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Copper-catalyzed 1,3-dipolar cycloaddition reaction of spirosolane-derived azide for the preparation of modified solasodine alkaloid

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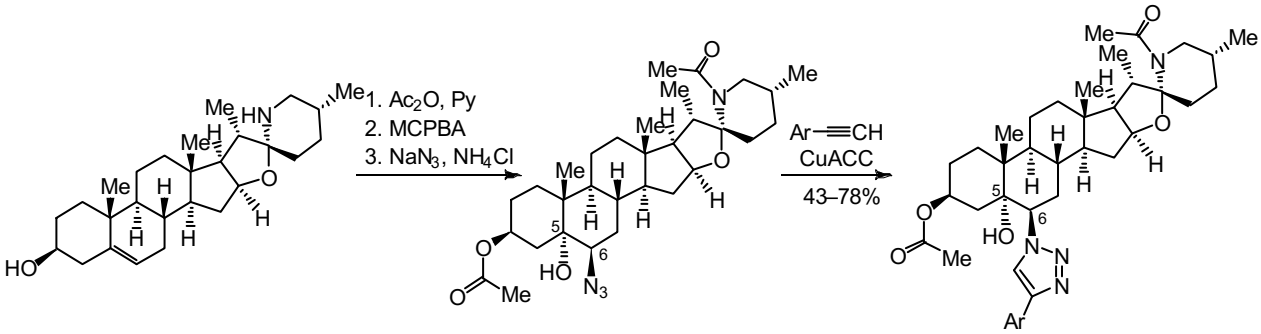


Modification of the steroidal alkaloid solasodine was performed by introduction of 1,2,3-triazolyl substituents at the C-6 atom of spirosolane ring system. The azidolysis of 5,6α-epoxysolasodine diacetate, formed as the major product during epoxidation of solasodine diacetate by the action of sodium azide in DMF in the presence of ammonium chloride, proceeded through the formation of 6β-azido-5α-hydroxysolasodine diacetate. The newly obtained azide was used in reactions with terminal alkynes in the presence of copper(I) bromide and *N*,*N*-diisopropylethylamine in DMF to synthesize the respective (22*R*,25*R*)-*N*,*O*-diacetyl-6β-[4-aryl-1,2,3-triazol-1-yl]-5α-hydroxyspirosolanes.

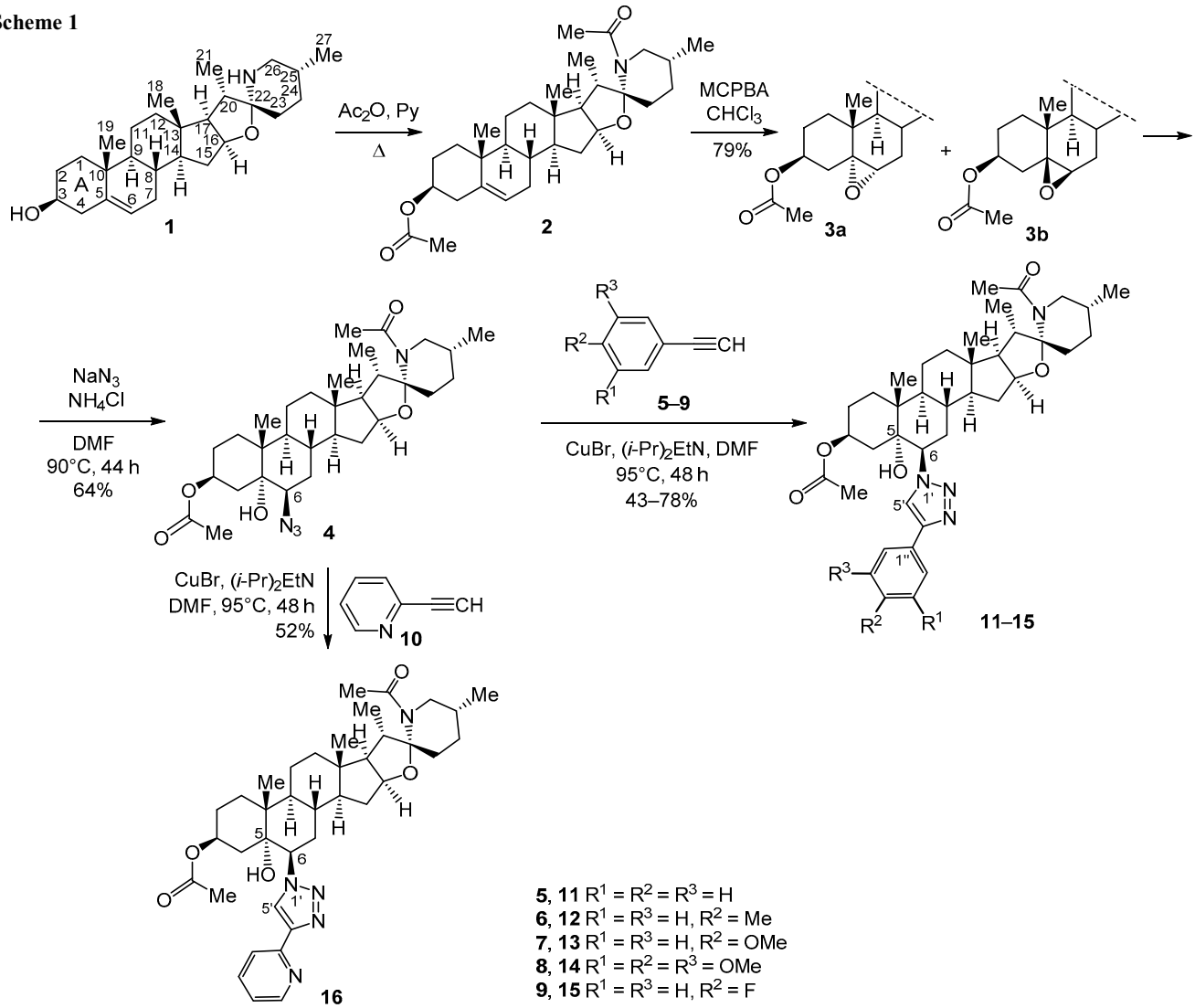
Keywords: solasodine, steroidal alkaloids, 1,2,3-triazoles, azidolysis, CuAAC reaction.

