Intramolecular Diels—Alder reaction of 4-(*N*-furfuryl)aminobut-1-enes. New approach to the synthesis of 6,8a-epoxyoctahydroisoquinoline (3-aza-11-oxatricyclo[6.2.1.0^{1,6}]undec-9-ene) derivatives

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The intramolecular Diels—Alder reaction of readily accessible 4-substituted 4-(*N*-furfuryl)aminobut-1-enes was studied and a new one-step method was developed for the synthesis of 6,8a-epoxy-1,2,3,4,4a,5,6,8a-octahydroisoquinoline (3-aza-11-oxatricyclo[6.2.1.0^{1,6}]undec-9-ene) derivatives. The [4+2]-cycloaddition proceeds stereoselectively to form *exo*-adducts. The influence of substituents at the nitrogen atom in 4-(*N*-furfuryl)aminobut-1-enes on the cycloaddition pathway was examined.

Key words: homoallylamines, intramolecular [4+2]-cycloaddition, furans, intramolecular Diels—Alder reaction, 6,8a-epoxyoctahydroisoquinolines, 3-aza-11-oxatricyclo[6.2.1.0^{1,6}]undec-9-enes.

Decahydroisoquinoline represents a major structural fragment of more than 500 various alkaloids.[1] However, the reactivity of hydrogenated 6,8a-epoxyisoquinolines, which are synthetic precursors of polyhydroxyperhydroisoquinolines, has not been adequately investigated. This is associated primarily with the lack of general and reliable procedures for the preparation of these compounds. One of the most efficient approaches to the synthesis of epoxyoctahydroisoquinolines involves the intramolecular [4+2]-cycloaddition of alkenylfurans. This reaction, which has been described for the first time in the study of photooxidation of furylcyclophane,[2] is efficient for the construction of hydrogenated derivatives of the isoindole,[3—7] indole, and quinoline series.[8—13] A versatile preparative method for the synthesis of hydrogenated indoles and quinolines[14] is based on the intramolecular [4+2]-cycloaddition of *N*-allyl(butenyl)-*N*-(α-furyl)urethanes.[8—13]

Examples of the use of the Diels—Alder reaction for the construction of octa(hexa)hydro-6,8a-epoxyisoquinoline systems are scarce.[15—19] This is associated with the ambiguity (compared to the synthesis of 5,7a-epoxyisoindoles) of the [4+2]-cycloaddition of tertiary furfurylbutenylamines as well as with the fact that some of these compounds are not easily accessible. The stereoselective synthesis of enantiomeric 6,8a-epoxy-1,2,3,4,4a,5,6,8a-octahydroisoquinolines has recently been described.[20]

We are carrying out systematic investigation into the reactivity of secondary homoallylamines, *viz.*, 4-substituted 4-*N*-aryl(aralkyl)aminobut-1-enes. Based on this class of compounds, preparative methods have been developed for the synthesis of tetrahydroquinolines,[21] benz-2-azepines,[22] 6-substituted and all-*cis* spiro-fused 2-phenylpiperidin-4-ols,[23] azetidines, and 1,2,3-oxathiazines.[24]

Recently, we have proposed an original approach to the synthesis of a new heterocyclic system, *viz.*, 3-spirofused 6,8a-epoxyoctahydroisoquinoline (3-aza-11-oxatricyclo[6.2.1.0^{1,6}]undec-9-ene), based on the *exo*-stereoselective intramolecular [4+2]-cyclization of 1-allyl-1-(*N*-furfuryl)aminocycloalkanes.[25]

The aim of the present study was to investigate the stereochemical features of this process and the electronic and steric effects of substituents in the allylic fragment and cyclizing agents (acid anhydrides and halides) (Scheme 1).

The starting azomethines, which were prepared by condensation of furfurylamine with cyclic ketones[23,26] (see Scheme 1), were not isolated in the individual state and were introduced into the reactions with the Grignard reagents directly after distillation of benzene from the reaction mixture.

Homoallylamines **1a—e** underwent partial cyclization into *exo*-epoxyoctahydroisoquinoline derivatives **2a—e** at

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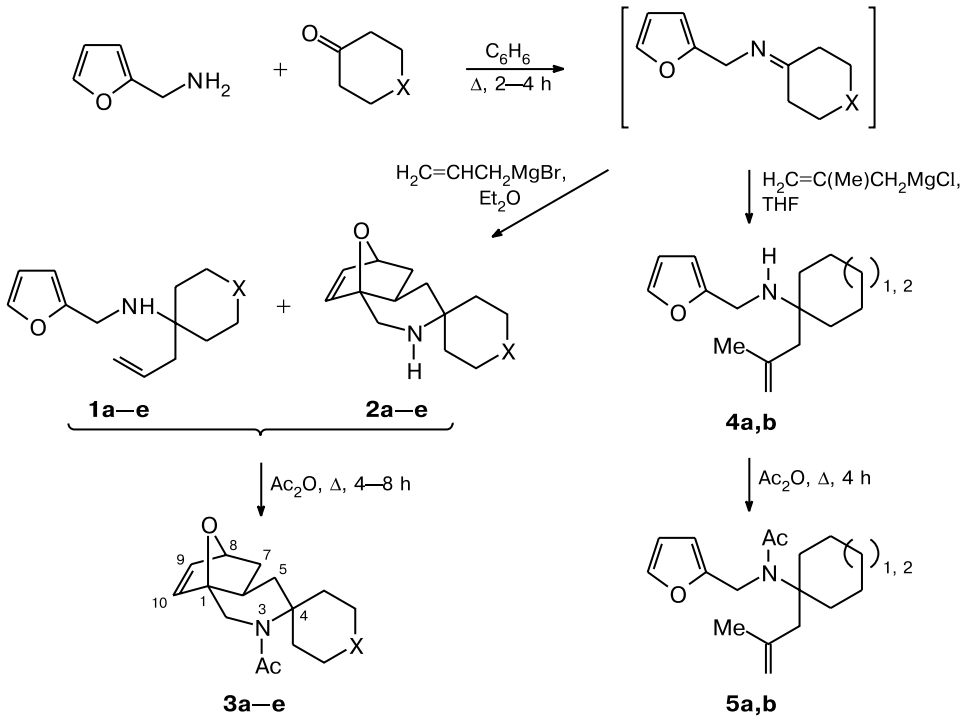
Scheme 1



1—3: X = bond (**a**), CH_2 (**b**), $(CH_2)_2$ (**c**), NMe (**d**), NEt (**e**)

160—200 °C. As a result, amines **1a—c,e** isolated by vacuum distillation were contaminated (according to the ^{1}H NMR spectroscopic data) with 5—9% of the corresponding tricyclic compounds **2a—c,e**. The exception is compound **1d** (X = NMe), which is contaminated with 25% of epoxyoctahydroisoquinoline **2d**. Adduct **2d** was isolated from the mixture in the individual state in 5% yield by crystallization. In other cases, we did not undertake attempts to isolate compounds **2** in the individual state. Apparently, thermal intramolecular cyclization of amines **1a—e** is an equilibrium reaction. However, attempts to increase the yield of tricyclic systems **2a—e** by refluxing furfurylamines **1a—e** in high-boiling solvents (*o*-xylene, pseudocumene, or durene) failed.

To the contrary, intramolecular cyclization of homoallylamines **1a—e** in boiling acetic anhydride, which involved *N*-acylation as the first step, proceeded readily and stereoselectively to give *exo*-Diels-Alder adducts **3a—e** in 48—71% yields (see Scheme 1).

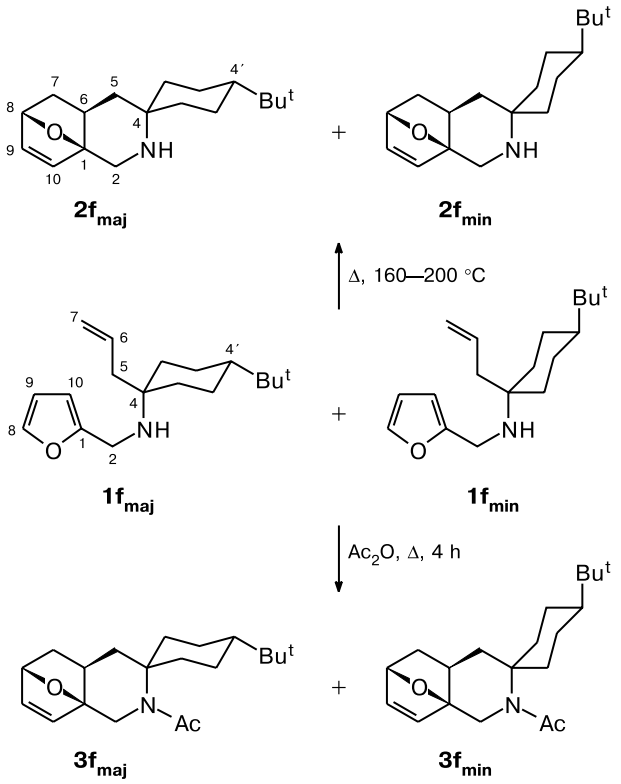
Refluxing of methallyl derivatives **4a,b** in acetic anhydride led only to acetylation of the N atom giving rise to amides **5a,b**. The fact that intramolecular cyclization does not occur is apparently attributable to destabilization of the transition state due to steric hindrance caused by the Me group of the methallyl fragment.

