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Synthesis of novel 1,2,3-triazolyl derivatives of pregnane, androstane and D-homoandrostane. Tandem "click" reaction/Cu-catalyzed D-homo rearrangement†

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Copper-catalyzed 1,3-dipolar cycloaddition has been employed in the reaction of steroidal azides with various terminal alkynes. A number of novel 1,2,3-triazolyl derivatives of pregnane, androstane and D-homoandrostane were obtained in high yield (70–98%). The developed synthetic protocols allowed us to attach the triazolyl moiety to both the side chain and the steroidal backbone directly, despite the steric hindrance exerted by the polycyclic system. The presence of Cu(II) was shown to evoke D-homo rearrangement under mild conditions. A rational choice of the copper precatalyst permitted us to carry out the "click" reaction either along with tandem D-homo rearrangement or in the absence of this process. The tendency of 16-heterosubstituted steroids to undergo D-homo rearrangement under Cu(II) catalysis was studied.

Introduction

17α-Hydroxylase-$C_{17,20}$-lyase (CYP17), a cytochrome P450 mono-oxygenase, is a key enzyme for androgen biosynthesis. It catalyzes both the hydroxylation of C17 and the cleavage of the C17–C20 bond of pregnanes to produce androst-4-ene-3,17-dione and dehydroepiandrosterone from progesterone and pregnenolone. Since the products of these transformations are known to stimulate the development of prostate cancer by binding to androgen receptor (AR), selective suppression of androgen biosynthesis became an important therapeutic strategy to inhibit tumor growth.[1] The large number of both steroidal and non-steroidal nitrogen-containing heterocycles capable of binding to heme iron and blocking the C17-hydroxylation were found to be potent inhibitors of CYP17. The use of a lipophilic steroid core with nitrogen-containing substituents as the basis for the construction of new CYP17 inhibitors has the benefit of both creation of fairly good fitting to a mostly hydrophobic active site of the enzyme[2] and providing increased cell membrane permeability. Though many nitrogen-containing steroidal inhibitors[3] were proposed, the most prominent inhibitory effect was observed for D-ring-modified steroids with heteroaryl[4] or azolyl[5] substituents. In 2011 abiraterone acetate (**1**) became the first steroidal CYP17 inhibitor to be approved by the FDA for the treatment of castrate-resistant prostate cancer,[6] while galeterone (**2a**), another CYP17 inhibitor with AR antagonistic and ablative activities, is currently undergoing Phase I/II clinical trials.[7]

Unfortunately, the synthesis of such compounds remains rather expensive and tedious[8] despite the great progress in Pd-[9,10] and Cu-catalyzed[11] cross-coupling with steroids. 17-(1,2,3-Triazolyl)-substituted steroid **2b**[5a] (Fig. 1) offers another possibility for development of synthetically friendly and cheap inhibitors of CYP17 since the 1,2,3-triazolyl moiety can be constructed through copper-catalyzed 1,3-dipolar azide–alkyne

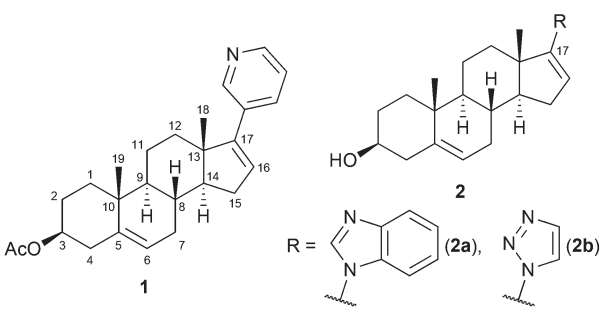

Fig. 1 Known steroidal CYP17 inhibitors containing the heterocyclic moiety.

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†Electronic supplementary information (ESI) available: Copies of the ^{1}H and ^{13}C NMR spectra for compounds **4**, **6**, **8–13**, **16**, **17a**, **17b**, **18a**, and **19c**. See DOI: 10.1039/c4ob00404c

cycloaddition (CuAAC). This reaction enables an efficient synthesis of 1,4-substituted 1,2,3-triazoles with excellent regioselectivity and almost complete absence of by-products, providing a high yield of the desired compound.[12] The introduction of a 1,2,3-triazolyl fragment[13] into steroid molecules has led to new biologically active compounds exhibiting anticancer,[14] anti-inflammatory,[15] antimicrobial,[16] and anti-HIV[17] effects. Due to the mild conditions of the CuAAC reaction, the 1,2,3-triazole moiety became a convenient linker in bioconjugation of steroid-like molecules with various natural compounds such as peptides,[18] carbohydrates,[14c,19] nucleosides,[17] and nucleic acids.[20]

Herein, we report the synthesis of new 1,2,3-triazolylsteroids bearing a heterocyclic moiety in the side chain as well as in the 16-C position of the steroidal backbone. The obtained compounds are of interest to medicinal chemistry as they are potential CYP17 inhibitors which can be applied for treating prostate diseases.

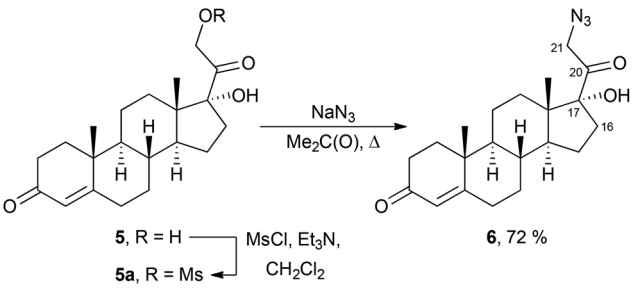
Results and discussion

Synthesis of azidosteroids

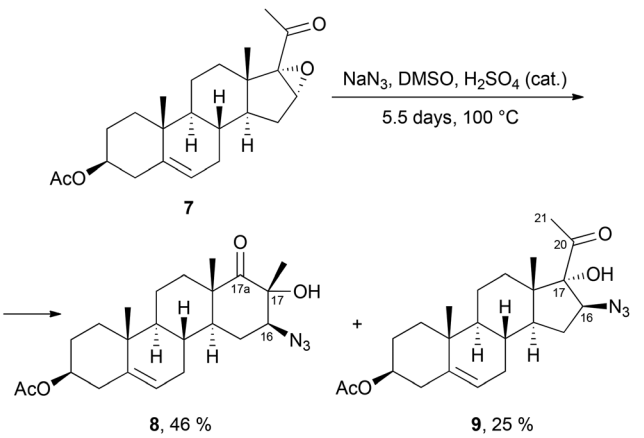
To prepare substrates for the CuAAC reaction we decided to introduce the azide moiety into the steroidal framework. This transformation was accomplished by modifying procedures presented in the literature. One of the synthetic routes to azidosteroids was nucleophilic ring opening of epoxides by sodium azide.[21] For example, a reaction of epoxide **3** with sodium azide in a MeCN–H_2O (1 : 1) mixture for 16 h at 100 °C followed by hydrolysis of the enol ether group afforded azidosteroid **4** in high yield (Scheme 1).

The introduction of the azide moiety into the 21-C position of the steroidal framework was performed by a two-step reaction sequence. Mesylation of cortexolone **5** followed by nucleophilic substitution of the mesyloxy group by sodium azide gave 21-azidosteroid **6** in good yield (Scheme 2). Although substitution of the 21-mesyloxy group is known to proceed at ambient temperature,[22] in our case the reaction was carried out under reflux in order to achieve full conversion and reduce the reaction time without lowering the yield.

The conditions used for nucleophilic ring opening of epoxide **3** appeared to be absolutely ineffective in a reaction of the more sterically hindered epoxide **7** (Scheme 3). Prolonged heating for 5.5 days in DMSO in the presence of catalytic amounts of sulfuric acid was required for the reaction to proceed completely.[21b] Under the conditions employed, azidosteroid **9** partially transforms to structural isomer **8** undergoing α-ketol rearrangement that leads to the expansion of 5-membered ring D of the steroidal backbone (so-called D-homo rearrangement). This process is rather typical for 17α-hydroxy-20-ketosteroids and can take place under both acid and base catalysis.[23] The mixture of isomers **8** and **9** was obtained in good yield (71%), and both compounds were isolated in pure state by column chromatography.



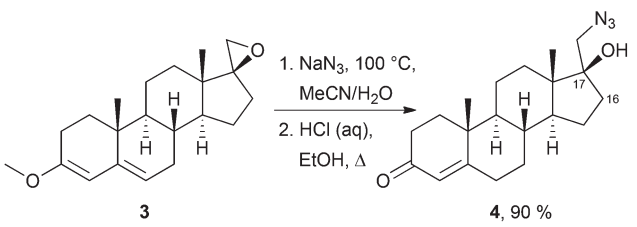
Scheme 2 Synthesis of 21-azidosteroid **6**.



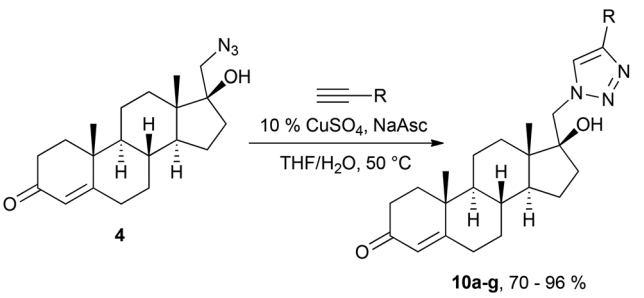
Scheme 3 Synthesis of 16β-azidosteroids **8** and **9**.

Copper-catalyzed 1,3-dipolar cycloaddition

The reaction of azidosteroid **4** with a number of terminal alkynes was performed successfully using a standard catalytic system for CuAAC comprising copper(II) sulfate and sodium ascorbate (NaAsc) in a mixture of THF and water (Scheme 4).

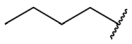
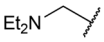
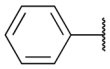
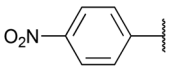
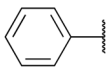
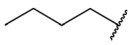


Scheme 1 Synthesis of 17α-(azidomethyl)steroid **4**.



Scheme 4 Synthesis of 17α-(triazolylmethyl)steroids **10**.

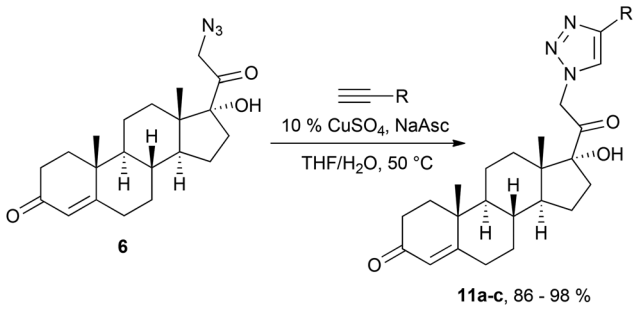
Table 1 Yields of triazolylsteroids in the CuAAC reaction of azidosteroids **4** and **6** with terminal alkynes[a]

Entry	Substrate	R	Product	Time (h)	Yield[b] (%)
1	**4**		**10a**	15	81
2	**4**		**10b**	15	93
3	**4**		**10c**	15	70
4	**4**		**10d**	16	96
5	**4**		**10e**	14	93
6	**4**		**10f**	15	89
7	**4**		**10g**	16	91
8	**6**		**11a**	14	86
9	**6**		**11b**	22	98
10	**6**		**11c**	22	98

[a] Reaction conditions: $CuSO_4 \cdot 5H_2O$ (10 mol%), NaAsc (40 mol%), 1-alkyne (1.2 equiv.), THF–H_2O (4 : 1), 50 °C, 14–22 h. [b] Isolated yield.