The steroidal alkaloid solasodine (**1**) is a readily available metabolite isolated from plants belonging to the *Solanum* genus.[1] The main source used for industrial production of this alkaloid is the kangaroo apple *Solanum laciniatum*.[2] Solasodine has been shown to possess various types of biological activity, including antimicrobial,[3] hepatoprotective,[4] analgesic,[5] anti-inflammatory,[6] antioxidative,[7] cytotoxic, and antitumor effects.[8] Solasodine significantly affects the central nervous system,[9] resulting in cognitive enhancement[9c] and anticonvulsant activity[9d] in animal models. For these reasons, there is interest in performing chemical modifications of solasodine. Modifications of the hydroxy group at the C-3 position have been used for the preparation of antitumor agents.[10] Transformations of alkaloid **1** into pregnanene- or pregnanediene-type compounds have also been described.[11] Some relatively more complex transformations at the C-2,3 atoms of the A ring in the steroid nucleus produced fused pyrazole and isoxazole derivatives, as well as converted the A ring of spirosolane **1** by forming lactone and lactam moieties.[12] The formation of diene motif in the B ring of the aforementioned alkaloid has been also described.[12b] In the current study, we present the synthesis of *N*,*O*-diacetyl-5α-hydroxy-6β-azidosolasodine and its transformations under the conditions of copper-catalyzed 1,3-dipolar cycloaddition reaction (CuAAC reaction).

It should be noted that there is also interest in structural modifications of alkaloid **1** at the C-5,6 atoms, since it is known that the teratogenic properties of jervanes, solanidanes, and spirosolanes are linked to the presence of a double bond between the C-5,6 atoms in the steroid ring system.[13]

The initial treatment of solasodine (**1**) with an excess of acetic anhydride in refluxing pyridine led to solasodine

Scheme 1



diacetate **2**,[14] the epoxidation of which in the presence of *m*-chloroperoxybenzoic acid gave a mixture of 5,6α- and 5,6β-epoxides **3a**,**b**[15] in 3:1 ratio (according to ^{1}H NMR spectrum of the reaction mixture) with an overall yield of 79% (Scheme 1). The attempt to separate the epoxides was not successful, therefore the ring opening step was performed using the mixture of epoxides.

Azidolysis of epoxides **3a**,**b** by the action of NaN_3 was achieved in DMF medium in the presence of NH_4Cl by following a previously published procedure.[16a] It is known that the presence of ammonium salt facilitates the nucleophilic substitution reaction by azide ion through coordination at the oxygen atom and weakening of the binding orbital in the oxygen–carbon bond of the epoxide group.[16b] As a result of this reaction followed by silica gel column chromatography, a new compound – 6β-azido-*N*,*O*-diacetyl-5α-hydroxysolasodine **4** was isolated in 64% yield (Scheme 1). The interaction of azide **4** with terminal alkynes (phenylacetylene (**5**), *p*-tolylacetylene (**6**), 4-methoxyphenylacetylene (**7**), 5-ethynyl-1,2,3-trimethoxybenzene (**8**), 4-fluorophenylacetylene (**9**), and 2-ethynylpyridine (**10**)) was achieved in DMF medium in the presence of CuBr and *N*,*N*-diisopropylethylamine upon heating to 95°C.

As a result of these reactions, (22*R*,25*R*)-*N*,*O*-diacetyl-5α-hydroxy-6β-[4-aryl(hetaryl)-1,2,3-triazol-1-yl]spirosolanes **11**–**16** were obtained in 78, 69, 71, 60, 43, and 52% yields, respectively. The reaction conditions for the 1,3-dipolar cycloaddition were selected on the basis of literature data on reactions between steroidal azido alcohols with terminal acetylenes,[17] which demonstrated the low reactivity of 6β-azido-5α,3β-dihydroxyandrostan-17-one under the commonly used conditions of CuAAC reactions,[18] using $CuSO_4$, sodium ascorbate, and aqueous CH_2Cl_2. According to the published data,[17] the target 1,2,3-triazole fragment was not formed under these conditions due the steric influence from the azide group (1,3-diaxial interaction between the azide functionality at the C-6 atom and the methyl group at the C-19 atom. An increase of the reaction temperature led to conformational changes in the steroid nucleus, associated with a change in the relative orientation of the azide group at the C-6 atom and the methyl group at the C-19 atom, as well as removal of the steric strain and reactivity enhancement. During the interaction of spiro-

solane azide **4** with arylacetylenes **9** and **10** in the presence of CuBr catalyst and *N*,*N*-diisopropylethylamine as a base, the yields of the CuAAC reaction deteriorated, and also the corresponding homocoupling products – 1,1'-buta-1,3-diyn-1,4-diylbis(4-fluorobenzene)[19] and 2,2'-buta-1,3-diyn-1,4-diyl-dipyridine[19] were isolated in 18 and 22% yields, respectively.