Unlike homoallylamines **1a—e**, 1-allyl-4-*tert*-butyl-1-(*N*-furfuryl)aminocyclohexane (**1f**) was prepared as a mixture of the major ($\mathbf{1f_{maj}}$) and minor ($\mathbf{1f_{min}}$) isomers due to the presence of the *tert*-butyl fragment, which hinders inversion of the cyclohexane ring (Scheme 2). According to the ^{13}C NMR spectroscopic data, isomer $\mathbf{1f_{maj}}$ with the equatorial orientation of the allyl substituent slightly predominated in the reaction mixture. The $\mathbf{1f_{min}}$: $\mathbf{1f_{maj}}$ ratio in the reaction mixture was ~45 : 55, *i.e.*, the addition of the Grignard reagent proceeded nonstereospecifically. Vacuum distillation of isomers of **1f** was also accompanied by partial intramolecular cyclization into epoxyoctahydroisoquinoline derivatives **2f** (after distillation, the **1f** : **2f** ratio was ~4 : 1, the total yield of compounds **1f** and **2f** was 65%). Unlike amines **1a—e**, refluxing of a mixture of **1f** and **2f** in *o*-xylene led to further cyclization. After heating for 5 h, the **1f** : **2f** ratio decreased to ~1 : 1 (more prolonged heating led to a decrease in the total yield of amines **1f** and **2f** and had virtually no effect on their ratio).

Cyclization of a mixture of isomeric allylamines **1f** and tricyclic compounds **2f** in boiling acetic anhydride proceeds readily and stereoselectively to give a mixture of isomers of **3f** in virtually quantitative yield; the ratio of these isomers corresponds to the ratio of isomers of **1f** in the starting mixture ($\mathbf{3f_{min}}$: $\mathbf{3f_{maj}} \approx 45 : 55$).

All isomers of compounds **1f**, **2f**, and **3f** were isolated in the individual state by column chromatography. Their spatial structures were established by ^{13}C NMR spectro-

Scheme 2



scopy on the assumption that the chair conformation of the cyclohexane ring with the equatorial orientation of the bulky *tert*-butyl substituent (a "conformational anchor") is retained in all the compounds under study. In this case, the orientation of the C(5)—C(4) bond in the major isomer differs from that in the minor isomer.

It is known[27,28] that in the ^{13}C NMR spectra of symmetrical isomeric dimethylcyclohexanes, the higher-field signal for the C atoms of the Me groups belongs to the isomer in which the diequatorial arrangement of the Me groups cannot occur. The upfield shift of the signal for the axial methyl carbon atom compared to the signal for the equatorial carbon atom, which was estimated based on the published data for isomeric 1,4-dimethylcyclohexanes,[28] is ~5 ppm.

A comparison of the ^{13}C chemical shifts for the analogous C atoms in the isomer pairs of **1f—3f** shows that the signal for the C(5) atom in the minor isomers is noticeably (by 5.4—8.3 ppm) shifted upfield (the numbering of atoms in the isomers of **1f** presented in Scheme 2 was changed for the ease of viewing, see Table 1), the differences in the chemical shifts of all other C atoms being substantially smaller. Taking into account the aforesaid, this fact is indicative of the axial orientation of the C(5)—C(4) bond in the minor isomers, which corresponds to the *cis* arrangement of the C(5) atom and the *tert*-butyl substituent.

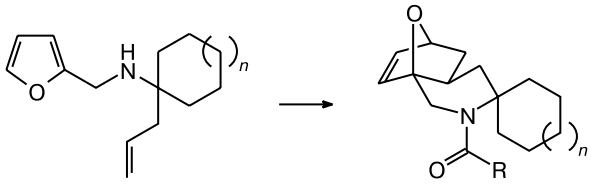
The stereochemistry of the epoxyoctahydroisoquinoline moiety is identical for the isomer pairs of **2f** and **3f** and was established by ^1H NMR spectroscopy (Tables 2 and 3). In the spectra of all compounds, the spin-spin coupling constants for analogous protons have similar values ($^3J_{H(7A),H(8)} < 1$ Hz, $^3J_{H(7B),H(8)} = 4.4—4.6$ Hz, $^3J_{H(6),H(7A)} = 7.7—7.3$ Hz, $^3J_{H(6),H(7B)} = 2.7—3.6$ Hz). According to the published data,[29] these constants are indicative of the *endo* orientation of the H(6) and H(7A) protons and the *exo* orientation of the H(7B) proton. The H(6) atom is in the axial orientation with respect to the piperidine ring, as evidenced by the large value of the vicinal spin-spin coupling constant between one of protons at the C(5) atom and the H(6) proton (^3J = 11.8—13.2 Hz).

We believe that the ease of intramolecular [4+2]-cycloaddition of amines **1** in acetic anhydride is attributable not to the Thorpe—Ingold effect associated with the "contraction" of the endocyclic angles[30] but to flattening of the amide fragment in the initially formed *N*-acyl derivative. This flattening increases ordering of the diene-dienophilic fragment of the molecule resulting in a decrease in the entropy of formation of the transition state.[31,32]

In recent studies[33—38] of intramolecular cyclization of *N*-R-*N*-allylfurfurylamines, the influence of the volume and electronic effects of the substituents R at the N atom on this process was examined. The yield of intramolecular cycloaddition adducts was found to increase substantially with increase in the volume of the substituent.

To estimate the influence of the substituent at the N atom on the formation of 6,8a-epoxyoctahydroisoquinolines **6a—e** and **7a—e**, we carried out the intramolecular cycloaddition of allylamines **1b,c** in propionic anhydride, a mixture of acetic anhydride and formic acid, chloroacetyl chloride, benzoyl chloride, and boiling xylene in the presence of an excess of trifluoroacetic anhydride (see the Experimental section). *N*-Acyl-substituted tricyclic compounds **6a—e** and **7a—e** were prepared in yields from 40 to 60% (Scheme 3).

Scheme 3



1b,c **6a—e**, **7a—e**

6, 7: R = H (**a**), Et (**b**), CH_2Cl (**c**), Ph (**d**), CF_3 (**e**)

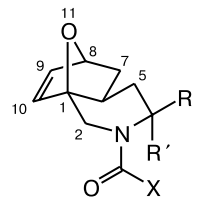
n = 1 (**1b**, **6a—e**), 2 (**1c**, **7a—e**)

Table 1. ^{13}C NMR spectra of compounds **1f**, **2f**, and **3f** ($CDCl_3$)[a]

Compound	δ ($^1J_{C,H}$/Hz)														
	C(1)	C(2)	C(4)	C(5)	Δ[b]	C(6)	C(7)	C(8)	C(9)	C(10)	C(2′)	C(6′)	C(3′)	C(5′)	C(4′)
1f$_{min}$	154.6	38.9 (134.5)	54.0	35.9 (~125)	8.3	133.9 (151.5)	117.8 (154.0, 157.0)	141.4 (201.5)	110.0 (174.0)	106.0 (174.0)	36.0 (125.5)		23.1 (~125)		47.7 (~125)
1f$_{maj}$	155.1	38.3 (134.0)	53.1	44.2 (125.0)		134.4 (151.5)	117.2 (154.0, 157.0)	141.2 (201.5)	110.0 (174.5)	105.7 (174.0)	35.1 (125.5)		21.8 (126.0)		47.9 (122.5)
2f$_{min}$	83.9	42.6 (132.5, 136.5)	51.0	37.5 (126.0)	8.1	30.1 (135.0)	35.0 (135.0)	78.4 (162.7)	137.3 (173.0)	135.7 (171.0)	41.3 (124.0)	30.9 (125.0)	22.9 (126.0)	22.6 (124.0)	48.0 (123.5)
2f$_{maj}$	83.9	42.4 (134.0)	50.2	45.6 (126.0)		30.4 (135.0)	35.0 (134.0)	78.5 (162.5)	137.3 (173.0)	135.9 (172.0)	41.0 (124.5)	29.6 (124.0)	22.0 (125.0)	21.7 (126.0)	48.6 (123.0)
3f$_{min}$	86.5	45.3 (138.0)	61.5	34.7 (128.0)	5.4	32.6 (134.5)	31.2 (135.0)	77.9 (162.5)	136.1 (~174)	136.1 (~174)	33.0 (128.5)	28.4 (128.5)	23.9 (126.0)	23.1 (126.0)	46.5 (126.0)
3f$_{maj}$	85.1	45.4 (137.0)	59.4	40.1 (129.0)		31.4 (135.0)	33.8 (135.0)	78.5 (163.5)	137.9 (174.0)	134.7 (172.0)	37.3 (125.0, 135.0)	34.0 (125.5)	22.9 (127.0)	21.7 (127.0)	47.4 (124.5)

[a] The chemical shifts of the C atoms of the 4′-*tert*-butyl and acetyl groups (δ, *J*/Hz): **1f$_{min}$**, 27.5 (C_3H_9, *J* = 124.5), 32.2 (C_{quat}); **1f$_{maj}$**, 27.5 (C_3H_9, *J* = 124.5), 32.3 (C_{quat}); **2f$_{min}$**, 27.4 (C_3H_9, *J* = 124.5), 32.1 (C_{quat}); **2f$_{maj}$**, 27.5 (C_3H_9, *J* = 124.5), 32.3 (C_{quat}); **3f$_{min}$**, 25.8 (CH_3, *J* = 128.0), 27.3 (C_3H_9, *J* = 124.5), 32.0 (C_{quat}), 171.0 (CO); **3f$_{maj}$**, 25.4 (CH_3, *J* = 128.0), 27.2 (C_3H_9, *J* = 124.5), 32.2 (C_{quat}), 173.2 (CO).
[b] The difference in the chemical shifts of the axial and equatorial C(5) atoms in the pairs of the corresponding isomers.

