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Synthetic Studies Towards a New Fulvestrant Analogue

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Πάντα ῥεῖ ὡς ποταμός

Abstract

A study towards the synthesis of a new fulvestrant analogue with improved bioavailability was carried out. In this work a twelve-step synthetic route starting from β-estradiol was optimized and a palladium (Pd)-catalyzed endo-selective Heck reaction for the functionalization of an advanced intermediate was investigated.

Abbreviations

Ac	Acetyl
Ar	Aryl
Bu	Butyl
calcd	Calculated
cat	Catalyzed
CI	Chemical ionization
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEPT	Distortionless enhancement of polarisation transfer
DIBAL-H	Diisobutylaluminum hydride
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
EI	Electron impact
eq.	Equivalent
ER	Estrogen receptor
ESI	Electrospray ionization
Et	Ethyl
FT	Fourier Transform
i	Iso
IR	Infrared
L	Ligand
Me	Methyl
MOM	Methoxymethyl
mp	Melting point
MS	Mass spectroscopy
NBS	N-Bromosuccinimide
NMR	Nuclear magnetic resonance
PG	Protecting group
Ph	Phenyl
PMA	Phosphomolybdic acid
Pr	Propyl
R	Organic substituent (if not otherwise specified)
rt	Room temperature
sat	Saturated
SM	Starting material
TBS	Butyldimethylsilyl
TCCA	Trichloroisocyanuric acid
Tf	Triflate (trifluoromethanesulfonate)
THF	Tetrahydrofuran
TMS	Trimethylsilyl

Contents

1. Introduction

1.1 Steroids[1]

Steroids are polycyclic organic compounds which contain a basic carbon framework consisting of four fused rings, where three cyclohexane rings (named rings A, B and C) form the skeleton of a perhydro-derivative of phenanthrene, while the D-ring has a cyclopentane structure. Hundreds of different steroids are found in Nature, where the archetype just described may contain unsaturations, an alkyl chain on C-17, an aromatic A-ring, hydroxyl groups, methyl groups or other functionalities; all of them are described using a specific numbering as shown in (Fig. 1).

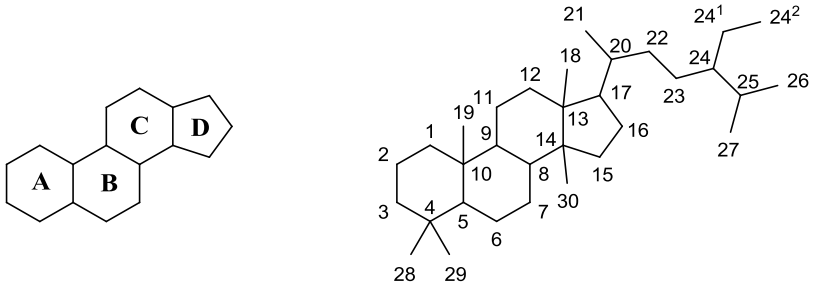
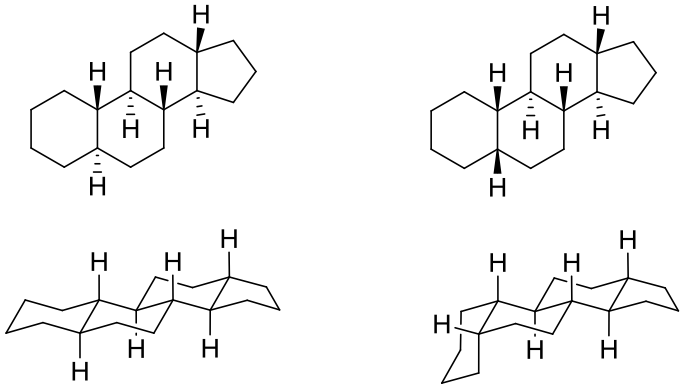


Fig. 1. Steroid skeleton and numbering

Each ring junction could be *cis* or *trans*, but it turns out that all steroids have all *trans* junctions except where rings A and B join which is sometimes *cis*. Examples are 5α-gonane (all *trans*) and 5β-gonane (rings A and B fused *cis*), the simplest existing steroids. (Fig. 2). Because of their structure, steroids cannot undergo a ring flip, so even the isomers of the simplest examples cannot interconvert.



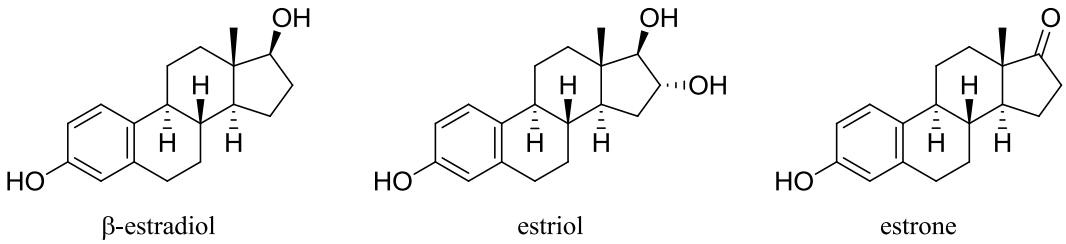
5α-gonane
cis A-B ring junction

5β-gonane
trans A-B ring junction

Fig. 2. Spatial arrangement of the steroidal core

1.1.1 Estrogens[2]

Estrogens are a group of steroid hormones that are important for sexual and reproductive development mainly in women. They are also referred to as female sex hormones. The term "estrogen" refers to all of the chemically similar hormones in this group, which include β-estradiol, estriol and estrone. (Fig. 3).



β-estradiol estriol estrone

Fig. 3. Estrogens

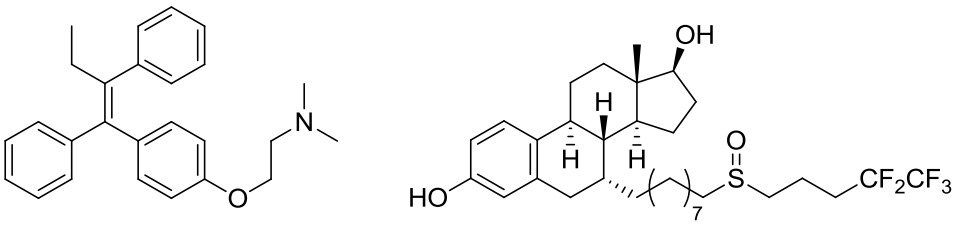
1.2 Fulvestrant in Breast Cancer Treatment

Breast cancer represents 25% of all cases of cancer in women, making it the leading form and resulting in more than 1.6 million cases annually and causing 522,000 deaths in 2012 in the USA[3,4]. Despite these numbers, breast cancer mortality has continuously decreased since the late 1970s in developed countries thanks to early detection and research for new drugs and treatments[5].

In this scenario hormone therapies represent an important treatment for hormone-receptor-positive breast cancer[6,7], i.e. a cancer formed by cells that receive signals from certain types of hormone that could promote their growth. If the carcinoma has receptors for estrogen is called estrogen-receptor-positive (or ER+), while it is called progesterone-receptor-positive (PR+) if it has progesterone receptors[8]. Roughly two out of every three breast cancer phenotypes test positive for hormone receptors, and this ratio becomes higher in older women than in younger women[9].

These findings have led to the development of molecules able to block estrogen-mediated cell signalling[10], ability called "antagonist effect", in order to fight ER+ breast carcinomas. For the last three decades, the most widely used drug as a hormonal therapy has been tamoxifen (Novaldex®), which indeed acts as an antagonist in the breast tissues and effectively treats patients, but it also acts as an agonist in other tissues[11,12].

This means that tamoxifen and its class of drugs could lead, as a side effect, to the development of resistance towards the primary treatment and to an increased risk of carcinomas in other parts of the body[11]. These drawbacks drove the research through the development of new drug molecules free of these undesired effects. (Fig. 4)

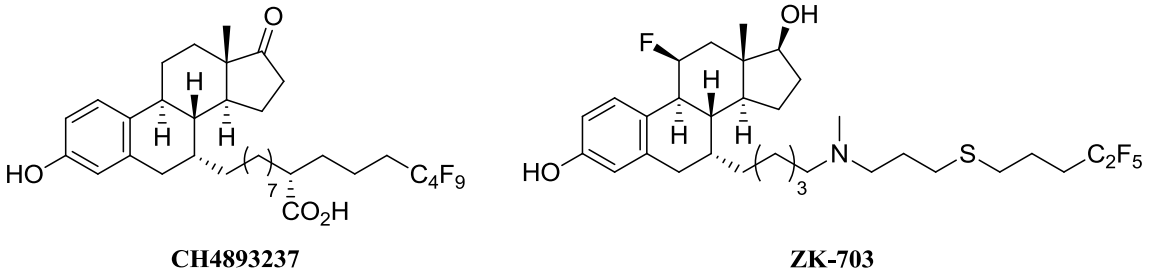


tamoxifen (Novaldex®) fulvestrant (Faslodex®)

Fig. 4. Examples of drugs used in hormonal therapy

Fulvestrant ('Faslodex®'), developed in 1987, is the first in a class of a new type of hormonal therapy: it acts as a 'pure' estrogen antagonist and therefore possesses no agonist effect[13]. Tamoxifen remains widely used against breast cancer, but fulvestrant has been proved to have other interesting properties in addition to its "pure antagonism".
Faslodex® is indeed quite active in the treatment of patients with ER+ breast carcinoma who didn't respond positively to other endocrine therapies, and also good results have been obtained using it in combination with other agents in order to increase its efficacy[14,15,16].

The main problem with fulvestrant is its low oral bioavailability, so it has to be injected intramuscularly. This implicates more pain for the patient as well as a higher risk of inflammation at the site of administration. For these reasons, research focused on the development of orally active pure estrogen-receptor antagonists, and efforts have been made to modify the alkyl side chain of fulvestrant. This led to the synthesis and biological assessment of compounds such as **CH4893237**[17] and **ZK-703**[18], for which research is still in progress[19] (Fig. 5).

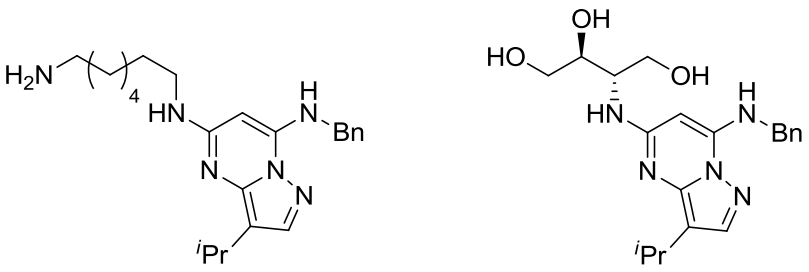


CH4893237 **ZK-703**

Fig. 5. Fulvestrant analogues with increased bioavailability

1.3 Previous Work

The issue of oral bioavailability has previously been faced in our laboratory on a different medicinal chemistry project. Our collaborators were interested in developing a selective cyclin-dependent kinase inhibitor[20]. A first analogue, **BS-181**, showed interesting inhibitory activity against a range of different kinases (Fig. 6), but the real achievement it turned out to be the substitution of the aminoalkyl fragment with a trihydroxy side chain, affording compound **BS-194**. This modification led to an important increase in the oral bioavailability without significant changes in the desired biological functions of the drug[21].

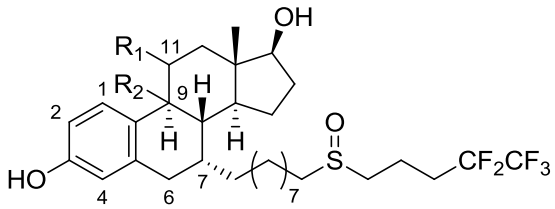


BS-181 **BS-184**

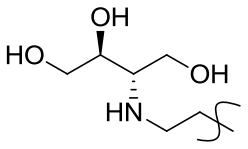
Fig. 6. Increase of the bioavailability of BS-181

These findings were therefore used in the design of a new analogue of fulvestrant, on which the same trihydroxyamino side chain was substituted onto the steroidal core of fulvestrant (compound **237**, Fig. 7). Instead of modifying the C-7 alkyl side chain, it was seen as a good idea to attach the bioavailability enhancing triol fragment *via* an ethylene linker on C-11 or on C-9 of the steroidal core.

Examples of modification of the C-11/C-9 position of estrogen derivatives have already been reported in the literature[22], but nothing concerning a similar compound carrying also the side chain on C-7 and C-11 functionalized with side chains. For this reason and for the advantages that it could offer, the synthesis of fulvestrant analogue **237** represents a very challenging synthetic goal.



