Synthetic methods towards steroid-ferrocene conjugates

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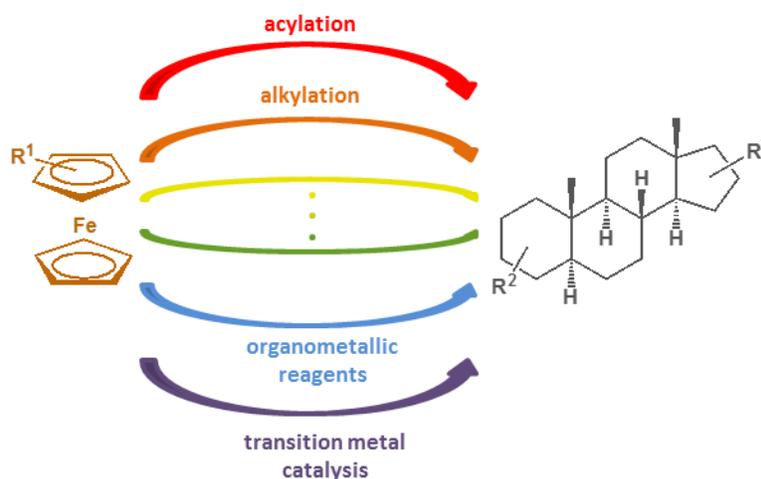**This paper is dedicated to Professor György Keglevich on the occasion of his 65th birthday**

Abstract

Steroid-ferrocene conjugates, in which a steroid skeleton is connected directly or via a linker group to the ferrocene moiety, have a broad scope of possible applications in medicinal or analytical chemistry as well as in materials science. They may integrate or even enhance many of the attractive properties of the components. Reactive functional groups of steroids and the ease in the conversion of ferrocene via aromatic substitution reactions offer a wide range of possibilities to attach the two skeletons to each other. This review summarizes the diverse methodologies used in the synthesis of conjugates, including classical organic reactions as well as the application of organometallic reagents and transition-metal catalyzed reactions.

Keywords: Steroids, ferrocene, organometallics, catalysis

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1. Introduction

Since its discovery, ferrocene (Fc) and its derivatives have been attracting much attention in catalysis, organic synthesis, new materials and supramolecular chemistry.[1] Ferrocene has high thermal stability, is stable in air, and soluble in all common organic solvents. It reacts as a strong electrophile and can easily be functionalized via usual aromatic substitution reactions that offer the possibility of further derivatization. The robustness of ferrocene is the result of its 18-electron structure. The hydrophobic neutral ferrocene form of orange color undergoes a mild and reversible oxidation by using electrochemical methods or common oxidizing agents to obtain the 17-electron hydrophilic cationic ferrocenium with purple color. The sandwich geometry is maintained upon one-electron removal. Due to its aromaticity and redox activity, the ferrocene moiety has drawn attention as a useful functionality in virtually any field of applied science. It has been used as a building block for the design of switchable functional systems[2], electro- and photo- responsive materials[3], in supramolecular chemistry[4] and for the construction of sensory devices.[5,6]

Beside the properties mentioned above, the lipophilic nature of ferrocene and the stability of the ferrocenyl group in aqueous, aerobic media have made ferrocene suitable for conjugation with pharmacophores.[7-9] Although ferrocene itself is nontoxic, the cytotoxicity of ferrocenium derivatives was discovered during the 1980s.[10] The anticancer effects are mainly attributed to the formation of reactive oxygen species (ROS) via the Fenton pathway[11] which induces DNA damage followed by cell death.[12] In the past decades, ferrocene derivatives with a broad range of biological activities, such as antimalarial, antitumor,[13,14] antiparasitic, antibacterial, antifungal, and antiviral[15] effects have been prepared.

In steroid-ferrocene conjugates a steroid skeleton is connected directly or via a linker group to the ferrocene moiety. These hybrid derivatives may incorporate some favorable properties of both components. Due to the hormonal activity of natural and synthetic steroid derivatives, great effort has been directed to explore the biological activity of their ferrocene derivatives, and the results have been summarized in some reviews.[7,14,16] One of them, concentrating especially on the anticancer activity of ferrocene-steroid hybrids, was published quite recently.[17] Beyond potential medicinal applications, the conjugates can also awaken

interest in analytical chemistry and materials science. The introduction of Fc into a steroid, e.g., estrogen, triggers an electrochemical response and may enable electrochemical detection. Coupled with a HPLC system, this methodology can be used to determine the concentration of the circulating hormone or the hormone bound to its receptor to assess receptor levels in tumors. Another advantage of Fc-labelling can be the enhancement of the sensitivity of ESI-MS analysis of steroids.[18] Steroid-Fc conjugates can be utilized to form redox-responsive gels, i.e., they may act as proamphiphiles which form vesicles upon oxidation to the ferrocenium moiety as a polar head group. These vesicles collapse when Fc(III) is reduced to Fc(II).[19,20] Steroid-Fc conjugates can also serve as useful intermediates to prepare ruthenium, rhenium or technetium analogues with potential application as radiopharmaceuticals.[21]

Reactive functional groups (such as hydroxyl, carbonyl, *etc*.) in certain positions of the steroid skeleton offer the possibility for simple derivatization, *e.g.,* via ester formation or carbonyl reactions. At the same time, the bulky ferrocenyl group may hamper steroid-receptor interactions which necessitates the use of linker groups or the introduction of the Fc moiety into less reactive positions. Sometimes the generation of C-C bonds can be favorable to obtain more stable conjugates. Accordingly, the use of organometallic reagents and, in the past decades, the application of transition-metal-catalyzed reactions, have come to the forefront of research. Some synthetic methodologies towards these compounds were summed up in 2013 as part of a review on the synthesis of transition-metal derivatives of steroids.[22]

This review intends to demonstrate the great variety of methodologies that have been successfully applied to obtain these derivatives from the 'classical' organic reactions to homogeneous catalytic procedures.

2. Synthesis of Steroid-ferrocene Conjugates via Classical Organic Reactions

2.1. Acylation of steroid alcohols

Acylation reactions leading mainly to esters and carbamates were carried out with various Fc-carboxylic acid derivatives (**1**-**12**, Figure 1). The main goal was to produce liquid crystals[23] or materials capable of sol-gel transitions.[24-26] Some compounds were synthesized for their potential biological activity.[27] Reactivities of various Fc-containing acylating agents were compared for the derivatization of steroid alcohols for gas chromatographic separation and GC-MS measurements,[28] to enable electrochemical detection in HPLC separations[29] or to enhance the efficiency of ES-MS analysis.[30]

Synthetic methodologies include acylation of steroid alcohols with chlorocarbonylferrocene (**1**, Figure 1) or ferrocenecarboxylic acid anhydride (**2**) (Table 1).
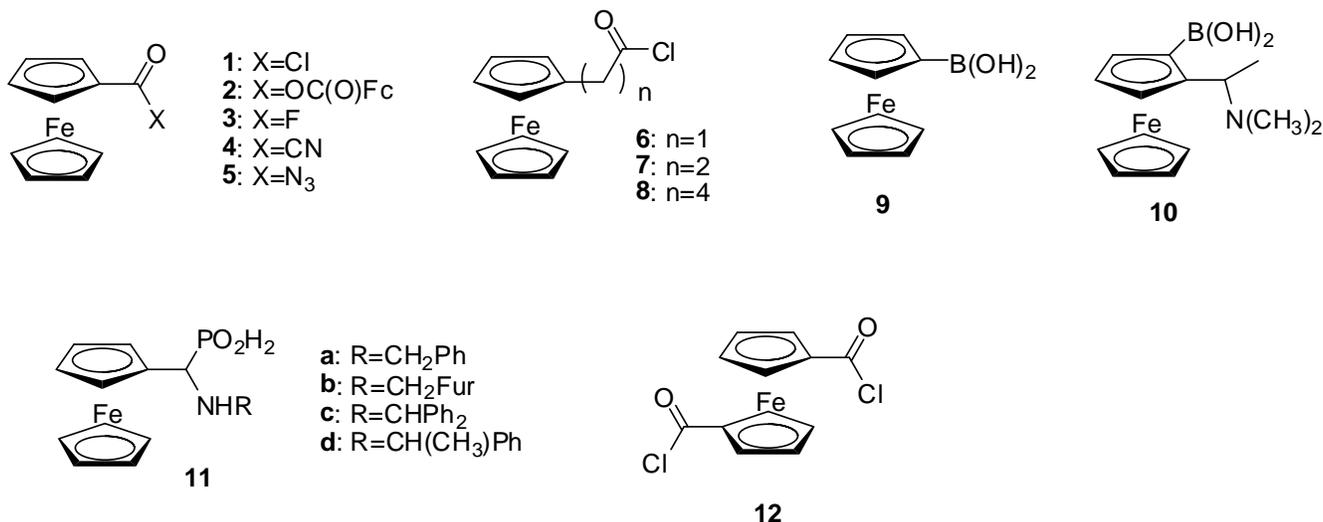
Figure 1. Reagents used for the acylation of steroid alcohols.

Acylation of estrone with one hydroxyl functionality leads to compound **13** with either of the acylation agents (entries 1, 3), but the reaction of estradiol can result in the formation of mono- or diester derivatives, depending on the reaction conditions (entries 2, 4-7). Using acid chloride **1** in less than equimolar amount, a mixture of estradiol-3-ferrocenecarboxylate (**14**) estradiol-3,17-bis(ferrocenecarboxylate) (**15**) and estradiol-17-ferrocenecarboxylate (**16**) was obtained (entry 5). The application of an excess of the reagent led to the biscarboxylate **15** in 81% yield (entry 6).[32] Estradiol-3-ferrocenecarboxylate (**14**) could be produced with excellent selectivity using fluorocarbonylferrocene (**3**, entry 7).[33] X-ray measurements confirmed that esterification occurred at C-3 with ferrocene positioned between the alpha and beta faces of the steroid. Compounds **13** and **14** were used to synthesize the corresponding [130]Ru-ruthenocene derivatives used to study the organ distribution of potential radiopharmaceuticals.[31]

Cholesterol esters were obtained in the reaction of the steroid with chlorocarbonylferrocene (**1**, entry 8), ferrocenecarboxylic acid anhydride (**2**, entry 9)[32] and chloride derivatives of ferroceneacetic acid (**6**, entry 10) and δ-ferrocenyl valeric acid (**8**, entry 11).[34] Interestingly, direct esterification of the acids with the DCC method failed according to the latter report. Testosterone was found to be much less reactive, the 17-carboxylate **21** was produced only in 13% yield (entry 12).[32]

Comparison of various derivatization agents for dehydroepiandrosterone (entries 13-15, Figure 2) in analytical applications proved the superiority of ferrocenoyl azide that leads to carbamate **23**. This reagent was shown to convert a wide range of steroidal substrates (e.g., methyl lithocholate, estrone, digitoxigenins, 3-epidigitoxigenin, digoxigenin) to the corresponding products in 10-30 minutes. Carbamates of cholesterol and stigmasterol (**20**, **24**) were obtained in 73 and 75% yields, respectively, after heating a mixture of the acyl azide **5** and the sterol in toluene at 90 °C for 10-30min (entries 16, 17).[30] ES-MS detection of the ferrocene-based derivatives proved facile, with the molecular radical cation of the derivative dominant in the spectrum.

Table 1. Acylation of steroid alcohols with carboxylic acid derivatives of ferrocene

| entry	reagent	reagent/steroid [mol/mol]	base	temp. [°C]	r. time	product	yield [%]	ref.
1	**2**	1	pyridine	rt	24h	**13**	67	31
2	**2**	1	pyridine	rt	24h	**14**	55	31
3	**1**	1	pyridine	rt	6-12h	**13**	40-45	27
4	**1**	1	pyridine	rt	6-12h	**14**	40-45	27
5	**1**	0.75	AgCN	rt. (then refl. in benzene)	3h (1h)	**14** **15** **16**	37 37 10	32
6	**1**	3.7	DMAP	rt	19h	**15**	81	32
7	**3**	0.67	DMAP	refl. in CH_2Cl_2	12h	**14**	85	33
8	**1**	2.4	pyridine	50	24h	**17**	60	32
9	**2**	1	pyridine	refl.	24h	**17**	57	32
10	**6**	1.2	pyridine	20	24h	**18**	38	34
11	**8**	1.2	pyridine	20	24h	**19**	43	34
12	**1**	1	pyridine	65	19h	**21**	13	32
13	**1**	1mikrog/50mikrog	pyridine	60	10 min	**22**	10[a]	29
14	**4**	1mikrog/50mikrog	Et₃N	60	10 min	**22**	5[a]	29
15	**5**	1mikrog/30mikrog	-	80	10 min	**23**	100[a]	29
16	**5**	1	-	90	10-30 min	**20**	73	30
17	**5**	1	-	90	10-30 min	**24**	75	30
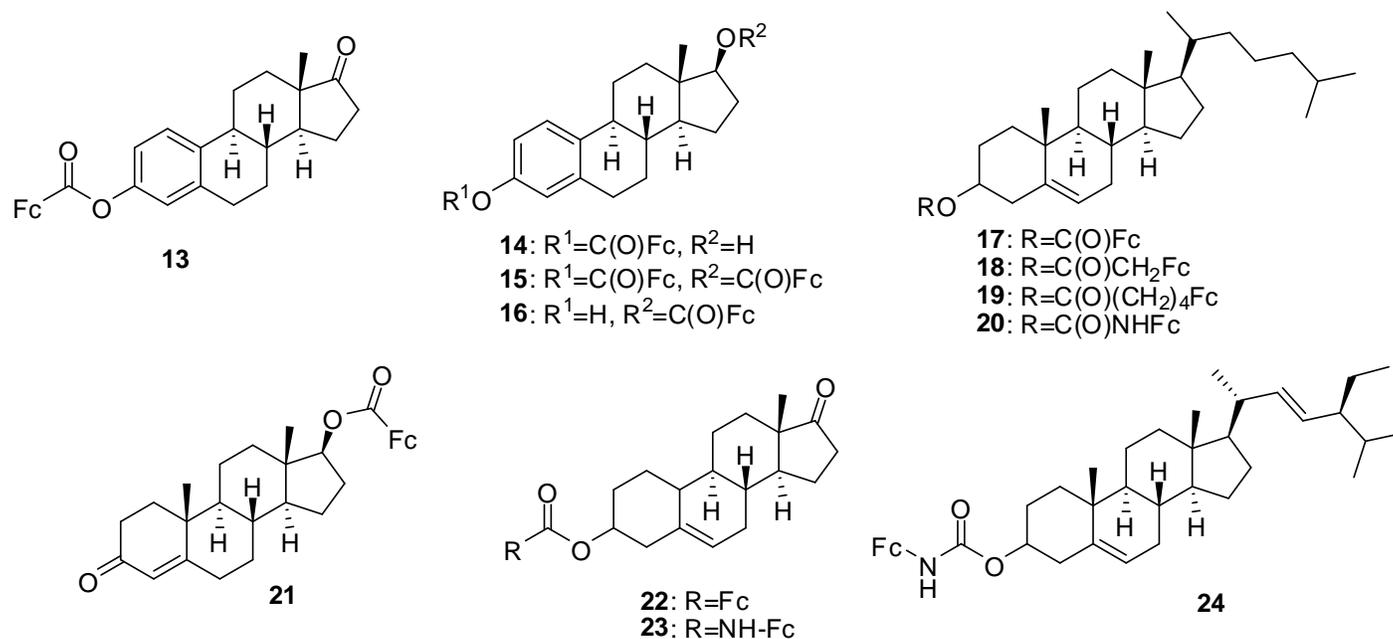
Figure 2. Products of acylation of steroid alcohols.

Efficiency of ES-MS analysis could also be enhanced by the formation of cyclic boronate esters from 2- or 4-hydroxyestradiol (**25**, **26**, Figure 3).[35] The methodology made it possible to analyze the isobaric catechol estrogens in the presence of one another. Ferroceneboronic acid (**9**) and *N,N*-dimethylaminoethyl ferroceneboronic acid (**10**) were used for the derivatization of diols for gas chromatographic separation and GC-MS measurements[28] to obtain esters **27-37** (Figure 2). In the case of compounds with two vicinal diol moieties, a mixture of mono- and diesters was formed in most cases. Acylation using ferroceneboronic acid (**9**) led to monoester **30**, together with diester **31** showing the higher reactivity of the 22,23-diol group. The ratio of products depended also on the choice of the acylating agent. While the 20,22-monoester **32** was the predominant product in the presence of reagent **9**, the use of boronic acid **10** led to a mixture of ester **33** and diester **34**.
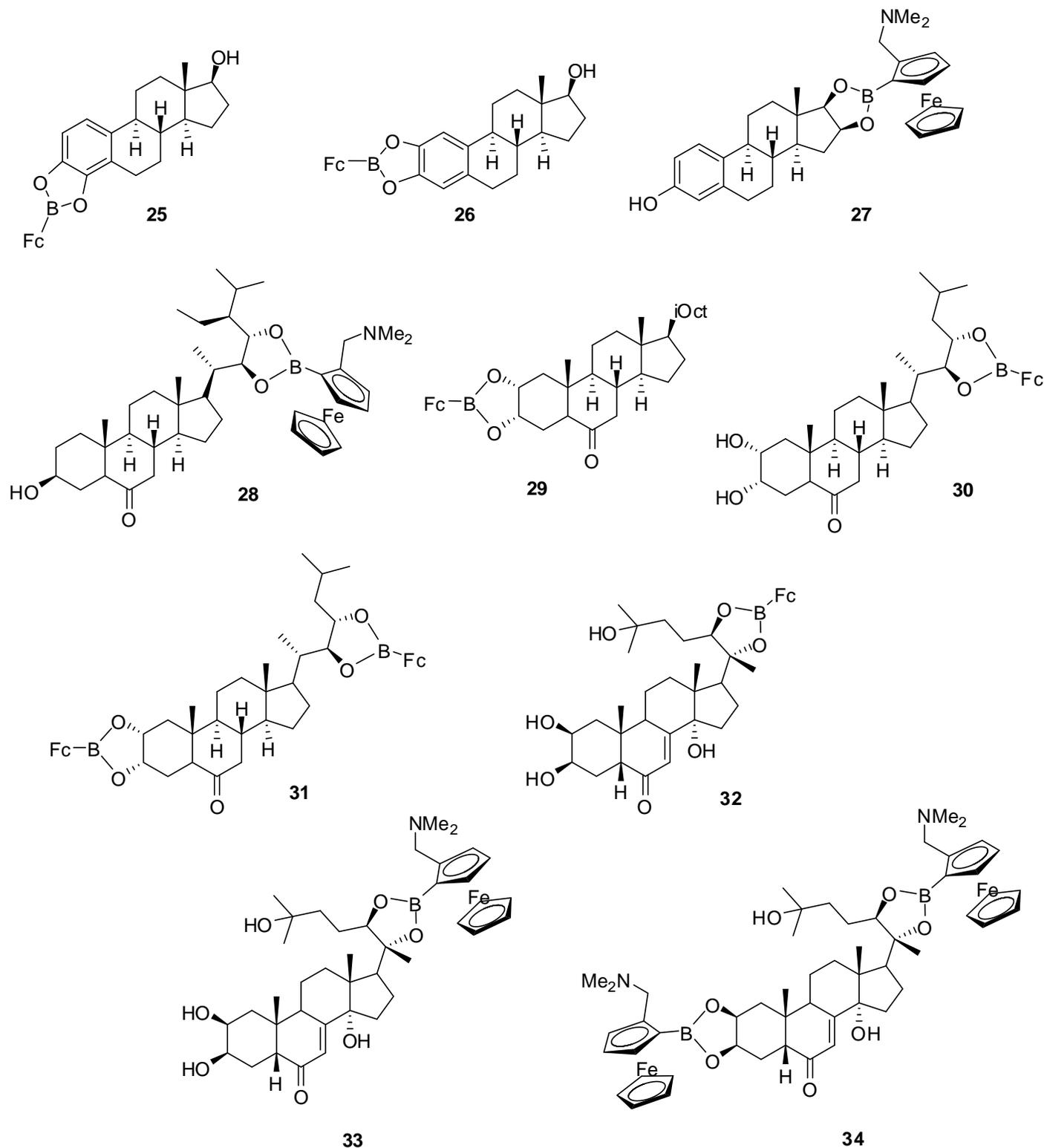
Figure 3. Boronate esters of steroidal diols.

