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Regio- and Stereoselective Functionalization of 16-Membered Lactone Aglycone of Spiramycin via Cascade Strategy

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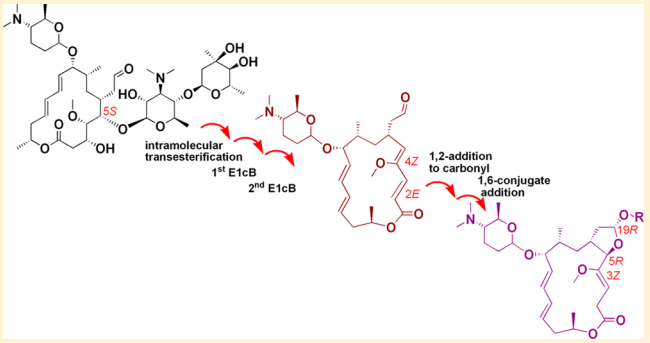
Supporting Information

ABSTRACT: Functionalization of 16-membered aglycone of spiramycin with the use of intramolecular cascade strategy yielded access to novel types of diastereopure bicyclic spiramycin derivatives containing tetrahydrofuran ring. Experimental results shows that a specific sequence of regio- and stereoselective transformations, based on the intramolecular transesterification, E1cB tandem eliminations, 1,2-addition to carbonyl, and 1,6-conjugate addition at the spiramycin aglycone, proceeds with the inversion of absolute configuration at C(5) stereogenic center. Performed cascade and multistep transformations have opened new possibilities in divergent modifications, not only spiramycin but also the whole family of leucomycin type antibiotics having a similar structure of 16-membered aglycone lactone ring.

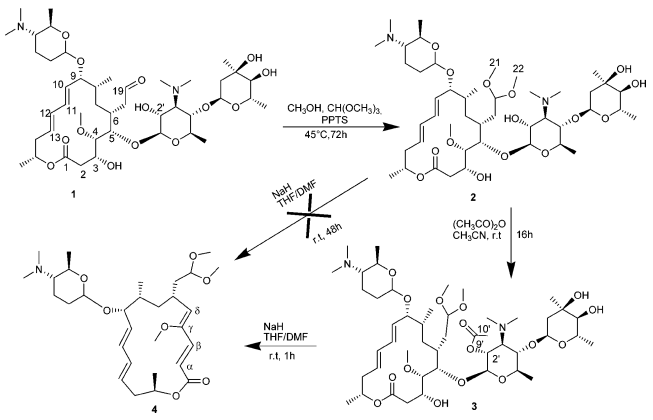


INTRODUCTION

Leucomycins (A_1–A_{15}) and spiramycins (I–III) have structurally similar 16-membered lactone aglycone and two of the same saccharides attached at the C(5) position—mycaminose and mycarose.[1] Spiramycins differ from leucomycins only in the presence of D-(+)-forosamine substituent at 9-OH hydroxyl group. Spiramycins are produced by *Streptomyces ambofaciens* as a mixture in which spiramycin I (compound **1**), shown in Scheme 1, is dominant (75–80%).[2] Spiramycins II and III have acetate or propionate at C(3) carbon, respectively. All of these types of antibiotics are widely used against upper and lower respiratory tracts infections and toxoplasmosis because of their good gastrointestinal tolerance and relatively rare side effects.[3] The mechanism of the action of leucomycins and spiramycins is based on their binding in the polypeptide exit tunnel, adjacent to the peptidyl transferase center, and in this way inhibiting protein synthesis by blocking the egress of nascent polypeptides.[4] The use of this class of antibiotics has been seriously limited because of the growing resistance of a number pathogens; therefore, the search for new and biologically active structural analogues of lactone macrolides is essential.[5] Up to now, much of the effort has been directed mainly toward modification of hydroxyls[6] via acylation, etherification, and epimerization; aldehyde[7] via reduction, reductive alkylation, or addition; diene moiety[8] via metathesis, epoxidation, allylic rearrangement or formation carbamates; nitrogens[9] of forosamine or mycaminose via oxidation and elimination of the mycarose sugar. The access to novel types of leucomycin and spiramycin derivatives is difficult because of the presence of many reactive functional groups in their structures, complicated intramolecular interactions, and steric as well as conformational factors, which result often in formation of different byproducts during modifications of these type of antibiotics.[10] Some building blocks of spiramycin aglycone can be obtained by, e.g., Noyori's protocol and Julia–Paris–Kocienski condensation, but the synthesis of the whole aglycone ring with the respective stereochemistry is not an easy task and is time-consuming as it requires multistep transformations.[11]

Cascade reactions are readily used in synthesis and modifications of structurally complexed natural products,

Scheme 1. Structure of Spiramycin I (compd 1) and Its Conversion into Novel Type of $\alpha,\beta,\gamma,\delta$-Unsaturated Lactone Aglycone Derivative 4



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when economy of time and labor as well as stereoselectivity of the reaction are desired.[12] Here, as a continuation of our interests in designing new analogues of lactone macrolides of useful antibacterial properties, we tested the cascade and multistep combined approach to get access to structurally diverse and novel derivatives built on spiramycin aglycone.

RESULTS AND DISCUSSION

As introduction of any new substituent near the lactone group of aglycone is difficult, in practice our efforts at the first stage were focused on obtaining an unsaturated lactone group within aglycone. At the first step, however, it was necessary to protect the aldehyde group against the Omura's bicyclization reaction which takes place at aglycone.[13] This protection was successfully achieved by treating of spiramycin I (compound **1**) with a mixture of trimethyl orthoformate, pyridinium *p*-toluenesulfonate (PPTS, as a catalyst), and methanol (Scheme 1). Detailed FT-IR spectra and ^{1}H−^{1}H NOESY analyses revealed that within the structures of compounds **1** and **2** in solution, the hydroxyls at C(3) and C(2′) are in close vicinity and are weak intramolecularly hydrogen-bonded (Supporting Information Figure 1S). Thus, in the next step we wanted to introduce an acetyl group at one of these hydroxyls, which could enable an intramolecular reaction. Optimization of the acetylation reaction in CH_3CN led to obtaining product **3**, whose ^{13}C NMR spectrum is shown in Figure 1. The presence

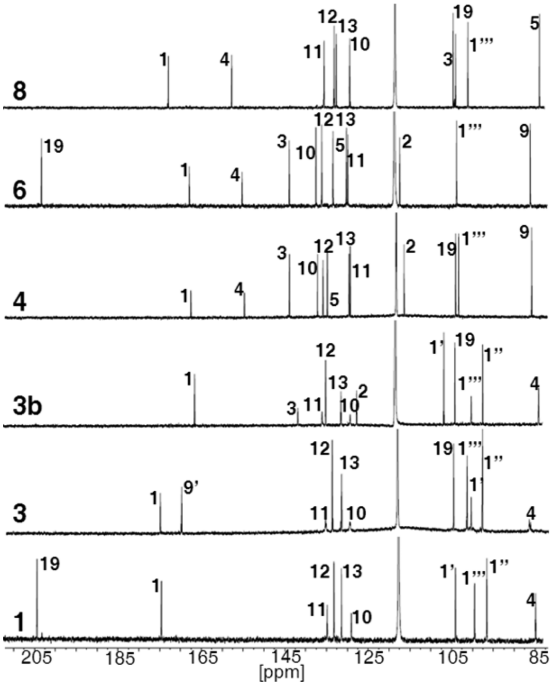

Figure 1. Comparison of ^{13}C NMR data of **1**, **3**, **3b**, **4**, **6**, and **8** above 85 ppm, recorded in CD_3CN.

of a resonance signal at 169 ppm together with ^{1}H−^{13}C HMBC correlation (Supporting Information Figure 2S) revealed that acetate was introduced in a regioselective way at mycaminose (Scheme 1). Treatment of compound **3** with NaH in THF/DMF mixture yielded a new product **4**, characterized by longer retention time (Figure 2). The structure of derivative **4** was determined on the basis of detailed 1D and 2D NMR, FT-IR, and HR MALDI-TOF MS studies (Supporting Information Figure 3S, experimental data) and visualized via B88-LYP DFT

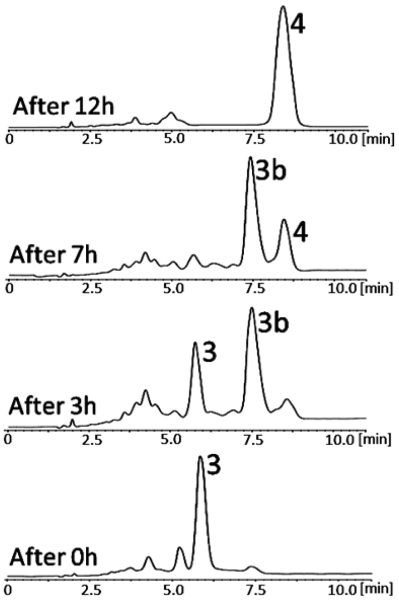

Figure 2. HPLC chromatograms of the reaction mixture showing stepwise transformation of **3** into **4** product (detection at λ_{max} = 232 nm; flow rate: 1 mL/min; mobile phase: CH_3CN:H_2O:CH_3COONH_4 55:35:10).

theoretical calculations, taking into account ^{1}H−^{1}H NOESY data (Supporting Information Figure 4S). In the ^{13}C NMR spectrum of the new derivative **4** (Figure 1), deshielding of C(2), C(3), C(4), and C(5) resonances and shielding of C(1) resonance indicated the presence of *α*,*β*,*γ*,*δ*-unsaturated lactone aglycone. Red shift of the band assigned to ν(C═O)$_{lactone}$ about 20 cm^{-1}, noted in the spectrum of **4**, relative to its position observed in the spectrum of **1**, is another strong confirmation of double unsaturated lactone moiety formation within structure of **4** (Figure 3). Analysis of ^{1}H−^{1}H NOESY

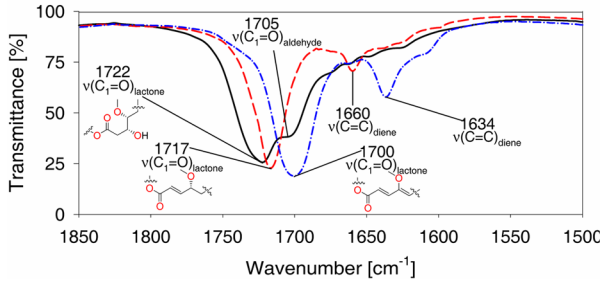

Figure 3. FT-IR spectra of **1** (black solid), **3b** (red dashed), and **4** (blue dash-dotted) in the range 1500−1850 cm^{-1}, recorded in CH_3CN.

spectrum (Supporting Information Figure 4S) revealed additionally that orientations of the lactone carbonyl and −OCH_3 groups relative to the —C(10)═C(11)−C(12)═C(13)— diene moiety are changed when compared to those present in spiramycin structure (Supporting Information Figure 1S). Contacts noted in the NOESY spectrum of **4** proved also that the newly formed double bond system, conjugated with lactone, has configurations (2*E*, 4*Z*), as shown in Supporting Information Figure 4S. This result demonstrates the diastereoselective course of the tandem eliminations. The change in the reaction conditions revealed that the conversion of **3** into **4**

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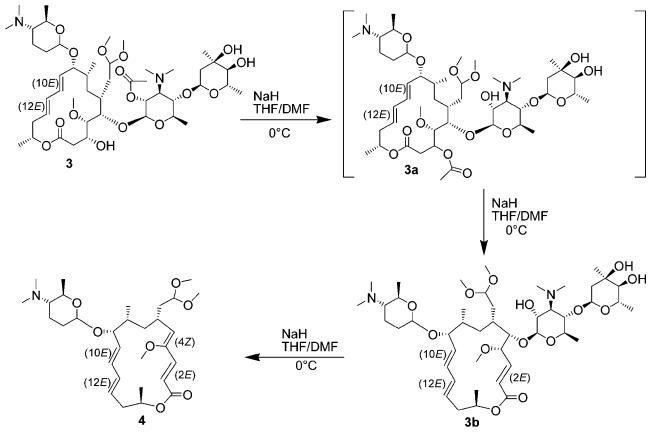
is stepwise, as shown by recorded HPLC chromatograms (Figure 2). Explanation of the mechanism of product **4** formation was possible after isolation of intermediate **3b** (Figure 2, Scheme 2). A significant shift of $\delta_{C(1)=O}$ signal from

Scheme 2. Cascade Transformation of 3 into New α,β,γ,δ-Unsaturated Aglycone Derivative 4 by Intramolecular Transesterification and Tandem E1cB Eliminations via Formation of Intermediates 3a and 3b



175.1 ppm (value for **3**) to 166.3 ppm (value for **3b**) is clear evidence of the formation of α,β-unsaturated lactone aglycone within **3b** intermediate. C(9′) carbon atom signal is not observed in the ^{13}C NMR spectrum of **3b** (Figure 1), and the difference in molecular weights between **3** and **3b** determined from MALDI-TOF mass spectra is 60 [Da], suggesting elimination of one acetate from derivative **3**. The question arises about the mechanism of formation of α,β-unsaturated lactone aglycone within **3b**. It should be underlined here that an attempt at direct conversion of **2** into **4** failed in the presence of NaH (Scheme 1). Conversions of **2** into **4** or **3** into **4** failed also when KOH was used as another base. Moreover, an attempt at addition of KOH to **1** did not yield α,β-unsaturated derivative of **1**, structurally analogous to **3b**, indicating the important role of acetate at C(2′) of mycaminose in the tandem eliminations at aglycone with formation of product **4**. In view of the earlier works on leucomycins having an hydroxyl group at C(3) position, a similar elimination was not observed under acidic or basic conditions.[6,7b,9] Thus, the newly formed double bond C(2)=C(3) in product **3b** appears at aglycone ring (Supporting Information Figure 5S) as a result of acetyl group migration from hydroxyl at C(2′) to the other one at C(3) and its subsequent elimination of E1cB type. Unfortunately, the first elimination proceeded so quickly that we were not able to notice the formation of product **3a** (Scheme 2) by HPLC monitoring (Figure 2). Thus, taking into account determined structures of products **3**, **3b**, and **4**, it can be concluded that the conversion of **3** into **4** is a result of cascade reactions based on intramolecular transesterification and the two tandem eliminations of E1cB type, as shown in Figure 4. The mechanism of E1cB elimination is only possible from the enolate form of lactone after migration of the acetyl from mycaminose saccharide to the hydroxyl at C(3) with the formation of **3a**. The elimination of acetate as a conjugate base leads to formation of monounsaturated lactone of the aglycone **3b** (Figure 4). Deprotonation of derivative **3b** at γ-position relative to carbonyl of lactone yields enolate having different orientation of the lactone and methoxyl group relative to that determined within earlier obtained derivatives **2** and **3**. After the conformational change and formation of **3b** enolate, the disaccharide moiety becomes oriented favorably to typical trans-elimination. At the next step the second elimination of disaccharide as a conjugate base via E1cB reaction gives product **4**. Modification of the above cascade reaction conditions allows its completion in 1 h. The overall yield of conversion **1** into **4** is about 21% (calculated relative to spiramycin I).