The composition and structure of the synthesized compounds were confirmed from data of IR, ^{1}H and ^{13}C NMR spectroscopy, and mass spectrometry. ^{1}H and ^{13}C NMR spectra of the synthesized compounds featured the characteristic signal set of spirosolane system and the substituent that was present. ^{1}H NMR spectrum of epoxides **3a**,**b** contained signals of the 6-CH proton at 2.85 ppm (doublet, J = 4.3 Hz) for the α-isomer and at 3.04 ppm (singlet) for the β-isomer. The relative amounts of isomeric epoxides **3a** and **3b** in the mixture were determined from the ratio of the integrated intensities of the aforementioned signals. The 6-CH proton of azide **4** gave a signal at 3.36 ppm in the form of a broadened singlet, pointing to its equatorial orientation and corresponding to the stereoelectronic requirements of *trans*-diaxial configuration of azide and hydroxy groups in azido alcohols that are obtained by epoxide ring opening.[16a] The presence of an azide substituent was also confirmed from IR spectral data (a strong absorption band at 2096 cm^{-1}, corresponding to the stretching vibrations of azide group).

The 1,2,3-triazole ring proton in ^{1}H NMR spectra of compounds **11**–**16** appeared as a singlet in the region of 7.74–8.19 ppm. The carbon atoms of this heterocycle gave ^{13}C NMR signals at 120.1–120.8 ppm (the C-5 atom was observed as a doublet in spectra acquired in JMOD experiment) and 145.8–147.1 ppm (singlet of the C-4 atom). These data confirmed the formation of 1,4-disubstituted 1*H*-1,2,3-triazoles as a result of CuAAC reaction.[20]

Thus, we report the first modification of steroidal alkaloid solasodine involving the introduction of a heterocyclic substituent at the C-6 position. We propose a method for the preparation of a new group of solasodine derivatives, in which the spirosolane nucleus and aromatic (heteroaromatic) system are connected through a linker with potential biological activity – a 1*H*-1,2,3-triazole ring.

Experimental

IR spectra were recorded on a Bruker Vector 22 FTIR spectrometer in KBr pellets. ^{1}H and ^{13}C NMR spectra were acquired on Bruker Avance 400 (400 and 100 MHz, respectively, compounds **12**–**14**) and Bruker Avance 600 (600 and 150 MHz, respectively, compounds **4**, **11**, **15**, **16**) spectrometers in $CDCl_3$, using TMS as internal standard. The structures of the obtained compounds were elucidated using ^{1}H and ^{13}C NMR spectra, two-dimensional ^{1}H–^{1}H NMR experiments (COSY, NOESY, mixing time 1 s, pulse delay 2 s), as well as two-dimensional heteronuclear NMR experiments (^{1}H–^{13}C COLOC, ^{1}H–^{13}C HMBC), relying on literature data for solasodine (**1**).[21] The multiplicity of ^{13}C NMR signals was determined from spectra acquired in the *J*-modulation (JMOD) mode. High-resolution mass spectra were recorded on a Thermo Scientific DFS mass spectrometer, vaporizer temperature 200–250°C, EI ionization (70 eV). The specific rotation values were measured on a PolAAr 3005 polarimeter and were expressed in (deg·ml)/(g·dm), with concentration in g per 100 ml of solution. Melting points were determined on a Stuart SMP30 hot stage apparatus. The reaction progress was controlled by TLC on Silufol UV-254 plates using $CHCl_3$ and 10:1 $CHCl_3$–EtOH mixture as eluents, with visualization in iodine chamber and under UV light. The reaction products were isolated by column chromatography using silica gel from Acros (0.035–0.240 mm).

The reagents used in this work – sodium azide, phenylacetylene (**5**), *p*-tolylacetylene (**6**), 4-methoxyphenylacetylene (**7**), 4-fluorophenylacetylene (**9**), 2-ethynylpyridine (**10**), 3-chloroperoxybenzoic acid (50–55%), CuBr, and *N*,*N*-diisopropylethylamine were purchased from Alfa Aesar. The solvents ($CHCl_3$, DMF, pyridine) were purified according to standard procedures. DMF was additionally distilled under argon flow immediately before use. Solasodine (**1**) was obtained from diosgenin,[22] mp 199–201°C (EtOH), $[\alpha]_D^{25}$ –98.5 (*c* 0.41, MeOH). Compounds **2**,[14] **3a**,**b**,[15] and 1,2,3-trimethoxy-5-ethynylbenzene (**8**)[23] were synthesized according to previously published procedures.

(2*R*,2a*R*,4*S*,5'*R*,6a*R*,6b*S*,8a*S*,8b*R*,9*S*,10*R*,11a*S*,12a*S*,12b*S*)-1'-Acetyl-2-azido-2a-hydroxy-5',6a,8a,9-tetramethyloctadecahydrospiro[naphtho[2',1':4,5]indeno[2,1-*b*]furan-10,2'-piperidin]-4-yl acetate (*N*,*O*-diacetyl-6β-azido-5α-hydroxysolasodine) (4). NaN_3 (114 mg, 1.75 mmol) and NH_4Cl (47 mg, 0.88 mmol) were added to a solution containing a mixture of solasodine diacetate α- and β-epoxides **3a**,**b** (451 mg, 0.88 mmol) in DMF (7 ml). The reaction mixture was stirred while heating to 90°C for 44 h, then poured onto a Petri dish for evaporation of DMF under ambient conditions. The residue was dissolved in $CHCl_3$ (30 ml), the solution was washed with saturated NaCl solution (3×15 ml), the organic extracts were combined and dried over anhydrous $MgSO_4$. The drying agent was removed by filtration, the solvent was evaporated at reduced pressure, the residue was separated by silica gel column chromatography (eluent petroleum ether – EtOAc, gradient from 100:1 to 10:1). The fraction containing the azide was recrystallized from 5:1 petroleum ether – EtOAc mixture. Yield 312 mg (64%), colorless fine crystalline powder, mp 220–223°C (EtOAc), $[\alpha]_D^{26}$ –91.2 (*c* 0.23, $CHCl_3$). IR spectrum, ν, cm^{-1}: 609, 665, 692, 717, 755, 804, 856, 871, 923, 966, 1002, 1031, 1068, 1135, 1160, 1178, 1245, 1321, 1363, 1380, 1405, 1432, 1454, 1631, 1731, 2096, 3411. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.90 (3H, s, 18-CH_3); 0.93 (3H, d, J = 7.0, 27-CH_3); 1.07 (3H, d, J = 6.6, 21-CH_3); 1.15 (3H, s, 19-CH_3); 1.16–1.23 (3H, m, 12,24-CH_2, 14-CH); 1.31–1.47 (5H, m, 1,11,15-CH_2, 9-CH); 1.56–1.61 (3H, m, 1,2,23-CH_2); 1.67–1.85 (8H, m, 2,4,7,12,23-CH_2, 8,17-CH); 1.92–2.01 (3H, m, 15,24-CH_2, 25-CH); 2.03 (3H, s, $OCOCH_3$); 2.12 (2H, m, 4-CH_2, 5-OH); 2.19 (3H, s, $NCOCH_3$); 2.84–2.87 (1H, m, 26-CH_2); 3.03–3.09 (1H, m, 20-CH); 3.36 (1H, br. s, 6-CH); 3.98–4.04 (1H, m, 26-CH_2); 4.16 (1H, ddd, J = 8.8, J = 7.4, J = 6.6, 16-CH); 5.09–5.14 (1H, m, 3-CH).