α-(Ferrocenyl)-aminomethanephosphonous acid derivatives were prepared (Scheme 1) to connect the ferrocenyl group and the steroid skeleton with the help of aminophosphonous acid, often found in biologically-active compounds.[36] Esters **35a–c** were obtained as mixtures of four diastereoisomers, which were clearly visible in ^{31}P NMR spectra as four well-separated signals. The ratio of diastereoisomers varied from

2:2:3:3 in the case of *N*-diphenylmethyl derivative **35c** to even 1:1:6:6 in the case of **35b**, while the use of *N*-(*R*)-α-methylbenzylamino(ferrocenyl) methane phosphonous acid as the acylating agent led to the formation of two diastereoisomers of **35d** in a 1:2 ratio.


a: R=CH$_2$Ph, **b**: R=CH$_2$Fur, **c**: R=CHPh$_2$, **d**: R=CH(CH$_3$)Ph
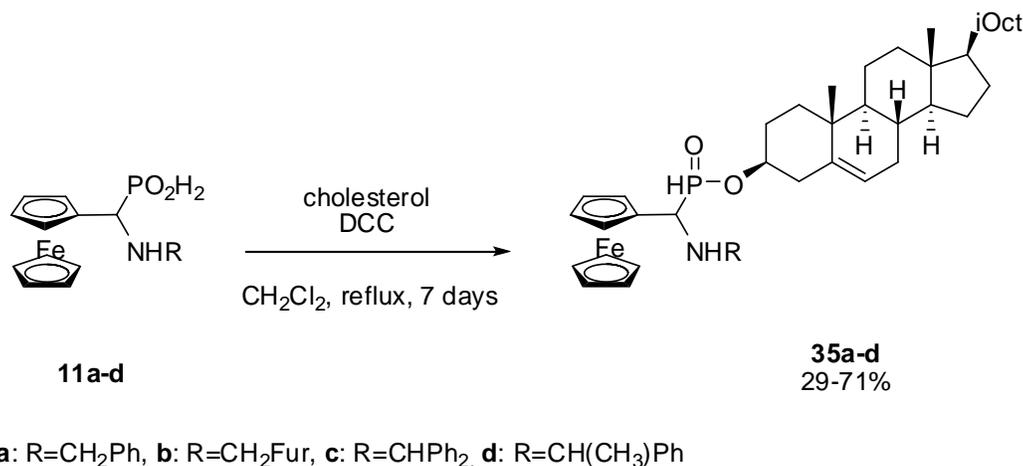
Scheme 1. Acylation of cholesterol with α-(ferrocenyl)-aminomethanephosphonous acid derivatives **11a-d**.

The ester functionality can be introduced to both cyclopentadienyl rings of ferrocene. 1,1'-Bis-(chlorocarbonyl)ferrocene (**12**) was prepared by the reaction of the acid with oxalyl chloride and a catalytic amount of pyridine.[37] The 1,1'-diesters of cholestanol (**36**, Scheme 2) and cholesterol (**37**) were obtained in moderate yields in the presence of triethylamine.
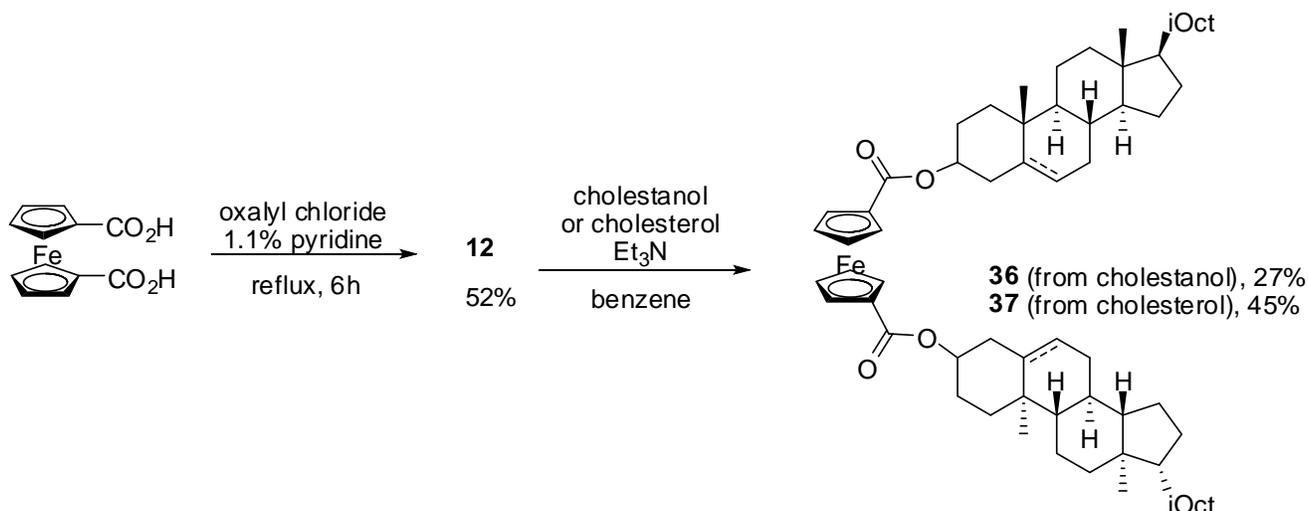

Scheme 2. Preparation of steroid diesters of ferrocenedicarboxylic acid (**36**, **37**).

Compound **40**, with succinic acid as the linker between the two components, was reported by Cais for potential use in metalloimmunoassays (Scheme 3).[38] Estradiol was converted to the 17β-hemisuccinate **38**. This carboxylic acid was connected to ferrocene *via* an amide bond using (aminomethyl)ferrocene (**39**) as the reagent. Unfortunately, no particulars of the synthetic methodology were disclosed.
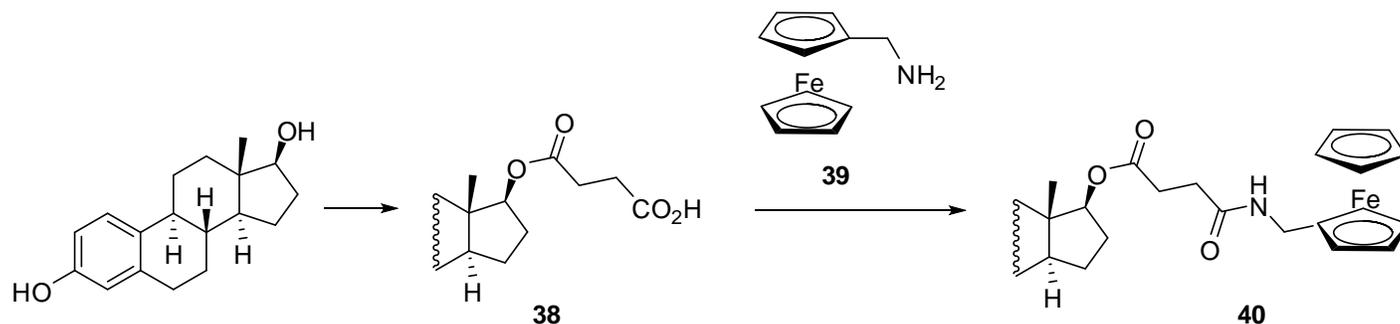
Scheme 3. Outline of the synthetic methodology leading to the ferrocene-steroid conjugate **40.**

Steroid-ferrocene conjugates have been designed to obtain redox-responsive gels. In these molecules, the steroid alcohols are connected to the ferrocene moiety *via* a suitable linker. Ester **41** was prepared by the acylation of cholesterol with *N*-protected glycine (Scheme 4).[24] After the removal of the protecting group, the amino derivative **42** was connected to ferrocene by an amide bond to produce conjugate **43**. According to SEM measurements, compound **43** self-assembled into different supramolecular structures in different solvents. Chemical oxidation of the ferrocenyl residue resulted in a phase transition from the gel state to the solution state.
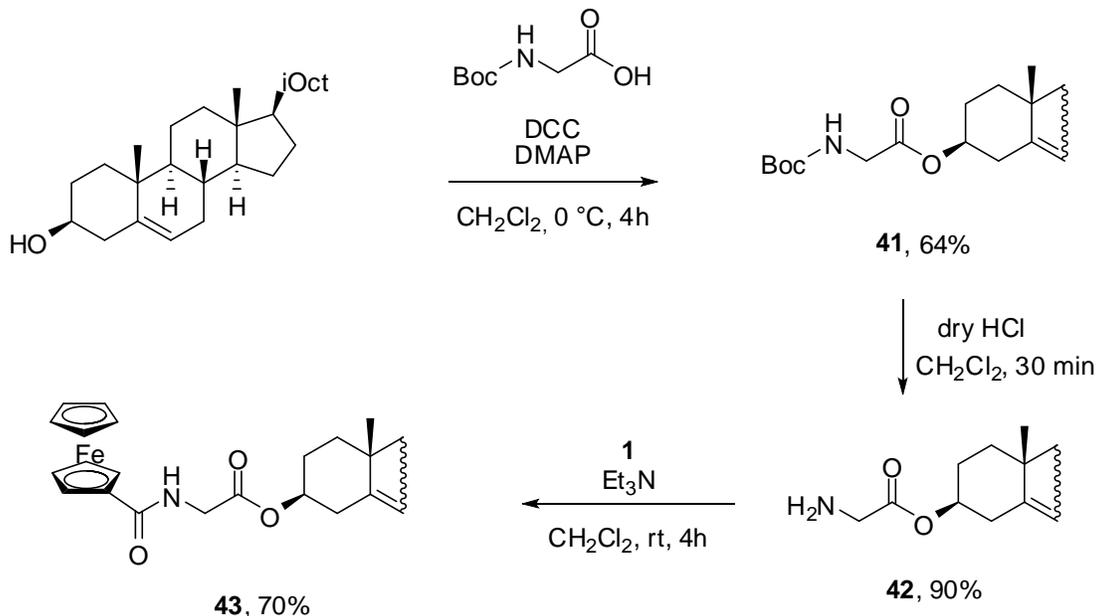

Scheme 4. Synthesis of steroid-Fc conjugate **43** with glycine as linker group.

Similarly, linker groups with amino functionalities were introduced into compounds **46a-d** (Scheme 5) to give them some hydrogen-bond formation sites, and to enhance their aggregation ability.[25] Sol–gel phase transitions of these conjugates could easily be triggered by chemical redox reaction, shear stress, sonication or change in the temperature.
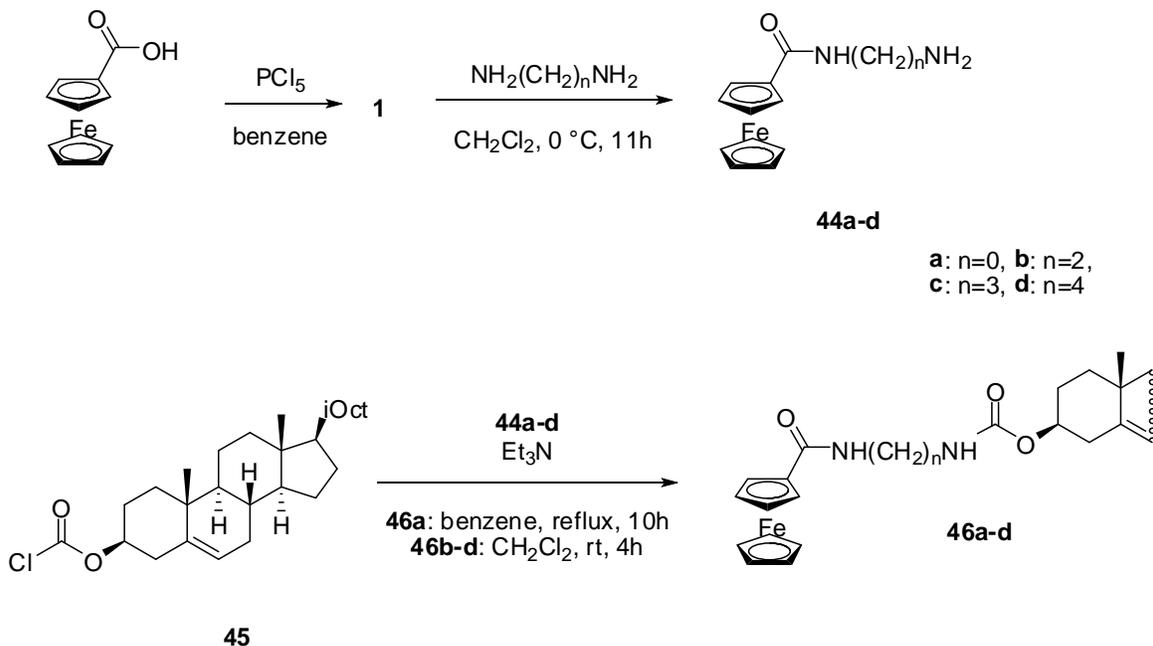
Scheme 5. Synthesis of conjugates **46a-d** with linker groups with amino functionalities.

In a similar fashion, conjugates containing two cholesteryl groups (**47**, **49**) were produced starting from 1,1'-*bis*(chlorocarbonyl)ferrocene (**12**) (Scheme 6).[26] Compound **47** was found to form a thixotropic gel, with a potential use in wastewater treatment. The methodology was proved to be very effective using iodine-contaminated water as a model system, combining the efficiency of liquid–liquid extraction and the simplicity of liquid–solid separation.
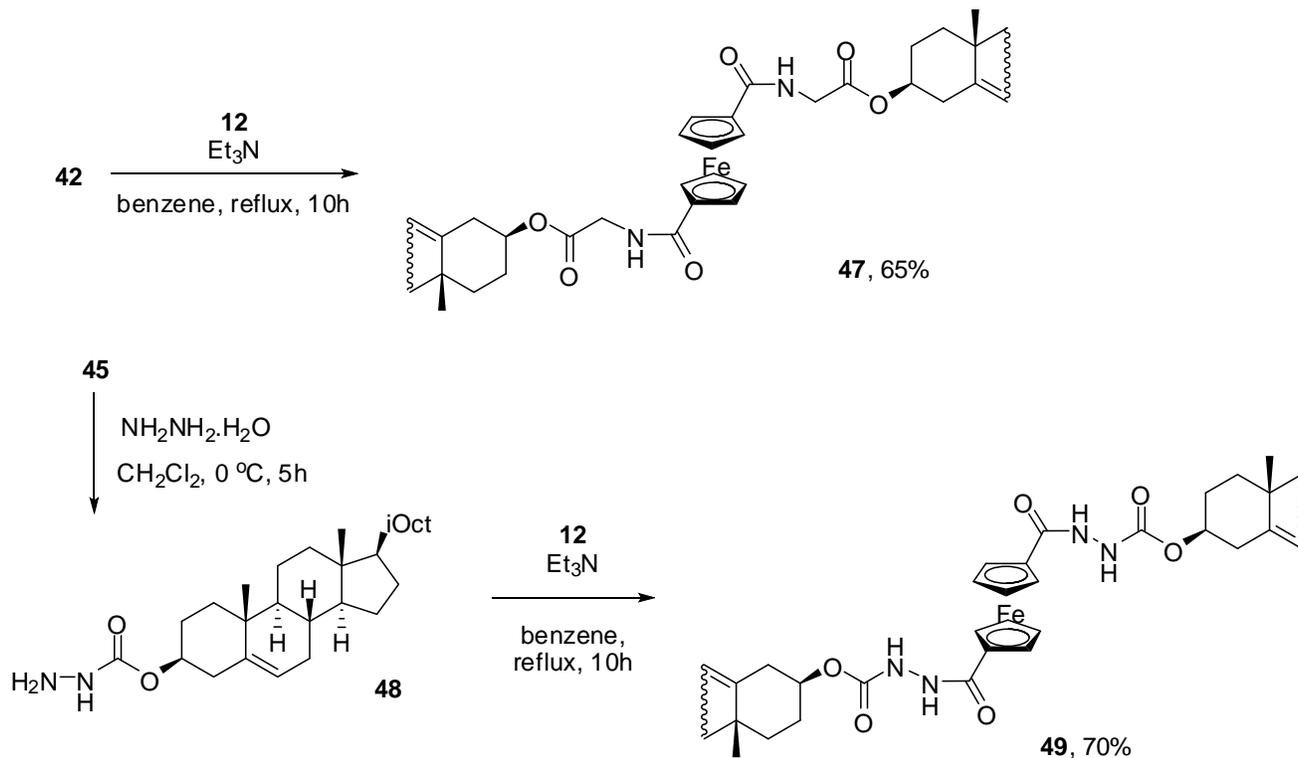
Scheme 6. Synthesis of conjugates **47** and **49** with two cholesteryl groups.

The application of 1,1'-*bis*(chlorocarbonyl)ferrocene (**12**) as the starting material offers the possibility to introduce two different groups on the cyclopentadienyl rings. Compound **51** was synthesized from cholest-5-en-3β-yl-4-(10-hydroxydecyloxy)benzoate (**50**) and hydroquinone monobenzyl ether (Scheme 7),[23] and was used as a building block of a first-generation dendritic core substituted with six mesomorphic ferrocene units (**52**). The dendrimer showed liquid-crystalline properties and exhibited a broad enantiotropic smectic A phase, as proven by polarized optical microscopy, differential scanning calorimetry, and X-ray diffraction studies.
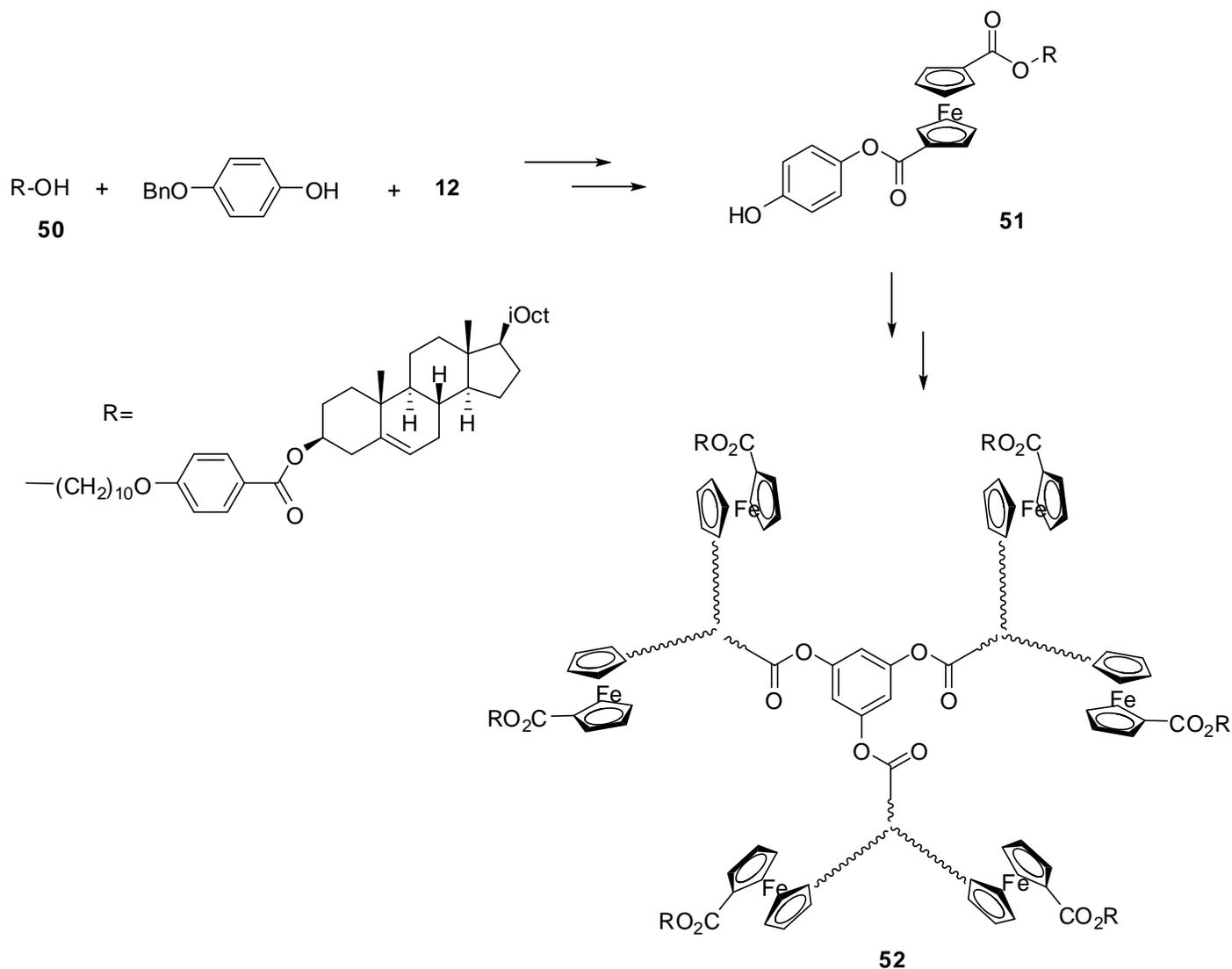

Scheme 7. Overview of the synthesis of liquid crystalline dendrimer **52** incorporating steroid-Fc conjugate **51** as a building block.