All reactions of substrate **4** proceeded under mild conditions affording 1,4-substituted 1,2,3-triazoles **10a–g** bearing both aliphatic (Table 1, entries 1–4) and aromatic (entries 5–7) fragments in high yield. Hydroxy (entries 1 and 2) and amino groups (entry 4) were tolerated by the reaction conditions. 4-Nitrophenylacetylene (entry 6), which is known to be a challenging substrate for some reactions due to a tendency to add nucleophiles, also reacted well. It is worth mentioning that a high yield (91%) was achieved in the reaction of **4** with ethynylferrocene (entry 7), though reactivity of azidosteroids is not always high in the case of alkynes bearing bulky substituents. For instance, 2-azidosteroid is known to react with ethynylferrocene in 64% yield, while the more sterically hindered 6-azidosteroid gives only trace amounts of the corresponding product.[24]

The standard catalytic system based on $CuSO_4 \cdot 5H_2O$ and NaAsc also allowed to synthesize 1,2,3-triazoles attached to the 21-C position of the steroidal backbone (Scheme 5). The corresponding 21-derivatives of 17α-hydroxyprogesterone **11a–c** were isolated in excellent yields (Table 1, entries 8–10). Thus, both substrates **4** and **6** bearing the azide moiety in the side



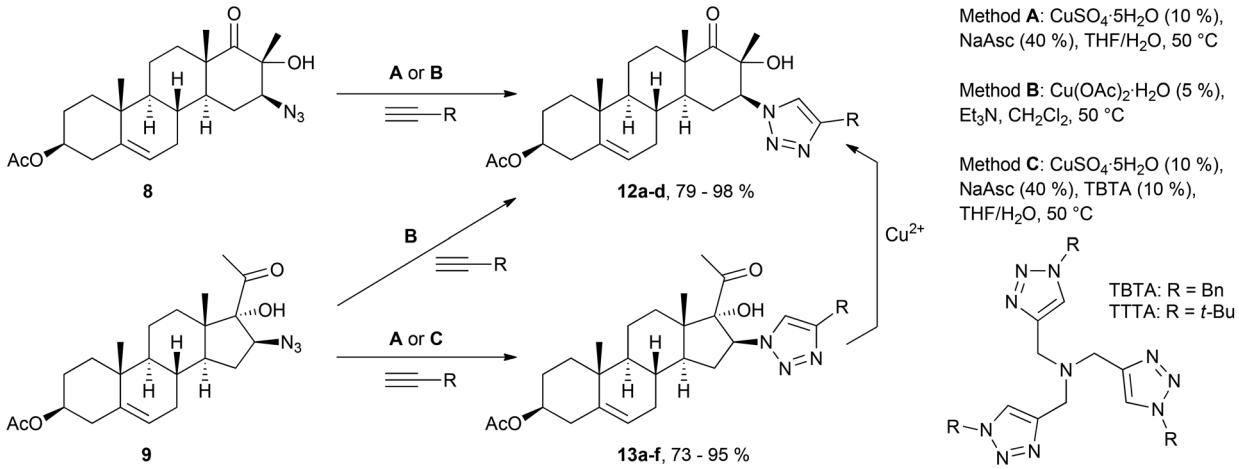
Scheme 5 Synthesis of 21-triazolylsteroids **11**.

chain reacted with terminal alkynes rather easily, and the steroid fragment did not exert a noticeable steric effect on their reactivity.

Attachment of the triazolyl moiety to C16 provides another convenient way to introduce a coordinating N-atom in the vicinity of the CYP17 active center. Since D-homo rearrangement is the expected metabolic degradation pathway of 17α-hydroxy-20-ketopregnanes **13** and D-homosteroids are known to exhibit valuable pharmacological properties,[25] both **9** and the corresponding D-homoandrostane **8** were studied in CuAAC. As was expected, the reaction of these more sterically hindered azidosteroids proceeded more slowly and proved sensitive to the composition of a catalytic system. The use of $CuSO_4 \cdot 5H_2O$ and NaAsc in aqueous THF (method **A**) allowed us to obtain product **12c** *via* reaction of azidosteroid **8** with propargyl alcohol (Scheme 6; Table 2, entry 3), but in the case of phenylacetylene conversion was only 48% after 14 h. Since copper carboxylates are known to accelerate the CuAAC reaction,[26] we applied presumably more active $Cu(OAc)_2 \cdot H_2O$ as a catalyst. Triethylamine was added to increase the solubility of the catalyst in CH_2Cl_2 and facilitate the formation of copper acetylide. This catalytic system (method **B**) appeared to be effective for both phenylacetylene and 1-hexyne (Table 2, entries 1 and 2). Alkyne with the diethylamino group also reacted smoothly (entry 4), though for propargyl alcohol the conversion was only 51% after 22 h.

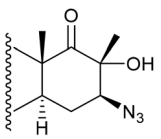
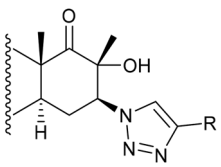
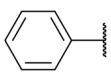
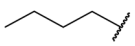
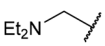
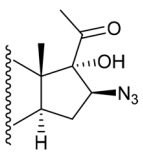
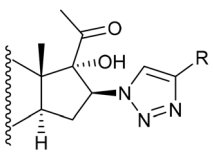
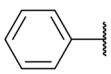
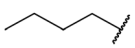
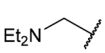
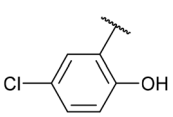
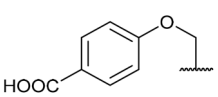
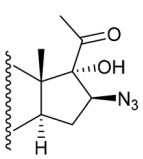
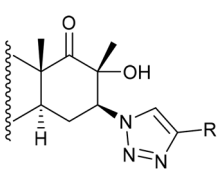
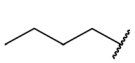
Reaction of azidosteroid **9** with phenylacetylene reached full conversion after 14 h when method **A** was used (Table 2, entry 5), while in the case of method **B**, the result was unexpected. Method **B** led to D-homo rearrangement product **12** instead of **13**, whereas this process did not take place in method **A** (Scheme 6). Thus, the reaction of azidosteroid **9** with 1-hexyne and propargyl alcohol in method **B** was complete after 22 h and furnished products **12b** and **12c**, respectively (Table 2, entries 11 and 12). The yields appeared to be even slightly better than for the same compounds synthesized from azidosteroid **8** (*cf.* entries 2 *vs.* 11 and 3 *vs.* 12 in Table 2).

As method **A** was not applicable for the reaction of azidosteroid **9** with some alkynes (*e.g.* the conversion in the case of propargyl alcohol was only 16%), it was intriguing to find a more effective catalytic system allowing to avoid D-homo rearrangement. Apparently, one should prevent the formation of copper(II) ions which possess higher Lewis acidity than



Scheme 6 Synthesis of 16β-triazolylsteroids **12** and **13**.

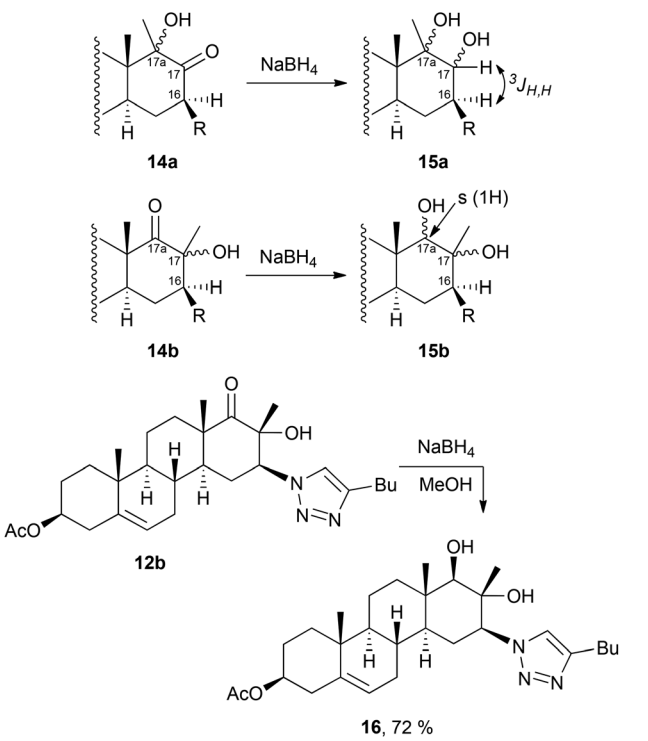
Table 2 Yields of triazolylsteroids in the CuAAC reaction of azidosteroids **8** and **9** with terminal alkynes[a]

Entry	Substrate	Product		R	Method	Time (h)	Isolated yield (%)
1	 **8**		**12a**		**B/A**	18/14	79/48[b]
2			**12b**		**B**	22	84
3			**12c**		**A/B**	14/22	84/51[b]
4			**12d**		**B**	20	81
5	 **9**		**13a**		**A**	14	95
6			**13b**		**C**	19	90
7			**13c**		**C/A**	20/14	94/16[b]
8			**13d**		**C**	20	95
9			**13e**		**C**	20	87
10			**13f**		**C**	20	73
11	 **9**		**12b**		**B**	22	90
12			**12c**		**B**	22	98

[a] Reaction conditions: A: $CuSO_4{\cdot}5H_2O$ (10 mol%), NaAsc (40 mol%), THF–H_2O (4 : 1), 50 °C, 14 h; B: $Cu(OAc)_2{\cdot}H_2O$ (5 mol%), Et_3N (1 equiv.), CH_2Cl_2, 50 °C, 18–22 h; C: $CuSO_4{\cdot}5H_2O$ (10 mol%), TBTA (10 mol%), NaAsc (40 mol%), THF–H_2O (4 : 1), 50 °C, 19–20 h. [b] ^1H NMR yield.

copper(I) ones, *i.e.* the reaction should be made in the presence of the reductant – sodium ascorbate. To increase the conversion of **9** we employed triazole-based chelating ligands that are well known to accelerate the CuAAC reaction and stabilize copper(I) species.[27] Thus, a catalytic system comprising $CuSO_4 \cdot 5H_2O$, tris(benzyltriazolylmethyl)amine (TBTA) and NaAsc (method **C**) allowed us to achieve a full conversion of azidosteroid **9**, suppress the D-homo rearrangement process, and isolate the corresponding products **13b** and **13c** in high yield (Table 2, entries 6 and 7). Tris(*tert*-butyltriazolylmethyl) amine (TTTA) while efficiently suppressing D-homo rearrangement led to incomplete conversion of azidosteroid **9**. Alkyne containing diethylamino group (entry 8), which could stabilize the copper(II) oxidation state and facilitate D-homo rearrangement, afforded exclusively product **13d** in excellent yield. Alkynes bearing acidic phenol and carboxyl moieties (entries 9 and 10) also afforded the corresponding products **13e** and **13f** in high yield.

To confirm the structure of the D-homo rearrangement product formed under conditions **B**, the carbonyl group in the D ring was reduced by $NaBH_4$ (Scheme 7). According to the literature,[23] D-homo rearrangement of 17α-hydroxy-20-ketosteroids can lead to one of the two regioisomers **14a** or **14b** depending on the substrate structure, relative stability of the products and reaction conditions. Since C*H*OH proton appears as a singlet at 3.36 ppm in the ^{1}H NMR spectrum of 1,2-diol **16**, the carbonyl group must be in 17a-C position, *i.e.* regioisomer **14b** formed (Scheme 7).

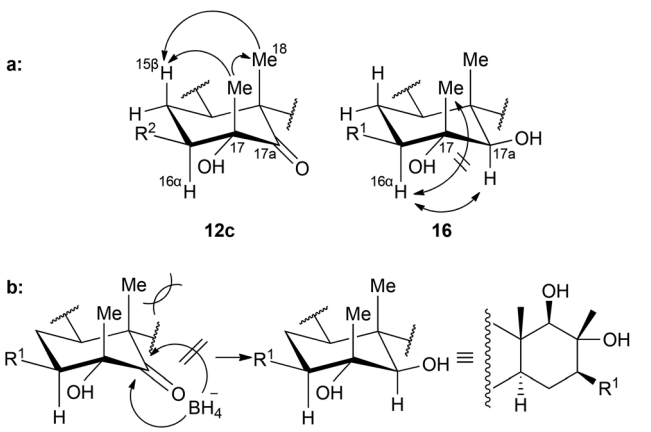


Scheme 7 Assignment of regiochemistry of D-homo rearrangement product.