Having product **4** with the protected aldehyde, which seemed to be a good acceptor in the Michael type addition, at first we subjected it to a reaction with propargyl alcohol in the presence of NaH. Instead of the expected products of 1,4- or 1,6-conjugate addition, we obtained compound **5** with the opened aglycone ring (Scheme 3), as revealed by HR MALDI-TOF and NMR data. Also the unsuccessful conjugate addition attempts with the other alcohols including methanol, ethanol, and propanol (data not shown) confirmed undesired opening of the aglycone lactone. DFT calculated structure of **4** (Figure 4) together with $^{1}H-^{1}H$ NOESY contacts (Supporting Information Figure 4S) revealed that the acetal protecting group of the aldehyde together with the methoxyl at C(4) are steric hindrances for the Michael type additions. Hence, at the next step we deprotected the aldehyde group at C(19) and obtained derivative **6**. It is noteworthy that vinyl methoxyl ether group at C(4) survived CHF_2COOH treatment during deprotection of acetal at C(19). Cleavage of vinyl type ethers occurs by protonation of the mesomeric structure at α position relative to ether group with formation of alkoxycarbocation. The probable protonation sites within structures **4** and **6** are at γ-position relative to lactone group. However, carbon at γ-position participates in conjugation with the lactone carbonyl, and therefore moiety at C(4) does not behave as a classical isolated vinyl ether. At the next step new derivative **6** was subjected to reactions with the structurally diverse alcohols as shown in Scheme 3. Analysis of the ^{13}C NMR spectra of products **7**−**12** shows the lack of C(19) carbon resonances of aldehyde at about 200 ppm, present in the spectrum of **6**. Furthermore, significant changes in the C(2)−C(5) chemical shifts together with deshielding of C(1) signal in the spectra of **7**−**12** indicates that after the reaction, the lactone group is no longer π−π conjugated and that only one double bond remained at this fragment of aglycone (Figure 1, Supporting Information Table 2S). Interestingly, C(19) resonances in the spectra of **7**−**12** are found in the region 101.2−105.3 ppm (Supporting Information Table 2S, Figure 1) characteristic of carbons of acetals. The $^{1}H-^{13}C$ HMBC spectra of **7**−**12** show significant long-range correlations between C(19) and H(23) and H(18) protons as well as a correlation H(19)−C(5) (Supporting Information Figure 6S). This result indicates that the alcohol part is attached at C(19) atom and that C(19) is linked via oxygen atom with C(5) position forming in this way an additional tetrahydrofuran ring fused with aglycone. Thus, at the first stage upon treatment of **6** with alcohol in the presence of NaH, the 1,2-addition of a respective alkoxylate to the carbonyl of the aldehyde takes place (Figure 4). As a consequence of this nucleophilic attack, a new alkoxylate at C(19) carbon atom is generated, and then it reacts as an excellent donor atom in intramolecular 1,6-conjugate addition giving enolate adduct of **6** (Figure 4). Hence, this addition is regioselective because carbon δ but not β, relative to lactone, is attacked by alkoxylate as Michael donor. In the $^{1}H-^{1}H$ NOESY spectra of compounds **7**−**12** the following key contacts were detected: H(5)/H(17), H(5)/H(23), and H(5)/H(7) indicat-

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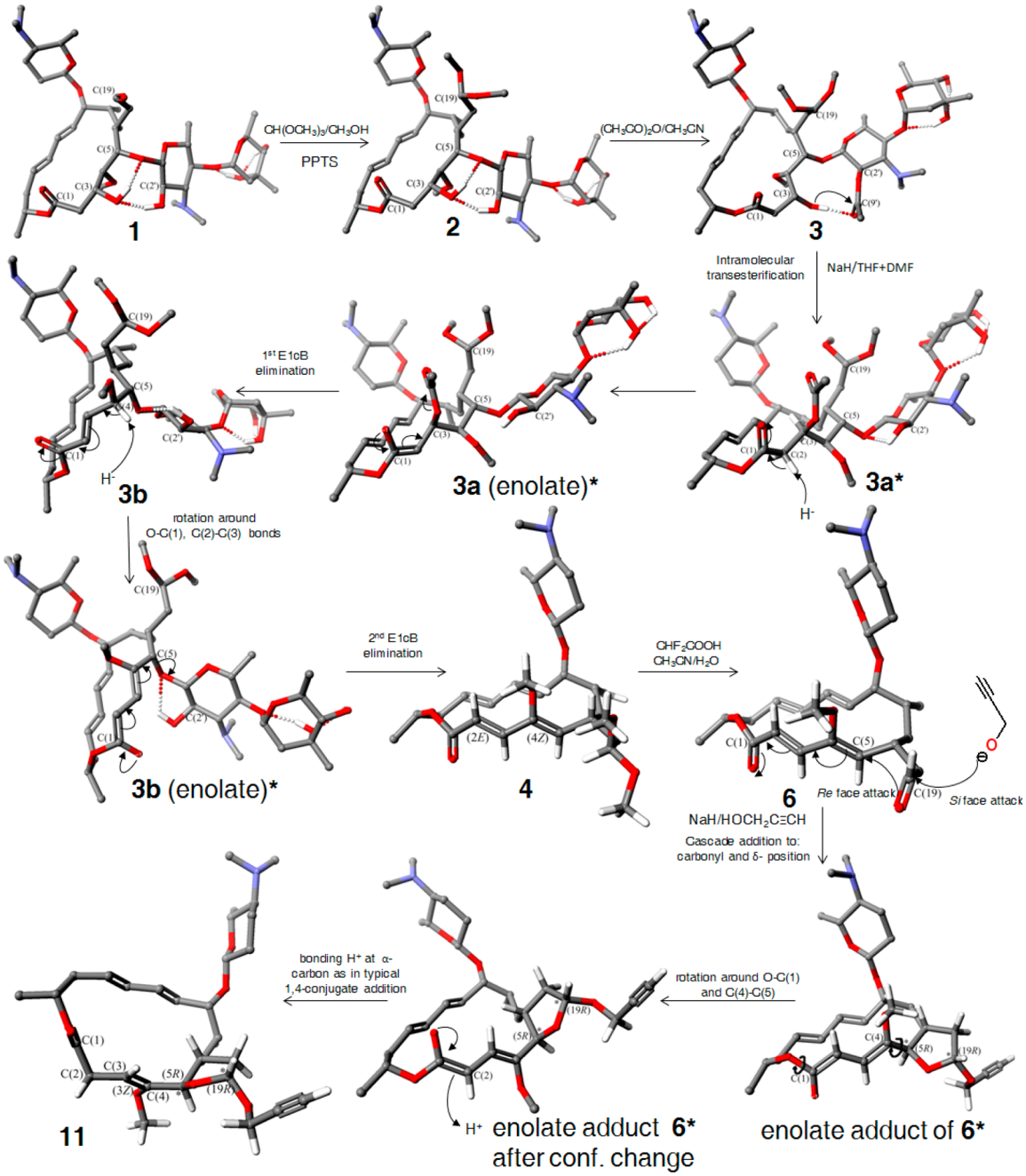

Figure 4. Conversion of **1** into **11** revealing complex stereochemical and conformational factors being a driving force for cascade modifications at aglycone, presented with the help of local energy minimum structures of intermediates* and the one of lowest energy structures of products **1**−**3**, **3b**, **4**, **6** and **11** which are in agreement with NOESY data, calculated by B88 LYP DFT method (*Scigress* package[14,15]); most of H's atoms were omitted for better clarity.

ing their mutual spatial vicinity (Figure 5). Additionally, the proton−proton contacts H(2)/H(17), H(2)/H(16), H(14)/H(16), H(14)/H(12), H(10)/H(12) as well as H(7)/H(10) revealed a common orientation for all of them, toward the bottom of the aglycone ring. Further contacts between protons H(6)/H(3), H(6)/H(11), and H(3)/H(11) indicated that they are oriented from the opposite side to that in which H(5), H(17), and H(7) protons are located; therefore, the configuration at C(5) is (5*R*). Knowing the absolute configurations at C(5) and C(6) and the orientation of H(6) proton relative to diene fragment, the additional contact between H(6) and H(19) indicated their similar orientation and configuration (19*R*). Thus, this cascade conversion of **6** into **7**−**12** gave exclusively one diastereomeric product of configurations (5*R*,19*R*), as indicated by key ^{1}H−^{1}H NOESY contacts discussed above (Figure 5) together with the other ones obtained from different fragments of the aglycone ring of **7**−**12** (Supporting Information Figure 4S). As visualized by one of the reactive conformations of compound **6** (Figure 4), the diastereoselective 1,2-addition of alkoxylate to aldehyde is only understandable when ones takes into account the forced orientation of the oxygen atom of aldehyde toward the bottom of aglycone ring, similarly to that of the carbonyl oxygen atom of lactone. This specific spatial arrangement of the aldehyde

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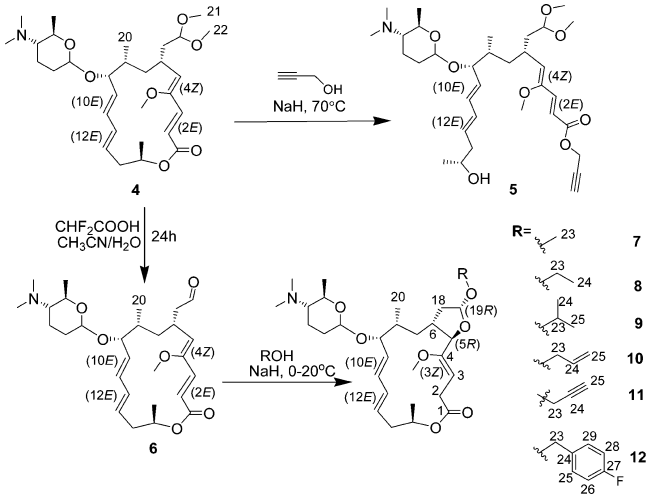
Scheme 3. Synthesis of Compounds 7−12 from 6 via Regio- and Stereoselective Cascade Intermolecular 1,2-Addition and Intramolecular 1,6-Conjugate Addition



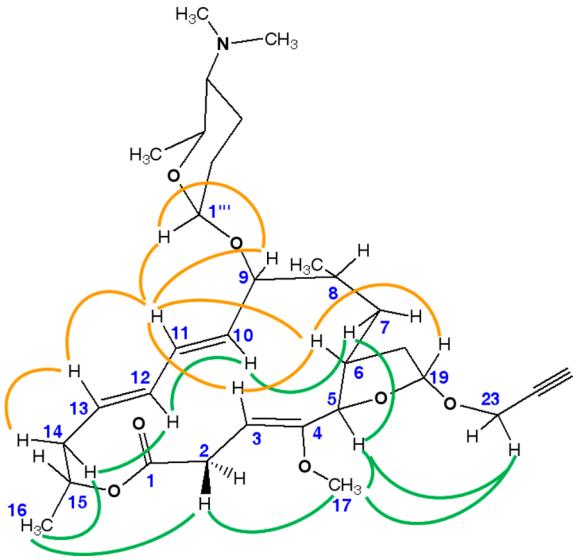


Figure 5. Key $^{1}H-^{1}H$ NOESY contacts (green−for H's oriented to the bottom of the aglycone ring; orange−for H's oriented above the aglycone ring) important for assignment of stereochemistry and conformation of cascade addition product **7−12**.

group, implied by the steric hindrance with the methoxyl group and a weak $\pi-\pi$ stabilizing interaction between C(19)=O and C(4)=C(5) moieties, together with *Si* face attack of the nucleophile via 1,2-addition mechanism at the carbonyl of aldehyde, explains the final formation of products **7−12** of (19*R*) configuration (Figure 4). The (5*R*) configuration, determined with the help of NOESY experiments, is a result of regioselective alkoxylate nucleophilic *Re* face attack from C(19) position at C(5) carbon (Figure 4). However, this addition is untypical with regard to the fact that the reaction starts as 1,6-conjugate addition and at the end the proton is bonded at α-carbon as in 1,4-conjugate addition. Exemplary ^{1}H NMR and $^{1}H-^{1}H$ COSY spectra of compound **9** revealed long-range correlations ($^{5}J_{H2a-H5}$ = 0.9 Hz, $^{5}J_{H2b-H5}$ = 1.3 Hz; Supporting Information Figure 7S and Table 1S), characteristic of couplings between protons in homoallylic system. Thus, on the basis of the above results and $^{1}H-^{13}C$ HMBC correlations, it is evidenced that in a result of 1,6-conjugate addition, the newly formed double bond appears between C(3) and C(4) carbon atoms. Knowing from NOESY experiments the opposite orientation of H(3) and CH_3(17) protons relative to the aglycone, the configuration of newly formed double bond C(3)=C(4) is (3*Z*). Explanation of an untypical termination of the 1,6-conjugate addition is the aglycone ring strain produced during bicyclization with the tetrahydrofuran ring formation. To reduce the strain within enolate adduct of **6** (Figure 4), a simultaneous rotation around O−C(1) and C(4)−C(5) bonds occurs within aglycone. Therefore, the proton is attached to α-carbon as in a typical 1,4-Michael type addition, yielding greater conformational freedom of the aglycone ring. As a consequence of the above-mentioned structural changes, the lactone carbonyl group within products **7−12** restores its orientation, similarly as in the parent compound spiramycin I (**1**) and its isolated derivatives **2** and **3b**.