2.2. Alkylation of steroid alcohols

Several ether derivatives were prepared to obtain chemically switchable membranes or vesicles. Ferrocene was chosen as a redox-active headgroup connected to the apolar steroid skeleton; thus, upon oxidation of ferrocene to ferrocenium, amphiphilic molecules can be formed. The first example, compound **54** was produced by the reaction of methyl iodide with the ferrocene derivative **53** leading to the formation of a carbocation via quaternization of the amine derivative. Carbocation formation was followed by alcoholysis by cholestanol (Scheme 8).[37] The same methodology was used to obtain the *bis*(ferrocenylmethyl)-estradiol

diether (**55**) with the 3,17 β-estradiol unit as a rigid spacer.[39] Vesicle formation was attempted with the neutral monomers **54**, **55**, but no aggregates could be detected by laser-light scattering. At the same time, electrochemical or chemical (Ce^{4+}) oxidation of the conjugates to the corresponding ferrocenium derivatives resulted in the formation of stable vesicles in water. The aggregates were found to collapse upon treating with aqueous dithionite solution to reduce Fe^{3+} to Fe^{2+}, and the monomers could be recovered and re-oxidized to form the vesicles, again. Electrochemical studies showed that the two headgroups of compound **55** could be oxidized independently; this was the first example of a redox-switchable, organometallic bolaamphiphile.
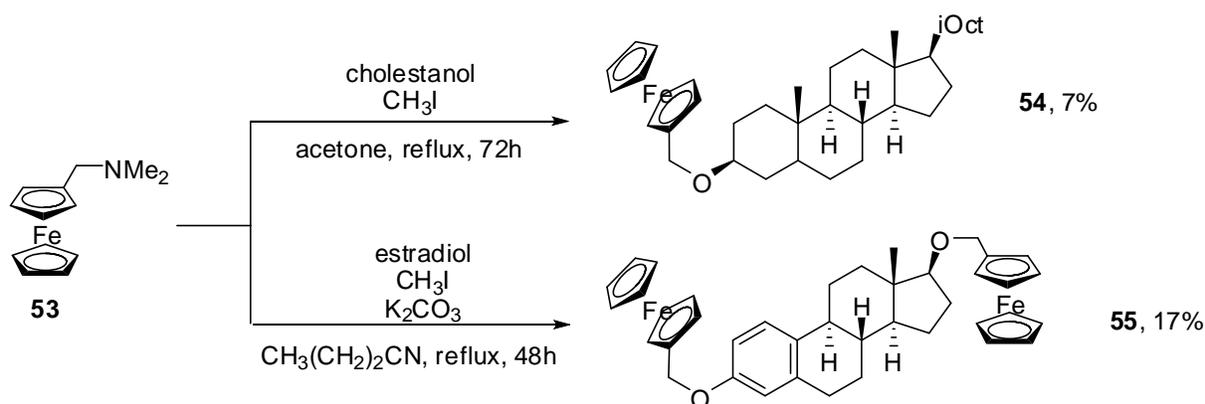

Scheme 8. Alkylation of steroid alcohols with (dimethylaminomethyl)ferrocene **53.**

(Ferrocenylmethyl)trimethylammonium iodide (**56**) was used as the alkylation agent by Sakač to produce ether derivatives of estradiol (**57**) and estrone (**59**) (Scheme 9).[40] Interestingly, the outcome of the reaction depended greatly on the choice of the solvent. Ethers **57** and **59** were the sole products in DMF, while ether formation was accompanied by *C*-alkylation in methanol. The latter reaction occurred preferentially at position 4 of the steroid core, leading to compounds **60** and **62**, although a 2-alkylated derivative (**61**) could also be detected in the reaction of estradiol. The authors offered two possible explanations for the *C*-alkylations. In protic solvents, the nucleophilicity of the phenoxide oxygen of the steroids is decreased because of hydrogen bonding, which may promote *C*-alkylation. Alternatively, electron transfer between the electron-rich phenoxide and the ferrocenylmethyl cation could yield two stable radicals that promote *C*-alkylation, *C*-reactivity being more pronounced in the case of the phenoxide radical compared to the anion. 4-(Ferrocenylmethyl)estra-1,3,5(10)-triene-3,17β-diol (**58**) was found to be more active against the hormone-dependent breast cancer cell line MCF-7 than doxorubicin, so A-ring substitution of steroidal estrogens is a plausible strategy for preparing steroid-ferrocene conjugates acting against tumor cells.

Ferrocenylmethanol (**62**) was the source of the ferrocenylmethyl cation in the alkylation of 7α-mercapto-estradiol (**63**) to obtain conjugate **64** (Scheme 10).[41] The 7α-position was chosen for conjugation to retain estrogen receptor affinity. The complex indeed behaved like estrogens. In low concentrations, it lacked cytotoxic effect; however, at higher concentrations, it became cytotoxic on MDA-MB-231 cells.
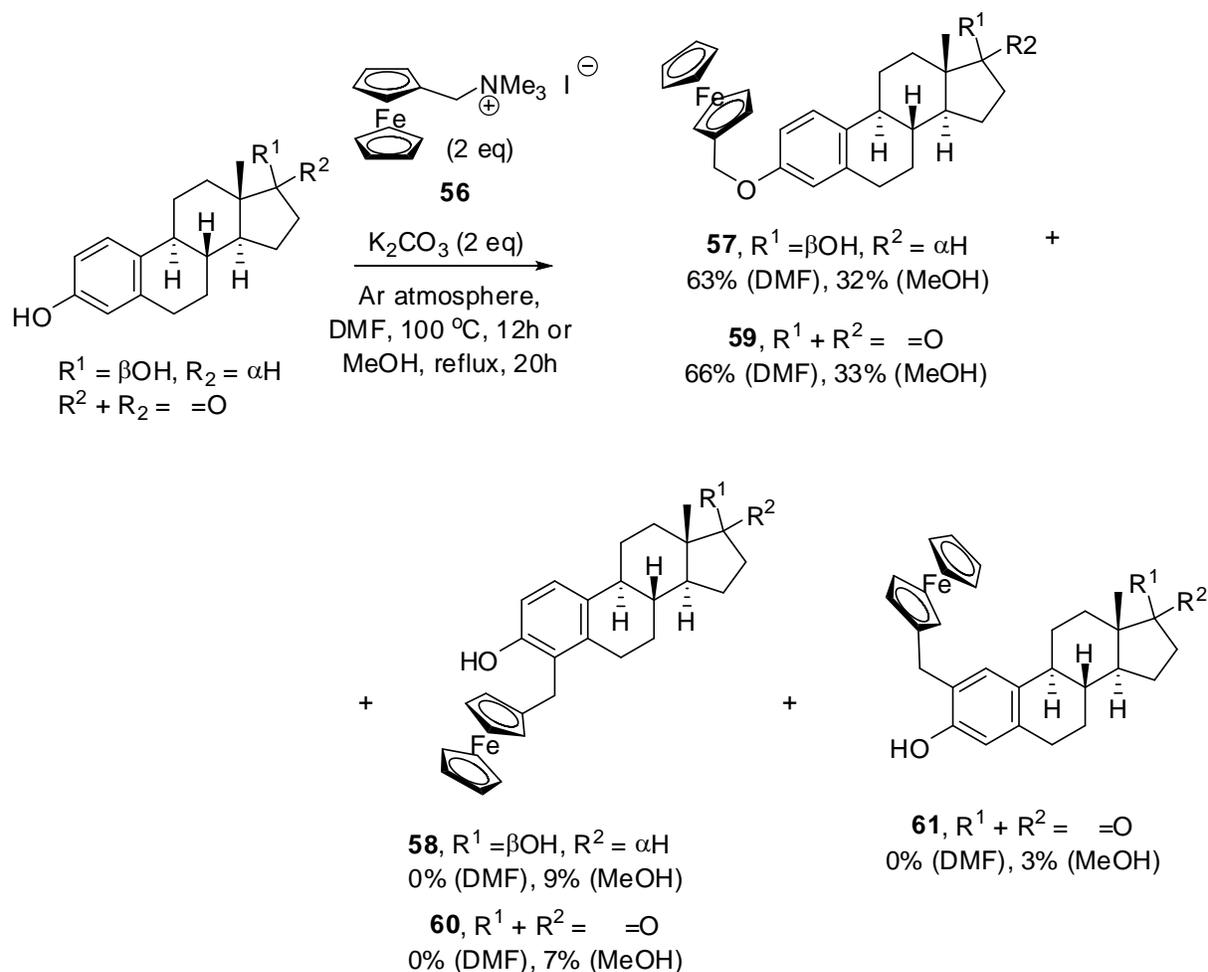
Scheme 9. Synthesis of *O*- and *C*-alkylated derivatives **57-61.**
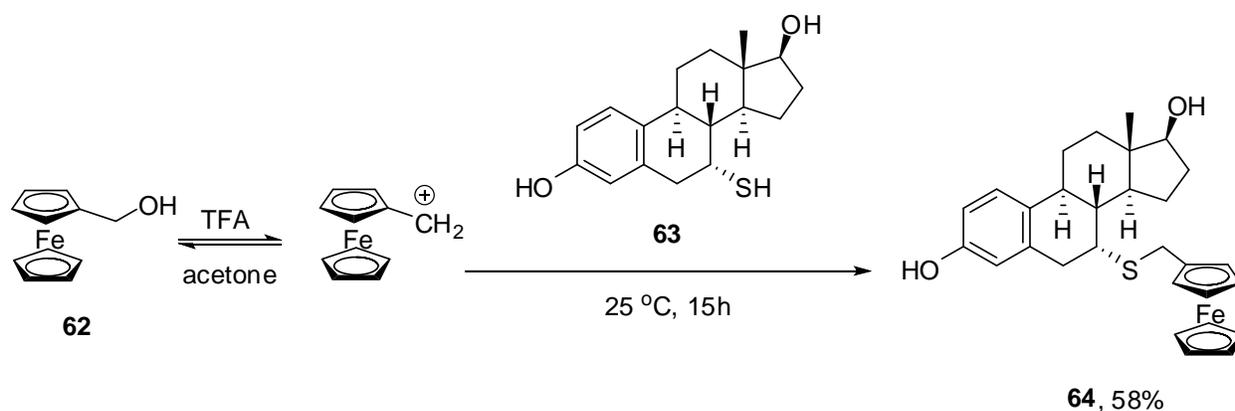

Scheme 10. Synthesis of thioether **64.**

The Fc moiety was attached to estrogens through a linker group by Cais to obtain compounds that can potentially be used in metalloimmunoassays.[42] First, 3-*O*-carboxymethyl ether derivatives **65a-c** were synthesized that were then converted to the active esters **66a-c** in the presence of *N*-hydroxysuccinimide (Scheme 11). The latter compounds were used as acylating agents to connect Fc via an amide bond to produce **67a-c.**
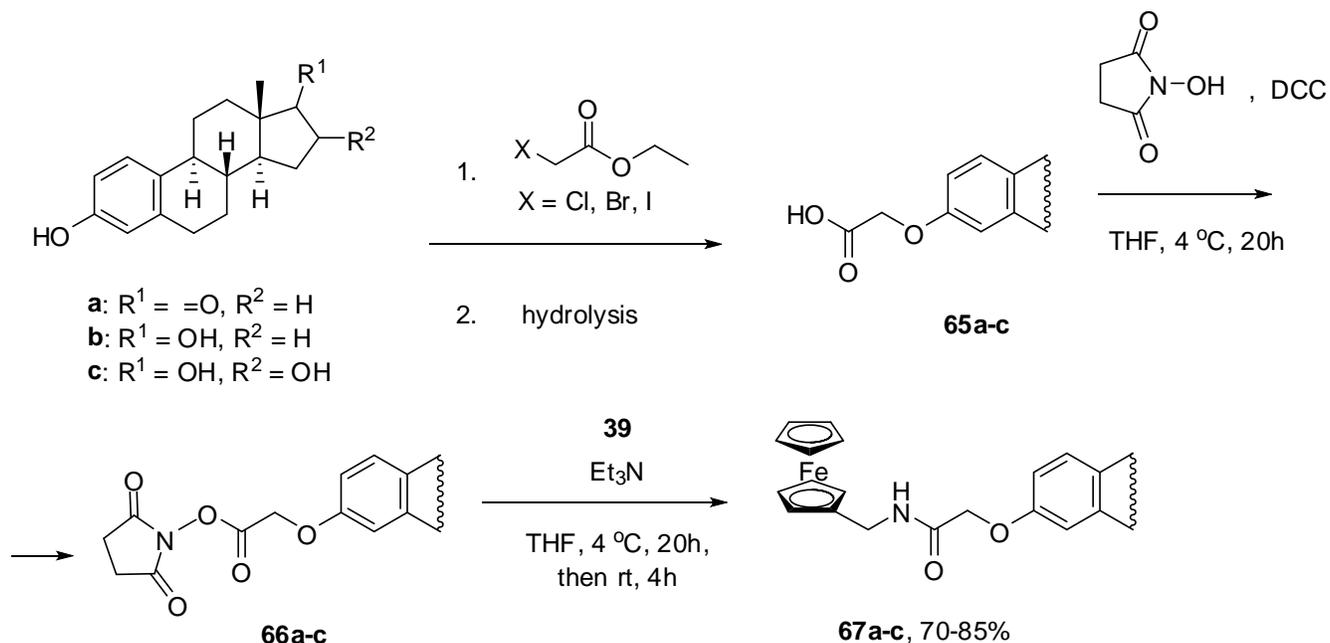
Scheme 11. Synthesis of Fc-estrone (**67a**), -estradiol (**67b**) and -estriol conjugates (**67c**) (DCC: *N,N'*-dicyclohexylcarbodiimide).

The cationic cholesterols **70**, **71** and **73**, **74**, synthesized by the reaction of cholest-5-en-3β-oxyethan-*N,N*-dimethylamine (**68**) with the appropriate 1-(ω-bromoalkyl)ferrocenes (**69**) or 1,1'-bis(1-(ω-bromoalkyl))ferrocenes (**72**) (Scheme 12) were shown to be capable of controlled gene transfection.[43] The conjugates formed mixed liposomes in the presence of 1,2-dioleoyl-*sn*-glycero-3-phosphatidyl ethanolamine. The vesicles possessing ferrocene in the reduced state induced an efficient gene-transfection capability using pEGFP-C3 plasmid DNA in three cell lines, even better than the commercial lipofectamine 2000. Redox activities of the co-liposomes and their lipoplexes could be regulated using the alkyl ferrocene moiety. This evidence suggests that these redox-driven systems could be used in gene-delivery applications where transfection needs to be performed partially or temporarily.
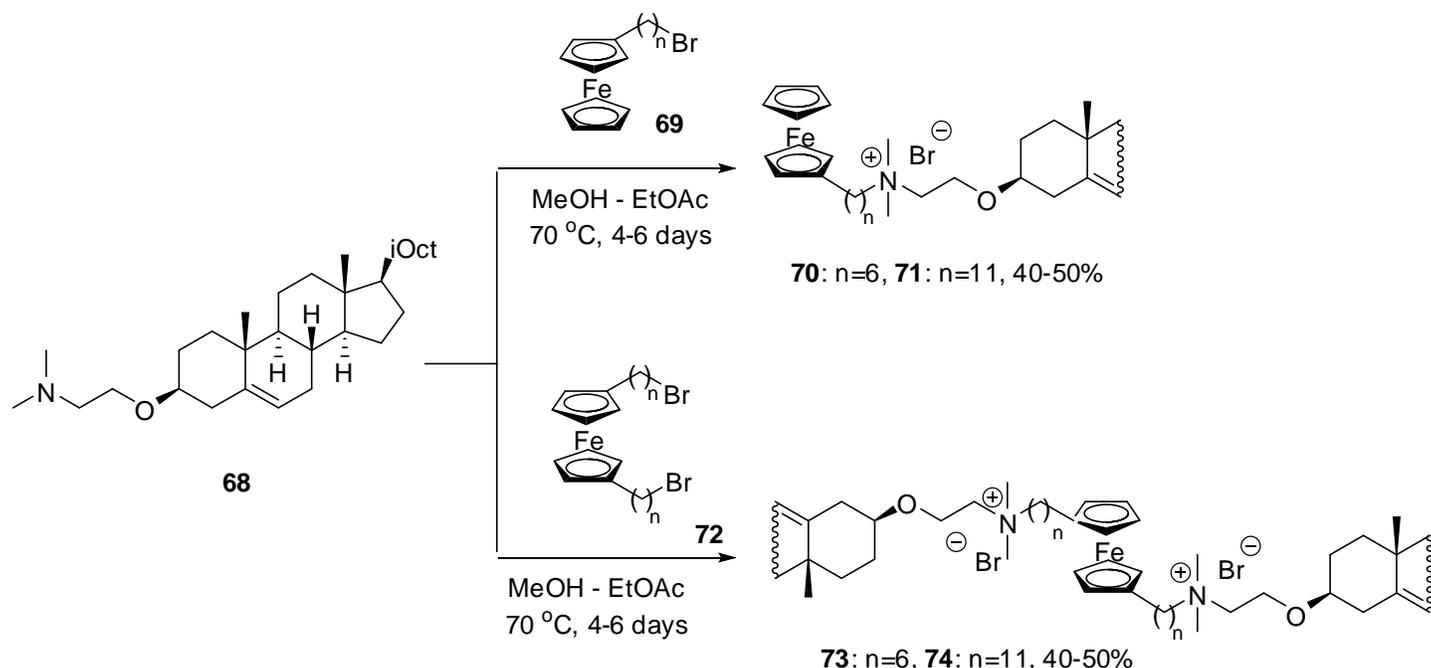
Scheme 12. Synthesis of cationic steroid-ferrocene conjugates **70**, **71** and **73**, **74**.

