Reactions of Some Terpenoids with CH-Acids in the Presence of Cs-β Zeolite

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Abstract—Reactions of some α,β-unsaturated ketones from terpenoid series with CH-acids in the presence of Cs-β zeolite were studied under various conditions. The variation of reaction conditions (heating, ultrasonic irradiation) strongly affected the reaction products ratio, and the effect was singular in each case and gave different results.

Extensive application of heterogeneous catalysts (among them zeolites) in the fine organic synthesis is an important line of investigation in the modern organic chemistry [1]. However although the zeolites were already for several decades used in the fine organic synthesis the application of basic zeolites for catalysis of significant synthetic processes of CH-acids (Michael and Knoevenagel reactions) was reported only recently [2–5]. As acceptors in these studies served commonly either aromatic aldehydes or the simplest α,β-unsaturated carbonyl compounds lacking substituents in the β-position, and the direction of the process was clear from the very beginning. Yet the relatively complex structure of the α,β-unsaturated carbonyl compounds of the terpenoid series provides a possibility for nucleophiles to attack both on the double carbon-carbon bond (Michael reaction) and on the carbonyl group (Knoevenagel reaction).

In the previous study [6] we investigated the reaction between some α,β-unsaturated carbonyl compounds of the terpenoid series with malononitrile catalyzed with the basic Cs-β zeolite. It was established that depending on the spatial loading of the carbonyl group and the β-position at the double C=C bond adjacent to the carbonyl the process took the route either of the Michael or Knoevenagel reaction, or tandem transformations occurred.

For instance, the ketones **I** and **II** with malononitrile in the presence of the Cs-β zeolite along concurrent Michael and Knoevenagel reactions afforded compounds **III–VI**. Therewith the Michael reaction resulted in tandem transformations yielding complex polyfunctional compounds **V** and **VI** containing a rich variety of reactive functional groups (Scheme 1). The assumed reaction

mechanism for compounds **V** and **VI** formation was supported by the fact that keeping compound **III** with malononitrile under the reaction conditions did not yield any products, and the dinitrile **III** was recovered intact.

The above reactions occurred at room temperature without solvent, the zeolite was used in catalytic amounts, and the reaction products were obtained in plausible yield considering the complex structure of these compounds (overall yield with respect to reacted ketone was 47–50%). The main drawback of the reactions described is the low rate. For instance, within 48 h the conversion of ketone **I** in reaction with malononitrile attained 73%.

In the present study we demonstrated that carrying out the reaction of ketone **I** with malononitrile at 60°C reduced the reaction time to 4 h (conversion 65%) providing somewhat lesser overall yield of compounds **III** and **V** (41% vs. 47% obtained in reaction performed at room temperature) (Table 1).

The use of microwave (commercial microwave oven of 850 W power) or ultrasonic (ultrasonic bath, 42 kHz, 130 W) irradiation at room temperature did not notably affect the reaction progress. Yet the combined application of heating to 60°C an d ultrasonic irradiation resulted in higher conversion (77%) at the same overall yield of 41% with respect to the reacted ketone.

The change in reaction conditions significantly affected the ratio of the reaction products. Whereas at room temperature compounds **III** and **V** were obtained in 5.7:1 ratio, at 60°C it was 2.7:1; here we also proved that compound **III** did not transform into substance **V** under the conditions of reaction. Apparently at higher temperature the relative rates of Michael and Knoevenagel reactions

Scheme 1.

$R = CH_3$ (**I, III, V**), CH_2CH_3 (**II, IV, VI**).
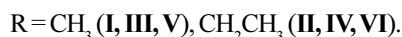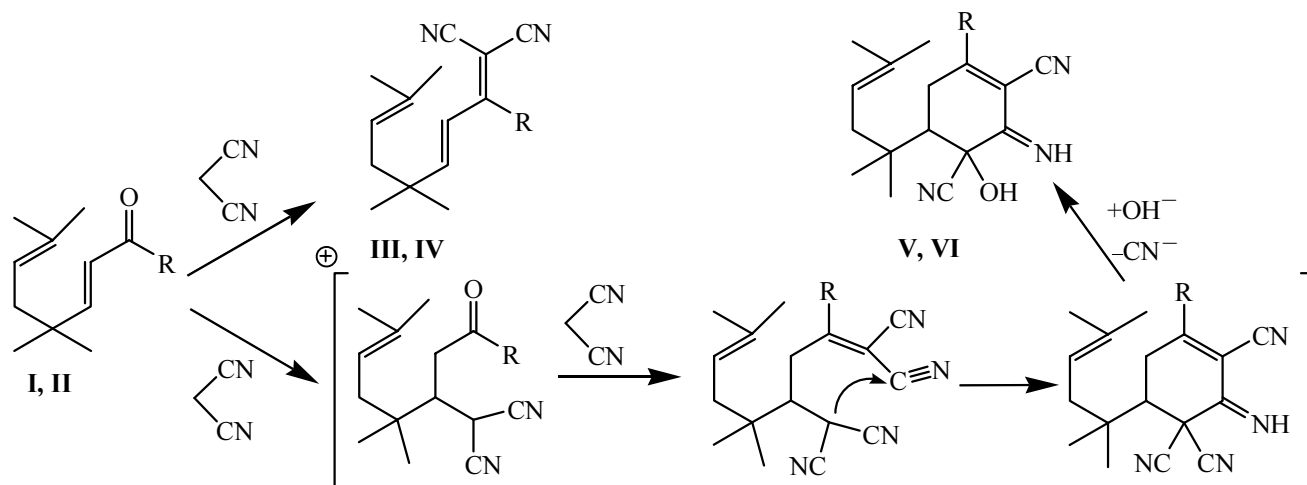
occurring in the first stage changed to the benefit of the former resulting in relative increase of compound **V** content in the reaction product. The application of ultrasonic irradiation further raised the relative content of compound **V** till the ratio of compounds **III** and **V** 1.6:1. However in theis case we found that dinitrile **III** reacted with malononitrile under the conditions of reaction yielding compound **V**.

