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Intramolecular [4+2] cycloaddition in *N*-allyl- and *N*-propargyl-α-furyl lactams

Dmitry S. Poplevin[1], Eugeniya V. Nikitina[1], Vladimir P. Zaytsev[1], Alexey V. Varlamov[1], Santosh G. Tilve[2], Fedor I. Zubkov[1]*

[1] *RUDN University, 6 Miklukho-Maklaya St., Moscow 117198, Russia; e-mail: fzubkov@sci.pfu.edu.ru*

[2] *Goa University, Taleigao Plateau, Goa 403206, India; e-mail: stilve@unigoa.ac.in*

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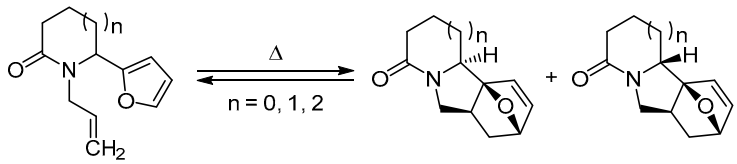


The size of nitrogen heterocycle in *N*-allyl- and *N*-propargyl-α-furyl lactams, as well as the nature of the unsaturated substituent linked to the nitrogen atom affected the possibility of thermal intramolecular [4+2] cycloaddition between multiple bond and the furan ring. *N*-Allyl-γ-(α-furyl)butyrolactam was shown to be unreactive at temperatures from 140 to 230°C. Substituted δ-valero- and ε-caprolactams underwent partial Diels–Alder cyclization, forming tautomeric mixtures that contained both the initial open-chain form and the cyclic form (diastereomeric 3a,6-epoxyisoindoles fused with an aza ring) in ratios between 19:81 and 55:45. *N*-Propargyl-α-furyl lactams did not participate in thermal IMDAF reaction regardless of the ring size and the temperature of the synthesis.

Keywords: epoxyisoindoles, furans, lactams, IMDAF reaction, intramolecular [4+2] cycloaddition.

Fused and substituted lactams are commonly found in plants and form structural part of molecules that show antibiotic, antitumor, anti-inflammatory, antifungal, antimicrobial, antiaggregant, cytotoxic, and other types of biological activity.[1] For these reasons, chemists are motivated to develop new, more effective routes for the synthesis of natural compounds, their derivatives, and pharmacophoric agents containing cyclic amide moieties, in order to obtain drugs with superior efficacy.

In the current work, we studied intramolecular Diels–Alder reaction of furans containing an unsaturated group (known as IntraMolecular Diels–Alder of Furan or IMDAF reaction) for the synthesis of new potentially biologically active heterocycles combining two privileged scaffolds (lactam and isoindole) in their structures. For our experiments, we selected large-scale industrial products: γ-butyrolactam, δ-valerolactam, and ε-caprolactam, which are used in the synthesis of widely known active pharmaceutical ingredients.

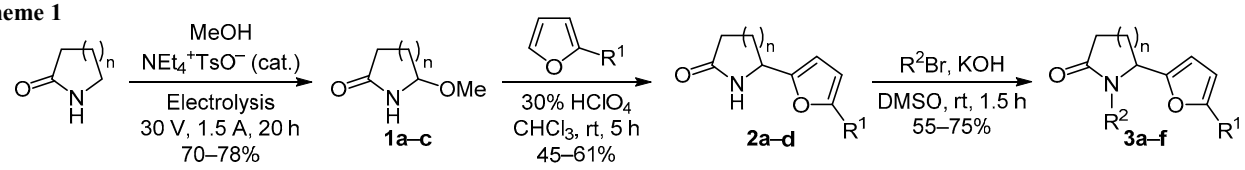
It should be noted that the Diels–Alder reaction in the series of furan derivatives, along with its tandem variants (for example, a sequence of *N*-acylation / [4+2] cycloaddition in 2-aminofurans and furfuryl amines) are well described in literature sources, but the overwhelming majority of examples covered by review articles[2] involve the cycloaddition of either furans activated with certain electron-donating substituents to various dienophiles or, on the contrary, the addition of dienophiles activated with electron-withdrawing groups to furans.

Thus, besides the aforementioned practical task we were also interested in gaining theoretical insights into the possibilities for using such weak dienophiles as allyl and propargyl substituents in IMDAF reaction with unactivated furans. Transformations of this type are rarely described in the literature.[3]

α-Methoxy-substituted γ-butyrolactam, δ-valerolactam, and ε-caprolactam **1a**–**c** were obtained according to the described procedures[4] by electrolysis of the appropriate cyclic amides in MeOH in an electrochemical cell equipped with graphite electrodes.[4d] We used tetraethylammonium *p*-toluenesulfonate as the background electrolyte, because it was stable under these conditions (Scheme 1).

Methoxy derivatives **1** after the evaporation of solvents were purified by silica gel column chromatography and then used in reactions with furan or 2-methylfuran. The best catalyst for electrophilic substitution among all of the

Scheme 1



R^1 = H, Me; R^2 = $CH_2CH{=}CH_2$, $CH_2C{\equiv}CH$; n = 1, 2, 3

tested options was $HClO_4$. When other catalysts were used (*p*-TsOH, HCl, and $BF_3{\cdot}OEt_2$), the yields of the target α-furyl lactams **2** were lower.[5]

Substituted furans **2** were isolated in moderate yields after chromatographic purification as viscous colorless oils (Table 1). ^{1}H NMR spectra of these compounds featured proton signals of furan rings in the range of 5.86–7.37 ppm with the spin-spin coupling constants $J_{3,4}$ = 2.0–3.0, $J_{5,4}$ = 1.7–2.0 Hz, as well as the proton signal of CH proton belonging to the aza ring manifested as a triplet or double doublet at 3.92–4.78 ppm with the spin-spin coupling of J = 5.1–7.6 Hz.

The alkylation of α-furyl lactams **2** with allyl bromide or propargyl bromide was performed according to the standard procedure[6] in DMSO in the presence of KOH at room temperature. This synthesis provided *N*-alkyl derivatives **3** (Scheme 1, Table 1). ^{1}H NMR spectra of *N*-allyl-substituted compounds **3a**–**d** additionally contained proton signals of their unsaturated groups in the range of 4.6–5.8 ppm (spin-spin coupling constants ^2J = 1.3–1.5, ^3J = 10.3–11.2, and 16.9–17.1 Hz), while the spectra of *N*-propargyl derivatives **3e**,**f** contained a triplet at 2.1–2.3 ppm (^4J = 2.1–2.5 Hz). We tested the obtained *N*-alkenylfurans **3** in a thermal intramolecular [4+2] cycloaddition reaction.