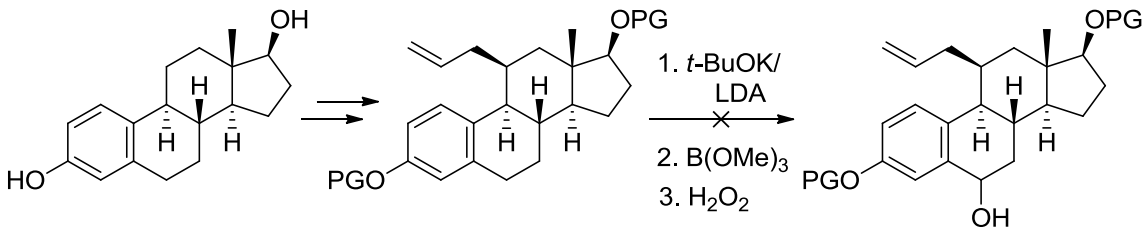
237a R_1 = trihydroxy side chain; R_2 = H
237b R_1 = H, R_2 = trihydroxy side chain



(trihydroxy side chain)

Fig. 7. Synthetic targets as new fulverstrant analogues

The synthesis of fulvestrant analogue **237** has been previously attempted in the Barrett group[23]. In the first attempt an allyl group was put in the C-11 position. Compounds **238a** and **238b** were obtained after a five-step sequence. In the next step efforts were made to oxidize the C-6 position, in order to introduce the alkyl side chain on the C-7 position. Unluckily, alcohol **239** was not obtained (Scheme 8)



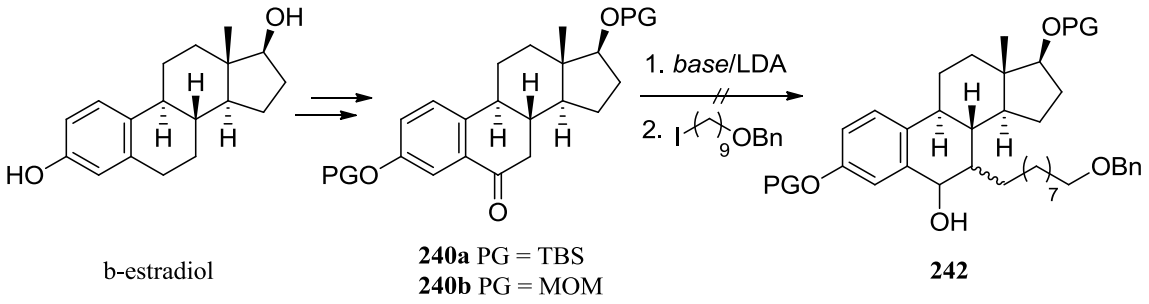
b-estradiol

238a PG = TBS
238b PG = Bn

239

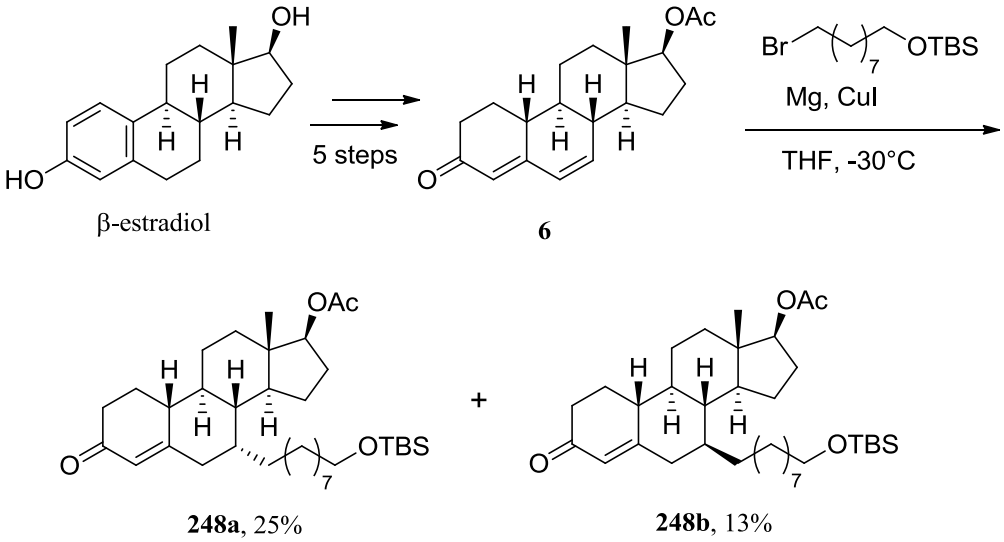
Scheme 8. First attempt in the synthesis of fulvestrant analogue 237

A second alternative approach for the synthesis of target molecule **237** was to install the alkyl side chain in an early stage[23] (Scheme 9). To do so, intermediates **240a** and **240b** were synthetizes in three steps, but the alkylation reaction to obtain compound **242** was unsuccessful.



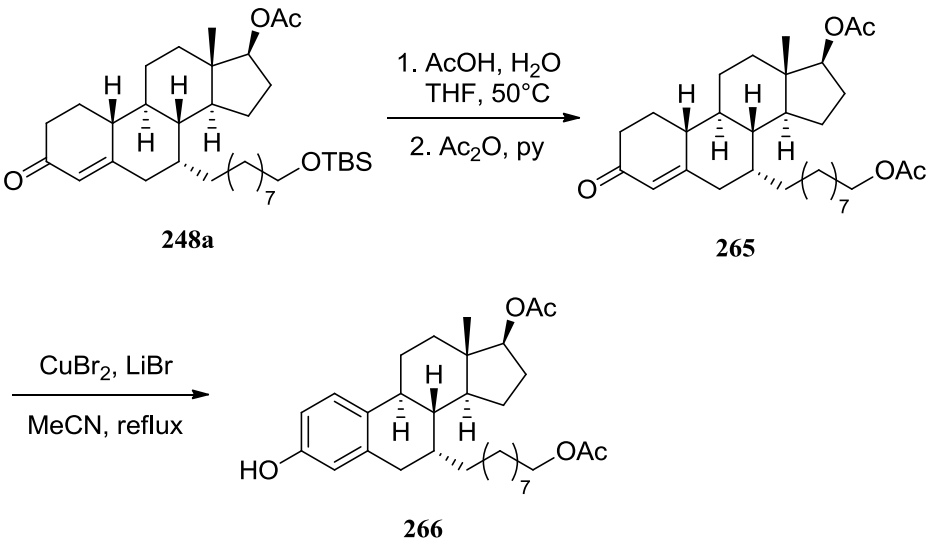
Scheme 9. Second attempt in the synthesis of fulvestrant analogue 237

The third attempt[24] that has been undertaken to reach synthetic target **237** was to attach the side chain on C-7 by way of a copper mediated 1,6-addition of the alkyl bromide below to dienone **6**. C-9 and C-11 positions have then to be oxidized connecting them with a double bond with DDQ. Dienone **6** was successfully synthetized in 5 steps, and also the conjugate addition was successful, giving compound **248a** (Scheme 10).



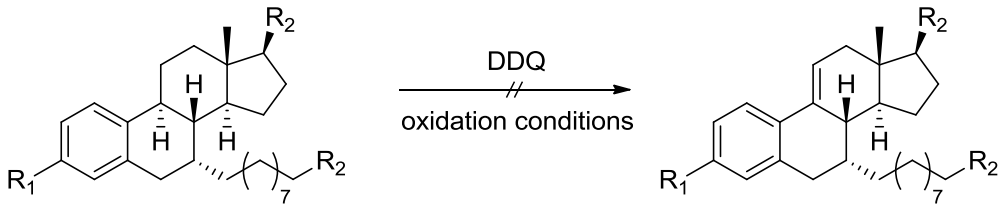
Scheme 10. Installation of the southern chain

The TBS protecting group in ketone **248a** was then hydrolyzed and acetylated in the same step to give alkylated enone **265**, that was subsequently successfully aromatized to phenolic steroid **266** (Scheme 11).



Scheme 11. Replacement of –OTBS group with acetate and aromatization

The next step was an oxidation carried out with DDQ, which afforded no desired product in any condition tested (Scheme 12).

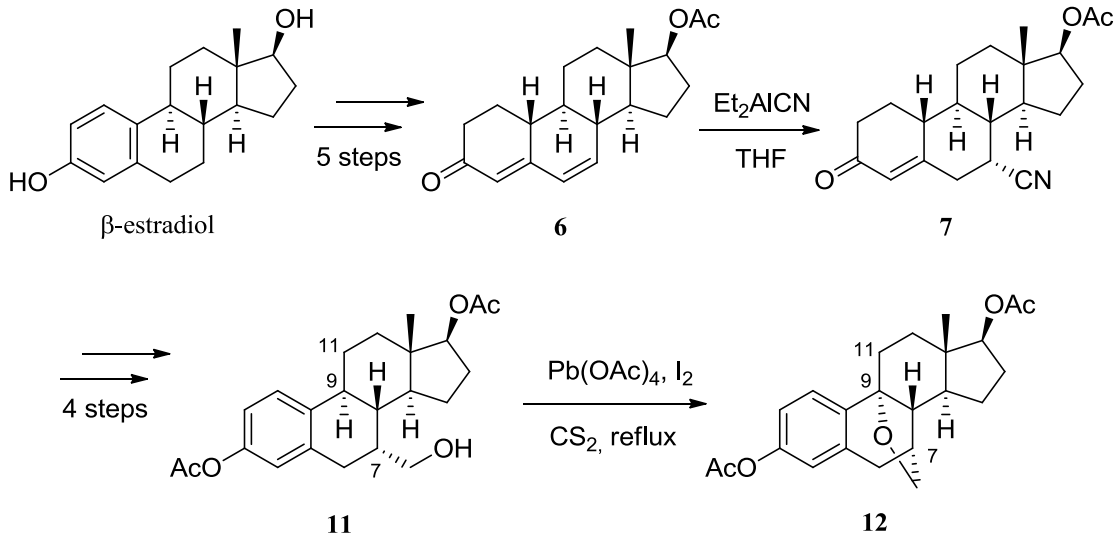


266 R_1 = OH, R_2 = OAc
273 R_1 = OBn, R_2 = OTBS

268 R_1 = OH, R_2 = OAc
274 R_1 = OBn, R_2 = OTBS

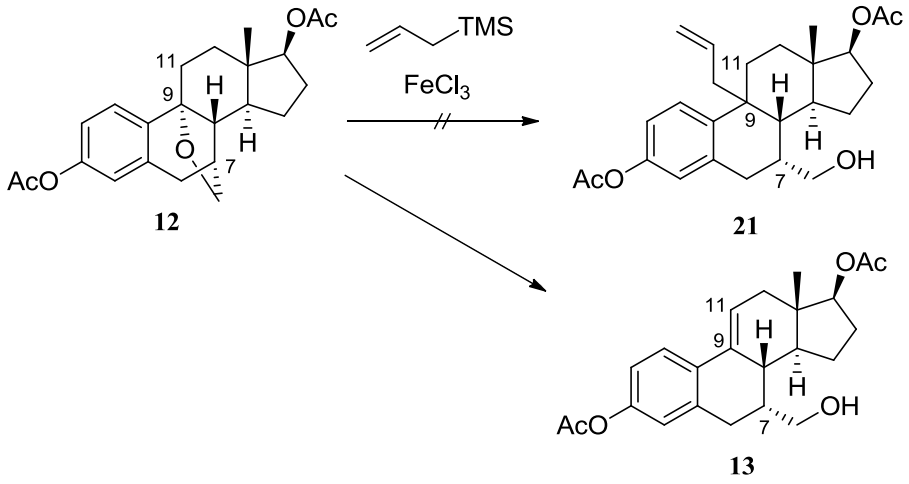
Scheme 12. DDQ oxidation

The fourth attempt[24] to synthetize fulvestrant analogue **237** was to introduce a functionalized carbon on the C-7 position and then use it to lead the way to the functionalization of C-9. Starting from β-estradiol, compound **6** was synthetized in 5 steps, then a carbon was added on C-7 position through a 1,6-conjugate addition of cyanide giving compound **7**. Alcohol **11** was synthetized in 4 more steps, but the real achievement was the success in the synthesis of ether **12**.



Scheme 13. Fourth try in the synthesis of fulvestrant analogue 237

At this point an allylation was attempted in order to functionalize ether **12** on the C-9 position with an allyl group. Unexpectedly, an elimination occurred instead, leading to alkene **13** (Scheme 14).

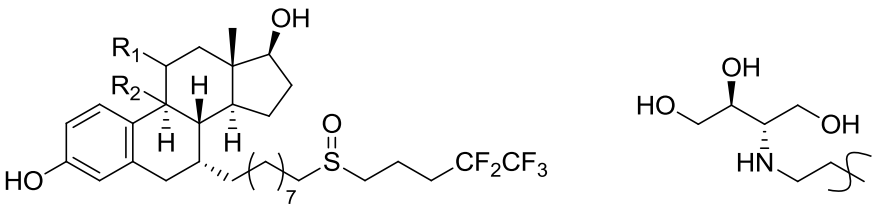


Scheme 14. Elimination reaction towards alkene 13

The synthesis of alkene **13** was a success in any case, but its potential role in the synthesis of fulvestrant analogues **237** wasn't further investigated.

2. Project Goals

This project is part of a study undertaken to increase fulvestrant bioavailability. The main goal is the synthesis of a novel intermediate as a step forward into the synthesis of fulvestrant analogues **237** (Fig. 7).

