Synthetic transformation of higher terpenoids
31.* Synthesis of 1,2,3-triazolyl-containing furan labdanoids and studies of their cytotoxic activity*

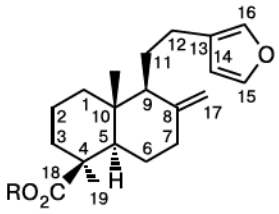
Yu. V. Kharitonov,[a] E. E. Shul´ts,[a] M. M. Shakirov,[a] M. A. Pokrovskii,[b] A. G. Pokrovskii,[b] and G. A. Tolstikov[a]†*

[a]N. N. Vorozhtsov Novosibirsk Institute of Organic Chemistry, Siberian Branch of the Russian Academy of Sciences, 9 prosp. Akad. Lavrent´eva, 630090 Novosibirsk, Russian Federation. Fax: +7 (383) 330 9752. E-mail: schultz@nioch.nsc.ru
[b]Novosibirsk State University, 2 ul. Pirogova, 630090 Novosibirsk, Russian Federation

16-(1-R-1,2,3-Triazol-4-ylethyl)-, 16-(1-R-1,2,3-triazol-4-ylmethoxymethyl)-, and 16-{2-(1-R-1,2,3-triazol-4-yl)-1-[(1-R-1,2,3-triazol-4-ylmethoxy)ethyl]}-substituted derivatives of methyl lambertianate were synthesized by 1,3-cycloaddition of labdanoid alkynes with azides. The compounds obtained possess considerable cytotoxicity toward the human tumor cell lines CEM-13, MT-4, and U-937. The most active compound, methyl 16-(2-{2-[(1-benzyl-1*H*-1,2,3-triazol-4-yl)acetyl]furan-3-yl}ethyl)lambertianate, was found to inhibit the viability of the tumor cells by 50% ($CCID_{50}$) in the concentration of 7—12 μmol L^{-1}.

Key words: lambertianic acid, labdanoid alkynes, azides, 1,3-cycloaddition, the Huisgen reaction, tumor cells, cytotoxicity.

Lambertianic acid (**1**) possessing antidepressant[2] and antiallergic[3] properties is of interest for the preparation of pharmacologically useful compounds. Modifications of lambertianic acid (**1**) and its methyl ester (**2**) at the furan ring with the introduction of nitrogen-containing heterocyclic fragments (5-oxo-2-phenyloxazolyl, 1,2,4-oxadiazolyl) performed earlier made it possible to synthesize compounds possessing cytotoxic activity in micromolar concentrations,[4] as well as promising cytostatic polychemiotherapy correctors.[5]



1, 2

R = H (**1**), Me (**2**)

In this connection, it seems of interest to synthesize and study new furan labdanoid derivatives containing various nitrogen substituents in their furan ring, in particular, the 1,2,3-triazole fragment. Such heterocyclic substituents are parts of compounds possessing antibacterial,[6] antiepileptic,[7] and antitumor[8] activity. Some triazolyl-substituted compounds were found to be selective inhibitors of the 2-type methionineaminopeptidase,[9] HIV-1 protease,[10] tyrosinkinase[11].

The present study is devoted to the synthesis of triazole-containing labdane diterpenoids and the studies *in vitro* of their cytotoxic properties. The synthesis of new methyl lambertianate heterocyclic derivatives was carried out by the copper-catalyzed 1,3-dipolar cycloaddition of alkyne-containing labdanoids **3a**,**b**, **4**, **5a**,**b** with different azides[12] (Scheme 1). Methyl 16-formyllambertianate (**6**) was used as the starting compound. The reaction of aldehyde **6** with propargyl bromide in the presence of activated zinc dust led to a mixture of diastereoisomeric homopropargylic alcohols **3a**,**b** (a ~1 : 1 ratio).[13] The ratio of alcohols **3a**,**b** was found from the ^{1}H NMR spectrum (using the ratio of integral intensities of the signals for protons H(17) in the spectra of acetates (**7a**,**b**)). Reduction of aldehyde **6** with sodium borohydride in methanol gives the corresponding 16-hydroxymethyl derivative **8**, whose reaction with propargyl bromide in the presence of sodium hydride gave the labdane-type propargylic furfuryl ether **4** (see Ref. 14). The reaction of hydroxyalkynes **3a**,**b** with propargyl bromide under similar conditions furnished the corresponding dialkynes **5a**,**b**. A single crystal of 1´(*R*)-diastereoisomer **5a** was studied by X-ray crystallography.[14]

The reaction of a mixture of alkynyl-substituted labdanoids **3a**,**b** with benzyl azide (**9**) in acetonitrile in the

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† Deceased.

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presence of diisopropylethylamine and catalytic amount of CuI gave a mixture of diastereomers **10a,b** in 80% yield (Scheme 2). Similarly treated, **3a,b** and methyl 2-azidoacetate (**11**) afforded a mixture of isomers **12a,b** in 82% yield.

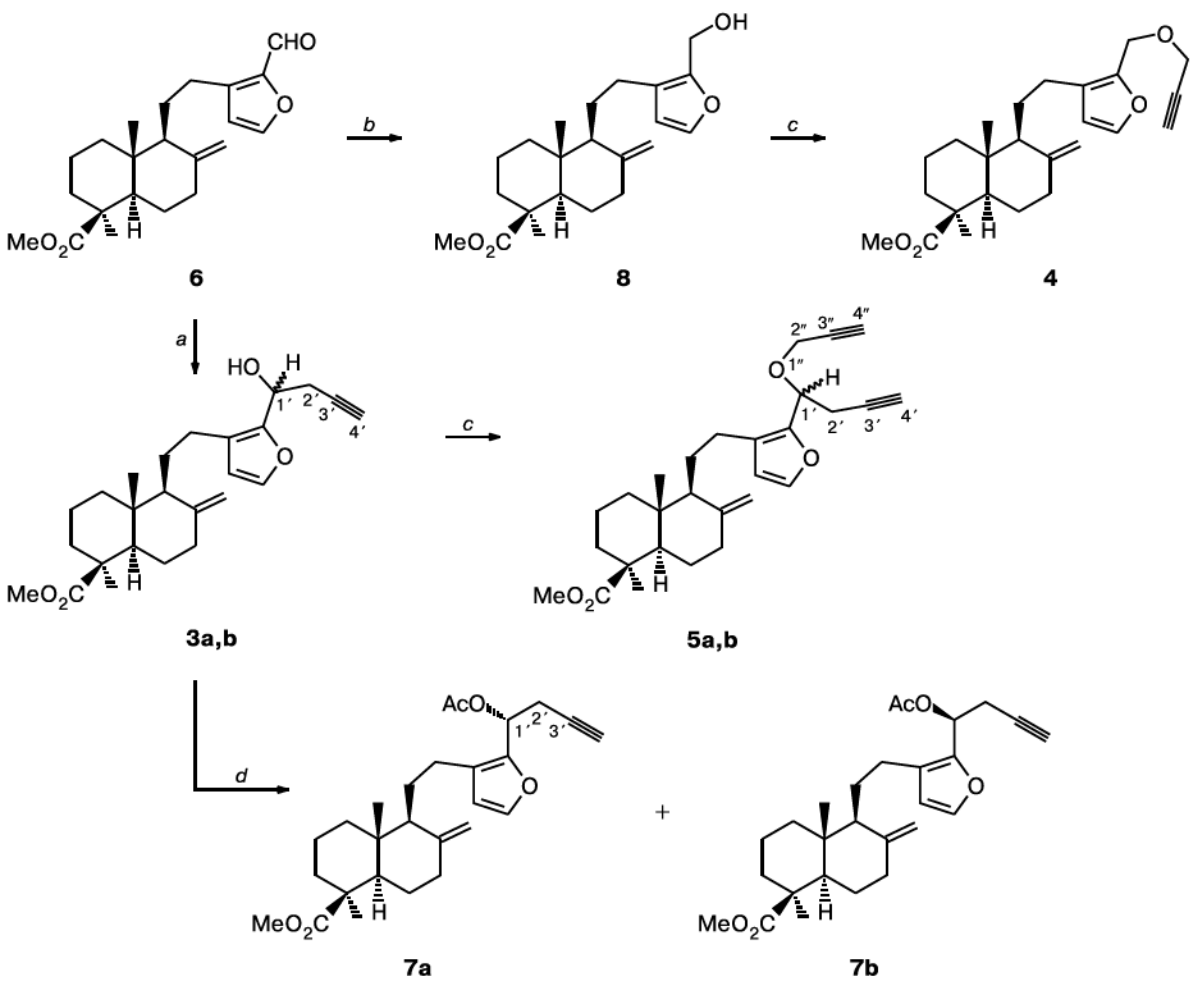
The oxidation of stereoisomeric alcohols **10a,b** with the Dess—Martin periodinane led to 1′-keto derivative **13** isolated in 65% yield. The dehydration of stereoisomeric alcohols **10a,b** upon treatment with methanesulfonyl chloride in the presence of triethylamine and catalytic amount of 4-dimethylaminopyridine[15] led to the individual (*E*)-triazolylvinyllabdanoid (**14**) (49% yield).

Alkynyllabdanoids **3a,b** smoothly reacted with 1,10-diazidodecane (**15**) in the presence of catalytic amount of $CuSO_4 \cdot 5H_2O$ and sodium ascorbate in a dilute solution of dichloromethane with the formation of stereoisomeric triazole lazides (**16a,b**) (73% yield) (Scheme 3).