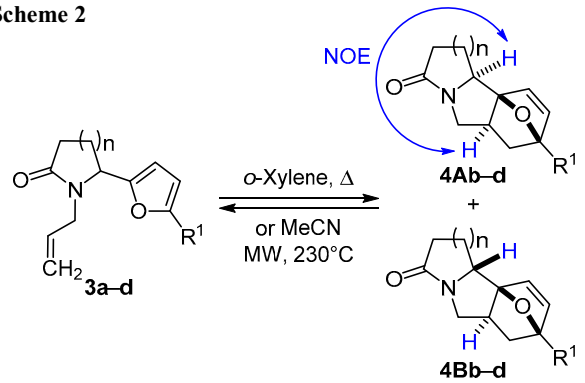
In order to optimize the conditions of the IMDAF reaction, we selected 1-allyl-6-(furan-2-yl)piperidin-2-one (**3b**) (Scheme 2), which was refluxed in *o*-xylene for 5 h and produced a mixture of the starting compound **3b** and two cyclic isomers **4Ab/4Bb** in 41:30:29 ratio according to ^{1}H NMR spectra (Table 2). Longer refluxing of this mixture for 8 h in *o*-xylene did not alter the ratio of tautomers, but was accompanied by gradual accumulation of unidentified polymeric products. Heating of piperidone **3b** in MeCN under the conditions of microwave irradiation (230°C, 10–11 bar, 30 min) shifted the equilibrium toward the cyclic forms **4Ab/4Bb**. According to ^{1}H NMR spectra acquired for $CDCl_3$ solutions at room temperature, the combined content of cyclic forms increased to 81%, compared to 59% achieved in *o*-xylene. Thus, the equilibrium composition of the reaction mixtures was achieved more rapidly in a microwave reactor and all subsequent experiments were performed under these conditions.

The treatment of *N*-allyl derivatives **3c**,**d** with microwave irradiation under analogous conditions also led to equilibrium mixtures of products **3c/4Ac/4Bc** and **3d/4Ad/4Bd**. At the same time, the position of tautomeric equilibrium was not substantially affected by the presence of a methyl group at position 5 of the furan ring, nor by increasing the size of the nitrogen heterocycle.

Table 1. Reaction conditions and yields of compounds **1a**–**c**, **2a**–**d**, **3a**–**f**

Compound	n	R^1	R^2	Yield, %
1a	1	–	–	70
1b	2	–	–	78
1c	3	–	–	73
2a	1	H	–	45
2b	2	H	–	51
2c	2	Me	–	57
2d	3	Me	–	61
3a	1	H	$CH_2CH{=}CH_2$	72
3b	2	H	$CH_2CH{=}CH_2$	62
3c	2	Me	$CH_2CH{=}CH_2$	75
3d	3	Me	$CH_2CH{=}CH_2$	55
3e	2	H	$CH_2C{\equiv}CH$	75
3f	2	Me	$CH_2C{\equiv}CH$	71

Scheme 2



In order to study the effect of reaction temperature on the composition of products arising from intramolecular [4+2] cycloaddition in *N*-allyl-6-(5-methylfuran-2-yl)-piperidin-2-one **3c**, we performed dynamic ^{1}H NMR studies (see the Supplementary information file). It was established that the IMDAF reaction proceeded at significant rate at temperatures above 50°C. After the reaction mixture was maintained in NMR ampoule for 5 min at 80°C, the content of compounds **3c**/**4Ac**/**4Bc** in $CDCl_2$–$CDCl_2$ solution was equal to 85:4:11. Heating of the solution for 5 min at 140°C changed the ratio to 71:9:20. The equilibrium was completely established over 8 h at 140°C, reaching 55:13:32 ratio of the components **3c**/**4Ac**/**4Bc**. This ratio of isomers was preserved upon cooling of the sample to room temperature within NMR spectrometer. It is interesting to note that the same exact

Table 2. Tautomeric mixtures of compounds **3** and **4** in $CDCl_3$ solutions at 22°C according to ^{1}H NMR spectra

Starting compound	n	R^1	Conditions	Isomer ratio, %
				3a/4Aa/4Ba
3a	1	H	*o*-xylene*	100:0:0
			MW**	100:0:0
				3b/4Ab/4Bb
3b	2	H	*o*-xylene*	41:30:29
			MW**	19:21:60
				3c/4Ac/4Bc
3c	2	Me	MW**	55:13:32
			$C_2D_2Cl_4$***	85:4:11
			$C_2D_2Cl_4$*[4]	55:13:32
				3d/4Ad/4Bd
3d	3	Me	MW**	49:14:35

* Refluxing in *o*-xylene, 5 h.
** Microwave irradiation in MeCN, 230°C, 10–11 bar, 30 min.
*** Heating in NMR ampoule with 1,1,2,2-tetrachloro-1,2-dideuterioethane at 80°C for 5 min.
*[4] Heating in NMR ampoule with 1,1,2,2-tetrachloro-1,2-dideuterioethane at 140°C for 8 h.

ratio of isomeric forms **3c**/**4Ac**/**4Bc** was detected when the reaction was performed in a microwave reactor for 30 min at 230°C (Table 2).

When the isomeric mixtures **3/4A/4B** that were thus obtained were separated by crystallization or silica gel column chromatography, only the open-chain form **3** could be isolated as an individual compound. The cyclic adducts **4A/4B** could not be isolated as pure samples, as there was always an impurity of the open-chain form **3**. This allows to assume that the retro Diels–Alder reaction occurred during the chromatographic separation or upon moderate heating of solutions containing the adducts **4A/4B**, leading to the formation of the thermodynamically more stable starting material **3**.