2.3 Other reactions of steroid alcohols

Ferrocene conjugates of cholesterol (**76**) and stigmasterol (**77**) (Scheme 13) were obtained by the replacement of the OH group with a (ferrocenyl)thioimidoyl moiety.[44] Mitsunobu reaction of the steroid alcohols with *N*-(ethoxycarbonyl)ferrocenecarbothioamide (**75**) was relatively slow compared to simple alcohols, such as benzyl alcohol. Good yields for steroid substrates could be obtained in days rather than hours. NMR measurements revealed inversion of the configuration at C-3, typical for the Mitsunobu reaction.
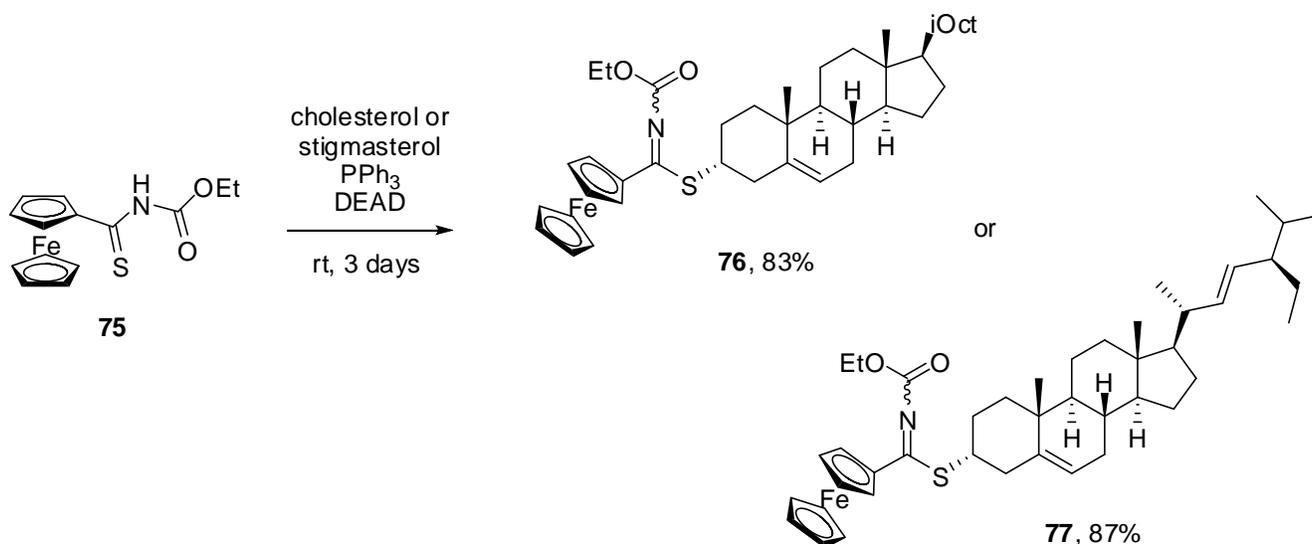
Scheme 13. Mitsunobu reaction of steroid alcohols leading to conjugates **76** and **77**.

Mono- (**81**) and bis cholesterol derivatives (**82**) were prepared in good yields by the isomerization reaction of Morita–Baylis–Hillman adducts **79** and **80** obtained as an inseparable mixture (ratio: 2:3) in the

reaction of 1,1'-ferrocene-dicarboxaldehyde (**78**) and acrylonitrile[45] (Scheme 14). Compound **82** was reported to show liquid crystalline properties.
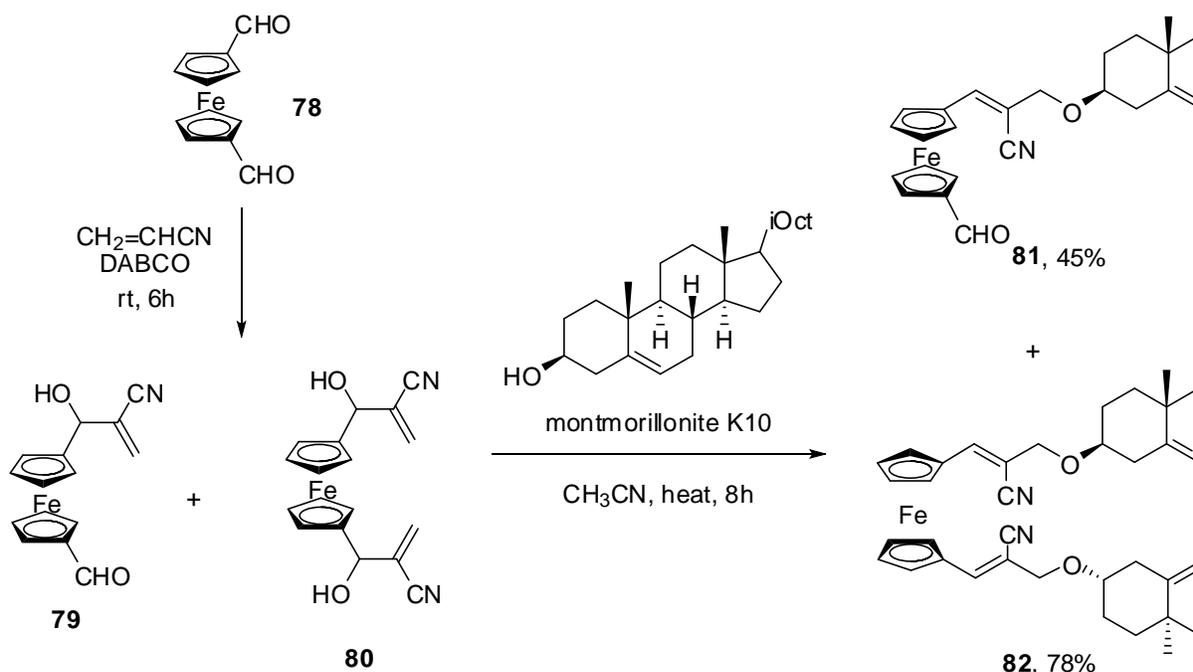
Scheme 14. Reaction of 1,1'-ferrocene-dicarboxaldehyde (**78**) with Morita–Baylis–Hillman adducts **79** and **80**.

2.4 Transformation of steroids with carbonyl functionality

Another common moiety of natural steroids is the carbonyl group that easily undergoes nucleophilic additions or aldol-type reactions. The first report for the derivatization of a steroid ketone appeared in 1970.[46] Hydrazones **86** and **87** were prepared in good-to-excellent yields by the reaction of ferrocenecarboxhydrazide (**85**) with androstanolone benzoate (**83**) or testosterone benzoate (**84**), respectively (Scheme 15). Unfortunately, these compounds (among other Fc derivatives connected to biomolecules in a similar fashion) were found to bear no significant biological activity, such as antibacterial, antifungal, or antiparasitic properties.
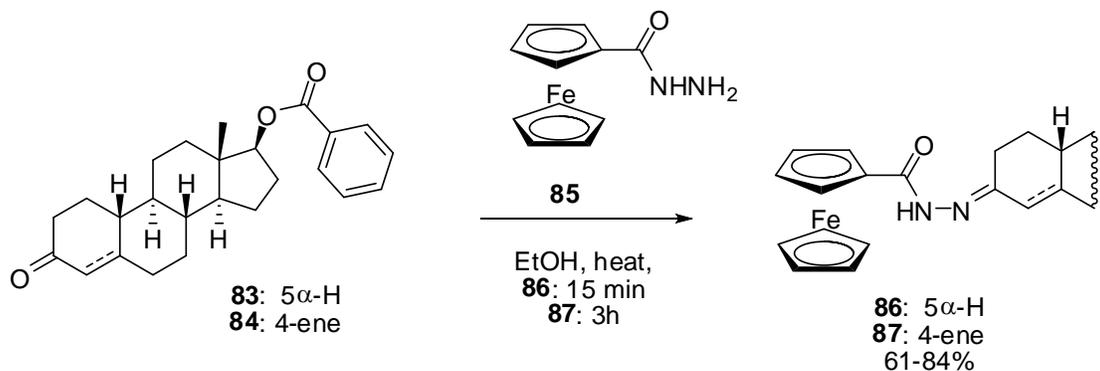

Scheme 15. Synthesis of hydrazones **86** and **87**.

Claisen-Schmidt condensation of steroidal ketones with ferrocenecarboxaldehyde (**88**) results in the formation of ferrocenylmethylidene derivatives, so the Fc moiety can be connected to different positions of the steroid skeleton by a C-C double bond. 16-Ferrocenylmethylidene estrone (**89**, Scheme 16) was prepared to be used as starting material to produce radiopharmaceuticals[47] or to carry out detailed structural investigations and bioactivity tests.[48] Single-crystal X-ray diffraction studies proved the *E* configuration of the product with the cyclopentadienyl ring adopting a coplanar conformation with the olefinic group of the α,β-unsaturated system. Interestingly, it could be isolated as two conformers in the solid state using different crystallization media, benzene and carbon tetrachloride. The conformer that co-crystallized with a benzene molecule had the Fc positioned on the alpha face of the steroid skeleton, while in the other one, co-crystallized with carbon tetrachloride, the Fc pointed to the beta face. At the same time, NMR data showed the presence of one species, indicating a low rotational energy barrier between the two conformers. According to biological tests, conjugate **89** was more cytotoxic on hormone-dependent MCF-7 and T-47D than on hormone-independent MDA-MB-231 breast cancer cell lines.
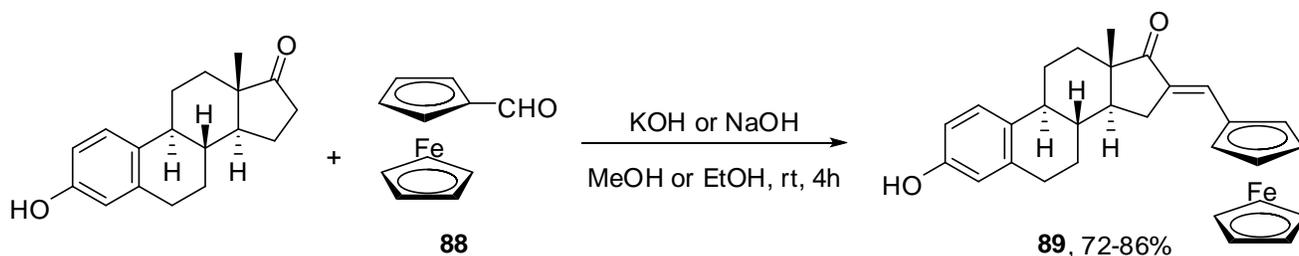

Scheme 16. Synthesis of 16-ferrocenylidene estrone (**89**).

The reduction of **89** with NaBH$_4$ led to diol **90**, while Pd-catalyzed hydrogenation resulted in the formation of a mixture of the two ferrocenylmethyl derivatives **91** and **92** (Scheme 17).[48] The 17β-ol (**92**) could be produced in 99% and 98% yields, respectively, by the NaBH$_4$ reduction[49] of ketone **91** or by the hydrogenation[48] of ferrocenylmethylidene conjugate **90**. The structures of products **90-92** were proven by X-ray crystallography.[48-50] According to docking studies, the steroid moiety is positioned in the estradiol-binding pocket of the estrogen receptor surrounded by the same hydrophobic core as 17β-estradiol, however, the position of the ferrocene is different depending on the structure of the conjugates. In the ferrocene conjugates **91, 92**, as well as in one conformer of **89** (obtained with crystallization from carbon tetrachloride), the hormone moieties adopt the same orientation as 17β-estradiol does. In the other conformer of **89,** and in **90**, the steroid skeletons are positioned opposite to the direction of the original hormone.[48]
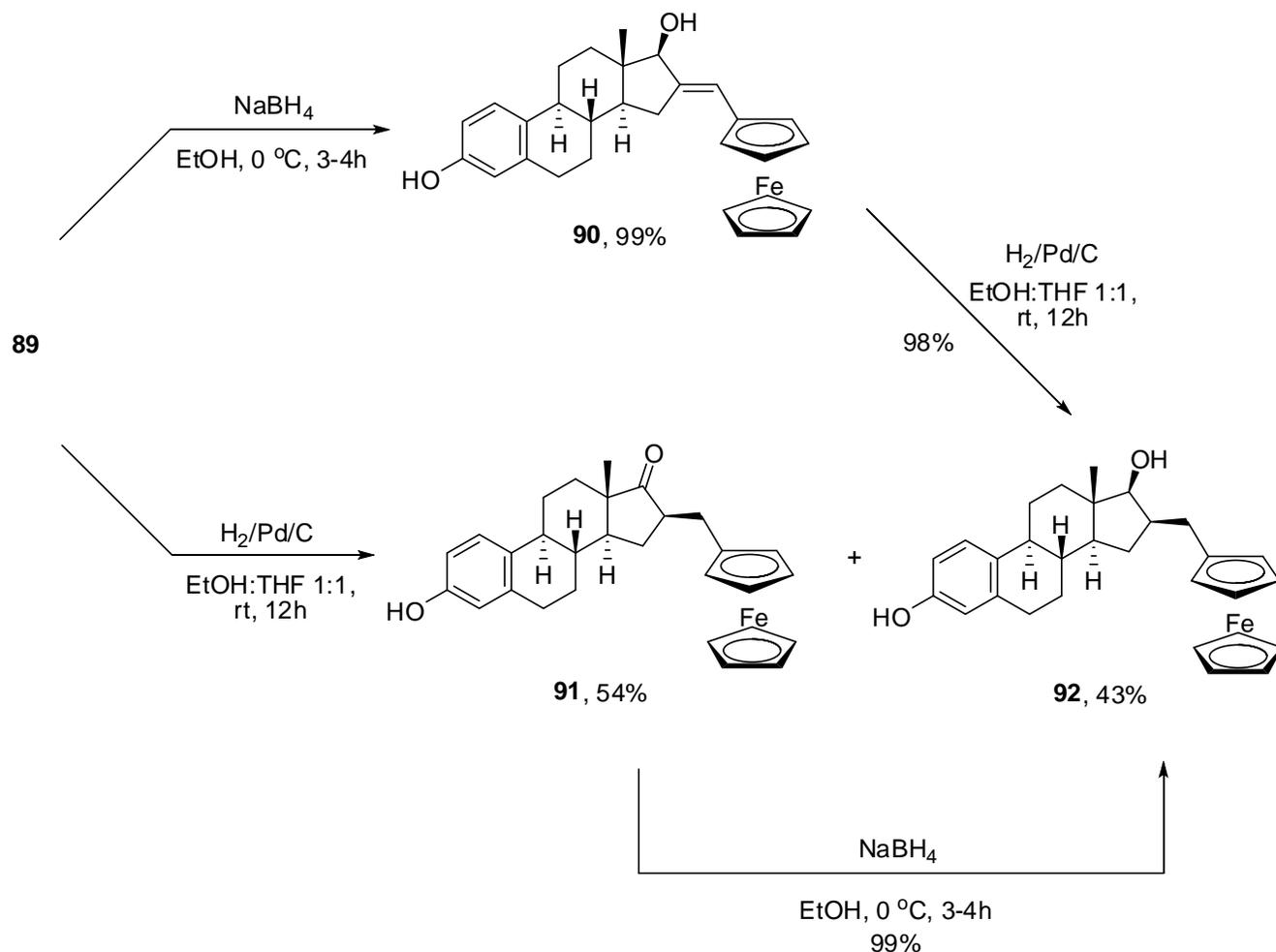
Scheme 17. Reduction of conjugate **89** under various conditions.

The estrone conjugate **89** served as a starting material to produce the radioactive [99mTc] derivative **94** (Scheme 18).[47] Organ-distribution studies showed a tumor/muscle [99mTc] concentration ratio of 3:1 in the case of MXT-mammary tumors in mice. It should be mentioned that the [99mTc] compound **94** could be obtained in better yield via route A than via route B.
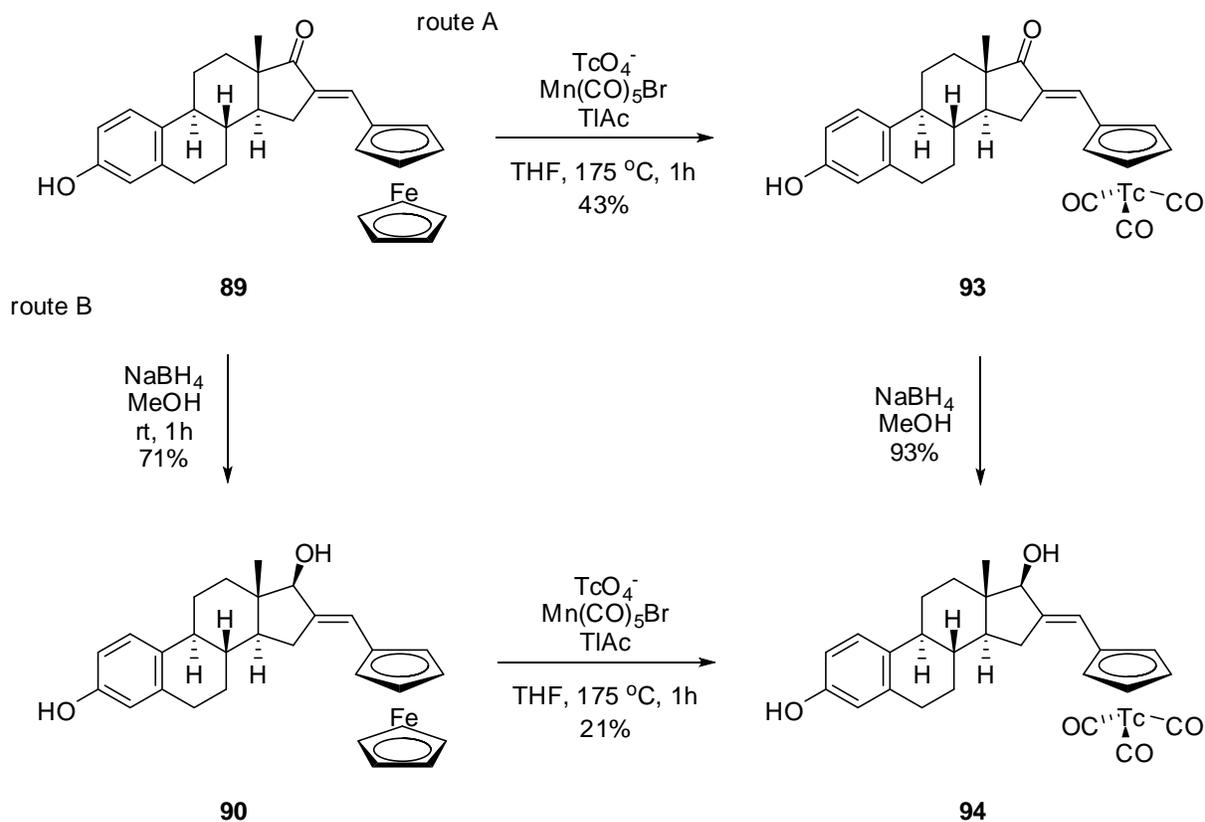
Scheme 18. Synthetic pathways toward the ^{99m}Tc compound **94**.