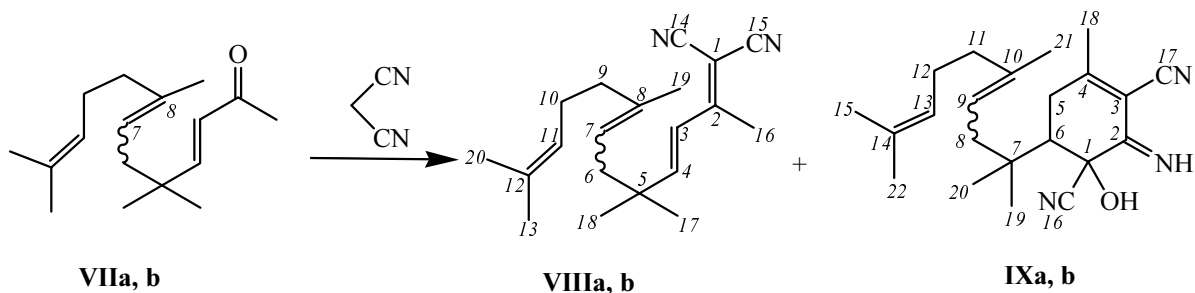In continuation of the study of the uncommon reaction we brought into reaction with malononitrile in the pres-

ence of Cs-β zeolite 5,5,8,12-tetramethyltrideca-3,7,11-trien-2-one (**VIIa, b**) (a mixture of *cis-* and *trans-*isomers in 1:1 ratio). The latter compound containds a structural block similar to that in compound **I** but with a bulky hydrocarbon substituent at the double bone $C^7=C^8$ (Scheme 2). We isolated from the reaction mixture the Knoevenagel reaction products **VIIIa, b** and polyfunctional compounds **IXa, b** similar to compounds **V** and **VI.**

Rate of 5,5,8,12-tetramethyltrideca-3,7,11-trien-2-one (**VIIa, b**) reaction with malononitrile at room temperature is even slower than that of ketone **I**. After storage of the reaction mixture for 168 h the conversion was only 39% with a good yield of compounds **VIIIa, b** and **IXa, b** on the reacted 5,5,8,12-tetramethyltrideca-3,7,11-trien-2-one (90%, Table 2); the products of Knovenagel reaction **VIIIa, b** prevailed.
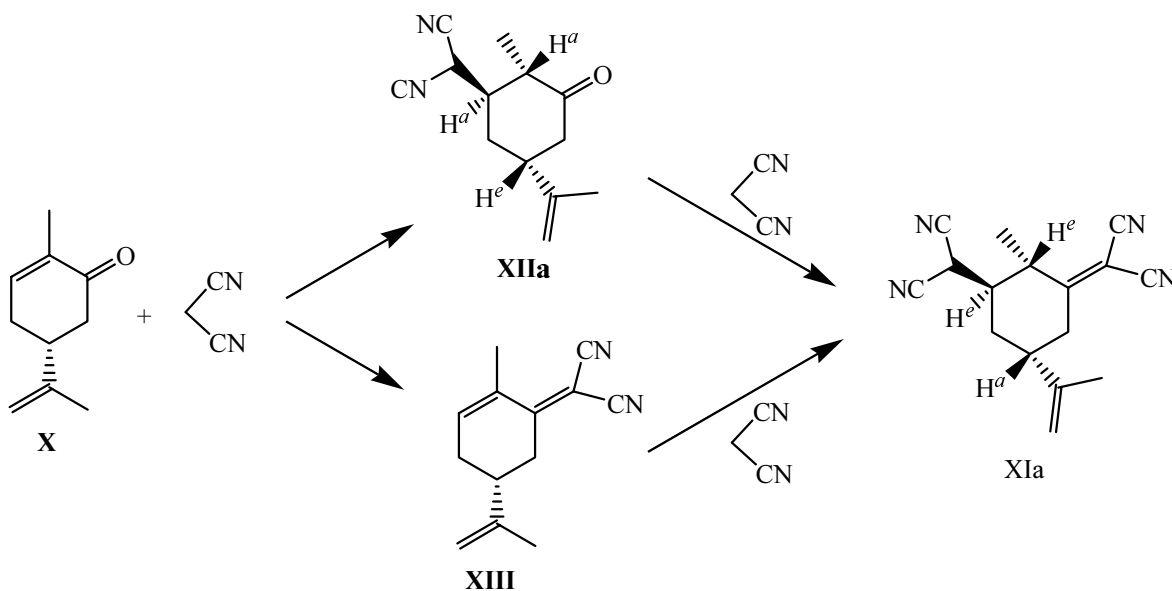
At raising the temperature to 60°C the reaction of compound **VIIa, b** was accelerated to reach conversion 52% within 5 h. However the overall yield of products **VIIIa, b** and **IXa, b** sharply decreased to 31%. As with ketone **I** at higher temperature the products ratio changed with growing relative content of compounds **IXa, b** at the expense of Knoevenagel reaction products **VIIIa, b.**

At combined heating and ultrasonic irradiation the overall yield of compounds **VIIIa, b** and **IXa, b** raised to 52% (at 45% conversion), and the yield of compounds **IXa, b** reduced from 8 to 3%. It should be noted that unlike compound **III** dinitriles **VIIIa, b** do not transform into compounds **IXa, b** under the reaction conditions even at ultrasonic irradiation. The reduced relative content of
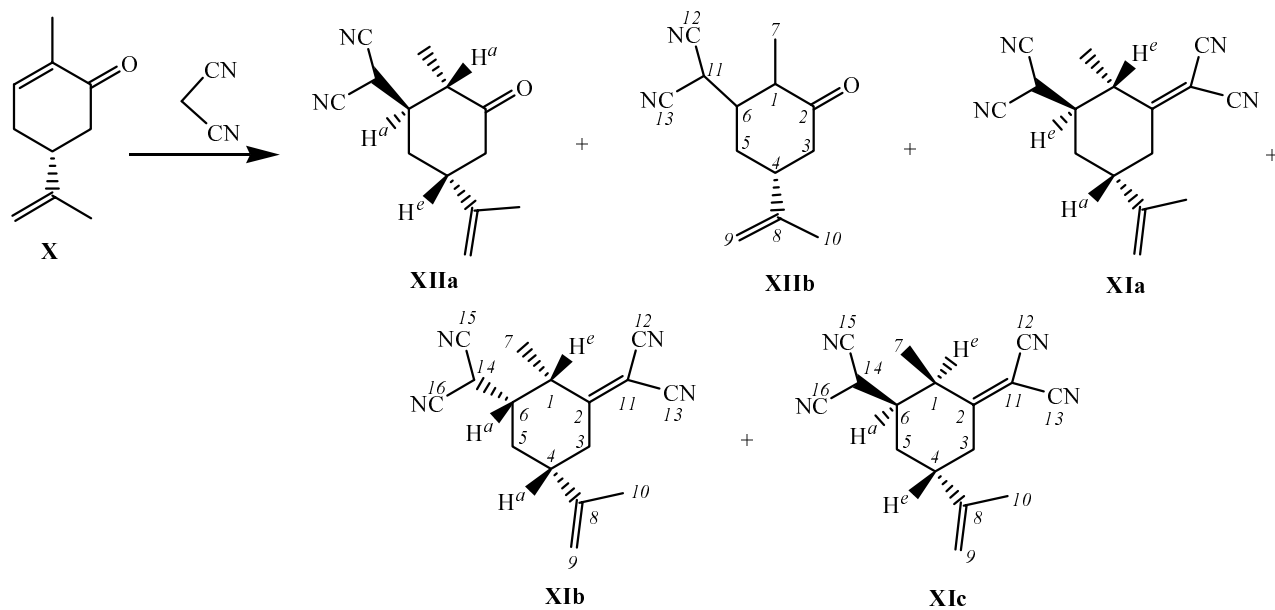
Table 1. Reaction of ketone **I** with malononitrile in the presence of basic zeolite Cs-β

Reaction conditions	Reaction time, h	Conversion, %	Yield (on reacted ketone), %		Ratio **III:V**
			III	**V**	
20°C	48	73	40	7	5.7
60°C	4	65	30	11	2.7
60°C, ultrasound	4	77	25	16	1.6

Table 2. Reaction of 5,5,8,12-tetramethyltrideca-3,7,11-trien-2-one (**VIIa, b**) with malononitrile in the presence of basic zeolite Cs-β

Reaction conditions	Reaction time, h	Conversion, %	Yield (on reacted ketone), %		Ratio **VIIIa, b: IXa, b**
			VIIIa, b	**IXa, b**	
20°C	168	39	84	6	14
60°C	5	52	23	8	2.9
60°C, ultrasound	5	45	49	3	16.3

Scheme 2.