The reaction of alkynes **3a,b** with (3*S*,4*R*,5*R*)-3-azido-1-ethoxycarbonyl-4,5-bis(methanesulfonyloxy)cyclohexene (**17**)[16] in the presence of CuI and diisopropylethylamine proceeds with the formation of a mixture of stereoisomeric 16-(2-{1-[(3-ethoxycarbonylphenyl)-1,2,3-triazol-4-yl]-1-hydroxyethyl})labdatrienes (**18a,b**) (85% yield) (Scheme 4). 1,3-Dipolar cycloaddition of azide **17** to the terpenoid alkyne **4** smoothly leads to 16-{[(3-ethoxycarbonylphenyl)-1*H*-triazol-4-yl]methoxymethyl}-labdatriene (**19**) (87% yield). As it is seen, the reaction proceeds through the elimination of sulfonyloxy substituents and aromatization. The easy formation of the aromatic azide from compound **17** was reported earlier in the work.[16]

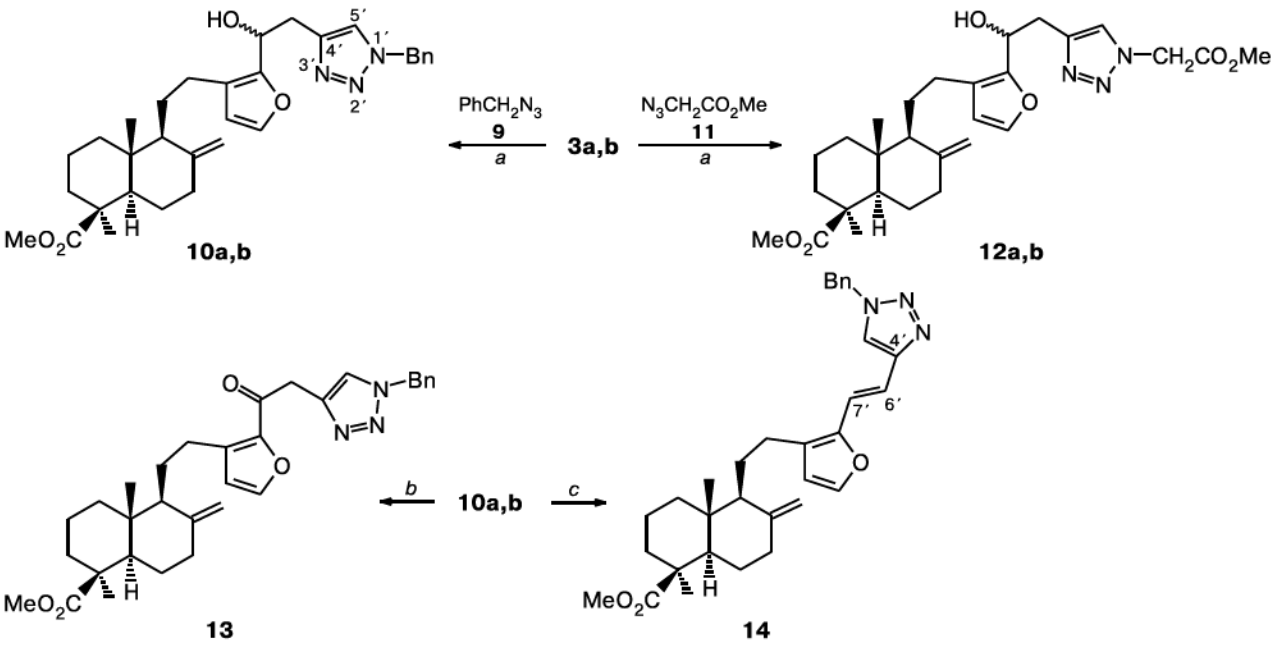
Nonsymmetric bis-1,2,3-triazoles possess valuable pharmacological properties.[17] This prompted us to synthesize labdanoid bis-triazoles based on dialkynes **5a,b**. The reaction of diastereomers of methyl 16-[(*4RS*)-5-oxaocta-1,7-diyn-4-yl]lambertianates **5a,b** with methyl 2-azidoacetate **11** (2 equiv.) leads to the corresponding bis-triazole-containing labdanoids **20a,b** (86% yield)

Scheme 1



Reagents and conditions: *a*. $BrCH_2C{\equiv}CH$, Zn, aq. NH_4Cl; *b*. $NaBH_4$, MeOH; *c*. $BrCH_2C{\equiv}CH$, NaH; *d*. Ac_2O, Py.

Scheme 2



Reagents and conditions: *a*. CuI, Pr^i_2NEt, MeCN, 20 °C; *b*. Dess—Martin periodinane, CH_2Cl_2, 20 °C; *c*. MsCl, Et_3N, DMAP, EtOAc, 0 °C, 1 h, then 20 °C, 1 h.

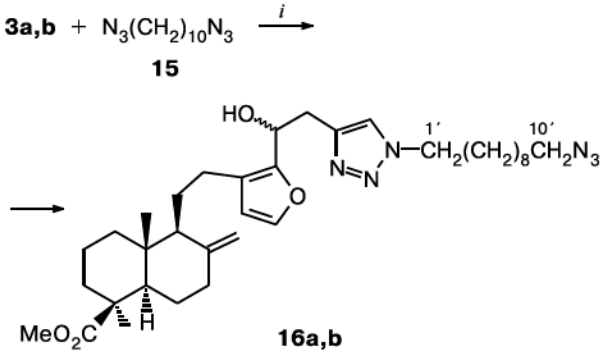
(Scheme 5). A mixture of 1′(*R*)- and 1′(*S*)-bis(1-aryltriazol-4-yl)-containing labdanoids **21a**,**b** (78% yield) was obtained by the reaction of dialkynes **5a**,**b** with azide **17**.

The structure of the compounds synthesized was established based on the combination of mass, IR, UV, and NMR spectral data. The IR spectra of compounds **16a**,**b** is featured by the presence of the absorption band of the azide group at 2097 cm^{-1}.

The formation of the 1,2,3-triazole ring in compounds **10a**,**b**, **12a**,**b**, **16a**,**b**, **18a**,**b**, and **19** was confirmed by the NMR spectral data. The ^1H NMR spectra exhibit a singlet related to proton H(5′) (δ 7.10—7.98). The signals for the carbon atoms of the triazole ring (C(4′) and C(5′)) in the ^{13}C NMR spectra were found in the region δ 144.73—145.38 (s) and 120.73—122.06 (d), respectively. The double sets of signals are observed in the spectra of mixtures of 1′(*R*)- and 1′(*S*)-stereoisomers **10a**,**b**, **12a**,**b**, **16a**,**b**, **18a**,**b**, **20a**,**b**, and **21a**,**b**. The ^1H and ^{13}C NMR spectra of stereoisomers **20a**,**b** and **21a**,**b** show the presence of two 1,2,3-triazole rings in the structure. For example, the ^1H NMR spectrum of compounds **20a**,**b** exhibits four singlets for the protons of the 1,2,3-triazole substituents (δ 7.33, 7.39, 7.48, and 7.50). These substituents in the ^{13}C NMR spectrum are represented by two doublets at δ 123.73 and 123.93 (C(5′)) and two singlets at δ 145.35 and 144.38 (C(4′)).

On going from 1-methyl-1,2,3-triazole[18] to triazoles **16a**,**b**, the signals for atoms N(1′), N(2′), and N(3′) in

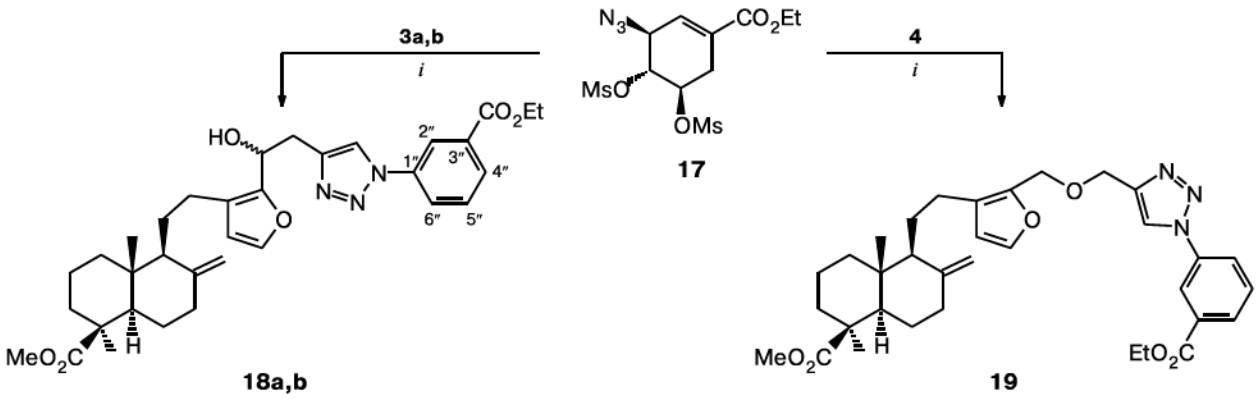
Scheme 3



Reagents and conditions: *i*. $CuSO_4 \cdot 5H_2O$, Na ascorbate, CH_2Cl_2, 40 °C.

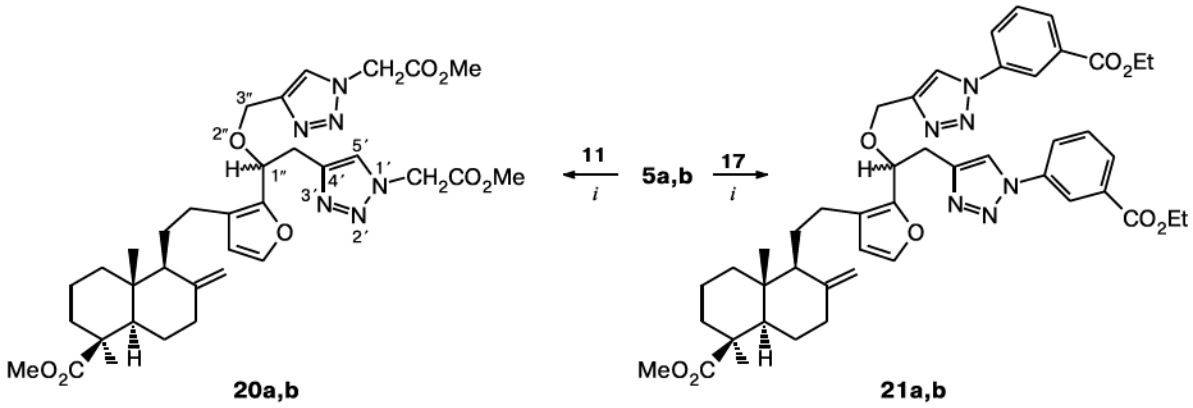
the ^{15}N NMR spectra shift upfield (Δδ ~12, 4, and 5, respectively). The signals for atoms N(1′), N(2′), and N(3′) are found as multiplets with the spin-spin coupling constant lying in the range 1.0—4.0 Hz with the CH_2 and H(5′) protons. The ^1H—^{13}C COLOC spectrum of compounds **10a**,**b** exhibits a cross-peak between the signals for protons H(5′) and the carbon atom of the benzyl CH_2 group. The features of the ^{15}N NMR spectrum and the interactions found in the 2D spectrum (for 1,2,3-triazoles **10a**,**b** taken as examples) indicate the formation of 4-substituted 1,2,3-triazoles and confirm the regioselectivity of

Scheme 4



Conditions: *i*. CuI, Pr^i_2NEt, MeCN, 20 °C.

Scheme 5



Conditions: *i*. CuI, Pr^i_2NEt, MeCN, 20 °C.

the reaction of the labdane-type alkynes with azides under consideration.