^{13}C NMR spectrum, δ, ppm: 16.4 (19,21-CH_3); 16.6 (18-CH_3); 18.4 (27-CH_3); 20.8 (C-11); 21.4 (OCO$\underline{C}H_3$); 23.7 (C-23); 24.4 (C-24); 25.2 (NCO$\underline{C}H_3$); 26.5 (C-2); 28.0 (C-25); 30.0 (C-8); 31.1 (C-7); 31.9 (C-15); 32.0 (C-1); 37.4 (C-4); 38.4 (C-20); 38.8 (C-10); 40.1 (C-12); 41.3 (C-13); 45.2 (C-9); 49.0 (C-26); 54.8 (C-14); 62.2 (C-17); 66.6 (C-6); 70.6 (C-3); 75.6 (C-5); 78.7 (C-16); 101.1 (C-22); 170.9 (O$\underline{C}OCH_3$); 171.0 (N$\underline{C}OCH_3$). Mass spectrum, *m*/*z* (I_{rel}, %): 556 (52), 542 (35), 541 (100), 498 (36), 487 (45), 180 (30), 156 (49), 155 (81), 114 (36), 43 (30). Found, *m*/*z*: 556.3619 $[M]^+$. $C_{31}H_{48}N_4O_5$. Calculated, *m*/*z*: 556.3623.

Preparation of (22*R*,25*R*)-*N*,*O*-diacetyl-5α-hydroxy-6β-[4-aryl-1,2,3-triazol-1-yl]spirosolanes 11–16 (General method). CuBr (10 mg, 0.07 mmol) and *N*,*N*-diisopropylethylamine (371 mg, 2.88 mmol) were added to a solution of azido alcohol **4** (200 mg, 0.36 mmol) and the appropriate terminal acetylene **5**–**10** (0.43 mmol) in DMF (10 ml). The reaction mixture was stirred with heating to 95°C for 48 h under argon flow, cooled, and poured onto a Petri dish for evaporation under ambient conditions. The residue was treated with $CHCl_3$ (20 ml), washed with saturated aqueous NaCl solution (3×15 ml), the organic extracts were combined and dried over anhydrous $MgSO_4$. The drying agent was filtered off and the solvent was removed by evaporation at reduced pressure using water aspirator. The oily residue was dissolved in a minimum amount of $CHCl_3$ and separated by silica gel column chromatography (eluent $CHCl_3$–EtOH, gradient from 100:1 to 10:1). The reaction products were isolated in the following sequence: compounds **11**–**16** (using 50:1 $CHCl_3$–MeOH as eluent), then compounds **5**–**8**, **10** (trace amounts) or compound **9** (20 mg) and the homocoupling products (in the reactions of compound **4** with alkynes **9**, **10**) – 1,4-bis-(4-fluorophenyl)buta-1,3-diyne[19] and 1,4-di(pyridin-2-yl)-buta-1,3-diyne.[19]

