B) = 13.4	7.52–7.38 (m)	–
6g	3.80 (d), 3.63 (d), *J* (H_A,H_B) = 13.4	7.45–7.01 (m)	3.88 (s), OCH_3
6h	3.32 (d), 3.56 (d), *J* (H_A,H_B) = 13.1	7-30–7.05 (m)	7.32 (d, α-H), 6.27 (dd, β-H), 6.13 (d, β′-H), $J_{\alpha,\beta}$ = 1.8, $J_{\alpha,\beta'}$ = 3.4
6i	3.30 (d), 3.40 (d), *J* (H_A,H_B) = 13.3	7.06–6.94 (m)	8.32 (d, α-H), 7.38 (dt, β-H), 7.10 (d, β′-H), 6.88 (dt, γ-H)
6j	3.64 (d), 3.53 (d), *J* (H_A,H_B) = 13.5	7.32–7.28 (m)	8.55(d, α′-H), 8.50 (dd, α-H), 7.73 (dt, γ-H), 7.23 (t, β-H), $J_{\gamma,\beta'}$ =7.7, $J_{\alpha,\beta}$ =6.2, $J_{\gamma,\alpha'}$ =1.8, $J_{\gamma,\alpha}$ =1.5
6k	3.66 (d), 3.51 (d), *J* (H_A,H_B) = 13.4	7.40–7.15 (m)	8.56 (AA′, α-H), 7.44–7.15 (BB′, β-H)

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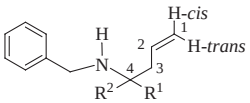
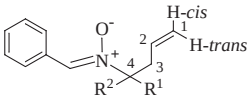
Table 3 ^{1}H NMR Spectra [$CDCl_3$/TMS, δ, *J* (Hz)] of 4-*N*-Benzylaminobut-1-enes **6a–l** and *N*-Benzylidene-*N*-butenylamino-*N*-oxides **7a–l** (continued)



6a-l



7a-l

Product	*N*–CH_AH_B (N=CH)	H_{arom}	Other Protons (R^1, R^2)
6l	3.68 (s)	7.22–7.13 (m)	1.23–1.18 [m, $(CH_2)_8$], 0.80 [t, CH_2CH_3, *J* (CH_3,CH_2) = 6.9]
7a	7.37 (s)	8.24, 7.45–7.35 (m)	2.53–1.54 [m, $(CH_2)_4$]
7b	7.39 (s)	8.30-7.45 (m)	2.35–1.35 [m, $(CH_2)_5$]
7c	7.38 (s)	8.29, 7.45–7.30 (m)	2.56–1.38 [m, $(CH_2)_6$]
7d	7.39 (s)	8.34, 7.48–7.30 (m)	2.38, 1.84–1.48 [m, $(CH_2)_7$]
7e	7.41 (s)	8.30, 7.52–7.40 (m)	2.20–1.20 [m, $(CH_2)_6$], 1.52 (s, 4-CH_3), 0.85 [t, CH_2CH_3, *J* (CH_3,CH_2) = 6.7]
7f	7.54 (s)	8.24, 7.41–7.35 (m)	7.58 ($H_{m,o}$), 7.40–7.35 (H_p)
7g	7.46 (s)	8.19, 7.40-7.30 (m)	7.47 ($H_{o,o'}$), 6.88 ($H_{m,m'}$), 3.78 (s, OCH_3)
7h[a]	7.41 (s)	8.22, 7.43–7.35 (m)	7.43 (d, α-H), 6.55 (d, β′-H), 6.41(dd, β-H), $J_{\alpha,\beta}$=1.8, $J_{\beta,\beta'}$ =3.4
7i	7.66 (s)	7.40–7.27 (m)	8.58 (d, α-H), 8.24 (t, β-H), 7.75 (d, β′-H), 7.72 (t, γ-H), $J_{\alpha,\beta}$ = 4.8, $J_{\beta,\gamma}$ =3.9, $J_{\beta',\beta}$ =1.2, $J_{\gamma,\alpha}$=1.7
7j	7.50 (s)	7.35–7.20 (m)	8.60 (d, α′-H), 8.50 (dd, α-H), 8.15 (t, β-H), 7.98 (dt, γ-H), $J_{\beta,\gamma}$ =7.7, $J_{\alpha,\beta}$ =6.5, $J_{\alpha',\gamma}$ =2.2, $J_{\alpha,\gamma}$=1.6
7k	7.51 (s)	8.23, 7.43–7.41 (m)	8.63 (α,α′-H), 7.49 (β,β′-H)
7l	7.26 (s)	8.18, 7.34–7.30 (m)	1.23–1.15 [m, $(CH_2)_8$], 0.78 [q, CH_3, *J* (CH_3,CH_2) = 6.7]

[a] Internal reference: HMDS (hexamethyldisilane).