The ^{1}H NMR spectra of compounds **18a,b**, **19**, and **21a,b** containing 1-(3-ethoxycarbonylphenyl)-1*H*-1,2,3-triazole substituent are distinguished by the presence of four signals for the protons of the aromatic substituent with characteristic splitting (for example, for **19**: 7.48 (t, 1 H, H(5″), J = 7.8 Hz); 7.88 (dd, 1 H, H(6″), J = 7.8 and 1.5 Hz); 7.98 (d, 1 H, H(4″), J = 7.8 Hz); 8.24 (d, 1 H, H(2″), J = 1.5 Hz)).

The spin-spin coupling constants between protons H(6′) and H(7′) (J = 16.1 Hz) indicate the formation of compound **14** with the (*E*)-configuration of the double bond.

Cytotoxic activity of the compounds synthesized was characterized by the concentration of the active compound inhibiting the viability of the tumor cells by 50% ($CCID_{50}$). To determine the $CCID_{50}$, we used the standard MTT-test, which made it possible to evaluate amount of live cells spectrophotometrically.[19]

The cytotoxic activity of labdanoids **3a,b**, **5a,b**, **7a,b**, **10a,b**, **12a,b**, **13**, **18a,b**, **19**, and **20a,b** is given in Table 1. Compounds **10a,b**, **18a,b** containing 2-[aryl(benzyl)-1,2,3-triazol-4-yl]-1-hydroxyethyl substituents at position C(16), as well as compound **12**, the labdane framework in which is bound to the triazole fragment with the ethanone linker, display the highest cytotoxicity toward the three lines of tumor cells. The cytotoxicity of these derivatives toward the human tumor cells five—six times exceeds the moderate cytotoxicity of lambertianic acid **1**. Compounds **18a,b** exhibit higher cytotoxicity than the corresponding triazololabdanoid **19** with oxabismethylene linker.

Note that cytotoxicity of acetylene derivatives **3a,b**, **5a,b**, and **7a,b** is selective toward lymphoid tumor cells MT-4 and CEM-13.

The results obtained indicate that the modification of labdanoids by the introduction of 2-[aryl(benzyl)-1,2,3-triazol-4-yl]-1-hydroxyethyl substituents at position C(16) of the molecules is a promising approach, since such

Table 1. Cytotoxic activity of new lambertianic acid derivatives

Compound	$CCID_{50}$/μmol L^{-1}		
	CEM-13	U-937	MT-4
3a,b	19±4.2	70±8.9	17±6.5
5a,b	13±7.5	60±11.2	11±4.8
7a,b	27±5.9	58±13.3	24±4.5
10a,b	12±3.7	16±4.7	18±4.2
12a,b	47±8.5	40±4.2	39±8.3
13	10±3.5	7±3.8	16±3.8
18a,b	24±6.9	8±3.4	21±6.6
19	41±7.5	36±7.2	76±9.4
20a,b	31±5.9	31±8.2	42±6.6
Lambertianic acid **1**	69.1	43.2	92.1

a transformation makes it possible to obtain compounds possessing considerably higher cytotoxicity to tumor cells than the starting compound.

In conclusion, we for the first time synthesized methyl lambertianate derivatives containing 1,2,3-triazole and bis(1,2,3-triazole) substituents. These compounds were found to possess considerable cytotoxic activity toward human tumor cells.

Experimental

^1H and ^{13}C NMR spectra for solutions of compounds in $CDCl_3$ were recorded on Bruker AV-300 (300.13 (^1H) and 75.47 MHz (^{13}C)), Bruker AV-400 (400.13 (^1H) and 100.78 MHz (^{13}C)), and Bruker AV-600 (600.30 (^1H) and 150.96 MHz (^{13}C)) spectrometers relative to $SiMe_4$. The ^{15}N NMR spectrum was obtained on a Bruker AV-600 spectrometer (60.84 MHz) relative to nitromethane (δ_N 0.0). In the description of the ^1H and ^{13}C NMR spectra, the labdane skeleton atoms numeration system given in structure **1** was used. The signals in the NMR spectra were assigned using different types of proton-proton and carbon-proton correlation spectroscopy (COSY, COXH, COLOC). The signal splittings in the ^{13}C NMR spectra were determined upon recording spectra in the J-mode.

A DFS Thermo Scientific high resolution mass spectrometer (EI 70 eV, injector temperature 230—280 °C) was used to record mass spectra and determine molecular weights and elemental composition of compounds.

IR spectra were recorded on a Vector-22 spectrometer. UV absorption spectra were obtained on an HP 8453 UV Vis spectrometer in ethanol. Specific rotation $[\alpha]_D^{20}$ was measured on a PolAAr3005 polarimeter. Melting points were determined on a SMF-38 heating stage. Elemental analysis was performed on a Carlo Erba 1106 CHN-analyzer.*

Reaction progress was monitored by TLC on Silufol UV-254 plates. Mixtures of chloroform—ethanol, 3 : 1; light petroleum—ethyl acetate, 10 : 1 were used as eluents. The spots were visualized by sprinkling the plates with 10% aq. H_2SO_4 with subsequent heating to 100 °C or under UV light. Reaction products were isolated by column chromatography on silica gel (Acros, 0.035—0.070 mm, pore diameter 6 nm), eluents chloroform—methanol, light petroleum—diethyl ether.

Freshly distilled solvents and reagents of pure grade were used. The synthesis of compounds **3a,b**,[13] **4**,[14] and **5a,b**[13] was performed as described earlier. Methyl 16-formyllabdatrienoate **6**,[20] methyl 16-(hydroxymethyl)lambertianate **8**,[20] as well as azides **9**,[21] **11**,[22] **15**,[23] and **17**[15] were obtained according to the known procedures.

Methyl (1*S*,4a*R*,5*S*,8a*R*)-5-{2-[2-(1(*R*)-acetoxybut-3-yn-1-yl)-furan-3-yl]ethyl}- and methyl (1*S*,4a*R*,5*S*,8a*R*)-5-{2-[2-(1(*S*)-acetoxybut-3-yn-1-yl)furan-3-yl]ethyl}-1,4a-dimethyl-6-methylidenedecahydronaphthalene-1-carboxylates (7a,b). Pyridine (2 mL) was added to a solution of compounds **3a,b** (0.35 g) in acetic anhydride (1 mL). The reaction mixture was stirred for 10 h, poured on ice, and extracted with chloroform (3×20 mL). The combined organic layers were washed with water (4×20 mL) and dried with $MgSO_4$. The solvent was evaporated, the residue was subjected to chromatography on silica gel (eluent light petroleum—diethyl ether, 4 : 1) to obtain a mixture of stereoisomers **7a,b** as an oil (98% yield). IR (neat), ν/cm^{-1}: 891, 968, 1024, 1157, 1232, 1373, 1460, 1506, 1645, 1724, 2853, 2926, 3271, 3306, 3462. UV, λ_{max}/nm (lgε): 220 (4.14), 254 (3.70). ^1H NMR (400.13 MHz), δ: 0.48 (s, 3 H, *C(20)H_3); 1.00 (m, 1 H, *H(1α)); 1.03 (m, 1 H, *H(3α)); 1.15 (s, 3 H, C(19)H_3); 1.16 (s, 3 H, C(19)H_3); 1.25 (m, 1 H, *H(5α)); 1.48 (m, 2 H, *H(2), *H(11)); 1.59 (br.s, 1 H, H(9)); 1.62 (br.s, 1 H, H(9)); 1.69 (m, 1 H, *H(11)); 1.75—1.79 (m, 3 H, *H(6), *H(1β), *H(2)); 1.82 (m, 1 H, *H(7α)); 1.91 (m, 1 H, *H(6)); 2.03 (s, 3 H, Ac); 2.03 (s, 3 H, Ac); 2.14 (dm, 1 H, *H(3β), J_{gem} = 12.7); 2.35—2.37 (m, 1 H, *H(12)); 2.41 (m, 1 H, *H(7β)); 2.53—2.65 (m, 1 H, *H(12)); 2.74—2.91 (m, 2 H, *H(2′)); 3.59 (s, 3 H, *OCH_3); 4.59 (s, 1 H, H(17)); 4.62 (s, 1 H, H(17)); 4.90 (s, 1 H, H(17)); 4.92 (s, 1 H, H(17)); 5.92 (d, 1 H, H(1′), J = 7.3 Hz); 5.96 (d, 1 H, H(1′), J = 7.1 Hz); 6.22 (d, 1 H, H(14), J = 1.2 Hz); 6.23 (d, 1 H, H(14), J = 1.2 Hz); 7.32 (d, 1 H, *H(15), J = 1.2 Hz). ^{13}C NMR, δ: 12.48, 12.52 (C(20)); 19.84 (*C(2)); 20.79, 20.81 (CO<u>C</u>H_3); 22.94, 22.97 (C(12)); 23.01, 23.13 (C(2′)); 24.52, 24.77 (C(11)); 26.18 (*C(6)); 28.70 (*C(19)); 38.10 (*C(3)); 38.60 (*C(7)); 38.94, 38.25 (C(1)); 40.10 (*C(10)); 44.18 (*C(4)); 51.01 (*OCH_3); 55.00, 55.40 (C(9)); 56.15, 56.17 (C(5)); 64.78, 64.87 (C(1′)); 70.14, 70.19 (C(4′)); 78.99, 79.13 (C(3′)); 106.40, 106.64 (C(17)); 111.49, 111.52 (C(14)); 124.64, 124.75 (C(13)); 142.17, 142.21 (C(15)); 145.42, 145.62 (C(16)); 147.47, 147.71 (C(8)); 169.57, 169.65 (<u>C</u>OCH_3); 177.59, 177.61 (C(18)). MS, m/z (I_{rel} (%)): 440 (1), 380 (10), 341 (30), 321 (10), 281 (17), 204 (12), 189 (26), 131 (55), 121 (100), 109 (25), 107 (30), 105 (27), 95 (30), 93 (28), 91 (36), 81 (48), 79 (27), 77 (27), 71 (33), 69 (30), 67 (27), 57 (53), 55 (56), 43 (76), 41 (55), 39 (16), 29 (20), 27 (13). HRMS, m/z: found: 440.2553 $[M]^+$; calculated for $C_{27}H_{36}O_5$ M = 440.2557.

Methyl (1*S*,4a*R*,5*S*,8a*R*)-5-(2-{2-[2(*R*)-(1-benzyl-1*H*-triazol-4-yl)-1(*R*)-hydroxyethyl]furan-3-yl}ethyl)- and methyl (1*S*,4a*R*,5*S*,8a*S*)-5-(2-{2-[2-(1-benzyl-1*H*-triazol-4-yl)-1(*S*)-hydroxyethyl]furan-3-yl}ethyl)-1,4a-dimethyl-6-methylidene-decahydronaphthalene-1-carboxylates (10a,b). Diisopropylethyl-

* Analytical and spectroscopic studies were performed in the Chemical Service Center of Collective Exploitation of SB of RAS.