(2*R*,2a*R*,4*S*,5'*R*,6a*R*,6b*S*,8a*S*,8b*R*,9*S*,10*R*,11a*S*,12a*S*,12b*S*)-1'-Acetyl-2a-hydroxy-5',6a,8a,9-tetramethyl-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)octadecahydrospiro[naphtho[2',1':4,5]-indeno[2,1-*b*]furan-10,2'-piperidin]-4-yl acetate ((22*R*,25*R*)-*N*,*O*-diacetyl-5α-hydroxy-6β-(4-phenyl-1,2,3-triazol-1-yl)-spirosolane) (11). Yield 184 mg (78%), yellow amorphous powder, $[\alpha]_D^{27}$ –73.6 (*c* 0.23, $CHCl_3$). IR spectrum, ν, cm^{-1}: 609, 678, 694, 723, 763, 802, 838, 865, 923, 966, 985, 1033, 1072, 1137, 1243, 1321, 1365, 1382, 1402, 1432, 1454, 1500, 1633, 1731, 2873, 2900, 2950, 3062, 3428. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.75 (3H, s, 19-CH_3); 0.94 (3H, d, *J* = 7.0, 27-CH_3); 1.00 (3H, s, 18-CH_3); 1.09 (3H, d, *J* = 6.6, 21-CH_3); 1.21–1.50 (6H, m, 1,7,11,12,24-CH_2, 14-CH); 1.53–1.63 (3H, m, 9-CH, 15,23-CH_2); 1.69 (1H, td, *J* = 11.0, *J* = 3.7, 1-CH_2); 1.76–1.83 (4H, m, 2,12,23-CH_2); 1.93–2.03 (5H, m, 4,11,15,23-CH_2, 25-CH); 2.04 (3H, s, $OCOCH_3$); 2.14 (1H, dd, *J* = 12.8, *J* = 4.8, 4-CH_2); 2.20–2.25 (2H, m, 7,24-CH_2); 2.23 (3H, s, $NCOCH_3$); 2.50–2.56 (1H, m, 8-CH); 2.80–2.88 (2H, m, 26-CH_2, 5-OH); 3.02–3.09 (1H, m, 20-CH); 4.04–4.10 (1H, m, 26-CH_2); 4.21 (1H, ddd, *J* = 8.6, *J* = 7.4, *J* = 6.4, 16-CH); 4.37 (1H, br. s, 6-CH); 5.16–5.21 (1H, m, 3-CH); 7.31–7.47 (3H, m, 3",4",5"-CH); 7.80–7.86 (2H, m, 2",6"-CH); 7.86 (1H, s, 5'-CH). ^{13}C NMR spectrum, δ, ppm: 15.7 (C-19); 16.3 (C-21); 16.8 (C-18); 18.5 (C-27); 21.0 (C-11); 21.5 (OCO$\underline{C}H_3$); 24.0 (C-23); 24.3 (C-24); 25.2 (NCO$\underline{C}H_3$); 26.5 (C-2); 28.0 (C-25); 30.6 (C-7); 31.6 (C-8); 31.8 (C-15); 32.5 (C-1); 38.4 (C-20); 38.5 (C-4); 38.8 (C-10); 40.3 (C-13); 41.5 (C-12); 45.5 (C-9); 48.9 (C-26); 55.3 (C-14); 62.1 (C-17); 65.3 (C-6); 70.7 (C-3); 76.1 (C-5); 78.8 (C-16); 101.2 (C-22); 120.7 (C-5'), 125.6 (C-2",6"); 128.2 (C-4"); 128.9 (C-3",5"); 130.4 (C-1"); 146.7 (C-4'); 171.1 (O$\underline{C}OCH_3$); 171.2 (N$\underline{C}OCH_3$). Mass spectrum, *m*/*z* (I_{rel}, %): 659 (41), 658 (100), 504 (30), 163 (31), 149 (29), 146 (58), 114 (41), 109 (26), 91 (28), 43 (32). Found, *m*/*z*: 658.4089 $[M]^+$. $C_{39}H_{54}N_4O_5$. Calculated, *m*/*z*: 658.4084.

(2*R*,2a*R*,4*S*,5'*R*,6a*R*,6b*S*,8a*S*,8b*R*,9*S*,10*R*,11a*S*,12a*S*,12b*S*)-1'-Acetyl-2a-hydroxy-5',6a,8a,9-tetramethyl-2-[4-(4-methylphenyl)-1*H*-1,2,3-triazol-1-yl]octadecahydrospiro[naphtho-[2',1':4,5]indeno[2,1-*b*]furan-10,2'-piperidin]-4-yl acetate ((22*R*,25*R*)-*N*,*O*-diacetyl-5α-hydroxy-6β-[4-(4-methylphenyl)-1,2,3-triazol-1-yl]spirosolane) (12). Yield 167 mg (69%), yellow amorphous powder, $[\alpha]_D^{25}$ –77.4 (*c* 0.24, $CHCl_3$). IR spectrum, ν, cm^{-1}: 609, 661, 727, 755, 796, 821, 877, 923, 966, 1033, 1072, 1137, 1164, 1245, 1322, 1365, 1380, 1400, 1452, 1498, 1580, 1610, 1635, 1654, 1731, 2873, 2950, 3065, 3398. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.74 (3H, s, 19-CH_3); 0.93 (3H, d, *J* = 6.4, 27-CH_3); 0.99 (3H, s, 18-CH_3); 1.08 (3H, d, *J* = 6.6, 21-CH_3); 1.21–1.80 (14H, m, 1,2,7,11,12,15,23,24-CH_2, 9,14,17-CH); 1.91–2.00 (5H, m, 4,11,15,23-CH_2, 25-CH); 2.03 (3H, s, $OCOCH_3$); 2.10–2.16 (1H, m, 4-CH_2); 2.19–2.24 (2H, m, 7,24-CH_2); 2.21 (3H, s, $NCOCH_3$); 2.38 (3H, s, CH_3); 2.50–2.56 (1H, m, 8-CH); 2.80–2.88 (2H, m, 26-CH_2, 5-OH); 3.05–3.10 (1H, m, 20-CH); 4.02–4.06 (1H, m, 26-CH_2); 4.20 (1H, ddd, *J* = 8.8, *J* = 7.3, *J* = 6.6, 16-CH); 4.36 (1H, br. s, 6-CH); 5.16–5.22 (1H, m, 3-CH); 7.23 (2H, d, *J* = 7.8, 3",5"-CH); 7.73 (2H, d, *J* = 7.8, 2",6"-CH); 7.80 (1H, s, 5'-CH). ^{13}C NMR spectrum, δ, ppm: 15.7 (19-CH_3); 16.3 (21-CH_3); 16.7 (18-CH_3); 18.5 (27-CH_3); 21.0 (C-11); 21.3 (CH_3 Ar); 21.5 (OCO$\underline{C}H_3$); 24.0 (C-23); 24.2 (C-24); 25.2 (NCO$\underline{C}H_3$); 26.4 (C-2); 27.9 (C-25); 30.6 (C-7); 31.5 (C-8); 31.8 (C-15); 32.5 (C-1); 38.3 (C-20); 38.4 (C-4); 38.8 (C-10); 40.2 (C-13); 41.5 (C-12); 45.4 (C-9); 48.8 (C-26); 55.3 (C-14); 62.0 (C-17); 65.1 (C-6); 70.7 (C-3); 76.1 (C-5); 78.8 (C-16); 101.2 (C-22); 120.4 (C-5'); 125.5 (C-2",6"); 127.5 (C-4"); 129.5 (C-3",5"); 138.0 (C-1"); 146.7 (C-4'); 171.0 (O$\underline{C}OCH_3$); 171.2 (N$\underline{C}OCH_3$). Mass spectrum, *m*/*z* (I_{rel}, %): 672 (78), 657 (26), 388 (94), 178 (56), 160 (63), 135 (96), 114 (43), 72 (44), 44 (79), 43 (100). Found, *m*/*z*: 672.4245 $[M]^+$. $C_{40}H_{56}N_4O_5$. Calculated, *m*/*z*: 672.4248.