Table 2. Chemical shifts (δ) of the protons in the ^{1}H NMR spectra of *N*-substituted epoxyoctahydroisoquinolines **3a—j**, **6a—e**, and **7a—e** ($CDCl_3$)



Compound	δ											
	H(2A)	H(2B)	H(5_{ax})	H(5_{eq})	H(6)	H(7_{ax})	H(7_{eq})	H(8)	H(9)	H(10)	X	R, R′
3a	4.03 (d)	3.94 (d)	1.42—1.79, 1.95—2.22 (both m)					4.91 (dd)	6.36 (dd)	6.09 (d)	2.10 (s, Me)	1.79—1.42, 2.22—1.95 (both m, 8 H, *cyclo*-C_5H_8)
3b	3.92 (d)	3.75 (d)	1.46 (dd)	1.86 (dd)	1.72 (m)	1.47 (dd)	1.38 (m)	4.86 (dd)	6.30 (dd)	6.12 (d)	2.11 (s, Me)	1.25, 2.64 (both m, 2 H, H(2)′); 1.35—1.50 (m, 6 H, H(3′), H(4′), H(5′)); 1.40, 2.84 (both m, 2 H, H(6′))
3c	4.04 (d)	3.47 (d)	*	1.96 (dd)	*	*	1.41 (dt)	4.90 (d)	6.32 (s)		2.14 (s, Me)	1.20—2.00, 2.57 (both m, 15 H, *cyclo*-C_7H_{12}, H(5_{ax}), H(6), H(7_{ax}))
3d	4.02 (d)	3.90 (d)	*	1.71 (br.d)	*	*	*	4.94 (dd)	6.39 (dd)	6.10 (d)	2.17 (s, Me)	1.83—1.90, 2.30—2.60 (both m, 4 H and 7 H each, H(5_{ax}), H(6), 2 H(7), piperidine); 2.26 (s, 3 H, NMe); 3.17 (m, 1 H, H(3′))
3e	4.04 (d)	3.89 (d)	*	*	3.21 (m)	*	1.43 (dt)	4.93 (br.d)	6.38 (dd)	6.08 (d)	2.16 (s, Me)	1.08 (t, 3 H, $C\underline{H}_3CH_2$); 1.35—1.90, 2.20—2.65 (m, 11 H, piperidine, 2 H(5), H(7_{ax}); 2.38 (q, 2 H, $C\underline{H}_2CH_3$)
3f$_{maj}$	4.05 (d)	3.78 (d)	1.72 (q)	1.45 (q)	1.84 (m)	1.36 (m)	1.42 (dd)	4.86 (dd)	6.32 (dd)	5.99 (d)	2.09 (s, Me)	0.77 (s, 9 H, Bu^t); 0.96, 2.35 (both m, 1 H each, C(6′)H_2); 1.01, 1.56 (both m, 1 H each, C(3′)H_2); 1.03 (m, 1 H, H(4′)); 1.03, 3.38 (both m, 1 H each, C(2′)H_2); 1.09, 1.54 (both m, 1 H each, C(5′)H_2)
3f$_{min}$	4.04 (d)	3.46 (d)	1.19 (m)	2.16 (q)	1.58 (m)	1.37 (m)	1.50 (dd)	4.85 (dd)	6.26 (dd)	6.28 (d)	2.11 (s, Me)	0.79 (s, 9 H, Bu^t); 1.12 (m, 1 H, H(4′)); 1.02, 1.61 (both m, 1 H each, C(3′)H_2); 1.11, 1.60 (both m, 1 H each, C(5′)H_2); 1.79, 2.34 (both m, 1 H each, C(6′)H_2); 1.60, 2.92 (both m, 1 H each, C(2′)H_2)
3g	5.01 (br.s)	3.35 (br.d)	1.35—1.80, 2.20—2.40 (both m)					4.87 (dd)	6.28 (br.d)	6.41 (d)	2.04 (s, 3 H)	~5.03 (br.s, 1 H, H(4)); 7.15—7.35 (m, Ph)

3h	4.39 (br.d)	3.67 (br.d)	1.25—1.50, 1.60—1.80, 1.90—2.05 (all m)					4.88 (br.d)	6.29 (dd)	6.24 (d)	2.04 (br.s, Me)	1.86 (s, Me); 7.15—7.35 (m, Ph)
3i	4.41 (br.s)	3.88 (d)	1.40, 1.58, 1.95—1.85 (all m)					4.91 (d)	6.36 (s, 2 H)		1.96 (s, Me)	2.15 (br.s, Me); 7.14 (t, H_o); 7.29—7.33, 7.50—7.60 (both m, Ar)
3j	4.39 (br.d)	4.11 (br.d)	2.37 (dd)	2.64 (dd)	1.40—1.50, 1.50—1.70 (both m)			4.93 (br.s)	6.32 (dd)	6.00 (d)	2.15 (br.s, Me)	7.05—7.50 (m, Ph)
6a	5.00 (d)	3.43 (d)	1.32 (dd)	2.11 (dd)	*	1.53 (dd)	1.41 (ddd)	4.93 (dd)	6.39 (dd)	6.07 (d)	8.44 (s, H)	1.86—1.98 (m, 11 H, *cyclo*-C_6H_{10}, H(6))
6b	3.98 (d)	3.81 (d)	*	1.93 (dd)	1.20—1.95 (m)			4.91 (dd)	6.34 (dd)	6.20 (d)	1.12 (t, $C\underline{H}_3CH_2$); 2.44 (m, $C\underline{H}_2CH_3$)	2.73, 2.92 (both m, 1 H each, *cyclo*-C_6H_{10}); 1.30, 1.40—1.54, 1.76 (all m, 12 H each, *cyclo*-C_6H_{10}, $H(5_{ax})$, H(6), 2 H(7))
6c	4.01 (d)	3.89 (d)	1.20—1.95 (m)					4.92 (dd)	6.37 (dd)	6.20 (d)	4.02, 4.31 (d, CH_2Cl)	1.20—1.95 (both m, 8 H, *cyclo*-C_6H_{10}); 2.97, 2.56 (both m, 1 H each, *cyclo*-C_6H_{10})
6d	3.94 (d)	3.85 (d)	1.25—1.75, 1.75—1.95 (both m)					4.89 (dd)	6.29 (dd)	5.99 (d)	7.40—7.52 (m, Ph)	1.75—1.95, 1.25—1.75 (both m, 8 H, *cyclo*-C_6H_{10}); 2.54, 3.19 (both m, 1 H each, *cyclo*-C_7H_{12})
6e	4.15 (d)	3.68 (d)	*	2.15 (dd)	*	*	*	4.93 (dd)	6.35 (dd)	6.27 (d)	—	1.35—1.80 (m, 11 H, *cyclo*-C_6H_{10}, $H(5_{ax})$, H(6), 2 H(7)); 2.70 (m, 2 H, *cyclo*-C_6H_{10})
7a	4.74 (d)	3.54 (d)	1.30—2.30 (m)					4.92 (dd)	7.38 (dd)	6.09 (d)	8.47 (s, H)	1.30—2.30 (m, 12 H, *cyclo*-C_7H_{12})
7b	4.06 (d)	3.46 (d)	1.90—2.00, 2.50—2.70 (both m)					4.88 (d)	6.30 (s)		1.14 (t, $C\underline{H}_3CH_2$) 2.30—2.50 (m, $C\underline{H}_2CH_3$)	1.25—1.90, 2.50—2.70 (both m, 12 H, *cyclo*-C_7H_{12})
7c	4.07 (d)	3.57 (d)	*	1.98 (dd)	*	*	1.42 (ddd)	4.91 (dd)	6.32 (dd)	6.41 (d)	4.03, 4.19 (d, CH_2Cl)	2.49, 2.63 (both m, 1 H each, *cyclo*-C_7H_{12}); 1.20—1.95 (m, 13 H, *cyclo*-C_7H_{12}, $H(5_{ax})$, H(6), $H(7_{eq})$)
7d	3.91 (d)	3.62 (d)	*	1.99 (dd)	*	*	*	4.88 (dd)	6.29 (dd)	6.20 (d)	7.36—7.44 (m, Ph)	1.43—1.93 (m, 13 H, *cyclo*-C_7H_{12}, $H(5_{ax})$, H(6), 2 H(7)); 2.60, 2.83 (both m, 1 H each, *cyclo*-C_7H_{12})
7e	4.25 (dq)	3.42 (d)	*	*	2.06 (dd)	*	*	4.91 (dd)	6.30 (dd)	6.37 (d)	—	1.20—2.00, 2.40—2.60 (both m, 16 H, *cyclo*-C_7H_{12}, 2 H(5), 2 H(7))

* The signals for the protons overlap with a complex multiplet of the H atoms of the cycloalkane ring.