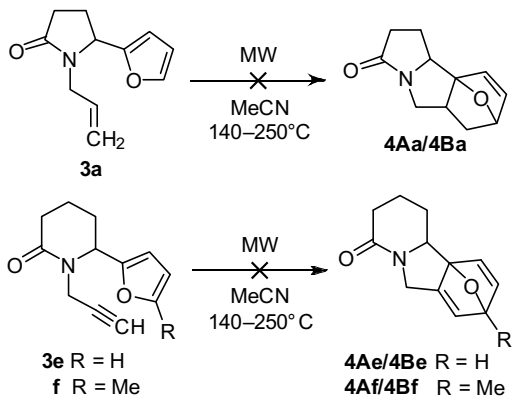
The assignment of NMR signals for mixtures of isomers **4** as belonging to the series **A** or **B** was based on the data obtained from two-dimensional NMR experiments and used analogies to related compounds.[7] In particular, fused epoxyisoindoles **4A** showed a NOESY cross peak between the closely positioned protons of CH groups, denoted with blue color in Scheme 2. Such a cross peak was absent in the series of isomers **4B**. The proton signal of NCH group was manifested as a double doublet at 3.72 (compound **4Bb**), 3.91 (compound **4Bc**), 4.57 (compound **4Bd**) and 3.93 (compound **4Ab**), 3.82 (compound **4Ac**), and 4.54 ppm (compound **4Ad**) (spin-spin coupling constants ^3J = 3.2–3.5, ^3J = 11.0–11.5 Hz), while the proton signal of $CH_2C\underline{H}{=}CH_2$ group in the same compounds was observed as a multiplet in the range of 1.88–2.15 ppm.

5-Furylpyrrolidinone **3a** did not undergo intramolecular [4+2] cycloaddition neither when heated in *o*-xylene nor under the conditions of microwave irradiation (230–250°C, 10–13 bar) (Scheme 3). Not even a trace of Diels–Alder adducts **4Aa/4Ba** could be detected in the reaction mixture by method of ^{1}H NMR spectroscopy. Apparently, this was associated with the high conformational strain arising from the fusion of four five-membered rings in the cycloaddition products. The construction of similar fused ring systems by using IMDAF reaction are quite seldom encountered in the literature.[8] Achieving a successful reaction always required the presence of an additional heteroatom (*S*, *O*, or *N*) in the pyrrolidine ring, which enhanced the conformational mobility both of the starting molecules and the obtained products.

It is known that triple bonds are generally less reactive toward cycloaddition than double bonds. Successful IMDAF reactions in the case of alkynylfurans, as a rule, require the presence of electron-withdrawing substituents at the triple bond,[9] even though there are some exceptions.[10]

N-Propargyl-6-furylpiperidinones **3e**,**f** under the conditions of microwave irradiation at up to 250°C merely underwent gradual resinification. According to the data of ^{1}H NMR spectroscopy, the obtained reaction mixtures did not contain any of the intramolecular cycloaddition products, compounds **4**.

Scheme 3



Thus, we have shown in the current work that *N*-allyl-α-furyl lactams featuring nitrogen heterocycles with size larger than 5 atoms participate in IMDAF reactions with the formation of tautomeric mixtures containing the starting *N*-allyl derivatives along with Diels–Alder reaction products. *N*-Propargyl-α-furyl lactams, regardless of the size of the nitrogen heterocycle, as well as 5-membered lactams do not undergo thermal intramolecular [4+2] cycloaddition up to 250°C even under the conditions of microwave irradiation.

Experimental

IR spectra were recorded for KBr pellets on an Infralum FT-801 FTIR spectrometer. ^{1}H NMR spectra were acquired on a JEOL JNM-ECA600 instrument (600 MHz) in $CDCl_3$, using TMS as internal standard. ^{13}C NMR spectra were recorded on a Bruker Avance 600 instrument (151 MHz) in $CDCl_3$, using the solvent signal (δ 77.4 ppm) or DMSO-d_6 multiplet (δ 40.0 ppm) as internal standards. The product ratio in the mixtures was determined from ^{1}H NMR spectra as the ratio of integrated intensities for the corresponding protons. Kinetic ^{1}H NMR experiments were performed in 1,1,2,2-tetrachloro-1,2-dideuterioethane ($C_2D_2Cl_4$), using the residual solvent signal of C_2DHCl_4 as internal signal (δ 5.89 ppm). Mass spectra were recorded on a Thermo

Trace DSQ mass spectrometer (EI ionization, 70 eV, source temperature 200°C, direct introduction of sample) or a Thermo Focus DSQ II GC-MS instrument (EI ionization, 70 eV, source temperature 200°C, carrier gas – helium, RTX-5MS column). Elemental analysis was performed on a Euro Vector EA 3000 CHNS-analyzer. Melting points were determined on an SMP 30 apparatus in open capillaries and were not corrected. TLC analysis was performed on Sorbfil PTSKh-AF-A plates, visualization with iodine vapor or $KMnO_4$ solution. The reagents were obtained from Acros Organics and Alfa Aesar and were used without additional purification, while the solvents were distilled prior to the syntheses.

Synthesis of α-methoxylactams 1a–c (General method). Tetraethylammonium *p*-toluenesulfonate (3.0 g, 0.007 mol) was added as background electrolyte to a solution of the commercially available lactam (0.2 mol) in MeOH (150 ml). The solution was cooled to 10–20°C, continuously stirred, and electrical current (1.5 A, 30 V) was passed between the graphite electrodes. Four electrodes with the diameter of 5 mm were used, with the submerged area equal to $6.9 \cdot 10^3$ mm^2. The design of the electrochemical cell has been described in the literature.[4d] The duration of electrolysis under these conditions was ~20 h. Subsequently, MeOH was removed by evaporation at reduced pressure, while the products were purified by silica gel column chromatography (column length 20 cm, particle size 0.035–0.07 mm, the eluent was hexane and 1:3 EtOAc–hexane). The characteristics of the obtained compounds **1a**–**c** were in agreement with published data.[11]

5-Methoxypyrrolidin-2-one (1a). Yield 16.1 g (70%), light-yellow oil, R_f 0.46 (EtOAc–hexane, 1:4) (R_f 0.65 (EtOAc–hexane, 1:3)[11a]).

6-Methoxypiperidin-2-one (1b). Yield 20.1 g (78%), colorless needles, mp 110–112°C (hexane–EtOAc) (mp 114–115°C (EtOAc)[11d]).

7-Methoxyazepan-2-one (1c). Yield 20.9 g (73%), light-yellow oil, R_f 0.39 (EtOAc–hexane, 1:4) (R_f 0.55 (EtOAc–hexane, 1:3)[11a]).

