Summary of Doctoral (PhD) Thesis

STEREOSELECTIVE SYNTHESIS OF STEROID HYBRIDS

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1. Introduction and aims

Steroids occur nearly everywhere in almost all living organisms and they play important roles from biological aspects. The preparation of semisynthetic and synthetic steroids and their biological evaluation have become a major field in pharmaceutical research. The therapeutic application of compounds with sterane skeleton for hormone-dependent diseases is getting increasingly widespread. Nowadays the synthesis of steroid hybrids seems to get outstanding significance. The reason is that this synthetic strategy is an inexhaustible tool to prepare novel drug candidates. A suitable carrier molecule and a naturally occurring or synthetic compound can be combined *via* a suitable linker and the novel hybrid compound with a unique structure thus prepared could exert new biological properties as well. Among cytostatic hybrid type compounds published previously many bear sterane skeleton. The receptor binding of the molecule could be influenced by the chemical nature of the linker. The synthetic method applied for the preparation of hybrid derivatives determines the position and the stereochemistry of the coupling molecular entities on the sterane core.

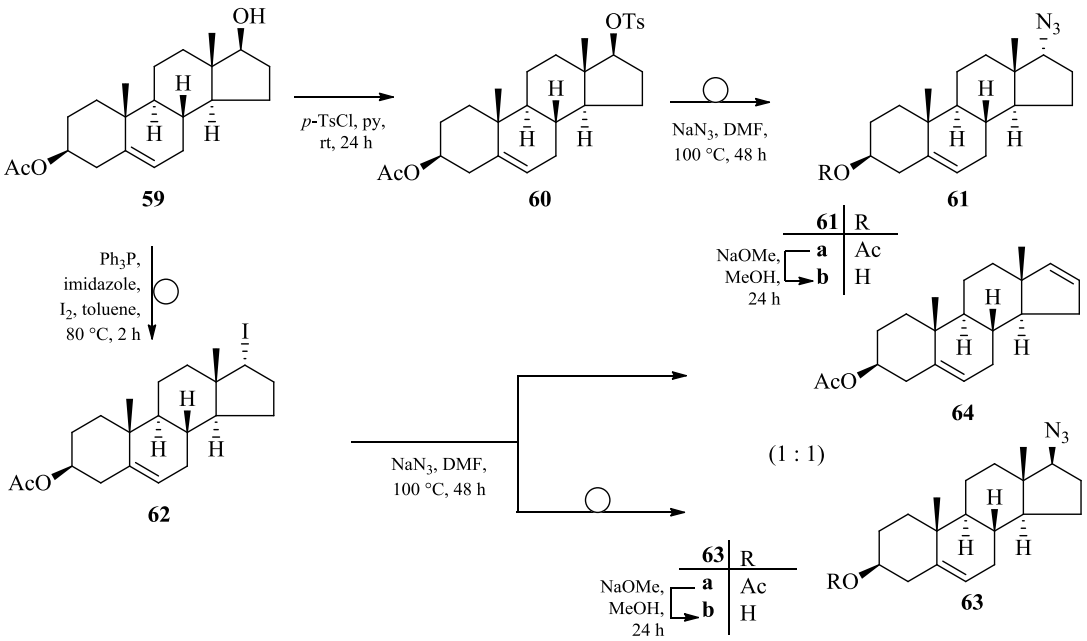
Relying on the results of previous studies, the purpose of my doctoral work was to synthesize a series of compounds with diverse structures for comprehensive pharmacological investigations. During the design of the desired types of compounds we have been bearing several viewpoints in mind. A comparative pharmacological investigation has not been obtained yet on stereoisomeric hybrid compounds. For this purpose, we planned to prepare and investigate substituted androstane derivatives bearing triazolyl group in both the 17α and 17β position. Our further goal was to synthesize all four possible isomers each of the 3-methoxy- and 3-benzyloxy-16-hydroxymethyl-17-hydroxyestra-1,3,5(10)-triene and to prepare 16-triazolylmethyl hybrids. The antiproliferative activity was expected to depend on the stereochemistry of the isomers. The results of the biological investigation could also be influenced by the presence of the 3-methoxy or the 3-benzyloxy substituents on the sterane framework. To expand our research on hybrid molecules bearing methylene linker, we aimed to build in a longer carbon linker. After the promising results achieved in the natural estrane series we attempted to take further examinations with the four possible isomers each of the 3-methoxy- and 3-benzyloxy-16-hydroxymethyl-17-hydroxy-13α-estra-1,3,5(10)-triene. Note that it is well-known in the literature that 13α-estrane derivatives may not possess estrogenic activity.

2. Experimental methods

For the preparation of the starting materials reactions were carried out in the molar range, whereas the synthesis of the derivatives was accomplished in the millimolar range. Conversions were monitored by thin-layer chromatography. Purification and isolation of the crude products were implemented by flash chromatography. The structures of all newly synthesized compounds were confirmed by ^{1}H NMR, ^{13}C NMR and in some cases 2D NMR experiments (HSQC, HMBC) were also performed for structure determination.

3. Scientific results*

3.1. Both the 3β-hydroxy-17α- and 3β-hydroxy-17β-azidoandrost-5-ene epimers (**61b** and **63b**) could be synthesized from 3β-acetoxy-17β-hydroxyandrost-5-ene **59** (Scheme 1). First, the esterification of 3β-acetoxy-17β-hydroxyandrost-5-ene **59** with *p*-toluenesulfonyl chloride furnished 3β-acetoxy-17β-tosyloxyandrost-5-ene (**60**). Then a Ts→N_3 exchange taking place *via Walden* inversion gave the 3β-acetoxy-17α-azidoandrost-5-ene (**61a**). Compound **59** under the conditions of the *Appel* reaction led to the 3β-acetoxy-17α-iodoandrost-5-ene (**62**), and then an I→N_3 exchange with inversion afforded the 3β-acetoxy-17β-azidoandrost-5-ene (**63a**).