Table 3. Spin coupling constants (J) of the protons in the ^{1}H NMR spectra of *N*-substituted epoxyoctahydroisoquinolines **3a—j**, **6a—e**, and **7a—e** ($CDCl_3$)

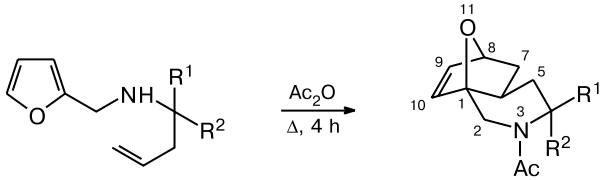
Compound	J/Hz										
	2A, 2B	5_{ax}, 5_{eq}	5_{eq}, 6	5_{ax}, 6	6, 7_{ax}	6, 7_{eq}	7_{ax}, 7_{eq}	7_{eq}, 8	8, 9	9, 10	X, R, and R´
3a	15.4	*	*	*	*	*	*	4.0	1.3	6.0	—
3b	15.4	13.5	5.1	12.5	7.6	3.4	11.3	4.5	1.7	5.8	—
3c	15.0	13.1	3.1	*	*	4.3	11.3	4.3	—	—	—
3d	15.6	*	*	*	*	*	*	4.3	1.8	5.8	—
3e	15.0	*	*	*	*	3.7	11.3	3.7	1.5	5.8	$^3J(CH_3CH_2)$ = 7.3
3f$_{maj}$	15.8	13.2	6.4	11.8	7.3	3.2	11.3	4.4	1.7	5.8	—
3f$_{min}$	15.1	13.8	3.4	13.0	7.7	3.6	11.0	4.4	1.5	5.8	—
3g	14.3	*	*	*	*	*	*	4.3	1.8	5.8	—
3h	14.7	*	*	*	*	*	*	4.3	1.5	5.8	—
3i	14.6	*	*	*	*	*	*	3.7	—	—	$^3J_{o,m} = {}^3J_{m,p}$ = 7.5
3j	15.0	14.3	4.6	12.2	*	*	*	—	1.5	5.8	—
6a	15.3	13.5	5.7	12.2	7.5	2.9	11.3	4.6	1.7	5.7	—
6b	15.3	13.4	4.9	*	*	*	*	4.5	1.2	5.5	$^3J(CH_3CH_2)$ = 7.3, $^2J(CH(A)H(B))$ = 15.3
6c	15.6	*	*	*	*	*	*	4.3	1.5	5.8	$^2J(CH_2Cl)$ = 12.8
6d	15.0	*	*	*	*	*	*	4.3	1.5	5.8	—
6e	15.6	13.4	4.0	*	*	*	*	4.3	1.2	5.8	—
7a	15.3	*	*	*	*	*	*	4.3	1.5	5.5	—
7b	15.3	*	*	*	*	*	*	4.3	—	—	$^3J(CH_3CH_2)$ = 7.3, $^2J(CH(A)H(B))$ = 16.5
7c	15.2	13.1	3.4			4.0	11.3	4.3	1.5	5.5	$^2J(CH_2Cl)$ = 12.2
7d	15.1	13.3	4.0	*	*	*	*	4.4	1.6	5.8	—
7e	15.3	13.1	*	*	*	2.4	*	4.3	1.2	6.1	$^5J(H(2A)CF_3)$ = 1.2

* Spin coupling constants were not measured due to overlap of the signals for the corresponding protons with the signals for the protons of the cycloalkane substituent.

The results of our study did not allow us to make an unambiguous conclusion about the influence of the substituents R on the cyclization process. The size of the annelated ring also has no substantial effect. It should only be noted that the yields of the corresponding *N*-acyl derivatives **3b** and **3c** were somewhat higher (~70%) than those of analogs containing other substituents R. The presence of electron-withdrawing groups at the N atom (R = CH_2Cl or CF_3) allows the cyclization temperature to be lowered.

Homoallylamines **1g—j**, which were prepared from acyclic aldehydes and ketones according to an analogous procedure, also undergo stereoselective cyclization in boiling acetic anhydride to form *exo*-adducts **3g—j** ($J_{7\text{-}exo,6\text{-}endo}$ = 3.4—4.0 Hz). Compounds **3g—j** were prepared in 34—70% yields (Scheme 4).

Scheme 4



1g—j **3g—j**

1, **3**	**g**	**h**	**i**	**j**
R^1	Ph	Ph	*p*-PhC_6H_4	Ph
R^2	H	Me	Me	Ph

According to the ^{1}H NMR spectroscopic data, tricyclic compounds **3h** and **3i** bearing different substituents R^1 and R^2 were prepared as the only geometrical isomer as regards the arrangement of the substituents relative to the epoxide bridge. Unfortunately, the ^{1}H NMR NOE experiments for octahydroisoquinolines **3h,i** did not allow us to unambiguously determine the orientations of the substituents at the C(4) atom. The interpretation of the ^{1}H NMR spectra of compound **3g** is complicated by a substantial broadening of the signals for the H(2) and H(4) protons due to hindered rotation of the acetyl group about the amide bond (CO—N). The nature of the solvent ($CDCl_3$, DMSO-d_6, CD_3OH, and C_6D_6) and heating of a sample in an NMR tube to 65 °C had no effect on the resolution of these signals. Therefore, we failed to measure the spin coupling constant $J_{4,5}$ and determine the orientation of the H(4) proton in the piperidine ring of amide **3g** (see Tables 2 and 3).

In conclusion, it should be noted that the reaction mixtures prepared by cyclization of all homoallylamines **1** in acetic anhydride contained impurities of acyclic

N-acetyl-substituted derivatives (results of TLC and ^{1}H NMR spectroscopy of crude reaction mixtures), which indicates that cycloaddition is reversible.

To summarize, we developed a new one-step preparative procedure for the synthesis of hydrogenated 6,8a-epoxyisoquinolines based on the intramolecular Diels—Alder reaction of readily accessible 4-(*N*-furfuryl)aminobut-1-enes. We made an attempt to estimate the influence of substituents in the starting furfurylalkenes on the rate of [4+2]-cycloaddition and demonstrated that the cyclizing agent has no effect on the yields of the target products.

Experimental

The reagents were purchased from Acros Organics. The IR spectra were recorded on UR-20 and Specord IR-75 spectrometers in KBr pellets (for crystalline compounds) or in a film (for oils). The mass spectra were obtained on Finnigan MAT95XL and Hewlett—Packard MS-5988 mass spectrometers with direct inlet of the sample into the ion source; the ionizing energy was 70 eV. The ^{1}H and ^{13}C NMR spectra were measured on Bruker WP-200 (200 MHz) and Varian Unity+400 (400 MHz for ^{1}H and 100.6 MHz for ^{13}C) instruments in $CDCl_3$, C_6H_6, or DMSO-d_6 at 23 °C. The ^{1}H NMR spectroscopic data for homoallylamines **1a—j** and **4a,b** are given in Tables 4 and 5. The chemical shifts were measured in the δ scale with Me_4Si as the internal standard. The AB systems in the ^{1}H NMR spectra are marked with asterisks. Thin-layer chromatography was carried out with the use of Silufol plates (visualization with iodine vapor). The yields, physicochemical characteristics, results of elemental analysis, and selected spectroscopic data for homoallylamines **1a—j** and **4a,b** and epoxyoctahydroisoquinolines **3a—j**, **6a—e**, and **7a—e** are given in Tables 6 and 7.

1-Allyl-1-*N*-furfurylaminocyclopentane (1a), -cyclohexane (1b), -cycloheptane (1c), 1-allyl-4-*tert*-butyl-1-*N*-furfurylaminocyclohexane (1f), 4-allyl-4-*N*-furfurylamino-1-methylpiperidine (1d), 4-allyl-1-ethyl-4-*N*-furfurylaminopiperidine (1e), 4-*N*-furfurylamino-4-phenylbut-1-ene (1g), 4-*N*-furfurylamino-4,4-diphenylbut-1-ene (1j), 4-*N*-furfurylamino-4-phenylpent-1-ene (1h), 4-*N*-furfurylamino-4-(biphenyl-4-yl)pent-1-ene (1i), 1-*N*-furfurylamino-1-methallylcyclohexane (4a), and 1-*N*-furfurylamino-1-methallylcycloheptane (4b) (general procedure). A solution of freshly distilled furfurylamine (0.2 mol) and the corresponding aldehyde or ketone (0.2 mol) in benzene (70 mL) was refluxed using a Dean—Stark trap for 1—4 h until the theoretical amount of water (~3.6 mL) was collected. If the separation of water proceeded slowly, several drops of glacial acetic acid were added. The solvent was removed under reduced pressure. Azomethines were used in the subsequent step without additional workup.