Synthesis of α-furyl lactams 2a–d (General method). A solution of the appropriate α-methoxy lactam **1a**–**c** (0.045 mol) in chloroform (60 ml) was stirred and treated by the addition of furan or 2-methylfuran (0.55 mol) and aqueous 30% $HClO_4$ solution (40 ml). The reaction mixture was stirred at room temperature for 5 h (control by TLC), neutralized by aqueous 10% NH_3 solution, the organic layer was separated, and the aqueous phase was extracted with chloroform (2×50 ml). The organic extracts were combined and dried over $MgSO_4$. The solids were removed by filtration and the extracts were evaporated. The products were purified by silica gel column chromatography (column length 20 cm, particle size 0.035–0.07 mm, the eluent was hexane and 1:3 EtOAc–hexane).

5-(Furan-2-yl)pyrrolidin-2-one (2a).[12] Yield 3.10 g (45%), yellow oil, R_f 0.65 (EtOAc–hexane, 1:3). IR spectrum, ν, cm^{-1}: 1580 (N–C=O), 3370 (N–H). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.18–2.25 (1H, m, 4-CH_2) and 2.34–2.40 (1H, m, 4-CH_2); 2.43–2.52 (2H, m, 3-CH_2); 4.78 (1H, dd, *J* = 5.1, *J* = 7.6, 5-CH); 6.22 (1H, br. d, *J* = 3.0, H-3 Fur); 6.32 (1H, dd, *J* = 2.0, *J* = 3.0, H-4 Fur); 7.13 (1H, br. s, NH), 7.37 (1H, d, *J* = 2.0, H-5 Fur). ^{13}C NMR spectrum, δ, ppm: 26.9; 29.9; 51.7; 106.0; 110.3; 142.4; 154.7; 178.7. Mass spectrum, *m*/*z* (I_{rel}, %): 151 $[M]^+$ (7), 146 (12), 134 (17), 133 (20), 122 (11), 106 (24), 94 (100), 79 (23), 77 (27), 66 (26), 39 (67). Found, %: C 63.40; H 5.90; N 9.20. $C_8H_9NO_2$. Calculated, %: C 63.58; H 6.00; N 9.37.

6-(Furan-2-yl)piperidin-2-one (2b). Yield 3.81 g (51%), pale-yellow needles, mp 85–86°C (EtOAc–hexane), R_f 0.61 (EtOAc–hexane, 1:3). IR spectrum, ν, cm^{-1}: 1581 (N–C=O), 3369 (N–H). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.77–1.83 (1H, m, 4-CH_2); 1.83–1.95 (2H, m, 5-CH_2); 2.06–2.15 (1H, m, 4-CH_2); 2.38–2.44 (2H, m, 3-CH_2); 4.63 (1H, t, *J* = 6.6, 6-CH); 6.22 (1H, d, *J* = 3.0, H-3 Fur); 6.27 (1H, br. s, NH); 6.33 (1H, dd, *J* = 1.7, *J* = 3.0, H-4 Fur); 7.37 (1H, d, *J* = 1.7, H-5 Fur). ^{13}C NMR spectrum, δ, ppm: 19.0; 27.4; 31.3; 50.8; 106.6; 110.4; 143.6; 154.3; 172.4. Mass spectrum, *m*/*z* (I_{rel}, %): 165 $[M]^+$ (6), 160 (20), 148 (19), 147 (29), 136 (19), 120 (30), 108 (97), 93 (20), 91 (29), 80 (31), 53 (56), 49 (31). Found, %: C 65.61; H 6.80; N 8.31. $C_9H_{11}NO_2$. Calculated, %: C 65.44; H 6.71; N 8.48.

6-(5-Methylfuran-2-yl)piperidin-2-one (2c). Yield 4.80 g (57%), yellow viscous oil, R_f 0.51 (EtOAc–hexane, 1:3). IR spectrum, ν, cm^{-1}: broad absorption band at 1599–1615 (N–C=O), 3415 (N–H). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.76–1.79 (1H, m, 5-CH_2); 1.87–1.95 (2H, m, 4-CH_2); 2.02–2.11 (1H, m, 5-CH_2); 2.26 (3H, s, CH_3); 2.38–2.44 (2H, m, 3-CH_2); 4.56 (1H, t, *J* = 6.7, 6-CH); 5.90 (1H, br. d, *J* = 3.0, H-4 Fur); 6.08 (1H, d, *J* = 3.0, H-3 Fur); 6.09 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 13.5; 19.0; 27.5; 31.4; 51.0; 106.1; 106.8; 151.9; 152.8; 172.1. Mass spectrum, *m*/*z* (I_{rel}, %): 179 $[M]^+$ (15), 174 (31), 162 (25), 161 (21), 150 (19), 134 (25), 122 (81), 107 (22), 105 (36), 94 (38), 67 (45), 63 (22), 49 (19). Found, %: C 66.85; H 7.37; N 7.95. $C_{10}H_{13}NO_2$. Calculated, %: C 67.02; H 7.31; N 7.82.

7-(5-Methylfuran-2-yl)azepan-2-one (2d). Yield 5.32 g (61%), yellow oil, R_f 0.49 (EtOAc–hexane, 1:3). IR spectrum, ν, cm^{-1}: 1602 (N–C=O), 3410 (N–H). ^{1}H NMR spectrum, δ, ppm (*J*, Hz) (signal of the NH group is not observed in the spectrum): 1.33–1.36 (1H, m, 5-CH_2); 1.64–1.70 (2H, m, 4,5-CH_2); 1.94–1.98 (1H, m, 4-CH_2); 2.19–2.26 (7H, m, 3,6-CH_2, CH_3); 3.92 (1H, t, *J* = 6.8, 7-CH); 5.86 (1H, d, *J* = 3.0, H-4 Fur); 5.92 (1H, d, *J* = 3.0, H-3 Fur). ^{13}C NMR spectrum, δ, ppm: 13.6; 25.3; 27.1; 32.7; 35.8; 38.9; 106.0; 106.2; 150.7; 153.9; 176.0. Mass spectrum, *m*/*z* (I_{rel}, %): 193 $[M]^+$ (12), 187 (2), 176 (11), 175 (100), 173 (4), 131 (6), 95 (5), 91 (6), 77 (5), 55 (4), 44 (11), 43 (30). Found, %: C 68.43; H 7.90; N 7.27. $C_{11}H_{15}NO_2$. Calculated, %: C 68.31; H 7.72; N 7.39.