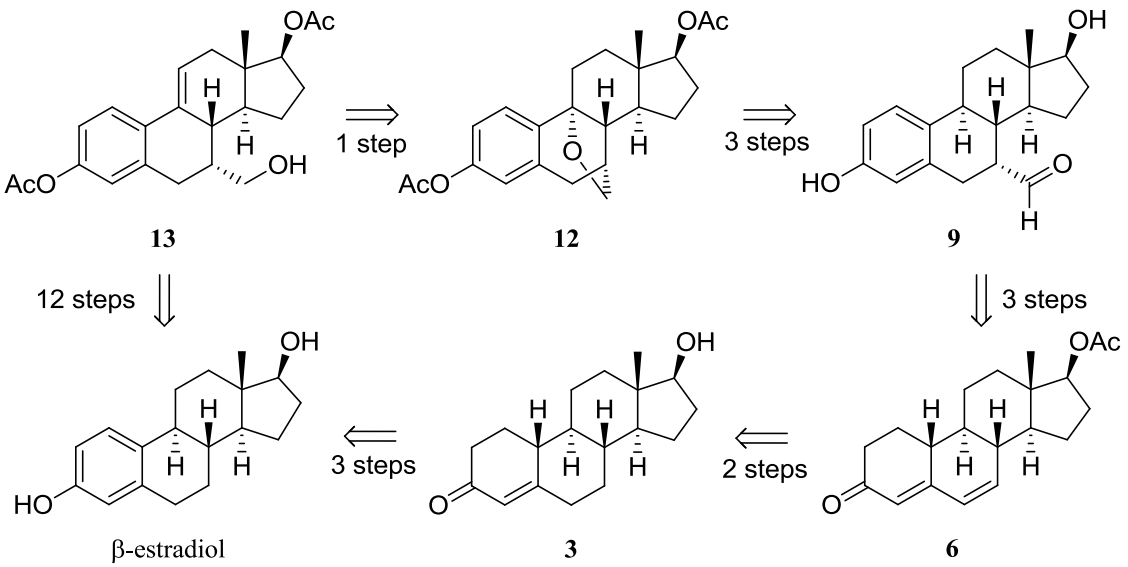


237a R_1 = trihydroxy side chain; R_2 = H
237b R_1 = H, R_2 = trihydroxy side chain

(trihydroxy side chain)

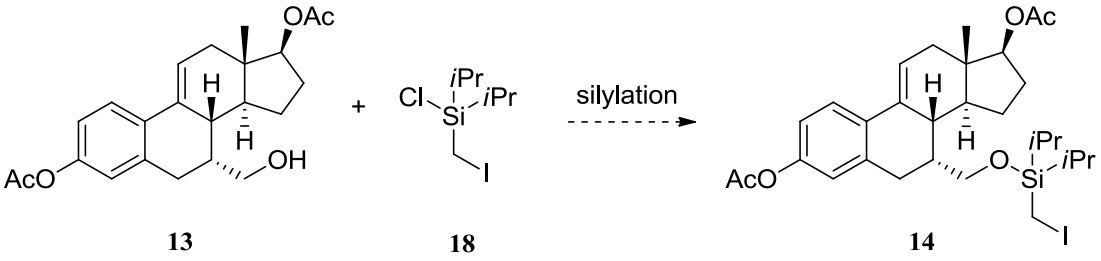
Fig. 7. Fulvestrant analogues 237

In previous work in Barrett research group[24,25], synthesis of alkenol **13** was achieved in twelve steps from commercially available β-estradiol (Scheme 15).



Scheme 15. Retrosynthesis towards alkenol 13 from β-estradiol

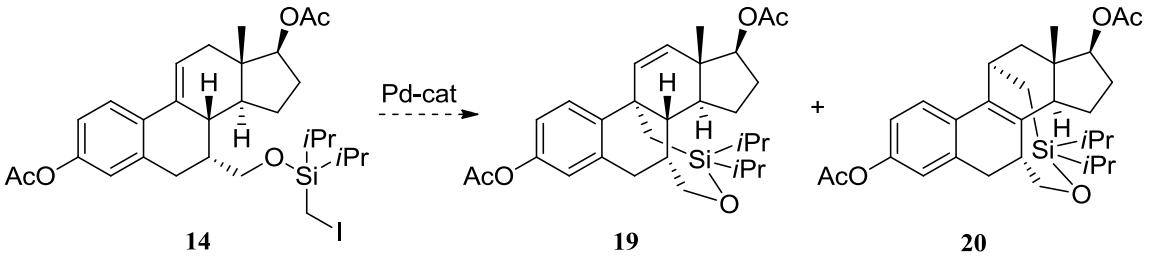
After synthetizing an appreciable amount of alkenol **13**, the purpose of this project was to synthetize silyl chloride **18** in three steps and use it to functionalize alkenol **13** to give silyl steroid **14** (scheme 16), a novel advanced intermediate[26].



13 **18** **14**

Scheme 16. Idea for the synthesis of a novel advanced intermediate 14

If the silylation of alkenol **13** is successful, an intramolecular modified Heck coupling[26] will be tried in order to get a bicyclic steroid such as **19** and/or **20** (Scheme 17).



14 **19** **20**

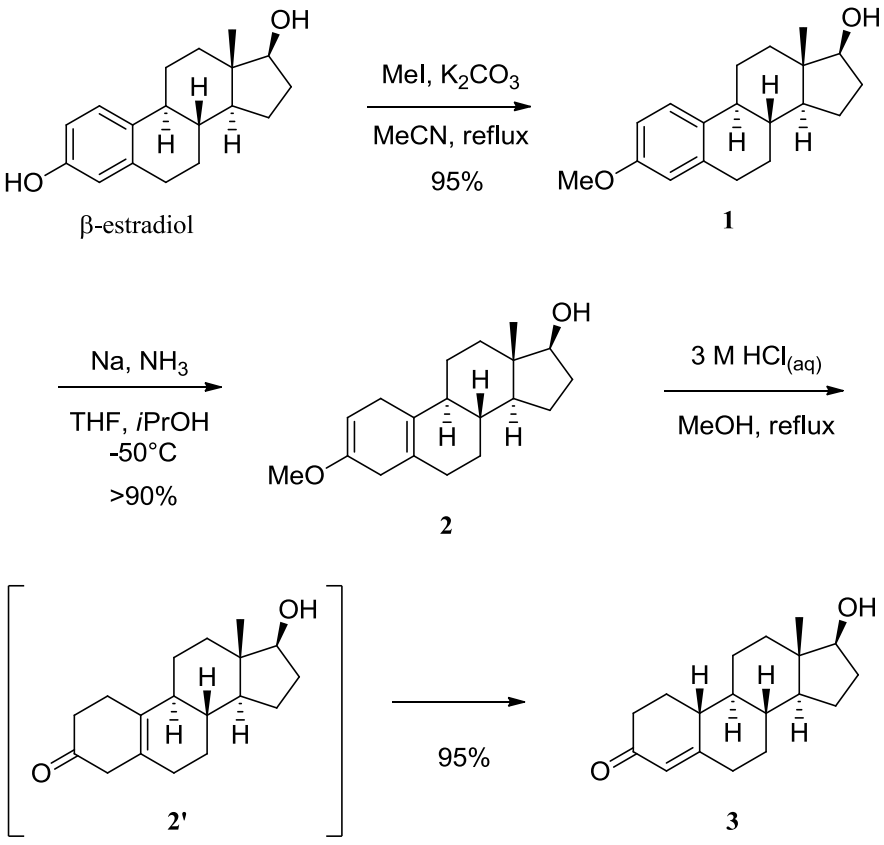
Scheme 17. Hypothesized products of the Heck Coupling

3. Results and Discussion

3.1 Synthesis of 19-nortestosterone (3)

For economic reasons, it was decided to synthetize commercially available 19-nortestosterone (**3**) from the much more cheaper and commercially available β-estradiol in three steps, following literature procedures[27,28] (Scheme 18).

Firstly, the methylation of the aromatic hydroxyl of β-estradiol was carried out. Methyl iodide and potassium carbonate were refluxed with the substrate in acetonitrile giving methyl ether **1** in 95% yield. The second step was the Birch reduction of aromatic compound **1** in order to obtain unconjugated diene **2**: sodium dissolved in liquid ammonia and THF in presence of isopropanol at -50°C gave desired product **2** in > 90% yield. Finally, enol ether **2** was hydrolyzed in aqueous acidic conditions to 19-nortestosterone **3** in 95% yield.

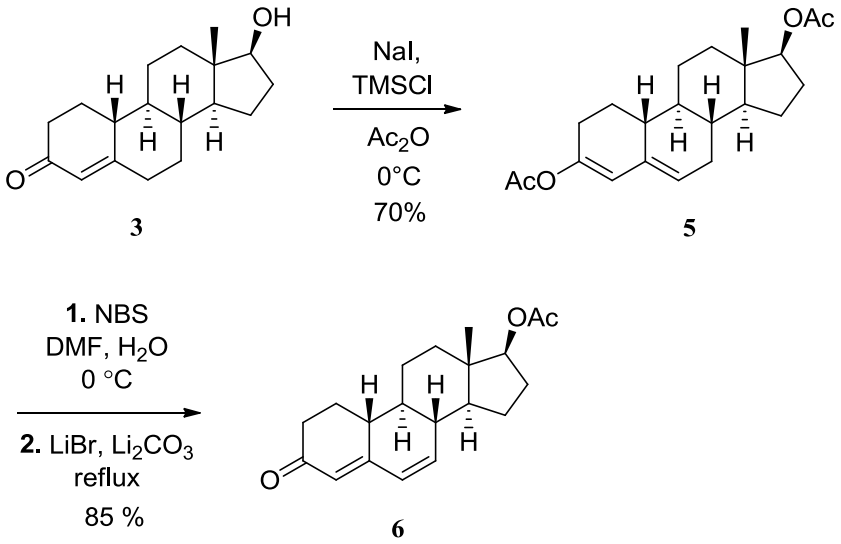


Scheme 18. Synthesis of 19-nortestosterone 3

This hydrolysis passes through an intermediate β,γ-unsaturated ketone **2'**, which isomerizes straight away to give the α,β-unsaturated ketone **3** as a result of the keto enol tautomerism.

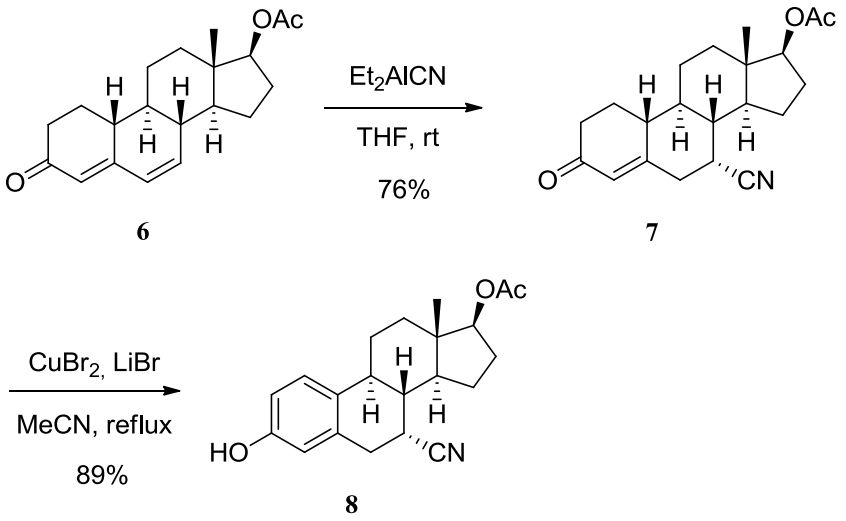
3.2 Functionalization of the C-7 Position

In the first step enone **3** was dissolved in acetic anhydride and treated with sodium iodide and trimethylsilyl chloride to give diacetate **5** in a single high-yielding step[29]. Treatment of **5** with NBS in presence of water, followed by heating and addition of base[30] led to the formation of α,β,γ,δ-unsaturated ketone **6** in 85% yield (Scheme 19).



Scheme 19. Synthesis of dienone 6

Dienone **6** underwent a hydrocyanation[31] to give nitrile **7** in 76% yield (Scheme 3). For this 1,6-conjugated addition of cyanide, one molar diethylaluminum cyanide solution in toluene was used as soluble and bulky source of CN^-, in order to achieve high diastereoselectivity in the product. The cyclic enone moiety in ketone **7** was then aromatized with cupric bromide and lithium bromide in refluxing acetonitrile[31], giving nitrile **8** in 89% yield (Scheme 20).