Absolute configuration of atoms 17-C and 17a-C in the products of tandem CuAAC/D-homo rearrangement reaction was established by 1D NOESY experiments (Scheme 8a). The presence of NOEs from the CH_3 group in the 17-C position to 15β-H and 18-CH_3 in **12c** suggests that they are in the same face. The absence of NOE between the axial proton 16-CH(triazole) and the CH_3 group in the 17-C position and the presence of NOE between 16-CH and 17a-C*H*OH protons confirmed the structure of 1,2-diol expressed by formula **16**. This configuration is consistent with a bottom face attack of $NaBH_4$ on the carbonyl group as the attack from the top face is less preferable due to a significant steric effect of the two methyl groups (Scheme 8b). The regio- and stereochemistry of D-homo rearrangement product were also confirmed by X-ray crystallographic analysis of deacetylated **12a** (Fig. 2).

The structure of rearranged products **12** is consistent with Lewis acid catalyzed D-homo rearrangement. Indeed, a complete isomerization of **13a** to **12a** was observed after 18 h not only under conditions used in method **B** but also in the presence of $Cu(OAc)_2 \cdot H_2O$ alone.

Although the detailed mechanism of the rearrangement is not quite clear even for "traditional" Lewis acids, all proposed pathways are very similar. Coordination of the metal ion or hydrogen bonding provides the necessary *syn* alignment of carbonyl and hydroxyl groups and facilitates 1,2-migration of



Scheme 8 (a) 1D NOESY experiments for **12c** and **16**; (b) assignment of stereochemistry of the D-homo rearrangement product.

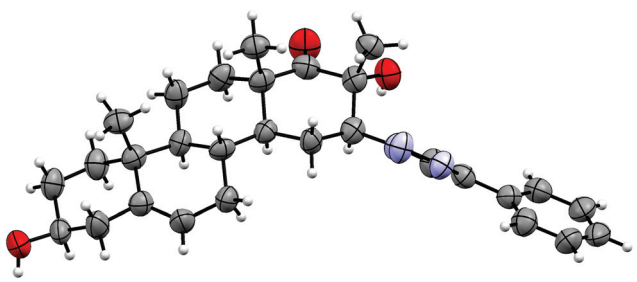
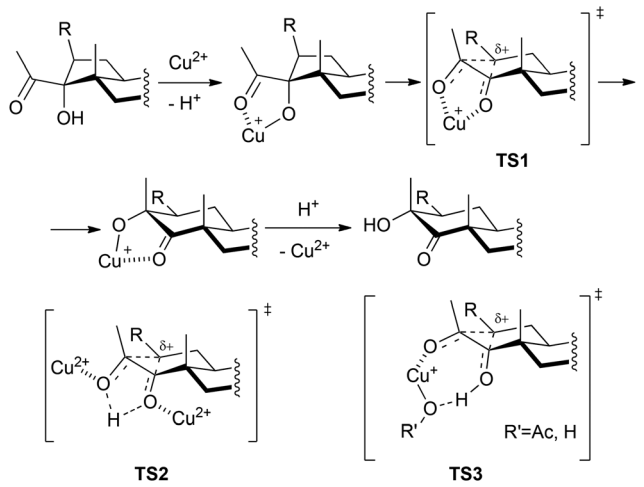


Fig. 2 X-ray crystal structure of deacetylated **12a**.



Scheme 9 Possible mechanism of Cu-catalyzed D-homo rearrangement.

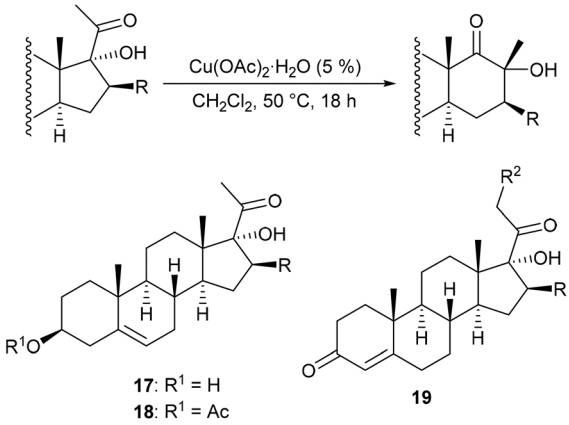
16-C *via* the chair-like transition state, resulting in a more stable 6-membered ring (Scheme 9).

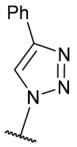
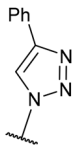
Apart from the "classical" mechanism involving 5-membered chelate (**TS1**),[28,29] more complex transition states were proposed. Thus, coordination of 2 BF_3 molecules with carbonyl and hydroxyl groups, connected by intramolecular hydrogen bond was assumed for BF_3-promoted D-homo rearrangement on the basis of NMR and kinetic data.[30] A 7-membered cyclic transition state featuring a hydrogen bond of the hydroxyl group with an oxygen ligand on the metal was predicted by DFT calculations for Al-catalyzed 1,2-hydride shift in hydrated glyoxal.[31] Therefore, analogous transition states **TS2** and **TS3** can be expected for the Cu-catalyzed D ring expansion.

The generality of the Cu(II)-catalyzed rearrangement was studied on various substrates containing a 17α-hydroxy-20-keto fragment (Table 3). D-Homo rearrangement was not observed for compounds **6** and **11a** (entries 3 and 4) bearing the azide and 1,2,3-triazolyl moiety in the 21-C position, respectively. Other 16-unsubstituted steroids **19a** and **19b** (entries 1 and 2) were also recovered unchanged after heating with 5 mol% $Cu(OAc)_2{\cdot}H_2O$ at 50 °C for 18 h. Thus, the nature of substituents on the migrating center was believed to be the main determinant of D-homo rearrangement. In order to understand the reason for the obtained compounds **13** to transform to **12** under copper(II) catalysis so easily, we investigated steroids bearing different heteroatoms in the 16-C position.

Regardless of the actual structure of the transition state, a shift of electron density induced by coordination of Lewis acid to α-ketol increases positive charge on the migrating 16-C atom. It is generally accepted that substituents on 16-C, capable of stabilizing partial positive charge in the transition state, facilitate D-homoannulation.[32] Thus, 16β-methyl-[33] and 16β-phenylsteroids[25b] rearrange under milder conditions than the corresponding unsubstituted derivatives. The same tendency was observed for the rearrangement of *p*-substituted 16α-benzoyloxysteroids.[33b]

Table 3 Cu-catalyzed D-homo rearrangement of 16-substituted steroids



Entry	Substrate	Parent structure	R^2	R	Conversion[a] (%)
1	**19a**	**19**	H	H	0
2	**19b**	**19**	OH	H	0
3	**6**	**19**	N_3	H	0
4	**11a**	**19**		H	0
5	**9**	**18**	—	N_3	100
6	**13a**	**18**	—		100
7	**17a**	**17**	—	Cl	6 23[b]
8	**18a**	**18**	—	OAc	0
9	**17b**	**17**	—	SPh	50 66[b]
10	**17b**	**17**	—	SPh	19[c]
11	**19c**	**19**	H	SCN	0[b]

[a] By ^{1}H NMR. [b] The mixture CH_2Cl_2–DMSO (4 : 1) was used as a solvent to increase substrate solubility. [c] 5 mol% $Cu(OTf)_2$ was used as a catalyst.

We believe that the lone pair of nitrogen atoms can stabilize the nearby cationoid center; therefore full conversion was obtained for 16β-azido and 16β-triazol-1-yl substituted compounds **9** and **13a** (Table 3, entries 5 and 6). However 16β-acetoxy substituted compound **18a** was isolated unchanged when treated with copper(II) acetate probably due to the combined effect of higher electronegativity of oxygen and the electron-withdrawing property of the acetyl group (entry 8). The phenylthio group produces a significant amount of rearranged product but the replacement of the almost electron-neutral phenyl group at sulfur (entry 9) with a strong electron-withdrawing cyano-group (entry 11) led to complete suppression of the rearrangement. Therefore copper

(II) acetate can be regarded as a rather weak Lewis acid capable of inducing D-homo rearrangement only with "activated" substrates.

The rearrangement of **17b** was attempted with more electrophilic copper(II) triflate (entry 10) but only 19% of the product was obtained. Since the increased electrophilicity of copper should favor the rearrangement *via* **TS2** (Scheme 9), this pathway is doubtful. Under the same conditions anhydrous $CuCl_2$ afforded only traces of D-homosteroid, whereas 47% conversion of **17b** was observed for hydrate $CuCl_2{\cdot}2H_2O$. In contrast, anhydrous $Cu(OAc)_2$ afforded even slightly higher conversion than $Cu(OAc)_2{\cdot}H_2O$ (58% *vs.* 50%). Thus, oxygen ligands on copper play a significant role in modulating the catalyst activity. These data are more consistent with transition state **TS3** where the hydrogen bond of α-ketol with a ligand bound to copper(II) is a distinct feature of the mechanism, though the pathway *via* "classical" transition state **TS1** cannot be definitely ruled out.

Conclusions

New types of 1,2,3-triazolyl steroids were prepared by the CuAAC reaction. Primary azides **4** and **6** were transformed to the corresponding products in high yields (70–98%) using standard conditions ($CuSO_4{\cdot}5H_2O$, NaAsc, THF–H_2O), while the reaction of more sterically hindered secondary azides **8** and **9** proved sensitive to the composition of the catalytic system. The use of $Cu(OAc)_2{\cdot}H_2O$ generally afforded more reliable results in these cases. Cu(II)-catalyzed α-ketol rearrangement was found to interfere in the coupling of **9** with 1-alkynes leading to exclusive formation of D-homoandrostanes **12** instead of **13** by a tandem CuAAC/rearrangement sequence. Prevention of Cu(I) oxidation and addition of TBTA led to acceleration of the CuAAC reaction and suppression of isomerization. Cu(II) appeared to be a rather weak Lewis acid that could facilitate D-homo rearrangement only of "activated" substrates. The compounds synthesized will be evaluated for their potential CYP17 inhibitory effect.

Experimental

General information

NMR spectra were recorded with a Bruker Avance 400 and an Agilent 400MR spectrometer (^{1}H 400 MHz, ^{13}C 100.6 MHz) at ambient temperature in $CDCl_3$ or in $CDCl_3$–DMSO-d_6, CCl_4–DMSO-d_6 and $CDCl_3$–CD_3OD mixtures for compounds with low solubility in $CDCl_3$. Chemical shifts are presented in ppm (δ scale) and referenced to hexamethyldisiloxane (δ = 0.05 ppm) in the ^{1}H NMR spectra and to the solvent signal in the ^{13}C NMR spectra. IR spectra were recorded with a Thermo Nicolet 200 FT-IR instrument in KBr pellets. MALDI-TOF spectra were recorded with a Bruker Daltonics UltraFlex instrument in a dithranol matrix using PEG 400 or PEG 600 as the internal standard. Elemental analyses were performed with an Elementar Vario MICRO cube apparatus. Column chromatography was carried out on Macherey–Nagel silica gel 60 (0.040–0.063 mm). Compounds **17a**,[34] **17b**,[35] **18a**[36] and **19c**[37] were prepared according to literature procedures.

Synthesis of azidosteroids

17α-(Azidomethyl)-17β-hydroxyandrost-4-en-3-one (4). In a vial with a screw cap, a mixture of **3** (1.572 g, 5.00 mmol), NaN_3 (1.30 g, 20.0 mmol), acetonitrile (5.0 mL), and water (5.0 mL) was stirred at 100 °C for 16 h. The solution was diluted with CH_2Cl_2 (50 mL), washed with water (2 × 50 mL), dried with anhydrous Na_2SO_4, and evaporated under vacuum. The residue was mixed with 95% ethanol (20 mL) and conc. HCl (1.0 mL) and stirred under reflux for 30 min. The solution was diluted with CH_2Cl_2 (100 mL), washed with satd. Na_2CO_3 (100 mL), water (2 × 100 mL), dried with anhydrous Na_2SO_4, and evaporated under vacuum. The residue was purified by column chromatography (eluent: CH_2Cl_2–MeOH = 50 : 1). Yield 1.551 g (90%). White solid; mp 154–156 °C (lit.,[21a] 153–155 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.72 (s, 1H, 4-CH), 3.52 (d, J = 12.1 Hz, 1H, CH_2N_3), 3.23 (d, J = 12.1 Hz, 1H, CH_2N_3), 2.47–2.30 (m, 3H), 2.26 (ddd, J = 14.7, 4.5, 2.5 Hz, 1H), 2.05–1.94 (m, 3H), 1.84 (m, 1H), 1.76–1.56 (m, 6H), 1.45 (qd, J = 12.6, 3.8 Hz, 1H), 1.36 (qd, J = 12.3, 7.1 Hz, 1H), 1.25–1.08 (m, 2H), 1.18 (s, 3H, 19-CH_3), 1.05–0.85 (m, 2H), 0.93 (s, 3H, 18-CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 199.4 [C(3)=O], 170.8 (5-C), 123.9 (4-CH), 83.2 (17-COH), 58.2 (CH_2N_3), 53.6, 50.7, 45.7 (quat.), 38.6 (quat.), 36.3, 35.7, 34.7, 33.9, 32.7, 31.7, 31.6, 23.5, 20.6, 17.3, 14.1; IR (KBr) ν = 3414 (OH), 2094 (N_3), 1657 (C=O) cm^{-1}; HRMS (MALDI-TOF) calcd for $C_{20}H_{30}NO_2$ $[M + H - N_2]^+$ 316.2277; found 316.2273.