VIIa, b   VIIIa, b   IXa, b

Scheme 3.

XIIa

X

XIII

XIa

Scheme 4.

X   XIIa   XIIb   XIa

XIb   XIc

Table 3. Reaction of (–)-carvone **X** with malononitrile in the presence of basic zeolite Cs-β

Reaction conditions	Reaction time, h	Conversion %	Compounds formed	Overall yield on reacted ketone, %
20°C	168	65	**XIa**	52
60°C	6	65	**XIa, b, XIIa, b**	76, [**XIa, b**]/[**XIIa, b**] = 1.8
60°C, ultrasound	6	67	**XIa–c, XIIa, b**	99, [**XIa–c**]/[**XIIa, b**] = 1.9

Table 4. Reaction of (–)-carvone **X** with ethyl cyanoacetate in the presence of basic zeolite Cs-β

Reaction conditions	Reaction time, h	Conversion, %	Compounds formed (yield on reacted ketone), %	Ratio **XIVa: XIVb, c**
20°C	96	64	**XIVa** (9), **XIVb, c** (42)	0.2
60°C	6	65	**XIVa** (45), **XIVb, c** (39)	1.2
60°C, ultrasound	6	76	**XIVa** (42), **XIVb, c** (33)	1.3

compounds **IXa, b** under ultrasonic irradiation is apparently due to their higher rate of tarring compared to compounds **VIIIa, b**.

Hence the longer hydrocarbon chain in going from ketone **I** to compound **VIIa, b** caused the rate reduction in the reaction with malononitrile and in the shift of products distribution toward those resulting from the Knoevenagel reaction. The variation of the process conditions also differently affects the reactions between malononitril and ketones **I** or **VIIa, b**.

Ketones **I** and **VIIa, b** do not react in the presence of the basic zeolite Cs-β with CH-acids weaker than malononitrile, like ethyl cyanoacetate, diethyl malonate, nitromethane, even under combined action of heating and ultrasonic irradiation.

Another interesting reaction we found formerly [6] was that of (–)-carvone **X** with malononitrile in the presence of Cs-β zeolite (Scheme 3). We demonstrated that the arising product **XI a** resulted from consecutive Michael and Knoevenagel reactions.

To clear up whether the initial attack of the CH-acid occurred at the double bond or the carbonyl group we carried out the reaction of the (–)-carvone with a small amount of malononitrile. We isolated from the reaction mixture both Michael reaction product **XIIa** and Knoevenagel reaction product **XIII**, and also compound **XIa**. Consequently the reaction proceeds via both possible intermediates. Unlike ketones **I**, **II**, and **VIIa, b** in this case regardless of the initial reaction (Michael or Knoevenagel) we obtained the same compound.

Compounds **XIa, XIIa**, and **XIII** formed stereoselectively and possessed an optical activity. The main disadvantage of these reactions same as with ketones **I**, **II**,

and **VIIa, b** was the low reaction rate. In reaction of (–)-carvone **X** with malononitrile the 65% conversion was attained in 168 h. We showed in the present study that the same process carried out at 60°C required 6 h to obtain the same conversion of 65%, but the stereoselectivity was lost (Scheme 4, Table 3).

We isolated from the reaction mixture 2 stereoisomeric products of the Michael reaction **XIIa, b** and 2 compounds resulting from tandem reactions of Michael and Knoevenagel **XIa, b.** The overall yield of the four compounds formed amounted to 72% vs. 52% at room temperature.

Combined application of heating and ultrasonic irradiation resulted at virtually the same conversion in an overall yield of the five arising compounds **XIa–c** and **XIIa, b** of 99% with respect to the reacted (–)-carvone.

Whereas in reaction at room temperature of (–)-carvone **X** with a little of malononitrile was obtained a single isomer of Michael reaction product, **XIIa**, and at 60°C **XIIa** and **XIIb** formed in comparable quantities, the ultrasonic irradiation gave rise to compound **XIIb** as the only product.

Unlike ketones **I** and **VIIa, b** (–)-carvone **X** reacted with ethyl cyanoacetate in the presence of Cs-β zeolite. This reaction was first performed by Knoevenagel in 1904 to obtain Michael reaction product in 25–33% yield depending on the catalyst used (diethylamine, piperidine) [7]. The reaction mixture was kept by Knoevenagel at room temperature for 168 h, then 6–8 h at 130°C. Judging from the distillation results, the reaction product was an isomer mixture whose composition was not investigated.

We found that the reaction of (–)-carvone **X** with ethyl cyanoacetate in the presence of Cs-β zeolite car-

Scheme 5.

X   XIVa   +   XIVb, c
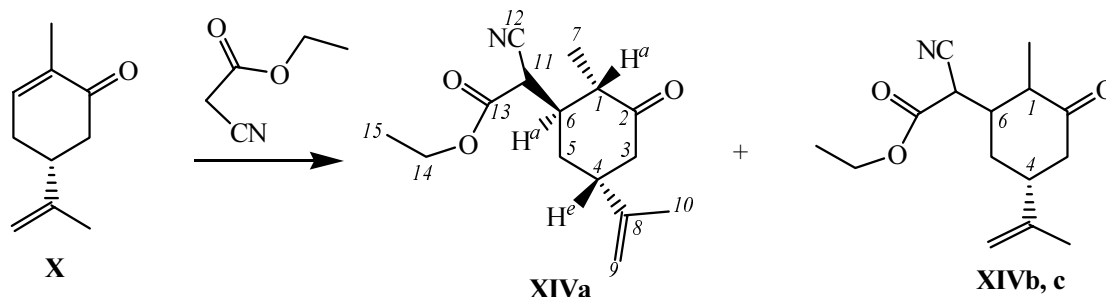
ried out for 96 h gave rise to 3 diastereomers **XIVa–c** (Scheme 5) in an overall yield 51% at 64% conversion (Table 4).

Whereas compound **XIVa** was isolated in pure form, we failed to separate compounds **XIVb** and **XIVc,** and they were analyzed as a mixture. Inasmuch as proton signals of H^1, H^4, and H^6 in the ^{1}H NMR spectrum of the mixture of **XIVb** and **XIVc** were overlapping it was impossible to measure their coupling constants with the neighboring protons and thus definitely reveal the cause of their isomerism: whether it was due to different position of substituents at one, two, or three at once carbon atoms (Scgeme 25).