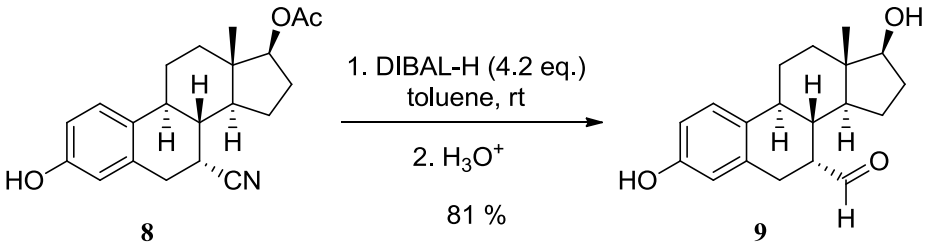
6 **7** **8**

Scheme 20. Synthesis of nitrile 8 from dienone 6

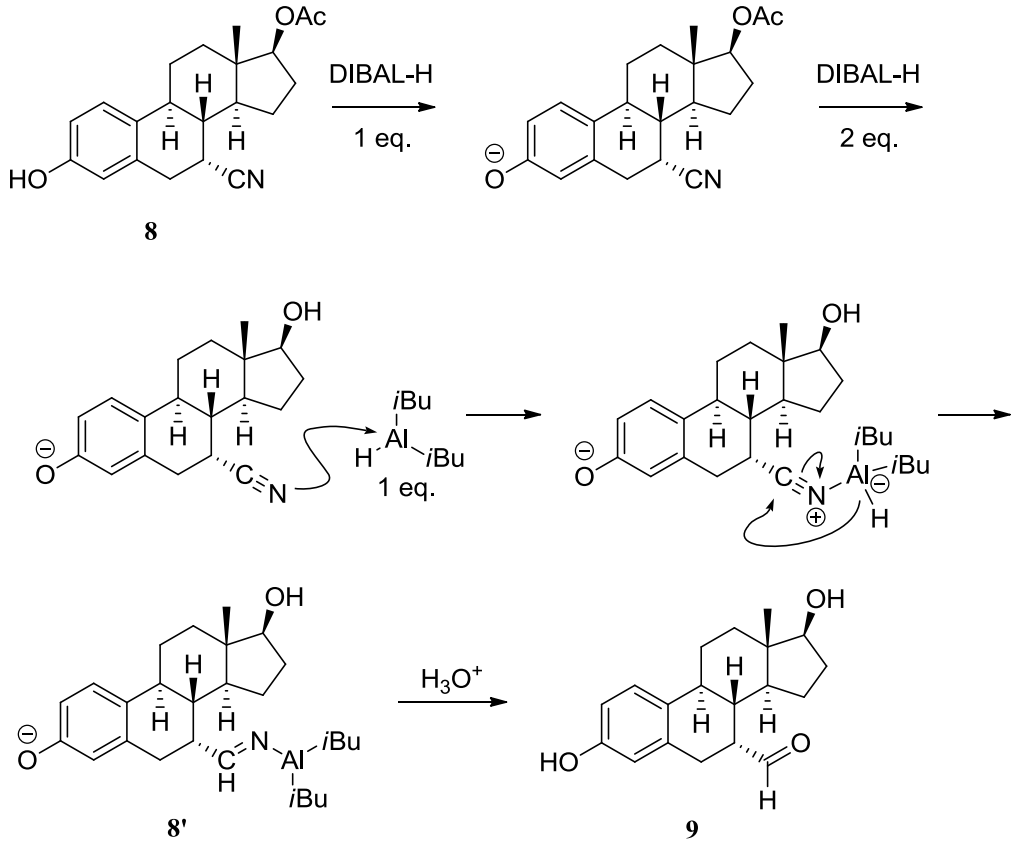
3.3 Functionalization of the C-9 and C-11 Positions

3.3.1 Reduction of Nitrile 8 with DIBAL-H

In previous works in the Barrett Group[24] and in the literature[31] the reduction of nitrile **8** to aldehyde **9** was carried out with 1.67 equivalents of DIBAL-H at room temperature. In our hands, attempted reproduction of these conditions gave aldehyde **9** in a yield that did not exceed 40%. Considering the reactivity of DIBAL-H and the presence of additional functionality in the substrate (i.e. an ester, a phenolic hydroxyl and a nitrile in the molecule), the number of equivalents of hydride was increased to 4.2: one equivalent would deprotonate the hydroxyl, two equivalents would reduce the ester to an alcohol and the fourth equivalent would actually reduce the aliphatic cyanide to an imine salt **8'**. This would hydrolyze to the corresponding aldehyde after aqueous work-up (Scheme 22). These modified reaction conditions proved effective and nitrile **8** was reduced to aldehyde **9** in 81% yield (Scheme 21).



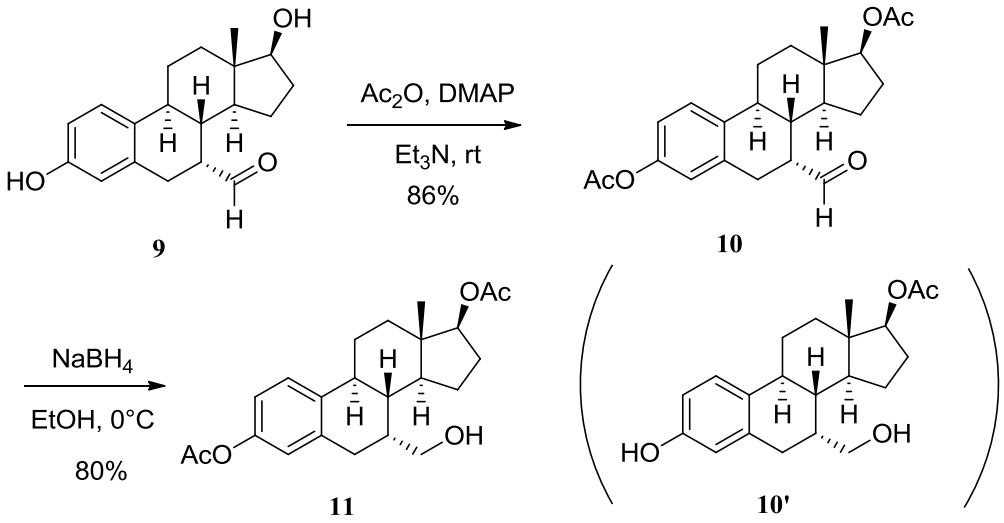
Scheme 21. Reduction of nitrile 8 to aldehyde 9



Scheme 22. Proposed mechanism for DIBAL-H reduction of 8 (deprotonation of phenolic hydroxyl, reduction of the ester and reduction of the nitrile are displayed in this order for explanatory reasons).

3.3.2 Reduction of Aldehyde 9 to Alcohol 11

First the two hydroxyl groups of aldehyde **9** were protected as diacetate **10** using acetic anhydride catalyzed by DMAP and a tertiary amine[31]. In the next step the aldehyde was reduced using sodium borohydride in ethanol at 0 °C[31] giving alcohol **11** (Scheme 23).

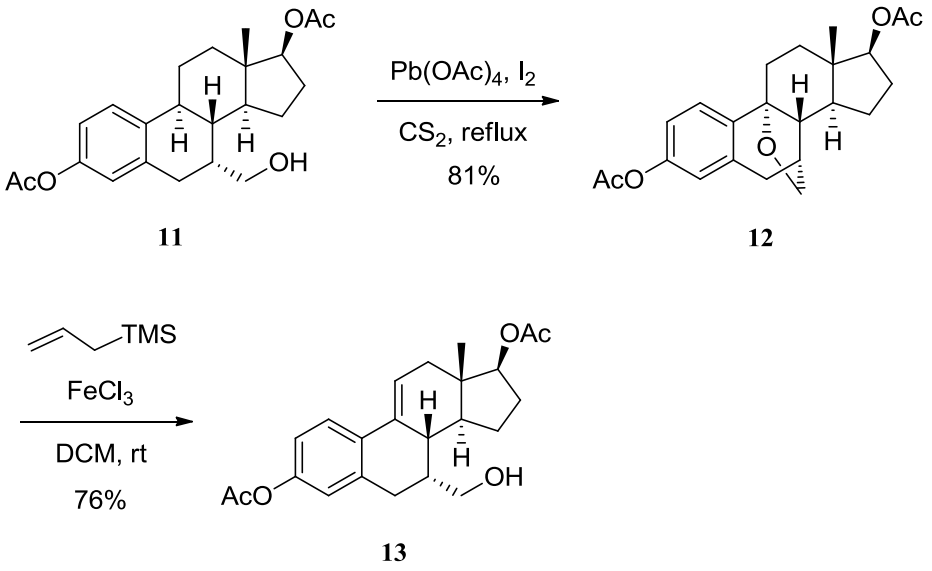


Scheme 23. Protection and reduction of alcohol 9 to aldehyde 11

During the course of this reaction alcohol **10'** was detected and isolated, as the basic conditions led to partial cleavage of the aromatic acetate. In an attempt to avoid this, the same reaction was performed in presence of a buffer salt (NaH_2PO_4), however no improvement was observed. On the other hand it was found that simply neutralizing the reaction mixture with a reverse quench into a saturated solution of ammonium chloride, the cleavage of the aromatic ester was reduced and alcohol **11** was obtained with a reproducible yield of 80%.

3.3.3 Synthesis of Alkenol 13

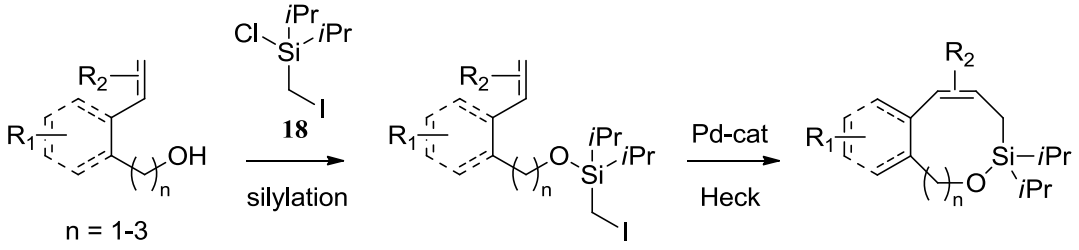
Following the conditions previously reported by the Barrett research group[24], alcohol **11** was oxidized to the benzylic ether **12** necessary for subsequent conversion to alkenol **13**. Thus alcohol **11** was refluxed with a mixture of lead (IV) acetate and iodine in carbon disulfide to give bicyclic ether **12** in 81% yield. After, substrate **12** was converted to alkenol **13** via an elimination reaction with iron (III) chloride and allyltrimethylsilane in dichloromethane[25] in 76% yield (Scheme 24).



Scheme 24. Synthesis of alkanol 13 from alcohol 11

3.4 Attempts Towards the Synthesis of the Silyloxycycle Steroid Derivative

With substrate **13** in hand, it was decided to investigate an intramolecular Heck reaction of this steroid derivative. According to the literature[26] an endo-selective palladium-catalyzed Heck reaction of iodomethylsilyl ethers of aliphatic alkenols has been developed to obtain silyloxycycles (Scheme 25).

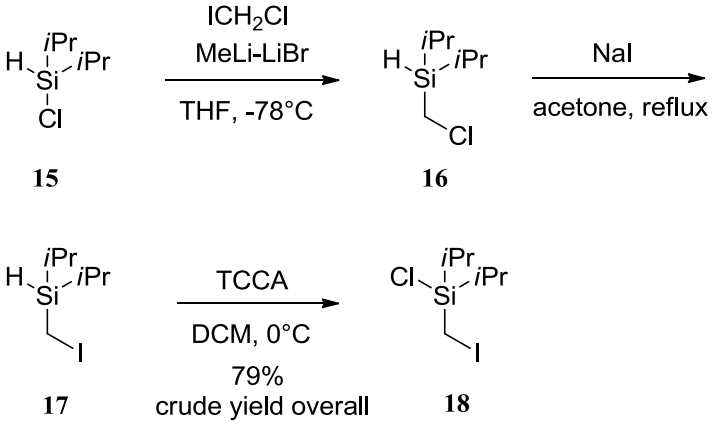


Scheme 25. Preparation of a Silyloxycycle using a Heck Coupling

3.4.1 Synthesis of Silylating Agent 18

Chloro(iodomethyl)diisopropylsilane **18** was synthetized from commercially available (chloro)diisopropylsilane **15** in three steps[26]. First substrate **15** was converted into silane **16** by reaction with chloroiodomethane and a complex of methyllithium and lithium

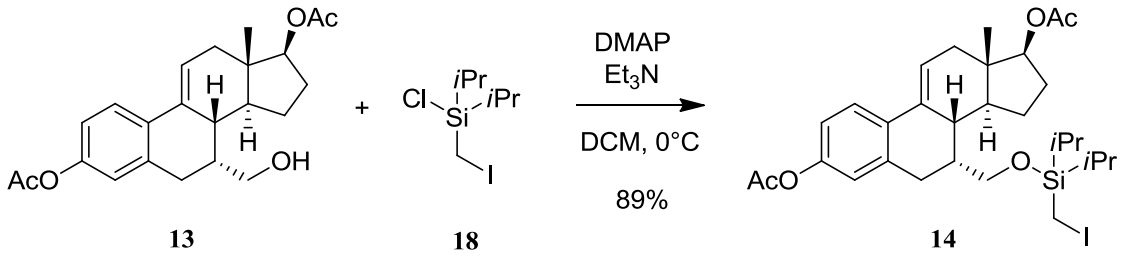
bromide in THF at -78 °C. Displacement of the chloride in compound **16** with iodide through a Finkelstein reaction gave (iodomethyl)diisopropylsilane **17**. In the last step substrate **17** was oxidized with trichloroisocyanuric acid (TCCA) in DCM at 0 °C to give chloro(iodomethyl)diisopropylsilane **18** with an overall crude yield of 79% (Scheme 26).



Scheme 26. Synthesis of silylating agent 18

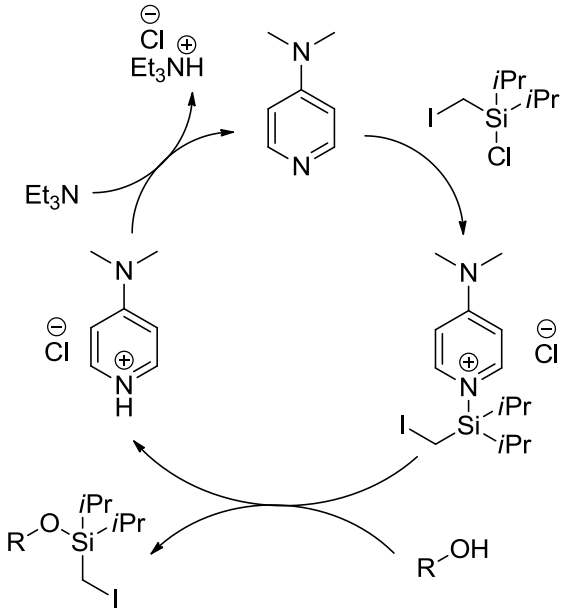
3.4.2 Silylation of Alkenol 13

Alkenol **13** was successfully silylated by reacting with silylating agent **18** in a DMAP catalyzed reaction with triethylamine in DCM at 0°C[26] giving iodomethylsilyl ether **14** in 89% yield (Scheme 27), a novel intermediate.