Freshly prepared azomethine was added under gentle reflux to a solution of allylmagnesium bromide (methallylmagnesium chloride for compounds **4a,b**), which was prepared from allyl bromide (methallyl chloride) (0.3 mol) and magnesium (0.6 mol), in anhydrous diethyl ether (a 1 : 1 THF—diethyl ether mixture for compounds **4a,b**) (200 mL). The reaction mixture was stirred at 25 °C for 1 h, cooled to 0 °C, and poured onto ice (100 mL). The resulting emulsion was destroyed by adding a saturated solution of ammonium chloride. The products were extracted with diethyl ether (3×100 mL), the extract was dried with $MgSO_4$, the solvent was distilled off, and the residue was fractionated *in vacuo*. Homoallylamines **1a—j** (in a mixture with epoxy derivatives **2a—j**) and **4a,b** were obtained as labile pale-yellow oils. The chromatographic mobilities of amines **1a—j** and **4a,b** were measured in a 1 : 3 ethyl acetate—hexane system.

After vacuum distillation of allylamine **1d**, the distillate partially crystallized. The crystals were filtered off, washed with cold hexane, and twice recrystallized from hexane. **1′-Methyl-6,8a-epoxyspiro[1,2,3,4,4a,5,6,8a-octahydroisoquinoline-3,4′-piperidine] (2d)** was obtained in 5% yield, m.p. 110—111 °C, R_f 0.16. Found (%): C, 71.58; H, 9.42; N, 11.90. $C_{14}H_{22}N_2O$. Calculated (%): C, 71.76; H, 9.46; N, 11.95. IR, ν/cm^{-1}: 1638 (C=C). ^{1}H NMR, δ: 1.05—2.05 (m, 10 H); 2.29 (s, 3 H, N(1′)Me); 2.35—2.50 (m, 4 H, H(3′) and H(5′)); 3.37 (s, 2 H, H(2)); 4.92 (dd, 1 H, H(8), J = 4.6 Hz, J = 1.7 Hz); 5.96 (d, 1 H, H(10), J = 5.5 Hz); 6.38 (dd, 1 H, H(9), J = 5.5 Hz, J = 1.7 Hz). MS, m/z (I_{rel} (%)): 234 [M]$^+$ (23), 205 (3), 176 (20), 163 (13), 138 (37), 122 (11), 111 (22), 110 (16), 109 (26), 96 (100), 81 (89), 70 (38), 53 (32).

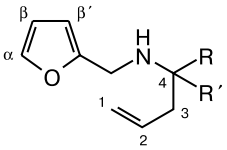
Vacuum distillation of **1f** afforded a mixture of isomers of allylamine **1f** and isoquinoline **2f**. According to the ^{1}H NMR spectroscopic data, the ratio of isomers $\mathbf{1f_{maj}}$ and $\mathbf{1f_{min}}$ was ~55 : 45, the **1f** : **2f** ratio being 4 : 1. The total yield was 65%, b.p. 154—160 °C (1 Torr). The resulting mixture was chromatographed on Al_2O_3 (15×1.5 cm) using a 1 : 100 ethyl acetate—hexane mixture as the eluent. Allylamines $\mathbf{1f_{maj}}$ and $\mathbf{1f_{min}}$ were isolated as pale-yellow oils.

4′-*tert*-Butyl-6,8-epoxyspiro[(1,2,3,4,4a,5,6,8a-octahydro)isoquinoline-1,3′-cyclohexanes] $\mathbf{2f_{maj}}$ and $\mathbf{2f_{min}}$ were prepared as colorless crystals.

Isoquinoline $\mathbf{2f_{maj}}$, the yield was 7%, m.p. 99—102.5 °C, R_f 0.29. Found (%): C, 78.72; H, 10.70; N, 5.21. $C_{18}H_{29}NO$. Calculated (%): C, 78.49; H, 10.61; N, 5.09. IR, ν/cm^{-1}: 1598 (C=C); 3295 (NH). ^{1}H NMR, δ: 0.82 (s, 9 H, Bu^t); 0.90 (m, 1 H, H(4′)); 0.90 and 2.20 (both m, 1 H each, 2 H(2′)); 1.16 (q, 1 H, H(5B), J = 13.2 Hz, J = 12.2 Hz); 1.20 and 1.48 (both m, 1 H each, 2 H(5′)); 1.26 and 1.36 (both m, 1 H each, 2 H(6′)); 1.35 (ddd, 1 H, H(7B), J = 11.2 Hz, J = 4.7 Hz, J = 2.7 Hz); 1.35 and 1.44 (both m, 1 H each, 2 H(3′)); 1.47 (q, 1 H, H(7A), J = 11.2 Hz, J = 7.5 Hz, $J \approx 0$ Hz); 1.53 (q, 1 H, H(5A), J = 13.2 Hz, J = 6.1 Hz); 1.74 (dddd, 1 H, H(6), J = 12.2 Hz, J = 7.5 Hz, J = 6.1 Hz, J = 2.7 Hz); 3.29* (1 H, H(2B), J = 15.2 Hz); 3.31* (1 H, H(2A), J = 15.2 Hz); 4.88 (q, 1 H, H(8), J = 4.6 Hz, J = 1.8 Hz); 5.93 (d, 1 H, H(10), J = 5.8 Hz); 6.32 (q, 1 H, H(9), J = 5.8 Hz, J = 1.8 Hz). MS, m/z (I_{rel} (%)): 275 [M]$^+$ (6), 266 (2), 234 (6), 176 (45), 163 (6), 154 (15), 122 (8), 91 (9), 80 (12), 81 (100), 79 (10), 77 (9), 67 (7), 57 (47), 53 (22), 43 (10), 41 (53), 39 (12).

Isoquinoline $\mathbf{2f_{min}}$, the yield was 3%, m.p. 127—129 °C, R_f 0.10. Found (%): C, 78.56; H, 10.60; N, 5.11. $C_{18}H_{29}NO$. Calculated (%): C, 78.49; H, 10.61; N, 5.09. IR, ν/cm^{-1}: 1610 (C=C); 3320 (NH). ^{1}H NMR, δ: 0.78 (s, 9 H, Bu^t); 0.82 (ddd, 1 H, H(5B), J = 13.5 Hz, J = 12.3 Hz, J = 1.5 Hz); 0.92 and 1.56 (both m, 1 H each, 2 H(3′)); 0.93 (m, 1 H, H(4′)); 1.00 and 2.15 (both m, 1 H each, 2 H(2′)); 1.06 and 1.50 (both m, 1 H each, 2 H(5′)); 1.28 and 1.32 (both m, 1 H each, 2 H(6′)); 1.35 (ddd, 1 H, H(7B), J = 11.2 Hz, J = 4.6 Hz, J = 2.7 Hz); 1.46 (q, 1 H, H(7A), J = 11.2 Hz, J = 7.6 Hz, $J \approx 0$ Hz); 1.62 (m, 1 H, H(6)); 2.16 (q, 1 H, H(5A), J = 13.5 Hz, J = 5.8 Hz); 3.25 (d, 1 H,

Table 4. Chemical shifts (δ) of the protons in the ^{1}H NMR spectra of solutions of homoallylamines **1a—j** and **4a,b** ($CDCl_3$)