CONCLUSIONS

Functionalization of the 16-membered aglycone of spiramycin, whose structure is common for all Leucomycin type antibiotics, using intramolecular cascade strategy, has been proposed. Regio- and stereoselective transformations, based on the sequence of several intramolecular reactions as transesterification, E1cB tandem eliminations, 1,2-addition to the carbonyl of aldehyde, and untypical 1,6-conjugate addition to $\alpha,\beta,\gamma,\delta$-unsaturated lactone, have opened new routes in multistep aglycone ring modifications of leucomycin type macrolide antibiotics. Diastereopure derivative **6** is a good starting point for further explorations toward a new class of leucomycins via the divergent synthesis approach using other structurally diverse nucleophiles containing carbon, sulfur, selenium, nitrogen, etc. rich-electron donor atoms. The obtained $\alpha,\beta,\gamma,\delta$-unsaturated lactone group within compound **6** can be also a site of metathetic transformations. Presented cascade regio- and stereoselective transformations yielding derivatives **7−12** enabled the inversion of configuration at C(5) stereogenic center, relative to that of the parent spiramycin. Deprotecting of the acetal moiety with opening of the tetrahydrofuran ring can be also a great opportunity to introduce, e.g., different saccharides at the carbon atom C(5) of the inversed absolute configuration. Our current works are focused on the use of derivative **11** in 1,3-dipolar azide−alkyne cycloaddition catalyzed by Cu^{+} ions with different mono- and disaccharaides containing azide group.

EXPERIMENTAL SECTION

General Experimental. Spiramycin, CH_3CN and CD_3CN for spectroscopic measurements, NaH, methanol, pyridynium *p*-toluenosulfonate, trimethyl orthoformate, ethanol, 2-isopropanol, propargyl alcohol, allyl alcohol, 4-fluorobenzyl alcohol, acetonitrile, difluoroacetate acid, acetic anhydride, THF, DMF used for the syntheses of new spiramycin derivatives, $CH_3COOC_2H_5$, Et_2O, NaCl, H_2O HPLC gradient grade, and CH_3CN HPLC gradient grade were purchased. HPLC separations were performed on C18 150 × 4.6 mm (5 μm) column at 25 °C using a variable wavelength UV−vis detector. The flow rates were 0.5 and 1 mL/min with injection volumes of 10 μL. Mixtures of water, acetonitrile, and 0.01 M ammonium acetate (acetonitrile-water, 50−50, v/v) at 35:55:10 H_2O/CH_3CN/buffer were used as the mobile phase, irrespectively, of the sample. The analytical wavelength was λ_{max} = 232 nm.

The FT-IR spectra of spiramycin and its new derivatives were recorded in CH_3CN solution. FT-IR measurements were performed

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with a spectrometer equipped with a DTGS detector and two-columnar purge gas generator at resolution 1 cm^{-1}, NSS = 150, range 4000−400 cm^{-1}. The Happ−Genzel apodization function was used.

The ^1H and ^{13}C measurements of spiramycin and its new derivatives were performed in CD_3CN 400 and 600 MHz spectrometers. The operating frequencies for ^1H measurements were 400.075 and 600.08 MHz; pulse width corresponding to the flip angle of 450; spectral width, swh = 9842.5 Hz; acquisition time at = 0.2 s; relaxation delay d_1 = 1.0 s; T = 293.0 K, TMS was used as the internal standard. No window function or zero filling was used. Digital resolution was 0.2 Hz/point. ^{13}C NMR spectra were recorded at the operating frequency 150.454 MHz; pulse width corresponding to the flip angle of 600; sw = 19 000 Hz; at = 1.8 s; d_1 = 1.0 s; T = 293.0 K and TMS as the internal standard. Line broadening parameters of 0.5 or 1 Hz were applied. ^1H and ^{13}C NMR resonances were unambiguously assigned on the basis of the $^1H-^{13}C$ HMBC, $^1H-^{13}C$ HSQC, $^1H-^1H$ COSY couplings.

DFT calculations with DGauss using the B88-LYP GGA energy functional of new spiramycin's derivatives were performed with the use of the *Scigress* F.J. 2.4 package (version EU 3.1.8, 2008−2014). DZVP basis set was used for the C, N, O, and H atoms. Models of structures of spiramycin derivatives were built on the basis of earlier determined X-ray structure of demycarosyl Leucomycin A_3 hydrobromide[15]. After construction of initial structures of **1**−**3**, **3b**, **4**, **6**, and **11**, according to experimentally obtained key proton−proton contacts for H(2), H(3), H(4), H(5), H(6), H(19), H(10), H(11), H(12), H(13), H(15), H(17), H(19), H(1′), H(2′), H(6′), H(1‴), and H(2‴) protons, structures were reoriented for further calculations. Then structures were subjected to MM3 and MO-G PM6 semiempirical initial optimizations, and finally the lowest energy calculations were performed with the use of B88-LYP DFT method at the gradient not exceeding 1 kcal/mol at one step. Among conformers of the lowest energy calculated for **1**−**3**, **3b**, **4**, **6**, and **11**, only the ones having interatomic proton−proton distances between 2.4 and 5.6 Å for which the above key proton−proton contacts were detected in NOESY spectra were selected and shown in Figure 4. Even when one of the important proton−proton contacts was not reflected in the calculated structure, the structure was rejected from further consideration. Reorientation one of **1**−**3**, **3b**, **4**, and **6** low-energy conformers and DFT local minimum energy calculations with the gradient not exceeding 0.1 kcal/mol at one step allowed visualization of the structures of intermediates: **3a***, **3a** (enolate)*, **3b** (enolate)*, enolate adduct of **6***, and enolate adduct **6** after conformational change. Low-energy structures, which were in total agreement with $^1H-^1H$ NOESY data, are shown in Figure 4, Supporting Information Figure 1S and Figure 4S. $H_f°$ values obtained for the calculated structures, shown in Figure 4, are the following: **1** $H_f°$ = −607.6 kcal/mol; **2** $H_f°$ = −652.52 kcal/mol; **3** $H_f°$ = −678.02 kcal/mol; **3a** $H_f°$ = −674.53 kcal/mol; **3a** (enolate) $H_f°$ = −695.97 kcal/mol; **3b** $H_f°$ = −612.39 kcal/mol; **3b** (enolate) $H_f°$ = −595.36 kcal/mol; **4** $H_f°$ = −256.85 kcal/mol; **6** $H_f°$ = −195.64 kcal/mol; **6** (enolate adduct) $H_f°$ = −255.06 kcal/mol; **6** (enolate adduct after conformational change) $H_f°$ = −242.56 kcal/mol; **11** $H_f°$ = −238.47 kcal/mol.

2-((4*R*,5*S*,6*S*,7*R*,9*R*,10*R*,11*E*,13*E*,16*R*)-6-(((2*S*,3*R*,4*R*,5*S*,6*R*)-5-(((2*S*,4*R*,5*S*,6*S*)-4,5-dihydroxy-4,6-dimethyltetrahydro-2*H*-pyran-2-yl)-oxy)-4-(dimethylamino)-3-hydroxy-6-methyltetrahydro-2*H*-pyran-2-yl)oxy)-10-(((5*S*,6*R*)-5-(dimethylamino)-6-methyltetrahydro-2*H*-pyran-2-yl)oxy)-4-hydroxy-5-methoxy-9,16-dimethyl-2-oxooxacyclohexadeca-11,13-dien-7-yl)acetaldehyde (spiramycin-compound **1**): mp 125−128 °C, ^1H NMR (600 MHz, CD_3CN, 25 °C), δ = 0.94 (d, $^3J_{H8,H20}$ = 6.6 Hz, 3H, 20-H), 1.08 (m, 1H, 7a-H), 1.14 (s, 3H, 7″-H), 1.15 (d, $^3J_{H5‴,H6‴}$ = 6.1 Hz, 3H, 6‴-H), 1.22 (d, $^3J_{H5′,H6′}$ = 6.2 Hz, 3H, 6′-H), 1.23 (d, $^3J_{H5″,H6″}$ = 6.2 Hz, 3H, 6″-H), 1.29 (d, 3H, 16-H), 1.35 (m, 1H, 2‴a-H), 1.45 (m, 1H, 3‴b-H), 1.46 (m, 1H, 7b-H), 1.75 (dd, ^2J = 14.4 Hz, 1H, 2″a-H), 1.81 (m, 1H, 2‴b-H), 1.81 (m, 1H, 3‴a-H), 1.91 (d, 1H, 2″b-H), 1.96 (m, 1H, 8-H), 2.13 (m, 1H, 4‴-H), 2.14 (m, 1H, 14a-H), 2.19 (s, 6H, 7‴-H, 8‴-H), 2.22 (m, 1H, 6-H), 2.31 (dd, $^3J_{H2,H3}$ = 1.4 Hz, 1H, 2b-H), 2.34(dd, $^3J_{H6,H18}$ = 3.4 Hz, 1H, 18b-H), 2.47 (s, 6H, 7′-H, 8′-H), 2.48 (m, 1H, 3′-H), 2.52 (m, 1H, 14b-H), 2.57 (dd, $^3J_{H2,H3}$ = 10.8 Hz, ^2J = 14.5 Hz, 1H, 2a-H), 2.77 (ddd, $^3J_{H18,H19}$ = 1.9 Hz, $^3J_{H6,H18}$ = 9.8 Hz, ^2J = 17.6 Hz, 1H, 18a-H), 2.87 (d, $^3J_{H4″,H5″}$ = 9.8 Hz, 1H, 4″-H), 3.15 (dd, $^3J_{H4,H5}$ = 9.0 Hz, 1H, 4-H), 3.21 (m, ^3J = 9.5, 1H, 4′-H), 3.28 (m, 1H, 5′-H), 3.47 (m, 1H, 5‴-H), 3.47 (s, 3H, 17-H), 3.47 (m, 1H, 2′-H), 3.76 (dt, $^3J_{H3,H4}$ = 1.8 Hz, 1H, 3-H), 3.92 (dd, $^3J_{H5,H6}$ = 1.9 Hz, 1H, 5-H), 4.08 (m, 1H, 9-H), 4.09 (m, 1H, 5″-H), 4.44 (m, 1H, 1′-H), 4.44 (m, 1H, 1‴-H), 5.06 (d, $^3J_{H1″,H2″}$ = 3.5 Hz, 1H, 1″-H), 5.19(ddq, $^3J_{H15,H16}$ = 6.4 Hz, $^3J_{H15,H14a}$ = 12.7 Hz, $^3J_{H15,H14b}$ = 3.3 Hz, 1H, 15-H), 5.58 (ddd, $^3J_{H13,H14a}$ = 11.0 Hz, $^3J_{H13,H14b}$ = 4.0 Hz, 1H, 13-H), 5.68 (dd, $3J_{H9,H10}$ = 9.5 Hz, $^3J_{H10,H11}$ = 15.1 Hz, 1H, 10-H), 6.08 (ddd, $^3J_{H12,H13}$ = 15.1 Hz, $^4J_{H12,H14b}$ = 1.6 Hz, 1H, 12-H), 6.21(dd, $^3J_{H11,H12}$ = 10.5 Hz, 1H, 11-H), 9.77 (t, 1H, 19-H), ^{13}C NMR (600 MHz, CD_3CN, 25 °C), δ= 15.5 (20-C), 18.7 (6″-C), 18.8 (3‴-C), 19.4 (6′-C), 19.5 (6‴-C), 20.4 (16-C), 25.7 (7″-C), 31.1 (6-C), 31.1 (7-C), 32.0 (8-C), 32.2 (2‴-C), 38.9 (2-C), 40.9 (7‴, 8‴-C), 41.9 (2″-C), 42.1 (14-C), 42.4 (7′, 8′-C), 43.7 (18-C), 61.9 (17-C), 65.9 (4‴-C), 69.2 (3-C), 69.5 (3′-C), 70.0 (15-C), 70.1 (3″-C), 72.4 (2′-C), 73.7 (5′-C), 76.0 (4′-C), 77.4 (4″-C), 66.5 (5″-C), 74.2 (5‴-C), 78.7 (9-C), 79.7 (5-C), 85.7 (4-C), 97.4 (1″-C), 100.3 (1‴-C), 104.8 (1′-C), 129.6 (10-C), 131.9 (13-C), 133.7 (12-C), 135.3 (11-C), 174.7 (1-C), 204.3 (19-C), (4*R*,5*S*,6*S*,7*R*,9*R*,10*R*,11*E*,13*E*,16*R*)-6-(((2*S*,3*R*,4*R*,5*S*,6*R*)-5-(((2*S*,4*R*,5*S*,6*S*)-4,5-dihydroxy-4,6-dimethyltetrahydro-2*H*-pyran-2-yl)-oxy)-4-(dimethylamino)-3-hydroxy-6-methyltetrahydro-2*H*-pyran-2-yl)oxy)-7-(2,2-dimethoxyethyl)-10-(((5*S*,6*R*)-5-(dimethylamino)-6-methyltetrahydro-2*H*-pyran-2-yl)oxy)-4-hydroxy-5-methoxy-9,16-dimethyloxacyclohexadeca-11,13-dien-2-one (compound **2**): spiramycin (500 mg, 0.59 mmol) and pyridinium *p*-toluenesulfonate (366.5 mg, 1.45 mmol) were stirred in a mixture of MeOH (10 mL) with trimethyl orthoformate (30 mL) at 45 °C. After 36 h, mixture was evaporated. Solid residue was dissolved in EtOAc and washed twice with saturated $NaHCO_3$. Ethyl acetate layer evaporation to dryness afforded product **2** as white solid (312 mg, 60%), mp 109−112 °C. HPLC R_t = 9.787 min. Anal. Calcd for $C_{45}H_{80}N_2O_{15}$: C, 60.79; H, 9.07; N, 3.15. Found: C, 60.83; H, 9.05; N, 3.14; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{45}H_{80}N_2O_{15}$: 888.5559; Found 888.5534.^1H NMR (600 MHz, CD_3CN, 25 °C), δ= 0.91 (d, $^3J_{H8,H20}$ = 6.7 Hz, 3H, 20-H), 0.999 (m, 1H, 7a-H), 1.11 (s, 3H, 7″-H), 1.16 (d, $^3J_{H5‴,H6‴}$ = 6.2 Hz, 3H, 6‴-H), 1.20 (d, 3H, 6″-H), 1.24 (d, $^3J_{H5′,H6′}$ =6.1 Hz, 3H, 6′-H), 1.26 (d, 3H, 16-H), 1.33 (m, 1H, 2‴a-H), 1.44 (m, 1H, 3‴b-H), 1.44 (m, 1H, 7b-H), 1.55 (ddd, $^3J_{H18b,H19}$ = 2.5 Hz, $^3J_{H6-H18}$ = 8.4 Hz, ^2J = 13.9 Hz, 1H, 18b-H),1.67 (m, 1H, 6-H), 1.73 (dd, ^2J = 14.4 Hz, 1H, 2″a-H), 1.79 (m, 1H, 3‴a-H), 1.80 (m, 1H, 2‴b-H), 1.81 (m, 1H, 18a-H), 1.89 (dd, $^3J_{H1″,H2″}$ = 1.2 1H, 2″b-H), 2.02 (m, 1H, 8-H), 2.10 (m, 1H, 4‴-H), 2.10 (m, 1H, 14a-H), 2.16 (s, 6H, 7‴-H, 8‴-H), 2.26 (m, 1H, 2b-H), 2.44 (s, 6H, 7′-H, 8′-H), 2.47 (m, 1H, 3′-H), 2.48 (m, 1H, 14b-H), 2.54 (dd, $^3J_{H2,H3}$ = 10.8 Hz, ^2J = 14.7 Hz, 1H, 2a-H), 2.84 (t, $^3J_{H4″,H5″}$ = 9.4 Hz, $^3J_{H4″,OH}$ = 9.4 Hz, 1H, 4″-H), 3.11 (dd, $^3J_{H3,H4}$ = 1.8, $^3J_{H4,H5}$ = 9.0 Hz, 1H, 4-H), 3.20 (t, ^3J = 9.5, 1H, 4′-H), 3.28 (s, 3H, 21-H), 3.30 (m, 1H, 5′-H), 3.36 (s, 3H, 22-H), 3.42 (s, 3H, 17-H), 3.43 (m, 1H, 5‴-H), 3.44 (m, 1H, 2′-H), 3.68 (d, 1H, 3-H), 3.96 (d, 1H, 5-H), 4.07 (dq, $^3J_{H5″-H6″}$ = 6.1 Hz, 1H, 5″-H), 4.20 (dd, $^3J_{H8-H9}$ = 4.2 Hz, $^3J_{H9-H10}$ = 9.5 Hz, 1H, 9-H), 4.43 (dd, $^3J_{H1‴-H2a‴}$ = 9.5 Hz, $^3J_{H1‴-H2b‴}$ = 2.0 Hz, 1H, 1‴-H), 4.48 (d, $^3J_{H18a,H19}$ = 7.7 Hz, 1H, 19-H), 4.48 (d, $^3J_{H1′-H2′}$ = 8.5 Hz, 1H, 1′-H), 5.05 (d, $^3J_{H1″,H2″}$ = 3.7 Hz, 1H, 1″-H), 5.17 (ddq, $^3J_{H15,H16}$ = 6.4 Hz, $^3J_{H15,H14a}$ = 12.8 Hz, $^3J_{H15,H14b}$ = 3.0 Hz, 1H, 15-H), 5.54 (ddd, $^3J_{H13,H14a}$ = 11.0 Hz, $^3J_{H13,H14b}$ = 4.2 Hz, 1H, 13-H), 5.65 (dd, $^3J_{H10,H11}$ = 15.0 Hz, 1H, 10-H), 6.04 (dd, $^3J_{H12,H13}$ = 15.1 Hz, $^4J_{H12,H14b}$ = 1.6 Hz, 1H, 12-H), 6.14 (dd, $^3J_{H11,H12}$ = 10.5 Hz, 1H, 11-H), ^{13}C NMR (600 MHz, CD_3CN, 25 °C), δ = 15.5 (20-C), 18.7 (6″-C), 18.7 (3‴-C), 19.6 (6′-C), 19.4 (6‴-C), 20.3 (16-C), 25.7 (7″-C), 31.6 (7-C), 31.8 (18-C), 31.9 (8-C), 32.2 (2‴-C), 32.1 (6-C), 39.0 (2-C), 40.9 (7‴, 8‴-C), 41.9 (2″-C), 42.2 (14-C), 42.4 (7′, 8′-C), 53.4 (21-C), 54.5 (22-C), 61.7 (17-C), 66.0 (4‴-C), 69.3 (3-C), 69.6 (3′-C), 70.0 (15-C), 70.1 (3″-C), 72.6 (2′-C), 73.8 (5′-C), 76.1 (4′-C), 77.4 (4″-C), 66.5 (5″-C), 74.3 (5‴-C), 78.8 (9-C), 79.6 (5-C), 85.8 (4-C), 97.3 (1″-C), 100.6 (1‴-C), 104.8 (19-C), 105.2 (1′-C), 129.6 (10-C), 131.7 (13-C), 133.8 (12-C), 135.5 (11-C), 175.0 (1-C),