Synthesis of *N*-allyl- and propargyl-substituted lactams 3a–f (General method). The appropriate furyl-substituted lactam **2** (0.006 mol) was added to a slurry of KOH (1.42 g, 0.024 mol) in DMSO (12 ml), followed by the addition of allyl or propargyl bromide (0.012 mol). The reaction mixture was stirred at room temperature for 1.5 h. The obtained solution was worked up by the addition of water (120 ml), and the obtained emulsion was extracted with dichloromethane (3×50 ml). The organic extracts were combined, dried over $MgSO_4$, and evaporated. The

obtained products were purified by silica gel chromatography (column length 30 cm, particle size 0.035–0.07 mm, eluent hexane and 1:2 EtOAc–hexane).

1-Allyl-5-(furan-2-yl)pyrrolidin-2-one (3a). Yield 0.83 g (72%), viscous pale-brown oil, R_f 0.45 (EtOAc–hexane, 1:2). IR spectrum, ν, cm^{-1}: 1617 (N–C=O). ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.17–2.23 (1H, m, 4-CH_2); 2.32–2.38 (1H, m, 4-CH_2); 2.46 (1H, ddd, *J* = 6.4, *J* = 9.8, *J* = 16.8, 3-CH_2); 2.63–2.69 (1H, dddd, *J* = 1.0, *J* = 6.4, *J* = 9.8, *J* = 16.8, 3-CH_2); 3.24 (1H, ddd, *J* = 1.0, *J* = 7.6, *J* = 15.1, CH_2CH=CH_2); 4.25–4.28 (1H, m, CH_2CH=CH_2); 4.68 (1H, dd, *J* = 4.5, *J* = 8.6, 5-CH); 5.08 (1H, dq, *J* = 17.1, *J* = 1.5, CH=CH_2); 5.13 (1H, dq, *J* = 10.2, *J* = 1.5, CH=CH_2); 5.60–5.67 (1H, m, CH=CH_2); 6.24 (1H, d, *J* = 3.3, H-3 Fur); 6.34 (1H, dd, *J* = 3.3, *J* = 1.5, H-4 Fur); 7.39 (1H, d, *J* = 1.5, H-5 Fur). ^{13}C NMR spectrum, δ, ppm: 24.6; 30.3; 43.4; 55.0; 108.3; 110.3; 117.9; 132.2; 142.8; 152.8; 174.6. Mass spectrum, *m*/*z* (I_{rel},%): 191 $[M]^+$ (2), 135 (4), 134 (8), 108 (32), 94 (46), 79 (84), 77 (51), 66 (30), 55 (25), 41 (100). Found, %: C 69.08; H 6.90; N 7.25. $C_{11}H_{13}NO_2$. Calculated, %: C 69.22; H 6.81; N 7.46.

1-Allyl-6-(furan-2-yl)piperidin-2-one (3b). Yield 0.76 g (62%), pale-yellow needles, mp 102–102.5°C (hexane–EtOAc), R_f 0.38 (EtOAc–hexane, 1:2). IR spectrum, ν, cm^{-1}: 1610 (N–C=O). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.70–1.74 (1H, m, 4-CH_2); 1.84–1.90 (1H, m, 4-CH_2); 1.97–2.03 (1H, m, 5-CH_2); 2.07–2.13 (1H, m, 5-CH_2); 2.44 (1H, ddd, *J* = 6.6, *J* = 10.3, *J* = 16.9, 3-CH_2); 2.52 (1H, dt, *J* = 10.3, *J* = 5.0, 3-CH_2); 3.21 (1H, dddd, *J* = 0.8, *J* = 7.4, *J* = 15.3, *J* = 8.3, CH_2CH=CH_2); 4.62 (1H, t, *J* = 5.0, 6-CH); 4.68–4.73 (1H, m, CH_2CH=CH_2); 4.92 (1H, dq, *J* = 16.9, *J* = 1.5, CH=CH_2); 5.28 (1H, dq, *J* = 10.3, *J* = 1.5, CH=CH_2); 5.42 (1H, m, CH=CH_2); 6.34 (1H, d, *J* = 3.1, H-4 Fur); 6.38 (1H, dd, *J* = 1.7, *J* = 3.1, H-3 Fur); 7.53 (1H, dd, *J* = 0.8, *J* = 1.7, H-5 Fur). ^{13}C NMR spectrum, δ, ppm: 17.8 (C-4); 32.0 (C-5); 35.1 (C-3); 47.5 (C-1 allyl); 54.2 (C-6); 107.5 (C-3 Fur); 110.2 (C-4 Fur); 117.1 (C-3 allyl); 132.8 (C-2 allyl); 142.2 (C-5 Fur); 153.7 (C-2 Fur), 170.0 (NCO). Mass spectrum, *m*/*z* (I_{rel}, %): 205 $[M]^+$ (3), 146 (2), 133 (4), 106 (7), 94 (24), 79 (11), 77 (16), 55 (25), 42 (29), 39 (100). Found, %: C 70.15; H 7.21; N 7.03. $C_{12}H_{15}NO_2$. Calculated, %: C 70.22; H 7.37; N 6.82.

1-Allyl-6-(5-methylfuran-2-yl)piperidin-2-one (3c). Yield 0.99 g (75%), pale-brown oil, R_f 0.42 (EtOAc–hexane, 1:2). IR spectrum, ν, cm^{-1}: 1622 (N–C=O). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.70–1.72 (1H, m, 4-CH_2); 1.88–1.90 (1H, m, 4-CH_2); 1.97–2.00 (1H, m, 5-CH_2); 2.07–2.09 (1H, m, 4-CH_2); 2.26 (3H, s, CH_3); 2.42 (1H, ddd, *J* = 6.4, *J* = 10.1, *J* = 16.4, 3-CH_2); 2.51 (1H, dt, *J* = 10.5, *J* = 5.1, 3-CH_2); 3.21 (1H, dddd, *J* = 0.7, *J* = 7.5, *J* = 8.5, *J* = 15.2, CH_2CH=CH_2); 4.54 (1H, t, *J* = 5.0, 6-CH); 4.68–4.71 (1H, m, CH_2CH=CH_2); 5.06 (1H, dq, *J* = 16.6, *J* = 1.4, CH=CH_2); 5.12 (1H, dq, *J* = 10.4, *J* = 1.4, CH=CH_2); 5.69–5.75 (1H, m, CH=CH_2); 5.90 (1H, d, *J* = 3.1, H-4 Fur); 6.02 (1H, d, *J* = 3.1, H-3 Fur). ^{13}C NMR spectrum, δ, ppm: 13.6; 23.8; 35.9; 39.9; 49.6; 51.0; 54.3; 96.0; 98.9; 106.1; 133.4; 151.7; 168.3. Mass spectrum, *m*/*z* (I_{rel}, %): 219 $[M]^+$ (12), 204 (1), 176 (6), 148 (8), 136 (19), 122 (32), 108 (100), 107 (40), 95 (14), 81 (19), 79 (25), 77 (22), 65 (13), 56 (19), 55 (44), 41 (54). Found, %: C 71.05; H 7.97; N 6.14. $C_{13}H_{17}NO_2$. Calculated, %: C 71.21; H 7.81; N 6.39.

