Synthesis of C7-Substituted Estra-1,3,5(10),6-Tetraen-3,17β-Diols

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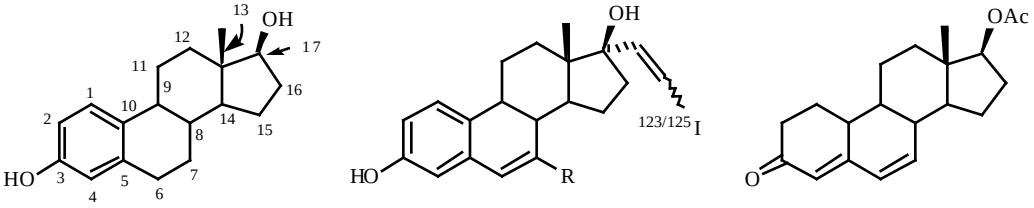
Abstract: A series of C7-substituted estra-1,3,5(10),6-tetraene-3,17β-diols were prepared as precursors to radiodiagnostic agents of breast cancer. The introduction of the olefin moiety at C6/C7 in the molecules was achieved through thermal elimination of the 6-hydroxy group in the corresponding estra-1,3,5(10)-triene-3,17β-diols.

Keywords: Estranes, steroids, conjugate addition, thermal dehydration.

INTRODUCTION

60-70% of breast cancer tumours are estrogen receptor positive [1]. The cells possess estrogen receptor ERα in concentrations much greater than normal breast tissue. Potentially, this opens ways to target the cancer cells with both diagnostics and therapeutic agents, where a steroid can act as drug delivery system. One of the prerequisites expected of such compounds is a good binding affinity to ERα. In our search for estradiol based radiodiagnostic agents for the detection of minimal breast cancer [2], we have investigated a series of 17α-iodovinyl substituted estra-1,3,5(10),6-tetraene-3,17β-diols **2** (Fig. **1**). It is known that C-7α substituted estradiols can exhibit a strong binding affinity to the estrogen receptor ERα [3,4]. C-7β substituted estradiols, while studied to a much lesser degree, are deemed to exhibit a poorer binding to ERα. For this reason it seemed of interest to focus on the behaviour of C7-substituted estra-1,3,5(10),6-tetraen-3,17β-diols, e.g. **3**, where the C7 substituent branches off from an sp^2 carbon of the steroidal framework (Fig. **1**) [5]. Former studies [5] have been limited to the synthesis of C7 substituted estratetraenediols with a protected, methylated phenolic function at C3 with the idea being that the prodrug would be demethylated *in vivo*. *In vitro* testing of the compounds, such as *in vitro* receptor binding affinity assays, however, are complicated by the protective group, and even comparative *in vitro* testing among differently substituted estradiol-3-methyl ethers may not necessarily reflect the behaviour of the estradiols themselves. In the following, the synthesis of a series of non-protected cyanoalkyl-, amidoalkyl-, and *N*-butyl-*N*-methylamidoalkylestra-1,3,5(10),6-tetraen-3,17β-diols is elaborated.

Various synthetic pathways to C7-substituted estradiols and estrones have been pursued. Initially, norandrostanes have been used as starting material, with the key step being a 1,6-addition of the chain comprising nucleophile to 17-protected 17β-hydroxy-19-norandrosta-4,6-dien-3-one **4** [3,6]. As the synthesis necessitates an aromatisation of ring A in the latter part of the sequence, later approaches to C7-substituted estradiols utilized either estrone, estradiol or related estranes such as equiline as starting material [5,7-9]. Recently, C7-substituted estradiols have been accessed *via* conjugate addition of a C7-chain electrophile to the enolates of 6-ketoestrane derivatives [5,8]. In the preparation of C7-substituted estra-1,3,5(10),6-tetraenes, the 6-keto group is reduced after the introduction of the substituent at C7 to the corresponding hydroxy group, which subsequently is eliminated under acidic conditions. The dehydration is unproblematic, when the phenolic function at C3 is protected as a methyl ether. However, if the tethered chain at C7 carries a terminal functionality such as a cyano or amide group, it should be a C_5 chain or longer for the dehydration to proceed smoothly. Against this background, we undertook the synthesis of non-protected C7-substituted



1
Estradiol

2 (R = H)
3 (R = -$(CH_2)_n$CN/CONR$_2$)

4

Fig. (1).