21-Methanesulfonyloxy-17α-hydroxypregn-4-ene-3,20-dione (5a). A solution of **5** (1.386 g, 4.00 mmol) in a mixture of CH_2Cl_2 (40 mL) and triethylamine (1.23 mL, 8.80 mmol) was cooled to 0 °C in an ice bath. Then methanesulfonyl chloride (0.341 mL, 4.40 mmol) was added dropwise, and the solution was stirred at rt for 1 h. The mixture was diluted with CH_2Cl_2 (50 mL) and subsequently washed with HCl (10%, 100 mL), satd. Na_2CO_3 (100 mL), and water (100 mL). The organic layer was dried with anhydrous Na_2SO_4, and the solvents were evaporated under vacuum. The product was used in the synthesis of **6** without further purification. Yield 1.645 g (97%). White solid; ^{1}H NMR (400 MHz, $CDCl_3$–DMSO-d_6) δ 5.70 (s, 1H, 4-CH), 5.39 (d, J = 18.1 Hz, 1H, 21-CH_2OMs), 5.36 (d, J = 18.1 Hz, 1H, 21-CH_2OMs), 3.18 (s, 3H, SO_2CH_3), 2.63 (m, 1H), 2.47–2.21 (m, 4H), 2.03 (m, 1H), 1.94–1.24 (m, 12H), 1.18 (s, 3H, 19-CH_3), 1.08 (qd, J = 13.0, 4.0 Hz, 1H), 0.97 (m, 1H), 0.66 (s, 3H, 18-CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$–DMSO-d_6) δ 204.9 [C(20)=O], 199.1 [C(3)=O], 170.9 (5-C), 123.3 (4-CH), 89.0 (17-COH), 72.8 (21-CH$_2$OMs), 52.8, 49.9, 47.7 (quat.), 38.6 (SO_2CH_3), 38.1 (quat.), 35.2 (2C), 33.9, 33.5, 32.4, 31.6, 29.8, 23.2, 20.3, 16.9, 14.2.

21-Azido-17α-hydroxypregn-4-ene-3,20-dione (6). A suspension of **5a** (1.645 g, 3.87 mmol) and NaN_3 (1.040 g, 16.0 mmol) in acetone (50 mL) was heated for 6 h under reflux with stirring. The mixture was diluted with CH_2Cl_2 (100 mL), washed

with water (2 × 100 mL), dried with anhydrous Na_2SO_4, and evaporated under vacuum. The residue was purified by column chromatography (eluent: CH_2Cl_2–MeOH = 20 : 1). Yield 1.071 g (74%). White solid; mp 201–203 °C (dec.); ^{1}H NMR (400 MHz, $CDCl_3$–DMSO-d_6) δ 5.69 (s, 1H, 4-CH), 4.48 (d, J = 18.7 Hz, 1H, 21-CH_2N_3), 3.95 (d, J = 18.7 Hz, 1H, 21-CH_2N_3), 2.67 (ddd, J = 14.7, 11.6, 3.2 Hz, 1H), 2.49–2.22 (m, 4H), 2.03 (dt, J = 13.4, 4.0 Hz, 1H), 1.94–1.22 (m, 12H), 1.18 (s, 3H, 19-CH_3), 1.08 (qd, J = 13.0, 4.0 Hz, 1H), 0.97 (td, J = 11.4, 4.2 Hz, 1H), 0.65 (s, 3H, 18-CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$–DMSO-d_6) δ 206.9 [C(20)═O], 198.8 [C(3)═O], 170.7 (5-C), 123.1 (4-CH), 88.8 (17-COH), 55.5 (21-CH_2N_3), 52.6, 49.7, 47.1 (quat.), 38.0 (quat.), 35.0 (2C), 33.5, 33.3, 32.2, 31.4, 29.9, 23.0, 20.1, 16.8, 14.3; IR (KBr) ν = 3506 (OH), 2109 (N_3), 1718 [C(20)═O], 1654 [C(3)═O] cm^{-1}; HRMS (MALDI-TOF) calcd for $C_{21}H_{30}N_3O_3$ [M + H]$^+$ 372.2282; found 372.2287; Anal. calcd for $C_{21}H_{29}N_3O_3$: C, 67.90; H, 7.87; N, 11.31; found C, 67.92; H, 7.79; N, 11.52.

3β-Acetoxy-16β-azido-17α-hydroxy-17β-methyl-D-homoandrost-5-en-17a-one (8) and 3β-acetoxy-16β-azido-17α-hydroxypregn-5-en-20-one (9). A mixture of **7** (1.128 g, 3.00 mmol), NaN_3 (3.942 g, 60.6 mmol), and H_2SO_4 (98%, 186 μL) in DMSO (36 mL) was stirred at 100 °C for 132 h. The mixture was diluted with CH_2Cl_2 (100 mL), washed with satd. Na_2CO_3 (100 mL), water (3 × 100 mL), dried with anhydrous Na_2SO_4, and evaporated under vacuum. The residue was subjected to column chromatography (eluent: hexanes–EtOAc = 4 : 1) to afford pure products **8** and **9**.

3β-Acetoxy-16β-azido-17α-hydroxy-17β-methyl-D-homoandrost-5-en-17a-one (8). Yield 571.2 mg (46%). White solid; mp 208–210 °C (lit.,[21b] 209–210 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.36 (d, J = 4.4 Hz, 1H, 6-CH), 4.58 (tt, J = 11.4, 4.7 Hz, 1H, 3-C*H*OAc), 4.18 (s, 1H, OH), 3.52 (dd, J = 12.5, 4.6 Hz, 1H, 16-CHN_3), 2.39–2.13 (m, 3H), 2.02 [s, 3H, OC(O)CH_3], 2.01–1.82 (m, 3H), 1.72–0.93 (m, 11H), 1.40 (s, 3H, 17-CCH_3), 1.10 (s, 3H, 18-CH_3), 1.01 (s, 3H, 19-CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 215.3 [C(17a)═O], 170.4 [O*C*(O)CH_3], 139.6 (5-C), 121.4 (6-CH), 79.7 (17-COH), 73.5 (3-*C*HOAc), 69.6 (16-CHN_3), 48.8, 47.2, 46.3 (quat.), 37.7, 36.8 (quat.), 36.5, 32.6, 31.5, 30.6, 27.5, 27.1, 22.7, 21.4, 19.2 (2C), 15.8; IR (KBr) ν = 3505 (OH), 2130 (N_3), 1730 (C═O, ester), 1700 (C═O, ketone) cm^{-1}.

3β-Acetoxy-16β-azido-17α-hydroxypregn-5-en-20-one (9). Yield 310 mg (25%). White solid; mp 141–143 °C (lit.,[21b] 142.5–144.5 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.37 (d, J = 4.0 Hz, 1H, 6-CH), 4.58 (tt, J = 11.5, 5.4 Hz, 1H, 3-C*H*OAc), 3.95 (dd, J = 8.0, 6.2 Hz, 1H, 16-CHN_3), 3.62 (s, 1H, OH), 2.44–2.25 (m, 3H), 2.38 (s, 3H, 21-CH_3), 2.06–1.94 (m, 1H), 2.02 [s, 3H, OC(O)CH_3], 1.90–1.80 (m, 2H), 1.72–1.36 (m, 9H), 1.11 (td, J = 14.0, 4.5 Hz, 1H), 1.05–0.93 (m, 1H), 1.02 (br s, 6H, 18-CH_3, 19-CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 208.3 [C(20)═O], 170.5 [O*C*(O)CH_3], 139.7 (5-C), 122.0 (6-CH), 89.1 (17-COH), 73.7 (3-*C*HOAc), 69.5 (16-CHN_3), 49.4, 48.6, 47.6 (quat.), 38.0, 36.9, 36.6 (quat.), 33.1, 31.7, 31.1, 30.5, 29.5, 27.6, 21.4, 19.9, 19.3, 15.3; IR (KBr) ν = 3330–3490 (OH), 2125 (N_3), 1740 (C═O, ester), 1715 (C═O, ketone) cm^{-1}.

General procedure for copper-catalyzed 1,3-dipolar cycloaddition

Method A: In a vial with a screw cap, azidosteroid (0.200 mmol), $CuSO_4$·5H_2O (5.0 mg, 20 μmol, 10 mol%), and water (0.2 mL) were mixed. Then THF (0.8 mL), terminal alkyne (0.240 mmol), and sodium ascorbate (16.7 mg, 80 μmol, 40 mol%) were subsequently added. The reaction mixture was stirred at 50 °C for 12–24 h, diluted with CH_2Cl_2 (25 mL), and washed with water (2 × 25 mL). The organic layer was dried with anhydrous Na_2SO_4, and the solvents were evaporated under vacuum. The residue was purified by column chromatography.

Method B: In a vial with a screw cap, azidosteroid (0.200 mmol), terminal alkyne (0.240 mmol), $Cu(OAc)_2$·H_2O (2.0 mg, 10 μmol, 5 mol%), and triethylamine (27.8 μL, 0.200 mmol) were mixed under an Ar atmosphere in CH_2Cl_2 (1.0 mL). The reaction mixture was stirred at 50 °C for 12–24 h, diluted with CH_2Cl_2 (25 mL), and washed with water (2 × 25 mL). The organic layer was dried with anhydrous Na_2SO_4, and the solvents were evaporated under vacuum. The residue was purified by column chromatography.

Method C: Synthesis was performed as described for method **A** with the addition of 10 mol% of tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine (TBTA).

17β-Hydroxy-17α-{[4-(hydroxymethyl)-1*H*-1,2,3-triazol-1-yl]-methyl}androst-4-en-3-one (10a). Synthesized according to method **A** from **4** (68.7 mg, 0.200 mmol) and propargyl alcohol (14.0 μL, 0.240 mmol); heating 15 h; eluent: CH_2Cl_2–MeOH = 10 : 1. Yield 65.0 mg (81%). White solid; mp 236 °C; ^{1}H NMR (400 MHz, $CDCl_3$–DMSO-d_6) δ 7.87 [s, 1H, CH(triazole)], 5.66 (s, 1H, 4-CH), 5.00 (br t, J = 5.8 Hz, 1H, OH), 4.64 (m, 3H, CH_2OH, OH), 4.44 (d, J = 13.7 Hz, 1H, CH_2N), 4.25 (d, J = 13.7 Hz, 1H, CH_2N), 2.48–2.22 (m, 4H), 2.04 (ddd, J = 13.5, 5.0, 3.2 Hz, 1H), 1.88 (m, 1H), 1.76–1.17 (m, 11H), 1.21 (s, 3H, 19-CH_3), 1.09 (td, J = 12.5, 4.4 Hz, 1H), 1.01–0.96 (m, 1H), 0.94 (s, 3H, 18-CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$–DMSO-d_6) δ 197.4 [C(3)═O], 169.6 (5-C), 146.6 [C(triazole)], 122.9 [CH(triazole)], 122.3 (4-CH), 80.7 (17-COH), 54.9, 54.6, 52.1, 49.0, 44.8 (quat.), 37.2 (quat.), 35.0, 34.2, 32.6, 31.3, 30.3 (2C), 29.5, 22.1, 19.2, 16.0, 13.1; HRMS (MALDI-TOF) calcd for $C_{23}H_{34}N_3O_3$ [M + H]$^+$ 400.2595; found 400.2598; Anal. calcd for $C_{23}H_{33}N_3O_3$: C, 69.14; H, 8.33; N, 10.52; found C, 69.00; H, 8.38; N, 10.37.