* The doubling of the signal in the spectra of a mixture of stereoisomers.

amine (0.21 mL, 1.2 mmol), benzyl azide **9** (0.48 g, 1.2 mmol), and CuI (0.012 g, 0.12 mmol) were sequentially added to a stirred solution of compounds **3a**,**b** (0.50 g, 1.2 mmol) in acetonitrile (10 mL) at 0 °C under argon. The temperature was raised to ambient, and the reaction mixture was stirred for 24 h. The solvent was evaporated *in vacuo*, the residue was dissolved in chloroform, washed with 2 *N* aqueous H_2SO_4 (2×50 mL), water (2×50 mL), aq. NH_4Cl/NH_4OH (9 g of NH_4Cl, 1 mL of NH_4OH, and 100 mL of H_2O) (2×50 mL), and water (2×50 mL), then dried with $MgSO_4$. The solvent was evaporated, the residue was subjected to column chromatography on silica gel (eluent chloroform—methanol, 100 : 1) to obtained a mixture of compounds **10a**,**b** (0.53 g, 80%) as an oil. IR (neat), ν/cm^{-1}: 754, 891, 988, 1034, 1047, 1134, 1157, 1227, 1454, 1643, 1720, 2847, 2945, 3078, 3144, 3397. ^{1}H NMR (400.13 MHz), δ: 0.45 (s, 3 H, *C(20)H_3); 0.95 (m, 1 H, *H(1α)); 0.99 (m, 1 H, *H(3α)); 1.13 (s, 3 H, C(19)H_3); 1.14 (s, 3 H, C(19)H_3); 1.23 (m, 1 H, *H(5α)); 1.47 (m, 2 H, *H(2), *H(11)); 1.51—1.57 (m, 2 H, *H(9), *H(11)); 1.72—1.80 (m, 3 H, *H(2), *H(6), *H(1β)); 1.80—1.89 (m, 1 H, *H(7α)); 1.94 (m, 1 H, *H(6)); 2.12 (m, 1 H, *H(3β)); 2.17 (m, 1 H, *H(12)); 2.36 (m, 1 H, *H(7β)); 2.37 (m, 1 H, H(12)); 2.46 (m, 1 H, H(12)); 3.06 (dd, 1 H, CH_2, J = 15.1 Hz, J = 4.8 Hz); 3.08 (dd, 1 H, CH_2, J = 15.1 Hz, J = 5.4 Hz); 3.31 (dd, 1 H, CH_2, J = 15.1 Hz, J = 8.0 Hz); 3.32 (dd, 1 H, CH_2, J = 15.1 Hz, J = 8.6 Hz); 3.59 (s, 3 H, *OCH_3); 4.49 (s, 1 H, H(17)); 4.53 (s, 1 H, H(17)); 4.84 (s, 1 H, H(17)); 4.84 (s, 1 H, H(17)); 4.94 (dd, 1 H, C<u>HOH</u>, J = 8.0 Hz, J = 5.4 Hz); 4.96 (dd, 1 H, C<u>HOH</u>, J = 8.6 Hz, J = 4.8 Hz); 5.44 (d, 2 H, CH_2Ph, J = 4.6 Hz); 5.45 (d, 2 H, CH_2 Ph, J = 2.5 Hz); 6.15 (d, 1 H, H(14), $J_{14,15}$ = 1.5 Hz); 6.16 (d, 1 H, H(14), $J_{14,15}$ = 1.5 Hz); 7.10 (s, 1 H, H(5′)); 7.14 (s, 1 H, H(5′)); 7.19 (m, 2 H, *H(2″), *H(6″)); 7.25 (m, 1 H, *H(15)); 7.33 (m, 3 H, *H(3″), *H(5″), *H(4″)). ^{13}C NMR, δ: 12.48 (*C(20)); 19.79 (*C(2)); 22.72, 22.90 (C(12)); 24.33, 24.55 (C(11)); 26.11 (*C(6)); 28.62, 28.66 (C(19)); 31.95, 32.02 (CH_2); 38.00, 38.03 (C(3)); 38.49, 38.57 (C(7)); 38.85, 38.89 (C(1)); 39.98, 40.02 (C(10)); 44.15 (*C(4)); 50.98, 51.00 (OCH_3); 53.87, 53.88 (CH_2Ph); 54.65, 55.04 (C(9)); 55.97, 56.09 (C(5)); 64.97 (*CHOH); 106.37, 106.44 (C(17)); 111.27, 111.41 (C(14)); 121.71 (*C(5′)); 121.96 (*C(13)); 127.78, 127.80 (*C(2″,6″)); 128.50, 128.51 (C(4″)); 128.91 (*C(5″,3″)); 134.60 (*C(1″)); 141.16, 141.21 (C(15)); 144.81, 144.90 (C(4′)); 147.66, 147.78 (C(8)); 149.52, 149.61 (C(16)); 177.61, 177.64 (C(18)). MS, m/z (I_{rel} (%)): 531 (4), 514 (10), 513 (12), 265 (11), 202 (24), 174 (12), 173 (86), 121 (20), 91 (100). HRMS, m/z: found: 531.3089 [M]$^+$; calculated for $C_{32}H_{41}N_3O_4$ M = 531.3092.

Methyl (1*S*,4a*R*,5*S*,8a*R*)-5-[2-(2-{1(*R*)-hydroxy-2-[1-(2-methoxy-2-oxoethyl)-1*H*-triazol-4-yl]ethyl}furan-3-yl)ethyl]- and methyl (1*S*,4a*R*,5*S*,8a*S*)-5-[2-(2-{1(*S*)-hydroxy-2-(1-(2-methoxy-2-oxoethyl)-1*H*-triazol-4-yl]ethyl}furan-3-yl)ethyl]-1,4a-dimethyl-6-methylidenedecahydronaphthalene-1-carboxylates (12a,b). Diisopropylethylamine (0.21 mL, 1.2 mmol), methyl 2-azidoacetate **11** (0.14 g, 1.2 mmol), and CuI (0.012 g, 0.12 mmol) were sequentially added to a stirred solution of compounds **3a**,**b** (0.50 g, 1.2 mmol) in acetonitrile (10 mL) at 0 °C under argon. The temperature was raised to ambient, and the reaction mixture was stirred for 24 h. The solvent was evaporated, the residue was dissolved in chloroform, washed with 2 *N* aq. H_2SO_4 (2×50 mL), water (2×50 mL), aq. NH_4Cl/NH_4OH (9 g of NH_4Cl, 1 mL of NH_4OH, and 100 mL of H_2O) (2×50 mL), water (2×50 mL), and dried with $MgSO_4$. The solvent was evaporated, the residue was subjected to chromatography on silica gel (eluent chloroform—methanol, 100 : 1) to obtain a mixture of compounds **12a**,**b** (0.52 g, 82%) as an oil. IR (neat), ν/cm^{-1}: 756, 891, 989, 1032, 1049, 1094, 1155, 1229, 1377, 1441, 1464, 1554, 1645, 1722, 1757, 2849, 2974, 2949, 3150, 3410. UV, λ_{max}/nm (lgε): 218 (3.91). ^{1}H NMR (400.13 MHz), δ: 0.46 (s, 3 H, *C(20)H_3); 0.95 (m, 1 H, *H(1α)); 0.99 (dt, 1 H, *H(3α), J = 12.9 Hz, J = 3.8 Hz); 1.14 (s, 3 H, C(19)H_3); 1.15 (s, 3 H, C(19)H_3); 1.23 (m, 1 H, *H(5α)); 1.45—1.49 (m, 2 H, *H(2), *H(11)); 1.54 (br.s, 1 H, H(9)); 1.56 (br.s, 1 H, H(9)); 1.65 (m, 1 H, *H(11)); 1.72, 1.77, 1.81 (all m, 3 H, *H(6), *H(1β), *H(2)); 1.83 (m, 1 H, *H(7α)); 1.94 (m, 1 H, *H(6)); 2.12 (m, 1 H, *H(3β), J_{gem} = 12.9 Hz); 2.24 (m, 1 H, *H(12)); 2.38 (m, 1 H, *H(7β)); 2.45 (m, 1 H, *H(12)); 2.79 (br.s, 1 H, OH); 2.85 (br.s, 1 H, OH); 3.14 (m, 1 H, CH_2); 3.15 (dd, 1 H, CH_2, J = 14.7 Hz, J = 5.2 Hz); 3.36 (dd, 1 H, CH_2, J = 14.7 Hz, J = 8.6 Hz); 3.35 (m, 1 H, CH_2); 3.58 (s, 3 H, *OCH_3); 3.78 (s, 3 H, *CH_2CO_2<u>CH_3</u>); 4.51 (s, 1 H, H(17)); 4.55 (s, 1 H, H(17)); 4.86 (s, 1 H, *H(17)); 4.99 (m, 1 H, *C<u>HOH</u>); 5.08 (d, 2 H, <u>CH_2</u>CO_2CH_3, J = 3.9 Hz); 5.11 (d, 2 H, <u>CH_2</u>CO_2CH_3, J = 3.9 Hz); 6.20 (d, 1 H, H(14), $J_{14,15}$ = 1.8 Hz); 6.21 (d, 1 H, H(14), $J_{14,15}$ = 1.8 Hz), 7.31 (d, 1 H, *H(15), $J_{14,15}$ = 1.8 Hz); 7.35 (s, 1 H, H(5′)); 7.40 (s, 1 H, H(5′)). ^{13}C NMR, δ: 12.49 (*C(20)); 19.82 (*C(2)); 22.77, 22.95 (C(12)); 24.34, 24.55 (C(11)); 26.15 (*C(6)); 28.64 (*C(19)); 31.92, 32.02 (CH_2); 38.03 (*C(3)); 38.52, 38.61 (*C(7)); 38.89, 38.93 (C(1)); 40.01, 40.05 (C(10)); 44.17 (*C(4)); 50.51, 50.68 (<u>CH_2</u>CO_2CH_3); 50.99 (*OCH_3); 52.87 (*CH_2CO_2<u>CH_3</u>); 54.70, 55.09 (C(9)); 56.03, 56.13 (C(5)); 64.93 (*CHOH); 106.41 (*C(17)); 111.38, 111.50 (C(14)); 122.06 (*C(5′)); 122.07 (*C(13)); 141.27, 141.32 (C(15)); 144.77, 144.86 (C(4′)); 147.73, 147.82 (C(8)); 149.64 (*C(16)); 166.61 (*CH_2<u>CO_2</u>CH_3); 177.66 (*C(18)). MS, m/z (I_{rel} (%)): 513 (1.7), 495 (10), 198 (12), 189 (12), 169 (27), 161 (11), 155 (85), 147 (11), 133 (12), 122 (12), 121 (100), 119 (20), 110 (12), 109 (26), 107 (31), 105 (23), 95 (16), 93 (18), 91 (31), 81 (32), 79 (26), 77 (17), 69 (10), 68 (15), 67 (20), 69 (12), 55 (30), 53 (15). HRMS, m/z: found: 513.2969 [M]$^+$; calculated for $C_{28}H_{39}N_3O_6$ M = 513. 2825.