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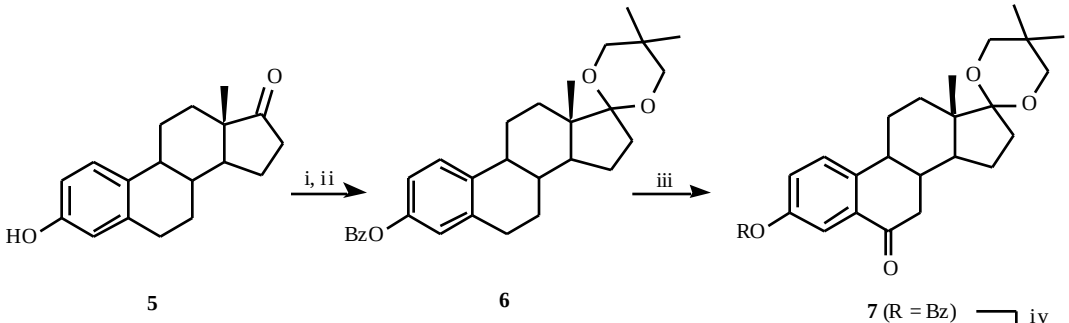


i. KOH, PhCOCl, CH_2Cl_2, H_2O, 0˚C (98%); ii. neopentyl glycol, *p*-TsOH, benzene, refl. (68%); iii. $KMnO_4$, $NaHCO_3$, Adogen 464, benzene, H_2O, 80˚C (31%); iv. KOH, MeOH, THF, H_2O, rt (92%); v. DHP, *p*-TsOH, CH_2Cl_2, rt (93%)

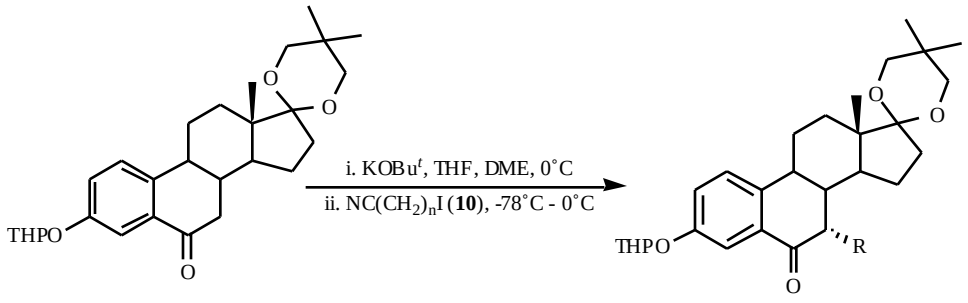
Scheme 1.

estra-1,3,5(10),6-tetraen-3,17β-diols following the latter synthetic approach utilizing the conjugate addition of ω-functionalized alkyliodides to a suitably protected 6-ketoestra-1,3,5(10)-trien-17-one.