At heating to 60°C the reaction time reduced to 6 h, and the conversion insignificantly increased. Therewith the overall yield of products grew from 51 to 84%. The higher temperature favored prevailing formation of compound **XIVa** whereas at the room temperature the dominant product were substances **XIVb, c**.

The ultrasonic irradiation resulted in higher conversion, but the overall yield of the Michael reaction products (calculated on the reacted ketone) reduced to 75%. The products ratio compared to that obtained at heating somewhat changed in favor of compound **XIVa**.

In contrast to reaction of (–)-carvone with malononitrile only products of Michael reactions are formed with ethyl cyanoacetate, no products of Knoevenagel reaction or tandem transformations were detected.

Hence our study of reactions of some terpenoid α,β-unsaturated ketones with CH-acids in the presence of the basic Cs-β zeolite under various conditions revealed that increase in the temperature from 20 to 60°C resulted in a sharp decrese in the reaction time at the comparable conversion. Whereas in reaction carried out at heating (–)-carvone with malononitrile and ethyl cyanoacetate afforded higher overall yield of products with respect to the reacted ketone, ketones **I** and **VIIa, b** with malononitrile provided less products apparently due to lower stability

of compounds under the reaction conditions. The combined application of heating and ultrasonic irradiation resulted as a rule in higher conversion of the initial ketones.

The change in reaction conditions strongly affects the ratio of the reaction products. Therewith this effect is inherent to each individual case, and the final results are various. Whereas in reaction of ketone **I** with malononitrile in the presence of the basic Cs-β zeolite more severe conditions (heating and especially ultrasonic irradiation) resulted in a higher yield of polyfunctional compound **V**, the same effect with compound **VIIa, b** was observed only when the process was carried out at 60°C, and the ultrasonic irradiation at 60°C led to nearly exclusive formation of the Knoevenagel reaction products **VIIIa, b**. The reaction of (–)-carvone with malononitrile under more stringent conditions resulted in the loss of stereoselectivity, yet in its reaction with ethyl cyanoacetate only a changed isomeric ratio was observed.

To the best of our knowledge no data was published on compounds **VIIIa, b, IXa, b, XIb, c**, and **XIIb**; compounds **XIVa–c** were isolated in 1904 apparently as isomer mixtures and were not characterized by spectral data. The structure of all compounds obtained was proved by ^{1}H and ^{13}C, IR, and mass spectra.

The chemical shifts of carbon atoms C^4–C^{13}, C^{17}–C^{20} in the ^{13}C NMR spectra of compounds **VIIIa** and **VIIIb** are similar to the corresponding data for *trans-* and *cis-*isomers of the initial ketone **VIIa, b** [8], and the data of ^{1}H and ^{13}C NMR spectra of compounds **IXa** and **IXb** are close to the respective characteristics of the related compounds [6].

The equatorial orientation of proton H^1 and the axial positions of protons H^4 and H^6 in the molecule of compound **XIb** follow from the values of the vicinal coupling constants ($^3J_{1,6}$ 4, $J_{4,3e}$, $J_{4,5a}$, $J_{6,5a}$ 13 Hz); therefore the substituents at the carbon atoms C^1, C^4, and C^6 are located in the mutual *cis*-configuration.

The axial position of proton H^6 in compound **XIc** follows from its vicinal coupling constant with proton H^{5a}

$(J_{6a,5a}$ 13 Hz), and equatorial position of protons H^1 and H^4 is evident from the vicinal coupling constants with the neighboring protons and from the remote W-coupling ($^3J_{1,6}$ 4, $^4J_{1,3e}$ 1.2, $^4J_{1,5e}$ 1.2 Hz; all vicinal constants for proton H^4 are smaller than 6.5 Hz). The above permits a conclusion that in **XIc** compound the substituents at atoms C^1 and C^6 are *cis* to each other and *trans* with respect to the substituent attached to C^4. The paramagnetic shift of H^1 proton in the ^1H NMR spectrum compared to the characteristic position of allyl protons (1.9–2.8 ppm) may be rationalized as due to the influence of the triple bond of the cyano group $C^{12}N$.

The axial orientation of H^1 and H^6 protons in the molecule of compound **XIVa** is evident from the value of their reciprocal coupling constant, and also from the value $^3J_{6,5a}$ 11 Hz. All coupling constants of H^4 proton with the protons of adjacent methylene groups are less than 6 Hz, consequently, the proton is in the equatorial position. Hence the substituents at atoms C^1 and C^4 are *cis* to each other and *trans* with respect to the substituent attached to C^6.

The values of vicinal coupling constants in the ^1H NMR spectra of compounds **XIIb** and **XIVb, c** indicate that their molecules in contrast to those of **XIb, c** and **XIVa** most probably exist in the *chair* conformation.

EXPERIMENTAL

^1H and ^{13}C NMR spectra were registered on spectrometer Bruker AM-400 at operating frequencies of 400.13 and 100.61 MHz respectively from solution of compounds in a mixture $CDCl_3$–CCl_4, ~1:1 by volume. The chloroform signals (δ_H 7.24, δ_C 76.90 ppm) served as internal standard. The structure of compounds was deduced from NMR spectra basing on the analysis of spin-spin coupling constants in the double resonance ^1H–^1H spectra and also from ^{13}C NMR spectra registered with selective and off-resonance decoupling from protons, differential spectra modulated with long-range coupling ^{13}C–^1H (LRJMD, $^nJ_{C,H}$ 10 Hz, $n = 2, 3$), and from two-dimensional spectra of ^{13}C–^1H heteronuclear correlation (COSY, $^1J_{C,H}$ 135 Hz). High-resolution mass spectra were measured on Finnigan MAT-8200 instrument, the specific rotation $[\alpha]_{580}$ was taken on spectrometer Polamat A from solutions in $CHCl_3$ at concentration g/100 ml of solution. IR spectra were recorded from solutions in CCl_4 on spectrometer Bruker Vector-22.

Reactions under ultrasonic irradiation were carried out with the use of ultrasonic bath Branson MTH-3510, 42 kHz, 130 W.

The purity of initial compounds was checked and reaction products were analyzed by GLC on Model 3700 instrument, quartz capillary column 15000×0.22 mm, stationary phase VC-30, flame-ionization detector, carrier gas helium, excessive pressure 1 at.

We used as catalyst zeolite Cs-β, whose preparation and properties are described in [6]. The zeolite was calcined for 2 h at 500°C just before use. The solvent was dried by passing through a column charged with calcined alumina. The reaction products were separated by column chromatography on silica gel (40–100 μ), eluent ethyl ether in hexane, from 0 to 90%.