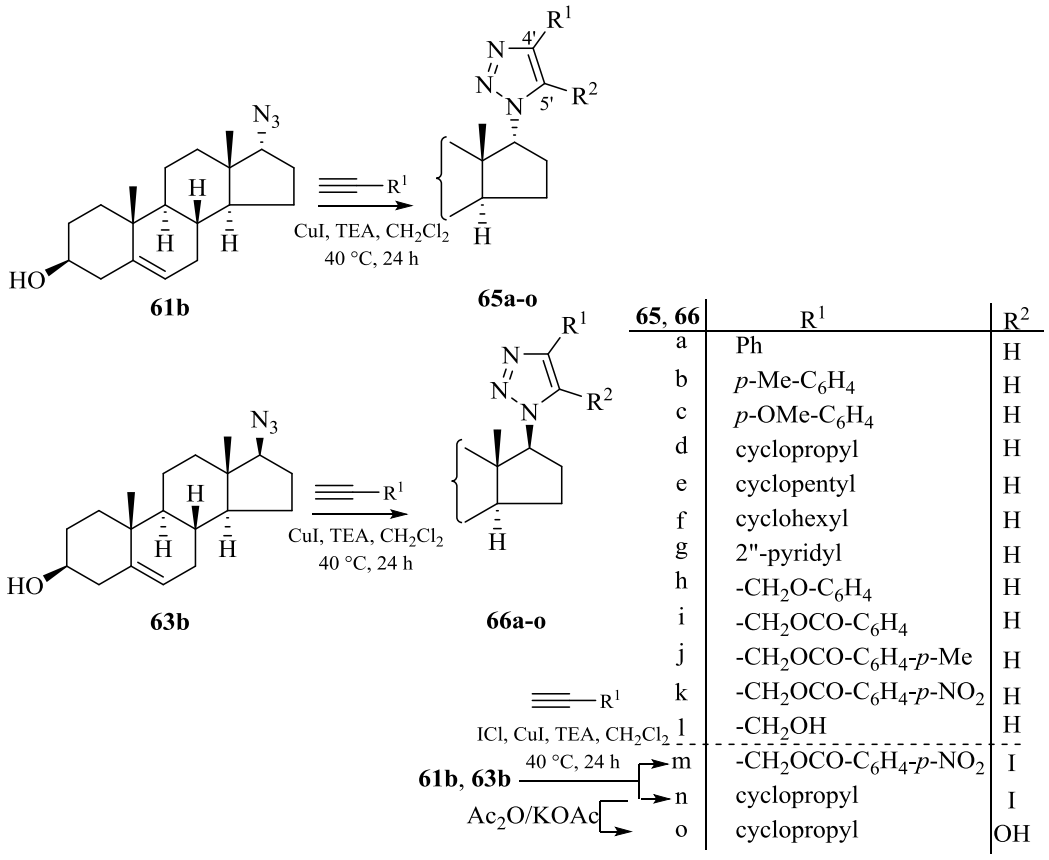
Scheme 1

* The numbering of the compounds is in accordance with that in the Ph.D Thesis

3.2. The Cu(I)-catalysed 1,3-dipolar cycloaddition performed with cycloalkyl- (**65d**–**f, 66 d**–**f**), aryl- (**65a**–**c**, **g** and **65a**–**c**, **g**) and aryloxymethyl-alkynes (**65h**–**m**, **66h**–**m**) on the 17α- and 17β-azide groups led to the corresponding triazolyl derivatives (**65a**–**n**, **66a**–**n**) with the heterocycle directly connected to the androstane skeleton (Scheme 2).

3.3. Alkaline hydrolysis of the 4'-benzoyloxymethyl triazoles (**65i**–**k** and **66i**–**k**) yielded the 4'-hydroxymethyltriazolyl derivatives (**65l**, **66l**) without the decomposition of the triazolyl ring (Scheme 2).

3.4. We found that during the click reactions [Cu(I)-catalysed alkyne–azide cycloaddition; CuAAC] with the use of 10 equivalents of CuI in the presence of triethylamine (TEA) and 1.5 equivalents of ICl, the 5'-iodotriazolyl derivatives (**65m**–**n** and **66m**–**n**) were formed with good yields (Scheme 2).