Scheme 27. Silylation of alkenol 13 with silylating agent 18

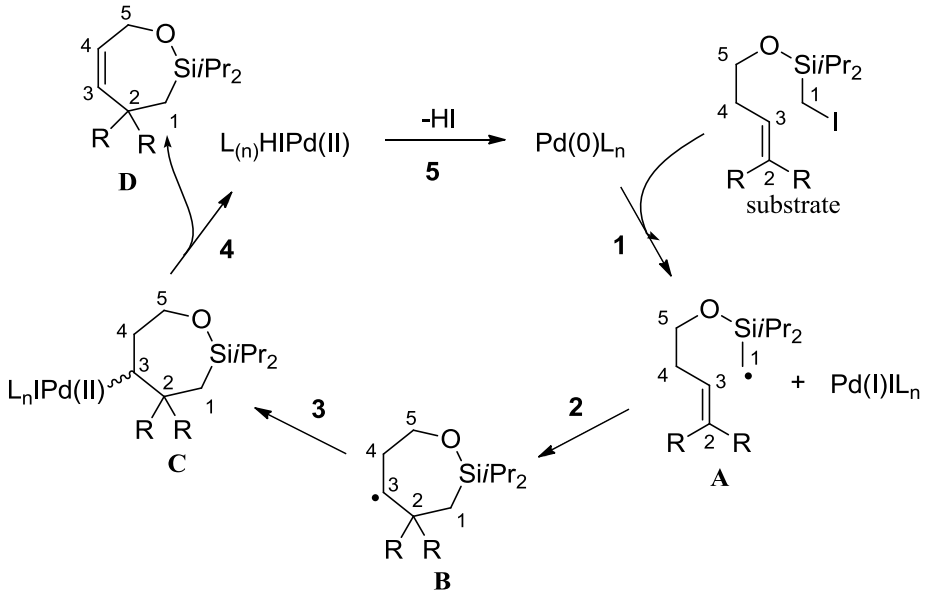
The silylation catalytic cycle that took place is shown in (Scheme 28). The silyl chloride is activated by DMAP, while the stoichiometric triethylamine neutralizes the HCl formally eliminated during the reaction.



Scheme 28. Silylation catalytic cycle with DMAP

3.4.3 The Silyl Methyl Heck Coupling

The silyl methyl Heck coupling is proposed to proceed via a hybrid-Pd-radical catalytic cycle[26] shown in (Scheme 29).



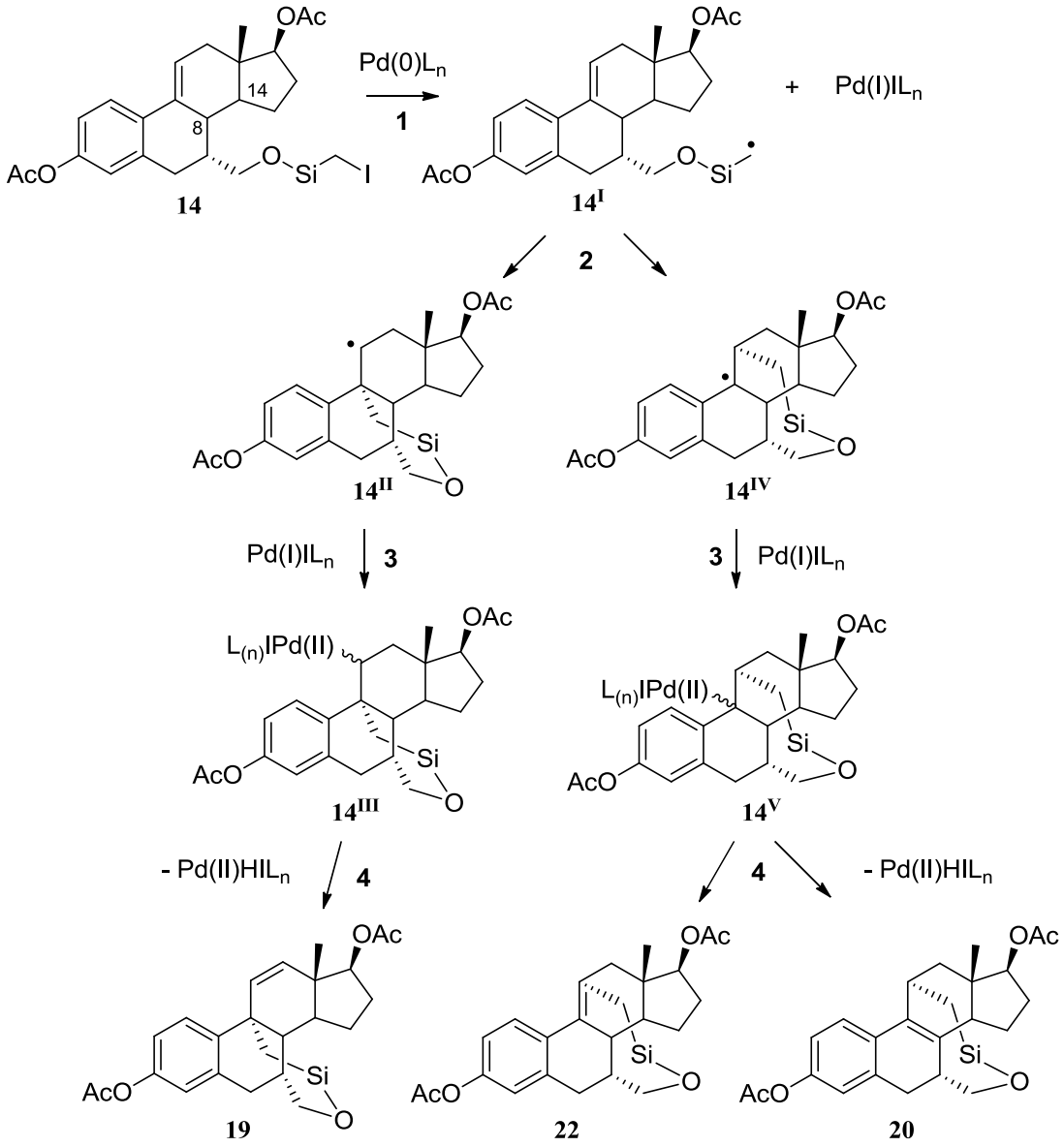
Scheme 29. Catalytic cycle for the silyl methyl Heck reaction

1. Oxidative addition of the substrate to the catalyst, followed by homolysis produces radical **A** and the Pd(I) species, avoiding a premature β-hydride elimination.
2. Cyclization of radical **A** can lead to cyclic radical **B**.
3. Recombination of radical **B** with Pd(I) species produces alkylpalladium species **C**.
4. β-hydride elimination of **C**, which can be induced with silver salts, gives product **D** and Pd(II) species.
5. Reductive elimination of HI, in the presence of a base, regenerate the catalytic species Pd(0).

Although 6-9 membered silyloxycycle with *endo* double bond are the most common products, silyloxycycles with *exo* double bond are almost always isolated as minor products and at times obtained as major products.

3.4.4 Possible products of the silyl methyl Heck reaction on substrate 14

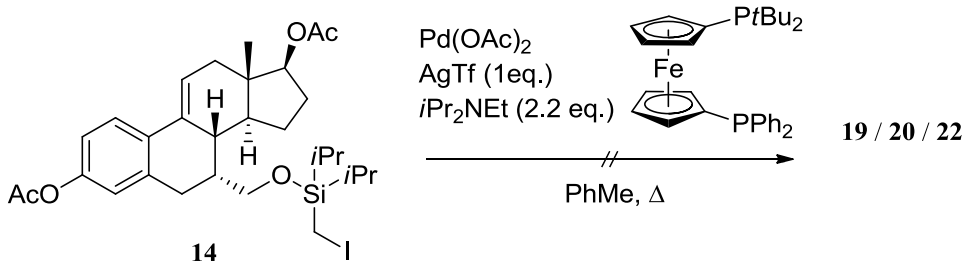
If the reaction were to work on substrate **14**, three products can be hypothesized, such as **19**, **20** and **22** (Scheme 30). Product **22** is very unlikely to form as its structure would be forbidden by the Bredt's rule.



Scheme 30. Possible products of the silyl methyl Heck reaction on substrate 14. The silicon atoms shown in the scheme are tetravalent, but two –*i*Pr substituents were omitted for drawing reasons.

3.4.5 Pd-catalyzed silyl methyl Heck reaction applied on substrate 14

After some consideration about possible products, the reaction was attempted on substrate **14** by treatment with palladium (II) acetate, silver triflate, diisopropylethylamine, 1-diphenylphosphino-1′-(di-*tert*-butylphosphino)ferrocene as ligand and toluene as solvent (scheme 31). The reaction was run in a sealed tube, under argon atmosphere in a glove box, and different conditions were screened (Tab 1). In each case the reaction was monitored by TLC analysis and was stirred up to 72 hours.



Scheme 31. Silyl methyl Heck reaction on substrate 14

Entry	Temperature	$Pd(OAc)_2$	Ligand	Results
1	110 °C	0.1 eq.	0.2 eq.	decomposition
2	135 °C	0.1 eq.	0.2 eq.	decomposition
3	135 °C	0.5 eq.	1.0 eq.	products not characterized

Tab 1. Screening

In one run (entry 3) two clear spot were detected by thin layer chromatography analysis. The reaction mixture was filtered through celite and a purification by flash column chromatography in DCM was attempted. Unfortunately, given the scale of the reaction and the instability of the product mixture, it was not possible to characterize any product in the isolated fractions.

It is possible that the reaction was unsuccessful because the 7 or 8 membered ring which would form would be too strained. This is because 4 of its atom would belong to the steroidal core and therefore are roughly on the same plane (Fig. 8)

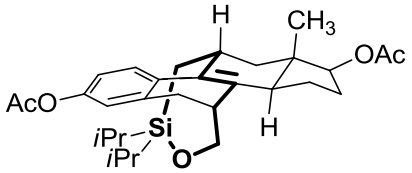
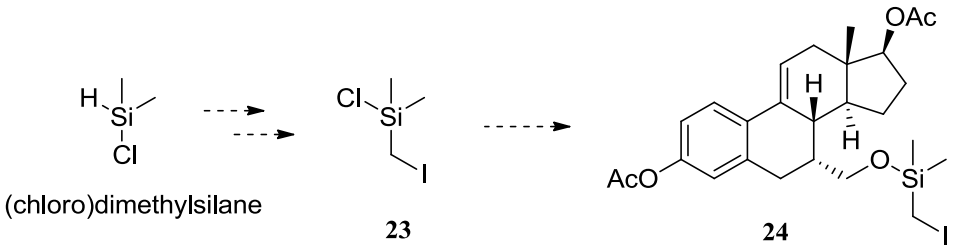


Fig. 8. Proposed 3D drawing of target molecule 20

3.5 Future work

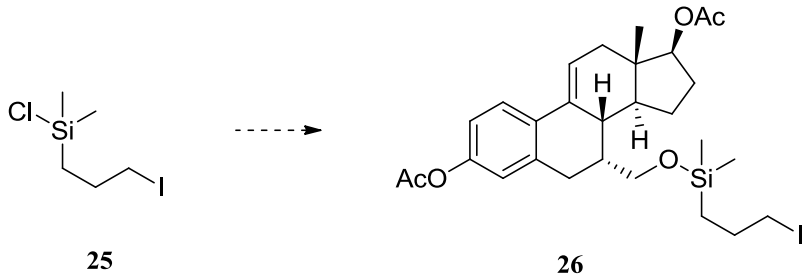
The Pd-catalyzed silyl methyl Heck reaction will be further investigated:

1. Conditions **3** will be run with a greater amount of substrate **14** to try to characterize the product.
2. The reaction will be run again without silver triflate. It is known that silver salts promote the β-elimination stage during the catalytic cycle, but in this case silver cation could induce a premature β-elimination between the oxidative addition and the homolysis, and such a thing would compromise the formation of radical **A** (Scheme 29).
3. In case the reaction was not successful due to steric hindrance, a less bulky silicon fragment can be synthetized and attached to alkenol **13**, i.e. with methyl groups instead of isopropyl ones. That would lead to a less hindered iodomethylsilyl ether such as compound **24** (Scheme 32).



Scheme 32. Proposed option with a less bulky silicon moiety

4. If the reaction did not work because the ring that would form would be too strained, a reasonable option would be to increase the number of carbon atoms between the iodine and the double bond (compound **26**) using a different silylating agent (**25**), in order to form a less strained ring (Scheme 33).