Methyl (1*S*,4a*R*,5*S*,8a*R*)-5-(2-{2-[2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)acetyl]furan-3-yl}ethyl)-1,4a-dimethyl-6-methylidenedecahydronaphthalene-1-carboxylate (13). Dess—Martin periodinane (0.44 g, 1.0 mmol) was added to a solution of compounds **10a**,**b** (0.50 g, 0.9 mmol) in dichloromethane (10 mL) under argon. The mixture was stirred for 24 h at room temperature, the solvent was evaporated, the residue was subjected to chromatography on silica gel (eluent light petroleum—diethyl ether, 1 : 1) to obtain compound **13** (0.33 g, 65%) as an oil, $[\alpha]_D^{20}$ +37.45 (*c* 0.33, $CHCl_3$). IR (neat), ν/cm^{-1}: 733, 754, 885, 1047, 1153, 1229, 1414, 1454, 1468, 1580, 1674, 1722, 2847, 2945, 3424. UV, λ_{max}/nm (lgε): 278 (3.75). ^{1}H NMR (400.13 MHz), δ: 0.46 (s, 3 H, C(20)H_3); 0.96—1.04 (m, 2 H, H(1α), H(3α)); 1.15 (s, 3 H, C(19)H_3); 1.26 (dd, 1 H, H(5α), J = 12.0 Hz, J = 2.8 Hz); 1.46* (m, 1 H, H(2)); 1.59* (m, 1 H, H(11)); 1.60 (m, 1 H, H(9)); 1.73, 1.77, 1.80 (all m, 3 H, H(6), H(1β), H(2)); 1.85 (m, 1 H, H(7α)); 1.95 (m, 1 H, H(6)); 2.13 (dm, 1 H, H(3β), J_{gem} = 13.2 Hz); 2.38 (m, 1 H, H(7β)); 2.65 (m, 1 H, H(12)); 2.91 (m, 1 H, H(12)); 3.58 (s, 3 H, OCH_3); 4.33 (s, 2 H, CH_2); 4.61 (s, 1 H, H(17)); 4.87 (s, 1 H, H(17)); 5.50 (s, 2 H, CH_2Ph); 6.43 (d, 1 H, H(14), $J_{14,15}$ = 1.6 Hz); 7.25 (m, 2 H, H(2″), H(6″)); 7.33—7.35 (m, 3 H, H(3″), H(5″) and H(4″)); 7.43 (d, 1 H, H(15), $J_{14,15}$ = 1.6 Hz); 7.58 (s, 1 H, H(5′)). ^{13}C NMR, δ: 12.45 (C(20)); 19.79 (C(2)); 23.60 (C(12)); 24.75

(C(11)); 26.12 (C(6)); 28.68 (C(19)); 36.10 (CH_2); 38.07 (C(3)); 38.58 (C(7)); 38.91 (C(1)); 40.15 (C(10)); 44.16 (C(4)); 51.01 (OCH_3); 54.02 ($\underline{CH_2}$Ph); 55.57 (C(9)); 56.13 (C(5)); 106.50 (C(17)); 114.55 (C(14)); 122.78 (C(5′)); 127.95 (C(2″), C(6″)); 128.51 (C(4″)); 128.92 (C(5″), C(3″)); 134.64 (C(1″)); 136.46 (C(13)); 140.89 (C(4′)); 144.71 (C(15)); 147.25 (C(8)); 147.53 (C(16)); 177.62 (C(18)); 186.04 (CO). MS, *m*/*z* (I_{rel} (%)): 356 (24), 341 (37), 312 (10), 300 (18), 299 (100), 281 (21), 192 (25), 189 (15), 181 (11), 173 (13), 161 (14), 151 (74), 149 (11), 148 (45), 147 (47), 146 (10), 133 (11), 122 (11), 121 (79), 120 (12), 119 (18), 109 (20), 107 (25), 106 (16), 105 (42), 95 (14), 93 (22), 91 (32), 81 (25), 79 (29), 77 (29), 67 (13), 65 (11), 55 (18), 53 (10), 41 (19). HRMS, *m*/*z*: found 529.6694 $[M]^+$; calculated for $C_{32}H_{39}N_3O_4$ M = 529.6699.

Methyl (1*S*,4a*R*,5*S*,8a*R*)-5-(2-{2-[(*E*)-2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)vinyl]furan-3-yl}ethyl)-1,4a-dimethyl-6-methylidenedecahydronaphthalene-1-carboxylate (14). Methanesulfonyl chloride (0.13 mL, 1.63 mmol) was added to a solution of compounds **10a**,**b** (0.43 g, 0.81 mmol) in ethyl acetate with stirring under argon, then the mixture was cooled to 0 °C, followed by addition of 4-dimethylaminopyridine (0.03 g, 0.24 mmol) and dropwise addition of Et_3N (0.23 mL, 1.63 mmol) with vigorous stirring. The reaction mixture was stirred for 1 h at 0 °C, and for another 1 h at room temperature, then diluted with 1 *N* aq. HCl (70 mL). The organic phase was separated, washed with aq. K_2CO_3 (pH = 8—9), and dried with $MgSO_4$. The solvent was evaporated *in vacuo*, the residue was subjected to column chromatography on silica gel (eluent light petroleum—diethyl ether) to obtain compound **14** (0.20 g, 49%) as an oil, $[\alpha]_D^{20}$ +43.26 (*c* 0.32, $CHCl_3$). IR (neat), ν/cm^{-1}: 739, 754, 893, 961, 982, 1047, 1155, 1229, 1454, 1643, 1720, 1759, 2849, 2945, 3429. UV, λ_{max}/nm (lgε): 312 (4.21). ^{1}H NMR (400.13 MHz), δ: 0.47 (s, 3 H, C(20)H_3); 0.94 (dt, 1 H, H(1α), *J* = 13.2 Hz, *J* = 4.6 Hz); 0.98 (dt, 1 H, H(3α), *J* = 13.3 Hz, *J* = 3.8 Hz); 1.13 (s, 3 H, C(19)H_3); 1.23 (dd, 1 H, H(5α), *J* = 12.0 Hz, *J* = 2.8 Hz); 1.45 (m, 1 H, H(2)); 1.57 (m, 2 H, H(9), H(11)); 1.67—1.70 (m, 1 H, H(11)); 1.73, 1.76, 1.80 (all m, 3 H, H(6), H(1β), H(2)); 1.83 (m, 1 H, H(7α)); 1.94 (m, 1 H, H(6)); 2.11 (dm, 1 H, H(3β), J_{gem} = 13.3 Hz); 2.32—2.39 (m, 2 H, H(7α), H(12)); 2.56 (m, 1 H, H(12)); 3.58 (s, 3 H, OCH_3); 4.58 (s, 1 H, H(17)); 4.89 (s, 1 H, H(17)); 5.48 (s, 2 H, CH_2Ph); 6.26 (d, 1 H, H(14), $J_{14,15}$ = 1.9 Hz); 6.83 (d, 1 H, H(6′), *J* = 16.1 Hz); 7.04 (d, 1 H, H(7′), *J* = 16.1 Hz); 7.26 (m, 2 H, H(2″), H(6″)); 7.27 (d, 1 H, H(15), $J_{14,15}$ = 1.9 Hz); 7.32, 7.33 (all m, 3 H, H(3″), H(5″), H(4″)); 7.36 (s, 1 H, H(5′)). ^{13}C NMR, δ: 12.46 (C(20)); 19.72 (C(2)); 22.98 (C(12)); 24.21 (C(11)); 26.05 (C(6)); 28.56 (C(19)); 37.94 (C(3)); 38.44 (C(7)); 38.81 (C(1)); 39.95 (C(10)); 44.07 (C(4)); 50.91 (OCH_3); 53.87 ($\underline{CH_2}$Ph); 54.65 (C(9)); 55.96 (C(5)); 106.36 (C(17)); 112.54 (C(14)); 113.04 (C(7′)); 116.46 (C(6′)); 119.90 (C(5′)); 124.58 (C(13)); 127.84 (C(2″), C(6″)); 128.51 (C(4″)); 128.89 (C(5″), C(3″)); 134.51 (C(1″)); 141.64 (C(15)); 146.46 (C(4′)); 147.66 (C(8)); 148.06 (C(16)); 177.51 (C(18)). MS, *m*/*z* (I_{rel} (%)): 513 (4), 189 (10), 158 (10), 130 (11), 128 (18), 121 (53), 119 (10), 115 (10), 109 (15), 107 (15), 105 (12), 93 (12), 92 (10), 91 (100), 85 (18), 83 (27), 81 (15), 79 (11), 77 (10), 65 (15), 55 (11), 43 (54). HRMS, *m*/*z*: found 513.2990 $[M]^+$; calculated for $C_{32}H_{39}N_3O_3$ M = 513.2986.