During the elaboration of our strategy, we mentioned that nitrone precursors are not only versatile and excellent building blocks in the preparation of novel heterocyclic structures by use of 1,3-dipolar cycloaddition, both in inter- and intramolecular version[25,26] or by use of the nucleophilic addition reactions,[27] but are also effective in trapping short-lived free radical species and potent antioxidants.[28–30] The effectiveness of radical scavengers in reducing oxidative stress within a living biological environment has not been established;[31] however, one molecule under investigation as a therapeutic agent is phenyl-*tert*-butylnitrone (PBN),[32] which has shown promising activity as a neuroprotector in certain animal models.[33] The design and synthesis of analogues of PBN are still needed. Moreover, their alicyclic analogues bearing a quaternary carbon at a nitrogen atom, are not accessible. Antioxidant activity of the obtained nitrones **7d–f** and **7i–l** showed that these compounds possess moderate potency (20–55% compared to BHT) as inhibitors of lipid peroxidation. It was established that nitrones **7i–k**, containing a pyridine ring possess a higher activity and that the replacement of the aromatic substituents at C-4 with spiroalkylidene fragment resulted in a decrease in potency.[34]

The heterobicyclic skeleton was then constructed by an intramolecular thermal cyclisation of nitrones **7a–h** and **7k**,**l** which proceeded smoothly in benzene or toluene to give the corresponding 2-substituted 6-*exo*-phenyl-1-aza-7-oxabicyclo[2.2.1]heptanes **8a–j** (Scheme 2). The intramolecular 1,3 dipolar cycloaddition of alkenylnitrones **7a–d** and **7f**,**g**,**l** occurs with a high degree of stereoselectivity with the formation of 2-spiroannulated 6-*exo*-phenyl-1-aza-7-oxabicyclo[2.2.1]heptanes **8a–d** or 2-*exo*-aryl(*n*-nonyl)-6-*exo*-phenyl-1-aza-7-oxabicyclo-[2.2.1]-heptanes **8f**,**g**,**j**, respectively, as the major isomeric products with yields ranging from 48 to 83%. These major 2-*exo*-, 6-*exo*-isomers were isolated and purified either by fractional crystallisation (**8a–c**,**f**,**g**) or by alumina column chromatography (**8d**,**e**,**j**)[35] (Table 4).

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Table 4 1-Aza-7-oxabicyclo[2.2.1]heptanes **8a**–**j** and 2,6-Disubstituted 4-hydroxypiperidines **9a**–**i**

Product[a]	Molecular Mass (*m*/z)		Mp (°C)[b]	R_f (Silufol UV_{254})	IR (cm^{-1}) ν_{NH}/ν_{OH}	Yield (%)
	Found ($M^{+\cdot}$)	Calcd				
8a	229	229	78–80	0.64[c]	–	50
8b	243	243	88–89	0.53[d]	–	83
8c	257	257	96–97	0.63[e]	–	48
8d	271	271	oil	0.65[e]	–	48
8e	287	287	oil	0.59[e]	–	75
8f	251	251	97–100	0.50[c]	–	60
8g	281	281	126–128	0.57[c]	–	56
8h	241	241	36–37	0.45[f]	–	34
8i	252	252	88–89	0.53[d]	–	36
8j	301	301	38–40	0.60[c]	–	73
9a	231	231	51–54	0.64[g]	3380/3240	75
9b	245	245	102.5–103.5	0.51[h]	3480/3280	76
9c	259	259	oil	0.54[g]	3385	78
9d	273	273	oil	0.60[g]	3338	75
9e	289	289	85–87	0.53[g]	3259	72
9f	253	253	113–114	0.57[g]	3275/3210	75
9g	283	283	101–103	0.44[h]	3400	66
9h	243	243	73.5–75.0	0.40[h]	3382	45
9i	303	303	68–70	0.53[g]	3285/3220	73

[a] All compounds showed satisfactory elemenatal analyses: C, ±0.26; H, ±0.18; N, ±0.13.
[b] Solvent for recrystallisation: EtOAc–hexane.
[c] EtOAc–hexane (1:5).
[d] EtOAc–acetone (2:1).
[e] EtOAc–hexane (1:10).
[f] EtOAc–hexane, (1:3).
[g] EtOAc–hexane, (1:1).
[h] EtOAc.

An intramolecular [3+2] cycloaddition reaction of nitrones **7h** and **7k** proceeded more slowly than that of nitrones **7a**–**d** and **7f**,**g** and resulted in the formation of considerable amounts of 2-*endo*-, 6-*exo*-substituted products. The ratio of 2-*exo*-, 6-*exo*-/2-*endo*-, 6-*exo*-isomers found by ^{1}H NMR in reaction mixtures is ~5:1. In these cases, the individual *exo*-, *exo*-isomers of 2-hetaryl substituted bicycles **8h**,**i** were isolated in moderate yields (34 and 36%) by fractional crystallisation of the reaction mixtures.

An intramolecular [3+2] cycloaddition reaction of nitrone **7e** proceeded with moderate stereoselectivity and led to bicycloheptane **8e**, which was characterized by GC-MS as a mixture of two isomers in a 2.2:1 ratio. However, the major isomer, identified as 2-*endo*-methyl-2-*exo*-*n*-heptyl-6-*exo*-phenyl-1-aza-7-oxabicyclo[2.2.1]heptane, was also successfully isolated by alumina column chromatography.

Due to the structural similarity, the mean signals in ^{1}H NMR spectra of dominant isomers of compounds **8a**–**j** were assigned largely on the basis of correlation to the chemical shifts and vicinal coupling constants in spectra of previously investigated 2-phenyl-1-aza-7-oxabicyclo[2.2.1]heptane[12] and 6-substituted 2-methyl-3-trimethylsilyl-1-aza-7-oxabicyclo[2.2.1]heptanes.[36]

Chemical shifts in spectra of compounds **8a**–**j** have been measured by irradiation of the samples in $CDCl_3$ and C_6D_6 solutions. Unfortunately, the results of irradiation in $CDCl_3$ were not clear enough to compare with those reported by Lumma[12] and Wuts.[36] For this reason we used C_6D_6 solution in order to determine the 4-H, 5-H_α, 5-H_β