Reaction of 5,5,8-trimethylnona-3,7-dien-2-one (I) with malononitrile at 60°C and under ultrasonic irradiation. To 0.04 g of zeolite Cs-β was added a solution of 0.15 g (2.3 mmol) of malononitrile in 2 ml of ethyl ether, the ether was distilled off, and 0.15 g (0.8 mmol) of ketone **I** was added thereto. (a) The mixture was heated at 60°C for 4 h, then the reaction products were washed from the catalyst with ethyl acetate. The separation by column chromatography afforded 0.053 g of the initial ketone **I** (conversion 65%), 0.037 g of 2-(1,4,4,7-tetramethylocta-2,6-dienylidene)malononitrile (**III**), yield on reacted ketone **I** 30%, and 0.017 g of 1-hydroxy-2-imino-4-methyl-6-(1,1,4-trimethylpent-3-enyl)-cyclohex-3-ene-1,3-dicarbonitrile (**V**), yield on reacted ketone **I** 11%.

(b) A flask with the mixture was placed into the ultrasonic bath heated to 60°C and was maintained under ultrasonic irradiation for 4 h. The reaction products were extracted from the catalyst with ethyl acetate. The separation by column chromatography afforded 0.035 g of the initial ketone **I** (conversion 65%), 0.037 g of dinitrile **III**, yield on reacted ketone **I** 25%, and 0.030 g of compound **V**, yield on reacted ketone **I** 16%.

Reaction of 2-(1,4,4,7-tetramethylocta-2,6-dienylidene)malononitrile (III) with malononitrile under ultrasonic irradiation. To 0.015 g of zeolite Cs-β was added a solution of 0.02 g (0.3 mmol) of malononitrile in 2 ml of ethyl ether, the ether was distilled off, and 0.018 g (0.08 mmol) of compound **III** was added. A flask with the mixture was placed into the ultrasonic bath heated to 60°C and was maintained under ultrasonic irradiation for 4 h. The reaction products were extracted from the catalyst with ethyl acetate. . The separation by column chromatography afforded 0.005 g of compound **V** (yield 22%).

Reaction of 5,5,8,12-tetramethyltrideca-3,7,11-trien-2-one (VIIa, b) with malononitrile at 20°C, 60°C, and under ultrasonic irradiation. To 0.04 g of zeolite Cs-β was added a solution of 0.20 g (3 mmol) of

malononitrile in 2 ml of ethyl ether, the ether was distilled off, and 0.15 g (0.6 mmol) of compound **VIIa, b** (a mixture of *cis*- and *trans*-isomers in 1:1 ratio) was added. (a) The mixture was kept for 168 h at 20°C and the products were extracted from the catalyst with ethyl acetate. The separation by column chromatography afforded 0.150 g of initial ketones **VIIa, b** in a mixture with 2-(1,4,4,7,11-pentamethyldodeca-2,6,10-trienylidene)malononitriles (**VIIIa, b**) in the weight ratio 1.6:1 (NMR data), and 0.005 g of 1-hydroxy-2-imino-4-methyl-6-(1,1,4,8-tetramethylnona-3,7-dienyl)cyclohex-3-ene-1,3-dicarbonitriles (**IXa, b**). The conversion of the initial ketone **VIIa, b** amounted to 39%, the calculated yield of compounds **VIIIa, b** with respect to reacted ketone was 84%, the yield of compounds **IXa, b** was 6%. The repeated separation of compounds **VIIa, b** and **VIIIa, b** on silica gel containing 20% of $AgNO_3$ (gradual elution with ethyl ether in hexane, from 5 to 95%) afforded 0.074 g of ketones **VIIa, b** and 0.056 g of compounds **VIIIa, b**, the yield on reacted ketone 80% in good agreement with the calculated yield.

(b) The mixture was heated at 60°C for 5 h, then the reaction products were washed from the catalyst with ethyl acetate. The separation by column chromatography afforded 0.093 g of a mixture containing initial ketone **VIIa, b** and compound **VIIIa, b** in 3.4:1 ratio (NMR data), and 0.009 g of compound **IXa, b**. The conversion of the initial ketone **VIIa, b** amounted to 52%, the calculated yield of compounds **VIIIa, b** with respect to reacted ketone was 23%, the yield of compounds **IXa, b** was 8%.

(c) A flask with the mixture was placed into the ultrasonic bath heated to 60°C and was maintained under ultrasonic irradiation for 4 h. The reaction products were extracted from the catalyst with ethyl acetate. . The separation by column chromatography afforded 0.122 g of a mixture containing initial ketone **VIIa, b** and compound **VIIIa, b** in 2.1:1 ratio (NMR data), and 0.003 g of compound **IXa, b**. The conversion of the initial ketone **VIIa, b** amounted to 45%, the calculated yield of compounds **VIIIa, b** with respect to reacted ketone was 49%, the yield of compounds **IXa, b** was 3%. NMR spectra of *trans*-isomer **VIIIa** and *cis*-isomer **VIIIb** were recorded from their mixtures in the ratio 1:1 and 1:0.6.

Compound VIIIa. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.09 s (6H, C^{17}H$_3$, C^{18}H$_3$), 1.56 m (3H, C^{19}H$_3$), 1.57 br.s (3H, C^{20}H$_3$), 1.65 m (3H, C^{13}H$_3$), 2.31 s (3H, C^{16}H$_3$), 1.95–2.07 m (2H^9, 2H^{10}), 2.08 br.d (2H^6, $J_{6,7}$ 8), 5.02 br.t (1H, H^{11}, $J_{11,10}$ 8), 5.04 br.t (1H, H^7, $J_{7,6}$ 8), 6.59 d (1H, H^4, $J_{4,3}$ 16) and 6.63 d (1H, H^3, $J_{3,4}$ 16), *AC* system. ^{13}C NMR spectrum, δ, ppm: 83.13 s (C^1), 169.32 s (C^2),

123.25 d (C^3), 158.87 d (C^4), 38.78 s (C^5), 40.30 t (C^6), 119.29 d (C^7), 138.29 s (C^8), 39.84 t (C^9), 26.48 t (C^{10}), 123.97 d (C^{11}), 131.45 C (C^{12}), 25.60 q (C^{13}), 111.94 s and 112.94 s (C^{14}, C^{15}), 17.98 q (C^{16}), 26.01 q and 26.15 q (C^{17}, C^{18}), 16.09 q (C^{19}), 17.58 q (C^{20}). Mass spectrum, *m/z* (I_{rel}, %): 296 (1) [*M*]$^+$, 175 (1.4), 160 (9), 137 (33), 112 (7.4), 95 (15.8), 81 (68.9), 69 (100), 55 (10), 41 (36). Found: *M* 296.22486. $C_{20}H_{28}N_2$. Calculated: *M* 296.22524.