Condensation reactions of a range of steroidal ketones with ferrocenecarboxaldehyde (**88**) led to the analogous derivatives of different hormones and anti-inflammatory drugs, such as conjugates of testosterone (**95**), methyltestosterone (**96**), androsterone (**97**) 17-hydroxypregnenolone (**98**), prednisolone (**99**), hydrocortisone (**100**),[51] *trans*-androsterone (**101**), pregnenolone(**101**), dehydroepiandrosterone (**103**)[52] (Figure 4). Chemical structures of **95-100** were determined based on HR ESI-MS and two-dimensional NMR spectroscopy. Unfortunately, the authors did not comment on the incorporation of two ferrocenyl units into methyltestosterone leading to the pentacyclic derivative **96**.[51] Crystallographic data confirmed that condensation was achieved at C-16 for **97** and **101**, and at C-21 for **102**. Ferrocene points towards the beta face of the steroid in compounds **97** and **101,** while in **102** it is positioned between the alpha and beta faces.[52]

The first two compounds (**95**, **96**) showed dose-dependent antiproliferative activity on HeLa cell lines and had similar potency to the standard anticancer drug, doxorubicin.[51] Conjugates **97**, **100** and **101** displayed moderate-to-high antiproliferative activity on colon cancer HT-29 and breast cancer MCF-7 cell lines with compound **97** exhibiting the highest activity on HT-29.[52] Conjugates **95-100** exerted moderate antioxidative effect.[51]
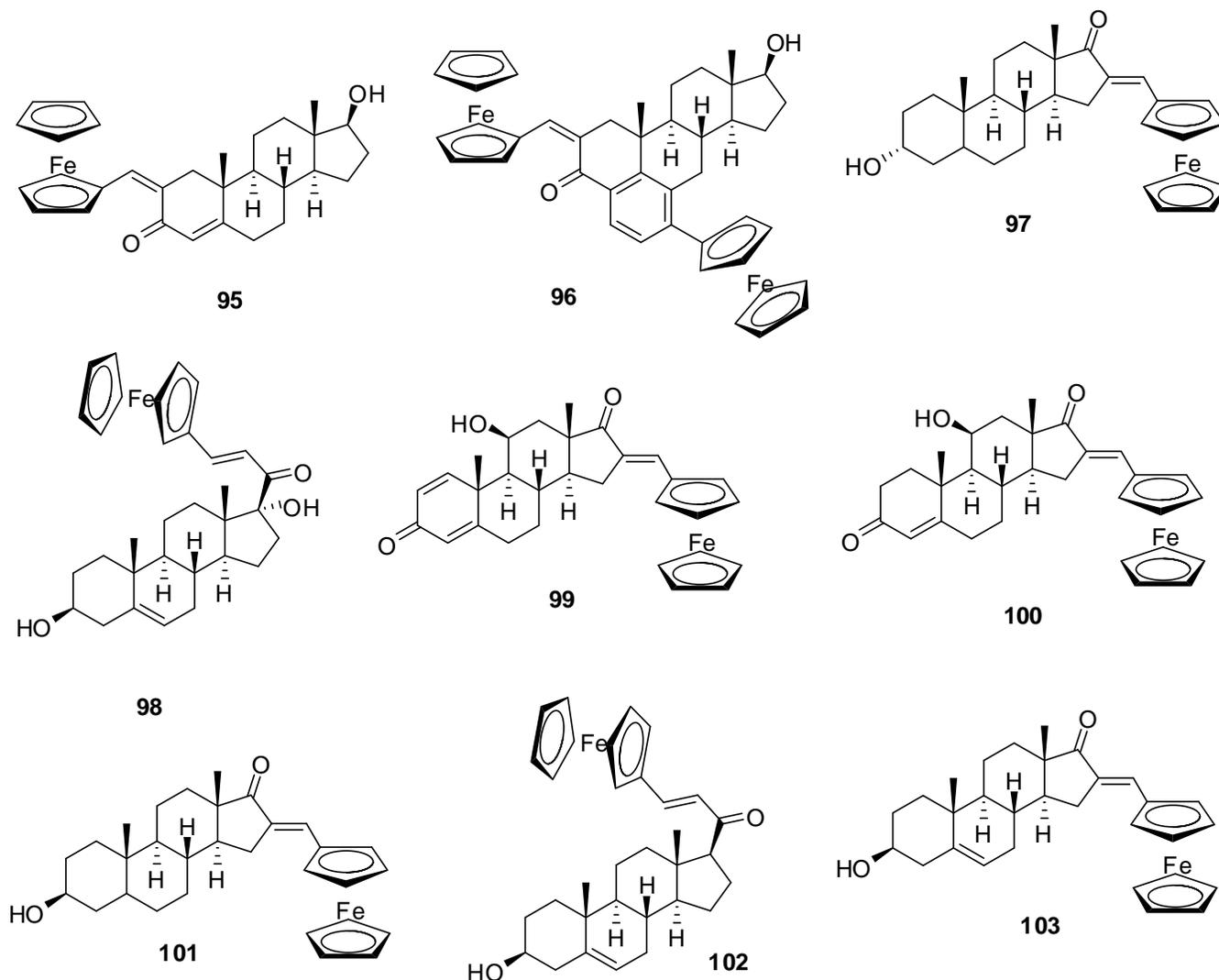
Figure 4. Structures of ferrocenylmethylidene derivatives **95-103.**

The 16-arylidene-3β,17β-diol **107** (Scheme 19) was prepared in order to evaluate its androgenic activity.[53] Deprotonation of the 3-protected dione **104** with sodium hydride was followed by the reaction with ferrocenecarboxaldehyde (**88**). The acetal of compound **105** was then quantitatively deprotected and diketone **106** was reduced using NaBH$_4$. According to NMR measurements the product (**107**) was obtained as a single diastereomer, and NOESY experiments proved the *E* configuration of the double bond. Unfortunately, the diol **107** had only a moderate effect on PC-3 hormone-independent prostate-cancer cells.
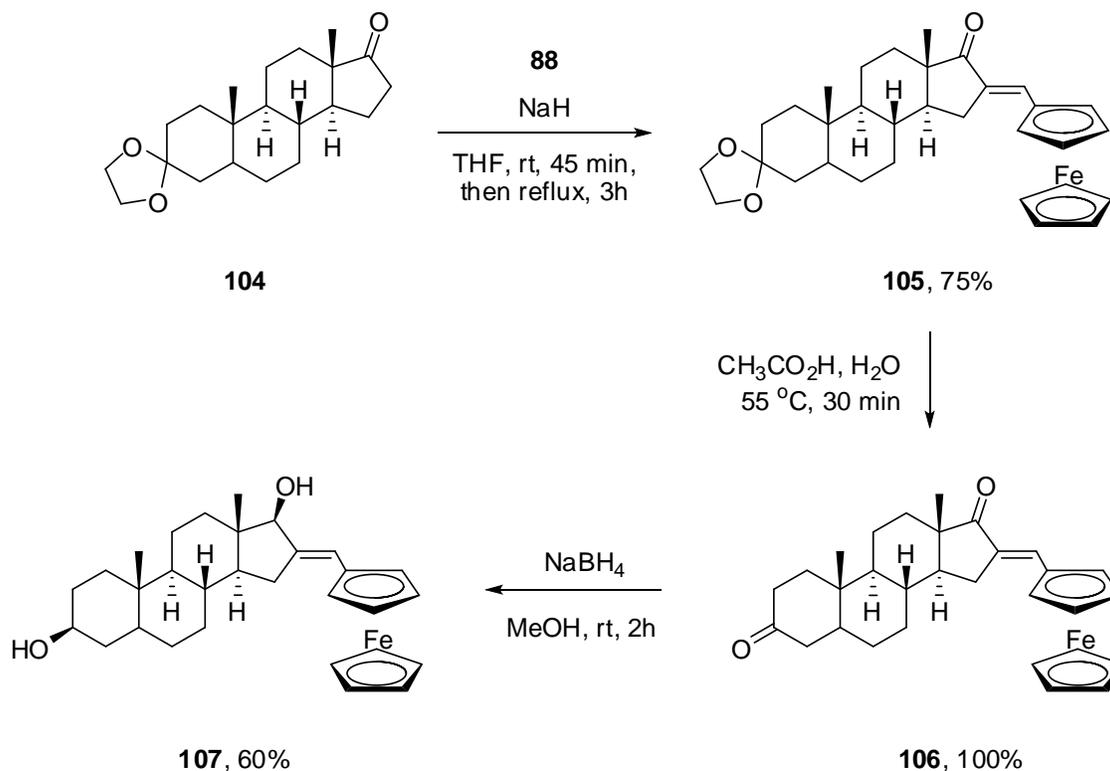
**Scheme 19.** Synthesis of the 16-arylidene-3β,17β-diol **107.**

Steroid-ferrocene derivatives **111** and **112** were obtained via the Claisen-Schmidt condensation of the corresponding 16-formyl steroids and acetylferrocene (**110**), carried out in a nBu-TMG (2-n-butyl-1,1,3,3-tetramethylguanidine) and ethylene glycol mixture (Scheme 20).[54] nBu-TMG can play a dual role of co-solvent and catalyst to substitute the usual alkali hydroxides. In similar reactions, both nBu-TMG and ethylene glycol can be recycled via the formation of a reversible ionic liquid in the presence of CO_2. The ionic-liquid form makes it possible to isolate the product by simple extraction. The ionic liquid can then be converted back into the original nBu-TMG / ethylene glycol mixture upon removal of CO_2, and can be used, again, in a next run by adding fresh reagents.
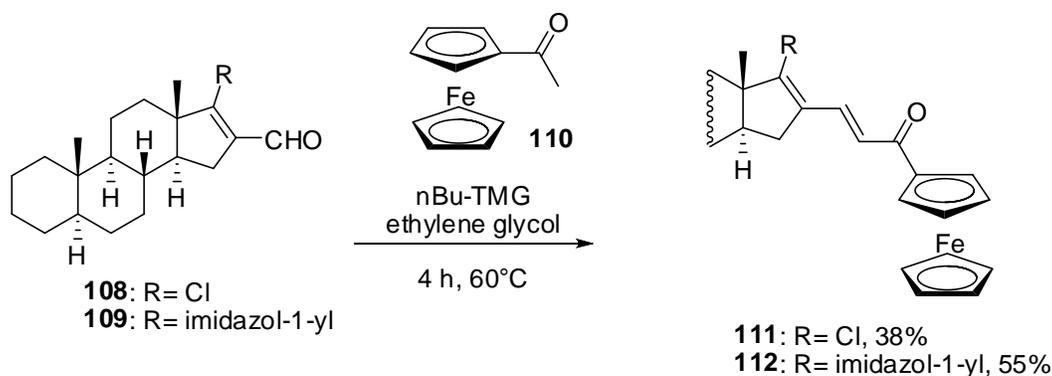
Scheme 20. Synthesis of conjugates **111** and **112** from 16-formyl steroids **108** and **109.**

2.5. Miscellaneous reactions

16-(Ferrocenylmethyl)amino-estratrienes **115a-f** (Scheme 21) exhibited broad antimicrobial activity, particularly against mycobacteria and multi-resistant staphylococci.[55] The conjugates were obtained by the condensation of the corresponding aminosteroids **113a-f** with ferrocenecarboxaldehyde (**88**) followed by reduction of the hydrazones **114a-f** with $NaBH_4$. The 3-(*N*-ferrocenylmethyl)amino-cholestanes **116a-c**, obtained by similar procedures, did not show antimicrobial effect. As ferrocenylmethylaminoethanol was also found to be inactive, the activity of the 16-ferrocenylmethylamino steroids **115a-f** was attributed to the combination of the ferrocenyl group and the estratriene steroid moiety.
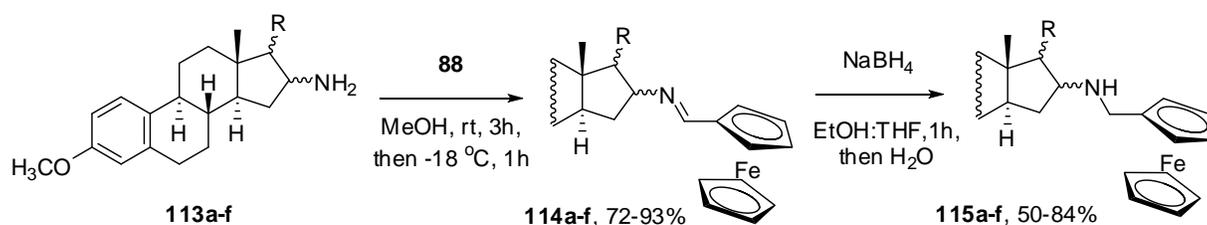

|	16-NH_2	R
a	β	β17-OH
b	α	β17-OH
c	β	α17-OH
d	α	α17-OH
e	β	H
f	α	H
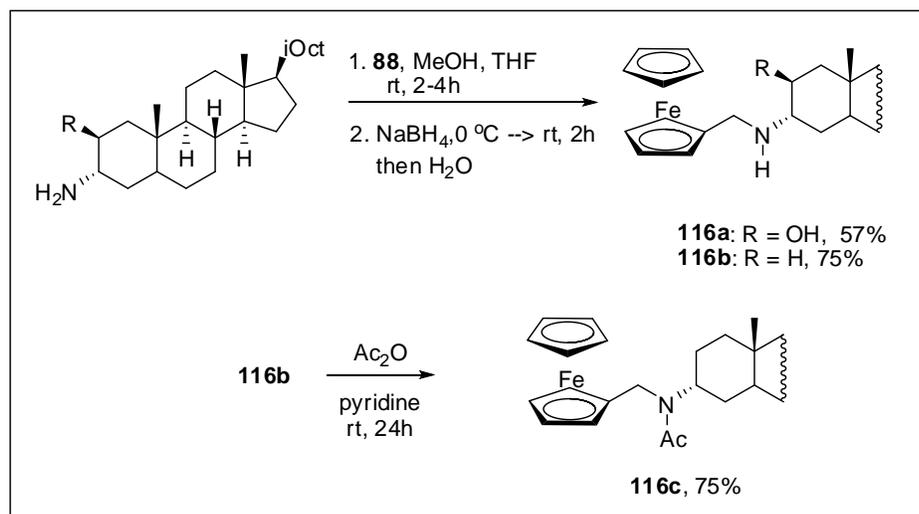
Scheme 21. Synthetic procedures towards (ferrocenylmethyl)amino-estranes **115a-f** and (ferrocenylmethyl)amino-cholestanes **116a-c**.

In order to enable electrochemical detection of steroid glucuronides after HPLC separation, condensation of glucuronides of estrone, estradiol and estriol (**117a-e**) with 2-ferrocenylethylamine (**118**) was effected in the presence of a water-soluble carbodiimide (EDC: *N*-Ethyl-*N'*-(3-dimethylaminopropyl)carbodiimide) and 1-hydroxybenzotriazole[56] (HOBt) (Scheme 22). The derivatization method was proved to be satisfactory for the determination of estrogen glucuronides in biological fluids with respect to selectivity and sensitivity.
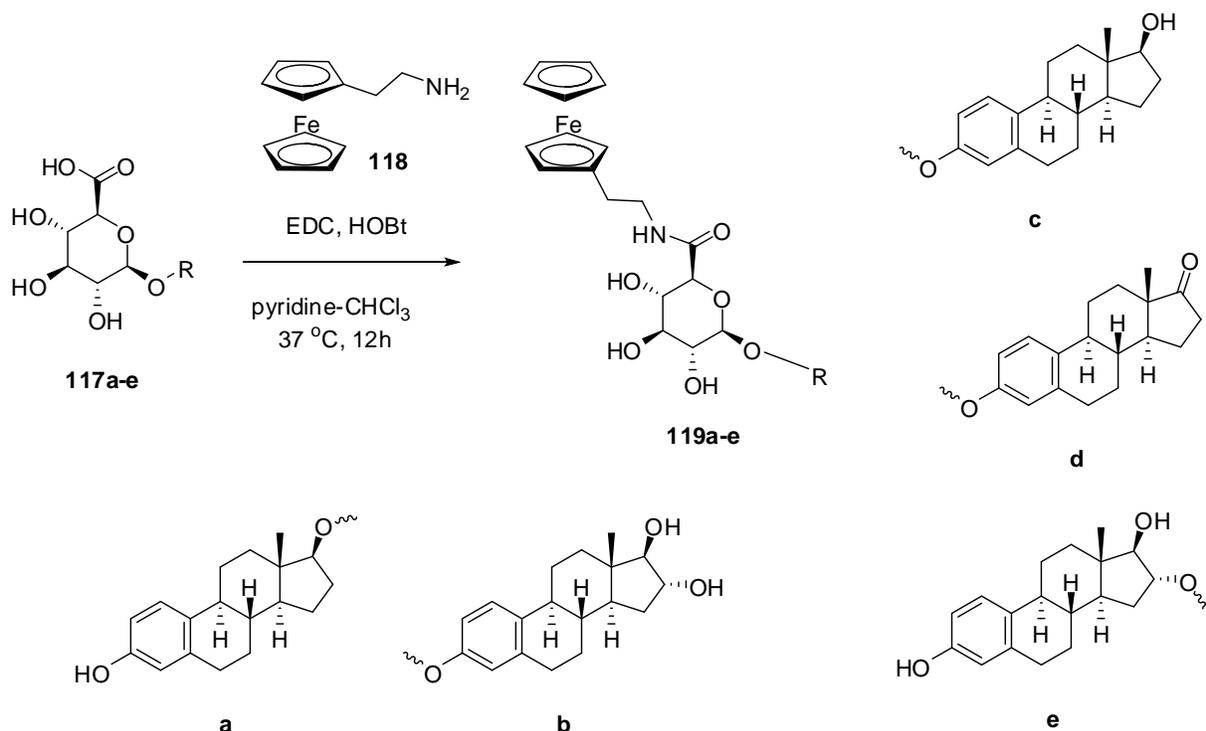
Scheme 22. Derivatization of estrogen glucuronides **117a-e.**

The acetoxy derivative of the pentacyclic triterpenoid ursolic acid (**120**) was converted to ferrocene derivatives **121** and **122** (Scheme 23).[57]
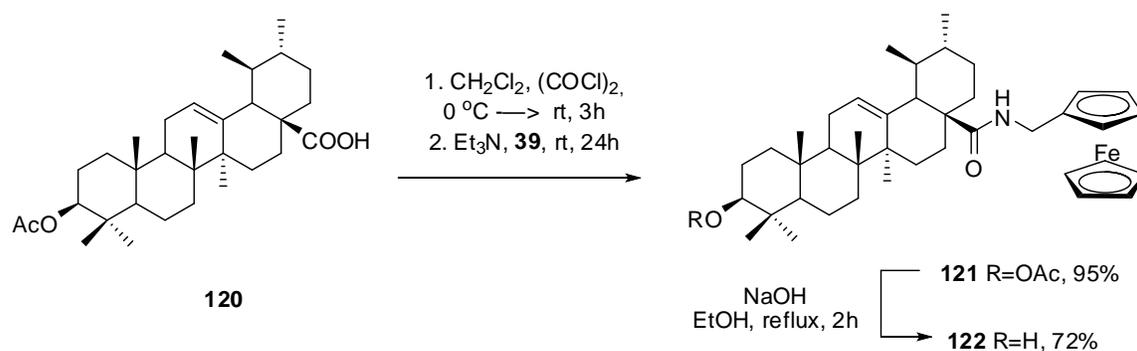

Scheme 23. Derivatization of a pentacyclic triterpenoid compound (**120**).

The acylation of aminomethylferrocene (**39**) was performed *via* the *in situ* formation of the corresponding acyl chloride obtained by the addition of oxalyl chloride. Unfortunately, the incorporation of the metallocene moiety into the ursolic acid derivatives did not increase the original aromatase-inhibitory activity of ursolic acid.

3. Synthesis of Steroid-ferrocene Conjugates using Organometallic Reagents

The Jaouen group developed several methodologies to connect the ferrocenyl moiety to the steroid skeleton by a C-C bond directly or via a linker group. The use of organometallic reagents or the application of transition metal catalyzed reactions (see section 4) resulted in a broad range of conjugates.

The 17α-ferrocenyl derivative **125** was found to be recognized by the estradiol receptor, although its apparent relative binding affinity decreased to 15%, with estradiol taken as 100%. Interestingly, while estradiol binds reversibly to its receptor, the introduction of the organometallic group resulted in an irreversible binding. Compound **125** was prepared in 29% yield by reaction of the protected estrone (**123**) with ferrocenyl lithium (**124**) (Scheme 24).[58]
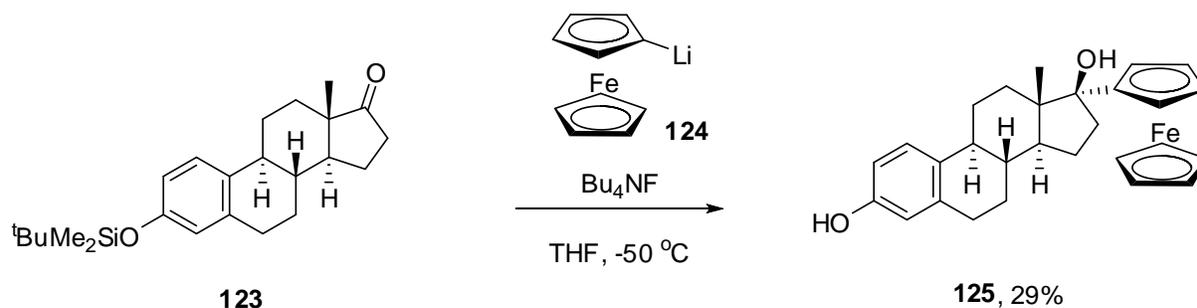
**Scheme 24.** Synthesis of 17 α-ferrocenylestradiol **125**.