Methyl (1*S*,4a*R*,5*S*,8a*R*)-5-[2-(2-{(*R*)-2-[1-(10-azidodecyl)-1*H*-1,2,3-triazol-4-yl]-1-hydroxyethyl}furan-3-yl)ethyl]- and methyl (1*S*,4a*R*,5*S*,8a*R*)-5-[2-(2-{(*S*)-1-(10-azidodecyl)-1*H*-1,2,3-triazol-4-yl]-1-hydroxyethyl}furan-3-yl)ethyl]-1,4a-dimethyl-6-methylidenedecahydronaphthalene-1-carboxylates (16a,b). 1,10-Diazidodecane **15** (0.28 g, 1.20 mmol), a solution of $CuSO_4 \cdot 5H_2O$ (0.063 g, 0.25 mmol) in H_2O (0.5 mL), and a solution of sodium ascorbate (0.25 g, 1.2 mmol) in H_2O (0.5 mL) were sequentially added to a solution of compounds **3a**,**b** (0.50 g, 1.2 mmol) in dichloromethane (20 mL) with stirring. The temperature was raised to 40 °C and stirring was continued for 10 h. The organic phase was separated, washed with water (3×50 mL), and dried with $MgSO_4$. The solvent was evaporated, the residue was subjected to chromatography on silica gel (eluent chloroform—methanol, 100 : 2) to obtain a mixture of compounds **16a**,**b** (0.57 g, 73%) as an oil. IR (neat), ν/cm^{-1}: 754, 891, 1034, 1047, 1138, 1155, 1215, 1228, 1248, 1449, 1466, 1643, 1722, 2097, 2855, 2932, 3370. UV, λ_{max}/nm (lgε): 282 (3.09), 301 (3.10). ^{1}H NMR (400.13 MHz), δ: 0.41 (s, 3 H, *C(20)H_3); 0.91 (m, 1 H, *H(1α)); 0.95 (dt, 1 H, *H(3α), *J* = 13.4 Hz, *J* = 3.8 Hz); 1.10 (s, 3 H, C(19)H_3); 1.11 (s, 3 H, C(19)H_3); 1.22 (m, 15 H, 7 *CH_2, *H(5α)); 1.41, 1.43 (all m, 2 H, *H(2), *H(11)); 1.53 (m, 3 H, *H(9), *CH_2); 1.65 (m, 1 H, *H(11)); 1.68, 1.72, 1.77, 1.79 (all m, 3 H, *H(6), *H(1β), *H(2)); 1.82 (m, 1 H, *H(7α)); 1.90 (m, 1 H, *H(6)); 2.08 (dm, 1 H, *H(3β), J_{gem} = 13.4 Hz); 2.17 (m, 1 H, *H(12)); 2.32 (m, 1 H, *H(7β)); 2.40 (m, 1 H, *H(12)); 3.06 (m, 1 H, CH_2); 3.07 (dd, 1 H, CH_2, *J* = 14.7 Hz, *J* = 5.4 Hz); 3.19 (t, 2 H, *C(10″)H_2, *J* = 7.0 Hz); 3.28 (dd, 1 H, CH_2, *J* = 14.7 Hz, *J* = 8.5 Hz); 3.29 (m, 1 H, CH_2); 3.53 (s, 3 H, *OCH_3); 4.20 (m, 2 H, *C(1″)H_2); 4.44 (s, 1 H, H(17)); 4.50 (s, 1 H, H(17)); 4.81 (s, 1 H, *H(17)); 4.91 (m, 1 H, *C$\underline{HOH}$); 6.14 (d, 1 H, *H(14), $J_{14,15}$ = 1.7 Hz); 7.24 (d, 1 H, *H(15), $J_{14,15}$ = 1.7 Hz); 7.11 (s, 1 H, H(5′)); 7.16 (s, 1 H, H(5′)). ^{13}C NMR, δ: 12.43 (*C(20)); 19.73 (*C(2)); 22.73, 22.87 (C(12)); 24.34, 24.52 (C(11)); 26.05 (*C(6)); 26.21 (*CH_2); 26.47 (*CH_2); 28.55 (*C(19)); 28.60 (*CH_2); 28.74 (*CH_2); 28.87 (*CH_2); 29.06 (*CH_2); 29.13 (*CH_2); 30.06 (*CH_2); 31.91, 31.96 (CHOH$\underline{CH_2}$); 37.94, 37.96 (C(3)); 38.43, 38.51 (C(7)); 38.78, 38.81 (C(1)); 39.92, 39.95 (C(10)); 44.07 (*C(4)); 49.97 (C(1″)); 50.94 (*OCH_3); 51.23 (C(10″)); 54.66, 54.98 (C(9)); 55.89, 56.00 (C(5)); 64.90 (*CHOH); 106.30, 106.37 (C(17)); 111.26, 111.37 (C(14)); 121.52 (*C(5′)); 121.87, 121.92 (C(13)); 141.04, 141.11 (C(15)); 144.19, 144.29 (C(4′)); 147.60, 147.70 (C(8)); 149.64, 149.70 (C(16)); 177.57 (*C(18)). ^{15}N (δ: −20.85 (N(2)); −35.60 (N(3)); −132.64 (N(1)); −204.86, −205.80 (N_3). MS, *m*/*z* (I_{rel} (%)): 622 (2), 606 (10), 293 (13), 189 (23), 188 (12), 181 (16), 175 (11), 173(11), 161 (17), 159 (13), 147 (10), 133 (15), 131 (10), 122 (13), 121(100), 119 (21), 109 (21), 107 (27), 105 (21), 95 (14), 93 (23), 91 (22), 81 (21), 79 (20), 77 (10), 67 (13), 55 (14), 41 (11). HRMS, *m*/*z*: found 622.4192 $[M]^+$; calculated for $C_{35}H_{54}O_4N_6$ M = 622.4201.

Methyl (1*S*,4a*R*,5*S*,8a*R*)-5-{2-[2-(1(*R*)-hydroxy-2-{1-[3-(ethoxycarbonyl)phenyl]-1*H*-triazol-4-yl}ethyl)furan-3-yl]ethyl}- and methyl (1*S*,4a*R*,5*S*,8a*S*)-5-{2-[2-(1(*S*)-hydroxy-2-{1-[3-(ethoxycarbonyl)phenyl]-1*H*-triazol-4-yl}ethyl)furan-3-yl]ethyl}-1,4a-dimethyl-6-methylidenedecahydronaphthalene-1-carboxylates (18a,b). Diisopropylethylamine (0.21 mL, 1.2 mmol), (3*S*,4*R*,5*R*)-3-azido-1-(ethoxycarbonyl)-4,5-bis(methanesulfonyloxy)cyclohexene **17** (0.48 g, 1.2 mmol), and CuI (0.012 g, 0.12 mmol) were sequentially added to a solution of compounds **3a**,**b** (0.50 g, 1.2 mmol) in acetonitrile (10 mL) at 0 °C under argon with stirring. The temperature was raised to ambient, and stirring was continued for 24 h. The solvent was evaporated, the residue was dissolved in chloroform (40 mL), washed with 2 *N* aq. H_2SO_4 (2×50 mL), water (2×50 mL), aq. NH_4Cl/NH_4OH

(9 g of NH_4Cl, 1 mL of NH_4OH, and 100 mL of H_2O) (2×50 mL), water (2×50 mL), and dried with $MgSO_4$. The solvent was evaporated, the residue was subjected to chromatography on silica gel (eluent chloroform—methanol, 100 : 1) to obtain a mixture of compounds **18a,b** (0.63 g, 85%) as an oil. IR (neat), ν/cm^{-1}: 675, 756, 814, 891, 1040, 1109, 1159, 1231, 1273, 1371, 1454, 1491, 1595, 1645, 1720, 2849, 2943, 3082, 3148, 3427. UV, λ_{max}/nm (lgε): 220 (3.83). ^{1}H NMR (400.13 MHz), δ: 0.34 (s, 3 H, *C(20)H$_3$); 0.86 (m, 1 H, *H(1α)); 0.89 (dt, 1 H, *H(3α), *J* = 13.4 Hz, *J* = 3.8 Hz); 1.05 (s, 3 H, C(19)H$_3$); 1.06 (s, 3 H, C(19)H$_3$); 1.16 (m, 1 H, *H(5α)); 1.35 (t, 5 H, *OCH$_2$CH$_3$, *H(2), *H(11), *J* = 7.0 Hz); 1.42 (br.s, 1 H, *H(9)); 1.50 (m, 1 H, *H(11)); 1.58—1.73 (m, 3 H, *H(6), *H(1β), *H(2)); 1.78 (dd, 1 H, *H(7α), *J* = 13.0 Hz, *J* = 3.6 Hz); 1.87 (dm, 1 H, *H(6), *J* = 12.5 Hz); 2.03 (m, 1 H, *H(3β)); 2.16 (m, 1 H, *H(12)); 2.29 (dt, 1 H, *H(7β), *J* = 12.1 Hz, *J* = 2.9 Hz); 2.41 (m, 1 H, *H(12)); 3.19 (dd, 1 H, *CH$_2$, *J* = 14.4 Hz, *J* = 5.7 Hz); 3.38 (dd, 1H, CH$_2$, *J* = 14.4 Hz, *J* = 5.7 Hz); 3.40 (dd, 1 H, CH$_2$, *J* = 14.4 Hz, *J* = 5.7 Hz); 3.51 (s, 3 H, *OCH$_3$); 4.34 (q, 2 H, *CH$_2$CH$_3$, *J* = 7.0 Hz); 4.41 (s, 1 H, H(17)); 4.47 (s, 1 H, H(17)); 4.79 (s, 1 H, *H(17)); 4.98 (t, 1 H, *CHOH, *J* = 5.7 Hz); 6.16 (d, 1 H, H(14), *J* = 1.6 Hz); 6.17 (d, 1 H, H(14), *J* = 1.6 Hz); 7.27 (d, 1 H, *H(15), *J* = 1.6 Hz); 7.50 (t, 1 H, H(5″), *J* = 8.1 Hz); 7.51 (t, 1 H, H(5″), *J* = 8.1 Hz); 7.67 (s, 1 H, H(5′)); 7.70 (s, 1 H, H(5′)); 7.87 (dm, 1 H, *H(6″), *J* = 8.1 Hz); 8.00 (d, 1 H, *H(4″), *J* = 8.1 Hz); 8.20 (t, 1 H, H(2″), *J* = 1.9 Hz); 8.21 (t, 1 H, H(2″), *J* = 1.9 Hz). ^{13}C NMR, δ: 12.38 (*C(20)); 14.16 (*OCH$_2$CH$_3$); 19.72 (*C(2)); 22.85 (*C(12)); 24.41, 24.47 (C(11)); 26.08 (*C(6)); 28.58 (*C(19)); 32.01 (*CH$_2$); 37.88, 37.94 (C(3)); 38.45, 38.49 (C(7)); 38.79 (*C(1)); 39.92 (*C(10)); 44.06 (*C(4)); 50.98 (*OCH$_3$); 54.79, 54.91 (C(9)); 55.96 (*C(5)); 61.46 (*OCH$_2$CH$_3$); 64.74, 64.84 (CHOH); 106.39 (*C(17)); 111.47 (*C(14)); 120.73, 120.80 (C(5′)); 122.18, 122.29 (C(13)); 124.22 (*C(6″)); 124.31 (*C(2″)); 129.25 (*C(4″)); 129.74 (*C(5″)); 131.97 (*C(3″)); 136.99 (*C(1″)); 141.25 (*C(15)); 145.38 (*C(4′)); 147.64 (*C(8)); 149.60 (*C(16)); 165.15 (*CO$_2$CH$_2$CH$_3$); 177.60 (*C(18)). MS, *m*/*z* (I_{rel} (%)): 589 (3), 571 (20), 543 (22), 341 (13), 339 (12), 315 (10), 308 (18), 307 (32), 295 (53), 294 (76), 280 (17), 266 (15), 249 (24), 248 (100), 231 (26), 222 (22), 221 (26), 220 (42), 202 (62), 174 (14), 147 (20), 130 (17), 121 (56), 119 (15), 119 (23), 107 (21), 105 (18), 93 (19), 91 (50), 81 (27), 79 (18), 77 (16), 65 (16), 55 (18), 41 (16), 29 (16). HRMS, *m*/*z*: found: 589.3141 [M]$^+$; calculated for $C_{34}H_{43}O_6N_3$ M = 589.3146.