1-Allyl-7-(5-methylfuran-2-yl)azepan-2-one (3d). Yield 0.76 g (55%), pale-brown oil, R_f 0.38 (EtOAc–hexane, 1:2). IR spectrum, ν, cm^{-1}: 1644 (N–C=O). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.32–1.35 (1H, m, 5-CH_2); 1.64–1.72 (1H, m, 5-CH_2); 2.00–2.06 (1H, m, 4-CH_2); 2.07–2.19 (1H, m, 4-CH_2); 2.24 (3H, s, CH_3); 2.30–2.38 (2H, m, 6-CH_2); 2.40–2.50 (2H, m, 3-CH_2); 3.23 (1H, dd, *J* = 7.6, *J* = 15.4, CH_2CH=CH_2); 4.54 (1H, t, *J* = 4.6, 7-CH); 4.68–4.71 (1H, m, CH_2CH=CH_2); 5.06–4.69 (1H, dq, *J* = 16.3, *J* = 1.3, CH=CH_2); 5.16 (1H, dq, *J* = 10.7, *J* = 1.3, CH=CH_2); 5.78–5.82 (1H, m, CH=CH_2); 5.85 (1H, d, *J* = 3.0, H-3 Fur); 5.91 (1H, br. d, *J* = 3.0, H-4 Fur). ^{13}C NMR spectrum, δ, ppm: 17.9; 19.2; 23.8; 27.2; 36.7; 43.3; 59.1; 109.2; 116.4; 117.1; 141.6; 150.7; 153.9; 172.9. Mass spectrum, *m*/*z* (I_{rel}, %): 233 $[M]^+$ (10), 190 (16), 162 (18), 150 (10), 136 (32), 122 (90), 121 (35), 109 (21), 95 (15), 93 (15), 91 (32), 79 (11), 70 (25), 69 (50), 55 (34), 41 (25). Found, %: C 71.75; H 7.99; N 6.24. $C_{14}H_{19}NO_2$. Calculated, %: C 72.07; H 8.21; N 6.00.

6-(Furan-2-yl)-1-(prop-2-yn-1-yl)piperidin-2-one (3e). Yield 0.91 g (75%), brown oil, R_f 0.44 (EtOAc–hexane, 1:2). IR spectrum, ν, cm^{-1}: 1678 (N–C=O). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.73–1.77 (1H, m, 4-CH_2); 1.88–1.92 (1H, m, 4-CH_2); 2.08–2.13 (2H, m, 5-CH_2); 2.18 (1H, t, *J* = 2.5, C≡CH); 2.43–2.55 (2H, m, 3-CH_2); 3.39 (1H, dd, *J* = 2.5, *J* = 17.4, NCH_2); 4.91 (1H, t, *J* = 5.1, 6-CH); 4.94 (1H, dd, *J* = 2.5, *J* = 17.4, NCH_2); 6.22 (1H, br. d, *J* = 3.3, H-3 Fur); 6.34 (1H, dd, *J* = 2.0, *J* = 3.3, H-4 Fur); 7.39 (1H, br. d, *J* = 2.0, H-5 Fur). ^{13}C NMR spectrum, δ, ppm: 18.1; 28.6; 32.2; 33.9; 54.2; 71.7; 78.8; 108.0; 110.3; 142.5; 152.9; 170.1. Mass spectrum, *m*/*z* (I_{rel}, %): 203 $[M]^+$ (6), 202 (16), 175 (5), 174 (11), 160 (1), 133 (20), 122 (11), 106 (24), 94 (100), 77 (22), 66 (24), 55 (27), 39 (65). Found, %: C 71.07; H 6.39; N 6.97. $C_{12}H_{13}NO_2$. Calculated, %: C 70.92; H 6.55; N 6.79.

6-(5-Methylfuran-2-yl)-1-(prop-2-yn-1-yl)piperidin-2-one (3f). Yield 0.92 g (71%), brown oil, R_f 0.39 (EtOAc–hexane, 1:2). IR spectrum, ν, cm^{-1}: 1665 (N–C=O). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.70–1.75 (1H, m, 4-CH_2); 1.91–1.94 (1H, m, 4-CH_2); 2.06–2.11 (1H, m, 5-CH_2); 2.20 (1H, t, *J* = 2.5, C≡CH); 2.27 (3H, s, CH_3); 2.40–2.56 (3H, m, 3,5-CH_2); 3.41 (1H, dd, *J* = 2.5, *J* = 17.1, NCH_2); 4.81 (1H, t, *J* = 5.1, 6-CH); 4.92 (1H, dd, *J* = 2.5, *J* = 17.1, NCH_2); 5.91 (1H, dq, *J* = 3.0, *J* = 1.0, H-4 Fur); 6.09 (1H, br. d, *J* = 3.0, H-3 Fur). ^{13}C NMR spectrum, δ, ppm: 13.7; 18.2; 28.7; 32.2; 33.8; 54.3; 71.6; 79.0; 106.1; 108.8; 150.9; 152.3; 170.2. Mass spectrum, *m*/*z* (I_{rel}, %): 217 $[M]^+$ (9), 216 (27), 202 (7), 174 (28), 160 (12), 148 (22), 147 (43), 146 (32), 136 (19), 121 (23), 120 (94), 108 (100), 107 (55), 91 (41), 77 (38), 65 (29), 55 (60), 43 (76), 39 (84). Found, %: C 72.02; H 6.83; N 6.28. $C_{13}H_{15}NO_2$. Calculated, %: C 71.87; H 6.96; N 6.45.

Intramolecular [4+2] cycloaddition in allyl derivatives 3b–d. A solution of *N*-allyl derivative **3b–d** (2.4 mmol) in MeCN (6 ml) was treated by microwave irradiation (230–250°C, 10–13 bar) for 30 min in an Anton Paar® micro-

wave oven. The products were isolated by removing the solvent at reduced pressure (Table 2). The composition and spectral properties of products obtained as a result of microwave irradiation are described below.