A similar, but more detailed synthetic procedure was reported in 1994, leading to the estradiol derivative **125** in 44% yield.[59] The X-ray investigation of the product proved the α-configuration of the ferrocenyl group pointing below the plane of the D ring, and also the formation of a hydrogen bond between the C-3 phenolic and C-17 hydroxyl groups. Such an intermolecular hydrogen bond had been found to be significant in the interaction of the parent estradiol with the hormonal receptor. The authors thought that this might explain why the 17α-ferrocenylestradiol derivative retained a relatively good affinity to the same receptor in spite of the bulky ferrocenyl substituent. They also showed that Fc-labelling of estradiol resulted in a more selective detection of the steroid after HPLC separation as it allowed the use of the electrochemical detector at low anodic potentials.[60]

Ferrocene conjugates of 17α-ethynyl steroid hormones were obtained by two different strategies using organometallic reagents. The ferrocenoyl-ethynyl compound **129** was prepared by reacting the lithium derivative of the deprotected 17α-ethynylestradiol **126** with amidoferrocene **127**, prepared according to the Weinreb method (Scheme 25).[61]
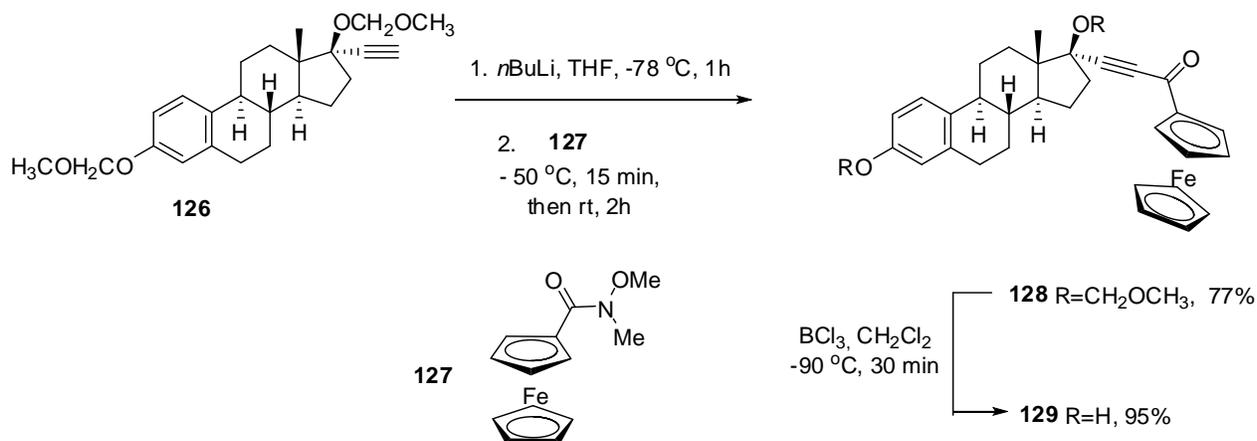
Scheme 25. Synthesis of Fc-estradiol conjugate **129**.

The steroid-ferrocene conjugate **129** was used as the starting material for the synthesis of ^{99m}Tc- (**130**) or Re-complexes (**131**) as potential radiopharmaceuticals via ligand transfer (Scheme 26).
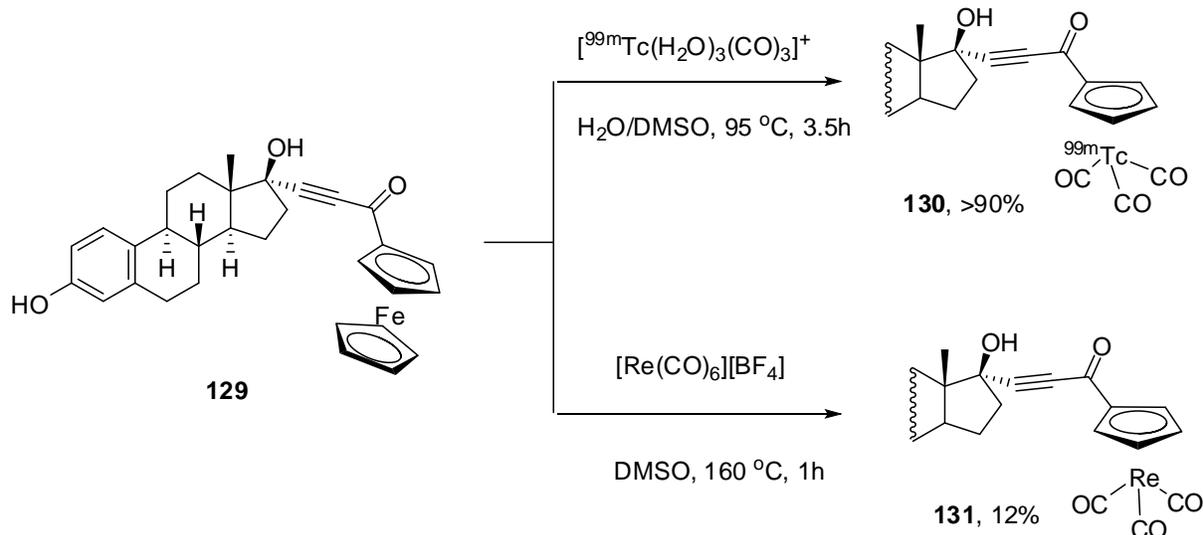
Scheme 26. Conversion of Fc-estradiol conjugate **129** to ^{99m}Tc- (**130**) or Re-(**131**) complexes.

      As another approach reported by the same group, the dihydrotestosterone (DHT) conjugate **134** was obtained *via* the reaction of the 3-protected steroid **104** with lithiated ethynylferrocene.[53] Exclusive formation of the 17α-ferrocenyl isomer **133** was observed in 39% yield (Scheme 27). The deprotection of the C-3 ketone was carried out quantitatively using a catalytic amount of PTSA (p-toluenesulfonic acid) to give the ferrocenyl DHT derivative **134** that was reduced in one step to give the androstanediol derivative **135**.
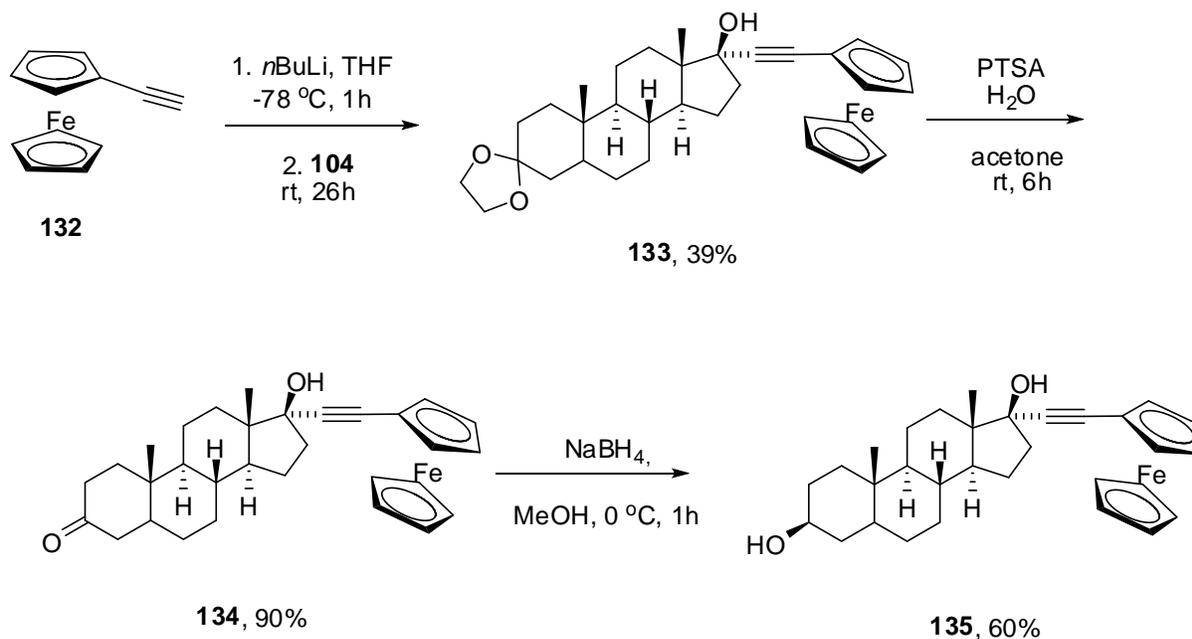
Scheme 27. Synthesis of Fc-DHT conjugate **134** and its reduction to the androstanediol derivative **135.**

Binding affinity to the androgene receptor was found to be low even for the 3-keto compound **134**. This means that there is not enough space in the binding pocket of the receptor to accommodate practically any substituent in the 17 α-position. In contrast to 3β-androstanediol that was described as the endogenous ligand for the beta form of the estrogen receptor (ERβ) in the prostate, the 3β-OH derivative **135** showed no affinity towards this receptor. At the same time, conjugates **134** and **135** were found to exert considerable antiproliferative effect on hormone independent PC-3 prostate-cancer cells.

Similar synthetic procedures were used by Wenzel in 1994[47] during the synthesis of the estradiol conjugate **136** by the addition of lithiated ethynylferrocene onto the carbonyl functionality of protected estrone **123**. Also, the Fc conjugate was proved to be a suitable starting material for the ^{99m}Tc-complex **137**.
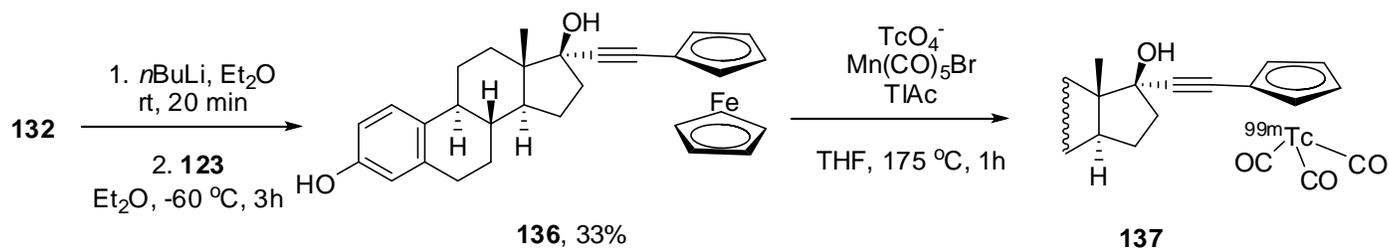
Scheme 28. Synthesis of estradiol conjugate **136** and its conversion to the ^{99m}Tc-complex **137.**

An interesting example of the application of organometallic reagents is the synthesis of a ring-C aromatic steroidal analogue connected to a ferrocenyl moiety (**139**, Scheme 29).[62] Chromium-carbene complexes possessing a π-system adjacent to the carbene carbon such as compound **138** may undergo an annulation reaction, in the present case with ethynylferrocene (**132**). Probably due to the vicinity of the aromatic structure, no diastereoselection was observed, and a 1:1 mixture of epimers was formed.
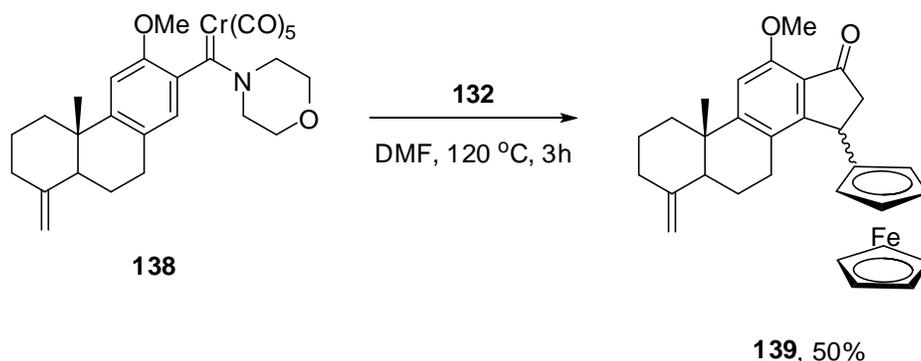
Scheme 29. Annulation of the chromium carbene complex **138** with ethynylferrocene **132**.

4. Transition Metal Catalysis in the Synthesis of Steroid-ferrocene Conjugates

Although facile C-C bond formation can be achieved by the application of organometallic reagents, the introduction of protecting groups is necessary to avoid side reactions. Transition-metal catalysis usually eliminates the need for protection-deprotection steps, so synthetic routes can be simplified. Both palladium[63] and copper[64] catalysts are widely used to produce steroid derivatives with ferrocene-steroid conjugates among them.

4.1. Palladium-catalyzed C-C coupling reactions

Stille-coupling, the reaction of alkenyl- or aryl halides with organotin reagents, was one of the first examples of palladium-catalyzed C-C couplings.[65] Recently, it has been superseded by other similar reactions, such as Sonogashira- and Suzuki couplings, mainly due to the toxicity of organotin compounds and some difficulties in product separation. Beside other methodologies for the synthesis of steroid-Fc conjugates, the Jaouen group prepared the testosterone derivative **143** by a Stille-coupling reaction between iodoferrocene **142** and the 17-ethynyltestosterone stannyl derivative **141**, which was obtained by heating ethynyltestosterone (**140**) with n-Bu₃SnOMe (Scheme 30).[53] It is worth noting that other iodo-organometallics, such as $(C_5H_4I)Re(CO)_3$ and $(C_5H_4I)Mn(CO)_3$ were more reactive than iodoferrocene. Conjugate **143** was found to have a significant antiproliferative effect on hormone independent PC-3 prostate cancer cells.
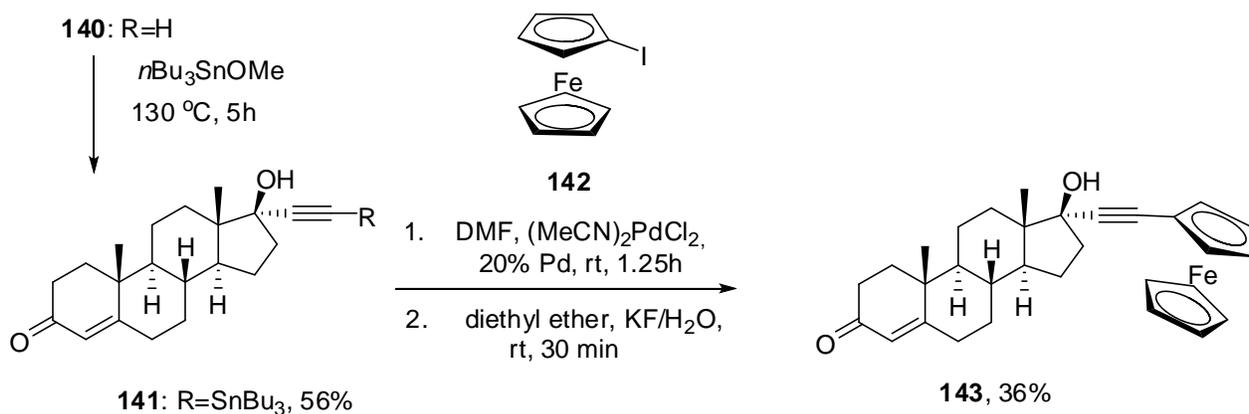

Scheme 30. Application of Stille coupling in the synthesis of conjugate **143**.

Another option for creating a C-C bond between the steroid and the ferrocenyl moiety is the Sonogashira coupling, involving the reaction of an aryl/alkenyl halide with a terminal acetylene in the presence of a palladium catalyst and a copper-salt as co-catalyst.[65] The ready availability of 17α-ethynyl steroids may make this approach especially attractive. In contrast to the route reported by Wenzel (Scheme 28),[47] conjugate **136** could be prepared without the protection of the hydroxyl groups, simply by coupling of ethynylestradiol (**144**) with iodoferrocene (**142**) (Scheme 31).[66] It was found to retain a satisfactory affinity for an antibody specific to estradiol and that it remains well-recognized by the two natural estrogen-receptor subtypes, ERα and ERβ.
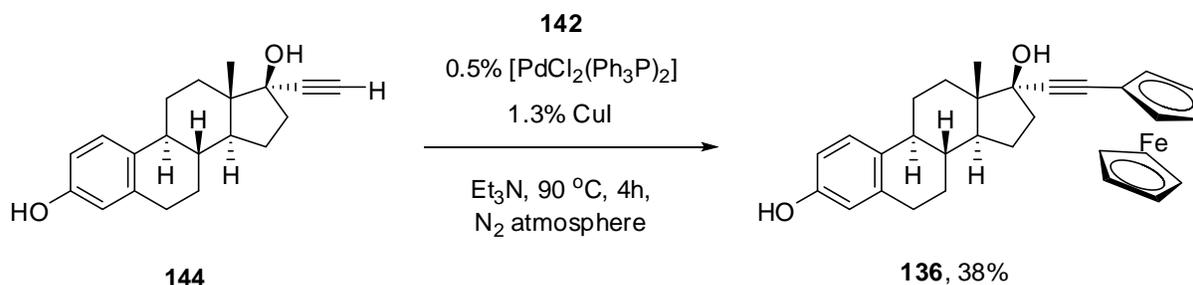
Scheme 31. Synthesis of ethynylestradiol conjugate **136** via Sonogashira coupling.

Because the receptor affinity of hormones is sensitive to the presence of substituents, an additional functional group on the cyclopentadienyl ring of the complexes was expected to modify their recognition by the receptor. Due to the planar chirality of 2-formyl-iodoferrocene (**145**), the Sonogashira reaction of 17α-ethynylestradiol (**144**) with racemic **145** led to a mixture of diastereomeric products that was difficult to separate.[67] The application of enantiopure 2-formyl- (**(S)-145** or **(R)-145**)),[67] or 3-formyl-iodoferrocenes (**(S)-146** or **(R)-146**))[68] in four separate coupling reactions (Scheme 32) resulted in the formation of products **(R)-147**, **(S)-147** or **(R)-148**, **(S)-148** as single isomers. Interestingly, neither **(S)-145** nor **(R)-145** could be coupled with a tributyltin derivative of **144** under the conditions of Stille coupling.
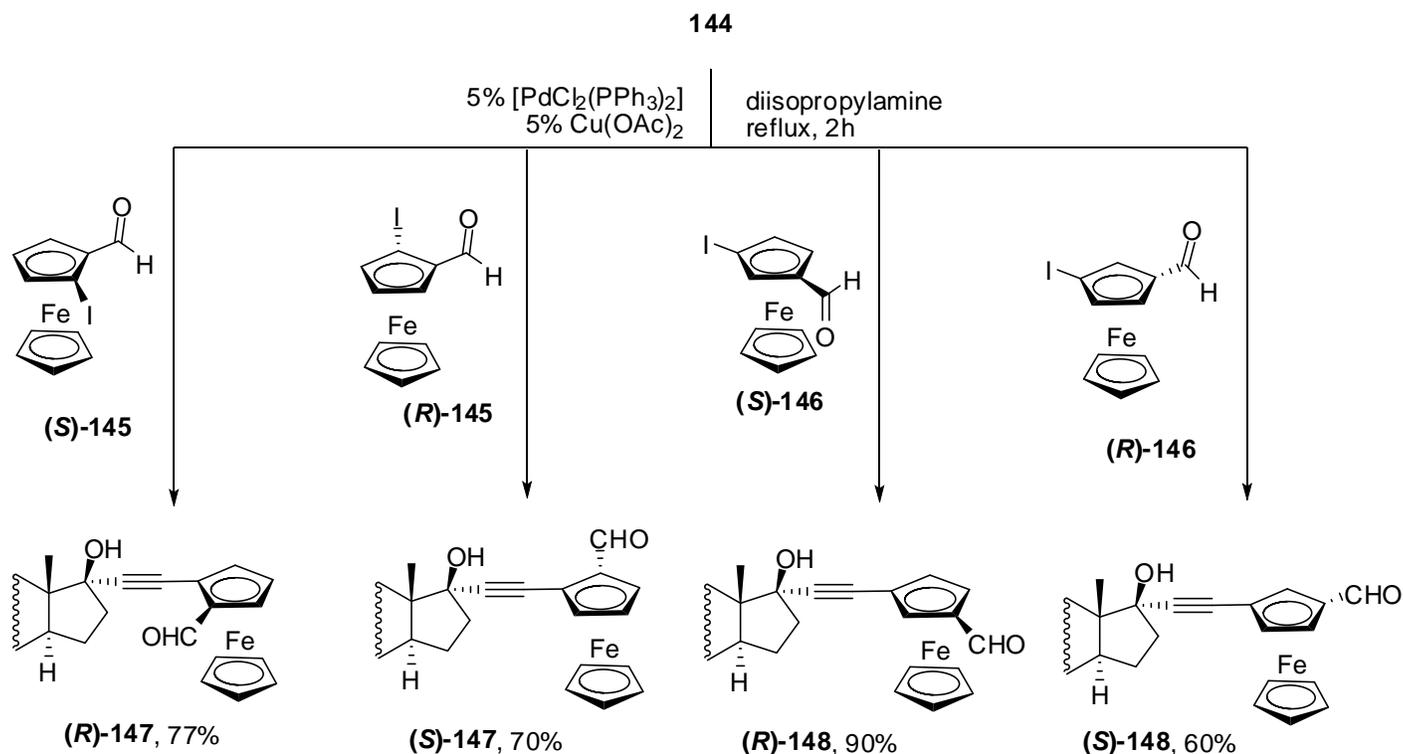
Scheme 32. Sonogashira coupling of 17α-ethynylestradiol (**144**) with formyl-iodoferrocenes.