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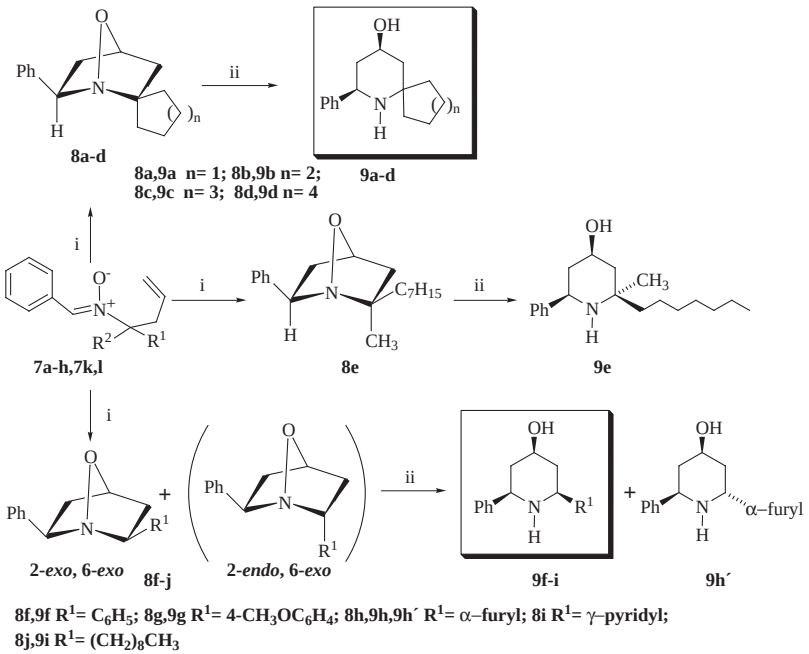
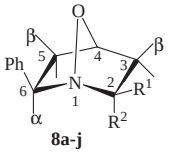


Scheme 2 *Reagents and Conditions*: i) benzene or toluene, reflux, 5–10 h; ii) 80% AcOH/Zn, 60–65 °C, 3–5 h.

and 6-H absorptions and their vicinal coupling constants (Tables 5, 6). Our detailed explications for these NMR experiments have been recently described[17] taking the 1-aza-6-phenyl-2-spiro-7-oxabicyclo[2.2.1]heptane-2,1′-cyclohexane **8b** as a model molecule. Thus, the *exo* relative stereochemistry of C-6 phenyl group in major isomers of all analysed bicycloheptanes was inferred by the values of coupling constants $J_{5,6}$ (7.0–8.3 and 4.3–5.5 Hz) which agreed with those determined previously ($J_{5\alpha,6\alpha}$ = 8.2–8.3 and $J_{5\beta,6\alpha}$ = 4.3–5.6 Hz).[12,36] The *exo*-orientation of C-2 substituents (phenyl, 4-methoxyphenyl, *n*-heptyl, α-furyl, γ-pyridyl) in bicycloheptanes **8f–j** has been established in the same manner ($J_{2\alpha,3\alpha}$ = 7.3–8.3 and $J_{2\alpha,3\beta}$ = 4.3–4.6 Hz).

Table 5 ^{1}H NMR Spectra [(δ, *J* (Hz)] of 1-Aza-7-oxabicyclo[2.2.1]heptanes **8a–j**



Product	Solvent[a]	2α-H	3α-H	3β-H	4-H	5a-H
8a	$CDCl_3$	–	1.47 (d) $J_{3a,3b}$ = 11.3	–[b]	4.97 (t, $J_{4,3\beta}$=5.2, $J_{4,5\beta}$=5.2)	2.14 (dd, $J_{5\alpha,5\beta}$ = 11.3, $J_{5\alpha,6\alpha}$ = 8.2)
	C_6D_6	–	0.87 (d, $J_{3\alpha,3\beta}$ = 11.3)	–[b]	4.40 (t, $J_{4,3\beta}$ = 4.9, $J_{4,5\beta}$ = 4.9)	-[b] ($J_{5\alpha,6\alpha}$ = 7.9)
8b	$CDCl_3$	–	1.23 (d, $J_{3\alpha,3\beta}$ = 11.3)	1.82 (dd, $J_{3\beta,4}$ = 5.3)	4.89 (dt, $J_{4,5\beta}$ = 2.6, $J_{4,5\alpha}$ = 2.6)[c]	~2.04 (m, $J_{5\alpha,6\alpha}$ = 6.3)[c]
	C_6D_6	–	0.58 (d, $J_{3\alpha,3\beta}$ = 11.3	1.34 (ddd, $J_{3\beta,4}$ = 5.2, $J_{3\beta,5\beta}$ = 2.4)	4.31 (t, $J_{4,3\beta}$ = 5.2, $J_{4,5\beta}$ = 5.2)	1.41 (dd, $J_{5\alpha,5\beta}$ = 11.3, $J_{5\alpha,6\alpha}$ = 8.2)
8c	$CDCl_3$	–	1.36 (d, $J_{3\alpha,3\beta}$ = 11.3)	1.77 (dd, $J_{3\beta,4}$ = 5.2)	4.86 (dt, $J_{4,5\beta}$ = 2.6)[c]	~2.03 (m, $J_{5\alpha,6\alpha}$ = 6.3)[c]

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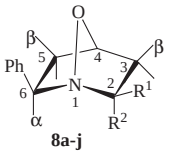
Table 5 ^{1}H NMR Spectra [(δ, *J* (Hz)] of 1-Aza-7-oxabicyclo[2.2.1]heptanes **8a–j** (continued)