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(2*S*,3*R*,4*S*,5*S*,6*R*)-5-(((2*S*,4*R*,5*S*,6*S*)-4,5-dihydroxy-4,6-dimethyltetrahydro-2*H*-pyran-2-yl)oxy)-2-(((4*R*,5*S*,6*S*,7*R*,9*R*,10*R*,11*E*,13*E*,16*R*)-7-(2,2-dimethoxyethyl)-10-(((5*S*,6*R*)-5-(dimethylamino)-6-methyltetrahydro-2*H*-pyran-2-yl)oxy)-4-hydroxy-5-methoxy-9,16-dimethyl-2-oxooxacyclohexadeca-11,13-dien-6-yl)oxy)-4-(dimethylamino)-6-methyltetrahydro-2*H*-pyran-3-yl acetate (compound **3**): Derivative **2** (312 mg, 0.34 mmol) was dissolved in acetonitrile (10 mL), and then acetic anhydride (0.091 mL, 0.96 mmol) was added. The mixture was stirred for 24 h at room temperature. Next the mixture was evaporated and extracted with ethyl acetate and saturated $NaHCO_3$. Ethyl acetate layer evaporation to dryness afforded white solid product **3** (315 mg, 95%), mp 103−106 °C. HPLC R_t = 11.360 min. Anal. Calcd for $C_{47}H_{82}N_2O_{16}$: C, 60.62; H, 8.88; N, 3.01. Found: C, 60.60; H, 8.90; N, 3.04; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{47}H_{82}N_2O_{16}$ 930.5664; Found 930.5643.^{1}H NMR (600 MHz, CD_3CN, 25 °C), δ= 0.87 (d, $^3J_{H8,H20}$ = 6.7 Hz, 3H, 20-H), 0.87 (m, 1H, 7a-H), 1.11 (s, 3H, 7″-H), 1.16 (d, $^3J_{H5‴,H6‴}$ = 6.2 Hz, 3H, 6‴-H), 1.20 (d, $^3J_{H5′,H6′}$ = 6.1 Hz, 3H, 6″-H), 1.26 (d, $^3J_{H5′,H6′}$ = 6.1 Hz, 3H, 6′-H), 1.27 (d, 3H, 16-H), 1.31 (m, 1H, 2‴a-H), 1.32 (m, 1H, 7b-H), 1.44 (m, 1H, 3‴b-H), 1.50 (ddd, $^3J_{H18b,H19}$ = 2.9 Hz, $^3J_{H6-H18}$ = 9.9 Hz, ^2J = 16.0 Hz, 1H, 18b-H),1.65 (m, 1H, 6-H), 1.74 (dd, ^2J = 14.5 Hz, 1H, 2″a-H), 1.74 (m, 1H, 18a-H), 1.79 (m, 1H, 3‴a-H), 1.79 (m, 1H, 2‴b-H), 1.90 (dd, $^3J_{H1″,H2″}$ = 1.2 1H, 2″b-H), 1.98 (m, 1H, 8-H), 2.00 (s, 3H, 10′-H), 2.08 (m, 1H, 14a-H), 2.09 (m, 1H, 4‴-H), 2.16 (s, 6H, 7‴-H, 8‴-H), 2.21 (dd, $^3J_{H2,H3}$ = 1.5, ^2J = 14.5 1H, 2b-H), 2.37 (s, 6H, 7′-H, 8′-H), 2.49 (m, 1H, 14b-H), 2.50 (dd, $^3J_{H2,H3}$ = 10.9 Hz, ^2J = 14.5 Hz, 1H, 2a-H), 2.83 (t, $^3J_{H3′,H4′}$ = 10.1, 1H, 3′-H), 2.83 (dd, $^3J_{H4″,H5″}$ = 11.6 Hz, $^3J_{H4″,OH}$ = 9.9 Hz, 1H, 4″-H), 3.03 (dd, $^3J_{H3,H4}$ = 1.8, $^3J_{H4,H5}$ = 9.0 Hz, 1H, 4-H), 3.26 (s, 3H, 21-H), 3.30 (dd, $^3J_{H4′,H5′}$ = 4.1, 1H, 4′-H), 3.35 (m, 1H, 5′-H), 3.36 (s, 3H, 22-H), 3.39 (s, 3H, 17-H), 3.42 (m, 1H, 5‴-H), 3.66 (d, 1H, 3-H), 3.91 (d, 1H, 5-H), 4.02 (m, 1H, 5″-H), 4.19 (dd, $^3J_{H8-H9}$ = 4.3 Hz, $^3J_{H9-H10}$ = 9.6 Hz, 1H, 9-H), 4.42 (dd, $^3J_{H1‴-H2a‴}$ = 9.6 Hz, $^3J_{H1‴-H2b‴}$ = 2.0 Hz, 1H, 1‴-H), 4.46 (d, $^3J_{H18a,H19}$ = 8.8 Hz, 1H, 19-H), 4.77 (d, $^3J_{H1′-H2′}$ = 7.8 Hz, 1H, 1′-H), 4.85 (dd, $^3J_{H2′,H3′}$ = 10.4 1H, 2′-H), 5.08 (d, $^3J_{H1″,H2″}$ = 3.8 Hz, 1H, 1″-H), 5.17 (ddq, $^3J_{H15,H16}$ = 6.4 Hz, $^3J_{H15,H14a}$ = 12.9 Hz, $^3J_{H15,H14b}$ = 2.7 Hz, 1H, 15-H), 5.52 (ddd, $^3J_{H13,H14a}$ = 11.0 Hz, $^3J_{H13,H14b}$ = 4.1 Hz, 1H, 13-H), 5.63 (dd, $^3J_{H10,H11}$ = 15.0 Hz, 1H, 10-H), 6.02 (dd, $^3J_{H12,H13}$ = 15.0 Hz, $^4J_{H12,H14b}$ = 1.6 Hz, 1H, 12-H), 6.12 (dd, $^3J_{H11,H12}$ = 10.6 Hz, 1H, 11-H), ^{13}C NMR (600 MHz, CD_3CN, 25 °C), δ = 15.4 (20-C), 18.8 (3‴-C), 19.4 (6″-C), 18.8 (6′-C), 19.4 (6‴-C), 20.3 (16-C), 21.9 (10′), 25.7 (7″-C), 31.2 (7-C), 31.7 (18-C), 31.7 (6-C), 31.9 (8-C), 32.3 (2‴-C), 38.7 (2-C), 40.9 (7‴, 8‴-C), 41.9 (2″-C), 41.9 (7′, 8′-C), 42.2 (14-C), 53.2 (21-C), 54.8 (22-C), 61.6 (17-C), 66.0 (4‴-C), 68.4 (3′-C), 69.4 (3-C), 69.9 (15-C), 70.1 (3″-C), 71.9 (2′-C), 73.6 (5′-C), 76.9 (4′-C), 77.4 (4″-C), 66.5 (5″-C), 74.3 (5‴-C), 77.2 (5-C), 78.5 (9-C), 86.6 (4-C), 97.8 (1″-C), 100.6 (1‴-C), 104.8 (19-C), 101.5 (1′-C), 129.6 (10-C), 131.6 (13-C), 133.8 (12-C), 135.5 (11-C), 169.9 (9′-C), 175.1 (1-C),