In comparison to conjugate **129** (Scheme 25), with a carbonyl functionality between the ethynyl group and the cyclopentadienyl ring, the formyl derivatives showed better affinity for the estrogen receptor. While the receptor does not differentiate between the two diastereomers (**R**)-**148** and (**S**)-**148**, the affinity of (**R**)-**147** is almost twice that of the *S* diastereomer (**S**)-**147**. The conjugates showed a proliferative effect on MCF-7 breast cancer cell lines, indicating estrogenic behavior.

Another option for a Sonogashira reaction of ferrocene derivatives with a steroid is the coupling of ethynylferrocene (**132**) as the alkyne reaction partner with a steroid bearing an appropriate substituent. The cholesterol derivative **150** was obtained in such a reaction with alkenyl-triflate **149** (Scheme 33) as a halide equivalent[69] that could be prepared easily from the corresponding ketone.
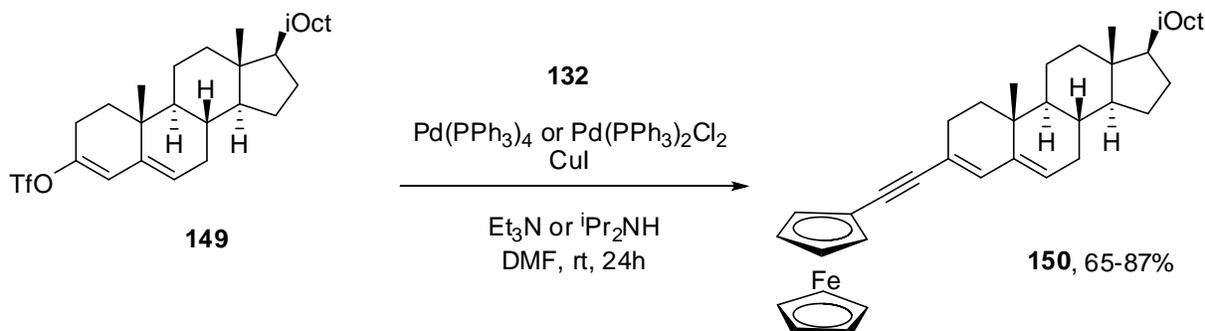
**Scheme 33.** Sonogashira coupling of triflate **149**.

4.2. Palladium catalyzed carbonylation reactions

In the presence of transition metals, carbon monoxide can be introduced directly into organic compounds. Thus, ketones, aldehydes or carboxylic acid derivatives can be obtained in one step from unsaturated compounds or from alkenyl/aryl halides or halide equivalents.[70] Sonogashira reactions, carried out under carbon monoxide (CO) instead of the usual inert atmosphere, lead to alkynyl ketones. This approach was applied in our group to convert 17α-ethynyl steroids **144**, **151** and **152** into Fc-conjugates **129**, **153** and **154** (Scheme 34).[71] A moderate CO pressure had to be used in order to convert iodoferrocene (**142**) into alkynyl ketones and to avoid homo-coupling of the terminal acetylene reaction partner. Although yields were moderate, 17α-ethynylestradiol (**144**) could be converted to alkynone **129** without protection of the 3-OH group.
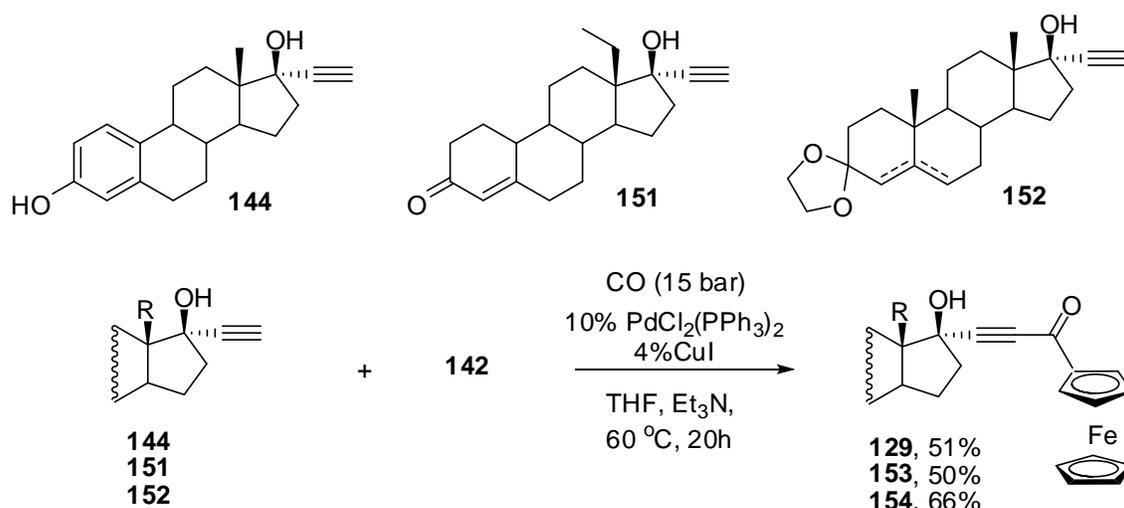
Scheme 34. Carbonylative Sonogashira reaction of 17α-ethynyl steroids **144**, **151** and **152**.

The two building blocks incorporating the steroid and the ferrocene skeleton, respectively, can be connected by an amide bond *via* aminocarbonylation reactions. Palladium-catalyzed aminocarbonylation involves the coupling reaction of an alkenyl/aryl halide or halide equivalent with a primary or secondary amine in carbon monoxide atmosphere. Alkenyl iodides **155a** and **155b**, prepared in two steps from an unnatural 13α-16-keto steroid (**154**) were converted to the corresponding ferrocene conjugates **156a** and **156b** by a reaction with (aminomethyl)ferrocene (**39**) under carbonylation conditions (Scheme 35).[72] As separation of the alkenyl iodides was found to be difficult, carbonylation was carried out using their 45/55 mixture and only the products **156a** and **156b** were isolated. Lower reactivity of **155a** was explained by a steric hindrance caused by the planar disposition and close proximity of the 17-methyl and 16-iodo groups. Aminocarbonylation was carried out under homogeneous conditions using Pd(OAc)₂ together with the PPh₃ ligand. The applicability of a heterogeneous, phosphine-free, silica-palladium catalyst was also tested. Somewhat lower yields, but greater selectivity towards **156b**, were obtained [with yields of 11% (**156a**) and 51% (**156b**)] with the latter catalyst. Also, it could be recycled with only a little decrease in the amount of the isolated products.
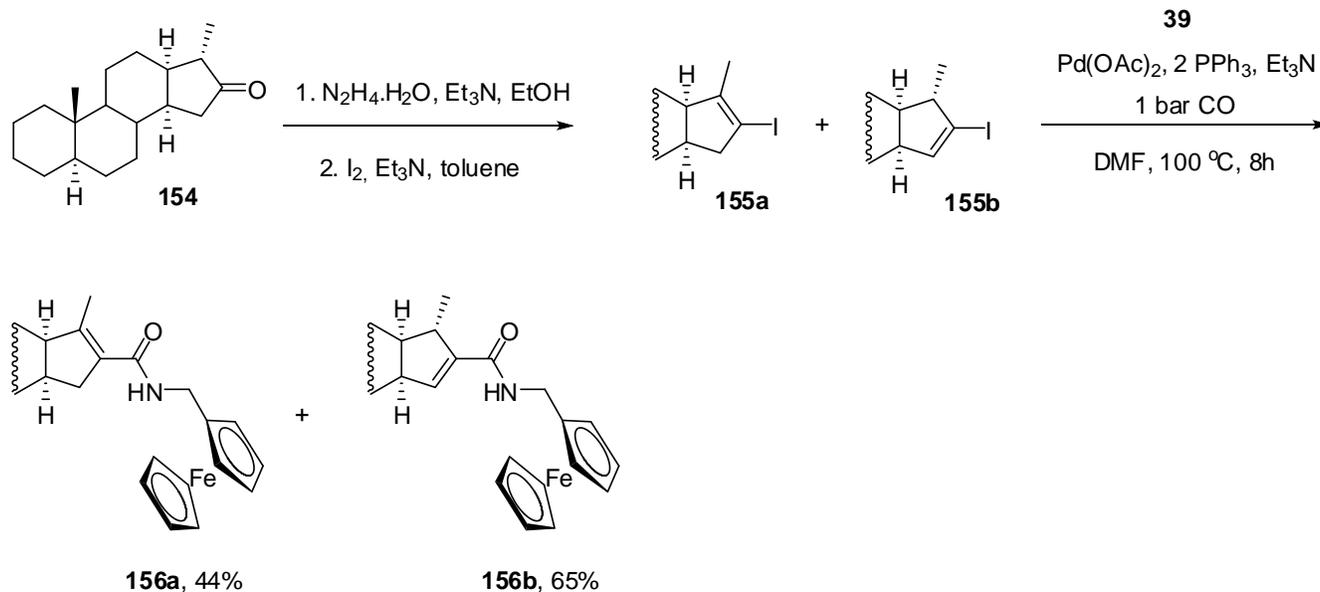
Scheme 35. Synthesis of conjugates **156a** and **156b** via aminocarbonylation.

Aminocarbonylation made it possible to connect the two skeletons via linkers that might possess biological activity themselves, such as β-lactam and chalcone structures. To prove the utility of the methodology, steroidal 17-iodo-16-enes with various functionalities (**157**-**160**, Figure 5) were reacted with 3-amino-azetidin-2-one **163** (Scheme 36)[73] and ferrocenyl-chalcone **168** (Scheme 37),[74] respectively. The products were obtained in good-to-excellent yields. Steroid-ferrocene-chalcone conjugate **172** was produced in good yield even starting from an enol triflate (**161**). It should be mentioned however, that the estrone triflate derivative **162** remained unreactive under the reaction conditions.
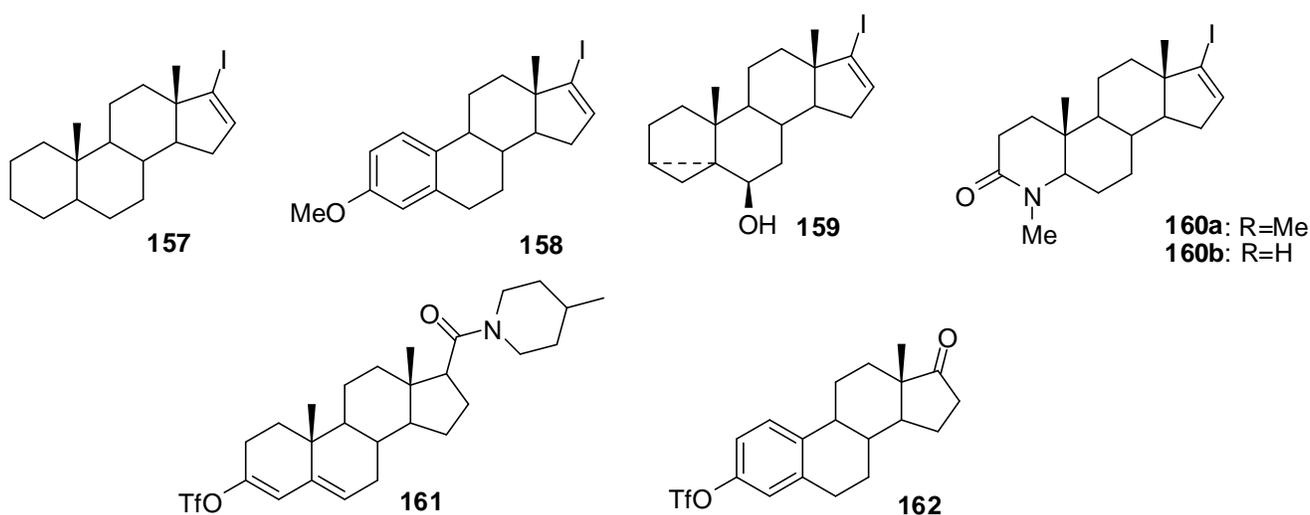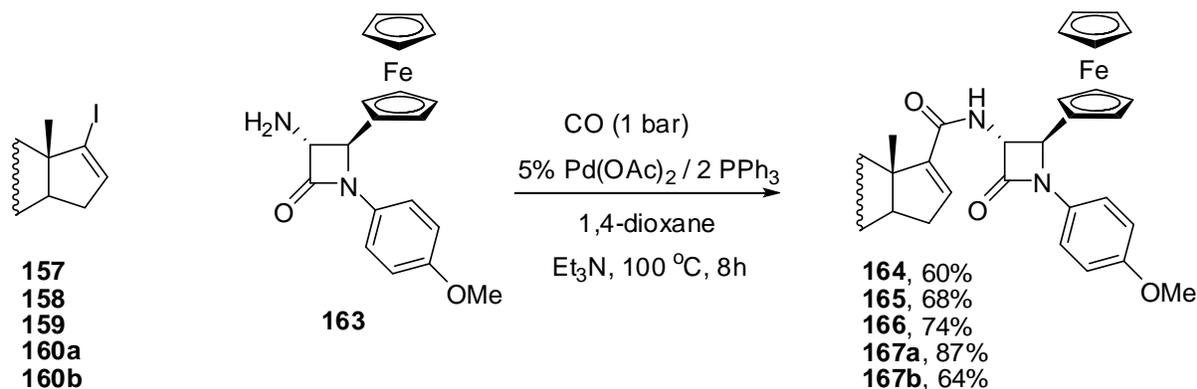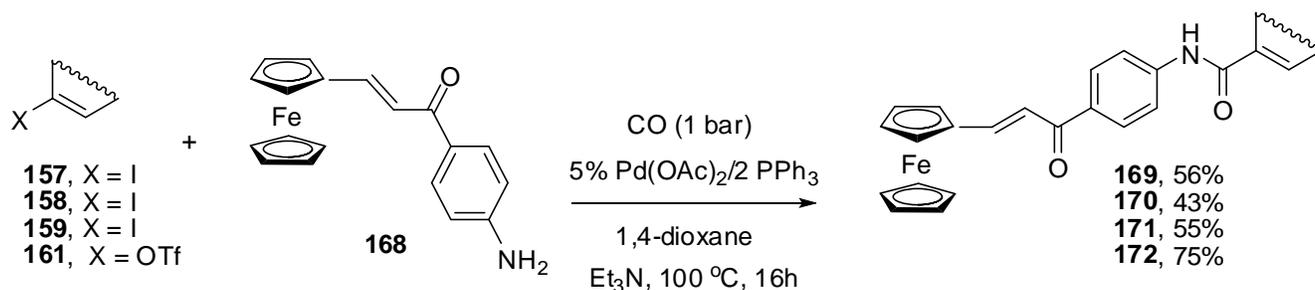

Figure 5. Steroidal halides and triflates used as substrates in aminocarbonylation reactions.

**Scheme 36.** Aminocarbonylation of steroidal 17-iodo-16-enes **157**-**160** with ferrocenyl β-lactam **163**.

Scheme 37. Aminocarbonylation of steroidal 17-iodo-16-enes **157**-**158** and enol triflate **161** with ferrocenyl chalcone **168**.

## 4.3 Copper-catalyzed azide-alkyne cycloaddition (CuAAC reaction)

The CuAAC reaction published by Sharpless[75] and Meldal[76] allows the direct synthesis of highly complex organic structures starting from simple, and readily available, building blocks. It involves the cycloaddition of organic azides and terminal alkynes leading to the exclusive formation of 1,4-disubstituted-1,2,3-triazoles. Although various Cu(I) salts and complexes can efficiently be used as catalysts, the simplest catalytic system consists of $CuSO_4$ and sodium ascorbate. The catalytically-active Cu(I) species is formed *in situ* from the Cu(II) salt in the presence of the ascorbate as the reducing agent. The reaction tolerates moisture and oxygen, can be carried out in environmentally friendly solvents, e.g., in water at ambient temperature, and often leads to the product, quantitatively. These features make this methodology especially attractive for the labelling of biomolecules.[77] Both steroids and ferrocene derivatives can easily be functionalized to introduce azide or alkyne moieties. That means that two different approaches can be used: either alkynyl steroids are reacted with ferrocenyl azides or *vice versa*, alkynylferrocenes and steroidal azides are used as substrates.

        The cycloaddition of racemic ferrocenyl azide **173** and 17α-ethynylsteroids **144**, **150** and **152** (Scheme 38) led, undoubtedly, to epimers of products **174**-**176**.[71] The epimers could not be separated by column chromatography, however, and gave identical R_f values when reaction mixtures were analyzed by TLC. The only sign of the presence of the two compounds was that the methine protons of the CH-CH₃ group of the side chain do not give a quartet as expected, but a more complicated multiplet. The small difference in the spectra in the two epimers was explained by the fact that the chiral center of the side chain is relatively far from those of the steroid skeleton. Triazoles **174**-**176**, as well as the conjugate 178,[78] were obtained in good-to-excellent yields.
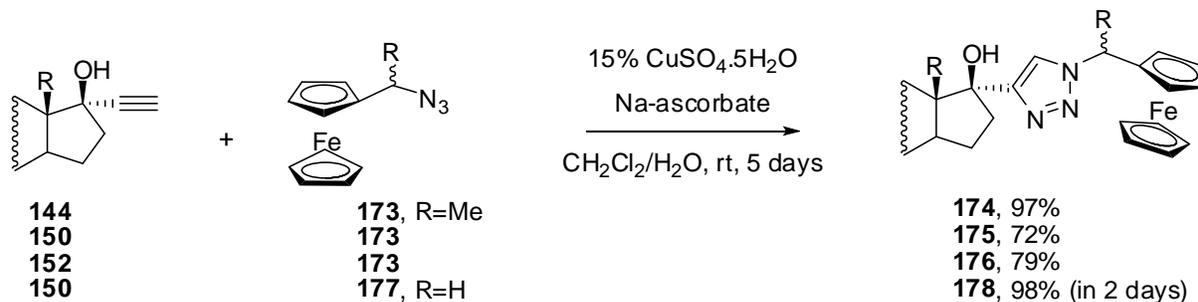
Scheme 38. Cycloaddition of 17α-ethynylsteroids with ferrocenyl azides.