17β-Hydroxy-17α-{[4-(1-hydroxy-1-methylethyl)-1*H*-1,2,3-triazol-1-yl]methyl}androst-4-en-3-one (10b). Synthesized according to method **A** from **4** (68.7 mg, 0.200 mmol) and 2-methylbut-3-yn-2-ol (23.3 μL, 0.240 mmol); heating 15 h; eluent: CH_2Cl_2–MeOH = 10 : 1. Yield 79.4 mg (93%). White solid; mp 129 °C; ^{1}H NMR (400 MHz, CCl_4–DMSO-d_6) δ 7.70 [s, 1H, CH(triazole)], 5.58 (s, 1H, 4-CH), 4.80 (s, 1H, OH), 4.62 (s, 1H, OH), 4.36 (d, J = 13.7 Hz, 1H, CH_2N), 4.14 (d, J = 13.7 Hz, 1H, CH_2N), 2.45–2.13 (m, 4H), 2.00 (m, 1H), 1.85 (m, 1H), 1.73–0.81 (m, 13H), 1.46 [s, 3H, C(CH_3)$_2$OH], 1.44 [s, 3H, C(CH_3)$_2$OH], 1.19 (s, 3H, 19-CH_3), 0.88 (s, 3H, 18-CH_3); ^{13}C NMR (100.6 MHz, CCl_4–DMSO-d_6) δ 196.8 [C(3)═O], 169.5 (5-C), 155.2 [C(triazole)],

123.2 (4-CH), 121.4 [CH(triazole)], 81.4 (17-COH), 67.1 [*C*(CH$_3$)$_2$OH], 55.5, 52.9, 49.6, 45.7 (quat.), 38.0 (quat.), 36.0, 35.1, 33.4, 32.1, 31.2, 30.9, 30.7, 30.4, 30.3, 23.0, 20.1, 16.9, 14.0; HRMS (MALDI-TOF) calcd for $C_{25}H_{37}N_3NaO_3$ [M + Na]$^+$ 450.2733; found 450.2732; Anal. calcd for $C_{25}H_{37}N_3O_3$: C, 70.22; H, 8.72; N, 9.83; found C, 69.88; H, 8.65; N, 9.62.

17β-Hydroxy-17α-[(4-butyl-1*H*-1,2,3-triazol-1-yl)methyl]androst-4-en-3-one (10c). Synthesized according to method **A** from **4** (68.7 mg, 0.200 mmol) and hex-1-yne (27.6 μL, 0.240 mmol); heating 15 h; eluent: CH_2Cl_2–Et_2O = 4 : 1. Yield 59.8 mg (70%). White solid; mp 95–96 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 [s, 1H, CH(triazole)], 5.72 (s, 1H, 4-CH), 4.42 (d, J = 13.7 Hz, 1H, CH_2N), 4.32 (d, J = 13.7 Hz, 1H, CH_2N), 2.69 (t, J = 7.7 Hz, 2H, CH_2Pr), 2.47–2.28 (m, 3H), 2.27 (ddd, J = 15.1, 4.7, 3.1 Hz, 1H), 2.02 (ddd, J = 13.4, 5.0, 3.2 Hz, 1H), 1.86 (m, 1H), 1.76–1.12 (m, 14H), 1.20 (s, 3H, 19-CH_3), 1.10–0.86 (m, 2H), 1.11–0.89 (m, 2H), 0.94 (s, 3H, 18-CH_3), 0.91 (t, J = 7.4 Hz, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 199.3 [C(3)═O], 170.9 (5-C), 147.8 [C(triazole)], 123.8 (4-CH), 122.9 [CH(triazole)], 82.6 (17-COH), 56.2, 53.5, 50.2, 46.0 (quat.), 38.5 (quat.), 36.2, 35.5, 33.7, 32.6 (2C), 31.4, 31.3, 30.8, 25.2, 23.4, 22.1, 20.4, 17.2, 14.0, 13.7; IR (KBr) ν = 3311 (OH), 1660 (C═O) cm^{-1}; HRMS (MALDI-TOF) calcd for $C_{26}H_{40}N_3O_2$ [M + H]$^+$ 426.3115; found 426.3110; Anal. calcd for $C_{26}H_{39}N_3O_2$: C, 73.37; H, 9.24; N, 9.87; found C, 73.32; H, 9.10; N, 9.72.

17β-Hydroxy-17α-({4-[(diethylamino)methyl]-1*H*-1,2,3-triazol-1-yl}methyl)androst-4-en-3-one (10d). Synthesized according to method **A** from **4** (68.7 mg, 0.200 mmol) and *N*,*N*-diethylpropargylamine (33.3 μL, 0.240 mmol); heating 16 h; eluent: CH_2Cl_2–MeOH = 10 : 1. Yield 87.3 mg (96%). Light-yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 [s, 1H, CH(triazole)], 5.73 (s, 1H, 4-CH), 4.43 [d, J = 13.8 Hz, 1H, CH_2N(triazole)], 4.33 [d, J = 13.8 Hz, 1H, CH_2N(triazole)], 3.84 (s, 2H, CH_2NEt$_2$), 3.20 (br s, 1H, OH), 2.59 [q, J = 7.0 Hz, 4H, N(CH_2CH$_3$)$_2$], 2.47–2.24 (m, 4H), 2.02 (ddd, J = 13.5, 4.9, 3.4 Hz, 1H), 1.86 (m, 1H), 1.76–0.77 (m, 14H), 1.20 (s, 3H, 19-CH_3), 1.10 [t, J = 7.0 Hz, 6H, N(CH$_2$CH_3)$_2$], 0.98 (s, 3H, 18-CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 199.3 [C(3)═O], 170.7 (5-C), 143.6 [C(triazole)], 125.2 [4-CH or CH(triazole)], 123.9 [4-CH or CH(triazole)], 82.7 (17-COH), 56.4, 53.6, 50.3, 47.4 (*C*H$_2$NEt$_2$), 46.6 [2C, N(*C*H$_2$CH$_3$)$_2$], 46.1 (quat.), 38.5 (quat.), 36.3, 35.6, 33.8, 33.0, 32.6, 31.5, 30.9, 23.5, 20.5, 17.3, 14.1 [2C, N(CH$_2$*C*H$_3$)$_2$], 11.4; HRMS (MALDI-TOF) calcd for $C_{27}H_{43}N_4O_2$ [M + H]$^+$ 455.3381; found 455.3387.

17β-Hydroxy-17α-[(4-phenyl-1*H*-1,2,3-triazol-1-yl)methyl]androst-4-en-3-one (10e). Synthesized according to method **A** from **4** (68.7 mg. 0.200 mmol) and phenylacetylene (26.4 μL, 0.240 mmol); heating 14 h; eluent: CH_2Cl_2–MeOH = 50 : 1. Yield 82.9 mg (93%). White solid; mp 282 °C (dec.); ^{1}H NMR (400 MHz, $CDCl_3$–DMSO-d_6) δ 8.19 [s, 1H, CH(triazole)], 7.81 [d, J = 7.8 Hz, 2H, 2,6-CH(Ph)], 7.40 [t, J = 7.8 Hz, 2H, 3,5-CH (Ph)], 7.29 [t, J = 7.6 Hz, 1H, 4-CH(Ph)], 5.69 (s, 1H, 4-CH), 4.56 (s, 1H, OH), 4.51 (d, J = 13.7 Hz, 1H, CH_2N), 4.32 (d, J = 13.7 Hz, 1H, CH_2N), 2.48–2.24 (m, 4H), 2.04 (ddd, J = 13.4, 5.0, 3.1 Hz, 1H), 1.88 (m, 1H), 1.78–0.92 (m, 13H), 1.21 (s, 3H, 19-CH_3), 0.97 (s, 3H, 18-CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$–DMSO-d_6) δ 198.1 [C(3)═O], 170.1 (5-C), 145.9 [C(triazole)], 130.1 [1-C(Ph)], 127.9 [2C, 3,5-CH(Ph)], 126.9 [4-CH(Ph)], 124.5 [2C, 2,6-CH(Ph)], 122.8 (4-CH), 121.4 [CH(triazole)], 81.3 (17-COH), 55.6, 52.7, 49.5, 45.4 (quat.), 37.7 (quat.), 35.5, 34.7, 33.0, 31.8, 31.0, 30.7, 30.1, 22.6, 19.7, 16.5, 13.5; IR (KBr) ν = 3630–3200 (OH), 1676 (C═O), 771 (Ar) cm^{-1}; HRMS (MALDI-TOF) calcd for $C_{28}H_{36}N_3O_2$ [M + H]$^+$ 446.2802; found 446.2798; Anal. calcd for $C_{28}H_{35}N_3O_2$: C, 75.47; H, 7.92; N, 9.43; found C, 75.62; H, 7.63; N, 9.22.

17β-Hydroxy-17α-{[4-(4-nitrophenyl)-1*H*-1,2,3-triazol-1-yl]-methyl}androst-4-en-3-one (10f). Synthesized according to method **A** from **4** (68.7 mg, 0.200 mmol) and (4-nitrophenyl) acetylene (35.3 mg, 0.240 mmol); heating 15 h; eluent: CH_2Cl_2–MeOH = 50 : 1. Yield 87.7 mg (89%). White solid; mp 249 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 [d, J = 8.7 Hz, 2H, 3,5-CH(Ar)], 8.22 [s, 1H, CH(triazole)], 7.99 [d, J = 8.7 Hz, 2H, 2,6-CH(Ar)], 5.72 (s, 1H, 4-CH), 4.56 (d, J = 13.7 Hz, 1H, CH_2N), 4.39 (d, J = 13.7 Hz, 1H, CH_2N), 2.60 (m, 1H), 2.47–2.24 (m, 4H), 2.03 (ddd, J = 13.3, 4.9, 3.3 Hz, 1H), 1.87 (m, 1H), 1.82–1.61 (m, 6H), 1.51 (qd, J = 12.9, 3.8 Hz, 1H), 1.57–1.17 (m, 4H), 1.20 (s, 3H, 19-CH_3), 1.10–0.91 (m, 2H), 1.01 (s, 3H, 18-CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 199.4 [C(3)═O], 170.7 (5-C), 147.1 [C(triazole) or 4-C(Ar)], 145.2 [C(triazole) or 4-C(Ar)], 137.0 [1-C(Ar)], 126.0 [2C, CH(Ar)], 124.2 [2C, CH(Ar)], 124.0 [CH(triazole) or 4-CH], 123.5 [CH(triazole) or 4-CH], 82.9 (17-COH), 56.5, 53.6, 50.3, 46.1 (quat.), 38.5 (quat.), 36.4, 35.6, 33.8, 33.3, 32.6, 31.5, 30.9, 23.5, 20.5, 17.3, 14.0; IR (KBr) ν = 3400 (OH), 1654 (C═O), 1517 (NO_2), 1334 (NO_2), 852 (C–N) cm^{-1}; HRMS (MALDI-TOF) calcd for $C_{28}H_{34}N_4NaO_4$ [M + Na]$^+$ 513.2478; found 513.2473; Anal. calcd for $C_{28}H_{34}N_4O_4$: C, 68.55; H, 6.99; N, 11.42; found C, 68.26; H, 6.93; N, 11.41.