Compound VIIIb. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.09 s (6H, C^{17}H$_3$, C^{18}H$_3$), 1.58 m (3H, C^{20}H$_3$), 1.66 m (3H, C^{13}H$_3$), 1.70 m (3H, C^{19}H$_3$), 2.32 s (3H, C^{16}H$_3$), 1.95–2.07 m (2H^9, 2H^{10}), 2.08 br.d (2H^6, $J_{6,7}$ 8), 5.01 t.m (1H, H^7, $J_{7,6}$ 8, $J_{7,9}$ 1.5), 5.06 m (1H, H^{11}), 6.58 d (1H, H^4, $J_{4,3}$ 16) and 6.63 d (1H, H^3, $J_{3,4}$ 16), *AC* system. ^{13}C NMR spectrum, δ, ppm: 83.13 s (C^1), 169.32 s (C^2), 123.39 d (C^3), 158.75 d (C^4), 38.41 C (C^5), 40.14 t (C^6), 119.72 d (C^7), 138.26 C (C^8), 31.91 t (C^9), 26.35 t (C^{10}), 123.88 d (C^{11}), 131.73 s (C^{12}), 25.60 q (C^{13}), 111.09 s and 112.94 s (C^{14}, C^{15}), 17.96 q (C^{16}), 26.01 q and 26.15 q (C^{17}, C^{18}), 23.50 q (C^{19}), 17.54 q (C^{20}).

NMR spectra of *trans*-isomer **IXa** and *cis*-isomer **IXb** were recorded from their mixtures in the ratio **IXa/IXb** ~1:0.6 and **IXa/IXb** ~ 0.8:1.

Compound IXa. IR spectrum, ν, cm^{-1}: 1580 (NH), 1647 (C=N), 2188, 2220 (Ca"N), 3357, 3399, 3479 (OH, NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.76 s and 0.85 s (6H, C^{19}H$_3$, C^{20}H$_3$), 1.56 m (3H, C^{21}H$_3$), 1.57 br.s (3H, C^{22}H$_3$), 1.65 m (3H, C^{15}H$_3$), 1.89 br.d (1H, H^8, $J_{8,9}$ 7.5), 1.94–2.03 m (2H^{11}), 2.05 m (2H^{12}), 2.22 d (3H, C^{18}H$_3$, $J_{18,5'}$ 1.2), 2.31 m (1H, H^6), 2.48 d.d (1H, H^5, $J_{5,5'}$ 18.5, $J_{5,6}$ 3), 2.53 d.d.d (1H, H$^{5'}$, *J* 18.5, $J_{5',6}$ 9, $J_{5',18}$ 1.2), 4.72 br.s (OH + NH), 5.04 t.M (1H, H^{13}, $J_{13,12}$ 7, $J_{13,15}$ 1.2, $J_{13,22}$ 1.2), 5.11 t.M (1H, H^9, $J_{9,8}$ 7.5, $J_{9,21}$ 1.2). ^{13}C NMR spectrum, δ, ppm: 71.99 s (C^1), 147.47 s (C^2), 104.53 s (C^3), 164.21 s (C^4), 32.12 t (C^5), 39.93 d (C^6), 40.31 s (C^7), 37.18 t (C^8), 119.75 d (C^9), 137.40 s (C^{10}), 39.93 t (C^{11}), 26.39 t (C^{12}), 124.09 d (C^{13}), 131.28 s (C^{14}), 25.57 q (C^{15}), 120.68 s (C^{16}), 113.92 s (C^{17}), 23.66 q (C^{18}), 23.98 q and 24.36 q (C^{19}, C^{20}), 16.08 q (C^{21}), 17.55 q (C^{22}). Mass spectrum, *m/z* (I_{rel}, %): 353 (4.6) [*M*]$^+$, 352 (7.8), 336 (3.5), 310 (1.6), 281 (2.8), 268 (5), 257 (2.1), 242 (5.9), 224 (25.3), 208 (23.8), 199 (16.5), 193 (8.7), 158 (46.6), 137 (12.7), 123 (19.4), 109 (30.1), 106 (39.8), 95 (15.89), 81 (39.3), 79 (48.8), 69 (62), 55 (34), 43 (100), 41 (73.7). Found: *M* 353.24584. $C_{22}H_{31}N_3O$. Calculated: *M* 353.24267.

Compound IXb. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.76 s and 0.87 s (6H, C^{19}H$_3$, C^{20}H$_3$), 1.58 br.s (3H, C^{22}H$_3$), 1.66 br.s (3H, C^{15}H$_3$), 1.69 m (3H, C^{21}H$_3$), 1.89 br.d (1H, H^8, $J_{8,9}$ 7.5), 1.94–2.03 m (2H^{11}), 2.05 m

(2H^{12}), 2.21 d (3H, C^{18}H$_3$, $J_{18,5'}$ 1.2), 2.32 d.d (1H, H^6, $J_{6,5'}$ 9, $J_{6,5}$ 2.5), 2.47 d.d (1H, H^5, $J_{5,5'}$ 18.5, $J_{5,6}$ 2.5), 2.53 d.d.d (1H, H$^{5'}$, J 18.5, $J_{5',6}$ 9, $J_{5',18}$ 1.2), 4.72 br.s (OH + NH), 5.07 m (1H, H^{13}), 5.11 t.m (1H, H^9, $J_{9,8}$ 7.5). ^{13}C NMR spectrum, δ, ppm: 71.95 s (C^1), 147.47 s (C^2), 104.53 s (C^3), 164.21 s (C^4), 32.11 t (C^5), 39.71 d (C^6), 40.31 s (C^7), 36.92 t (C^8), 120.11 d (C^9), 137.54 s (C^{10}), 31.89 t (C^{11}), 26.26 t (C^{12}), 123.99 d (C^{13}), 131.56 C (C^{14}), 25.57 q (C^{15}), 120.68 C (C^{16}), 113.91 C (C^{17}), 23.63 q (C^{18}), 24.14 q and 24.56 q (C^{19}, C^{20}), 23.55 q (C^{21}), 17.52 q (C^{22}).

Reaction of (–)-carvone (X) with malononitrile malononitrile at 60°C and under ultrasonic irradiation. To 0.04 g of zeolite Cs-β was added a solution of 0.15 g (2.3 mmol) of malononitrile in 2 ml of ethyl ether, the ether was distilled off, and 0.15 g (1 mmol) of ketone **X** was added thereto. (a) The mixture was heated at 60°C for 6 h, then the reaction products were washed from the catalyst with ethyl acetate. The separation by column chromatography afforded 0.052 g of initial (–)-carvone (**X**) (conversion 65%), 0.084 g of a mixture of compounds **XIa** and **XIb** in the ratio 0.9 : 1 (NMR data), overall yield on the reacted (–)-carvone 49%, and 0.038 g of a mixture of compounds **XIIa** and **XIIb** in the ratio 1 : 1.5 (NMR data), overall yield on the reacted (–)-carvone 27%.

(b) A flask with the mixture was placed into the ultrasonic bath heated to 60°C and was maintained under ultrasonic irradiation for 6 h. The reaction products were extracted from the catalyst with ethyl acetate. The separation by column chromatography afforded 0.050 g of initial (–)-carvone (**X**) (conversion 67%), 0.114 g of a mixture of compounds **XIa**–**c** in the ratio 4.2 : 3.6 : 1 (NMR data), overall yield on the reacted (–)-carvone 65%, and 0.049 g of a mixture of compounds **XIIa** and **XIIb** in the ratio 1 : 7.2 (NMR data), overall yield on the reacted (–)-carvone 34%.