1-Allyl-6-(furan-2-yl)piperidin-2-one (3b), (6a*RS*,8*RS*,10a*RS*,10b*RS*)-1,2,3,6,6a,7,8,10b-octahydro-4*H*-8,10a-epoxypyrido[2,1-*a*]isoindol-4-one (4Ab) and (6a*RS*,8*RS*,10a*RS*,10b*SR*)-1,2,3,6,6a,7,8,10b-octahydro-4*H*-8,10a-epoxypyrido[2,1-*a*]isoindol-4-one (4Bb) (a mixture of compounds; in $CDCl_3$ solution the ratio of **3b**/**4Ab**/**4Bb** was equal to 19:21:60 according to ^{1}H NMR data). All spectral data are given for the isomeric mixture. Yellow oil. IR spectrum, ν, cm^{-1}: 1654 (N–C=O). The characteristics of piperidine **3b** are given above. ^{1}H NMR spectrum of isomer **4Ab**, δ, ppm (*J*, Hz): 1.61 (1H, dd, *J* = 6.2, *J* = 11.6, 7-CH_2); 1.68–1.85 (3H, m, 1,2,7-CH_2); 1.95–2.05 (3H, m, 1,2,3-CH_2); 2.15–2.46 (2H, m, 3-CH_2, 6a-CH); 3.28 (1H, dd, *J* = 8.1, *J* = 12.3, 6-CH_2); 3.78 (1H, dd, *J* = 9.4, *J* = 12.3, 6-CH_2); 3.93 (1H, dd, *J* = 3.3, *J* = 11.0, 10b-CH); 5.05 (1H, dd, *J* = 1.5, *J* = 6.2, 8-CH); 6.31 (1H, d, *J* = 5.9, 10-CH); 6.41 (1H, dd, *J* = 1.5, *J* = 5.9, 9-CH). ^{13}C NMR spectrum of isomer **4Ab**, δ, ppm (the assignment of specific carbon signals was based on a set of two-dimensional NMR experiments COSY, HSQC, HMBC, NOESY): 20.9 (C-2); 23.8 (C-1); 31.0 (C-3); 33.4 (C-7); 39.0 (C-6a); 50.6 (C-6); 58.7 (C-10b); 79.7 (C-8); 96.2 (C-10a); 132.7 (C-10); 138.3 (C-9); 169.5 (C-4). ^{1}H NMR spectrum of isomer **4Bb**, δ, ppm (*J*, Hz): 1.36 (1H, dd, *J* = 6.2, *J* = 11.6, 7-CH_2); 1.68–1.85 (3H, m, 1,2,7-CH_2); 1.95–2.05 (3H, m, 1,2,3-CH_2); 2.15–2.46 (2H, m, 3-CH_2, 6a-CH); 3.18 (1H, dd, *J* = 8.1, *J* = 12.3, 6-CH_2); 3.72 (1H, dd, *J* = 3.3, *J* = 11.0, 10b-CH); 4.47 (1H, dd, *J* = 9.4, *J* = 12.3, 6-CH_2); 4.98 (1H, dd, *J* = 1.5, *J* = 6.2, 8-CH); 6.12 (1H, d, *J* = 5.9, 10-CH); 6.36 (1H, dd, *J* = 1.5, *J* = 5.9, 9-CH). ^{13}C NMR spectrum of isomer **4Bb**, δ, ppm: 20.2 (C-2); 26.1 (C-1); 30.2 (C-3); 32.0 (C-7); 41.0 (C-6a); 49.4 (C-6); 58.9 (C-10b); 80.1 (C-8); 99.2 (C-10a); 132.8 (C-10); 137.1 (C-9); 168.2 (C-4). Mass spectrum, *m*/*z* (I_{rel}, %): 205 [M]$^+$ (15), 203 (3), 146 (2), 133 (4), 106 (7), 94 (24), 79 (11), 77 (16), 55 (25), 42 (29), 39 (100). Found, %: C 70.37; H 7.61; N 6.43. $C_{12}H_{15}NO_2$. Calculated, %: C 70.22; H 7.37; N 6.82.

6-(5-Methylfuran-2-yl)piperidin-2-one (3c), (6a*RS*,8*RS*,10a*RS*,10b*RS*)-8-methyl-1,2,3,6,6a,7,8,10b-octahydro-4*H*-8,10a-epoxypyrido[2,1-*a*]isoindol-4-one (4Ac) and (6a*RS*,8*RS*,10a*RS*,10b*SR*)-8-methyl-1,2,3,6,6a,7,8,10b-octahydro-4*H*-8,10a-epoxypyrido[2,1-*a*]isoindol-4-one (4Bc) (a mixture of compounds; in $CDCl_3$ solution the ratio of **3c**/**4Ac**/**4Bc** was equal to 55:13:32 according to ^{1}H NMR data). (All spectral data are given for this isomeric mixture.) Yellow oil, R_f 0.42 (EtOAc–hexane, 1:2). IR spectrum, ν, cm^{-1}: 1661 (N–C=O). The characteristics of piperidine **3c** are given above. ^{1}H NMR spectrum of isomer **4Ac**, δ, ppm (*J*, Hz): 1.49–1.53 (1H, m, 2-CH_2); 1.64 (3H, s, CH_3); 1.69–1.74 (1H, m, 2-CH_2); 1.89–1.96 (1H, m, 7-CH_2); 1.98–2.07 (4H, m, 1,3,7-CH_2, 6a-CH); 2.28–2.34 (1H, m, 6-CH_2); 2.41–2.54 (2H, m, 1,3-CH_2); 3.23 (1H, dd, *J* = 7.6, *J* = 15.1, 6-CH_2); 3.82 (1H, dd, *J* = 3.5, *J* = 11.1, 10b-CH); 6.30 (1H, d, *J* = 5.6, 9-CH), 6.36 (1H, d, *J* = 5.6, 10-CH). ^{1}H NMR spectrum of isomer **4Bc**, δ, ppm (*J*, Hz): 1.49–1.53 (1H, m, 2-CH_2); 1.64 (3H, s, CH_3); 1.69–1.74 (1H, m, 2-CH_2); 1.89–1.96 (1H, m, 7-CH_2); 1.98–2.07 (4H, m, 1,3,7-CH_2, 6a-CH); 2.28–2.34 (1H, m, 6-CH_2); 2.41–2.54 (2H, m, 1,3-CH_2); 3.38 (1H, dd, *J* = 8.6, *J* = 12.1, 6-CH_2); 3.91 (1H, dd, *J* = 3.3, *J* = 11.2, 10b-CH); 6.26 (1H, d, *J* = 5.6, 9-CH); 6.40 (1H, d, *J* = 5.6, 10-CH). ^{13}C NMR spectrum of isomers **4Ac**, **4Bc**, δ, ppm (*J*, Hz): 13.6; 17.9; 19.3; 20.3; 20.9; 23.8; 26.1; 28.7; 30.3; 31.0; 32.1; 35.8; 39.9; 42.5; 44.4; 47.5; 47.8; 49.6; 50.8; 54.3; 59.1; 88.0; 88.3; 96.0; 98.9; 106.2; 106.3; 108.3; 117.0; 133.0; 133.3; 133.4; 140.4; 141.6; 151.7; 152.0; 168.4; 169.6; 170.2. Mass spectrum, *m*/*z* (I_{rel}, %): 219 [M]$^+$ (12), 204 (19), 176 (6), 148 (8), 136 (19), 122 (32), 108 (100), 107 (40), 95 (14), 81 (19), 79 (25), 77 (22), 65 (13), 56 (19), 55 (44), 41 (54). Found, %: C 71.53; H 8.13; N 6.64. $C_{13}H_{17}NO_2$. Calculated, %: C 71.21; H 7.81; N 6.39.