17β-Hydroxy-17α-[(4-ferrocenyl-1*H*-1,2,3-triazol-1-yl)methyl]-androst-4-en-3-one (10g). Synthesized according to method **A** from **4** (68.7 mg, 0.200 mmol) and ethynylferrocene (50.4 mg, 0.240 mmol); heating 16 h; eluent: CH_2Cl_2–MeOH = 50 : 1. Yield 101.2 mg (91%). Orange solid; mp 235 °C (dec.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 [s, 1H, CH(triazole)], 5.73 (s, 1H, 4-CH), 4.77 (br s, 1H, C_5H_4), 4.73 (br s, 1H, C_5H_4), 4.42 (d, J = 13.8 Hz, 1H, CH_2N), 4.32 (m, 3H, 1H, CH_2N + 2H, C_5H_4), 4.07 (s, 5H, C_5H_5), 2.91 (s, 1H, 17-COH), 2.48–2.24 (m, 4H), 2.01 (ddd, J = 13.5, 4.6, 3.8 Hz, 1H), 1.90–0.87 (m, 14H), 1.19 (s, 3H, 19-CH_3), 1.00 (s, 3H, 18-CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 199.4 [C(3)═O], 170.7 (5-C), 146.4 [C(triazole)], 124.0 (4-CH), 121.2 [CH(triazole)], 83.0 (17-COH), 75.9 (quat., C_5H_4), 69.8 (5C, C_5H_5), 68.9 (2C, C_5H_4), 66.74 (1C, C_5H_4), 66.69 (1C, C_5H_4), 56.3, 53.6, 50.3, 46.1 (quat.), 38.6 (quat.), 36.4, 35.7, 33.9, 33.3, 32.7, 31.5, 31.0, 23.5, 20.5, 17.3, 14.1; HRMS (MALDI-TOF) calcd for $C_{32}H_{39}FeN_3NaO_2$ [M + Na]$^+$ 576.2289; found 576.2292; Anal. calcd for $C_{32}H_{39}FeN_3O_2$: C, 69.44; H, 7.10; N, 7.59; found C, 69.61; H, 7.21; N, 7.57.

21-(4-Phenyl-1*H*-1,2,3-triazol-1-yl)-17α-hydroxypregn-4-ene-3,20-dione (11a). Synthesized according to method **A** from **6** (74.3 mg, 0.200 mmol) and phenylacetylene (26.4 μL, 0.240 mmol); heating 14 h; eluent: CH_2Cl_2–MeOH = 20 : 1. Yield 81.2 mg (86%). White solid; mp 254–255 °C; ^{1}H NMR (400 MHz, $CDCl_3$–DMSO-d_6) δ 7.89 [s, 1H, CH(triazole)], 7.83 [d, J = 7.2 Hz, 2H, 2,6-CH(Ph)], 7.41 [t, J = 7.2 Hz, 2H, 3,5-CH

(Ph)], 7.32 [t, J = 6.9 Hz, 1H, 4-CH(Ph)], 5.74 (d, J = 18.4 Hz, 1H, 21-CH_2N), 5.71 (s, 1H, 4-CH), 5.38 (d, J = 18.4 Hz, 1H, 21-CH_2N), 4.57 (br s, 1H, OH), 2.68 (t, J = 12.9 Hz, 1H), 2.49–2.20 (m, 4H), 2.11–1.97 (m, 2H), 1.94–0.79 (m, 12H), 1.18 (s, 3H, 19-CH_3), 0.66 (s, 3H, 18-CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$–DMSO-d_6) δ 204.0 [C(20)═O], 199.2 [C(3)═O], 170.9 (5-C), 147.1 [C(triazole)], 130.1 [1-C(Ph)], 128.5 [2C, 3,5-CH(Ph)], 127.8 [4-CH(Ph)], 125.4 [2C, 2,6-CH(Ph)], 123.4 (4-CH), 121.4 [CH(triazole)], 89.3 (17-COH), 56.6 (21-CH_2N), 52.8, 50.1, 47.6 (quat.), 38.2 (quat.), 35.3 (2C), 33.9, 33.6, 32.4, 31.7, 30.3, 23.3, 20.4, 17.0, 14.6; HRMS (MALDI-TOF) calcd for $C_{29}H_{36}N_3O_3$ $[M + H]^+$ 474.2751; found 474.2748; Anal. calcd for $C_{29}H_{35}N_3O_3$: C, 73.54; H, 7.45; N, 8.87; found C, 73.36; H, 7.31; N, 8.71.

21-(4-Butyl-1*H*-1,2,3-triazol-1-yl)-17α-hydroxypregn-4-ene-3,20-dione (11b). Synthesized according to method **A** from **6** (74.3 mg, 0.200 mmol) and hex-1-yne (27.6 μL, 0.240 mmol); heating 22 h; eluent CH_2Cl_2–MeOH = 20 : 1. Yield 88.8 mg (98%). White solid; mp 115–117 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 [s, 1H, CH(triazole)], 5.72 (s, 1H, 4-CH), 5.71 (d, J = 18.4 Hz, 1H, 21-CH_2N), 5.30 (d, J = 18.4 Hz, 1H, 21-CH_2N), 4.62 (br s, 1H, OH), 2.70 [t, J = 7.6 Hz, 2H, CH_2Pr], 2.67 (m, 1H), 2.48–2.23 (m, 4H), 2.09–1.97 (m, 2H), 1.92–1.56 (m, 9H), 1.51–0.80 (m, 7H), 1.18 (s, 3H, 19-CH_3), 0.91 (t, J = 7.3 Hz, 3H, CH_2CH_3), 0.66 (s, 3H, 18-CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 204.1 [C(20)═O], 199.8 [C(3)═O], 171.5 (5-C), 148.1 [C(triazole)], 123.7 (4-CH), 122.6 [CH(triazole)], 89.8 (17-COH), 56.8 (21-CH_2N), 53.2, 50.4, 48.1 (quat.), 38.5 (quat.), 35.6 (2C), 34.4, 33.8, 32.7, 31.9, 31.3, 30.6, 25.1, 23.5, 22.2, 20.6, 17.3, 14.9, 13.7; HRMS (MALDI-TOF) calcd for $C_{27}H_{39}N_3NaO_3$ $[M + Na]^+$ 476.2889; found 476.2888; Anal. calcd for $C_{27}H_{39}N_3O_3$: C, 71.49; H, 8.67; N, 9.26; found C, 71.70; H, 8.86; N, 8.70.

21-[4-(Hydroxymethyl)-1*H*-1,2,3-triazol-1-yl]-17α-hydroxypregn-4-ene-3,20-dione (11c). Synthesized according to method **A** from **6** (74.3 mg, 0.200 mmol) and propargyl alcohol (14.0 μL, 0.240 mmol); heating 22 h; eluent: CH_2Cl_2–MeOH = 10 : 1. Yield 84.2 mg (98%). White solid; mp 248–251 °C; ^{1}H NMR (400 MHz, $CDCl_3$–DMSO-d_6) δ 7.65 [s, 1H, CH(triazole)], 5.68 (s, 1H, 4-CH), 5.66 (d, J = 18.6 Hz, 1H, 21-CH_2N), 5.30 (d, J = 18.6 Hz, 1H, 21-CH_2N), 4.70 (s, 2H, CH_2OH), 4.22 (br s, 2H, OH), 2.63 (m, 1H), 2.49–2.22 (m, 4H), 2.11–1.95 (m, 2H), 1.93–0.78 (m, 12H), 1.19 (s, 3H, 19-CH_3), 0.63 (s, 3H, 18-CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$–DMSO-d_6) δ 203.5 [C(20)═O], 198.1 [C(3)═O], 170.2 (5-C), 147.4 [C(triazole)], 122.9 [4-CH or CH(triazole)], 122.7 [4-CH or CH(triazole)], 88.4 (17-COH), 55.7 (21-CH_2N), 55.0 (CH_2OH), 52.2, 49.3, 46.8 (quat.), 37.5 (quat.), 34.6 (2C), 33.0, 32.9, 31.7, 31.0, 29.6, 22.6, 19.7, 16.4, 13.9; HRMS (MALDI-TOF) calcd for $C_{24}H_{34}N_3O_4$ $[M + H]^+$ 428.2544; found 428.2544; Anal. calcd for $C_{24}H_{33}N_3O_4$: C, 67.42; H, 7.78; N, 9.83; found C, 67.33; H, 7.77; N, 9.77.

3β-Acetoxy-16β-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-17α-hydroxy-17β-methyl-D-homoandrost-5-en-17a-one (12a). Synthesized according to method **B** from **8** (41.6 mg, 0.100 mmol) and phenylacetylene (13.2 μL, 0.120 mmol); heating 18 h; eluent: CH_2Cl_2–Et_2O = 20 : 1. Yield 40.7 mg (79%). White solid; mp >300 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 [s, 1H, CH(triazole)], 7.85 [d, J = 7.8 Hz, 2H, 2,6-CH(Ph)], 7.41 [t, J = 7.6 Hz, 2H, 3,5-CH(Ph)], 7.31 [t, J = 7.2 Hz, 1H, 4-CH(Ph)], 5.36 (m, 1H, 6-CH), 4.59 (tt, J = 11.7, 4.5 Hz, 1H, 3-C*H*OAc), 4.41 (dd, J = 12.6, 3.8 Hz, 1H, 16-CH), 4.31 (br s, 1H, OH), 2.65 (q, J = 12.9 Hz, 1H, 15β-CH), 2.51 (m, 1H, 15α-CH), 2.40–2.23 (m, 3H), 2.04 (m, 1H), 2.02 [s, 3H, OC(O)CH_3], 1.92–1.83 (m, 2H), 1.80–1.42 (m, 6H), 1.37–0.98 (m, 3H), 1.23 (s, 3H, 17-CCH_3), 1.08 (s, 3H, 18-CH_3), 1.05 (s, 3H, 19-CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 215.1 [C(17a)═O], 170.5 [O*C*(O)CH_3], 147.2 [C(triazole)], 139.5 (5-C), 130.6 [1-C(Ph)], 128.8 [2C, CH(Ph)], 128.1 [4-CH(Ph)], 125.7 [2C, CH(Ph)], 121.5 [2C, 6-CH, CH(triazole)], 78.6 (17-COH), 73.5 (3-*C*HOAc), 68.9 (16-CH), 48.9, 48.0, 46.7 (quat.), 37.7, 36.8 (quat.), 36.6, 32.7, 31.6, 30.8, 27.6, 25.6, 22.9, 21.4, 19.3 (2C), 15.9; HRMS (MALDI-TOF) calcd for $C_{31}H_{40}N_3O_4$ $[M + H]^+$ 518.3013; found 518.3018; Anal. calcd for $C_{31}H_{39}N_3O_4$: C, 71.93; H, 7.59; N, 8.12; found C, 71.71; H, 7.57; N, 7.74.

3β-Acetoxy-16β-(4-butyl-1*H*-1,2,3-triazol-1-yl)-17α-hydroxy-17β-methyl-D-homoandrost-5-en-17a-one (12b). Synthesized according to method **B** from **8** (83.1 mg, 0.200 mmol) and hex-1-yne (27.6 μL, 0.240 mmol); heating 22 h. Yield 83.5 mg (84%). Synthesized according to method **B** from **9** (83.1 mg, 0.200 mmol) and hex-1-yne (27.6 μL, 0.240 mmol); heating 22 h; eluent: CH_2Cl_2–MeOH = 100 : 1. Yield 89.2 mg (90%). White solid; mp 234–236 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 [s, 1H, CH(triazole)], 5.35 (m, 1H, 6-CH), 4.58 (m, 1H, 3-C*H*OAc), 4.32 (dd, J = 12.9, 4.3 Hz, 1H, 16-CH), 4.29 (s, 1H, OH), 2.72 [m, 2H, CH_2Pr], 2.61 (q, J = 13.5 Hz, 1H, 15β-CH), 2.45 (m, 1H, 15α-CH), 2.38–2.22 (m, 3H), 2.05–1.97 (m, 1H), 2.02 [s, 3H, OC(O)CH_3], 1.93–1.83 (m, 2H), 1.79–1.43 (m, 8H), 1.37 (sextet, J = 7.5 Hz, 2H, CH_2CH_3), 1.32–0.98 (m, 3H), 1.22 (s, 3H, 17-CCH_3), 1.04 (s, 3H, 18-CH_3), 1.03 (s, 3H, 19-CH_3), 0.92 (t, J = 7.4 Hz, 3H, CH_2CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 215.2 [C(17a)═O], 170.4 [O*C*(O)CH_3], 147.8 [C(triazole)], 139.5 (5-C), 122.4 [CH(triazole)], 121.4 (6-CH), 78.6 (17-COH), 73.5 (3-*C*HOAc), 68.5 (16-CH), 48.9, 47.9, 46.7 (quat.), 37.7, 36.8 (quat.), 36.5, 32.7, 31.6, 31.5, 30.7, 27.5, 25.5, 25.3, 22.8, 22.2, 21.3, 19.23, 19.18, 15.8, 13.8; HRMS (MALDI-TOF) calcd for $C_{29}H_{43}N_3NaO_4$ $[M + Na]^+$ 520.3151; found 520.3153; Anal. calcd for $C_{29}H_{43}N_3O_4$: C, 69.99; H, 8.71; N, 8.44; found C, 70.12; H, 8.94; N, 8.27.