(2*R*,2a*R*,4*S*,5'*R*,6a*R*,6b*S*,8a*S*,8b*R*,9*S*,10*R*,11a*S*,12a*S*,12b*S*)-1'-Acetyl-2a-hydroxy-2-[4-(4-methoxyphenyl)-1*H*-1,2,3-triazol-1-yl]-5',6a,8a,9-tetramethyloctadecahydrospiro[naphtho[2',1':4,5]indeno[2,1-*b*]furan-10,2'-piperidin]-4-yl acetate ((22*R*,25*R*)-*N*,*O*-diacetyl-5α-hydroxy-6β-[4-(4-methoxyphenyl)-1,2,3-triazol-1-yl]spirosolane) (13). Yield 176 mg (71%), yellowish amorphous powder, $[\alpha]_D^{25}$ –46.6 (*c* 0.34, $CHCl_3$). IR spectrum, ν, cm^{-1}: 613, 663, 755, 796, 836, 867, 923, 968, 985, 1033, 1072, 1108, 1137, 1176, 1247, 1286, 1303, 1322, 1365, 1380, 1454,

1498, 1520, 1584, 1633, 1731, 2873, 2950, 3050, 3428. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.76 (3H, s, 19-CH_3); 0.94 (3H, d, *J* = 6.4, 27-CH_3); 1.00 (3H, s, 18-CH_3); 1.09 (3H, d, *J* = 6.6, 21-CH_3); 1.21–1.62 (9H, m, 1,7,11,12,15,23,24-CH_2, 9,14-CH); 1.69 (1H, td, *J* = 14.1, *J* = 3.4, 1-CH_2); 1.75–1.82 (4H, m, 2,12-CH_2, 17-CH); 1.93–2.02 (5H, m, 4,11,15,23-CH_2, 25-CH); 2.04 (3H, s, $OCOCH_3$); 2.11 (1H, dd, *J* = 12.4, *J* = 4.0, 4-CH_2); 2.18–2.24 (2H, m, 7,24-CH_2); 2.23 (3H, s, $NCOCH_3$); 2.50–2.56 (1H, m, 8-CH); 2.78–2.89 (2H, m, 26-CH_2, 5-OH), 3.05–3.10 (1H, m, 20-CH); 3.85 (3H, s, OCH_3); 4.02–4.06 (1H, m, 26-CH_2); 4.20 (1H, ddd, *J* = 8.6, *J* = 7.1, *J* = 6.6, 16-CH); 4.33 (1H, br. s, 6-CH); 5.14–5.21 (1H, m, 3-CH); 6.97 (2H, d, *J* = 8.6, 3",5"-CH); 7.74 (1H, s, 5'-CH); 7.78 (2H, d, *J* = 8.6, 2",6"-CH). ^{13}C NMR spectrum, δ, ppm: 15.7 (C-19); 16.4 (C-21); 16.8 (C-18); 18.5 (C-27); 21.1 (C-11); 21.4 ($OCOCH_3$); 24.1 (C-23); 24.4 (C-24); 25.2 ($NCOCH_3$); 26.5 (C-2); 28.0 (C-25); 30.7 (C-7); 31.6 (C-8); 31.9 (C-15); 32.6 (C-1); 38.5 (C-4,20); 38.9 (C-10); 40.3 (C-13); 41.5 (C-12); 45.6 (C-9); 49.0 (C-26); 55.3 (C-14); 55.4 (OCH_3); 62.2 (C-17); 65.2 (C-6); 70.7 (C-3); 76.2 (C-5); 78.9 (C-16); 101.2 (C-22); 114.3 (C-2",6"); 120.1 (C-5'); 123.2 (C-1"), 127.0 (C-3",5"); 146.5 (C-4'), 159.6 (C-4"); 171.0 ($OCOCH_3$); 171.1 ($NCOCH_3$). Mass spectrum, *m/z* (I_{rel}, %): 688 (31), 556 (79), 176 (55), 175 (57), 163 (76), 162 (62), 149 (59), 132 (66), 114 (100), 43 (92). Found, *m/z*: 688.4197 $[M]^+$. $C_{40}H_{56}N_4O_6$. Calculated, *m/z*: 688.4194.