Compound	δ									
	$H(1)_{cis}$	$H(1)_{trans}$	H(2)	H(3)	NCH_2	Furan H			NH	R and R′
						α	β	β′		
1a	5.09 (dd)	5.05 (dd)	5.82 (m)	2.26 (d)	3.66 (s)	7.29 (dd)	6.24 (dd)	6.10 (d)	1.73 (br.s)	1.25—1.75 (m, 8 H, *cyclo*-C_5H_8)
1b	5.10 (dd)	5.08 (dd)	5.86 (m)	2.21 (d)	3.68 (s)	7.33 (dd)	6.29 (dd)	6.15 (dd)	—	1.25—1.70 (m, 10 H, *cyclo*-C_6H_{10})
1c	5.09 (m)	5.07 (m)	5.85 (m)	2.20 (dt)	3.68 (s)	7.32 (dd)	6.28 (dd)	6.14 (dd)	—	1.25—1.95 (m, 12 H, *cyclo*-C_7H_{12})
1d	5.13 (m)	5.09 (m)	5.85 (m)	2.22 (d)	3.68 (s)	7.34 (dd)	6.30 (dd)	6.17 (m)	1.19 (br.s)	1.56—1.67 (m, 4 H, C(3′)H_2); 2.28 (m, 4 H, C(2′)H_2); 2.35—2.48 (s, 3 H, NMe)
1e	5.11 (m)	5.09 (m)	5.85 (m)	2.22 (d)	3.68 (s)	7.34 (dd)	6.29 (dd)	6.15 (dd)	—	1.08 (t, 3 H, $NCH_2C\underline{H}_3$); 1.61 (m, 4 H, C(3′)H_2); 2.30—2.60 (m, 4 H, C(2′)H_2); 2.41 (q, 2 H, $NC\underline{H}_2CH_3$)
1f$_{maj}$	5.07 (m)	5.04 (m)	5.86 (m)	2.12 (d)	3.63 (s)	7.32 (d)	6.28 (dd)	6.15 (d)	—	0.84 (s, 9 H, Bu^t); 0.90 (m, 1 H, H(4′)); 1.23, 1.50 (both m, 2 H each, C(3′)H_2, C(5′)H_2); 1.23, 1.75 (both m, 2 H each, C(2′)H_2, C(6′)H_2)
1f$_{min}$	5.11 (m)	5.10 (m)	5.81 (m)	2.28 (d)	3.73 (s)	7.31 (d)	6.26 (dd)	6.12 (d)	—	0.84 (s, 9 H, Bu^t); 0.98 (m, 1 H, H(4′)); 1.12, 1.62 (both m, 2 H each, C(3′)H_2, C(5′)H_2); 1.30, 1.73 (both m, 2 H each, C(2′)H_2, C(6′)H_2)
1g	5.04 (m)	5.06 (m)	5.68 (m)	2.40 (m)	3.67, 3.51 (both d)	7.33 (d)	6.28 (dd)	6.06 (d)	1.85 (s)	7.35—7.20 (m, 5 H, Ph); 3.66 (t, H)
1h	5.04 (dd)	5.06 (dd)	5.65 (m)	2.50 (d)	3.58, 3.45 (both d)	7.32 (d)	6.27 (dd)	6.11 (d)	1.70 (br.s)	1.50 (s, Me); 7.40—7.60 (m, 5 H, Ph)
1i	5.08 (dd)	5.10 (br.d)	5.68 (ddt)	2.54 (m)	3.60, 3.49 (both d)	7.33 (d)	6.28 (dd)	6.13 (d)	1.81 (s)	1.53 (s, Me); 7.42 (t, 1 H, H_o); 7.52—7.61 (m, 8 H, *p*-PhC_6H_4)
1j	5.02 (m)	5.00 (m)	5.53 (m)	3.09 (d)	3.44 (s)	7.29 (d)	6.26 (dd)	6.11 (d)	1.85 (br.s)	7.05—7.45 (m, 10 H, 2 Ph)
4a	4.90 (m)	4.70 (m)	1.84 (br.s, Me)	2.17 (br.s)	3.69 (s)	7.33 (dd)	6.29 (dd)	6.15 (dd)	—	1.20—1.70 (m, 10 H, *cyclo*-C_6H_{10})
4b	4.90 (m)	4.71 (m)	1.84 (br.s, Me)	2.18 (br.s)	3.72 (s)	7.32 (dd)	6.29 (dd)	6.15 (dd)	—	1.35—1.70 (m, 12 H, *cyclo*-C_7H_{12})

H(2B), J = 15.2 Hz); 3.43 (d, 1 H, H(2A), J = 15.2 Hz); 4.84 (q, 1 H, H(8), J = 4.6 Hz, J = 1.7 Hz); 5.90 (d, 1 H, H(10), J = 5.8 Hz); 6.30 (q, 1 H, H(9), J = 5.8 Hz, J = 1.7 Hz). MS, m/z (I_{rel} (%)): 275 $[M]^+$ (8), 266 (4), 176 (18), 154 (19), 122 (8), 91 (11), 80 (12), 81 (100), 79 (8), 77 (9), 67 (7), 57 (39), 53 (17), 43 (10), 41 (60), 39 (13).

3-Acetylspiro[3-aza-11-oxatricyclo[6.2.1.0^{1,6}]undec-9-ene-4,1′-cyclopentane] (3a), -cyclohexane] (3b), -cycloheptane] (3c), -4′-methylpiperidine] (3d), -4′-ethylpiperidine] (3e), -4′-*tert*-butylcyclohexane] (3f); 3-acetyl-3-aza-11-oxatricyclo[6.2.1.0^{1,6}]undec-9-ene-[4-phenyl] (3g), -4,4-diphenyl] (3j), -4-methyl-4-phenyl] (3h), -4-(biphenyl-4-yl)-4-methyl-4] (3i) (general procedure). Homoallylamine **1a—j** or **4a,b** (0.1 mol) was refluxed in a 20-fold molar excess of acetic anhydride for 3—6 h (TLC control). An excess of the anhydride was distilled off under reduced pressure, the residue was poured into water (200 mL), and $NaHCO_3$ was added to pH 9—10. The reaction mixture was extracted with ethyl acetate (3×70 mL) and the extract was dried with $MgSO_4$. After removal of the solvent, the residue was recrystallized from a hexane—ethyl acetate mixture. Tricyclic compounds **3a—j** were prepared as colorless crystals. *N*-Acyl derivatives **5a,b**, which were obtained as pale-yellow oils, were purified by chromatography on Al_2O_3 (hexane as the eluent).

Table 5. Spin-spin coupling constants (J) of protons in the ^{1}H NMR spectra of solutions of homoallylamines **1a—j** and **4a,b** ($CDCl_3$)

Compound	J/Hz									
	$J_{1,1}$	$J_{1cis,2}$	$J_{1trans,2}$	$J_{2,3}$	$J_{3A,4}$	$J_{NCH(A)H(B)}$	J of furan H atoms			Other J
							α,β	α,β´	β,β´	
1a	1.3	10.4	17.1	7.4	—	—	2.1	0.5	3.4	—
1b	2.4	11.0	16.5	7.3	—	—	1.8	0.6	3.1	—
1c	≈2.4	≈11.0	≈16.2	7.3	—	—	1.8	0.9	3.4	$J_{1´,3´cis} = J_{1´,3´trans} = 1.0$
1d	1.3	10.2	16.9	7.4	—	—	1.8	0.8	3.2	—
1e	2.4	10.7	16.5	7.3	—	—	1.8	0.9	3.1	$^3J(CH_3CH_2) = 7.0$
1f$_{maj}$	2.4	10.3	17.0	7.4	—	—	1.9	0.9	3.2	—
1f$_{min}$	2.3	10.5	16.8	7.4	—	—	1.9	0.9	3.2	—
1g	2.1	9.8	16.8	6.4	7.0	14.7	1.8	—	3.1	—
1h	2.1	10.4	16.8	7.6	—	13.7	1.8	—	3.1	—
1i	1.8	10.2	17.4	7.4	—	13.6	1.8	—	3.0	$J_{o,m} = J_{m,p} = 7.6$
1j	2.1	≈10.1	≈17.4	7.0	—	*	1.5	—	3.1	—
4a	1.7	3.3		—	—	—	1.8	0.9	3.4	—
4b	1.7	3.1		—	—	—	1.8	0.9	3.1	—

* Spin coupling constants were not measured.

Table 6. Yields and physicochemical characteristics of homoallylamines **1a—j** and **4a,b**

Compound	Yield (%)	M.p. /°C (p/Torr)	R_f	Molecular weight		Found / Calculated (%)			Molecular formula	IR, ν/cm^{-1}	
				Found, $[M]^+$	Calculated	C	H	N		C=C	NH
1a	62	133—138 (8.0)	0.50[a]	205	205	76.09 / 76.06	9.30 / 9.33	6.83 / 6.82	$C_{13}H_{19}NO$	1614	3327
1b	71	127—129 (2.0)	0.63[b]	219	219	76.70 / 76.67	9.58 / 9.65	6.35 / 6.39	$C_{14}H_{21}NO$	1632	3335
1c	67	154—157 (7.0)	0.65[b]	233	233	77.23 / 77.21	9.90 / 9.93	6.00 / 6.00	$C_{15}H_{23}NO$	1640	3340
1d	45	130—134 (2.0)	0.23[c]	234	234	71.81 / 71.76	9.37 / 9.46	11.96 / 11.95	$C_{14}H_{22}N_2O$	1630	3325
1e	61	127—136 (3.0)	0.32[d]	248	248	72.60 / 72.54	9.69 / 9.74	11.30 / 11.28	$C_{15}H_{24}N_2O$	1638	3332
1f$_{maj}$	25	154—160 (1.0)	0.54[a]	275	275	78.67 / 78.49	10.61 / 10.61	5.00 / 5.09	$C_{18}H_{29}NO$	1633	3340
	42										
1f$_{min}$	17		0.43[a]	275	275	78.49 / 78.49	10.52 / 10.61	5.11 / 5.09	$C_{18}H_{29}NO$	1635	3330
1g	72	118—120 (2.0)	0.47[a]	186 $[M - 41]^+$	227	79.30 / 79.26	7.45 / 7.54	6.17 / 6.16	$C_{15}H_{17}NO$	1645	3342
1h	55	157—159 (3.0)	0.48[a]	241	241	79.39 / 79.63	7.89 / 7.94	5.75 / 5.80	$C_{16}H_{19}NO$	1642	3320
1i	46	176—180 (4.0)	0.60[b]	317	317	83.12 / 83.24	7.25 / 7.30	4.37 / 4.41	$C_{22}H_{23}NO$	1636	3338
1j	28	167—171 (2.0)	0.62[a]	303	303	83.08 / 83.13	6.94 / 6.98	4.59 / 4.62	$C_{21}H_{21}NO$	1653	3320
4a	63	116—117.5 (1.0)	0.67[a]	218 $[M - 15]^+$	233	77.00 / 77.21	9.85 / 9.93	6.03 / 6.00	$C_{15}H_{23}NO$	1645	3347
4b	62	136—138 (1.5)	0.55[a]	232 $[M - 15]^+$	247	77.56 / 77.68	10.00 / 10.19	5.72 / 5.66	$C_{16}H_{25}NO$	1627	3367

[a] Ethyl acetate—hexane (1 : 3).
[b] Ethyl acetate—hexane (1 : 2).
[c] Pr^iOH—NH_4OH (25%) (1 : 1).
[d] Ethyl acetate.