3β-Acetoxy-16β-[4-(hydroxymethyl)-1*H*-1,2,3-triazol-1-yl]-17α-hydroxy-17β-methyl-D-homoandrost-5-en-17a-one (12c). Synthesized according to method **A** from **8** (83.1 mg, 0.200 mmol) and propargyl alcohol (14.0 μL, 0.240 mmol); heating 14 h. Yield 79.0 mg (84%). Synthesized according to method **B** from **9** (83.1 mg, 0.200 mmol) and propargyl alcohol (14.0 μL, 0.240 mmol); heating 22 h; eluent: CH_2Cl_2–MeOH = 20 : 1. Yield 92.1 mg (98%). White solid; mp 274–275 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 [s, 1H, CH(triazole)], 5.35 (m, 1H, 6-CH), 4.80 (br s, 2H, CH_2OH), 4.58 (tt, J = 12.1, 4.8 Hz, 1H, 3-C*H*OAc), 4.38 (s, 1H, OH), 4.37 (dd, J = 12.6, 4.2 Hz, 1H, 16-CH), 3.03 (s, 1H, OH), 2.60 (q, J = 13.4 Hz, 1H, 15β-CH), 2.44 (m, 1H, 15α-CH), 2.38–2.21 (m, 3H), 2.05–1.98 (m, 1H), 2.02 [s, 3H, OC(O)CH_3], 1.95–1.83 (m, 2H), 1.77–1.41 (m, 6H), 1.34–0.98 (m, 3H), 1.22 (s, 3H, 17-CCH_3), 1.04 (br s, 6H, 18-CH_3, 19-CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 214.9 [C(17a)═O], 170.5 [O*C*(O)CH_3], 147.0 [C(triazole)], 139.6 (5-C), 123.5

[CH(triazole)], 121.4 (6-CH), 78.5 (17-COH), 73.5 (3-*C*HOAc), 68.8 (16-CH), 56.4 (CH_2OH), 48.9, 47.9, 46.7 (quat.), 37.7, 36.8 (quat.), 36.5, 32.7, 31.6, 30.7, 27.6, 25.6, 22.8, 21.3, 19.2 (2C), 15.9; ^{1}H NMR (400 MHz, $CDCl_3$–CD_3OD) δ 7.79 [s, 1H, CH(triazole)], 5.35 (m, 1H, 6-CH), 4.73 (s, 2H, CH_2OH), 4.57 (tt, J = 11.1, 4.9 Hz, 1H, 3-C*H*OAc), 4.38 (s, 1H, OH), 4.43 (dd, J = 12.9, 4.1 Hz, 1H, 16-CH), 3.08 (br s, 2H, OH), 2.57 (q, J = 13.4 Hz, 1H, 15β-CH), 2.40 (m, 1H, 15α-CH), 2.37–2.20 (m, 3H), 2.04–1.98 (m, 1H), 2.02 [s, 3H, OC(O)CH_3], 1.93–1.83 (m, 2H), 1.78–1.40 (m, 6H), 1.32 (ddd, J = 12.9, 10.3, 2.7 Hz, 1H, 14-CH), 1.26–0.98 (m, 2H), 1.21 (s, 3H, 17-CCH_3), 1.04 (s, 3H, 19-CH_3), 1.03 (s, 3H, 18-CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$–CD_3OD) δ 214.8 [C(17a)═O], 170.6 [O*C*(O)CH_3], 147.0 [C(triazole)], 139.3 (5-C), 123.7 [CH(triazole)], 121.3 (6-CH), 78.3 (17-COH), 73.5 (3-*C*HOAc), 68.5 (16-CH), 55.7 (CH_2OH), 48.7 (9-CH), 47.6 (14-CH), 46.6 (13-C), 37.5, 36.6 (10-C), 36.3, 32.5, 31.4, 30.5, 27.4, 25.5 (15-CH or 17-C*C*H_3), 22.6 (15-CH or 17-C*C*H_3), 21.2, 19.1, 19.0, 15.8 (18-CH_3); HRMS (MALDI-TOF) calcd for $C_{26}H_{37}N_3NaO_5$ $[M + Na]^+$ 494.2631; found 494.2614; Anal. calcd for $C_{26}H_{37}N_3O_5$: C, 66.22; H, 7.91; N, 8.91; found C, 66.10; H, 8.12; N, 8.79.

3β-Acetoxy-16β-{4-[(diethylamino)methyl]-1*H*-1,2,3-triazol-1-yl}-17α-hydroxy-17β-methyl-D-homoandrost-5-en-17a-one (12d). Synthesized according to method **B** from **8** (62.3 mg, 0.150 mmol) and *N*,*N*-diethylpropargylamine (24.7 μL, 0.180 mmol); heating 20 h; eluent: CH_2Cl_2–MeOH = 10 : 1. Yield 63.7 mg (81%). White solid; mp 249–250 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 [s, 1H, CH(triazole)], 5.35 (m, 1H, 6-CH), 4.58 (tt, J = 11.5, 4.8 Hz, 1H, 3-C*H*OAc), 4.38 (dd, J = 12.9, 4.0 Hz, 1H, 16-CH), 3.98 (d, J = 14.2 Hz, 1H, CH_2NEt$_2$), 3.92 (d, J = 14.2 Hz, 1H, CH_2NEt$_2$), 2.74–2.62 [m, 4H, N(CH_2CH$_3$)$_2$], 2.58 (q, J = 13.2 Hz, 1H, 15β-CH), 2.44 (m, 1H, 15α-CH), 2.39–2.21 (m, 3H), 2.06–1.97 (m, 1H), 2.02 [s, 3H, OC(O)CH_3], 1.92–1.83 (m, 2H), 1.78–1.42 (m, 6H), 1.34–0.98 (m, 4H), 1.22 (s, 3H, 17-CCH_3), 1.10 [t, J = 7.1 Hz, 6H, N(CH$_2$CH_3)$_2$], 1.04 (s, 3H, 18-CH_3), 1.03 (s, 3H, 19-CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 214.9 [C(17a)═O], 170.4 [O*C*(O)CH_3], 142.2 [C(triazole)], 139.5 (5-C), 125.2 [CH(triazole)], 121.4 (6-CH), 78.4 (17-COH), 73.4 (3-*C*HOAc), 68.7 (16-CH), 48.8, 47.9, 47.0, 46.7 (quat.), 46.5 [2C, N(*C*H$_2$CH$_3$)$_2$], 37.7, 36.8 (quat.), 36.5, 32.7, 31.5, 30.7, 27.5, 25.5, 22.8, 21.3, 19.2 (2C), 15.9, 11.1 [2C, N(CH$_2$*C*H$_3$)$_2$]; HRMS (MALDI-TOF) calcd for $C_{30}H_{46}N_4NaO_4$ $[M + Na]^+$ 549.3417; found 549.3425.

3β-Acetoxy-16β-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-17α-hydroxypregn-5-en-20-one (13a). Synthesized according to method **A** from **9** (83.1 mg, 0.200 mmol) and phenylacetylene (26.4 μL, 0.240 mmol); heating 14 h; eluent: CH_2Cl_2–MeOH = 50 : 1. Yield 98.1 mg (95%). White solid; mp >300 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 [d, J = 7.3 Hz, 2H, 2,6-CH(Ph)], 7.79 [s, 1H, CH(triazole)], 7.41 [t, J = 7.5 Hz, 2H, 3,5-CH(Ph)], 7.32 [t, J = 7.4 Hz, 1H, 4-CH(Ph)], 5.39 (d, J = 4.7 Hz, 1H, 6-CH), 4.97 (t, J = 9.0 Hz, 1H, 16-CH), 4.61 (m, 1H, 3-C*H*OAc), 4.50 (s, 1H, OH), 2.61 (td, J = 12.5, 9.7 Hz, 1H, 15β-CH), 2.48 (ddd, J = 12.5, 8.4, 5.2 Hz, 1H, 15α-CH), 2.39–2.26 (m, 2H), 2.08 (m, 1H), 2.03 [s, 3H, OC(O)CH_3], 1.92–1.55 (m, 8H), 1.59 (qd, J = 13.4, 4.3 Hz, 1H), 1.67 (s, 3H, 21-CH_3), 1.33–1.01 (m, 3H), 1.14 (s, 3H, 18-CH_3), 1.06 (s, 3H, 19-CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 208.8 [C(20)═O], 170.5 [O*C*(O)CH_3], 147.9 [C(triazole)], 139.8 (5-C), 130.2 [1-C(Ph)], 128.8 [2C, CH(Ph)], 128.3 [4-CH(Ph)], 125.7 [2C, CH(Ph)], 121.9 (6-CH), 120.9 [CH(triazole)], 90.4 (17-COH), 73.7 (3-*C*HOAc), 71.3 (16-CH), 49.3, 49.2 (quat.), 48.7, 38.0, 36.9, 36.6 (quat.), 31.9, 31.7, 30.9, 30.6, 27.9, 27.6, 21.4, 20.1, 19.3, 15.9; HRMS (MALDI-TOF) calcd for $C_{31}H_{40}N_3O_4$ $[M + H]^+$ 518.3013; found 518.3020; Anal. calcd for $C_{31}H_{39}N_3O_4$: C, 71.93; H, 7.59; N, 8.12; found C, 72.02; H, 7.78; N, 8.12.

3β-Acetoxy-16β-(4-butyl-1*H*-1,2,3-triazol-1-yl)-17α-hydroxypregn-5-en-20-one (13b). Synthesized according to method **C** from **9** (58.2 mg, 0.140 mmol) and hex-1-yne (19.3 μL, 0.168 mmol); heating 19 h; eluent: CH_2Cl_2–MeOH = 50 : 1. Yield 62.4 mg (90%). White solid; mp 164–166 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 [s, 1H, CH(triazole)], 5.38 (d, J = 3.9 Hz, 1H, 6-CH), 4.92 (t, J = 8.7 Hz, 1H, 16-CH), 4.60 (tt, J = 11.7, 4.6 Hz, 1H, 3-C*H*OAc), 2.71 [t, J = 7.6 Hz, 2H, CH_2Pr], 2.60 (td, J = 12.8, 9.3 Hz, 1H, 15β-CH), 2.43 (ddd, J = 12.8, 8.6, 5.2 Hz, 1H, 15α-CH), 2.38–2.25 (m, 2H), 2.07 (m, 1H), 2.03 [s, 3H, OC(O)CH_3], 1.91–1.54 (m, 10H), 1.62 (s, 3H, 21-CH_3), 1.48 (qd, J = 13.0, 4.5 Hz, 1H), 1.36 (sextet, J = 7.3 Hz, 2H, $CH_2CH_2CH_3$), 1.29–1.13 (m, 4H), 1.10 (s, 3H, 18-CH_3), 1.05 (s, 3H, 19-CH_3), 0.91 (t, J = 7.3 Hz, 3H, CH_2CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 209.0 [C(20)═O], 170.5 [O*C*(O)CH_3], 148.1 [C(triazole)], 139.7 (5-C), 122.3 [CH(triazole)], 121.8 (6-CH), 89.7 (17-COH), 73.6 (3-*C*HOAc), 71.0 (16-CH), 49.2, 48.7 (quat.), 48.4, 37.9, 36.8, 36.5 (quat.), 31.9, 31.6, 31.4, 30.9, 30.7, 28.1, 27.6, 25.1, 22.2, 21.3, 20.1, 19.2, 15.6, 13.7; HRMS (MALDI-TOF) calcd for $C_{29}H_{43}N_3NaO_4$ $[M + Na]^+$ 520.3151; found 520.3147; Anal. calcd for $C_{29}H_{43}N_3O_4$: C, 69.99; H, 8.71; N, 8.44; found C, 69.84; H, 8.79; N, 8.19.