8a-j

Product	Solvent[a]	2α-H	3α-H	3β-H	4-H	5a-H
	C_6D_6	–	0.74 (d, $J_{3\alpha,3\beta}$ = 11.3)	1.32 (ddd, $J_{3\beta,4}$ = 5.2, $J_{3\beta,5\beta}$ = 2.2)	4.31 (t, $J_{4,5\beta}$ = 5.2)	1.42 (dd, $J_{5\alpha,5\beta}$ = 11.3, $J_{5\alpha,6\alpha}$ = 8.3)
8d	$CDCl_3$	–	1.34 (d, $J_{3\alpha,3\beta}$ = 11.3)	1.75 (dd, $J_{3\beta,4}$ = 5.2)	4.88 (dt, $J_{4,5\beta}$ = 2.6)[c]	~2.04 (m, $J_{5\alpha,6\alpha}$ = 6.3)[c]
	C_6D_6	–	0.74 (d, $J_{3\alpha,3\beta}$ = 11.3)	1.32 (ddd, $J_{3\beta,4}$ = 5.2, $J_{3\beta,5\beta}$ = 2.2)	4.31 (t, $J_{4,5\beta}$ = 5.2)	1.42 (dd, $J_{5\alpha,5\beta}$ = 11.3, $J_{5\alpha,6\alpha}$ = 8.3)
8e	$CDCl_3$	–	2.03 (m, $J_{3\alpha,3\beta}$ = 11.3)	2.15 (dd, $J_{3\beta,4}$ = 2.6)[c]	4.83 (t, $J_{4,5\beta}$ = 2.6)*c*	~2.03 (m, $J_{5\alpha,6\alpha}$ = 7.0)
	C_6D_6	–	0.88 (d, $J_{3\alpha,3\beta}$ = 11.3)	–[b] $J_{3\beta,4}$ = 5.2	4.34 (t, $J_{4,5\beta}$ = 5.2)	1.49 (dd, $J_{5\alpha,5\beta}$ = 11.4, $J_{5\alpha,6\alpha}$ = 8.3)
8f	$CDCl_3$	4.10 (dd, $J_{2\alpha,3\alpha}$ = 8.2, $J_{2\alpha,3\beta}$ = 4.6)	2.27 (dd, $J_{3\alpha,3\beta}$ = 11.0)	2.09 (ddd, $J_{3\beta,4}$ = 4.9)	5.09 (t, $J_{4,5\beta}$ = 4.9)	2.27 (dd, $J_{5\alpha,5\beta}$ = 11.0, $J_{5\alpha,6\alpha}$ = 8.2)
	C_6D_6	3.53 (dd, $J_{2\alpha,3\alpha}$ = 8.2, $J_{2\alpha,3\beta}$ = 4.6)	1.48 (dd, $J_{3\alpha,3\beta}$ = 11.0)	1.61 (ddd, $J_{3\beta,4}$ = 4.7)	4.40 (t, $J_{4,5\beta}$ = 4.7)	1.48 (dd, $J_{5\alpha,5\beta}$ = 11.0, $J_{5\alpha,6\alpha}$ = 8.2)
8g	$CDCl_3$	4.07 (dd, $J_{2\alpha,3\alpha}$ = 8.2, $J_{2\alpha,3\beta}$ = 4.5)	2.25 (dd, $J_{3\alpha,3\beta}$ = 11.2)	2.07 (ddd, $J_{3\beta,4}$ = 4.9)	5.10 (t, $J_{4,5\beta}$ = 4.9)	2.27 (dd, $J_{5\alpha,5\beta}$ = 11.2, $J_{5\alpha,6\alpha}$ = 8.2)
	C_6D_6	3.48 (dd, $J_{2\alpha,3\alpha}$ = 8.2, $J_{2\alpha,3\beta}$ = 4.3)	1.45 (dd, $J_{3\alpha,3\beta}$ = 11.0)	1.70–1.50[b] ($J_{3\beta,4}$ = 4.6)	4.39 (t, $J_{4,5\beta}$ = 4.6)	1.45 (dd, $J_{5\alpha,5\beta}$ = 11.0, $J_{5\alpha,6\alpha}$ = 8.2)
8h	C_6D_6	3.60 (dd, $J_{2\alpha,3\alpha}$ = 8.2, $J_{2\alpha,3\beta}$ = 4.6)	1.26 (dd, $J_{3\alpha,3\beta}$ = 11.6)	1.79 (m, $J_{3\beta,4}$ = 4.9, $J_{3\beta,5\beta}$ = 2.4)	4.34 (t, $J_{4,5\beta}$ = 4.9)	1.33 (dd, $J_{5\alpha,5\beta}$ = 11.6, $J_{5\alpha,6\alpha}$ = 8.2)
8i	$CDCl_3$	4.09 (dd, $J_{2\alpha,3\alpha}$ = 8.3, $J_{2\alpha,3\beta}$ = 4.6)	2.32 (dd, $J_{3\alpha,3\beta}$ = 11.8)	2.1–1.9[b] ($J_{3\beta,4}$ = 4.9)	5.09 (t, $J_{4,5\beta}$ = 4.9)	2.29 (dd, $J_{5\alpha,5\beta}$ = 11.8, $J_{5\alpha,6\alpha}$ = 8.3)
	C_6D_6	3.21 (t, $J_{2\alpha,3\alpha}$ = 6.5, $J_{2\alpha,3\beta}$ = 6.5)[c]	~1.30 (m)	~1.30 (m)	4.27 (m)	1.38 (dd, $J_{5\alpha,5\beta}$ = 11.6, $J_{5\alpha,6\alpha}$ = 8.2)
8j	$CDCl_3$	2.79 (m, $J_{2\alpha,3\alpha}$ = 7.3, $J_{2\alpha,3\beta}$ = 4.4)	1.71 (dd, $J_{3\alpha,3\beta}$ = 11.5)	1.48 (m, $J_{3\beta,4}$ = 4.9)	4.84 (t, $J_{4,5\beta}$ = 4.8)	1.88 (m, $J_{5\alpha,5\beta}$ = 11.6, $J_{5\alpha,6\alpha}$ = 8.3)

[a] Internal refernce: TMS.
[b] Overlapped with other protons.
[c] Coupling constants were measured using the first order NMR spectra approximation.