(3*E*,5*S*,6*S*,7*R*,9*R*,10*R*,11*E*,13*E*,16*R*)-6-(((2*S*,3*R*,4*R*,5*S*,6*R*)-5-(((2*S*,4*R*,5*S*,6*S*)-4,5-dihydroxy-4,6-dimethyltetrahydro-2*H*-pyran-2-yl)oxy)-4-(dimethylamino)-3-hydroxy-6-methyltetrahydro-2*H*-pyran-2-yl)oxy)-7-(2,2-dimethoxyethyl)-10-(((5*S*,6*R*)-5-(dimethylamino)-6-methyltetrahydro-2*H*-pyran-2-yl)oxy)-5-methoxy-9,16-dimethyloxacyclohexadeca-3,11,13-trien-2-one (compound **3b**): Derivative **3** (315 mg, 0.32 mmol) was dissolved in 12 mL of THF/DMF (12:4), and then 8.1 mg (0.34 mmol) of NaH was added. The reaction was performed at 0 °C. After 4 h 2 mL of acetone was added, and the mixture was evaporated. The solid residue was dissolved in diethyl ether and washed with saturated $NaHCO_3$. Diethyl ether layer evaporation and purification by column chromatography (EtOAc) afforded white powder of product **3b** (135 mg, 44%), mp 58−61 °C. HPLC R_t = 15.134 min. HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{45}H_{79}N_2O_{14}$ Calcd: 871,5526; Found 871.5520. Anal. Calcd for $C_{45}H_{78}N_2O_{14}$: C, 62.05; H, 9.03; N, 3.22. Found C, 62.00; H, 8.99; N, 3.20. ^{1}H NMR (600 MHz, CD_3CN, 25 °C), δ= 0.92 (d, $^3J_{H8,H20}$ = 6.7 Hz, 3H, 20-H), 0.98 (m, 1H, 7a-H), 1.14 (s, 3H, 7″-H), 1.18 (d, $^3J_{H5‴,H6‴}$ = 6.1 Hz, 3H, 6‴-H), 1.23 (d, 3H, 6″-H), 1.27 (d, $^3J_{H5′,H6′}$ = 6.2 Hz, 3H, 6′-H), 1.32 (d, $^3J_{H15-H16}$ = 6.2, 3H, 16-H), 1.34 (m, 1H, 2‴a-H), 1.45 (m, 1H, 6-H), 1.46 (m, 1H, 7b-H), 1.47 (m, 1H, 3‴b-H), 1.62 (dd, $^3J_{H18a,H19′}$ = 8.2 Hz, ^2J = 13.8 Hz, 1H, 18a-H), 1.75 (dd, ^2J = 14.4 Hz, 1H, 2″a-H), 1.79 (m, 1H, 3‴a-H), 1.81 (m, 1H, 2‴b-H), 1.90 (m, 1H, 2″b-H), 1.90 (m, 1H, 18b-H),2.01 (m, 1H, 8-H), 2.12 (m, 1H, 4‴-H), 2.07 (m, 1H, 14b-H), 2.19 (s, 6H, 7‴-H, 8‴-H), 2.47 (s, 6H, 7′-H, 8′-H), 2.48 (m, 1H, 3′-H), 2.48 (m, 1H, 14a-H), 2.86 (t, $^3J_{H4″,H5″}$ = 10.0 Hz, $^3J_{H4″,OH}$ = 10.0 Hz, 1H, 4″-H), 3.19 (s, 3H, 17-H), 3.22 (dd, ^3J = 9.0, ^3J = 10.0, 1H, 4′-H), 3.32 (m, 1H, 5′-H), 3.33 (s, 3H, 21-H), 3.34 (s, 3H, 22-H), 3.45 (dq, $^3J_{H4‴-H5‴}$ = 9.5 Hz, $^3J_{H5‴-H6‴}$ = 6.1 Hz, 1H, 5‴-H), 3.52 (ddd, $^3J_{H2′-H3′}$ = 10.2 Hz, $^3J_{H2′-OH}$ = 1.4 Hz, 1H, 2′-H), 3.73 (d, 1H, 5-H), 3.83 (t, $^3J_{H4,H5}$ = 9.1 Hz, 1H, 4-H), 4.10 (dq, $^3J_{H5″-H6″}$ = 6.2 Hz, 1H, 5″-H), 4.17 (dd, $^3J_{H8-H9}$ = 4.2 Hz, $^3J_{H9-H10}$ = 9.4 Hz, 1H, 9-H), 4.45 (dd, $^3J_{H1‴-H2a‴}$ = 9.5 Hz, $^3J_{H1‴-H2b‴}$ = 1.8 Hz, 1H, 1‴-H), 4.50 (d, $^3J_{H1′-H2′}$ = 7.6 Hz, 1H, 1′-H), 4.57 (d, $^3J_{H18a,H19}$ = 3.4 Hz, 1H, 19-H), 5.07 (d, $^3J_{H1″,H2″}$ = 3.7 Hz, 1H, 1″-H), 5.17 (ddq, $^3J_{H15,H16}$ = 6.3 Hz, $^3J_{H15,H14a}$ = 12.7 Hz, $^3J_{H15,H14b}$ = 3.2 Hz, 1H, 15-H), 5.49 (ddd, $^3J_{H13,H14a}$ = 10.9 Hz, $^3J_{H13,H14b}$ = 4.5 Hz, 1H, 13-H), 5.63 (dd, $^3J_{H10,H11}$ = 14.7 Hz, 1H, 10-H), 5.94 (d, $^3J_{H2,H3}$ = 15.2 Hz, 1H, 2-H), 6.12 (ddd, $^3J_{H12,H13}$ = 14.8 Hz, $^4J_{H12,H14b}$ = 1.2 Hz, 1H, 12-H), 6.08 (dd, $^3J_{H11,H12}$ = 10.6 Hz, 1H, 11-H), 6.34 (dd, $^3J_{H2-H3}$ = 15.5 Hz, $^3J_{H3-H4}$ = 9.0 Hz, 1H, 3-H), ^{13}C NMR (600 MHz, CD_3CN, 25 °C), δ = 15.5 (20-C), 18.8 (3‴-C), 19.4 (6″-C), 18.7 (6′-C), 19.3 (6‴-C), 20.4 (16-C), 25.7 (7″-C), 30.4 (7-C), 30.7 (18-C), 31.6 (8-C), 32.2 (2‴-C), 32.6 (6-C), 40.9 (7‴, 8‴-C), 41.9 (2″-C), 42.1 (14-C), 42.4 (7′, 8′-C), 52.9 (21-C), 53.9 (22-C), 56.3 (17-C), 66.0 (4‴-C), 70.0 (3′-C), 70.2 (15-C), 70.2 (3″-C), 72.5 (2′-C), 73.9 (5′-C), 75.7 (4′-C), 77.4 (4″-C), 66.5 (5″-C), 74.3 (5‴-C), 77.9 (9-C), 82.9 (4-C), 83.9 (5-C), 97.3 (1″-C), 100.0 (1‴-C), 103.9 (19-C), 106.6 (1′-C), 127.5 (2-C), 129.0 (10-C), 131.2 (13-C), 134.9 (12-C), 135.8 (11-C), 141.6 (3-C), 166.3 (1-C),

(3*E*,5*Z*,7*R*,9*R*,10*R*,11*E*,13*E*,16*R*)-7-(2,2-dimethoxyethyl)-10-(((5*S*,6*R*)-5-(dimethylamino)-6-methyltetrahydro-2*H*-pyran-2-yl)oxy)-5-methoxy-9,16-dimethyloxacyclohexadeca-3,5,11,13-tetraen-2-one (compound **4**): Derivative **3** (315 mg, 0.32 mmol) was dissolved in 12 mL of THF/DMF (3:1) mixture, and then NaH (81 mg, 3.37 mmol) was added. After 1 h 2 mL of acetone was added, and the mixture was evaporated. The solid residue was dissolved in diethyl ether and washed twice with saturated $NaHCO_3$. Diethyl ether layer evaporation to dryness afforded product **4** as white solid (150 mg, 83%), mp 126−129 °C. HPLC R_t = 16.920 min. Anal. Calcd for $C_{30}H_{49}NO_7$: C, 67.26; H, 9.22; N, 2.61. Found C, 67.25; H, 9.20; N, 2.63; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{30}H_{49}NO_7$ 535.3509; Found 535.3487.^{1}H NMR (600 MHz, CD_3CN, 25 °C), δ= 1.00 (d, $^3J_{H8,H20}$ = 6.3 Hz, 3H, 20-H), 1.10 (d, $^3J_{H5″,H6″}$ = 6.1 Hz, 3H, 6‴-H1.12 (m, 1H, 8-H), 1.12 (m, 1H, 7a-H), 1.28 (m, 1H, 2‴a-H), 1.29 (d, 3H, 16-H), 1.40 (m, 1H, 3‴b-H), 1.50 (m, 1H, 7b-H), 1.51 (ddd, $^3J_{H6-H18}$ = 9.4 Hz, $^3J_{H18b-H19}$ = 4.5 Hz, 1H, 18b-H),1.69 (ddd, $^3J_{H18a,H19}$ = 7.3 Hz, $^3J_{H6,H18}$ = 5.0 Hz ^2J = 13.9 Hz, 1H, 18a-H), 1.79 (dq, ^2J = 12.7 Hz, $^3J_{H3a‴-H4‴}$ = 3.7 Hz, $^3J_{H3a‴-H2‴}$ = 3.7 Hz, 1H, 3‴a-H), 1.83 (m, 1H, 2‴b-H), 2.07 (ddd, $^3J_{H4‴-H3b‴}$ = 11.7 Hz, $^3J_{H4‴-H5‴}$ = 9.4 Hz, $^3J_{H3a‴-H4‴}$ = 3.8 Hz, 1H, 4‴-H), 2.14 (s, 6H, 7‴-H, 8‴-H), 2.27 (dt, ^2J = 13.6 Hz, 1H, 14a-H), 2.42 (m, 1H, 14b-H), 2.58 (m, 1H, 6-H), 3.24 (s, 3H, 21-H), 3.24 (s, 3H, 22-H), 3.37 (dq, $^3J_{H4‴-H5‴}$ = 9.4 Hz, $^3J_{H5‴-H6‴}$ = 6.1 Hz, 1H, 5‴-H), 3.58 (s, 3H, 17-H), 3.74 (dd, $^3J_{H8-H9}$ = 1.4 Hz, $^3J_{H9-H10}$ = 8.7 Hz, 1H, 9-H), 4.28 (dd, $^3J_{H1‴-H2a‴}$ = 9.5 Hz, $^3J_{H1‴-H2b‴}$ = 2.1 Hz, 1H, 1‴-H), 4.33 (dd, 1H, 19-H), 4.96 (ddq, $^3J_{H15,H16}$ = 6.3 Hz, $^3J_{H15,H14a}$ = 12.4 Hz, $^3J_{H15,H14b}$ = 3.2 Hz, 1H, 15-H), 5.05 (d, $^3J_{H5-H6}$ = 10.8 Hz, 1H, 5-H), 5.35 (ddd, $^3J_{H13,H14a}$ = 11.0 Hz, $^3J_{H13,H14b}$ = 3.9 Hz, 1H, 13-H), 5.63 (d, $^3J_{H2,H3}$ = 15.6 Hz, 1H, 2-H), 5.75 (dd, $^3J_{H10,H11}$ = 15.0 Hz, 1H, 10-H), 5.84 (dd, $^3J_{H11,H12}$ = 10.3 Hz, 1H, 11-H), 6.15 (ddd, $^3J_{H12,H13}$ = 14.8 Hz, $^4J_{H12,H14b}$ = 1.5 Hz, 1H, 12-H), 6.96 (dd, 1H, 3-H), ^{13}C NMR (600 MHz, CD_3CN, 25 °C), δ= 18.8 (3‴-C), 19.5 (6‴-C), 20.2 (20-C), 21.2 (16-C), 31.9 (2‴-C), 33.6 (6-C), 38.0 (7-C), 39.2 (18-C), 39.4 (8-C), 40.9 (7‴, 8‴-C), 42.2 (14-C), 52.9 (21-C), 53.0 (22-C), 60.4 (17-C), 65.9 (4‴-C), 70.6 (15-C), 74.3 (5‴-C), 85.7 (9-C), 103.3 (1‴-C), 104.0 (19-C), 116.3 (2-C), 129.2 (11-C), 129.5 (13-C), 134.7 (5-C), 135.8 (12-C), 137.1 (10-C), 143.8 (3-C), 154.6 (4-C), 167.4 (1-C), prop-2-yn-1-yl(2*E*,4*Z*,6*R*,8*R*,9*R*,10*E*,12*E*,15*R*)-6-(2,2-dimethox-

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yethyl)-9-(((5*S*,6*R*)-5-(dimethylamino)-6-methyltetrahydro-2*H*-pyran-2-yl)oxy)-15-hydroxy-4-methoxy-8-methylhexadeca-2,4,10,12-tetraenoate (compound **5**): Derivative **4** (130 mg, 0.26 mmol) was dissolved in propargyl alcohol (3 mL), and then NaH (1.5 mg) was added. The reaction was performed at 70 °C. After 72 h the mixture was extracted twice with diethyl ether and saturated $NaHCO_3$. The organic layer evaporation and purification by column chromatography (EtOAc) afforded compound **5** as pale yellow oil (27 mg, 19%). HPLC R_t = 11.600 min. Anal. Calcd for $C_{33}H_{53}NO_8$: C, 66.98; H, 9.03; N, 2.37. Found C, 66.95; H, 9.05; N, 2.36; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{33}H_{53}NO_8$ 591.3771; Found 591.3759. ^{1}H NMR (600 MHz, CD_3CN, 25 °C), δ= 0.83 (d, $^3J_{H8,H20}$ = 6.8 Hz, 3H, 20-H), 1.09 (d, $^3J_{H15,H16}$ = 6.2 Hz 3H, 16-H), 1.12 (d, $^3J_{H5''',H6'''}$ = 6.2 Hz, 3H, 6‴-H), 1.15 (m, 1H, 7a-H), 1.31 (m, 1H, 7b-H), 1.35 (m, 1H, 2‴a-H), 1.41 (m, 1H, 3‴b-H), 1.47 (m, 1H, 18b-H), 1.62 (m, 1H, 8-H), 1.70 (ddd, $^3J_{H18a,H19}$ = 7.3 Hz, $^3J_{H6,H18}$ = 4.9 Hz, ^2J = 13.9 Hz, 1H, 18a-H), 1.78 (m, 1H, 3‴a-H), 1.82 (m, 1H, 2‴b-H), 2.1 (m, 1H, 4‴-H), 2.15 (s, 6H, 7‴-H, 8‴-H), 2.16 (m, 2H, 14-H), 2.78 (t, $^4J_{H23,H25'}$ = 2.5 Hz 1H, 25-H), 2.81 (m, 1H, 6-H), 3.23 (s, 3H, 22-H), 3.24 (s, 3H, 21-H), 3.40 (dd, $^3J_{H4'',H5'''}$ = 9.5 Hz, $^3J_{H5''',H6'''}$ = 6.2 Hz, 1H, 5‴-H), 3.61 (s, 3H, 17-H), 3.71 (m, 1H, 15-H), 3.89 (ddd, $^4J_{H9,H11}$ = 1.1 Hz, $^3J_{H8,H9}$ = 5.0 Hz, $^3J_{H9,H10}$ = 7.1 Hz, 1H, 9-H), 4.31 (dd, $^3J_{H18b,H19}$ = 4.3 Hz, $^3J_{H18a,H19}$ = 7.3, 1H, 19-H), 4.37 (dd, $^3J_{H1'''-H2a'''}$ = 9.2 Hz, $^3J_{H1'''-H2b'''}$ = 1.9 Hz, 1H, 1‴-H), 4.74 (d, $^4J_{H23,H25}$ = 2.5 Hz, 2H, 23-H), 5.27 (d, $^3J_{H5-H6}$ = 10.4 Hz, 1H, 5-H), 5.51 (dd, $^3J_{H10,H11}$ = 14.7, $^3J_{H9,H10}$ = 7.1 Hz, 1H, 10-H), 5.67 (dt, $^3J_{H12,H13}$ = 14.5 Hz, $^3J_{H13,H14}$ = 7.4 Hz, 1H, 13-H), 5.98 (d, $^3J_{H2,H3}$ = 15.5 Hz, 1H, 2-H), 6.06 (m, 1H, 12-H), 6.13 (ddd, $^3J_{H11,H12}$ = 10.5 Hz, $^3J_{H10,H11}$ = 14.7 Hz, $^4J_{H9,H11}$ = 1.1 Hz, 1H, 11-H), 7.09 (d, $^3J_{H2,H3}$ = 15.5 Hz, 1H, 3-H), ^{13}C NMR (600 MHz, CD_3CN, 25 °C), δ= 15.2 (20-C), 18.8 (3‴-C), 19.4 (6‴-C), 23.3 (16-C), 31.3 (6-C), 32.1 (2‴-C), 35.4 (8-C), 39.2 (7-C), 39.5 (18-C), 40.9 (7‴, 8‴-C), 43.2 (14-C), 52.6 (23-C), 53.0 (21-C), 53.1 (22-C), 60.6 (17-C), 65.9 (4‴-C), 67.8 (15-C), 74.3 (5‴-C), 76.1 (25-C), 79.0 (24-C), 83.0 (9-C), 101.5 (1‴-C), 103.8 (19-C), 116.5 (2-C), 131.4 (10-C), 131.7 (13-C), 132.8 (12-C), 132.9 (11-C), 134.6 (5-C), 142.7 (3-C), 154.3 (4-C), 166.7 (1-C),