Scheme 33. Proposed option with a silicon

In case the Heck coupling will not give any positive result, alkenol **13** remains a valuable advanced intermediate. Many options can be evaluated in order to functionalize the double bond and attach a substituent on C-9 or C-11 (Fig. 9)

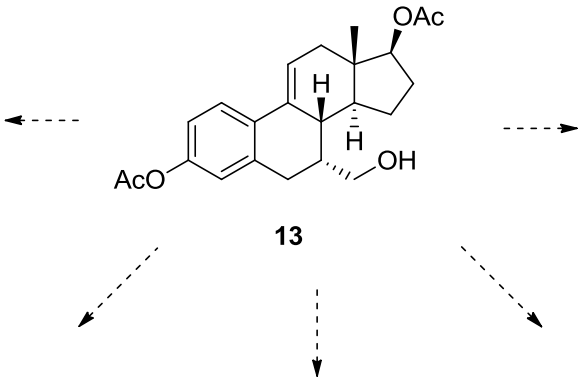


Fig. 9. Advanced intermediate 13

4. Experimental

4.1 General Procedures

All reagents and solvents were supplied from commercial sources, and used as supplied unless otherwise indicated. Reactions requiring anhydrous conditions were conducted in oven-dried glassware under an inert atmosphere (nitrogen or argon), and using anhydrous solvents. DCM, Et_3N, and pyridine were distilled over CaH_2. THF was distilled over Na/benzophenone. MeOH was distilled over $Mg(OMe)_2$. Anhydrous chemicals were obtained commercially.

All reactions were monitored by thin-layer chromatography (TLC) using Merck silica gel 60 F254 plates (0.25mm). TLC plates were visualized using UV light (254nm) and/or by staining in vanillin or PMA, as appropriate.

Flash column chromatography was performed using silica gel (Sigma-Aldrich) 40-63 μm 60 Å with a solvent system that will be described in the relevant procedure.

Infrared spectra were recorded neat on a Perkin Elmer Frontier FT-IR Spectrometer. Reported absorptions are strong or medium strength unless stated otherwise and given in wavenumbers (cm^{-1}).

^{1}H and ^{13}C NMR were recorded on a Bruker Avance 400 spectrophotometer at 400 MHz and 100 MHz respectively and on a Bruker Avance 500 at 500 MHz and 125 MHz respectively. Chemical shifts (δ) are quoted in ppm (parts per million) downfield from tetramethylsilane, referenced to residual solvent signals: ^{1}H δ = 7.26 ($CHCl_3$); ^{13}C δ = 77.16 ($CDCl_3$). Carbon multiplicities were determined by DEPT experiments. The signal multiplicity is quoted as follow: coupling constant (*J*), singlet (s), doublet (d), triplet (t), quadruplet (q), quintuplet (quin), sextet (sext), septet (sep) broad (br), apparent (app), multiplet (m), double-doublet (dd), double-double-doublet (ddd).

Low and high resolution mass spectra (ESI, CI) were recorded by the Imperial College London Department of Chemistry Mass Spectroscopy Service using a Micromass Autospec Premier and Micromass LCT Premier spectrometer.

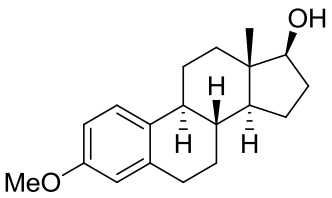
Melting points were determined using a Leica VMTG heated-stage microscope and are uncorrected.

Specific rotations $[\alpha]^{D}$ were recorded on a Perkin-Elmer 214 polarimeter at 589 nm

(Na D-line) with a path length of 0.5 dm. Concentrations (*c*) are quoted in g/100 mL and specific rotations are quoted in units of deg●$dm^{-1}cm^3g^{-1}$ at the indicated temperature (in °C).

4.2 Synthesis

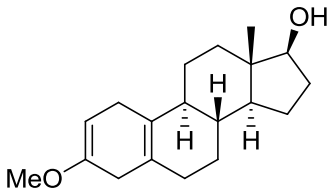
(8*R*,9*S*,13*S*,14*S*,17*S*)-3-methoxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-*6H*-cyclopenta[*α*]phenanthren-17-ol (1)



To a solution of β-estradiol (5.0 g, 18.36 mmol, 1.0 eq.) in acetonitrile (200 mL) was added potassium carbonate (12.69 g, 91.8 mmol, 5.0 eq.) and methyl iodide (15.64 g, 110.2 mmol, 6.0 eq.). This mixture was refluxed for 16 h, then cooled at room temperature and the solvent was evaporated *in vacuo*. The solid residue was suspended in water (200 mL) and the aqueous layer extracted with DCM (3 x 50 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent removed *in vacuo* giving crude compound **1** >90% pure by NMR. Purification by flash column chromatography (pentane : ethyl acetate, 80 : 20) afforded methyl ether **1** (4.99 g, 95% yield) as a white solid.

R_f 0.58 (pentane : ethyl acetate, 70 : 30); mp 80–82 °C; $[\alpha]_D^{28}$ +10 (*c* 1.00, $CHCl_3$); IR (thin film) 3460 (br), 2932, 2847, 1613, 1506, 1252 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.21 (d, 1H, *J* = 8.5 Hz, Ar-*H*), 6.71 (dd, 1H, *J* = 8.5, 2.8 Hz, Ar-*H*), 6.63 (d, 1H, *J* = 2.8 Hz, Ar-*H*), 3.78 (s, 3H, Ar-OCH_3), 3.76–3.69 (m, 1H, C*H*OH), 2.93–2.78 (m, 2H), 2.37–2.26 (m, 1H), 2.25–2.06 (m, 2H), 1.99–1.91 (m, 1H), 1.91–1.84 (m, 1H), 1.75–1.65 (m, 1H), 1.57–1.13 (m, 8H), 0.78 (s, 3H, CCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 157.4, 38.0, 132.6, 126.3, 113.8, 111.5, 81.9, 55.2, 50.0, 43.9, 43.3, 38.8, 36.7, 30.6, 29.8, 27.2, 26.3, 23.1, 11.0; HRMS (ES+) m/z: $[M+H]^+$ calcd for $C_{19}H_{27}O_2$ 287.2011, found 287.2023. The analytical data are consistent with the data reported in the literature.

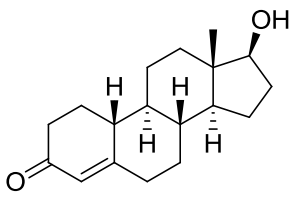
(8*R*,9*S*,13*S*,14*S*,17*S*)-3-methoxy-13-methyl-4,6,7,8,9,11,12,13,14,15,16,17-dodecahydro-*1H*-cyclopenta[*α*]phenanthren-17-ol (2)



A solution of protected phenol **1** (12.2 g, 42.6 mmol, 1.0 eq.) in isopropanol (40 mL) and THF (80 mL) was added to liquid ammonia (500 mL) at –78 °C. The resulting white viscous suspension was stirred vigorously for 10 min. with an oversized stir bar, then sodium (10.78 g, 468.6 mmol, 11.0 eq.) was added in small pieces over 10 min giving the mixture a deep blue colour. The reaction mixture was allowed to warm up between -55 and -45 °C and after 1.30 h the reduction is completed. Methanol (80 mL) was added slowly to quench the reaction, and the mixture was allowed to reach room temperature in an open flask. The residue was suspended in water (300 mL) and the aqueous layer extracted with DCM (3 x 50 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent removed *in vacuo* giving cyclohexadiene **2** as a white solid, more than 95% pure by NMR (12.16 g, >90% yield).

R_f 0.42 (pentane : ethyl acetate, 70 : 30); $[\alpha]_D^{28}$ +31 (*c* 1.00, $CHCl_3$); IR (thin film) 3381 (br), 2916, 2867, 1656, 1448, 1053 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.64 (t, 1H, *J* = 3.3 Hz, C=C*H*), 3.76–3.61 (app t, 1H, *J* = 8.4 Hz, C*H*OH), 3.55 (s, 3H, OCH_3), 2.91–2.81 (m, 1H), 2.77–2.45 (m, 3H), 2.19–2.00 (m, 2H), 1.97–1.79 (m, 3H), 1.67-1.72 (m, 1H), 1.65–1.57 (m, 3H), 1.48–1.02 (m, 8H), 0.76 (s, 3H, CCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.6, 127.9, 125.0, 90.6, 81.9, 53.8, 49.9, 45.5, 43.3, 38.9, 37.0, 34.1, 30.6, 30.5, 28.3, 26.7, 25.4, 23.0, 11.2; HRMS (CI) m/z: $[M]^+$ calcd for $C_{19}H_{28}O_2$ 288.2089, found 288.2076. The analytical data are consistent with the data reported in the literature.

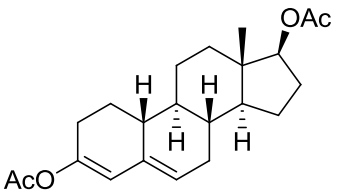
(8*R*,9*S*,10*R*,13*S*,14*S*,17*S*)-17-hydroxy-13-methyl-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-*1H*-cyclopenta[*α*]phenanthren-3(*2H*)-one (3)



Diene **2** (12.16 g, 42.16 mmol, 1.0 eq.) was heated in methanol (260 mL) at reflux. Aqueous HCl solution (3 M, 155 mL) was added and the reaction mixture was refluxed for 30 min turning from colourless to yellow. Water (300 mL) was added and the mixture was extracted with DCM (3 × 100 mL). The combined organic extracts were dried over $MgSO_4$, concentrated *in vacuo* and the residue was purified by flash column chromatography (pentane : ethyl acetate, 50 : 50 → ethyl acetate) to give enone **3** (11.0 g, 95% yield) as an orange foam.

R_f 0.29 (pentane : ethyl acetate, 50 : 50); $[\alpha]_D^{28}$ +52 (*c* 1.00, $CHCl_3$); IR (thin film) 3405 (br), 2924, 2864, 1655, 1618, 1055 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.83 (s, 1H, C=C*H*), 3.67 (app t, 1H, *J* = 8.4 Hz, C*H*OH), 2.51–2.36 (m, 2H), 2.34–2.19 (m, 3H), 2.16–2.02 (m, 2H), 1.91–1.78 (m, 3H), 1.66–1.23 (m, 8H), 1.15–0.98 (m, 3H), 0.81 (s, 3H, CCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.9, 166.6, 124.6, 81.7, 49.7, 49.6, 43.0, 42.6, 40.5, 36.5, 36.4, 35.5, 30.7, 30.4, 26.6, 26.1, 23.2, 11.0; HRMS (ES+) m/z: $[M+H]^+$ calcd for $C_{18}H_{27}O_2$ 275.2011, found 275.2026. The analytical data are consistent with the data reported in the literature.

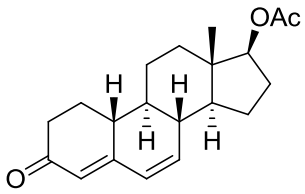
(8*R*,9*S*,10*R*,13*S*,14*S*,17*S*)-13-methyl-2,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-*1H*-cyclopenta[*α*]phenanthrene-3,17-diyl diacetate (5)



A solution of enone **3** (11.0 g, 40.1 mmol, 1 eq.) and 4 equiv of sodium iodide (24.0 g, 160.4 mmol, 4.0 eq.) in acetic anhydride (300 mL) was treated with trimethylsilyl chloride (17,4 mL, 160.4 mmol, 4.0 eq.) at 0 °C under a nitrogen atmosphere for 2 h. The reaction mixture was dried under reduced pressure, then the residue was dissolved in ethyl acetate. The solution was washed with 2% sodium thiosulfate, with a saturated solution of $NaHCO_3$ and dried over $MgSO_4$. After filtration the residue was purified by flash column chromatography (pentane : ethyl acetate, 90 : 10) to give diacetate **5** (10.1 g, 70% yield) as a white solid.

R_f 0.40 (pentane : ethyl acetate, 90 : 10); mp 148–150 °C; lit: mp 165–169 °C; $[\alpha]_D^{28}$ -139 (*c* 1.00, $CHCl_3$); IR (thin film) 2916, 2880, 2818, 1756, 1729, 1205 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.76 (s, 1H, C=C*H*), 5.47 (s, 1H, C=C*H*), 4.62 (app t, 1H, *J* = 8.4 Hz, C*H*OAc), 2.52–2.39 (m, 1H), 2.23–2.08 (m, 4H), 2.13 (s, 3H, COCH_3), 2.04 (s, 3H, COCH_3), 1.95–1.83 (m, 2H), 1.79–1.59 (m, 4H), 1.52–1.18 (m, 7H), 1.14-1.06 (m, 2H), 0,99-0,88 (m, 1H), 0.82 (s, 3H, CCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 169.2, 148.7, 134.6, 123.7, 117.6, 82.8, 50.3, 43.6, 42.6, 40.6, 36.7, 36.6, 30.9, 28.0, 27.5, 27.2, 26.3, 23.3, 21.2, 21.1, 11.9; HRMS (ES+) m/z: $[M+H]^+$ calcd for $C_{22}H_{31}O_4$ 359.2222, found 359.2201. The analytical data are consistent with the data reported in the literature.

(8*R*,9*S*,10*R*,13*S*,14*S*,17*S*)-13-methyl-3-oxo-2,3,8,9,10,11,12,13,14,15,16,17-dodecahydro-*1H*-cyclopenta[*α*]phenanthren-17-yl acetate (6)

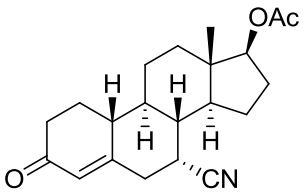


Diacetate **5** (8.22 g, 22.93 mmol, 1 eq.) was suspended in a mixture of DMF (53 mL) and water (1.5 mL) at 0°C, then *N*-bromosuccinimide (4.33 gm, 24,31 mmol, 1.06 eq.) was added over 30 min. giving a cloudy solution. At the end of the addition the reaction mixture was stirred at 0°C for other 45 min., after which it becomes clear. To the resulting solution were added LiBr (0.868 g, 10.0 mmol, 1.99 eq.) and Li_2CO_3 (1.76 g, 23.79 mmol, 4.74 eq.) and the mixture was heated at 110 °C for 1 h (it turns brown). After the suspension cooled down, the salts were removed by filtration and the solution was treated with a mixture of water (300 mL) and acetic acid (26 mL) turning from dark brown to bright orange. The solution was extracted three times with DCM (3 x 150 mL) and the combined organic extracts were washed with a saturated solution of $NaHCO_3$ and then with brine. The organic solution was then dried over $MgSO_4$, filtered and evaporated to dryness to give **6** (6.13 g, 85% yield) as an amber gummy solid.