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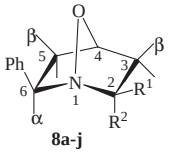
Table 6 ^{1}H NMR spectra [δ, *J* (Hz)] of 1-Aza-7-oxabicyclo[2.2.1]heptanes **8a**–**j**



8a-j

Product	Solvent[a]	5β-H	6α-H	H_{arom}	Other Protons (R^1, R^2)
8a	$CDCl_3$	–[b]	4.32 (dd, $J_{6\alpha,5\beta}$ = 5.2)	7.42, 7.35–7.20 (m)	1.95–1.59 (m)
	C_6D_6	–[b]	4.01 (dd, $J_{6\alpha,5\beta}$ = 5.2)	7.40, 7.22-6.85 (m)	2.15–1.15 (m)
8b	$CDCl_3$	~2.04 (m, $J_{5\beta,6\alpha}$ = 6.3)[c]	4.50 (t, $J_{5\alpha,6\alpha}$ = 6.3,[c] $J_{5\beta,6\alpha}$ = 6.3)[c]	7.47–7.11 (m)	1.96–1.17 (m)
	C_6D_6	1.63 (dddd, $J_{5\beta,6\alpha}$ = 4.3)	4.14 (dd, $J_{6\alpha,5\beta}$ = 4.3, $J_{6\alpha,5\alpha}$ = 8.2)	7.44, 7.20–6.90 (m)	1.25–0.95 (m)
8c	$CDCl_3$	~2.03 (m, $J_{5\beta,6\alpha}$ = 6.3)[c]	4.48 (t)	7.45, 7.35–7.10 (m)	2.28–1.24 (m)
	C_6D_6	1.62 (dddd, $J_{5\beta,6\alpha}$ = 4.3)	4.14 (dd)	7.48, 7.15–6.93 (m)	2.36 (dd), 1.78–0.93 (m)
8d	$CDCl_3$	~2.04 (m, $J_{5\beta,6\alpha}$ = 6.3)[c]	4.50 (t)	7.45, 7.35–7.15 (m)	2.30–1.25 (m)
	C_6D_6	1.62 (dd, $J_{5\beta,6\alpha}$ = 4.3)	4.14 (dd)	7.48, 7.15–6.90 (m)	2.36 (dd), 1.80–0.90 (m)
8e	$CDCl_3$	~2.03 (m, $J_{5\beta,6\alpha}$ = 5.5)	4.44 (dd)	7.42, 7.35–7.10 (m)	1.30 (s, 2-CH_3), 0.88 (t, CH_2CH_3), 2.04–1.26 [m, $(CH_2)_5$]
	C_6D_6	1.62 (dddd, $J_{5\beta,6\alpha}$ = 4.3)	4.14 (dd)	7.43, 7.20–6.90 (m)	0.87 (s, 2-CH_3), 0.78 (t, CH_2CH_3), 1.85–0.76 [m, $(CH_2)_5$]
8f	$CDCl_3$	2.09 (ddd, $J_{5\beta,6\alpha}$ = 4.6)	4.10 (dd)	7.45, 7.41–7.08 (m)	–
	C_6D_6	1.61 (ddd, $J_{5\beta,6\alpha}$ = 4.6)	3.53 (dd)	7.45, 7.25–6.95 (m)	–
8g	$CDCl_3$	2.09 (ddd, $J_{5\beta,6\alpha}$ = 4.5)	4.10 (dd)	6.90, 7.49–7.15 (m)	3.80 (s, OCH_3)
	C_6D_6	1.50–1.70[b] ($J_{5\beta,6\alpha}$ = 4.3)	3.50 (dd)	6.76, 7.50–6.95 (m)	3.22 (s, OCH_3)
8h	C_6D_6	1.48 (ddt, $J_{5\beta,6\alpha}$ = 4.9)	3.41 (dd)	7.35, 7.15–6.90 (m)	7.01 (dd, α-H), 6.22 (m, β-H), 6.00 (dd, β′-H), $J_{\alpha,\beta}$ = 1.8, $J_{\alpha,\beta'}$ = 0.9, $J_{\beta,\beta'}$ = 3.4
8i	$CDCl_3$	2.1–1.9,[b] $J_{5\beta,6\alpha}$ = 4.6)	4.07 (dd)	7.50–7.15 (m)	8.53 (AA′, α-Pyr)
	C_6D_6	1.52 (m, $J_{5\beta,6\alpha}$ = 4.9)	3.39 (dd)	7.38, 7.40–7.10 (m)	8.49 (AA′, α-Pyr), 7.05 (BB′-β-Pyr)
8j	$CDCl_3$	2.02 (dd, $J_{5\beta,6\alpha}$ = 4.8)	3.79 (dd)	7.32, 7.25–7.10 (m)	1.81 [m, $CH_2(CH_2)_7$], 1.64–1.61 (m, 2-CH_{2B}), 1.37–1.34 (m, 2-CH_{2A}), 0.80 [t, $(CH_2)_8CH_3$, *J* (CH_3,CH_2) = 6.7]

[a] Internal refernce: TMS.
[b] Overlapped with other protons.
[a] Coupling constants were measured using the first order NMR spectra approximation.