2-((3*E*,5*Z*,7*R*,9*R*,10*R*,11*E*,13*E*,16*R*)-10-(((5*S*,6*R*)-5-(dimethylamino)-6-methyltetrahydro-2*H*-pyran-2-yl)oxy)-5-methoxy-9,16-dimethyl-2-oxooxacyclohexadeca-3,5,11,13-tetraen-7-yl)acetaldehyde (compound **6**): Derivative **4** (150 mg, 0.28 mmol) was dissolved in 10 mL of H_2O/CH_3CN (50:50), and then CHF_2COOH (0.09 mL, 1.4 mmol) was added to the mixture at room temperature. After 24 h acetonitrile was evaporated, and the aqueous layer was washed with diethyl ether and saturated $NaHCO_3$. Diethyl ether layer evaporation to dryness afforded white solid product **6** (130 mg, 95%), mp 105−107 °C. HPLC R_t = 12.094 min. Anal. Calcd for $C_{28}H_{43}NO_6$: C, 68.68; H, 8.85; N, 2.86. Found C, 68.65; H, 8.87; N, 2.87; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{28}H_{43}NO_6$ 489.3090; Found 489.3079.^{1}H NMR (600 MHz, CD_3CN, 25 °C), δ= 1.05 (d, $^3J_{H8,H20}$ = 6.5 Hz, 3H, 20-H), 1.13 (d, 3H, 6‴-H), 1.16 (m, 1H, 8-H),), 1.15 (m, 1H, 7a-H), 1.31 (m, 1H, 2‴a-H), 1.32 (d, 3H, 16-H), 1.43 (m, 1H, 3‴b-H), 1.59 (m, 1H, 7b-H), 1.79 (dq, ^2J = 12.9 Hz, $^3J_{H3a'''-H4'''}$ = 3.7 Hz, $^3J_{H3a'''-H2'''}$ = 3.7 Hz, 1H, 3‴a-H), 1.85 (m, 1H, 2‴b-H), 2.10 (m, 1H, 4‴-H), 2.17 (s, 6H, 7‴-H, 8‴-H), 2.30 (m, 1H, 14b-H), 2.40 (m, 1H, 14a-H), 2.45 (ddd, $^3J_{H6-H18}$ = 7.5 Hz, $^3J_{H18b-H19}$ = 2.0 Hz, 1H, 18b-H), 2.52 (ddd, $^3J_{H18a,H19}$ = 2.0 Hz, $^3J_{H6,H18}$ = 6.3 Hz ^2J = 16.6 Hz, 1H, 18a-H), 3.02 (m, 1H, 6-H), 3.40 (dq, $^3J_{H4'''-H5'''}$ = 9.4 Hz, $^3J_{H5'''-H6'''}$ = 6.1 Hz, 1H, 5‴-H), 3.61 (s, 3H, 17-H), 3.79 (dd, $^3J_{H8-H9}$ = 1.6 Hz, $^3J_{H9-H10}$ = 8.6 Hz, 1H, 9-H), 4.31 (dd, $^3J_{H1'''-H2a'''}$ = 9.6 Hz, $^3J_{H1'''-H2b'''}$ = 2.1 Hz, 1H, 1‴-H), 4.97 (ddq, $^3J_{H15,H16}$ = 6.2 Hz, $^3J_{H15,H14a}$ = 12.4 Hz, $^3J_{H15,H14b}$ = 3.1 Hz, 1H, 15-H), 5.12 (d, $^3J_{H5-H6}$ = 10.7 Hz, 1H, 5-H), 5.40 (ddd, $^3J_{H13,H14a}$ = 11.0 Hz, $^3J_{H13,H14b}$ = 4.0 Hz, 1H, 13-H), 5.69 (d, $^3J_{H2,H3}$ = 15.7 Hz, 1H, 2-H), 5.80 (dd, $^3J_{H10,H11}$ = 15.4 Hz, 1H, 10-H), 5.88 (dd, $^3J_{H11,H12}$ = 10.3 Hz, 1H, 11-H), 6.18 (ddd, $^3J_{H12,H13}$ = 15.0 Hz, $^4J_{H12,H14b}$ = 1.5 Hz, 1H, 12-H), 6.99 (dd, 1H, 3-H), 9.68 (t, 1H, 19-H), ^{13}C NMR (600 MHz, CD_3CN, 25 °C), δ = 19.2 (3‴-C), 19.9 (6‴-C), 20.6 (20-C), 21.6 (16-C), 32.3 (6-C), 32.4 (2‴-C), 38.1 (7-C), 40.2 (8-C), 41.3 (7‴, 8‴-C), 42.6 (14-C), 50.0 (18-C), 60.9 (17-C), 66.3 (4‴-C), 71.2 (15-C), 74.7 (5‴-C), 86.1 (9-C), 103.7 (1‴-C), 117.4 (2-C), 129.8 (11-C), 130.2 (13-C), 133.3 (5-C), 136.1 (12-C), 137.4 (10-C), 143.9 (3-C), 152.2 (4-C), 167.8 (1-C), 203.2 (19-C),

(2*R*,3a*R*,5*R*,6*R*,7*E*,9*E*,12*R*,16*Z*,17a*R*)-6-(((5*S*,6*R*)-5-(dimethylamino)-6-methyltetrahydro-2*H*-pyran-2-yl)oxy)-2,17-dimethoxy-5,12-dimethyl-2,3,3a,4,5,6,11,12,15,17a-decahydro-14*H*-furo[2,3-*f*][1]-oxacyclohexadecin-14-one (compound **7**): Derivative **6** (130 mg, 0.26 mmol) was dissolved in CH_3OH (3 mL), and then NaH (1.5 mg) was added. After 1 h the mixture was extracted twice with diethyl ether and saturated $NaHCO_3$. The organic layer evaporation and purification by column chromatography (EtOAc) afforded colorless oil product **7** (62 mg, 45%). HPLC R_t = 14.534 min. Anal. Calcd for $C_{29}H_{47}NO_7$: C, 66.77; H, 9.08; N, 2.68. Found C, 66.78; H, 9.05; N, 2.70; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{29}H_{47}NO_7$ 521.3353; Found 521.3332.^{1}H NMR (600 MHz, CD_3CN, 25 °C), δ= 0.94 (d, $^3J_{H8,H20}$ = 6.8 Hz, 3H, 20-H), 1.11 (m, 1H, 7a-H), 1.17 (d, $^3J_{H5''',H6'''}$ = 6.2 Hz, 3H, 6‴-H), 1.26 (d, $^3J_{H8,H20}$ = 6.0 Hz, 3H, 16-H), 1.35 (m, 1H, 2‴a-H), 1.38 (m, 1H, 7b-H), 1.46 (m, 1H, 3‴b-H), 1.70 (dt, $^3J_{H18a,H19}$ = 5.3 Hz, $^3J_{H6,H18}$ = 5.3 Hz, ^2J = 12.1 Hz, 1H, 18a-H), 1.83 (m, 1H, 2‴b-H), 1.83 (m, 1H, 3‴a-H), 1.97 (m, 1H, 8-H),), 2.13 (m, 1H, 6-H), 2.13 (m, 1H, 14b-H), 2.13 (m, 1H, 18b-H), 2.13 (m, 1H, 4‴-H), 2.19 (s, 6H, 7‴-H, 8‴-H), 2.47 (m, 1H, 14a-H), 2.85 (ddd, $^3J_{H2b,H3}$ = 5.7 Hz, ^2J_H = 15.2 Hz $^5J_{H2b,H5}$ = 1.3 Hz,1H, 2b-H), 3.13 (dd, $^3J_{H2a,H3}$ = 7.8 Hz, ^2J_H = 15.2 Hz 1H, 2a-H), 3.31 (s, 3H, 23-H), 3.48 (m, 1H, 5‴-H), 3.62 (s, 3H, 17-H), 3.93 (d, $^3J_{H5-H6}$ = 9.4 Hz, 1H, 5-H), 4.15 (dd, $^3J_{H8-H9}$ = 4.5 Hz, $^3J_{H9-H10}$ = 9.3 Hz, 1H, 9-H), 4.46 (dd, $^3J_{H1'''-H2a'''}$ = 9.3 Hz, $^3J_{H1'''-H2b'''}$ = 1.5 Hz, 1H, 1‴-H), 4.79 (dd, $^3J_{H2a,H3}$ = 7.8 Hz, $^3J_{H2b,H3}$ = 5.7 Hz, 1H, 3-H), 4.96 (d, $^3J_{H18a,H19}$ = 5.3 Hz, 1H, 19-H), 5.13 (m, 1H, 15-H), 5.58 (ddd, $^3J_{H12,H13}$ = 14.9 Hz, $^3J_{H13,H14a}$ = 10.8 Hz, $^3J_{H13,H14b}$ = 4.2 Hz, 1H, 13-H), 5.64 (dd, $^3J_{H10,H11}$ = 15.2 Hz, $^3J_{H9,H10}$ = 9.3 Hz, 1H, 10-H), 6.05 (dd, $^3J_{H12,H13}$ = 14.9 Hz, $^3J_{H11,H12}$ = 10.8 Hz, 1H, 12-H), 6.18 (dd, $^3J_{H10,H11}$ = 15.2 Hz, $^3J_{H11,H12}$ = 10.5 Hz, 1H, 11-H), ^{13}C NMR (600 MHz, CD_3CN, 25 °C), δ = 15.8 (20-C), 18.8 (3‴-C), 19.5 (6‴-C), 20.6 (16-C), 32.2 (2‴-C), 32.2 (2-C), 34.6 (8-C), 36.1 (7-C), 38.8 (6-C), 39.3 (18-C), 40.9 (7‴, 8‴-C), 41.6 (14-C), 55.0 (23-C), 58.6 (17-C), 66.0 (4‴-C), 69.6 (15-C), 74.3 (5‴-C), 80.4 (9-C), 83.9 (5-C), 100.9 (1‴-C), 104.3 (3-C), 105.3 (19-C), 129.1 (10-C), 132.4 (13-C), 132.9 (12-C), 135.3(11-C), 157.4 (4-C), 172.6 (1-C),