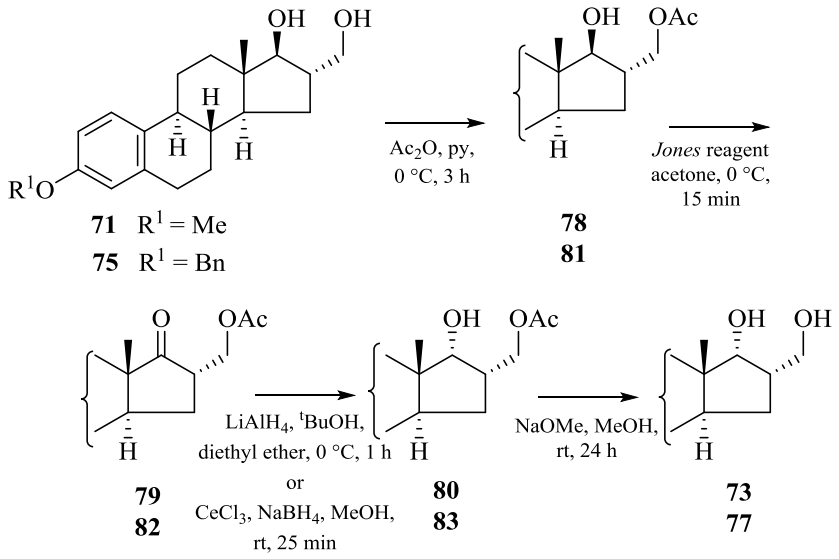


65, 66	R^1	R^2
a	Ph	H
b	*p*-Me-C_6H_4	H
c	*p*-OMe-C_6H_4	H
d	cyclopropyl	H
e	cyclopentyl	H
f	cyclohexyl	H
g	2"-pyridyl	H
h	-CH_2O-C_6H_4	H
i	-CH_2OCO-C_6H_4	H
j	-CH_2OCO-C_6H_4-*p*-Me	H
k	-CH_2OCO-C_6H_4-*p*-NO_2	H
l	-CH_2OH	H
m	-CH_2OCO-C_6H_4-*p*-NO_2	I
n	cyclopropyl	I
o	cyclopropyl	OH

Scheme 2

3.5. Acetolysis of the 5'-iodotriazolyl compounds (**65n**, **66n**) in acetic anhydride in the presence of KOAc followed by alkaline hydrolysis yielded 5'-hydroxytriazolyl derivatives (**65o**, **66o**) (Scheme 2).

3.6. We developed a novel synthetic pathway for the synthesis of 3-methoxy- and 3-benzyloxy-16-hydroxymethyl-17β-hydroxyestra-1,3,5(10)-trienes. The selective acetylation of the primary hydroxyl function of the 3-methoxy- and 3-benzyloxy-16α-hydroxymethyl-17β-hydroxyestra-1,3,5(10)-triene compounds (**71**, **75**) furnished the 16α-acetoxymethyl derivatives (**78**, **81**). *Jones* oxidation of these compounds (**78**, **81**) led to the transformation of the 17-hydroxy group to 17-keto function (**79**, **82**). Reduction of the 17-keto group with lithium tri-*tert*-butoxyaluminum hydride generated *in situ* in diethyl ether solution yielded the 16α-acetoxymethyl-17α-hydroxy and the 17α-acetoxymethyl-17β-hydroxy compounds in ratio of 4:1. The products then were deacetylated by the *Zemplén* method to yield the yet missing 16α-hydroxymethyl-17α-hydroxyestra-1,3,5(10)-triene isomers (**73**, **77**) in both the 3-methoxy and 3-benzyloxy series (Scheme 3). According to our laboratory experiences, this method could be used efficiently only in smaller batches.

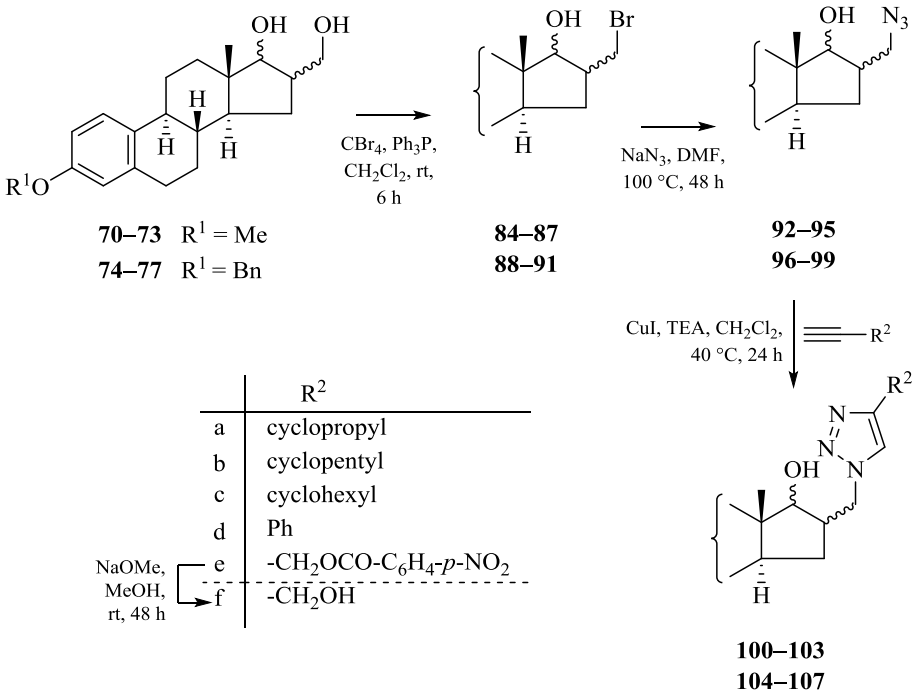


Scheme 3

3.7. We found that the 16α-acetoxymethyl-17-keto compounds (**79**, **82**) under the conditions of the *Luche* reduction, that is, reduction with $NaBH_4$ in the presence of $CeCl_3$, furnished the corresponding *pseudo-axial* 17α-hydroxy derivatives. The resulting 3-methoxy- and 3-benzyloxy-16α-hydroxymethyl-17α-hydroxyestra-1,3,5(10)-triene compounds (**73**, **77**) were isolated in good yields (Scheme 3).