NMR spectra of compound **XIb** were recorded in a mixture with previously described [6] compound **XIa** (isomer ration 1.1 : 1 respectively).

Compound XIb. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.23 d (3H, C^{7}H$_3$, $J_{7,1}$ 7), 1.67 d.d.d (1H, H^{5a}, $J_{5a,5e}$ 13, $J_{5a,4a}$ 13, $J_{5a,6a}$ 13), 1.77 br.s (3H, C^{10}H$_3$), 2.03 d.d.d (1H, H^{5e}, J 13, $J_{5e,4a}$ 4, $J_{5e,6a}$ 3), 2.20 d.d.d.d (1H, H^{4a}, $J_{4a,3a}$ 13, $J_{4a,5a}$ 13, $J_{4a,5e}$ 4, $J_{4a,3e}$ 3.5), 2.38 d.d (1H, H^{3a}, $J_{3a,3e}$ 14, $J_{3a,4a}$ 13), 2.38 m (1H, H^{6a}, $J_{6a,5a}$ 13, $J_{6a,14}$ 8, $J_{6a,1e}$ 4, $J_{6a,5e}$ 3), 2.98 d.m (1H, H^{3e}, J 14, $J_{3e,4a}$ 3.5), 3.51 q.d (1H, H^{1e}, $J_{1e,7}$ 7, $J_{1e,6a}$ 4), 3.77 d (1H, H^{14}, $J_{14,6a}$ 8), 4.86 br.s and 4.91 m (2H^9, *J*<1.5 Hz). ^{13}C NMR spectrum, δ, ppm: 38.24 d (C^1), 182.12 s (C^2), 34.22 t (C^3), 44.11 d (C^4),

28.23 t (C^5), 40.94 d (C^6), 12.70 q (C^7), 144.50 s (C^8), 112.06 t (C^9), 20.14 q (C^{10}), 84.57 s (C^{11}), 110.52 s and 110.87 s (C^{12}, C^{13}), 26.06 d (C^{14}), 110.90 s and 111.10 s (C^{15}, C^{16}).

Compound XIc. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.26 d (3H, C^{7}H$_3$, $J_{7,1}$ 7), 1.77 br.s (3H, C^{10}H$_3$), 1.94 d.d.d (1H, H^{5a}, $J_{5a,5e}$ 14, $J_{5a,6a}$ 13, $J_{5a,4e}$ 5), 2.16 d.m (1H, H^{5e}, J 14, $J_{5e,6a}$ 3, $J_{5e,4e}$ 3, $J_{5e,3e}$ 2, $J_{5e,1e}$ 1.2), 2.42 d.d.d.d (1H, H^{6a}, $J_{6a,5a}$ 13, $J_{6a,14}$ 8.5, $J_{6a,1e}$ 4, $J_{6a,5e}$ 3), 2.66 d.d.d (1H, H^{3a}, $J_{3a,3e}$ 16, $J_{3a,4e}$ 6.5, $J_{3a,1e}$ 1), 2.85 m (1H, H^{4e}, $J_{4e,3a}$ 6.5, $J_{4e,5a}$ 5, $J_{4e,5e}$ 3, $J_{4e,3e}$ 2), 3.27 d.d.d.d (1H, H^{3e}, J 16, $J_{3e,4e}$ 2, $J_{3e,5e}$ 2, $J_{3e,1e}$ 1.2), 3.48 br.q.d (1H, H^{1e}, $J_{1e,7}$ 7, $J_{1e,6a}$ 4), 3.70 d (1H, H^{14}, $J_{14,6a}$ 8.5), 4.67 br.d (1H, H^9, $J_{9,4e}$ 2), 5.03 s (1H, H$^{9'}$, $J_{9',4e}$ 1.2, $J_{9',10}$ 1). ^{13}C NMR spectrum, δ, ppm: 38.33 d (C^1), 182.54 s (C^2), 32.30 t (C^3), 39.35 d (C^4), 25.02 t (C^5), 36.31 d (C^6), 13.27 q (C^7), 143.68 s (C^8), 113.66 t (C^9), 22.06 q (C^{10}), 86.37 s (C^{11}), 110.33 s and 111.02 s (C^{12}, C^{13}), 26.09 d (C^{14}), 110.71 s and 111.12 s (C^{15}, C^{16}).

Compound XIIb. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.19 d (3H, C^{7}H$_3$, $J_{7,1}$ 7), 1.76 m (3H, C^{10}H$_3$, *J*<1.5 Hz), 2.08 d.d.d.m (1H, H^5, $J_{5,5'}$ 14, $J_{5,4}$ 7.5, $J_{5,6}$ 4), 2.18 d.d.d (1H, H$^{5'}$, J 14, $J_{5',6}$ 8, $J_{5',4}$ 4.5), 2.48 d.d.d.d (1H, H^3, $J_{3,3'}$ 15, $J_{3,4}$ 7, J 1.2, 0.5), 2.60 d.d.d (1H, H$^{3'}$, J 15, $J_{3',4}$ 5.5, J 0.5), 2.71 d.d.d.d (1H, H^6, $J_{6,11}$ 8.5, $J_{6,5'}$ 8, $J_{6,1}$ 5, $J_{6,5}$ 4), 2.77 m (1H, H^4), 2.83 q.d (1H, H^1, J 7, $J_{1,6}$ 5), 3.66 d (1H, H^{11}, $J_{11,6}$ 8.5), 4.74 m and 4.91 m (2H^9, *J*<1.5 Hz). ^{13}C NMR spectrum, δ, ppm: 45.95 d (C^1), 209.22 s (C^2), 42.68 t (C^3), 39.58 d (C^4), 28.98 t (C^5), 38.69 d (C^6), 11.51 q (C^7), 144.92 s (C^8), 112.66 t (C^9), 21.10 q (C^{10}), 24.47 d (C^{11}), 111.54 s and 111.56 s (C^{12}, C^{13}).

Reaction of (–)-carvone (X) ([α]$_D^{20}$ = –61°) with ethyl cyanoacetate. To 0.06 g of zeolite Cs-β was added a solution of 0.30 g (4.5 mmol) of ethyl cyanoacetate in 2 ml of ethyl ether, the ether was distilled off, and 0.30 g (2 mmol) of ketone **X** was added thereto. (a). The mixture was kept for 168 h at 20°C and the products were extracted from the catalyst with ethyl acetate. The separation by column chromatography afforded 0.109 g of a mixture of initial ketone **X** (conversion 64%), 0.031 g of ethyl 2-cyano-2-(5-isopropenyl-2-methyl-3-oxocyclohexyl)acetate (**XIVa**) (yield 9% with respect to reacted (–)-carvone), and 0.140 g of isomer mixture **XIVb, c** in the ratio 1:0.7 (NMR data). The overall yield on reacted (–)-carvone was 42%.