Table 7. Yields and physicochemical characteristics of epoxyoctahydroisoquinolines **3a—j**, **6a—e**, and **7a—e**

Compound	Yield (%)	M.p.[a] /°C	R_f	Molecular weight	Found / Calculated (%)			Molecular formula	IR, ν/cm^{-1}	
					C	H	N		C=C	NCO
3a	48	88—89	0.28[b]	247	72.62 72.84	8.34 8.56	5.81 5.66	$C_{15}H_{21}NO_2$	1630	
3b	71	134—135	0.62[c]	261	73.36 73.53	8.79 8.87	5.24 5.36	$C_{16}H_{23}NO_2$	1630	
3c	68	135—136	0.26[b]	275	74.27 74.14	9.15 9.15	5.26 5.09	$C_{17}H_{25}NO_2$	1623	
3d	50	98.5—101	0.11[d]	276	69.40 69.53	8.81 8.75	10.10 10.14	$C_{16}H_{24}N_2O_2$	1650	
3e	48	113—114	0.21[c]	290	70.52 70.31	8.98 9.02	9.55 9.65	$C_{17}H_{26}N_2O_2$	1674	1729
3f$_{maj}$	27	175.5—177	0.39[e]	317	75.71 75.67	9.90 9.84	4.40 4.41	$C_{20}H_{31}NO_2$	1640	
3f$_{min}$	19	189.5—191	0.28[e]	317	75.64 75.67	9.81 9.84	4.48 4.41	$C_{20}H_{31}NO_2$	1620	
3g	34	117—118	0.47[c]	269	75.58 75.81	7.20 7.11	5.25 5.20	$C_{17}H_{19}NO_2$	1639	
3h	37	152—153	0.13[b]	283	76.48 76.29	7.59 7.47	4.75 4.94	$C_{18}H_{21}NO_2$	1646	
3i	38	151—152	0.31[f]	359	80.07 80.19	6.90 7.01	3.94 3.90	$C_{24}H_{25}NO_2$	1633	
3j	42	150.5—152	0.14[b]	345	80.11 79.97	6.49 6.71	4.00 4.05	$C_{23}H_{23}NO_2$	1640	
6a	22	Oil	0.21[g]	247	73.00 72.84	8.63 8.56	5.37 5.66	$C_{15}H_{21}NO_2$	1647	
6b	52	58—60	0.26[b]	275	74.11 74.14	9.20 9.15	5.04 5.09	$C_{17}H_{25}NO_2$	1637	
6c	40	89.5—90.5	0.50[f]	295	64.97 64.97	7.48 7. 50	4.57 4.74	$C_{16}H_{22}NO_2Cl$	1647	
6d	61	157.5—159	0.37[b]	323	78.07 77.98	7.69 7.79	4.28 4.33	$C_{21}H_{25}NO_2$	1633	
6e	40	46—47	0.53[b]	315	60.77 60.94	6.08 6.39	4.49 4.44	$C_{16}H_{20}NO_2F_3$	1685	
7a	23	107—109	0.24[c]	261	73.48 73.53	8.88 8.87	5.27 5.36	$C_{16}H_{23}NO_2$	1626	
7b	56	85.5—87	0.48[e]	289	74.83 74.70	9.35 9.40	4.90 4.84	$C_{18}H_{27}NO_2$	1648	
7c	38	121—122.5	0.44[e]	309	66.03 65.90	7.68 7.81	4.57 4.52	$C_{17}H_{24}NO_2Cl$	1653	
7d	56	173.5—175	0.42[b]	337	78.55 78.30	8.27 8.06	4.32 4.15	$C_{22}H_{27}NO_2$	1633	
7e	40	93.5—97.5	0.50[b]	329	62.11 61.99	6.80 6.73	4.01 4.25	$C_{17}H_{22}NO_2F_3$	1697	1651

[a] From an ethyl acetate—hexane mixture.
[b] Ethyl acetate—hexane (1 : 3).
[c] Ethyl acetate.
[d] EtOH—NH_4OH (25%) (5 : 1).
[e] Ethyl acetate—hexane (1 : 1).
[f] Ethyl acetate—hexane (1 : 2).
[g] Ethyl acetate—hexane (2 : 1).

Compound **3a**. MS, m/z (I_{rel} (%)): 247 $[M]^+$ (18), 206 (10), 204 (6), 164 (6), 126 (15), 122 (9), 82 (7), 81 (100), 53 (6), 43 (11), 41 (5).

Compound **3b**. MS, m/z (I_{rel} (%)): 261 $[M]^+$ (63), 246 (2), 220 (19), 218 (13), 204 (34), 176 (12), 140 (40), 122 (14), 121 (29), 98 (10), 81 (100), 80 (9), 43 (25), 40 (26).

Compound **3c**. MS, *m/z* (I_{rel} (%)): 276 (5), 275 $[M]^+$ (45), 260 (4), 234 (12), 204 (24), 176 (11), 154 (41), 135 (18), 122 (11), 112 (9), 82 (9), 81 (100), 53 (10), 43 (18), 41 (11).

Compound **3d**. MS, *m/z* (I_{rel} (%)): 276 $[M]^+$ (10), 247(3), 233 (58), 138 (40), 136 (20), 122 (13), 110 (20), 109 (25), 97 (13), 96 (100), 94 (18), 81 (62), 72 (17), 70 (30), 53 (27), 44 (22), 43 (83), 42 (46).

Compound **3e**. MS, *m/z* (I_{rel} (%)): 290 $[M]^+$ (27), 275 (10), 261 (8), 248 (14), 247 (100), 152 (42) 150 (18), 124 (14), 123 (13), 122 (21), 110 (64), 108 (14), 85 (14), 84 (25), 58 (12), 43 (17), 42 (15).

Epoxyisoquinoline **3f** was prepared as a mixture of isomers $\mathbf{3f_{maj}}$ and $\mathbf{3f_{min}}$ in a total yield of 65%. The mixture was resolved by column chromatography on Al_2O_3 (30×2 cm) using a 1 : 20 ethyl acetate—hexane system as the eluent.

Compound $\mathbf{3f_{maj}}$. MS, *m/z* (I_{rel} (%)): 317 $[M]^+$ (13), 260 (29), 218 (16), 196 (15), 177 (16), 176 (26), 140 (10), 81 (100), 57 (19), 43 (16), 41 (15).

Compound $\mathbf{3f_{min}}$. MS, *m/z* (I_{rel} (%)): 317 $[M]^+$ (18), 276 (14), 260 (19), 218 (11), 196 (26), 177 (17), 176 (15), 140 (10), 81 (100), 57 (18), 43 (14), 41 (13).

Compound **3g**. MS, *m/z* (I_{rel} (%)): 269 $[M]^+$ (16), 228 (8), 227 (26), 210 (12), 208 (15), 188 (9), 186 (8), 146 (7), 138 (33), 104 (13), 96 (46), 91 (19), 81 (100), 53 (12), 43 (21).

Compound **3h**. MS, *m/z* (I_{rel} (%)): 283 $[M]^+$ (2), 268 (1), 161 (4), 162 (6), 129 (6), 117 (7), 103 (10), 91 (20), 81 (60), 77 (22), 65 (10), 53 (17), 43 (100), 41 (13), 39 (8).

Compound **3i**. MS, *m/z* (I_{rel} (%)): 359 $[M]^+$ (16), 302 (10), 276 (5), 238 (20), 220 (14), 205 (12), 196 (22), 194 (11), 180 (15), 179 (19), 178 (18), 167 (8), 165 (18), 163 (10), 152 (16), 96 (8), 81 (100), 43 (15).

Compound **3j**. MS, *m/z* (I_{rel} (%)): 345 $[M]^+$ (25), 302 (2), 283 (3), 252 (29), 251 (20), 224 (20), 182 (34), 180 (12), 178 (16), 165 (34), 129 (16), 128 (15), 115 (12), 91 (35), 81 (100), 77 (28), 53 (23), 43 (73), 41 (10).

Compound **5a**, the yield was 69%, R_f 0.49 (ethyl acetate—hexane, 1 : 1). Found (%): C, 74.23; H, 9.11; N, 5.02. $C_{17}H_{25}NO_2$. Calculated (%): C, 74.14; H, 9.15; N, 5.09. IR, ν/cm^{-1}: 1633 (C=C and C=O). ^{1}H NMR, δ: 1.15—1.35 and 1.40—1.60 (both m, 10 H, $(CH_2)_5$); 1.74 (br.s, 3 H, C(2)Me); 2.18 (s, 3 H, C(O)Me); 2.74 (s, 2 H, H(3)); 4.44 (br.s, 2 H, NCH_2); 4.66 and 4.86 (both m, 1 H each, H(1)); 6.19 (dd, 1 H, H(γ), J = 0.9 Hz, J = 3.1 Hz); 6.33 (dd, 1 H, H(β), J = 1.8 Hz, J = 3.1 Hz); 7.35 (br.d, 1 H, H(α), J = 1.8 Hz). MS, *m/z* (I_{rel} (%)): 275 $[M]^+$ (1), 221 (5), 220 (36), 178 (14), 140 (4), 121 (5), 96 (3), 82 (7), 81 (100), 69 (3), 53 (7), 43 (6), 41 (3).