3.8. The stereoisomers of the 3-methoxy- and 3-benzyloxy-16-hydroxymethyl-17-hydroxyestra-1,3,5(10)-triene (**70**–**77**) were transformed in the *Appel* reaction to give the

corresponding 16-bromomethyl derivatives (**84**–**91**) (Scheme 4). The subsequent nucleophilic substitution, a Br→N_3 exchange, provided the 16-azidomethyl stereoisomers (**92**–**95** and **96**–**99**), which were used as starting materials for the CuAAC reaction.



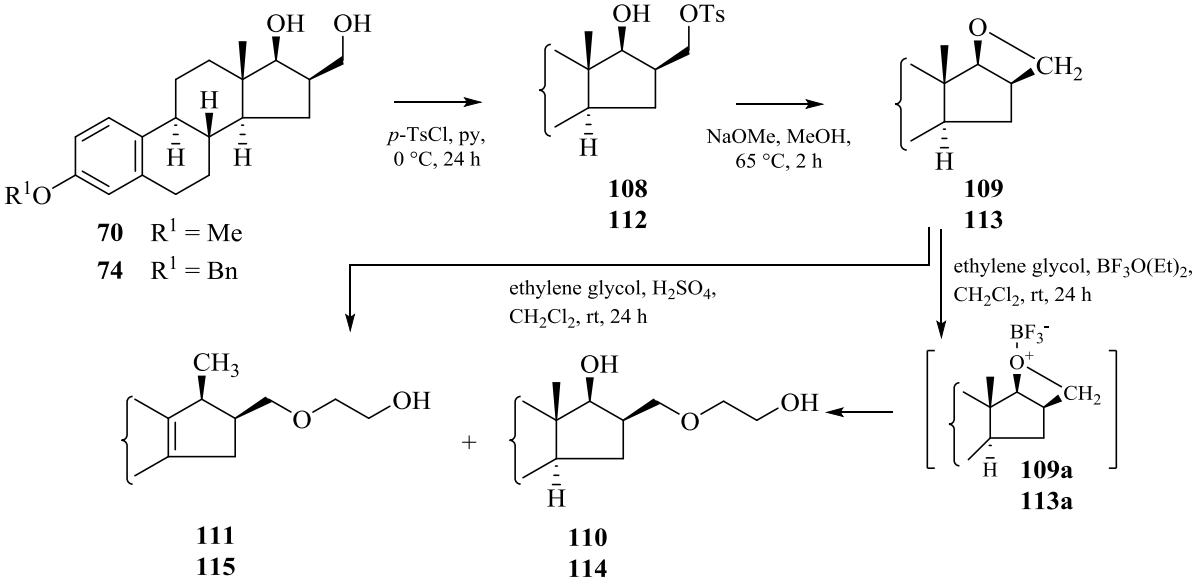
Scheme 4

3.9. The azide-alkyne cycloaddition of the four possible stereoisomers each of the 3-methyl- and 3-benzyloxy-16-azidomethyl-17-hydroxyestra-1,3,5(10)-triene (**92**–**95** and **96**–**99**) gave the corresponding triazolyl derivatives (**100**–**107**) with the heterocycle attached to the sterane framework through a methylene linker.

3.10. We found that the coupling constants of the 17-H peak in the ^{1}H NMR spectra of the synthesized 3-methyl- and 3-benzyloxy-16-azidomethyl-17-hydroxyestra-1,3,5(10)-triene (**92**–**95** and **96**–**99**) stereoisomers and their triazolyl derivatives (**100**–**107**) showed the following tendency:

$J_{16\alpha H,17\alpha H}$	>	$J_{16\beta H,17\alpha H}$	>	$J_{16\beta H,17\beta H}$	>	$J_{16\alpha H,17\beta H}$
~ 9.5 Hz		~ 7.0 Hz		~ 5.0 H		~ 0–1 Hz
(**92**, **96**, **100**, **104**)		(**93**, **97**, **101**, **105**)		(**95**, **99**, **103**, **107**)		(**94**, **98**, **102**, **106**)

3.11. The solvolytic reaction of 3-methoxy- and 3-benzyloxy-16β-tosyloxymethyl-17β-hydroxyestra-1,3,5(10)-trienes (**108**, **112**) led to derivatives with an oxetane ring condensed to the ring D (**109**, **113**) through neighbouring group participation (Scheme 5). These cyclic ethers (**109**, **113**) are suitable synthon equivalents for the preparation of derivatives with longer linkers. Their synthesis has been facilitated by the transformation of the cyclic ethers in the presence of *Lewis* acids like $BF_3 \cdot OEt_2$ to form oxonium complexes (**109a**, **113a**). The latter are known to undergo ring cleavage in a solvolytic reaction with α,ω-diols. In our case, ring cleavage was carried out with ethylene glycol to synthesize **110** and **114** with a three-carbon alkoxy linker in the 16β position. If the transformation is carried out with *Brønsted* acid, the ring cleavage of the oxonium complexes (**109a**, **113a**) occurs with *Wagner–Meerwein* rearrangement yielding the 16β-[(2'-oxa)-ω-hydroxyalkyl]-17β-methylestra-1,3,5(10),13(14)-tetraen-3-ethers (**111**, **115**).