(b) The mixture was heated at 60°C for 6 h, then the reaction products were washed from the catalyst with ethyl acetate. The separation by column chromatography afforded 0.105 g of initial (–)-carvone (**X**) (conversion 65%), 0.155 g of compound **XIVa** (yield 45% with

respect to reacted (–)-carvone), and 0.134 g of isomer mixture **XIVb, c** in the ratio 1:0.7 (NMR data). The overall yield on reacted (–)-carvone was 39%.

(c) A flask with the mixture was placed into the ultrasonic bath heated to 60°C and was maintained under ultrasonic irradiation for 6 h. The reaction products were extracted from the catalyst with ethyl acetate. The separation by column chromatography afforded 0.072 g of initial (–)-carvone (**X**) (conversion 76%), 0.167 g of compound **XIVa** (yield 42% with respect to reacted (–)-carvone), and 0.133 g of isomer mixture **XIVb, c** in the ratio 1:0.7 (NMR data). The overall yield on reacted (–)-carvone was 33%.

Compound XIVa, $[\alpha]_{580}^{20}$ +19.4 (C 3.1). ^{1}H NMR spectrum, δ, ppm (J, Hz): 1.07 d (3H, C^7H_3, $J_{7,1}$ 6.5), 1.30 t (3H, $C^{15}H_3$, $J_{15,14}$ 7), 1.67 br.s (3H, $C^{10}H_3$), 1.93 d.d.d.d (1H, H^{5e}, $J_{5e,5a}$ 14, $J_{5e,4e}$ 4, $J_{5e,6a}$ 4, $J_{5e,3e}$ 2), 2.00 d.d.d (1H, H^{5a}, $J_{5a,5e}$ 14, $J_{5a,6a}$ 11, $J_{5a,4e}$ 4.5), 2.24 d.d.d.d (1H, H^{6a}, $J_{6a,1a}$ 12, $J_{6a,5a}$ 11, $J_{6a,5e}$ 4, $J_{6a,11}$ 4), 2.35 d.q (1H, H^{1a}, $J_{1a,6a}$ 12, $J_{1a,7}$ 6.5), 2.53 d.d.d (1H, H^{3a}, $J_{3a,3e}$ 15, $J_{3a,4e}$ 6, $J_{3a,1a}$ 1.2), 2.70 d.d.d (1H, H^{3e}, $J_{3e,3a}$ 15, $J_{3e,4e}$ 3, $J_{3e,5e}$ 2), 2.78 m (1H, H^{4e}), 3.75 d (1H, H^{11}, $J_{11,6a}$ 4), 4.26 q (2H^{14}, $J_{14,15}$ 7), 4.66 m and 4.87 m (2H^9, J < 1.5 Hz). ^{13}C NMR spectrum, δ, ppm: 47.26 d (C^1), 208.89 C (C^2), 43.85 t (C^3), 39.46 d (C^4), 29.38 t (C^5), 39.71 d (C^6), 11.30 q (C^7), 145.19 C (C^8), 113.19 t (C^9), 21.68 q (C^{10}), 41.36 d (C^{11}), 114.23 s (C^{12}), 165.22 s (C^{13}), 62.97 t (C^{14}), 13.88 q (C^{15}). Mass spectrum, m/z (I_{rel}, %): 263 (42) $[M]^+$, 218 (3.3), 207 (2.6), 192 (7.4), 180 (2.8), 166 (3.1), 162 (4.6), 150 (100), 135 (36.6), 122 (12.7), 109 (45.9), 95 (34.1), 81 (18.3), 67 (48.6), 55 (28.8), 41 (31.4). Found: M 263.15175. $C_{15}H_{21}NO_3$. Calculated: M 263.15213.

NMR spectra of compounds **XIVb** and **XIVc** were registered from their mixture containing them in the ratio 1:0.7 respectively. **Compound XIVb**. ^{1}H NMR spectrum, δ, ppm (J, Hz): 1.03 d (3H, C^7H_3, $J_{7,1}$ 7), 1.25 t (3H, $C^{15}H_3$, $J_{15,14}$ 7), 1.70 br.s (3H, $C^{10}H_3$), 1.95 d.d.d (1H, H^5, $J_{5,5'}$ 14, $J_{5,4}$ 8.5, $J_{5,6}$ 4), 2.05 d.d.d.d (1H, $H^{5'}$, J 14, $J_{5',6}$ 7, $J_{5',4}$ 4, $J_{5',3}$ 1), 2.35 d.d.m (1H, H^3, $J_{3,3'}$ 14.5, $J_{3,4}$ 8.5), 2.53 br.d.d (1H, $H^{3'}$, J 14.5, $J_{3',4}$ 5.5), 2.58 q.d.d (1H, H^1, $J_{1,7}$ 7, $J_{1,6}$ 5, $J_{1,3}$ 1.2), 2.75 m (2H, H^4, H^6), 3.37 d (1H, H^{11}, $J_{11,6}$ 8), 4.20 q (2H^{14}, $J_{14,15}$ 7), 4.67 br.s and 4.80 m (2H^9, J < 1.5 Hz). ^{13}C NMR spectrum, δ, ppm:

46.60 d (C^1), 209.95 s (C^2), 43.32 t (C^3), 40.06 d (C^4), 29.92 t (C^5), 38.31 d (C^6), 11.36 q (C^7), 145.71 s (C^8), 111.53 t (C^9), 20.83 q (C^{10}), 38.50 d (C^{11}), 115.19 s (C^{12}), 165.17 s (C^{13}), 62.85 t (C^{14}), 13.68 q (C^{15}).

Compound XIVc. ^{1}H NMR spectrum, δ, ppm (J, Hz): 1.13 d (3H, C^7H_3, $J_{7,1}$ 7), 1.26 t (3H, $C^{15}H_3$, $J_{15,14}$ 7), 1.65 br.C (3H, $C^{10}H_3$), 1.80 m (1H, H^5, $J_{5,5'}$ 14, J 6, 4), 1.89 d.d.d (1H, $H^{5'}$, J 14, 8.5, 5), 2.38 m (1H, H^3, $J_{3,3'}$ 14.5, $J_{3,4}$ 6.5, J 1.2, 0.5), 2.52 d.d (1H, $H^{3'}$, $J_{3',3}$ 14.5, J 5.5), 2.62–2.71 m (3H, H^1, H^4, H^6), 3.35 d (1H, H^{11}, $J_{11,6}$ 8.5), 4.20 q (2H^{14}, $J_{14,15}$ 7), 4.65 m and 4.81 m (2H^9, J < 1.5 Hz). ^{13}C NMR spectrum, δ, ppm: 46.18 d (C^1), 210.19 s (C^2), 42.14 t (C^3), 39.64 d (C^4), 28.67 t (C^5), 37.47 d (C^6), 11.66 q (C^7), 145.35 s (C^8), 112.26 t.

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