(2*R*,2a*R*,4*S*,5'*R*,6a*R*,6b*S*,8a*S*,8b*R*,9*S*,10*R*,11a*S*,12a*S*,12b*S*)-1'-Acetyl-2a-hydroxy-5',6a,8a,9-tetramethyl-2-[4-(3,4,5-trimethoxyphenyl)-1*H*-1,2,3-triazol-1-yl]octadecahydrospiro[naphtho[2',1':4,5]indeno[2,1-*b*]furan-10,2'-piperidin]-4-yl acetate ((22*R*,25*R*)-*N*,*O*-diacetyl-5α-hydroxy-6β-[4-(3,4,5-trimethoxyphenyl)-1,2,3-triazol-1-yl]spirosolane) (14). Yield 161 mg (60%), yellowish amorphous powder, $[\alpha]_D^{24}$ –60.1 (*c* 0.25, $CHCl_3$). IR spectrum, ν, cm^{-1}: 609, 623, 665, 681, 756, 800, 856, 924, 966, 1009, 1034, 1068, 1088, 1107, 1128, 1178, 1242, 1363, 1381, 1410, 1429, 1460, 1498, 1589, 1655, 1732, 2873, 2943, 3138, 3425. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.79 (3H, s, 19-CH_3); 0.93 (3H, d, *J* = 6.5, 27-CH_3); 0.99 (3H, s, 18-CH_3); 1.09 (3H, d, *J* = 6.8, 21-CH_3); 1.21–1.61 (9H, m, 1,7,11,12,15,23,24-CH_2, 9,14-CH); 1.67 (1H, td, *J* = 14.2, *J* = 3.2, 1-CH_2); 1.75–1.87 (4H, m, 2,12-CH_2, 17-CH); 1.93–2.02 (5H, m, 4,11,15,23-CH_2, 25-CH); 2.04 (3H, s, $OCOCH_3$); 2.10 (1H, dd, *J* = 12.1, *J* = 4.2, 4-CH_2); 2.08–2.16 (2H, m, 7,24-CH_2); 2.23 (3H, s, $NCOCH_3$); 2.52–2.60 (1H, m, 8-CH); 2.78–2.89 (2H, m, 26-CH_2, 5-OH); 3.02–3.08 (1H, m, 20-CH); 3.85 (3H, s, OCH_3); 3.95 (6H, 2OCH_3); 4.05–4.09 (1H, m, 26-CH_2); 4.20 (1H, ddd, *J* = 8.4, *J* = 7.0, *J* = 6.6, 16-CH); 4.30 (1H, br. s, 6-CH); 5.14–5.21 (1H, m, 3-CH); 7.09 (2H, s, 2",6"-CH); 7.76 (1H, s, 5'-CH). ^{13}C NMR spectrum, δ, ppm: 15.7 (C-19); 16.3 (C-21); 16.7 (C-18); 18.5 (C-27); 21.0 (C-11); 21.5 ($OCOCH_3$); 24.0 (C-23); 24.3 (C-24); 25.2 ($NCOCH_3$); 26.4 (C-2); 27.9 (C-25); 30.8 (C-7); 31.5 (C-8); 31.8 (C-15); 32.5 (C-1); 38.3 (C-4); 38.6 (C-20); 38.8 (C-10); 40.24 (C-13); 41.5 (C-12); 45.5 (C-9); 48.8 (C-26); 55.3 (C-14); 56.4 (OCH_3); 61.0 (2OCH_3); 62.1 (C-17); 65.5 (C-6); 70.7 (C-3); 76.1 (C-5); 78.8 (C-16); 101.2 (C-22); 103.0 (C-2",6"); 120.8 (C-5'); 126.0 (C-1"); 138.2 (C-3",5"); 146.5 (C-4'); 153.7 (C-4"); 171.1 ($OCOCH_3$); 171.2 ($NCOCH_3$). Mass spectrum, *m/z* (I_{rel}, %): 748 (10), 513 (90), 453 (65), 435 (58), 264 (57), 235 (100), 220 (55), 163 (58), 114 (79), 109 (53). Found, *m/z*: 748.4415 $[M]^{+\cdot}$ $C_{42}H_{60}N_4O_8$. Calculated, *m/z*: 748.4406.

(2*R*,2a*R*,4*S*,5'*R*,6a*R*,6b*S*,8a*S*,8b*R*,9*S*,10*R*,11a*S*,12a*S*,12b*S*)-1'-Acetyl-2-[4-(4-fluorophenyl)-1*H*-1,2,3-triazol-1-yl]-2a-hydroxy-5',6a,8a,9-tetramethyloctadecahydrospiro-[naphtho-[2',1':4,5]indeno[2,1-*b*]furan-10,2'-piperidin]-4-yl acetate ((22*R*,25*R*)-*N*,*O*-diacetyl-5α-hydroxy-6β-[4-(4-fluorophenyl)-1,2,3-triazol-1-yl]spirosolane) (15). Yield 104 mg (43%), yellowish amorphous powder, $[\alpha]_D^{24}$ –65.1 (*c* 0.25, $CHCl_3$). IR spectrum, ν, cm^{-1}: 611, 663, 696, 757, 813, 840, 865, 923, 966, 1033, 1072, 1137, 1157, 1243, 1322, 1365, 1380, 1400, 1452, 1496, 1582, 1610, 1655, 1731, 2873, 2900, 2950, 3045, 3432. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.74 (3H, s, 19-CH_3); 0.93 (3H, d, *J* = 6.8, 27-CH_3); 1.00 (3H, s, 18-CH_3); 1.08 (3H, d, *J* = 6.8, 21-CH_3); 1.21–1.49 (6H, m, 1,7,11,12,24-CH_2, 14-CH); 1.53–1.62 (3H, m, 9-CH, 15,23-CH_2); 1.68 (1H, td, *J* = 13.0, *J* = 3.4, 1-CH_2); 1.76–1.83 (4H, m, 2,12-CH_2, 17-CH); 1.91–2.02 (5H, m, 4,11,15,23-CH_2, 25-CH); 2.04 (3H, s, $OCOCH_3$); 2.14 (1H, dd, *J* = 12.4, *J* = 4.2 , 4-CH_2); 2.08–2.16 (2H, m, 7-CH_2, 24-CH_2); 2.21 (3H, s, $NCOCH_3$); 2.52–2.60 (1H, m, 8-CH); 2.78–2.89 (2H, m, 26-CH_2, 5-OH); 3.08–3.12 (1H, m, 20-CH); 4.00–4.06 (1H, m, 26-CH_2); 4.20 (1H, ddd, *J* = 8.4, *J* = 7.2, *J* = 6.6, 16-CH); 4.36 (1H, br. s, 6-CH); 5.18–5.25 (1H, m, 3-CH); 7.13 (2H, d, *J* = 8.4, 3",5"-CH); 7.82 (2H, dd, J_{HH} = 8.4, J_{HF} = 5.5, 2",6"-CH); 7.81 (1H, s, 5'-CH). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 15.9 (C-19); 16.3 (C-21); 16.8 (C-18); 18.5 (C-27); 21.0 (C-11); 21.5 ($OCOCH_3$); 24.0 (C-23); 24.3 (C-24); 25.2 ($NCOCH_3$); 26.5 (C-2); 27.9 (C-25); 30.6 (C-7); 31.5 (C-8); 31.8 (C-12); 32.5 (C-1); 38.3 (C-20); 38.4 (C-4); 38.8 (C-10); 40.3 (C-13); 41.5 (C-15); 45.5 (C-9); 49.0 (C-26); 55.3 (C-14); 62.1 (C-17); 65.3 (C-6); 70.7 (C-3); 76.1 (C-5); 78.8 (C-16); 101.2 (C-22); 115.9 (C-3",5"); 120.5 (C-5'); 126.6 (C-1"); 127.4 (C-2",6"); 145.8 (C-4'); 162.6 (J_{CF} = 241.2, C-4"); 171.0 ($OCOCH_3$); 171.1 ($NCOCH_3$). Mass spectrum, *m/z* (I_{rel}, %): 677 (53), 676 (100), 453 (27), 264 (77), 213 (47), 164 (98), 163 (61), 162 (48), 126 (29), 114 (61). Found, *m/z*: 676.3995 $[M]^+$. $C_{39}H_{53}FN_4O_5$. Calculated, *m/z*: 676.3999.