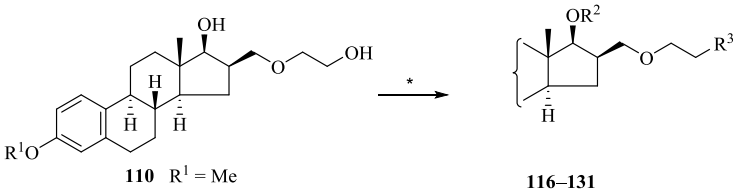


Scheme 5

3.12. Compounds with the ω-hydroxyalkyl linker (**110**, **114**) transformed in the *Appel* reaction led to the corresponding iodoalkyl derivatives (**116**, **120**), which were suitable alkylating agents in the selective alkylation of L-ascorbic acid (2-deoxy-2-keto gulonic acid γ-lactone) and salicylic acid (Scheme 6; **117**–**123**).

3.13. Nucleophilic substitution of the ω-iodoalkyl compounds (**116**, **120**) with NaN_3 furnished the ω-azidoalkyl derivatives (**124**, **125**) (Scheme 6). The terminal azide functions

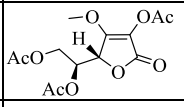
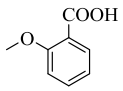
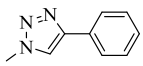
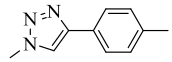
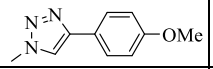
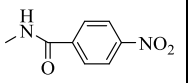
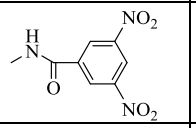
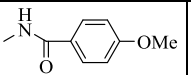
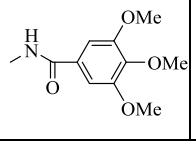
were capable of reacting under CuAAC conditions to provide terminal, disubstituted 1,2,3-triazoles (**126a**–**c** and **127a**–**c**).



110 R^1 = Me
114 R^1 = Bn

116–131

*1. I_2, Ph_3P, CH_2Cl_2, rt, 24 h
2. L-ascorbic acid/salicylic acid, DMSO, 60 °C, 6 h
3. Ac_2O, py, 24 h
4. NaN_3, DMF, 100 °C, 5 h
5. appropriate alkyne, CuI, TEA, CH_2Cl_2, 40 °C, 24 h
6. N_2H_4 x H_2O, Raney-Ni, EtOH, 0 °C, 30 min
7. appropriate carboxylic acid, HOBT, HBTU, DIPEA, DMF, rt, 3 h

	R^3	R^2
110 **114**	OH	H
116 **120**	I	H
118 **122**		OAc
119 **123**		H
124 **125**	N_3	H
126a **127a**		H
126b **127b**		H
126c **127c**		H
128 **129**	NH_2	H
130a **131a**		H
130b **131b**		H
130c **131c**		H
130d **131d**		H