Methyl (1*S*,4a*R*,5*S*,8a*R*)-5-(2-{2-[({1-[3-(ethoxycarbonyl)-phenyl]-1*H*-1,2,3-triazol-4-yl}methoxy)methyl]furan-3-yl}ethyl)-1,4a-dimethyl-6-methylidenedecahydronaphthalene-1-carboxylate (19). Diisopropylethylamine (0.21 mL, 1.25 mmol), (3*S*,4*R*,5*R*)-3-azido-1-(ethoxycarbonyl)-4,5-bis(methanesulfonyloxy)cyclohexene **17** (0.48 g, 1.21 mmol), and CuI (0.012 g, 0.13 mmol) were sequentially added to a stirred solution of compound **4** (0.5 g, 1.25 mmol) in acetonitrile (10 mL) at 0 °C under argon. The temperature of the reaction mixture was raised to ambient, and it was stirred for 24 h. The solvent was evaporated, the residue was dissolved in chloroform, washed with 2 *N* aq. H_2SO_4 (2×50 mL), water (2×50 mL), aq. NH_4Cl/NH_4OH (9 g of NH_4Cl, 1 mL of NH_4OH, and 100 mL of H_2O) (2×50 mL), and water (2×50 mL), then dried with $MgSO_4$. The solvent was evaporated, the residue was subjected to chromatography on silica gel (eluent chloroform) to obtain compound **19** (0.64 g, 87%) as an oil, $[\alpha]_D^{20}$ +24.10 (*c* 2.7, $CHCl_3$). IR (neat), ν/cm^{-1}: 741, 891, 1074, 1153, 1229, 1382, 1449, 1466, 1643, 1724, 2849, 2934, 2943, 3306. UV, λ_{max}/nm (lgε): 222 (4.34), 250 (3.83). ^{1}H NMR (300.13 MHz), δ: 0.36 (s, 3 H, C(20)H$_3$); 0.84 (m, 1 H, H(1α)); 0.87 (dt, 1 H, H(3α), *J* = 12.9 Hz, *J* = 4.1 Hz); 1.03 (s, 3 H, C(19)H$_3$); 1.30 (t, 5 H, OCH$_2$CH$_3$, H(5α), H(2), *J* = 7.0 Hz); 1.47 (m, 2 H, H(9), H(11)); 1.59 (m, 1 H, H(11)); 1.62, 1.66 (both m, 3 H, H(6), H(1b), H(2)); 1.73 (m, 1 H, H(7α)); 1.84 (dm, 1 H, H(6), *J* = 12.5 Hz); 2.01 (dm, 1 H, H(3β), J_{gem} = 12.9 Hz); 2.20 (m, 1 H, H(12)); 2.27 (m, 1 H, H(7β)); 2.45 (m, 1 H, H(12)); 3.47 (s, 3 H, OCH$_3$); 4.30 (q, 2 H, OCH$_2$CH$_3$, *J* = 7.0 Hz); 4.41 (s, 2 H, OCH$_2$); 4.46 (s, 1 H, H(17)); 4.62 (s, 2 H, FuCH$_2$O); 4.76 (s, 1 H, H(17)); 6.15 (d, 1 H, H(14), $J_{14,15}$ = 1.8 Hz); 7.23 (d, 1 H, H(15), $J_{14,15}$ = 1.8 Hz); 7.48 (t, 1 H, H(5″), *J* = 7.8 Hz); 7.88 (dm, 1 H, H(6″), *J* = 7.8 Hz); 7.98 (d, 1 H, H(4″), *J* = 7.8 Hz); 7.98 (s, 1 H, H(5′)); 8.24 (d, 1 H, H(2″), *J* = 1.5 Hz). ^{13}C NMR, δ: 12.12 (C(20)); 13.82 (OCH$_2$CH$_3$); 19.41 (C(2)); 22.73 (C(12)); 24.06 (C(11)); 25.75 (C(6)); 28.21 (C(19)); 37.61 (C(3)); 38.15 (C(7)); 38.47 (C(1)); 39.61 (C(10)); 43.70 (C(4)); 50.56 (OCH$_3$); 54.33 (C(9)); 55.61 (C(5)); 61.04 (OCH$_2$CH$_3$); 61.83 (OCH$_2$); 62.81 (FuCH$_2$O); 106.92 (C(17)); 111.06 (C(14)); 120.24 (C(5′))*; 120.50 (C(6″))*; 123.96 (C(2″)); 124.20 (C(13)); 129.01 (C(4″)); 129.45 (C(5″)); 131.71 (C(3″)); 136.64 (C(1″)); 141.66 (C(15)); 145.72 (C(4′)); 146.32 (C(16)); 147.39 (C(8)); 164.61 (CO$_2$CH$_2$CH$_3$); 177.05 (C(18)). MS, *m*/*z* (I_{rel} (%)): 589 (0.5), 248 (11), 232 (15), 231 (100), 202 (11), 121 (12), 94 (10). HRMS, *m*/*z*: found 589.3143 [M]$^+$; calculated for $C_{34}H_{43}O_6N_3$ M = 589.3146.

Methyl (1*S*,4a*R*,5*S*,8a*R*)-5-{2-[2-(2-[1-(2-methoxy-2-oxoethyl)-1*H*-1,2,3-triazol-4-yl]-1(*S*)-{[1-(2-methoxy-2-oxoethyl)-1*H*-triazol-4-yl]methoxy}ethyl)furan-3-yl]ethyl}- and methyl (1*S*,4a*R*,5*S*,8a*R*)-5-{2-[2-(2-[1-(2-methoxy-2-oxoethyl)-1*H*-1,2,3-triazol-4-yl]-1(*R*)-{[1-(2-methoxy-2-oxoethyl)-1*H*-triazol-4-yl]methoxy}ethyl)furan-3-yl]ethyl}-1,4a-dimethyl-6-methylidenedecahydronaphthalene-1-carboxylates (20a,b). Diisopropylethylamine (0.42 mL, 2.4 mmol), methyl 2-azidoacetate **11** (0.35 g, 3.1 mmol), and CuI (0.012 g, 0.12 mmol) were sequentially added to a solution of compounds **5a,b** (0.54 g, 1.2 mmol) in acetonitrile (10 mL) at 0 °C under argon. The temperature was raised to ambient, and the mixture was stirred for 24 h. The solvent was evaporated, the residue was dissolved in chloroform, washed with 2 *N* aq. H_2SO_4 (2×50 mL), water (2×50 mL), aq. NH_4Cl/NH_4OH (9 g of NH_4Cl, 1 mL of NH_4OH, and 100 mL of H_2O) (2×50 mL), and water (2×50 mL), then dried with $MgSO_4$. The solvent was evaporated, the residue was subjected to chromatography on silica gel (eluent chloroform—methanol, 100 : 1) to obtain a mixture of compounds **20a,b** (0.52 g, 86%) as an oil. IR (neat), ν/cm^{-1}: 756, 802, 893, 993, 1049, 1091, 1155, 1227, 1367, 1441, 1464, 1510, 1555, 1643, 1720, 1757, 2851, 2874, 2953, 3081, 3148. UV, λ_{max}/nm (lgε): 220 (4.03). ^{1}H NMR (400.13 MHz), δ: 0.44 (s, 3 H, *C(20)H$_3$); 0.98 (m, 2 H, *H(1α), *H(3α)); 1.12 (s, 3 H, *C(19)H$_3$); 1.23 (d, 1 H, *H(5α), *J* = 13.7 Hz); 1.43, 1.47 (both m, 2 H, *H(2), *H(11)); 1.52 (br.s, 1 H, *H(9)); 1.58 (m, 1 H, *H(11)); 1.70, 1.73, 1.89 (all m, 3 H, *H(6), *H(1β), *H(2)); 1.85 (m, 1 H, *H(7α)); 1.93 (dm, 1 H, *H(6), *J* = 13.7 Hz); 2.10 (dm, 1 H, *H(3β), J_{gem} = 13.2 Hz); 2.24 (m, 1 H, *H(12)); 2.33 (m, 1 H, *H(7β)); 2.49 (m, 1 H, *H(12)); 3.10 (m, 1 H, *CH$_2$); 3.40 (m, 1 H, *CH$_2$); 3.56 (s, 3 H, *OCH$_3$); 3.74 (s, 6 H, *2CH$_2$CO$_2$CH$_3$); 4.36 (d, 1 H, OCH$_2$, *J* = 12.1 Hz); 4.38 (d, 1 H, OCH$_2$, *J* = 12.1 Hz); 4.47—4.54 (m, 1 H, *OCH$_2$); 4.50 (s, 1 H, *H(17)); 4.64 (m, 1 H, *CHOH); 4.82 (s, 1 H, *H(17)); 5.11 (s, 4 H, *CH$_2$CO$_2$CH$_3$);

6.23 (s, 1 H, *H(14)); 7.33 (s, 1 H, *H(15)); 7.33 (s, 1 H, H(5′)); 7.39 (s, 1 H, H(5′)); 7.48 (s, 1 H, H(5′)); 7.50 (s, 1 H, H(5′)). ^{13}C NMR, δ,: 12.46, 12.50 (C(20)); 19.79, 19.81 (C(2)); 22.85, 22.88 (C(12)); 24.37, 24.42 (C(11)); 26.14 (*C(6)); 28.64, 28.66 (C(19)); 30.82 (*CH_2); 38.02, 38.04 (C(3)); 38.55 (*C(7)); 38.90, 38.92 (C(1)); 40.04, 40.11 (C(10)); 44.16 (*C(4)); 50.41 (*$\underline{CH_2}CO_2CH_3$); 50.47 (*$\underline{CH_2}CO_2CH_3$); 51.00 (*OCH_3); 52.78 (*$2CH_2CO_2\underline{CH_3}$); 54.98, 55.07 (C(9)); 56.02, 56.05 (C(5)); 61.72, 61.82 (CHOH); 71.08, 71.40 (OCH_2); 106.41, 106.50 (C(17)); 111.20 (*C(14)); 123.73 (*C(5′)); 123.93 (*C(5′)); 124.58, 124.61 (C(13)); 141.97, 142.00 (C(15)); 145.35 (*C(4′)); 145.38 (*C(4′)); 146.67, 146.80 (C(16)); 147.64, 147.66 (C(8)); 166.77 (*$CH_2\underline{C}O_2CH_3$); 167.04 (*$CH_2\underline{C}O_2CH_3$); 177.64 (*C(18)). MS, *m*/*z* (*I*$_{rel}$ (%)): 666 (1.1), 513 (19), 512 (64), 496 (36), 495 (74), 467 (18), 315 (36), 263 (18), 218 (23), 190 (32), 189 (19), 158 (23), 155 (68), 147 (28), 131 (28), 128 (19), 126 (100), 121 (72), 119 (19), 109 (19), 107 (27), 105 (24), 98 (39), 93 (26), 91 (43), 84 (20), 81 (33), 79 (24), 72 (21), 68 (20), 67 (18), 55 (26), 45 (21), 44 (22), 42 (26), 41 (31). HRMS, *m*/*z*: found 666.3366 $[M]^+$; calculated for $C_{34}H_{46}O_8N_6$ M = 666.3372.