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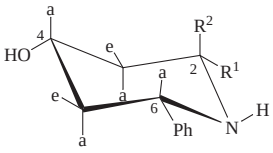
Finally, reductive cleavage of the N–O bond of heterocyclic bicycles **8a**–**j** was performed with a 5–6 fold excess of zinc in the presence of 80% acetic acid at 60–65 °C. Under these reaction conditions, all major individual isomers of the above mentioned bicycloheptanes have been subjected to this reduction, except for the compound **8h** which has been treated as a mixture of isomers. The reductive cleavage of the N–O bridged bond proceeded smoothly with the formation of all-R-*cis*-substituted 4-hydroxypiperidines **9a**–**g** and **9i** (Scheme 2). Of all bicycles underwent reductive cleavage, only the cleavage of **8i** with pyridyl substituent resulted in a complex mixture of products that is probably due to the formation of appropriate di- and tetrahydropyridines as final byproducts of partial and total reduction of the pyridine ring. For this reason, the nitrones **7i** and **7j** with β- and α-pyridyl substituents were not transformed to respective bicycles. Reductive cleavage of the N–O bond of molecule **8h** (as a mixture of isomers) also led to a mixture of isomers **9h** and **9h′** in 4:1 ratio (determined by ^{1}H NMR), from which only major isomer **9h** was successfully isolated by fractional crystallisation of the reaction mixture. New all-*cis*-R-substituted 4-hydroxypiperidines **9a**–**i** are fully characterized by physical and spectral methods (Table 4). Analysis of the ^{1}H NMR spectra of these piperidines showed that the C-4 hydroxyl ($J_{3a,4a} = J_{4a,5a}$ = 11.3–12.3 Hz, $J_{3e,4a} = J_{4a,5e}$ = 4.3–5.5 Hz), C-6 phenyl ($J_{5a,6a}$ = 11.3–12.4 Hz) and C-2 R^1 (phenyl, 4-methoxyphenyl, furyl, *n*-nonyl) ($J_{2a,3a}$ = 11.2-11.6 Hz) substituents are all oriented equatorially. Together, these facts were taken as evidence for the all-*cis* stereochemistry of obtained piperidines **9a**–**i** with the chair conformation (Tables 7, 8). The structure of all-*cis*-4-hydroxy-6-phenyl-2-(*n*-nonyl)piperidine (**9i**) was confirmed also by COSY and NOESY techniques. It was also established by ^{1}H NMR spectrum of the mixture of isomers **9h** and **9h′**, that the minor isomer **9h′** has the furyl and hydroxyl groups in *trans* configuration ($J_{2e,3a}$ = 5.8, $J_{2e,3e}$ = 1.7 Hz).

Table 7 ^{1}H NMR Spectra [$CDCl_3$/TMS, δ, *J* (Hz)] 2,6-Disubstituted 4-Hydroxypiperidines **9a**–**i**