(2*R*,2a*R*,4*S*,5'*R*,6a*R*,6b*S*,8a*S*,8b*R*,9*S*,10*R*,11a*S*,12a*S*,12b*S*)-1'-Acetyl-2a-hydroxy-5',6a,8a,9-tetramethyl-2-[4-(pyridin-2-yl)-1*H*-1,2,3-triazol-1-yl]octadecahydrospiro[naphtho-[2',1':4,5]indeno[2,1-*b*]furan-10,2'-piperidin]-4-yl acetate ((22*R*,25*R*)-*N*,*O*-diacetyl-5α-hydroxy-6β-[4-(pyridin-2-yl)-1,2,3-triazol-1-yl]spirosolane) (16). Yield 123 mg (52%), brownish amorphous powder, $[\alpha]_D^{25}$ –44.2 (c 0.29, $CHCl_3$). IR spectrum, ν, cm^{-1}: 619, 665, 692, 752, 784, 836, 867, 921, 966, 1033, 1072, 1153, 1245, 1321, 1365, 1380, 1405, 1436, 1471, 1550, 1571, 1604, 1635, 1731, 2873, 2937, 2950, 3056, 3419. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.77 (3H, s, 19-CH_3); 0.93 (3H, d, *J* = 6.6, 27-CH_3); 0.99 (3H, s, 18-CH_3); 1.10 (3H, d, *J* = 6.6, 21-CH_3); 1.19–1.46 (6H, m, 1,7,11,12,24-CH_2, 14-CH); 1.55–1.63 (3H, m, 9-CH, 15,23-CH_2); 1.69 (1H, td, *J* = 12.7, *J* = 2.8, 1-CH_2); 1.75–1.82 (4H, m, 2,12-CH_2, 17-CH); 1.91–1.99 (5H, m, 4,11,15,23-CH_2,

25-CH); 2.03 (3H, s, $OCOCH_3$); 2.16 (1H, dd, J = 12.6, J = 4.0, 4-CH_2); 2.16–2.24 (2H, m, 7,24-CH_2); 2.24 (3H, s, $NCOCH_3$); 2.54–2.62 (1H, m, 8-CH); 2.78–2.89 (2H, m, 26-CH_2, 5-OH); 2.98–3.06 (1H, m, 20-CH); 4.06–4.12 (1H, m, 26-CH_2); 4.20 (1H, ddd, J = 8.2, J = 7.3, J = 6.8, 16-CH); 4.38 (1H, br. s, 6-CH); 5.16–5.22 (1H, m, 3-CH); 7.25 (1H, d, J = 6.5, 6"-CH); 7.80 (1H, dd, J = 7.2, J = 6.8, 4"-CH); 8.19 (1H, s, 5'-CH); 8.23 (1H, dd, J = 7.2, J = 6.5, 5"-CH); 7.82 (1H, d, J = 6.8, 3"-CH). ^{13}C NMR spectrum, δ, ppm: 15.7 (C-19); 16.4 (C-21); 16.8 (C-18); 18.4 (C-27); 21.1 (C-11); 21.5 ($OCOCH_3$); 24.0 (C-23); 24.4 (C-24); 25.2 ($NCOCH_3$); 26.5 (C-2); 28.0 (C-25); 30.7 (C-7); 31.5 (C-8); 31.8 (C-15); 32.6 (C-1); 38.3 (C-20); 38.3 (C-4); 38.8 (C-10); 40.3 (C-13); 41.5 (C-12); 45.5 (C-9); 48.7 (C-26); 55.4 (C-14); 62.1 (C-17); 65.5 (C-6); 70.7 (C-3); 76.0 (C-5); 78.9 (C-16); 101.2 (C-22); 120.3 (C-5'); 122.9 (C-6"); 123.4 (C-4"); 137.1 (C-5"); 147.1 (C-4'); 149.2 (C-3"); 150.1 (C-1"); 172.0 ($OCOCH_3$); 171.2 ($NCOCH_3$). Mass spectrum, m/z (I_{rel}, %): 659 (7), 513 (12), 265 (16), 264 (100), 236 (16), 192 (11), 57 (11), 43 (59), 41 (15), 39 (14). Found, m/z: 659.4041 $[M]^+$. $C_{38}H_{53}N_5O_5$. Calculated, m/z: 659.4046.

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