(2*R*,3a*R*,5*R*,6*R*,7*E*,9*E*,12*R*,16*Z*,17a*R*)-6-(((5*S*,6*R*)-5-(dimethylamino)-6-methyltetrahydro-2*H*-pyran-2-yl)oxy)-2-ethoxy-17-methoxy-5,12-dimethyl-2,3,3a,4,5,6,11,12,15,17a-decahydro-14*H*-furo[2,3-*f*][1]-oxacyclohexadecin-14-one (compound **8**): Derivative **6** (130 mg, 0.26 mmol) was dissolved in C_2H_5OH (3 mL), and then NaH (1.5 mg) was added. After 1 h the mixture was extracted twice with diethyl ether and saturated $NaHCO_3$. The organic layer evaporation and purification by column chromatography (EtOAc) afforded colorless oil product **8** (66 mg, 47%). HPLC R_t = 17.026 min. Anal. Calcd $C_{30}H_{49}NO_7$: C, 67.26; H, 9.22; N, 2.61. Found C, 67.28; H, 9.20; N, 2.60; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{30}H_{49}NO_7$ 535.3509; Found 535.3499.^{1}H NMR (600 MHz, CD_3CN, 25 °C), δ= 0.94 (d, $^3J_{H8,H20}$ = 6.8 Hz, 3H, 20-H), 1.11 (m, 1H, 7a-H), 1.17 (d, $^3J_{H5''',H6'''}$ = 6.2 Hz, 3H, 6‴-H), 1.19 (t, $^3J_{H23a,H24}$ = 7.0 Hz, $^3J_{H23b,H24'''}$ = 7.1 Hz, 3H, 24-H), 1.26 (d, $^3J_{H8,H20}$ = 6.3 Hz, 3H, 16-H), 1.36 (m, 1H, 2‴a-H), 1.41 (m, 1H, 7b-H), 1.48 (m, 1H, 3‴b-H), 1.69 (dt, $^3J_{H18a,H19}$ = 5.4 Hz, $^3J_{H6,H18a}$ = 5.4 Hz, ^2J = 12.3 Hz, 1H, 18a-H), 1.82 (m, 1H, 3‴a-H), 1.84 (m, 1H, 2‴b-H), 1.97 (m, 1H, 8-H), 2.08 (dd, $^3J_{H6,H18b}$ = 6.5 Hz, ^2J = 12.3 Hz, 1H, 18b-H), 2.14 (m, 1H, 4‴-H), 2.15 (m, 1H, 14b-H), 2.19 (s, 6H, 7‴-H, 8‴-H), 2.21 (m, 1H, 6-H), 2.46 (m, 1H, 14a-H), 2.86 (ddd, $^3J_{H2b,H3}$ = 6.0 Hz, ^2J = 15.1 Hz $^5J_{H2b,H5}$ = 1.4 Hz, 1H, 2b-H), 3.11 (ddd, $^3J_{H2a,H3}$ = 7.9 Hz, ^2J = 15.1 Hz, $^5J_{H2b,H5}$ = 0.8 Hz, 1H, 2a-H), 3.44 (dq, $^3J_{H23b,H24}$ = 7.1 Hz, ^2J = 9.6 Hz, 1H, 23b-H), 3.49 (dq, $^3J_{H4''',H5'''}$ = 9.3 Hz, $^3J_{H5''',H6'''}$ = 6.2 Hz, 1H, 5‴-H), 3.61 (s, 3H, 17-H), 3.69 (dq, $^3J_{H23a,H24}$ = 7.0 Hz, ^2J = 9.6 Hz, 1H, 23a-H), 3.90 (dd, $^3J_{H5-H6}$ = 9.7 Hz, $^4J_{H3-H5}$ = 0.8 Hz, 1H, 5-H), 4.16 (dd, $^3J_{H8-H9}$ = 4.5 Hz, $^3J_{H9-H10}$ = 9.3 Hz, 1H, 9-H), 4.47 (dd, $^3J_{H1'''-H2a'''}$ = 9.4 Hz, $^3J_{H1'''-H2b'''}$ = 2.0 Hz, 1H, 1‴-H), 4.81 (ddd, $^3J_{H2a,H3}$ = 7.9 Hz, $^3J_{H2b,H3}$ = 6.0 Hz, $^4J_{H3,H5}$ = 0.8 Hz, 1H, 3-H), 5.07 (d, $^3J_{H18a,H19}$ = 5.4 Hz, 1H, 19-H), 5.12 (m, 1H, 15-H), 5.58 (ddd, $^3J_{H12,H13}$ = 15.1 Hz, $^3J_{H13,H14a}$ = 10.9 Hz, $^3J_{H13,H14b}$ = 4.1 Hz, 1H, 13-H), 5.64 (dd, $^3J_{H10,H11}$ = 15.2 Hz,

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$^{3}J_{H9,H10}$ = 9.0 Hz, 1H, 10-H), 6.05 (ddd, $^{3}J_{H12,H13}$ = 15.1 Hz, $^{3}J_{H11,H12}$ = 10.5 Hz, $^{4}J_{H12,H14b}$ = 1.8 Hz, 1H, 12-H), 6.18 (dd, $^{3}J_{H10,H11}$ = 15.2 Hz, $^{3}J_{H11,H12}$ = 10.5 Hz, 1H, 11-H), ^{13}C NMR (600 MHz, CD_3CN, 25 °C), δ = 15.6 (24-C), 15.8 (20-C), 18.8 (3‴-C), 19.5 (6‴-C), 20.5 (16-C), 32.2 (2‴-C), 32.7 (2-C), 34.6 (8-C), 36.0 (7-C), 39.0 (6-C), 39.4 (18-C), 40.9 (7‴, 8‴-C), 41.5 (14-C), 58.5 (17-C), 63.2 (23-C), 66.0 (4‴-C), 69.6 (15-C), 74.3 (5‴-C), 80.5 (9-C), 83.6 (5-C), 100.8 (1‴-C), 103.8 (19-C), 104.4 (3-C), 129.1 (10-C), 132.4 (13-C), 132.9 (12-C), 135.3(11-C), 157.4 (4-C), 172.6 (1-C),

(2*R*,3a*R*,5*R*,6*R*,7*E*,9*E*,12*R*,16*Z*,17a*R*)-6-(((5*S*,6*R*)-5-(dimethylamino)-6-methyltetrahydro-2*H*-pyran-2-yl)oxy)-2-isopropoxy-17-methoxy-5,12-dimethyl-2,3,3a,4,5,6,11,12,15,17a-decahydro-14*H*-furo[2,3-*f*][1]oxacyclohexadecin-14-one (compound **9**): Derivative **6** (130 mg, 0.26 mmol) was dissolved in of 2-propyl alcohol (3 mL), and then NaH (1.5 mg) was added. After 1 h the mixture was extracted twice with diethyl ether and saturated $NaHCO_3$. The organic layer evaporation and purification by column chromatography (EtOAc) yielded product **9** as colorless oil (61 mg, 42%). HPLC R_t = 19.560 min. Anal. Calcd for $C_{31}H_{51}NO_7$: C, 67.73; H, 9.35; N, 2.55. Found: C, 67.70; H, 9.38; N=2.52; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{31}H_{51}NO_7$ 549.3666; Found 549.3655 ^{1}H NMR (600 MHz, CD_3CN, 25 °C), δ= 0.94 (d, $^{3}J_{H8,H20}$ = 6.8 Hz, 3H, 20-H), 1.13 (m, 1H, 7a-H), 1.13 (d, $^{3}J_{H23,H25}$ = 6.2 Hz, 3H, 25-H), 1.16 (d, $^{3}J_{H23,H24}$ = 6.3 Hz, 3H, 24-H), 1.18 (d, $^{3}J_{H5‴,H6‴}$ = 6.2 Hz, 3H, 6‴-H), 1.26 (d, $^{3}J_{H8,H20}$ = 6.4 Hz, 3H, 16-H), 1.36 (m, 1H, 2‴a-H), 1.40 (m, 1H, 7b-H), 1.48 (m, 1H, 3‴b-H), 1.67 (dt, $^{3}J_{H18a,H19}$ = 5.2 Hz, $^{3}J_{H6,H18a}$ = 5.2 Hz, ^{2}J = 12.2 Hz, 1H, 18a-H), 1.83 (m, 1H, 3‴a-H), 1.83 (m, 1H, 2‴b-H), 1.97 (m, 1H, 8-H), 2.02 (dd, $^{3}J_{H6,H18b}$ = 6.4 Hz, ^{2}J = 12.2 Hz, 1H, 18b-H), 2.15 (m, 1H, 4‴-H), 2.15 (m, 1H, 14b-H), 2.19 (s, 6H, 7‴-H, 8‴-H), 2.25 (m, 1H, 6-H), 2.47 (m, 1H, 14a-H), 2.86 (ddd, $^{3}J_{H2b,H3}$ = 6.1 Hz, ^{2}J = 15.1 Hz $^{5}J_{H2b,H5}$ = 1.3 Hz, 1H, 2b-H), 3.11 (ddd, $^{3}J_{H2a,H3}$ = 7.8 Hz, ^{2}J = 15.1 Hz, $^{5}J_{H2b,H5}$ = 0.9 Hz, 1H, 2a-H), 3.49 (dq, $^{3}J_{H4‴,H5‴}$ = 9.4 Hz, $^{3}J_{H5‴,H6‴}$ = 6.2 Hz, 1H, 5‴-H), 3.61 (s, 3H, 17-H), 3.88 (m, 1H, 23-H), 3.88 (m, 1H, 5-H), 4.16 (dd, $^{3}J_{H8-H9}$ = 4.6 Hz, $^{3}J_{H9-H10}$ = 9.4 Hz, 1H, 9-H), 4.47 (dd, $^{3}J_{H1‴-H2a‴}$ = 9.4 Hz, $^{3}J_{H1‴-H2b‴}$ = 1.9 Hz, 1H, 1‴-H), 4.83 (ddd, $^{3}J_{H2a,H3}$ = 7.8 Hz, $^{3}J_{H2b,H3}$ = 6.1 Hz, $^{4}J_{H3,H5}$ = 0.8 Hz, 1H, 3-H), 5.11 (ddq, $^{3}J_{H15,H16}$ = 6.4 Hz, $^{3}J_{H14a,H15}$ = 12.8 Hz, $^{3}J_{H14b,H15}$ = 3.2 Hz, 1H, 15-H), 5.19 (d, $^{3}J_{H18a,H19}$ = 5.2 Hz, 1H, 19-H), 5.57 (ddd, $^{3}J_{H12,H13}$ = 15.1 Hz, $^{3}J_{H13,H14a}$ = 10.8 Hz, $^{3}J_{H13,H14b}$ = 4.1 Hz, 1H, 13-H), 5.64 (dd, $^{3}J_{H10,H11}$ = 15.2 Hz, $^{3}J_{H9,H10}$ = 9.4 Hz, 1H, 10-H), 6.05 (ddd, $^{3}J_{H12,H13}$ = 15.1 Hz, $^{3}J_{H11,H12}$ = 10.5 Hz, $^{4}J_{H12,H14b}$ = 1.7 Hz, 1H, 12-H), 6.17 (dd, $^{3}J_{H10,H11}$ = 15.2 Hz, $^{3}J_{H11,H12}$ = 10.5 Hz, 1H, 11-H), ^{13}C NMR (600 MHz, CD_3CN, 25 °C), δ= 15.7 (20-C), 18.8 (3‴-C), 19.4 (6‴-C), 20.5 (16-C), 22.8 (25-C), 23.7 (24-C), 32.1 (2‴-C), 32.1 (2-C), 34.4 (8-C), 35.9 (7-C), 39.0 (6-C), 39.6 (18-C), 40.9 (7‴, 8‴-C), 41.5 (14-C), 58.4 (17-C), 65.9 (4‴-C), 68.8 (23-C), 69.5 (15-C), 74.3 (5‴-C), 80.4 (9-C), 83.3 (5-C), 100.7 (1‴-C), 101.6 (19-C), 104.0 (3-C), 129.0 (10-C), 132.4 (13-C), 132.8 (12-C), 135.4 (11-C), 157.4 (4-C), 172.5 (1-C),

(2*R*,3a*R*,5*R*,6*R*,7*E*,9*E*,12*R*,16*Z*,17a*R*)-2-(allyloxy)-6-(((5*S*,6*R*)-5-(dimethylamino)-6-methyltetrahydro-2*H*-pyran-2-yl)oxy)-17-methoxy-5,12-dimethyl-2,3,3a,4,5,6,11,12,15,17a-decahydro-14*H*-furo[2,3-*f*][1]oxacyclohexadecin-14-one (compound **10**): Derivative **6** (130 mg, 0.26 mmol) was dissolved in allyl alcohol (3 mL), and then NaH (1.5 mg) was added. After 1 h the mixture was extracted twice with diethyl ether and saturated $NaHCO_3$. The organic layer evaporation and purification by column chromatography (EtOAc) yielded colorless oil product **10** (74 mg, 51%). HPLC R_t = 14.694 min. Anal. Calcd for $C_{31}H_{49}NO_7$: C, 67.98; H, 9.02; N, 2.56. Found C, 67.96; H, 9.05; N, 2.55; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{31}H_{49}NO_7$ 547.3509; Found 547.3488.^{1}H NMR (600 MHz, CD_3CN, 25 °C), δ= 0.95 (d, $^{3}J_{H8,H20}$ = 6.0 Hz, 3H, 20-H), 1.12 (m, 1H, 7a-H), 1.18 (d, $^{3}J_{H5‴,H6‴}$ = 4.3 Hz, 3H, 6‴-H), 1.26 (d, $^{3}J_{H8,H20}$ = 6.4 Hz, 3H, 16-H), 1.39 (m, 1H, 2‴a-H), 1.39 (m, 1H, 7b-H), 1.48 (m, 1H, 3‴b-H), 1.73 (dt, $^{3}J_{H18a,H19}$ = 5.4 Hz, $^{3}J_{H6,H18a}$ = 5.4 Hz, ^{2}J = 12.2 Hz, 1H, 18a-H), 1.83 (m, 1H, 3‴a-H), 1.83 (m, 1H, 2‴b-H), 1.97 (m, 1H, 8-H), 2.14 (m, 1H, 18b-H), 2.14 (m, 1H, 4‴-H), 2.14 (m, 1H, 14b-H), 2.19 (s, 6H, 7‴-H, 8‴-H), 2.23 (m, 1H, 6-H), 2.47 (m, 1H, 14a-H), 2.86 (ddd, $^{3}J_{H2b,H3}$ = 6.0 Hz, ^{2}J = 15.1 Hz $^{5}J_{H2b,H5}$ = 1.7 Hz, 1H, 2b-H), 3.12 (dd, $^{3}J_{H2a,H3}$ = 7.9 Hz, ^{2}J = 15.1 Hz, 1H, 2a-H), 3.49 (m, 1H, 5‴-H), 3.61 (s, 3H, 17-H), 3.93 (d, $^{3}J_{H5,H6}$ = 9.7 Hz, 1H, 5-H), 3.97 (m, 1H, 23a-H), 4.16 (m, 1H, 23b-H), 4.16 (m, 1H, 9-H), 4.47 (dd, $^{3}J_{H1‴-H2a‴}$ = 9.3 Hz, $^{3}J_{H1‴-H2b‴}$ = 2.3 Hz, 1H, 1‴-H), 4.81 (dd, $^{3}J_{H2a,H3}$ = 7.9 Hz, $^{3}J_{H2b,H3}$ = 6.0 Hz, 1H, 3-H), 5.11 (d, $^{3}J_{H18a,H19}$ = 5.4 Hz, 1H, 19-H), 5.12 (m, 1H, 15-H), 5.17 (dd, $^{3}J_{H24,H25b}$ = 12.4 Hz, ^{2}J = 1.7 Hz, 1H, 25b-H), 5.30 (dd, $^{3}J_{H24,H25a}$ = 17.5 Hz, ^{2}J = 1.7 Hz, 1H, 25a-H), 5.57 (ddd, $^{3}J_{H12,H13}$ = 15.0 Hz, $^{3}J_{H13,H14a}$ = 10.9 Hz, $^{3}J_{H13,H14b}$ = 4.4 Hz, 1H, 13-H), 5.64 (dd, $^{3}J_{H10,H11}$ = 15.2 Hz, $^{3}J_{H9,H10}$ = 9.2 Hz, 1H, 10-H), 5.96 (dddd, $^{3}J_{H23a,H24}$ = 6.1 Hz, $^{3}J_{H23b,H24}$ = 3.5 Hz, $^{3}J_{H24,H25a}$ = 17.5 Hz, $^{3}J_{H24,H25b}$ = 12.4 Hz, 1H, 24-H), 6.05 (dd, $^{3}J_{H12,H13}$ = 15.0 Hz, $^{3}J_{H11,H12}$ = 10.5 Hz, 1H, 12-H), 6.18 (dd, $^{3}J_{H10,H11}$ = 15.2 Hz, $^{3}J_{H11,H12}$ = 10.5 Hz, 1H, 11-H), ^{13}C NMR (600 MHz, CD_3CN, 25 °C), δ= 15.8 (20-C), 18.8 (3‴-C), 19.5 (6‴-C), 20.6 (16-C), 32.2 (2‴-C), 32.2 (2-C), 34.6 (8-C), 36.0 (7-C), 38.9 (6-C), 39.4 (18-C), 40.9 (7‴, 8‴-C), 41.5 (14-C), 58.6 (17-C), 66.0 (4‴-C), 68.5 (23-C), 69.6 (15-C), 74.3 (5‴-C), 80.4 (9-C), 83.9 (5-C), 100.8 (1‴-C), 103.5 (19-C), 104.5 (3-C), 116.6 (25-C), 129.1 (10-C), 132.4 (13-C), 132.9(12-C), 135.3 (11-C), 136.1 (24-C), 157.3 (4-C), 172.5 (1-C),