Compound **5b**, the yield was 67%, R_f 0.36 (ethyl acetate—hexane, 1 : 1). Found (%): C, 74.58; H, 9.41; N, 4.80. $C_{18}H_{27}NO_2$. Calculated (%): C, 74.70; H, 9.40; N, 4.84. IR, ν/cm^{-1}: 1627 (C=C and C=O). ^{1}H NMR, δ: 1.37—1.48 (m, 12 H, $(CH_2)_6$); 1.71 (br.s, 3 H, C(2)Me); 2.23 (s, 3 H, C(O)Me); 2.64 (s, 2 H, H(3)); 4.44 (br.s, 2 H, NCH_2); 4.62 and 4.83 (both m, 1 H each, 2 H(1)); 6.20 (dd, 1 H, H(γ), J = 0.8 Hz, J = 3.2 Hz); 6.34 (dd, 1 H, H(β), J = 1.7 Hz, J = 3.2 Hz); 7.35 (dd, 1 H, H(α), J = 1.7 Hz, J = 0.8 Hz). MS, *m/z* (I_{rel} (%)): 234 $[M - 55]^+$ (25), 192 (12), 140 (3), 135 (3), 96 (6), 95 (3), 82 (6), 81 (100), 67 (3), 55 (3), 53 (7), 43 (6), 41 (4).

3-Formylspiro[3-aza-11-oxatricyclo[6.2.1.0^{1,6}]undec-9-ene-4,1′-cyclohexane] (6a), -cycloheptane] (7a) (general procedure). Acetic anhydride (4.2 mL, 0.045 mol) was added to a solution of homoallylamines **1b,c** (0.015 mol) in HCOOH (6 mL, 0.145 mol). The reaction mixture was refluxed for 5 h, poured into water (100 mL), alkalified with sodium hydrogencarbonate to pH 9—10, and extracted with diethyl ether (3×50 mL). The organic phases were combined and dried with $MgSO_4$. After removal of the solvent, the residue was chromatographed on Al_2O_3 (20×4 cm) using a 1 : 5 ethyl acetate—hexane mixture as the eluent. Tricyclic compounds **6a** and **7a** were prepared as a brown oil and colorless crystals, respectively.

Compound **6a**. MS, *m/z* (I_{rel} (%)): 247 $[M]^+$ (12), 206 (18), 166 (8), 151 (6), 125 (28), 122 (8), 96 (8), 81 (100), 79 (10), 53 (10), 44 (64), 41 (12), 28 (20).

Compound **7a**. MS, *m/z* (I_{rel} (%)): 261 $[M]^+$ (4), 242 (2), 220 (5), 204 (2), 167 (3), 140 (10), 135 (5), 125 (15), 122 (7), 113 (4), 95 (10), 91 (5), 82 (7), 81 (100), 79 (6), 67 (8), 55 (9), 53 (13), 41 (18).

3-Propionylspiro[3-aza-11-oxatricyclo[6.2.1.0^{1,6}]undec-9-ene-4,1′-cyclohexane] (6b), -cycloheptane] (7b) (general procedure). Homoallylamine **1b,c** (0.1 mol) was refluxed in a 20-fold molar excess of propionic anhydride for 4 h. An excess of the anhydride was removed under reduced pressure, the residue was poured into water (200 mL), and the mixture was neutralized with sodium hydrogencarbonate; pH was brought to 9—10. The mixture was extracted with ethyl acetate (3×70 mL). The organic extracts were combined and dried with $MgSO_4$. After removal of the solvent, the residue was recrystallized from hexane. Tricyclic compounds **6b** and **7b** were prepared as colorless crystals.

Compound **6b**. MS, *m/z* (I_{rel} (%)): 276 (12), 275 $[M]^+$ (78), 234 (14), 219 (12), 218 (44), 178 (16), 176 (18), 154 (43), 122 (11), 121 (21), 98 (8), 81 (100), 79 (7), 57 (6), 41 (6).

Compound **7b**. MS, *m/z* (I_{rel} (%)): 290 (2), 289 $[M]^+$ (8), 260 (6), 232 (4), 218 (12), 196 (18), 183 (14), 182 (100), 181 (36), 176 (8), 168 (19), 154 (10), 112 (7), 91 (17), 81 (52), 28 (15).

3-Chloroacetylspiro[3-aza-11-oxatricyclo[6.2.1.0^{1,6}]undec-9-ene-4,1′-cyclohexane] (6c), -cycloheptane] (7c) (general procedure). Triethylamine (4 mL, 0.03 mol) was added to a solution of homoallylamine **1b,c** (0.018 mol) in acetonitrile (25 mL). Chloroacetyl chloride (2.1 mL, 0.027 mol) was added to the reaction mixture at 5 °C. The reaction mixture was stirred at ~20 °C for 4 h (TLC control), poured into water (100 mL), and extracted with diethyl ether (3×50 mL). The organic phases were combined and dried with $MgSO_4$. After removal of the solvent, the residue was chromatographed on Al_2O_3 (30×3 cm) using a 1 : 100 ethyl acetate—hexane mixture as the eluent. Tricyclic compounds **6c** and **7c** were obtained as colorless crystals.

Compound **6c**. MS, *m/z* (I_{rel} (%)): 297 (0.34), 295 $[M]^+$ (1), 261 (2), 260 (9), 256 (3), 254 (8), 174 (4), 138 (3), 122 (5), 121 (4), 91 (2), 82 (6), 81 (100), 79 (4), 67 (3), 53 (6), 41 (4).

Compound **7c**. MS, *m/z* (I_{rel} (%)): 309 $[M]^+$ (2), 274 (29), 188 (8), 135 (9), 122 (8), 95 (8), 81 (100), 77 (5), 67 (8), 55 (6), 53 (9), 41 (9).

3-Benzoylspiro[3-aza-11-oxatricyclo[6.2.1.0^{1,6}]undec-9-ene-4,1′-cyclohexane] (6d), -cycloheptane] (7d) (general procedure). Benzoyl chloride (2.62 g, 2.2 mL, 0.019 mol) was added dropwise to a solution of amines **1b,c** (0.0125 mol) and triethylamine (9.10 g, 0.09 mol) in toluene (50 mL). The reaction mixture was refluxed for 2—3 h, poured into water (200 mL), alkalified with sodium hydrogencarbonate, and extracted with ethyl acetate. The organic phase was dried with $MgSO_4$, the solvent was distilled off, and the residue (brown oil) was triturated in a hexane—diethyl ether mixture (1 : 1, v/v). The crystals

that formed were filtered off and recrystallized from a hexane—ethyl acetate mixture. Adducts **6d** and **7d** were obtained as colorless crystals.

Compound **6d**. MS, m/z (I_{rel} (%)): 323 $[M]^+$ (2), 282 (2), 266 (2), 158 (5), 144 (3), 122 (6), 106 (12), 105 (100), 91 (10), 81 (86), 79 (17), 78 (10), 77 (92), 67 (10), 53 (24), 51 (15), 41 (20), 39 (9).

Compound **7d**. MS, m/z (I_{rel} (%)): 338 (10.7), 337 $[M]^+$ (44), 296 (10), 266 (23), 232 (11), 216 (44), 158 (5), 135 (8), 122 (6), 106 (8), 105 (100), 95 (5), 81 (85), 79 (6), 77 (44), 67 (7), 53 (8), 51 (5), 41 (7).

3-Trifluoroacetylspiro[3-aza-11-oxatricyclo[6.2.1.0^{1,6}]undec-9-ene-4,1′-cyclohexane] (6e), -cycloheptane] (7e) (general procedure). Trifluoroacetic anhydride (9.8 mL, 0.07 mol) was added dropwise to a solution of homoallylamines **1b,c** (0.019 mol) in *o*-xylene (20 mL). The reaction mixture was boiled for 5 h and poured into water (100 mL); pH was brought to 9—10 by adding a 25% aqueous solution of ammonia. The mixture was extracted with diethyl ether (3×70 mL). The organic extracts were combined and dried with $MgSO_4$. After removal of the solvents, the residue was chromatographed on Al_2O_3 (25×3 cm) using hexane as the eluent. Tricyclic compounds **6e** and **7e** were obtained as colorless crystals.

Compound **6e**. MS, m/z (I_{rel} (%)): 315 $[M]^+$ (3), 275 (2), 274 (13), 272 (3), 234 (2), 193 (2), 122 (5), 107 (2), 94 (3), 91 (3), 82 (5), 81 (100), 79 (5), 77 (4), 69 (3), 53 (7), 41 (4).

Compound **7e**. MS, m/z (I_{rel} (%)): 329 $[M]^+$ (2), 288 (8), 272 (3), 258 (2), 248 (2), 136 (3), 122 (3), 107 (2), 95 (6), 91 (3), 82 (5), 81 (100), 79 (3), 77 (3), 67 (4), 55 (3), 53 (4), 41 (4).

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