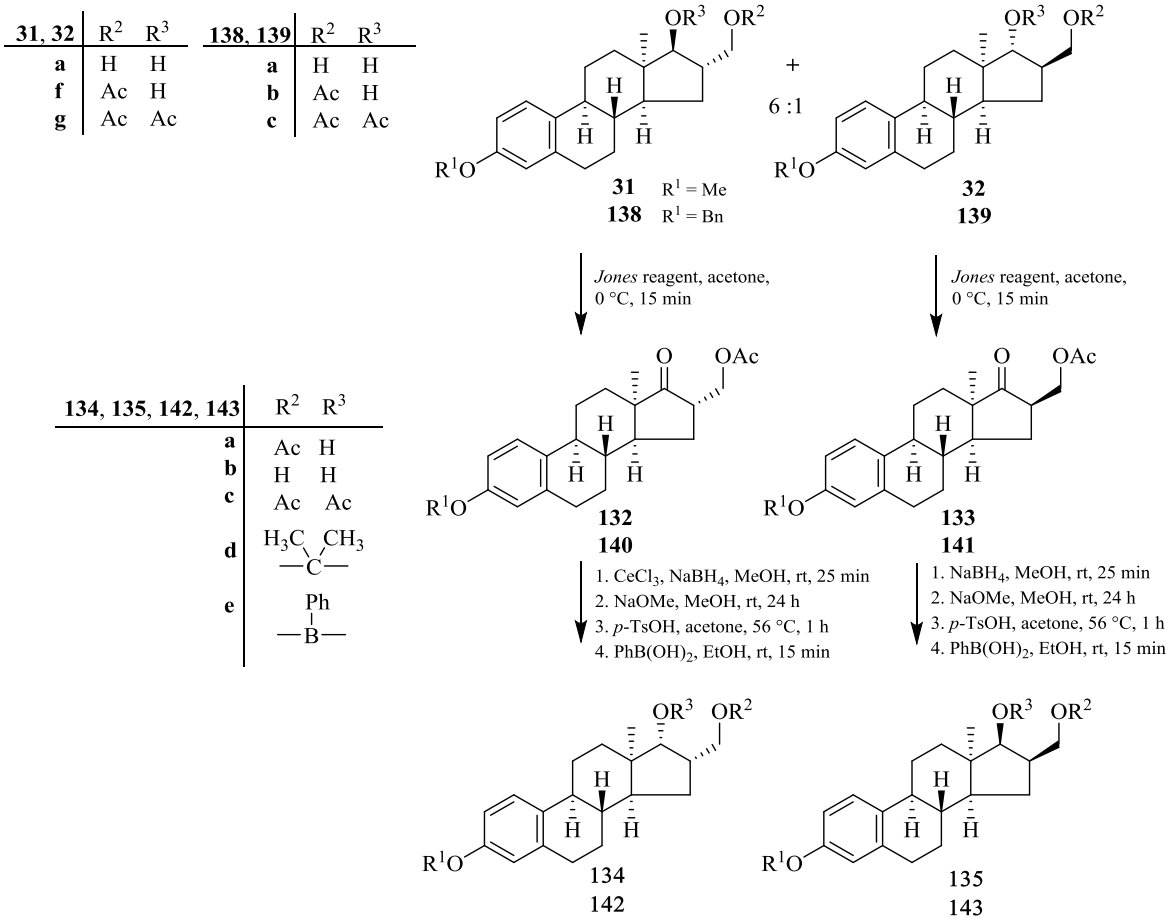
Scheme 6

3.14. The reduction of the terminal azide function of **124** and **125** with hydrazine hydrate in the presence of Raney-Ni catalyst in ethanol gave the corresponding ω-aminoalkyl derivatives (**128**, **129**). Then several hybrid carboxamides were synthesized. Acylations were performed with the use of aromatic carboxylic acids and well-known peptide coupling agents (Scheme 6; **130a**–**d** and **131a**–**d**).

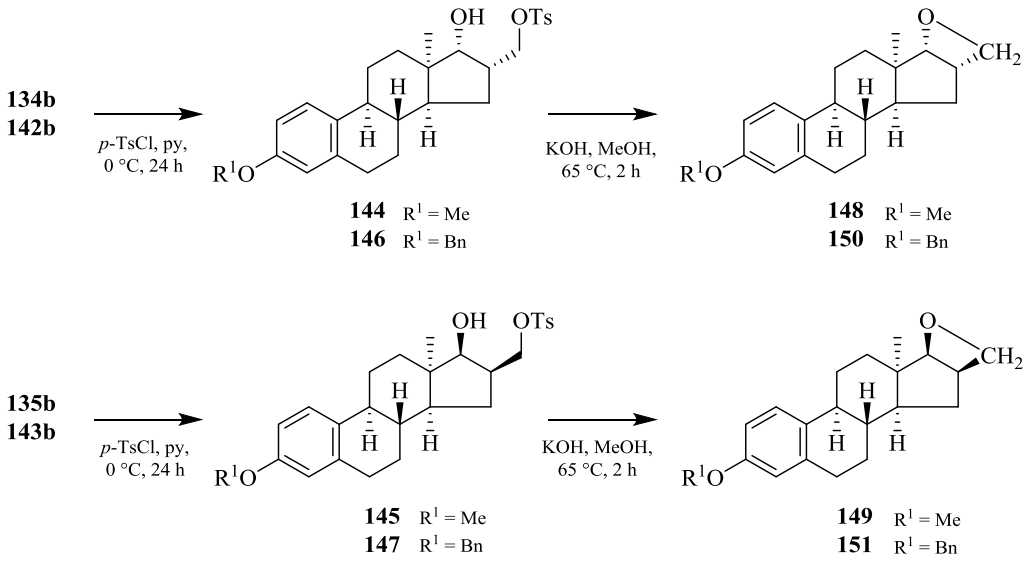
3.15. *Jones* oxidation of the separated *trans* 16-acetoxymethyl-17-hydroxy derivatives (**31f**, **32f** and **138b**, **139b**), the subsequent *Luche* or $NaBH_4$ reduction of the corresponding compounds and deacetylation by the *Zemlén* method gave *cis*-diols **134b**, **135b** and **142b**, **143b**. By these reaction steps the synthesis of the full isomer series of the 3-methoxy- and the 3-benzyloxy-16-hydroxymethyl-17-hydroxy-13α-estra-1,3,5(10)-triene was completed (Scheme 7).

3.16. According to our earlier investigations on the natural estrane series, we set out the selective esterification of the primary hydroxy function of the 16β,17β- (**135b**, **143b**) and 16α,17α-diols (**134b**, **142b**) with 13-*epi*-estrane skeleton. The alkaline reaction of the

1,3-tosylhydrins (**144**–**147**) leads to the formation of oxetanes (**148**–**151**) condensed to ring D in the 13α-estrane series as well. The process can be regarded as a neighbouring group participation, which is characterized as (O^--4) by the general symbol (Scheme 8).