3β-Acetoxy-16β-[4-(hydroxymethyl)-1*H*-1,2,3-triazol-1-yl]-17α-hydroxypregn-5-en-20-one (13c). Synthesized according to method **C** from **9** (58.2 mg, 0.140 mmol) and propargyl alcohol (9.8 μL, 0.168 mmol); heating 20 h; eluent: CH_2Cl_2–MeOH = 20 : 1. Yield 62.0 mg (94%). White solid; mp 219–221 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 [br s, 1H, CH(triazole)], 5.37 (m, 1H, 6-CH), 4.98 (m, 1H, 16-CH), 4.74 (br s, 2H, CH_2OH), 4.60 (tt, J = 11.3, 4.9 Hz, 1H, 3-C*H*OAc), 3.86 (br s, 2H, OH), 2.54–2.24 (m, 4H), 2.05 (m, 1H), 2.03 [s, 3H, OC(O)CH_3], 1.92–1.40 (m, 8H), 1.82 (s, 3H, 21-CH_3), 1.38–0.78 (m, 4H), 1.04 (s, 3H, 19-CH_3), 0.98 (s, 3H, 18-CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 209.9 [C(20)═O], 170.6 [O*C*(O)CH_3], 147.7 [C(triazole)], 139.7 (5-C), 129.1 [CH(triazole)], 121.8 (6-CH), 89.1 (17-COH), 73.7 (3-*C*HOAc), 71.5 (16-CH), 55.8 (CH_2OH), 49.2, 48.4 (quat.), 48.2, 37.9, 36.8, 36.5 (quat.), 31.9, 31.7, 31.1 (2C), 28.8, 27.6, 21.4, 20.3, 19.2, 15.4; HRMS (MALDI-TOF) calcd for $C_{26}H_{38}N_3O_5$ $[M + H]^+$ 472.2806; found 472.2802; Anal. calcd for $C_{26}H_{37}N_3O_5$: C, 66.22; H, 7.91; N, 8.91; found C, 66.18; H, 8.06; N, 8.74.

3β-Acetoxy-16β-{4-[(diethylamino)methyl]-1*H*-1,2,3-triazol-1-yl}-17α-hydroxypregn-5-en-20-one (13d). Synthesized according to method **C** from **9** (62.3 mg, 0.150 mmol) and *N*,*N*-diethylpropargylamine (24.7 μL, 0.180 mmol); heating 20 h; eluent: CH_2Cl_2–MeOH = 10 : 1. Yield 74.9 mg (95%). White solid; mp 163–166 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 [s, 1H,

CH(triazole)], 5.38 (m, 1H, 6-CH), 5.12 (br s, 1H, OH), 4.97 (t, J = 9.0 Hz, 1H, 16-CH), 4.60 (m, 1H, 3-C*H*OAc), 4.02 (d, J = 14.1 Hz, 1H, CH_2NEt$_2$), 3.96 (d, J = 14.1 Hz, 1H, CH_2NEt$_2$), 2.78 [q, J = 7.0 Hz, 4H, N(CH_2CH$_3$)$_2$], 2.59–2.26 (m, 4H), 2.12–1.98 (m, 1H), 2.03 [s, 3H, OC(O)CH$_3$], 1.93–1.53 (m, 7H), 1.52 (qd, J = 13.2, 8.8 Hz, 1H), 1.85 (s, 3H, 21-CH$_3$), 1.38–0.79 (m, 4H), 1.21 [t, J = 7.0 Hz, 6H, N(CH$_2$C*H*$_3$)$_2$], 1.04 (s, 3H, 19-CH$_3$), 0.98 (s, 3H, 18-CH$_3$); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 209.3 [C(20)═O], 170.4 [O*C*(O)CH$_3$], 141.4 [C(triazole)], 139.7 (5-C), 125.7 [CH (triazole)], 121.9 (6-CH), 89.3 (17-COH), 73.7 (3-*C*HOAc), 71.2 (16-CH), 49.2, 48.4 (quat.), 48.2, 47.1 (*C*H$_2$NEt$_2$), 46.5 [2C, N (*C*H$_2$CH$_3$)$_2$], 38.0, 36.8, 36.5 (quat.), 31.9, 31.4, 31.10, 31.05, 28.8, 27.6, 21.3, 20.3, 19.2, 15.3, 10.6 [2C, N(CH$_2$*C*H$_3$)$_2$]; HRMS (MALDI-TOF) calcd for $C_{30}H_{46}N_4NaO_4$ $[M + Na]^+$ 549.3417; found 549.3423.

3β-Acetoxy-16β-[4-(5-chloro-2-hydroxyphenyl)-1*H*-1,2,3-triazol-1-yl]-17α-hydroxypregn-5-en-20-one (13e). Synthesized according to method **C** from **9** (62.3 mg, 0.150 mmol) and 4-chloro-2-ethynylphenol (27.5 mg, 0.180 mmol); heating 20 h; eluent: CH_2Cl_2–MeOH = 50 : 1. Yield 74.5 mg (87%). White solid; mp 157–159 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 10.70 [br s, 1H, 2-COH(Ar)], 7.88 [s, 1H, CH(triazole)], 7.37 [d, J = 2.3 Hz, 1H, 6-CH(Ar)], 7.37 [dd, J = 8.7, 2.3 Hz, 1H, 4-CH(Ar)], 7.37 [d, J = 8.7 Hz, 1H, 3-CH(Ar)], 5.38 (m, 1H, 6-CH), 5.00 (t, J = 8.9 Hz, 1H, 16-CH), 4.61 (tt, J = 11.6, 4.7 Hz, 1H, 3-C*H*OAc), 4.24 (br s, 1H, 17-COH), 2.56–2.45 (m, 2H), 2.40–2.27 (m, 2H), 2.13–1.99 (m, 1H), 2.04 [s, 3H, OC(O)CH$_3$], 1.93–1.56 (m, 7H), 1.51 (qd, J = 13.1, 4.3 Hz, 1H), 1.76 (s, 3H, 21-CH$_3$), 1.34 (m, 1H), 1.26–0.98 (m, 3H), 1.08 (s, 3H, 18-CH$_3$ or 19-CH$_3$), 1.06 (s, 3H, 18-CH$_3$ or 19-CH$_3$); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 208.3 [C(20)═O], 170.7 [O*C*(O)CH$_3$], 154.3 [2-COH(Ar)], 146.3 [C(triazole)], 139.7 (5-C), 129.4, 125.4, 124.1 (quat.), 121.7 (6-CH), 120.5, 119.0, 115.0 (quat.), 89.9 (17-COH), 73.7 (3-*C*HOAc), 71.7 (16-CH), 49.2, 48.8 (quat.), 48.5, 37.9, 36.8, 36.6 (quat.), 31.9, 31.8, 30.9, 30.8, 28.3, 27.6, 21.4, 20.2, 19.2, 15.7; HRMS (MALDI-TOF) calcd for $C_{31}H_{39}ClN_3O_5$ $[M + H]^+$ 568.2573; found 568.2588.

3β-Acetoxy-16β-{4-[(4-carboxyphenoxy)methyl]-1*H*-1,2,3-triazol-1-yl}-17α-hydroxypregn-5-en-20-one (13f). Synthesized according to method **C** from **9** (62.3 mg, 0.150 mmol) and 4-(prop-2-yn-1-yloxy)benzoic acid (31.7 mg, 0.180 mmol); heating 20 h; eluent: CH_2Cl_2–MeOH = 50 : 1. Yield 64.8 mg (73%). White solid; mp 247–248 °C; ^{1}H NMR (400 MHz, CDCl$_3$–CD$_3$OD) δ 8.00 [d, J = 8.9 Hz, 2H, 3,5-CH(Ar)], 7.75 [s, 1H, CH(triazole)], 7.00 [d, J = 8.9 Hz, 2H, 2,6-CH(Ar)], 5.38 (m, 1H, 6-CH), 5.25 (s, 2H, CH$_2$O), 4.96 (t, J = 9.1 Hz, 1H, 16-CH), 4.60 (m, 1H, 3-C*H*OAc), 2.91 (br s, 2H, OH), 2.47–2.26 (m, 3H), 2.17 (td, J = 13.1, 9.9 Hz, 1H, 15β-CH), 2.08–1.99 (m, 1H), 2.03 [s, 3H, OC(O)CH$_3$], 1.93–1.54 (m, 7H), 1.48 (qd, J = 13.1, 4.7 Hz, 1H), 1.42–1.36 (m, 1H), 1.93 (s, 3H, 21-CH$_3$), 1.27–0.99 (m, 3H), 1.04 (s, 3H, 19-CH$_3$), 0.88 (s, 3H, 18-CH$_3$); ^{13}C NMR (100.6 MHz, CDCl$_3$–CD$_3$OD) δ 209.5 [C(20)═O], 170.8 [O*C*(O)CH$_3$], 169.0 (COOH), 162.0 [1-C(Ar)], 142.8 [C(triazole)], 139.6 (5-C), 132.0 [2C, 3,5-CH(Ar)], 123.7 [CH(triazole)], 122.9 [4-C (Ar)], 121.7 (6-CH), 114.3 [2C, 2,6-CH(Ar)], 88.9 (17-COH), 73.8 (3-*C*HOAc), 71.5 (16-CH), 61.8 (CH$_2$O), 49.1, 48.2 (quat.), 48.1, 37.8, 36.7, 36.5 (quat.), 31.9, 31.8, 31.0, 30.9, 28.6, 27.5, 21.3, 20.3, 19.2, 15.5; HRMS (MALDI-TOF) calcd for $C_{33}H_{42}N_3O_7$ $[M + H]^+$ 592.3017; found 592.3021; Anal. calcd for $C_{33}H_{41}N_3O_7$: C, 66.99; H, 6.98; N, 7.10; found C, 67.31; H, 6.88; N, 6.83.

3β-Acetoxy-16β-(4-butyl-1*H*-1,2,3-triazol-1-yl)-17β-methyl-D-homoandrost-5-ene-17α,17aβ-diol (16). NaBH$_4$ (104 mg, 2.79 mmol) was gradually added to a suspension of **12b** (104.3 mg, 0.210 mmol) in anhydrous methanol (5.0 mL). The mixture was stirred for 30 min at rt, diluted with CH_2Cl_2 (25 mL), washed with water (2 × 25 mL), dried with anhydrous Na_2SO_4, and evaporated under vacuum. The residue was subjected to column chromatography (eluent: CH_2Cl_2–MeOH = 20 : 1) to afford the pure product. Yield 75.5 mg (72%). White solid; mp >250 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.44 [s, 1H, CH(triazole)], 5.34 (m, 1H, 6-CH), 4.58 (tt, J = 11.1, 4.7 Hz, 1H, 3-C*H*OAc), 4.34 (dd, J = 12.8, 3.5 Hz, 1H, 16-CH), 3.36 (s, 1H, 17a-C*H*OH), 3.06 (br s, 2H, OH), 2.71 [t, J = 7.6 Hz, 2H, CH_2Pr], 2.37–2.24 (m, 2H), 2.21–2.09 (m, 2H), 2.07–1.82 (m, 4H), 2.02 [s, 3H, OC(O)CH$_3$], 1.69–1.44 (m, 6H), 1.36 (sextet, J = 7.5 Hz, 2H, CH$_2$CH_2CH$_3$), 1.30–1.20 (m, 1H), 1.17–0.96 (m, 4H), 1.02 (s, 3H, 19-CH$_3$), 0.92 (t, J = 7.3 Hz, 3H, CH$_3$), 0.889 (s, 3H, 17-CCH$_3$ or 18-CH$_3$), 0.886 (s, 3H, 17-CCH$_3$ or 18-CH$_3$); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 170.6 [O*C*(O)CH$_3$], 147.3 [C(triazole)], 139.6 (5-C), 121.64 (6-CH), 121.56 [CH(triazole)], 84.0 (17a-CHOH), 76.2 (17-COH), 73.7 (3-*C*HOAc), 67.5 (16-CH), 49.3, 48.6, 38.2 (quat.), 37.8, 37.2, 36.8 (quat.), 36.6, 31.8, 31.5, 30.2, 27.6, 26.5, 25.2, 22.3, 21.4, 19.2 (2C), 17.4, 13.8, 11.3; HRMS (MALDI-TOF) calcd for $C_{29}H_{46}N_3O_4$ $[M + H]^+$ 500.3483; found 500.3476; Anal. calcd for $C_{29}H_{45}N_3O_4$: C, 69.71; H, 9.08; N, 8.41; found C, 70.09; H, 9.25; N, 8.19.

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