9a-i

Product	2*a*-H	3*a*-H	3*e*-H	4*a*-H	5*a*-H
9a	–	1.41 (t, $J_{3a,3e}$ = 11.6, $J_{3a,4a}$ = 11.6)	1.88 (ddd, $J_{3e,4a}$ = 4.3, $J_{3e,5e}$ = 2.4)	3.84 (tt, $J_{4a,5a}$ = 11.6, $J_{4a,5e}$ = 4.3)	1.39 (q, $J_{5a,5e}$ = 11.6, $J_{5a,6a}$ = 11.6)
9b	–	1.14 (t, $J_{3a,3e}$ = 11.6, $J_{3a,4a}$ = 11.6)	2.04 (ddd, $J_{3e,4a}$ = 4.6, $J_{3e,5e}$ = 2.4)	4.00 (tt, $J_{4a,5a}$ = 11.6, $J_{4a,5e}$ = 4.6)	1.39 (q, $J_{5a,5e}$ = 11.6, $J_{5a,6a}$ = 11.6)
9c	–	1.13 (t, $J_{3a,3e}$ = 11.6, $J_{3a,4a}$ = 11.6)	2.00 (ddd, $J_{3e,4a}$ = 4.6, $J_{3e,5e}$ = 2.4)	3.93 (tt, $J_{4a,5a}$ = 11.6, $J_{4a,5e}$ = 4.6)	1.34 (q, $J_{5a,5e}$ = 11.6, $J_{5a,6a}$ = 11.6)
9d	–	1.08 (t, $J_{3a,3e}$ = 11.6, $J_{3a,4a}$ = 11.6)	2.06 (ddd, $J_{3e,4a}$ = 4.6, $J_{3e,5e}$ = 2.4)	3.98 (tt, $J_{4a,5a}$ = 11.6, $J_{4a,5e}$ = 4.6)	1.34 (q, $J_{5a,5e}$ = 11.6, $J_{5a,6a}$ = 11.6)
9e	–	1.63 (dd, $J_{3a,3e}$ = 12.1, $J_{3a,4a}$ = 11.4)	2.13 (dd, $J_{3e,4a}$ = 4.6)	3.99 (ddd, $J_{4a,5a}$ = 12.3, $J_{4a,5e}$ = 5.5)	1.51 (q, $J_{5a,5e}$ = 12.1, $J_{5a,6a}$ = 12.4)
9f	3.84 (dd, $J_{2a,3a}$ = 11.3, $J_{2a,3e}$ = 2.1)	1.54 (ddd, $J_{3a,3e}$ = 11.3, $J_{3a,4a}$ = 11.3)	2.16 (ddd, $J_{3e,4a}$ = 4.6)	3.93 (tt, $J_{4a,5a}$ = 11.3, $J_{4a,5e}$ = 4.6)	1.54 (ddd, $J_{5a,5e}$ = 11.3, $J_{5a,6a}$ = 11.3)
9g	3.84 (dd, $J_{2a,3a}$ = 11.6, $J_{2a,3e}$ = 2.5)	1.56 (q, $J_{3a,3e}$ = 11.6, $J_{3a,4a}$ = 11.6)	2.16 (m, $J_{3e,4a}$ = 4.9)	3.93 (tt, $J_{4a,5a}$ = 11.6, $J_{4a,5e}$ = 4.9)	1.56 (q, $J_{5a,5e}$ = 11.6, $J_{5a,6a}$ = 11.6)
9h	3.96 (br dd, $J_{2a,3a}$ = 11.6, $J_{2a,3e}$ = 2.4)	1.68 (q, $J_{3a,3e}$ = 11.6, $J_{3a,4a}$ = 11.6)	2.31 (ddt, $J_{3e,4a}$ = 4.6, $J_{3e,5e}$ = 2.4)	3.91 (tt, $J_{4a,5a}$ = 11.6, $J_{4a,5e}$ = 4.6)	1.58 (q, $J_{5a,5e}$ = 11.6, $J_{5a,6a}$ = 11.6)
9h′	4.51 (2*e*-H, br dd, $J_{2e,3a}$ = 5.8, $J_{2e,3e}$ = 1.7)	1.91 (ddd, $J_{3a,3e}$ = 12.8, $J_{3a,4a}$ = 11.6)	2.46 (m, $J_{3e,4a}$ = 4.6, $J_{3e,5e}$ = 2.4)	4.10 (tt, $J_{4a,5a}$ = 11.6, $J_{4a,5e}$ = 4.6)	1.62 (q, $J_{5a,5e}$ = 11.6, $J_{5a,6a}$ =11.6)
9i	2.60 (m, $J_{2a,3a}$=11.2, $J_{2a,3e}$=2.8)	1.06 (q, $J_{3a,3e}$ = 11.6, $J_{3a,4a}$ = 11.3)	1.92 (ddd, $J_{3e,4a}$ = 4.6, $J_{3e,5e}$ = 2.2)	3.68 (ddd, $J_{4a,5a}$ = 11.0, $J_{4a,5e}$ = 4.6)	1.36 (q, $J_{5a,5e}$ = 11.3, $J_{5a,6a}$ = 11.3)

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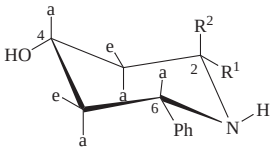
Table 8 ^{1}H NMR Spectra [$CDCl_3$/TMS, δ, *J* (Hz)] 2,6-Disubstituted 4-Hydroxypiperidines **9a–i**



9a-i

Product	5*e*-H	6*a*-H	6-Ph	Other Protons (R^1, R^2)
9a	2.09 (ddt, $J_{5e,6a}$ = 2.4)	3.75 (dd)	7.48–7.12 (m)	1.78–1.46 (m)
9b	2.14 (ddt, $J_{5e,6a}$ = 2.4)	3.87 (dd)	7.35 (m)	1.79–1.20 (m)
9c	2.11 (ddt, $J_{5e,6a}$ = 2.4)	3.82 (dd)	7.50–7.15 (m)	1.90–1.35 (m)
9d	2.13 (ddt, $J_{5e,6a}$ = 2.4)	3.86 (dd)	7.47–7.05 (m)	2.15–1.23 (m)
9e	2.16 (dd, $J_{5e,6a}$ = 2.4)	3.92 (dd)	7.30–7.15 (m)	4.79 (s, 1 H, OH), 3. 45 (s, NH), 1.92 (s, CH_3), 1.30–1.20 [m, $(CH_2)_6$], 0.86 (t, CH_2CH_3)
9f	2.16 (ddd, $J_{5e,6a}$ = 2.1)	3.84 (dd)	7.50–7.15 (m)	7.50–7.15 (m)
9g	2.16 (m, $J_{5e,6a}$ = 2.5)	3.82 (dd)	6.86, 7.48–7.19 (m)	6.86, 7.48–7.19 (m), 3.79 (s, OCH_3)
9h	2.15 (ddt, $J_{5e,6a}$ = 2.4)	3.81 (dd)	7.45–7.23 (m)	7.32 (dd, α-H, *J* = 1.8, 0.8), 6.30 (dd, β-H, *J* = 3.1, 1.8), 6.20 (dd, β′-H, *J* = 3.1, 0.8)
9h′	2.08 (ddt, $J_{5e,6a}$ = 2.4)	3.77 (dd)	7.45–7.23 (m)	7.32 (dd, α-H, *J* = 1.8, 0.8), 6.35 (dd, β-H, *J* = 3.1, 1.8), 6.23 (dd, β′-H, *J* = 3.1, 0.8)
9i	2.00 (ddd, $J_{5e,6a}$ = 2.3)	3.56 (dd)	7.30–7.15 (m)	1.30–1.11 [m, $(CH_2)_8$], 0.80 (t, CH_2CH_3)

In summary, a family of the phenyl 4-hydroxypiperidine derivatives at position C-6 with different substituents and variable steric size spirocyclic fragments at position C-2 has been synthesized following the molecular modelling of some relevant dendrobate alkaloids to study their pharmacological properties. The results given here represent an original approach using accessible homoallylic amines as starting materials to prepare stereoselectively 2,6-disubstituted 4-hydroxypiperidines, including new all-*cis*-2-spiro-4-hydroxy-6-phenylpiperidines as well as the all-*cis*-4-hydroxy-6-phenyl-2-*n*-nonylpiperidine.