Scheme 7

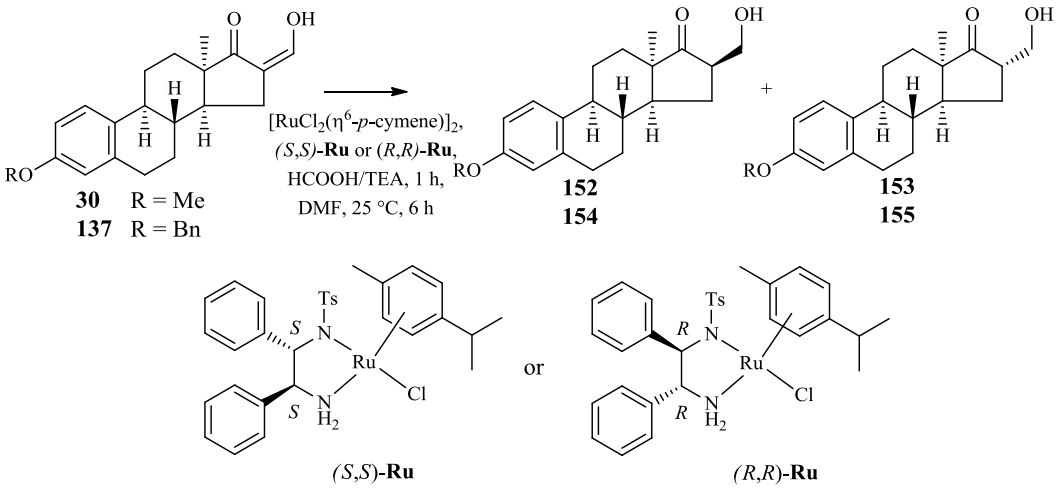


Scheme 8

3.17. All four possible isomers each of the 3-methoxy- and 3-benzyloxy-16-acetoxymethyl-17-acetoxy-13α-estra-1,3,5(10)-triene (**31g**, **32g**, **134c**, **135c** and **138c**, **139c**, **142c**, **143c**) have been investigated by 2D NMR techniques, such as HSQC and HMBC. The chemical shifts and the coupling constants of the carbons in the α-, β- or γ-positions are sensitive to differences in the configuration of the C-16 and C-17 atoms. A characteristic tendency has been observed in the ^{1}H NMR spectra of all compounds. The *tertiary* C-17 atom bears only a single proton, which is visible as a singlet in every proton spectrum. Nevertheless, the coupling constants are different because of the difference in the dihedral angle in accordance with the *Karplus* equation. In the case of compounds bearing a β-acetoxy group on C-17, the coupling constant of the C-17 hydrogen is 5.0 Hz. In turn, if the acetoxy group is in α-position, the coupling constant is 9.0 Hz. This statement is valid for both the 3-methoxy- and the 3-benzyloxy-*epi*-estrane series. Thus the regularities observed between the coupling constants of the 17-H are the following:

$J_{16\alpha H,17\alpha H}$	=	$J_{16\beta H,17\alpha H}$	<	$J_{16\alpha H,17\beta H}$	=	$J_{16\beta H,17\beta H}$
~ 5.0 Hz		~ 5.0 Hz		~ 9.0 H		~ 9.0 Hz
(**135c, 143c**)		(**31g, 138c**)		(**32g, 139c**)		(**134c, 142c**)

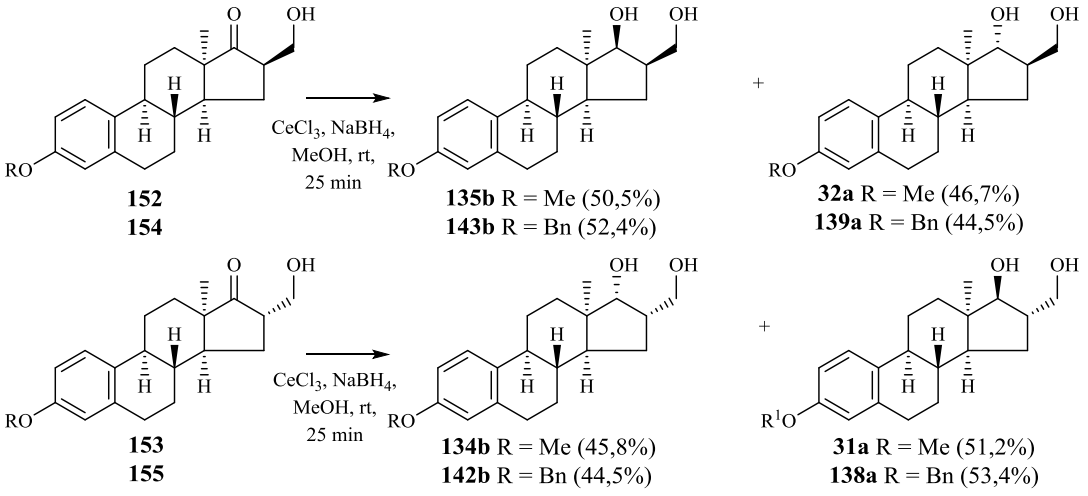
3.18. The transfer hydrogenation of 3-methoxy- and 3-benzyloxy-16-hydroxymethylidene-13α-estra-1,3,5(10)-trien-17-ones (**30**, **137**) in the presence of Ru(*S*,*S*-Ts-DPEN)(*para*-cymene)Cl [(*S*,*S*)-**Ru**] or Ru(*R*,*R*-Ts-DPEN)(*para*-cymene)Cl [(*R*,*R*)-**Ru**] its enantiomer gave diastereomeric mixtures of 3-methoxy- and 3-benzyloxy-16-hydroxymethyl-13α-estra-1,3,5(10)-trien-17-ones (**152**–**155**). The purification of the formed 16-hydroxymethyl-17-keto isomers (**152**–**155**) has been achieved by column chromatography and related data are summarized in the table of Scheme 9.



Start. mat.	Chiral cat.	Products (%)	16β:16α ratio	Yield (%)
30	*(S,S)*-**Ru**	**152** (18.0) + **153** (81.1)	1 : 4.50	99.1
30	(*R,R)*-**Ru**	**152** (27.5) + **153** (69.4)	1 : 2.52	96.9
137	*(S,S)*-**Ru**	**154** (17.9) + **155** (79,0)	1 : 4.45	97.7
137	*(R,R)*-**Ru**	**154** (28.1) + **155** (70.4)	1 : 2.50	98.5

Scheme 9

3.19. The reduction of the 16β-hydroxymethly-17-keto isomers (**152**, **154**) by the *Luche* method gave two compounds for each. The expected 16β,17β stereoisomers (**135b**, **143b**) and the **32a**, **139a** 16β,17α isomers were obtained in almost equal amounts. Similarly, under the same conditions, the reduction of 16α-hydroxymethyl-17-ketones (**153**, **155**) yielded the 16α,17α isomers (**134b**, **142b**) and the 16α,17β (**31a**, **138a**) isomers were also obtained in equal amounts (Scheme 10). The two-step transfer hydrogenation/reduction is a procedure of unprecedented convenience and efficiency for the preparation of all isomers of the 16-hydroxymethyl-17-hydroxy compounds compared to the classical synthetic pathway.