Methyl (1*S*,4a*R*,5*S*,8a*R*)-5-{2-[2-(2-[1-(3-ethoxycarbonylphenyl)-1*H*-triazol-4-yl}-1(*S*)-{[1-(3-ethoxycarbonylphenyl)-1*H*-1,2,3-triazol-4-yl]methoxy}ethyl)furan-3-yl}ethyl}- and methyl (1*S*,4a*R*,5*S*,8a*R*)-5-{2-[2-(2-[1-(3-ethoxycarbonylphenyl)-1*H*-triazol-4-yl}-1(*R*)-{[1-(3-ethoxycarbonylphenyl-1*H*-1,2,3-triazol-4-yl]methoxyethyl)furan-3-yl]ethyl}-1,4a-dimethyl-6-methylidenedecahydronaphthalene-1-carboxylates (21a,b). Diisopropylethylamine (0.21 mL, 1.21 mmol), (3*S*,4*R*,5*R*)-3-azido-1-(ethoxycarbonyl)-4,5-bis(methanesulfonyloxy)cyclohexene **17** (0.47 g, 1.21 mmol), and CuI (0.01 g, 0.10 mmol) were sequentially added to a solution of compounds **5a**,**b** (0.27 g, 0.61 mmol) in acetonitrile (10 mL) at 0 °C under argon. The temperature of the reaction mixture was raised to ambient, and it was stirred for 24 h. The solvent was evaporated, the residue was dissolved in chloroform, washed with 2 *N* aq. H_2SO_4 (2×50 mL), water (2×50 mL), aq. NH_4Cl/NH_4OH (9 g of NH_4Cl, 1 mL of NH_4OH, and 100 mL of H_2O) (2×50 mL), and water (2×50 mL), then dried with $MgSO_4$. The solvent was evaporated, the residue was subjected to chromatography on silica gel (eluent chloroform—methanol, 100 : 1) to obtain a mixture of compounds **21a**,**b** (0.39 g, 78%) as an oil. Found (%): C, 67.84; H, 6.52; N, 9.98. $C_{46}H_{54}N_6O_8$. Calculated (%): C, 67.46; H, 6.65; N, 10.26. IR (neat), ν/cm^{-1}: 675, 757, 893, 1045, 1111, 1164, 1229, 1270, 1375, 1458, 1497, 1594, 1644, 1720, 2849, 2943, 3142, 3437. UV, λ_{max}/nm (lgε): 222 (3.85). ^{1}H NMR (300.13 MHz), δ: 0.36 (s, 3 H, *C(20)H_3); 0.86 (m, 1 H, *H(1α)); 0.92 (dt, 1 H, *H(3α), *J* = 13.3 Hz, *J* = 4.0 Hz); 1.07 (s, 3 H, C(19)H_3); 1.09 (s, 3 H, C(19)H_3); 1.14 (dd, 1 H, *H(5α), *J* = 11.7 Hz, *J* = 2.5 Hz); 1.37 (t, 3H, *$CH_2\underline{CH_3}$, *J* = 7.1 Hz); 1.38 (t, 4 H, *$CH_2\underline{CH_3}$, *H(2), *J* = 7.1 Hz); 1.47 (m, 2 H, *H(9), *H(11)); 1.54 (m, 1 H, *H(11)); 1.60, 1.65, 1.69 (all m, 3 H, *H(6), *H(1β), *H(2)); 1.76 (dm, 1 H, *H(7α), *J* = 14.1 Hz); 1.88 (m, 1 H, *H(6)); 1.98—2.08 (m, 1 H, *H(3β)); 2.18—2.25 (m, 1 H, *H(12)); 2.28 (m, 1 H, *H(7β)); 2.41—2.52 (m, 1 H, *H(12)); 3.15 (m, 1 H, *CH_2); 3.28 (dd, 1 H, *CH_2, *J* = 14.7 Hz, *J* = 6.4 Hz); 3.53 (s, 3 H, OCH_3); 3.54 (s, 3 H, OCH_3); 4.37 (q, 2 H, *$O\underline{CH_2}CH_3$, *J* = 7.1 Hz); 4.39 (q, 2 H, *$O\underline{CH_2}CH_3$, *J* = 7.1 Hz); 4.42 (s, 1 H, H(17)); 4.48 (s, 1 H, H(17)); 4.53 (d, 1 H, $C\underline{H_2}O$, *J* = 12.5 Hz); 4.54 (d, 1 H, $C\underline{H_2}O$, *J* = 12.5 Hz); 4.61 (d, 1 H, $C\underline{H_2}O$, *J* = 12.5 Hz); 4.62 (d, 1 H, $C\underline{H_2}O$, *J* = 12.5 Hz); 4.79 (m, 1 H, *CHO); 4.81 (s, 1 H, *H(17)); 6.25 (d, 1 H, *H(14), $J_{14,15}$ = 1.6 Hz); 7.40 (d, 1 H, *H(15), $J_{14,15}$ = 1.6 Hz); 7.55 (t, 2 H, *H(5″), *J* = 8.1 Hz); 7.68 (s, 1 H, H(5′)); 7.73 (s, 1 H, H(5′)); 7.88 (s, 1 H, *H(5′)); 7.91 (m, 2 H, *H(6″)); 8.02 (td, 1 H, *H(4″), *J* = 8.1 Hz, *J* = 2.0 Hz); 8.06 (td, 1 H, *H(4″), *J* = 8.1 Hz, *J* = 2.0 Hz); 8.27 (t, 1 H, *H(2″), *J* = 2.0 Hz); 8.28 (t, 1 H, *H(2″), *J* = 2.0 Hz). ^{13}C NMR, δ: 12.34, 12.39 (C(20)); 14.18 (*$OCH_2\underline{CH_3}$); 14.19 (*$OCH_2\underline{CH_3}$); 19.72, 19.75 (C(2)); 22.92, 22.96 (C(12)); 24.37, 24.46 (C(11)); 26.09 (*C(6)); 28.59 (*C(19)); 30.63, 30.73 (CH_2); 37.87, 37.96 (C(3)); 38.48, 38.52 (C(7)); 38.84, 38.90 (C(1)); 39.97, 40.06 (C(10)); 44.07, 44.10 (C(4)); 50.98 (*OCH_3); 54.91, 55.16 (C(9)); 55.93, 56.01 (C(5)); 61.76 (*$O\underline{CH_2}CH_3$); 61.85 (*$O\underline{CH_2}CH_3$); 61.43, 64.48 ($CHO\underline{CH_2}$); 71.62, 71.91 ($\underline{CH}OCH_2$); 106.30, 106.50 (C(17)); 111.33 (*C(14)); 120.23, 120.48 (C(5′)); 120.70, 120.80 (C(5′)); 125.08, 125.14 (C(13)); 124.10 (*C(6″)); 124.23 (*C(6″)); 124.42 (*2C(2″)); 129.18 (*C(4″)); 129.44 (*C(4″)); 129.74 (*C(5″)); 129.80 (*C(5″)); 132.02, 132.06 (C(3″)); 132.09 (*C(3″)); 136.96, 137.05 (C(1″)); 125.13 (*C(1″)); 144.96, 145.03 (C(4′)); 145.94 (*C(4′)); 142.07 (*C(15)); 146.59, 146.70 (C(16)); 147.58, 147.74 (C(8)); 165.10 (*$\underline{C}O_2CH_2CH_3$); 165.16 (*$\underline{C}O_2CH_2CH_3$); 177.55, 177.58 (C(18)).

Cell cultures. Cytotoxicity of compounds under study was determined on the human tumor cell lines MT-4, CEM (human T-cell leukemia cells), and U-937 (human monocyte cells). The cells were cultured in the RPMI-1640 medium containing 10% of the cattle embryo blood serum, L-glutamine (2 mmol L^{-1}), gentamicin (80 μg mL^{-1}), and lincomycin (30 mg mL^{-1}), at 37 °C in the atmosphere of 5% CO_2 in an incubator. The tested compounds were dissolved in DMSO and added to the cell culture in the required concentrations. Three wells were used for each concentration: 0.1, 1, 10, and 100 μg mL^{-1}. The cells incubated without addition of tested compounds were used as a control. The cells were cultured for 72 h. An aqueous solution of the MTT-reagent, *i.e.*, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (5 mg mL^{-1}), was filtered through a filter (0.22 μm, Flow laboratories, England) and added into each tested culture in the ratio 1 : 10 (v/v), the mixture was incubated for 3—4 h at 37 °C in a CO_2-incubator. After the incubation was complete, the supernatant was carefully evaporated, then DMSO (in 100 μL portions) was added into each analyzed well. A precipitate was re-suspended and incubated for 30 min in dark at room temperature until crystals of formazane were completely dissolved.

Optical density (*D*) of the samples was measured on a Bio-Rad 680 multi-well spectrophotometer (USA) at the wavelength of 490 nm. The percentage of cell growth inhibition was determined using the following formula:

$$100 - D_{av}^{exp}/D_{av}^{contr} \cdot 100,$$

where D_{av}^{exp} is the average *D* value in the trial, D_{av}^{contr} is the average *D* value in the control. The value obtained for the control triplet (the first three wells without addition of compounds, parallel for each tested experimental agent) was set at 100%. An average value and average error were calculated for each concentration of the analyzed compound. Using the results obtained, a diagram of the dependence of cell viability (%) from the concentration of the tested cytotoxic compound was constructed, a doze inhibiting the cell viability by 50% ($CCID_{50}$) was determined, as well as a standard error (SE) for this index ($CCID_{50}$). Statistical processing of the results was performed using the Microsoft Excel-2007, STATISTICA 6.0, and GraphPad Prism

5.0 programs. The results are given as an average value ± a deviation from the average. Reliability of differences (p) was estimated using the Student t test. The differences with $p \leq 0.05$ were considered as reliable. The experimental results are given as the data average values obtained from three independently conducted experiments.

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