1-Allyl-7-(5-methylfuran-2-yl)azepan-2-one (3d), (3*RS*,4a*RS*,11a*RS*,11b*RS*)-3-methyl-3,4,4a,5,9,10,11,11a-octahydro-3,11b-epoxyazepino[2,1-*a*]isoindol-7(8*H*)-one (4Ad) and (3*RS*,4a*RS*,11a*SR*,11b*RS*)-3-methyl-3,4,4a,5,9,10,11,11a-octahydro-3,11b-epoxyazepino[2,1-*a*]-isoindol-7(8*H*)-one (4Bd) (a mixture of compounds; in $CDCl_3$ solution the ratio of **3d**/**4Ad**/**4Bd** was equal to 49:14:35 according to ^{1}H NMR data). (All spectral data are given for the isomeric mixture). Beige oil. R_f 0.38 (EtOAc–hexane, 1:2). IR spectrum, ν, cm^{-1}: 1629 (N–C=O). The characteristics of azepine **3d** are given above. ^{1}H NMR spectrum of isomer **4Ad**, δ, ppm (*J*, Hz): 1.25 (1H, dd, *J* = 7.2, *J* = 11.1, 4-CH_2); 1.31–1.36 (1H, m, 4-CH_2); 1.64–1.72 (2H, m, 10-CH_2); 1.88–1.98 (3H, m, 9,11-CH_2, 4a-CH); 1.99–2.08 (1H, m, 9-CH_2); 2.16 (1H, m, 11-CH_2); 2.24 (3H, s, CH_3); 2.31–2.53 (3H, m, 5,8-CH_2); 3.22 (1H, dd, *J* = 7.1, *J* = 15.1, 5-CH_2); 4.54 (1H, dd, *J* = 3.2, *J* = 11.5, 11a-CH); 5.85 (1H, d, *J* = 5.7, 2-CH); 5.91 (1H, d, *J* = 5.7, 1-CH). ^{1}H NMR spectrum of isomer **4Bd**, δ, ppm (*J*, Hz): 1.21 (1H, dd, *J* = 7.3, *J* = 11.1, 4-CH_2); 1.31–1.36 (1H, m, 4-CH_2); 1.64–1.72 (2H, m, 10-CH_2); 1.88–1.98 (3H, m, 9,11,-CH_2, 4a-CH); 1.99–2.08 (1H, m, 9-CH_2); 2.16 (1H, m, 11-CH_2); 2.26 (3H, s, CH_3); 2.31–2.53 (4H, m, 5,8-CH_2); 4.57 (1H, dd, *J* = 3.2, *J* = 11.5, 11a-CH); 5.85 (1H, d, *J* = 5.7, 2-CH); 5.90 (1H, d, *J* = 5.7, 1-CH). ^{13}C NMR spectrum of isomers **4Ad**, **4Bd**, δ, ppm: 13.7 (2C); 17.9; 19.2; 20.3; 20.9; 23.8, 24.5 (2C); 25.6; 28.7; 31.0; 32.1; 32.7; 36.7; 38.9; 41.9; 43.3; 47.5; 50.9; 54.3 (2C); 55.2; 59.1; 106.0; 106.1; 106.2 (2C); 108.3; 109.2; 116.4; 117.1; 133.0; 134.4; 141.6; 150.7; 151.7; 152.0; 153.9; 170.3; 172.9 (2C). Mass spectrum, *m*/*z* (I_{rel}, %): 233 [M]$^+$ (10), 190 (16), 162 (18), 150 (10), 136 (32), 122 (90), 121 (35), 109 (21), 95 (15), 93 (15), 91 (32), 79 (11), 70 (25), 69 (50), 55 (34), 41 (25). Found, %: C 72.35; H 7.94; N 6.34. $C_{14}H_{19}NO_2$. Calculated, %: C 72.07; H 8.21; N 6.00.

Determination of cyclization reaction kinetics for compound 3c. An ampoule containing 5% solution of compound **3c** in $C_2D_2Cl_4$ was heated while placed inside NMR spectrometer. After every temperature increase by 10°C (2–3 min), the sample was thermostated and maintained for 5 min, then ^{1}H NMR spectrum was acquired. The spectra were acquired within the temperature

range from 30 to 140°C. When the temperature reached 140°C, the sample was maintained at that temperature, while ^{1}H NMR spectra were acquired every 30 min for a total of 12 h. There were no visible changes in the obtained spectra after 8 h.

A Supplementary information file containing ^{1}H and ^{13}C NMR spectra of the synthesized compounds, two-dimensional COSY, HMBC, HSQC, NOESY spectra for the mixtures of isomers **3b/4Ab/4Bb** and dynamic ^{1}H NMR spectra for the isomeric mixture of **3c/4Ac/4Bc** at different temperatures is available at the journal website at http://link.springer.com/journal/10593.

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