R_f 0.27 (pentane : ethyl acetate, 70 : 30); mp 88–90 °C; $[\alpha]_D^{27}$ +36 (*c* 1.00, $CHCl_3$); IR (thin film) 2971, 2945, 2860, 1729, 1663, 1248 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.20–6.14 (m, 2H, 2 × C=C*H*), 5.77 (d, 1H, *J* = 1.9 Hz, C=C*H*), 4.65 (app t, 1H, *J* = 8.4 Hz, C*H*OAc), 2.55–2.50 (m, 1H), 2.37–2.12 (m, 5H), 2.04 (s, 3H, COCH_3), 1.85–1.78

(m, 3H), 1.60–1.41 (m, 3H), 1.36–1.05 (m, 4H), 0.86 (s, 3H, CC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.0, 171.1, 158.7, 141.3, 128.9, 124.4, 82.1, 47.7, 45.9, 43.4, 41.1, 40.8, 37.7, 36.4, 27.3, 26.9, 25.0, 22.9, 21.1, 11.8; HRMS (ES+) m/z: $[M+H]^+$ calcd for $C_{20}H_{27}O_3$ 315.1960, found 315.1947. The analytical data are consistent with the data reported in the literature.

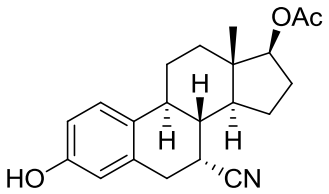
(7*R*,8*R*,9*S*,10*R*,13*S*,14*S*,17*S*)-7-cyano-13-methyl-3-oxo-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-*1H*-cyclopenta[*α*]phenanthren-17-yl acetate (7)



Diethylaluminium cyanide (1.0 M in toluene, 11.8 mL, 3.71 eq.) was added to a solution of dienone **6** (1.0 g, 3.18 mmol, 1.0 eq.) in THF (51 mL) and the reaction mixture was stirred at room temperature for 1 h. Cold $NaOH_{(aq)}$ (0.5 M, 150 mL) was added and the mixture was extracted with DCM (3 × 100 mL). The combined organic extracts were washed with water (150 mL), dried over MgSO4 and concentrated *in vacuo*. The crude product was purified by flash column chromatography (pentane : ethyl acetate, 50 : 50) to afford aliphatic nitrile **7** (0.824 g, 76% yield) as a white foam.

R_f 0.34 (pentane : ethyl acetate, 50 : 50); $[\alpha]_D^{25}$ +28 (*c* 1.00, $CHCl_3$); IR (thin film) 2946, 2864, 2240, 1728, 1669, 1241 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.93 (s, 1H, C=C*H*), 4.65 (app t, 1H, *J* = 8.6, C*H*OAc), 3.01–2.97 (m, 1H, C*H*CN), 2.75 (dd, 1H, *J* = 14.8, 2.3 Hz, CH_aH$_b$CHCN), 2.58–2.49 (m, 1H, CH$_a$$H_b$CHCN), 2.48-2.39 (m, 1H), 2.33–2.17 (m, 3H), 2.14–2.04 (m, 1H), 2.02 (s, 3H, COCH_3), 1.97–2.89 (m, 1H), 1.82–1.20 (m, 10H), 0.84 (s, 3H, CCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.6, 170.9, 158.5, 127.9, 118.9, 81.9, 47.0, 44.7, 43.0, 42.1, 41.2, 37.4, 36.4, 35.9, 31.6, 27.2, 26.3, 25.8, 22.6, 21.0, 12.0; HRMS (ES+) m/z: $[M+MeCN+H]^+$ calcd for $C_{23}H_{31}N_2O_3$ 383.2335, found 383.2355. The analytical data are consistent with the data reported in the literature.

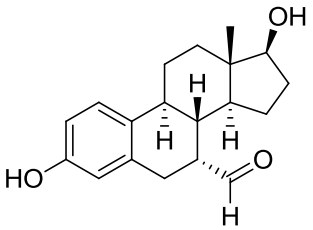
(7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-7-cyano-3-hydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-*6H*-cyclopenta[*α*]phenanthren-17-yl acetate (8)



$CuBr_2$ (3.91 g, 1.96 eq.) and LiBr (0.74 g, 1.0 eq.) were added to a suspension of aliphatic cyanide **7** (3.06 g, 8.96 mmol, 1.0 eq.) in acetonitrile (41 mL) and the reaction mixture was refluxed for 20 min. under argon atmosphere. The salts were removed by filtration and the mixture was stirred with saturated $NaHCO_{3(aq)}$ (200 mL) for 1 h. The solution was extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were washed with brine (300 mL), dried over MgSO4 and concentrated *in vacuo*. The crude product was purified by flash column chromatography (pentane : ethyl acetate, 60 : 40 → 50 : 50) to afford phenolic compound **8** (2,71 g, 89% yield) as a white-pink solid.

R_f 0.59 (pentane : ethyl acetate, 50 : 50); $[\alpha]_D^{29}$ +17 (*c* 1.00, $CHCl_3$); IR (thin film) 3374 (br), 2940, 2244, 1735, 1245 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, 1H, *J* = 8.4 Hz, Ar-*H*), 6.69 (dd, 1H, *J* = 8.4, 2.7 Hz, Ar-*H*), 6.56 (d, 1H, *J* = 2.7 Hz, Ar-*H*), 4.98 (s, 1H, Ar-O*H*), 4.74 (dd, 1H, *J* = 8.0, 9.1 Hz, C*H*OAc), 3.20–3.03 (m, 2H), 2.70–2.60 (m, 1H), 2.45–2.22 (m, 2H), 2.06 (s, 3H, COCH_3), 1.95–1.15 (m, 9H), 0.83 (s, 3H, CCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 154.1, 132.7, 130.0, 127.2, 120.2, 115.3, 114.2, 82.2, 47.0, 43.2, 39.4, 39.2, 36.3, 32.6, 28.5, 27.4, 26.2, 22.6, 21.1, 12.0; The mass of the product could not be found by HRMS. The analytical data are consistent with the data reported in the literature.

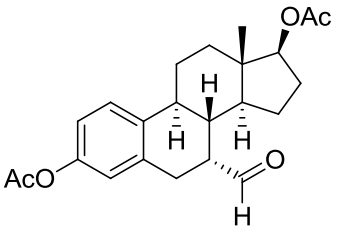
(7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-*6H*-cyclopenta[*α*]phenanthrene-7-carbaldehyde (9)



A solution of DIBAL-H (1.0 M in toluene, 1.24 mL, 4.2 eq.) was added to a solution of cyanide **8** (100 mg, 0.295 mmol, 1.0 eq.) in toluene (2.9 mL) at 0°C and the reaction mixture was stirred vigorously at room temperature for 3 h. Methanol (2.1 mL) and $HCl_{(aq)}$ (2 M, 1.2 mL) were added slowly and the mixture was stirred at room temperature for 30 min. The suspension was partitioned between ethyl acetate (50 mL) and water (50 mL) and extracted with ethyl acetate (2 × 100 mL). The combined organic extracts were washed with brine (100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography (pentane : ethyl acetate, 50 : 50) to afford aldehyde **9** (72 mg, 81% yield) as a white solid.

R_f 0.36 (pentane : ethyl acetate, 50 : 50); $[\alpha]_D^{29}$ +20 (*c* 1.00, MeOH); IR (thin film) 3242 (br), 2931, 1705, 1226, 1011 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.83 (d, 1H, *J* = 2.0 Hz, C*H*O), 7.16 (d, 1H, *J* = 8.5 Hz, Ar-*H*), 6.65 (dd, 1H, *J* = 8.4, 2.7 Hz, Ar-*H*), 6.62 (d, 1H, *J* = 2.6 Hz, Ar-*H*), 4.7 (br s, 1H, Ar-O*H*), 3.78 (app t, 1H, *J* = 8.3 Hz, C*H*OH), 3.17 (d, 1H, *J* = 17.3 Hz, Ar-CH_aH$_b$), 3.00 (dd, 1H, *J* = 17.3, 6.2 Hz, Ar-CH$_a$$H_b$), 2.72 (m, 1H), 2.45–2.33 (m, 2H), 2.23–2.15 (m, 1H), 1.96–1.84 (m, 3H), 1.68–1.43 (m, 4H), 1.33–1.24 (m, 2H, C*H*), 0.90-0.83 (m, 1H), 0.80 (s, 3H, CCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.7, 153.9, 135.3, 131.4, 127.2, 115.5, 113.7, 81.7, 46.9, 46.4, 43.8, 41.2, 39.7, 36.6, 30.5, 30.2, 27.4, 23.0, 10.6; HRMS (ES+) m/z: $[M+H]^+$ calcd for $C_{19}H_{25}O_3$ 301.1798, found 301.1799. The analytical data are consistent with the data reported in the literature.

(7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-7-formyl-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-*6H*-cyclopenta[*α*]phenanthrene-3,17-diyl diacetate (10)

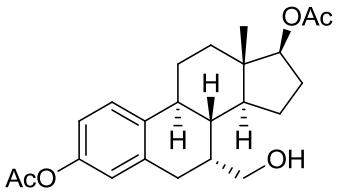


Aldehyde **9** (1.0 g, 3.33 mmol, 1.0 eq.) was suspended in DCM (20 mL), then Et_3N (2.3 mL, 16.6 mmol, 5 eq.) was added to give a clear solution. A catalytic amount of DMAP (40.3 mg, 0.33 mmol, 0.1 eq.) was added the solution was cooled to 0 °C. Acetic anhydride (0.94 mL, 9.99 mmol, 3 eq.) was added dropwise to the cold solution and the

reaction mixture was stirred for 1.30 h. Saturated $NaHCO_{3(aq)}$ was added until pH remained basic. 100 mL of DCM were added, the organic phase collected, washed with a 10% solution of citric acid in water and washed with saturated $NaHCO_{3(aq)}$ again. The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography (pentane : ethyl acetate, 70 : 30) to afford diacetate **10** (1.10 g, 86% yield) as a white foam.

R_f 0.71 (pentane : ethyl acetate, 2 : 1); $[\alpha]_D^{27}$ +28 (*c* 1.00, $CHCl_3$); IR (thin film) 2931, 1760, 1726, 1204, 1012 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.84 (s, 1H, C*H*O), 7.32–7.27 (m, 1H, Ar-*H*), 6.92–6.85 (m, 2H, 2 × Ar-*H*), 4.73 (dd, 1H, *J* = 9.1, 7.6 Hz, C*H*OAc), 3.21 (d, 1H, *J* = 17.2 Hz, Ar-CH_aH_b), 3.03 (dd, 1H, *J* = 17.4, 6.4 Hz, Ar-CH_aH_b), 2.79–2.70 (m, 1H), 2.58–2.44 (m, 1H), 2.44–2.31 (m, 1H), 2.31–2.24 (m, 1H), 2.28 (s, 3H, COCH_3), 2.06 (s, 3H, COCH_3), 1.97–1.83 (m, 3H), 1.81–1.68 (m, 1H), 1.67–1.33 (m, 4H), 0.84 (s, 3H, CCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.2, 171.1, 169.7, 148.8, 136.4, 135.3, 127.1, 121.8, 119.4, 82.3, 46.5, 46.1, 43.3, 40.3, 39.6, 36.6, 29.8, 27.4, 26.9, 23.1, 21.1 (2C), 11.5; HRMS (CI) m/z: $[M+NH_4]^+$ calcd for $C_{23}H_{32}NO_5$ 402.2280, found 402.2291. The analytical data are consistent with the data reported in the literature.

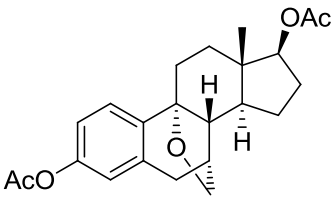
(7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-7-(hydroxymethyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-*6H*-cyclopenta[*α*]phenanthrene-3,17-diyl diacetate (11)



$NaBH_4$ (0.36 g, 9.63 mmol, 1.9 eq.) was added to a solution of aldehyde **10** (1.95 g, 5.07 mmol, 1.0 eq.) in EtOH (60 mL) at 0 °C and the reaction mixture was stirred for 30 min. The solution was poured into 250 mL of saturated ammonium chloride, washed with aqueous $NaHCO_3$ solution (10%) and extracted with ethyl acetate (3 × 200 mL). The combined organic extracts were washed with brine (200 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography (pentane : ethyl acetate, 60 : 40) to afford alcohol **11** (1.57 g, 80% yield) as a white foam.