An organic/inorganic hybrid material comprising a silica support and a polymer with imidazolium moieties was prepared for the immobilization of a copper catalyst. Although the catalyst retained its activity in the CuAAC reaction of the steroidal alkyne **144** and azidomethyferrocene **177** in three runs, product **179** was obtained in low yield (Scheme 39).[79] It should be mentioned that, under the same conditions, total conversion was observed in the cycloaddition of phenylacetylene and benzyl azide in 7 subsequent runs. Comparison of these results, and also data obtained by other alkynes and azides, showed that, in contrast to homogeneous phase reactions, steric hindrance in both reaction partners retarded cycloaddition in the presence of the heterogeneous catalyst considerably.
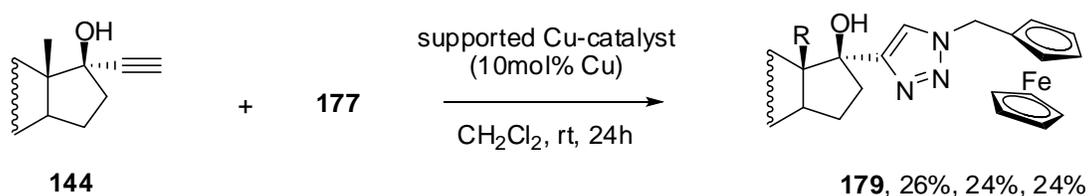
Scheme 39. Cycloaddition reaction in the presence of a heterogeneous catalyst.

The alkyne functionality was introduced to steroids **180-183** *via* an aminocarbonylation reaction of steroidal iodoalkenes **157-160** with propargylamine (Scheme 40).[80] Triazoles **184-187** were obtained in good yields as non-separable mixtures of epimeric products, similarly to the reactions depicted in Scheme 38. This was attributed to the flexible linker and the long distance between the chiral centers of the side chain and the steroid skeleton.
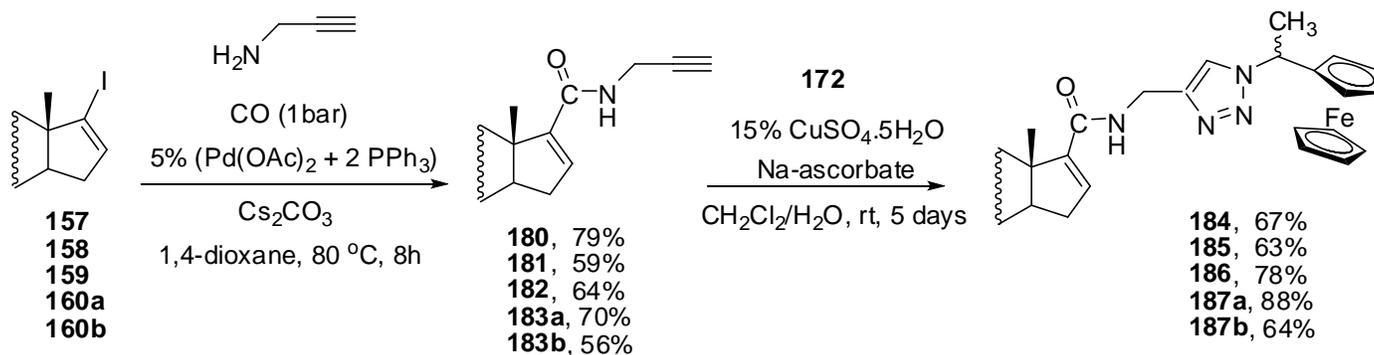
Scheme 40. Conversion of steroidal iodoalkenes **157-160** to ferrocenyltriazoles **184-187**.

The same approach was used during the synthesis of the 13-epi derivative **188** (Scheme 41). It was found to decrease the activation of TRPV1 receptor on TRG neurons, probably by influencing the lipid rafts surrounding the receptors in the plasma membrane of neurons.[72]
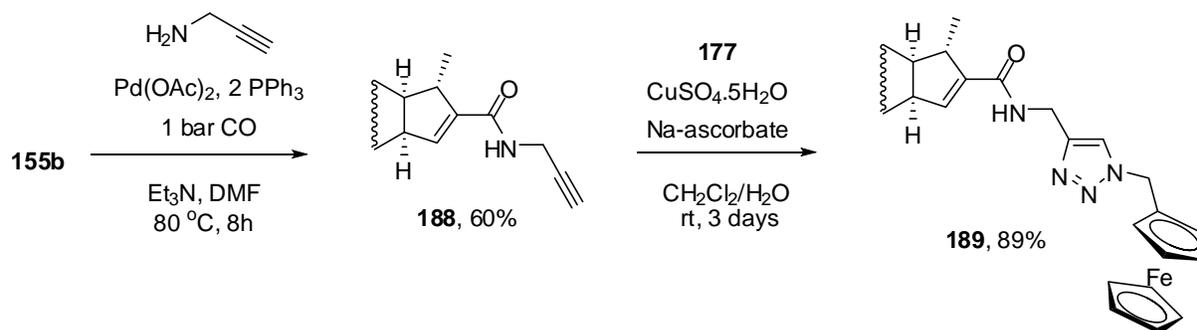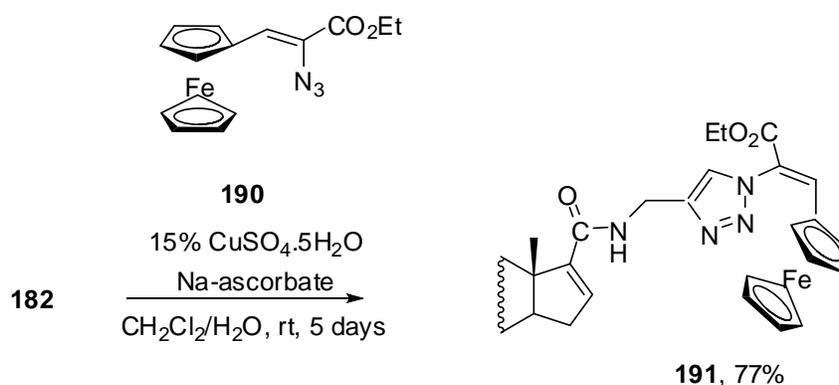

Scheme 41. Synthesis of triazol **189** from an alkenyl iodide with unnatural skeleton (**155b**).

The ferrocenyl alkenyl azide (**190**) also underwent the azide–alkyne cycloaddition with carboxamide **182** leading to triazol **191** (Scheme 42)[80] in good yield, comparable to those obtained with azide **173**.

Scheme 42. Cycloaddition of propargylamide **182** and ferrocenyl azide **190**.

Although the CuAAC is usually reported not to be hindered by bulky substituents, considerably different reactivity was observed for steroidal azides **192**, **196** and **199** (Scheme 43).[81] Ferrocene-labeled steroids with triazole groups attached directly to the 16β- (**194**) and 2β- positions (**197**) were obtained in good yields with ethynylferrocene (**132**) as the reaction partner, however, the target compound was detected only in trace amounts by TLC under the same conditions starting from **199**. According to the computational studies, the azido group is in the least hindered position in the 16β-azido-steroid **192**. Flipping of ring A of steroid **196** into a twisted boat conformer with the 2β-azido group in the equatorial position is still feasible. At the same time, there is a great difference in the free energies of the twisted boat and the chair conformations of the B ring in steroid **199**, in favor of the latter structure. Therefore, steric hindrance cannot be relieved by a conformational change in compound **199,** which may result in a considerably lower reactivity. It should be mentioned that the cycloaddition of alkyne **193** with a more distant ferrocenyl moiety led to the products in acceptable yields (57-67%) from all of the steroid substrates.
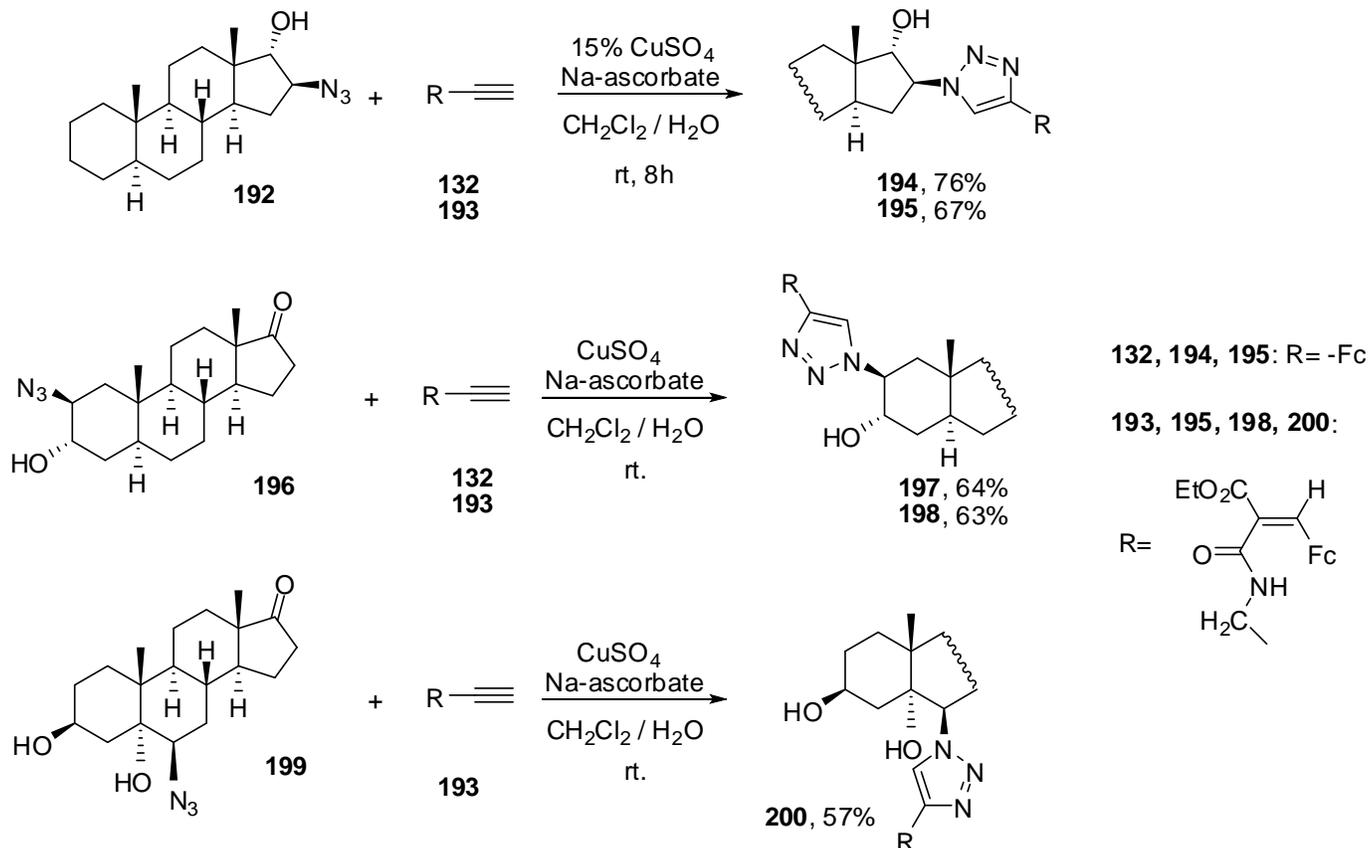
Scheme 43. Ferrocenyl triazole derivatives produced from steroidal azides **192**, **196** and **199**.

Three triazolyl-ferrocene derivatives (**179**, **195** and **197**) were found to be potent inhibitors of steroid sulfatase, a key enzyme in estrogen biosynthesis, and displayed stronger affinities to the enzyme than the substrate estrone-3-sulfate itself.[78] Compound **197** is bound in a reversible manner, whereas the C-16 (**195**) and C-17 derivatives (**179**) are irreversible inhibitors. Related non-ferrocenyl compounds were found to exert lower potency.

With a similar methodology, the azide derivative of cholesterol (**202**) was 'clicked' with ferrocenyl chalcone **201** to produce triazol **203** (Scheme 44).[82] Unfortunately, conjugate **204** was completely inactive against all the tested bacteria (*E. coli, S. aureus, A. flavus*, and *C. albicans.*).
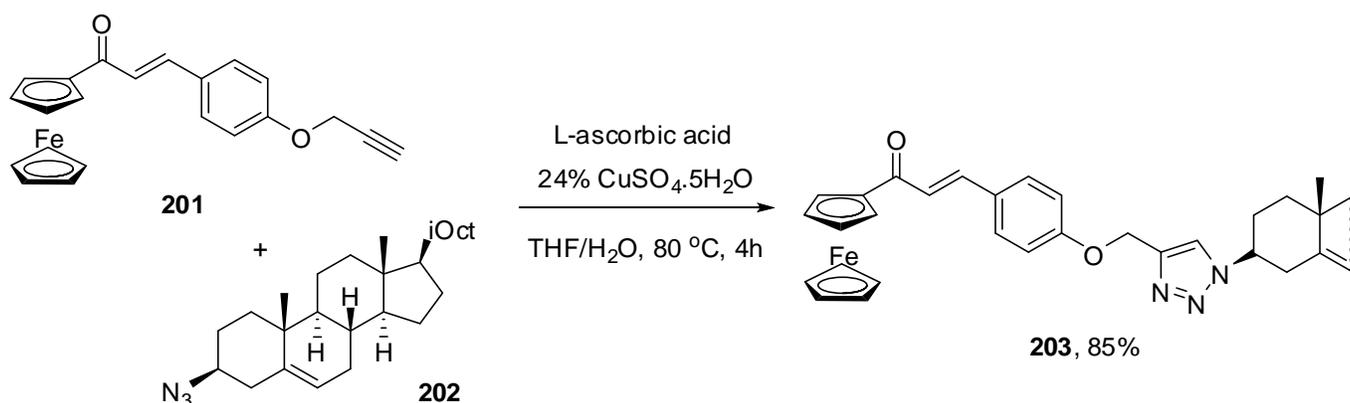
Scheme 44. CuAAC reaction of cholesteryl azide and alkynyl ferrocene **201**.

In order to prove suitability of sequential bioconjugation of polypeptides, ethynylferrocene (**132**) and 17α-ethynylestradiol (**144**) were introduced site-specifically into a *N*-substituted glycine peptoid oligomer scaffold to obtain conjugate **204** (Figure 5).[83] The ferrocene core of **204** showed a significant decrease in redox potential when compared to ethynylferrocene. This was attributed to the altered electronic environment established by the extended conjugation of the ferrocene cyclopentadiene group with the 1,2,3-triazole ring.
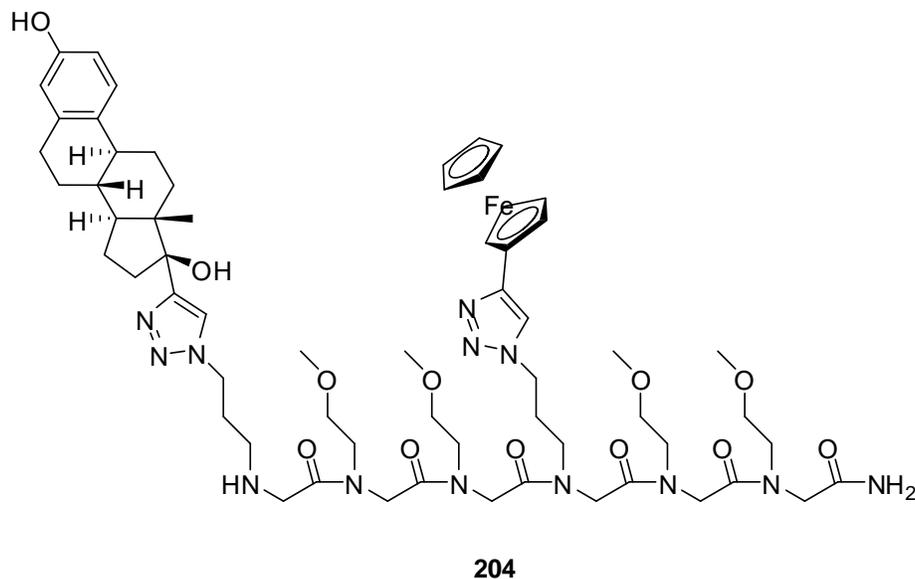

204

Figure 5. Oligopeptide **204** obtained by a click reaction of ethynylferrocene and 17α-ethynylestradiol and an oligopeptide with azide functionalities.

5. Synthesis of Ferrocenestrone

A completely different approach was used by Kotora *et al*.[84] to obtain a steroid-ferrocene conjugate. They synthesized the first steroid analogue possessing a ferrocene moiety integrated within the steroid framework. Ferrocenestrone **208** was produced starting from the chiral methyl ether **205** (Scheme 45). Planar chirality on the ferrocene moiety resulted in a selective formation of stereocenters during the Diels–Alder reaction, leading to **207** that ensured selectivity in further steps. Biological tests showed no activation of estrogen, androgen and progesterone receptors in the presence of compound **208**.
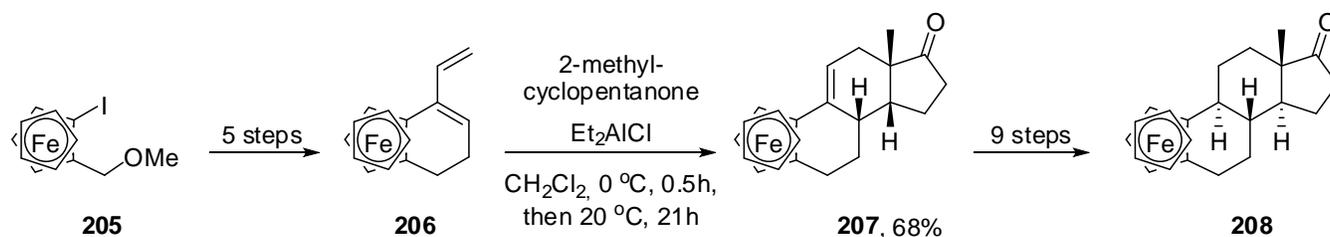
Scheme 45. Schematic route towards ferrocenestrone **208**.

6. Conclusions

Since the 1970s, when the first reports appeared on the synthesis of steroid-ferrocene conjugates, synthetic organic chemistry has undergone a great development, which is reflected in the methodologies utilized recently to connect the two skeletons. Of course, simple reactions such as esterification, *O*-alkylation, etc., are still used efficiently in many fields, e.g., increasing the efficiency of analytical methods. The application of organometallic reagents or transition-metal catalysis offer the possibility to create linkers with high stability (*e.g.*, to form C-C bonds between the two components). Moreover, transition-metal catalysis that has already become a general tool in synthetic organic chemistry, may lead to shortened reaction pathways and may result in more selective reactions.

There are several promising properties of steroid-ferrocene conjugates that need to be exploited further, and that may necessitate to introduce the ferrocene moiety into such positions of the steroid skeleton that are more difficult to functionalize, e.g., to facilitate ligand-receptor interactions. At the same time, most of the reactions discussed in the present report seem to be suitable to carry out even these more difficult transformations.

Acknowledgements

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Authors' Biographies

Márk Váradi received his B.Sc. degree in Chemistry in 2020, the same year he began his M.Sc. studies at the Faculty of Engineering of the University of Pannonia. He finished his M.Sc. course in 2022, and started his PhD in organic chemistry right afterwards. During his bachelor years, he dealt with the primary photochemistry of lanthanide porphyrin complexes and their application as homogeneous catalysts in oxidation reactions. During his master's studies he was involved in the synthesis of ferrocene-functionalised heterocycles. He also studied host-guest interactions of the products by spectroscopic and electrochemical methods. He received the Award of the Council of Commerce and Industry of Veszprém County and the Prize of Excellence of the Hungarian Chemical Society for his MSc thesis. During his PhD studies, he continues his research involving the synthesis of novel ferrocene derivatives.

Rita Skoda-Földes completed her PhD studies on the topic of homogeneous catalytic hydrosilylation reactions at the University of Veszprém (now University of Pannonia), Hungary under the supervision of Professor László Kollár and Professor Bálint Heil. After receiving her PhD degree in 1991, she turned her attention to homogeneous catalytic functionalisation of steroids. She was appointed Associate Professor in 1998 and Full Professor in 2009 at the University of Pannonia, where she was Head of the Department of Organic Chemistry between 2010-2020. Since 2020, she is the leader of the Organic Synthesis and Catalysis Research Group at the same University. The main focuses of her current research are the application of ionic liquids in

homogeneous and heterogeneous catalytic reactions, palladium-catalysed coupling and carbonylation reactions and functionalisation of steroids and ferrocene derivatives.