All reagents were purchased from Merck-Schuchardt and Aldrich Chemical Co. All solvents were used without further purification. Melting points were determined using a Fisher-Johns melting point apparatus and are uncorrected. IR spectra were obtained on a Perkin-Elmer 599B-FTIR and UR-20 spectrometers as KBr pellets for solid or as thin film for oils. ^{1}H NMR spectra were recorded on a Bruker WP-200 or WH-400 spectrometers for solutions (2%) in $CDCl_3$ or C_6D_6 at 30 °C and using TMS or HMDS (hexamethyldisilane) as internal standard. Chemical shifts are reported in ppm units, and coupling constants (*J*) are quoted in Hz. Mass spectra were obtained by electron impact at 70 eV on a Varian MAT-112 and Kratos MS25 RF mass or Finnegan MAT95XL spectrometers. Microanalyses were performed on a Perkin Elmer 2400 Series II analyzer. The purity of the obtained substances and the composition of the reaction mixtures were controlled by TLC Silufol UV_{254} plates. The separation of the final products was carried out by column chromatography on Al_2O_3 or by fractional crystallisation.

4-Substituted 4-*N*-Benzylaminobut-1-enes 6a–l; General Procedure

The imine **5a–l** (0.30 mol) was slowly added dropwise at reflux to a stirred solution of allylmagnesium bromide, prepared from allyl bromide (39 mL, 0.45 mol) and Mg turnings (22.0 g, 0.90 mol) in Et_2O (300 mL) or THF (300 mL) (for **5i–k**). After the addition of the Schiff base, the reaction mixture was stirred for 1 h at r.t. The cooled mixture was taken up in sat. aq NH_4Cl solution (300 mL) under ice cooling and extracted with Et_2O (3 × 100 mL). The organic layer was dried (Na_2SO_4) and concentrated. The residue was distilled in vacuo to give the product **6a–l** as colourless oils. Tables 1, 2 and 3 contain the yields and some physical and spectral properties of these compounds.

N-Benzylidene-*N*-3-butenylamino-*N*-oxides 7a–l; General Procedure

Aq H_2O_2 (50%, 34 mL, 0.60 mol) was added dropwise at 20 °C[37] to a solution of the homoallylamine **6a–l** (0.20 mol) and

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$Na_2WO_4 \cdot 2H_2O$ (0.33 g, 0.01 mol) in a mixture of acetone–H_2O (9:1, 150 mL). The reaction mixture was stirred at r.t. for 2–4 d (TLC control) and then diluted with H_2O (400 mL). The organic products were extracted with Et_2O (5 × 70 mL). The combined organic layers were washed with H_2O (2 × 100 mL), dried ($MgSO_4$) and concentrated. Evaporation of the solvent and column chromatography (3 × 7 cm) on alumina (EtOAc–hexane, 1:10, as eluent) gave the pure nitrones. For **7a**–**h**,**k** the residue solidified on standing. Further crystallisation from hexane–Et_2O gave the corresponding nitrones as colourless crystals. Tables 1, 2 and 3 contain the yields and some physical and spectral properties of these compounds.

1-Aza-7-oxabicyclo[2.2.1]heptanes 8a–j; General Procedure

A solution of nitrones **7a–l** (0.10 mol) and benzene or toluene (100 mL) was refluxed for 5–10 h (monitoring by TLC). Evaporation of the solvent left crude products as viscous oils. In all cases the major isomer could be easily separated by simple short column chromatography on alumina (4 × 3 cm, EtOAc–hexane, 1:10, as eluent, for **8d**,**e**,**j)**, or by fractional crystallisation of the reaction mixture from hexane–EtOAc (all other compounds). Tables 4, 5 and 6 contain the yields and some physical and spectral properties of these compounds.

2,6-Disubstituted 4-Hydroxypiperidines 9a–i; General Procedure

To a solution of **8a**–**j** (40 mmol) in 80% AcOH (150 mL) was added Zn powder (15.7 g, 0.24 mol). After stirring for 3–5 h at 60–65 °C the transparent reaction mixture was cooled to r.t. The precipitate of $Zn(AcO)_2$ was filtered. The residue after removal of AcOH in vacuo was combined with the precipitate of $Zn(AcO)_2$ and dissolved in H_2O (150 mL). A solution of 25% NH_4OH was added until the solution became clear (pH ~10–11). The mixture was then extracted with $CHCl_3$ (3 × 100 mL). The combined extracts were washed twice with 5% NH_4OH solution (100 mL), dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography on alumina (for **9c**–**e**,**i)** or by fractional crystallisation from a mixture of hexane–EtOAc (all other compounds). Tables 4 and 7, 8 contain the yields and some physical and spectral properties of these compounds

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(34) The detailed results from these studies will be published elsewhere.
(35) The exact composition of the formed stereoisomeric mixtures has not been studied.
(36) Wuts, P. G. M.; Jung, Y.-W. *J. Org. Chem.* **1988**, *53*, 1957.
(37) The reaction conditions used (20 °C) allow the oxidation of the homoallylamines.

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