Scheme 10

4. Scientific publications forming the basis of the thesis

1. **Kiss, A.**; Herman, B. E.; Görbe, T.; Mernyák, E.; Molnár, B.; Wölfling, J.; Szécsi, M.; Schneider, Gy.
   Synthesis of novel 17-triazolyl-androst-5-en-3-ol epimers *via* Cu(I)-catalyzed azide-alkyne cycloaddition and their inhibitory effect on 17α-hydroxylase/$C_{17,20}$-lyase
   Steroids **2018**, *135*, 79–91.

   IF: 2.523

2. **Kiss, A.**; Mernyák, E.; Wölfling, J.; Sinka, I.; Zupkó, I.; Schneider, Gy.
   Stereoselective synthesis of the four 16-hydroxymethyl-3-methoxy- and 16-hydroxymethyl-3-benzyloxy-13α-estra-1,3,5(10)-trien-17-ol isomers and their antiproliferative activities
   Steroids **2018**, *134*, 67–77.

   IF: 2.523

3. **Kiss, A.**; Mernyák, E.; Wölfling, J.; Szöllősi, Gy.; Schneider, Gy.
   Improved stereoselective synthesis of 3-methoxy- and 3-benzyloxy-16-hydroxymethyl-13α-estra-1,3,5(10)-trien-17-ol isomers by transfer hydrogenation using chiral Ru catalysts
   Reac. Kinet. Mech. Cat. **2018**, *125*, 47–53.

   IF: 1.515

4. **Kiss, A.**; Wölfling, J.; Mernyák, E.; Frank, É.; Gyovai, A.; Kulmány, Á.; Zupkó, I.; Schneider, Gy.
   Stereoselective synthesis of new type steroid hybrid molecules and their antiproliferative activities
   Steroids **2018**, submitted manuscript

5. **Kiss, A.**; Wölfling, J.; Mernyák, E.; Frank, É.; Benke, Zs.; Senobar Tahaei, S. A.; Mahó, S.; Zupkó, I.; Schneider, Gy.
   Stereocontrolled synthesis of the four possible 3-methoxy- and 3-benzyloxy-16-triazolylmethylestra-17-ol hybrids and their antiproliferative activites
   Steroids **2018**, submitted manuscript

Total IF: 6.561

5. Scientific lectures and posters forming the basis of the thesis

Lectures:

1. **Kiss, A.**; Wölfling, J.; Schneider, Gy.
   Sztereoizomer hibrid molekulák előállítása az ösztrán sorban
   MTA Szteroid- és Terpenoidkémiai Munkabizottsági ülése, Szeged, Hungary, 27 November 2017.

2. **Kiss, A.**
   Hybrids and conjugates at the focus of steroid research
   1st Hungarian-Norwegian Summer School on Bioactive Substance Research, *University of Tromsø*, Tromsø, Norway, 15 July 2017.

3. **Kiss, A.**; Schneider, Gy.
   A 16-hidroximetil-13-*epi*-ösztradiol-3-éterek sztereoszelektív átalakítása
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2. **Kiss, A.**; Benke, Zs.; Zupkó, I.; Wölfling, J.; Schneider, Gy.
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   MKE Vegyészkonferencia, Hajdúszoboszló, Hungary, 19–21 June 2017.

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   New 16-substituted estrone hybrids
   IXth Joint Meeting in Medicinal Chemistry, Athens, Greece, 7–10 June 2015.

6. Scientific publications not forming the basis of the thesis

1. Fröhlich, T.; **Kiss, A.**; Wölfling, J.; Mernyák, E.; Kulmány, Á.; Minorics, R.; Zupkó, I.; Leidenberger, M.; Friedrich, O.; Kappes, B.; Hahn, F.; Marschall, M.; Schneider, Gy.; Tsogoeva, S.
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2. Gyovai, A.; Minorics, R.; **Kiss, A.**; Mernyák, E.; Schneider, Gy.; Szekeres, A.; Kerekes, E.; Ocsovszki, I.; Zupkó, I.
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   17β-Priazolil és -pirazolinil-szteroidok szintézise
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Total IF: 13.614

7. Scientific lectures and posters not forming the basis of the thesis

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1. **Kiss, A.**; Schneider, Gy.; Wölfling, J.
   Ösztron hibrid származékok szintézise
   Tudományos Diákköri Konferencia, helyi forduló, Szeged, Hungary, 29 April 2014.

2. **Kiss, A.**; Schneider, G.; Wölfling, J.
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3. **Kiss, A.**; Kovács, I.; Schneider, Gy.; Zupkó, I.; Wölfling, J.
   Synthesis of steroid-carboxylic acid conjugates
   "Research Cooperation of the University of Szeged and the University of Novi Sad in Development of Anticancer Drug Compounds" (RECODAC), Szeged, Hungary, 20 September 2013.

4. **Kiss, A.**; Kovács, I. J.; Schneider, G.; Zupkó, I.; Wölfling, J.
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   Richter Gedeon Plc., Budapest, Hungary, 29 October 2013.

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   FAMÉ 2016: Magyar Farmakológiai, Anatómus, Mikrocirkulációs és Élettani Társaságok Közös Tudományos Konferenciája, Pécs, Hungary, 1–4 June 2016.

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