(2*R*,3a*R*,5*R*,6*R*,7*E*,9*E*,12*R*,16*Z*,17a*R*)-6-(((5*S*,6*R*)-5-(dimethylamino)-6-methyltetrahydro-2*H*-pyran-2-yl)oxy)-17-methoxy-5,12-dimethyl-2-(prop-2-yn-1-yloxy)-2,3,3a,4,5,6,11,12,15,17a-decahydro-14*H*-furo[2,3-*f*][1]oxacyclohexadecin-14-one (compound **11**): Derivative **6** (130 mg, 0.26 mmol) was dissolved in propargyl alcohol (3 mL), and next NaH (1.5 mg) was added. After 8 h the mixture was extracted twice with diethyl ether and saturated $NaHCO_3$. The organic layer evaporation and purification by column chromatography (EtOAc) yielded colorless oil product **11** (64 mg, 44%). HPLC R_t = 16.414 min. Anal. Calcd for $C_{31}H_{47}NO_7$: C, 68.23; H, 8.68; N, 2.57. Found C, 68.25; H, 8.70; N, 2.54; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{31}H_{47}NO_7$ 545.3353; Found 545.3333.^{1}H NMR (600 MHz, CD_3CN, 25 °C), δ= 0.97 (d, $^{3}J_{H8,H20}$ = 6.8 Hz, 3H, 20-H), 1.06 (m, 1H, 7a-H), 1.23 (d, $^{3}J_{H5‴,H6‴}$ = 6.0 Hz, 3H, 6‴-H), 1.26 (d, $^{3}J_{H8,H20}$ = 6.2 Hz, 3H, 16-H), 1.43 (m, 1H, 3‴b-H), 1.46 (m, 1H, 2‴a-H), 1.46 (m, 1H, 7b-H), 1.68 (dt, $^{3}J_{H18a,H19}$ = 5.4 Hz, $^{3}J_{H6,H18a}$ = 5.4 Hz, ^{2}J = 12.3 Hz, 1H, 18a-H), 1.82 (m, 1H, 3‴a-H), 1.86 (m, 1H, 2‴b-H), 1.86 (m, 1H, 8-H), 2.13 (m, 1H, 14b-H), 2.18 (m, 1H, 18b-H), 2.20 (m, 1H, 4‴-H), 2.22 (s, 6H, 7‴-H, 8‴-H), 2.29 (m, 1H, 6-H), 2.42 (t, $^{4}J_{H23,H25}$ = 2.3 Hz, 1H, 25-H), 2.43 (m, 1H, 14a-H), 2.95 (dd, $^{3}J_{H2b,H3}$ = 6.0 Hz, ^{2}J = 15.7 Hz, 1H, 2b-H), 3.14 (dd, $^{3}J_{H2a,H3}$ = 7.6 Hz, ^{2}J = 15.7 Hz, 1H, 2a-H), 3.43 (dq, $^{3}J_{H4‴,H5‴}$ = 11.9 Hz, $^{3}J_{H5‴,H6‴}$ = 6.0 Hz, 1H, 5‴-H), 3.63 (s, 3H, 17-H), 3.90 (d, $^{3}J_{H5,H6}$ = 9.4 Hz, 1H, 5-H), 4.10 (dd, $^{3}J_{H8-H9'}$ = 4.3 Hz, $^{3}J_{H9-H10'}$ = 9.0 Hz, 1H, 9-H), 4.22 (dd, ^{2}J = 16.0 Hz, $^{4}J_{H23a,H25}$ = 2.3 Hz, 1H, 23a-H), 4.28 (dd, ^{2}J = 16.0 Hz, $^{4}J_{H23b,H25}$ = 2.3 Hz, 1H, 23b-H), 4.38 (m, 1H, 1‴-H), 4.87 (dd, $^{3}J_{H2a,H3}$ = 7.6 Hz, $^{3}J_{H2b,H3}$ = 6.0 Hz, 1H, 3-H), 5.14 (m, 1H, 15-H), 5.29 (d, $^{3}J_{H18a,H19}$ = 5.4 Hz, 1H, 19-H), 5.57 (ddd, $^{3}J_{H12,H13}$ = 15.0 Hz, $^{3}J_{H13,H14a}$ = 10.6 Hz, $^{3}J_{H13,H14b}$ = 4.2 Hz, 1H, 13-H), 5.64 (dd, $^{3}J_{H10,H11}$ = 15.3 Hz, $^{3}J_{H9,H10}$ = 9.0 Hz, 1H, 10-H), 6.01 (m, 1H, 12-H), 6.23 (dd, $^{3}J_{H10,H11}$ = 15.3 Hz, $^{3}J_{H11,H12}$ = 10.4 Hz, 1H, 11-H), ^{13}C NMR (600 MHz, CD_3CN, 25 °C), δ= 15.8 (20-C), 18.3 (3‴-C), 18.9 (6‴-C), 20.3 (16-C), 31.2 (2‴-C), 31.7 (2-C), 34.9 (8-C), 35.3 (7-C), 37.7 (6-C), 38.9 (18-C), 40.6 (7‴, 8‴-C), 40.9 (14-C), 53.7 (23-C), 58.6 (17-C), 64.7 (4‴-C), 68.7 (15-C), 73.8 (5‴-C), 74.0 (25-C), 79.7 (24-C), 81.0 (9-C), 84.5 (5-C), 101.0 (1‴-C), 101.2 (19-C), 104.8 (3-C), 128.2 (10-C), 130.8 (13-C), 132.1 (12-C), 134.0 (11-C), 155.8 (4-C), 171.7 (1-C),

(2*R*,3a*R*,5*R*,6*R*,7*E*,9*E*,12*R*,16*Z*,17a*R*)-6-(((5*S*,6*R*)-5-(dimethylamino)-6-methyltetrahydro-2*H*-pyran-2-yl)oxy)-2-((4-fluorobenzyl)oxy)-17-methoxy-5,12-dimethyl-2,3,3a,4,5,6,11,12,15,17a-decahydro-14*H*-furo[2,3-*f*][1]oxacyclohexadecin-14-one (compound **12**): Derivative **6** (130 mg, 0.26 mmol) was dissolved in 4-fluorobenzyl alcohol (3 mL), and then NaH (1.5 mg) was added. After 3 h the mixture was extracted twice with diethyl ether and saturated $NaHCO_3$. The organic layer evaporation and purification by column chromatography (EtOAc) afforded product **12** as colorless oil (87 mg, 55%). HPLC R_t= 28.600 min. Anal. Calcd for $C_{34}H_{48}FNO_7$: C, 67.86; H, 8.04; N, 2.33; F, 3.16; Found C, 67.84; H, 8.03; N, 2.34; F, 3.18; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{34}H_{48}FNO_7$ 601.3415; Found 601.3403.^{1}H NMR (600 MHz, CD_3CN, 25 °C), δ= 0.95 (d, $^{3}J_{H8,H20}$ = 6.8 Hz, 3H, 20-H), 1.16 (m, 1H, 7a-H), 1.15 (m, 3H, 6‴-H), 1.28 (d,

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$^{3}J_{H8,H20}$ = 6.4 Hz, 3H, 16-H), 1.35 (m, 1H, 2‴a-H), 1.42 (m, 1H, 7b-H), 1.45 (m, 1H, 3‴b-H), 1.73 (dt, $^{3}J_{H18a,H19}$ = 5.1 Hz, $^{3}J_{H6,H18a}$ = 5.1 Hz, ^{2}J = 12.4 Hz, 1H, 18a-H), 1.80 (m, 1H, 3‴a-H), 1.84 (m, 1H, 2‴b-H), 1.99 (m, 1H, 8-H), 2.16 (m, 1H, 18b-H), 2.12 (ddd, $^{3}J_{H3b‴,H4‴}$ = 11.8 Hz, $^{3}J_{H4‴,H5‴}$ = 5.9 Hz, $^{3}J_{3a‴,H4‴}$ = 4.0 Hz, 1H, 4‴-H), 2.16 (m, 1H, 14b-H), 2.18 (s, 6H, 7‴-H, 8‴-H), 2.32 (m, 1H, 6-H), 2.49 (m, 1H, 14a-H), 2.87 (ddd, $^{3}J_{H2b,H3}$ = 5.7 Hz, ^{2}J = 15.1 Hz, $^{5}J_{H2b,H5}$ = 1.5 Hz, 1H, 2b-H), 3.17 (ddd, $^{3}J_{H2a,H3}$ = 8.1 Hz, ^{2}J = 15.1 Hz, $^{5}J_{H2a,H5}$ = 0.9 Hz, 1H, 2a-H), 3.46 (dq, $^{3}J_{H4‴,H5‴}$ = 9.4 Hz, $^{3}J_{H5‴,H6‴}$ = 6.1 Hz, 1H, 5‴-H), 3.64 (s, 3H, 17-H), 4.00 (d, $^{3}J_{H5,H6}$ = 9.6 Hz, 1H, 5-H), 4.15 (dd, $^{3}J_{H8,H9}$ = 4.6 Hz, $^{3}J_{H9,H10}$ = 9.4 Hz, 1H, 9-H), 4.41 (d, ^{2}J = 11.4 Hz, 23b-H), 4.45 (dd, $^{3}J_{H1‴–H2a‴}$ = 9.4 Hz, $^{3}J_{H1‴–H2b‴}$ = 2.0 Hz, 1H, 1‴-H), 4.71 (d, ^{2}J = 11.4 Hz, 1H, 23a-H), 4.86 (ddd, $^{3}J_{H2a,H3}$ = 8.1 Hz, $^{3}J_{H2b,H3}$ = 5.7 Hz, $^{4}J_{H3,H4}$ = 0.9 Hz, 1H, 3-H), 5.18 (d, $^{3}J_{H18a,H19}$ = 5.1 Hz, 1H, 19-H), 5.16 (m, 1H, 15-H), 5.56 (ddd, $^{3}J_{H12,H13}$ = 14.8 Hz, $^{3}J_{H13,H14a}$ = 10.8 Hz, $^{3}J_{H13,H14b}$ = 4.1 Hz, 1H, 13-H), 5.66 (dd, $^{3}J_{H10,H11}$ = 14.9 Hz, $^{3}J_{H9,H10}$ = 9.4 Hz, 1H, 10-H), 6.07 (ddd, $^{3}J_{H12,H13}$ = 14.8 Hz, $^{3}J_{H11,H12}$ = 10.5 Hz, $^{4}J_{H12,14b}$ = 1.6 Hz, 1H, 12-H), 6.13 (dd, $^{3}J_{H10,H11}$ = 14.9 Hz, $^{3}J_{H11,H12}$ = 10.5 Hz, 1H, 11-H), 7.13 (m, 2H, 26-H, 28-H), 7.41 (m, 2H, 25-H, 29-H), ^{13}C NMR (600 MHz, CD_3CN, 25 °C), δ = 15.7 (20-C), 18.7 (3‴-C), 19.4 (6‴-C), 20.5 (16-C), 32.2 (2‴-C), 32.2 (2-C), 34.4 (8-C), 35.9 (7-C), 38.8 (6-C), 39.4 (18-C), 40.9 (7‴, 8‴-C), 41.5 (14-C), 58.5 (17-C), 65.9 (4‴-C), 68.5 (23-C), 69.6 (15-C), 74.2 (5‴-C), 80.4 (9-C), 83.8 (5-C), 100.7 (1‴-C), 103.4 (19-C), 104.3 (3-C), 115.9 (J = 21.8 Hz, 26,28-C), 129.1 (10-C), 130.9 (J = 8.0 Hz, 25,29-C), 132.4 (13-C), 132.9 (12-C), 134.8 (J = 3.2 Hz, 24-C), 135.4 (11-C), 157.3 (4-C), 163.0 (d, J = 242.0 Hz, 27-C), 172.6 (1-C).

■ ASSOCIATED CONTENT

Supporting Information

Copy of FT-IR and NMR spectra of spiramycin and its new derivatives (**2**–**12**); selected HSQC, HMBC, and ^{1}H–^{1}H NOESY correlation spectra together with proton–proton contacts marked on DFT calculated structures; *XYZ* coordinates of structures shown in Figure 4. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00847.

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Notes

The authors declare no competing financial interest.

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