R_f 0.40 (pentane : ethyl acetate, 60 : 40); $[\alpha]_D^{27}$ +32 (*c* 1.00, $CHCl_3$); IR (thin film) 3447 (br), 2935, 1760, 1730, 1206, 1024 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, 1H, *J* = 8.3 Hz, Ar-*H*), 6.85 (dd, 1H, *J* = 8.3, 2.0 Hz, Ar-*H*), 6.82 (d, 1H, *J* = 2.0 Hz, Ar-*H*), 4.69 (dd, 1H, *J* = 9.0, 7.8 Hz, C*H*OAc), 3.75 (dd, 1H, *J* = 10.1, 3.9 Hz, C$H_a$$H_b$OH), 3.46 (app t, 1H, *J* = 10.1, CH$_a$$H_b$OH), 3.01 (dd, 1H, *J* = 17.2, 1.9 Hz, Ar-C$H_a$$H_b$), 2.93 (m, 1H, Ar-CH$_a$$H_b$), 2.40–2.17 (m, 3H), 2.28 (s, 3H, COCH_3), 2.14–2.01 (m, 1H), 2.06 (s, 3H, COCH_3), 1.95–1.69 (m, 3H), 1.63–1.26 (m, 6H), 0.82 (s, 3H, CCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 169.8, 148.6, 136.7, 136.5, 127.1, 122.4, 118.9, 82.5, 60.7, 46.6, 43.2, 40.1, 38.9, 36.9, 35.9, 32.5, 27.5, 27.2, 22.8, 21.2, 21.1, 11.8; HRMS (ES+) m/z: $[M+H]^+$ calcd for $C_{23}H_{31}O_5$ 387.2171, found 387.2184. The analytical data are consistent with the data reported in the literature.

(7*R*,8*R*,9*R*,13*S*,14*S*,17*S*)-13-methyl-6,7,8,11,12,13,14,15,16,17-decahydro-9,7-(epoxymethano)cyclopenta[*α*]phenanthrene-3,17-diyl diacetate (12)

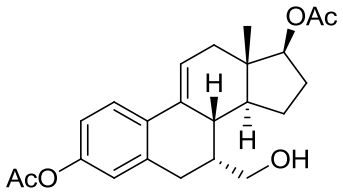


To a solution of alcohol **11** (1.57 g, 4.06 mmol, 1.0 eq.) in carbon disulfide (125 mL) was added iodine (1.03 g, 4.06 mmol 1.0 eq.) and lead tetraacetate (7.38 g, 16.65 mmol, 4.1 eq.) and the reaction mixture was refluxed for 1 h. The solvent was evaporated *in vacuo* and the residue was dissolved in DCM (200 mL), washed with aqueous NaS_2O_3 (10% wt, 3 × 100 mL), brine (100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography (pentane : ethyl acetate, 70 : 30) to afford benzylic ether **12** (1.27 g, 81% yield) as a white foam.

R_f 0.43 (pentane : ethyl acetate, 70 : 30); $[\alpha]_D^{30}$ –31 (*c* 1.00, $CHCl_3$); IR (thin film) 2936, 1753, 1730, 1247, 1201 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, 1H, *J* = 8.2 Hz, Ar-*H*), 6.90–6.82 (m, 2H, 2 × Ar-*H*), 4.67 (dd, 1H, *J* = 9.0, 7.8 Hz, C*H*OAc), 4.09 (ddd, 1H, *J* = 8.4, 5.9, 2.3 Hz, C$H_a$$H_b$O), 3.61 (d, 1H, *J* = 8.6 Hz, CH$_a$$H_b$O), 3.13 (app d, 1H, *J* = 16.9 Hz, Ar-C$H_a$$H_b$), 2.86 (dd, 1H, *J* = 17.1, 2.1 Hz, Ar-CH$_a$$H_b$), 2.58–2.37 (m, 2H), 2.28 (s, 3H, COCH_3), 2.35–2.21 (m, 1H), 2.12-2.00 (m, 1H), 2.05 (s, 3H, COCH_3), 2.00–1.92 (m, 1H), 1.81–1.70 (m, 2H), 1.65–1.51 (m, 2H), 1.47–1.37 (m, 2H), 0.79 (s, 3H, CCH_3);

^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1, 169.6, 149.8, 140.3, 136.2, 124.9, 122.2, 119.0, 82.2, 79.6, 71.1, 46.7, 42.2, 42.0, 38.3, 37.5, 32.6, 27.6, 26.2, 23.5, 21.1 (2C), 10.6; HRMS (ES+) m/z: $[M+H]^+$ calcd for $C_{23}H_{29}O_5$ 385.2015, found 385.2008. The analytical data are consistent with the data reported in previous work in Barrett research group[24].

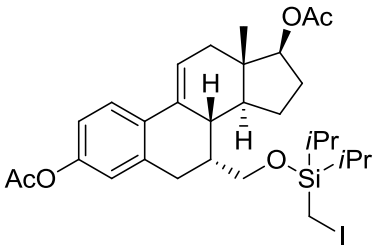
(7*R*,8*R*,13*S*,14*S*,17*S*)-7-(hydroxymethyl)-13-methyl-7,8,12,13,14,15,16,17-octahydro-*6H*-cyclopenta[*α*]phenanthrene-3,17-diyl diacetate (13)



To a stirring solution of benzyl ether **12** (500 mg, 1.3 mmol, 1 eq.) in DCM (30 mL), $FeCl_3$ (253 mg, 1.56 mmol, 1.2 eq.) and allyltrimethylsilane (1.49 g, 13.0 mmol, 10 eq.) were added and the mixture was stirred at room temperature for 30 min. The reaction was quenched with saturated $NaHCO_3$ and extracted with DCM (2 x 25 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give alcohol **13** (378 mg, 76% yield) as a white solid.

R_f 0.23 (pentane : ethyl acetate, 20 : 10); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, 1H, *J* = 8.6 Hz, Ar-*H*), 6.88–6.81 (m, 2H, 2 × Ar-*H*), 6.35-6.29 (m, 1H, C=C*H*), 4.77 (app t, 1H, *J* = 8.6 Hz, C*H*OAc), 3.66 (dd, 1H, *J* = 10.7, 4.6 Hz, C*H*$_a$H$_b$OH), 3.61 (app t, 1H, *J* = 9.9 Hz, CH$_a$*H*$_b$OH), 3.06 (dd, 1H, *J* = 16.8, 1.9 Hz, Ar-C*H*$_a$H$_b$), 2.96 (dd, 1H, *J* = 16.7, 4.8 Hz, Ar-CH$_a$*H*$_b$), 2.47–2.39 (m, 1H), 2.28 (s, 3H, COC*H*$_3$), 2.26–2.17 (m, 3H), 2.07 (s, 3H, COC*H*$_3$), 1.96–1.84 (m, 1H), 1.76–1.56 (m, 3H), 1.52–1.40 (m, 1H), 1.35 (br s, 1H), 0.80 (s, 3H, CC*H*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3, 169.8, 149.6, 135.2, 131.8, 131.7, 124.5, 122.8, 121.0, 119.51, 82.7, 61.1, 42.9, 41.6, 41.1, 39.3, 36.1, 33.0, 29.8, 27.7, 23.9, 21.3, 11.8; HRMS (ES+) m/z: $[M+H]^+$ calcd for $C_{23}H_{29}O_5$ 385.2015, found 385.2025.

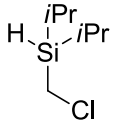
(7*R*,8*R*,13*S*,14*S*,17*S*)-7-((((iodomethyl)diisopropylsilyl)oxy)methyl)-13-methyl-7,8,12,13,14,15,16,17-octahydro-*6H*-cyclopenta[*α*]phenanthrene-3,17-diyl diacetate (14)



To a stirred mixture of DMAP (10.8 mg, 0.088 mmol, 0.1 eq.), chloro(iodomethyl)diisopropylsilane (257 mg, 0.884 mmol, 1 eq.), Et_3N (0.15 mL, 0.884 mmol, 1 eq.) and DCM (2 mL), alcohol **13** (340 mg, 0.886 mmol, 1 eq.) in 0.7 mL of DCM was added at 0°C under argon atmosphere. The mixture was stirred until completion of the reaction (1 h 30 min) as judged by TLC. After completion the mixture was quenched with saturated ammonium chloride solution and extracted with DCM (3 x 25 mL). The combined organic layer was dried with $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography in DCM to give silylated steroid **14** (89% yield) a viscous colourless oil.

R_f 0.60 (pentane : ethyl acetate, 90 : 10); $[\alpha]_D^{27}$ +5 (*c* 1.00, $CHCl_3$); IR (thin film) 2943, 2866, 1764, 1734, 1491, 1370, 1242, 1202, 1098 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, 1H, *J* = 8.7 Hz, Ar-*H*), 6.85 (dd, 1H, *J* = 8.7, 2.5 Hz, Ar-*H*), 6.81 (d, 1H, *J* = 2.5 Hz, Ar-*H*), 6.32 (m, 1H, C=C*H*), 4.77 (app t, 1H, *J* = 8.7 Hz, C*H*OAc), 3.75 (dd, 1H, *J* = 10.0, 5.4 Hz, CH_aH$_b$OSi), 3.37 (dd, 1H, *J* = 10.0, 8.7 Hz, CH$_a$$H_b$OSi), 3.06 (dd, 1H, *J* = 16.8, 1.8 Hz, Ar-CH_aH$_b$), 2.93 (dd, 1H, *J* = 16.6, 4.9 Hz, Ar-CH$_a$$H_b$), 2.46–2.38 (m, 1H), 2.32-2.15 (m, 3H), 2.27 (s, 3H, COCH_3), 2.07 (s, 3H, COCH_3), 1.96 (s, 2H, CH_2I), 1.96–1.88 (m, 1H), 1.83–1.73 (m, 1H), 1.68-1.56 (m, 1H), 1.52-1.40 (m, 1H), 1.20-1.10 (m, 2H), 1.10-1.04 (m, 4H), 1.04-0.94 (m, 12H, 2 x CH(CH_3)$_2$), 0.79 (s, 3H, CCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2 (Cq), 169.6 (Cq), 149.6 (Cq), 135.5 (Cq), 131.9 (Cq), 131.7 (Cq), 124.4, 122.7, 120.9, 119.3, 82.7, 62.4 (CH_2), 43.0, 41.6 (Cq), 41.2, 39.4 (CH_2), 36.4, 33.3 (CH_2), 27.7 (CH_2), 24.0, 21.3 (CH_2), 17.8, 17.6, 12.4, 12.3, 11.7, -20.8 (CH_2I); HRMS (ES+) m/z: $[M+H]^+$ calcd for $C_{30}H_{44}O_5SiI$ 639.2003, found 639.2007.

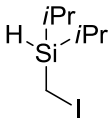
(chloromethyl)diisopropylsilane (16)



To a solution of dichlorodiisopropylsilane (5 g, 33.17 mmol, 1 eq.) and chloroiodomethane (8.78 g, 49.76 mmol, 1.5 equiv) in THF (41 mL) was added a solution of MeLi-LiBr complex (1.5 M in ether, 33.2 mL, 60 mmol, 1.5 eq.) dropwise at -78 °C. The reaction mixture was stirred at -78 °C for 1 h and then allowed to warm to room temperature before quenching with saturated ammonium chloride solution. The aqueous layer was extracted with pentane. The combined organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The crude product, (chloromethyl)diisopropylsilane, was used for the next step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.63 (app quint, 1H, J = 2.4 Hz, Si*H*), 2.95 (d, 2H, J = 2.3 Hz, CH_2Cl), 1.23-1.13 (m, 2H, 2 x C*H*(CH_3)$_2$), 1.12-1.05 (m, 12H, 2 x CH(CH_3)$_2$).

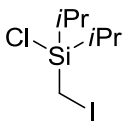
(iodomethyl)diisopropylsilane (17)



To a solution of NaI (15 g, 99.5 mmol, 3 eq.) in ACS standard acetone (30 mL) was added crude (chloromethyl)diisopropylsilane in acetone (5 mL). The reaction mixture was refluxed at 85 °C for 1h. The reaction was allowed to cool to room temperature before quenching with saturated solution of $Na_2S_2O_3$.The aqueous layer was extracted with pentane. The combined organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The crude product, iodomethyl)diisopropylsilane, a pale yellow oil, 7.04 g, (83 % yield over 2 steps) was used for the next step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.82 (app quint, 1H, J = 2.7 Hz, Si*H*), 2.05 (d, 2H, J = 2.9 Hz, CH_2I), 1.22-1.12 (m, 2H, 2 x C*H*(CH_3)$_2$), 1.11-1.06 (m, 12H, 2 x CH(CH_3)$_2$).

chloro(iodomethyl)diisopropylsilane (18)



To a solution of TCCA (1.14 g, 4.92 mmol, 0.36 eq.) in dry DCM (31 mL) under argon was added crude (chloromethyl)diisopropylsilane (3.5 g, 13.7 mmol, 1 eq.) in DCM (4

mL) dropwise at 0 °C for 1 h. The mixture was allowed to warm to room temperature and was then filtered through celite and concentrated. The residue was then dissolved in pentane and re-filtered through celite and then concentrated to give crude chloro(iodomethyl)diisopropylsilane (3.81 g, yield 96%) as a pink/purple oil. The crude product, >95% purity by NMR, was used for the next step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.22 (s, 2H, CH_2I), 1.43 (sep, 2H, J = 7.5 Hz, 2 x CH(CH_3)$_2$), 1.16-1.10 (m, 12H, 2 x CH(CH_3)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.4, 17.1, 13.6, -20.7. The analytical data are consistent with the data reported in the literature.

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