RESULTS AND DISCUSSION

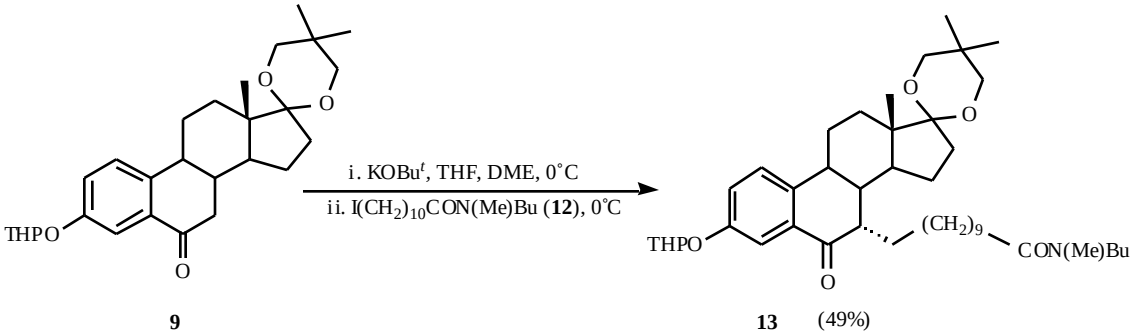
Commercially estrone was chosen as starting material. Initially, a good choice of protective groups for the keto group at C17 and phenolic function at C3 is essential. While the choice of the dimethyldioxane as protective group for C17 was straightforward, the selection of the protective group for HO(C3) was much less so. From previous experiments, it was evident that deprotection of a steroidal methyl ether at the final stages of the sequence, i.e. by BBr_3 or TMSI, would only lead to success in a limited number of cases. The use of the benzyloxy group would mean a subsequent selective reductive cleavage, which at the stage of the C7 substituted estra-1,3,5(10),6-tetraene is not possible. Interestingly, it has been shown that hydrogenation of such molecules leads to hydrogenation of the C6/C7 olefin moiety concomittant with the debenzylation, to give selectively the C7β-substituted estra-1,3,5(10)-triene-3-ols [10]. Additionally, the benzyloxy group is partially oxidized in the preparation of the 6-ketoestrone derivatives. Acetoxy- and trimethylsiloxy protective groups are too labile in the oxidation of the compound to the 6-keto derivatives. For this reason the tetrahydropyranyloxy group was chosen as protective group for HO(C3). With this choice, the envisaged sequence to the C7-substituted estra-1,3,5(10),6-tetraen-3,17β-diols was planned as follows: a) protection of HO(C3) and C17; b) oxidation of C6 to the 6-ketoderivative; c) conjugate addition of an ω-cyanoalkyl iodide or an ω-*N*-butyl-*N*-methylamidoalkyl iodide to the 6-keto derivative; d) reduction of the 6-keto group; e) acidic dehydration of the 6-hydroxy group with concomittant deprotection of HO(C3) and C17; f) facultative manipulation of the terminal functionality of the C7 side chain; g) addition of an ethynyl group to C17, both as a means to further the binding affinity of the molecule to the estrogen receptor and as a possible anchor for a radiolabel.

Initial experiments to synthesize 3-*O*-THP-estra-1,3,5(10)-triene-3-ol-17-one 17-acetal from estrone (**5**) gave the desired compound only in low yield, independently of whether the acetalisation followed the protection of HO(C3) with THP or whether the reactions were carried out in reverse order. Rather than optimize the conditions for the above reaction, it was deemed more opportune to operate *via* the estrone 3-benzoate and to change protective groups just before the introduction of the C7 side chain. Thus, estrone (**5**) was reacted with benzoyl chloride (KOH, water, 0ºC) to estrone 3-benzoate, which was acetalized with neopentyl glycol (NPG, benzene, *p*-TsOH) to **6**. A number of methods for the preparation of 6-ketoestrane derivatives of type **7** from suitably protected estrone and estradiol have been



using $NC(CH_2)_4I$ (**10a**) to obtain **11a** [R = $(CH_2)_4CN$]: 40%
using $NC(CH_2)_5I$ (**10b**) to obtain **11b** [R = $(CH_2)_5CN$]: 43%
using $NC(CH_2)_6I$ (**10c**) to obtain **11c** [R = $(CH_2)_6CN$]: 38%

Scheme 2.

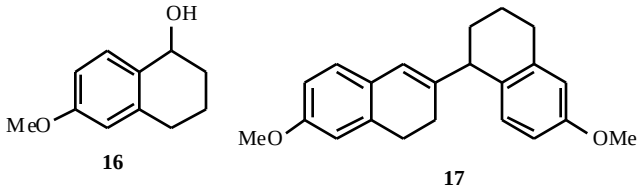


9 **13** (49%)

Scheme 3.

described in the literature [11]. The authors have found the benzylic oxidation to proceed best with $KMnO_4$ at 80ºC using PTC conditions (benzene and aq. $NaHCO_3$ with Adogen 464® as phase transfer catalyst) (Scheme **1**).

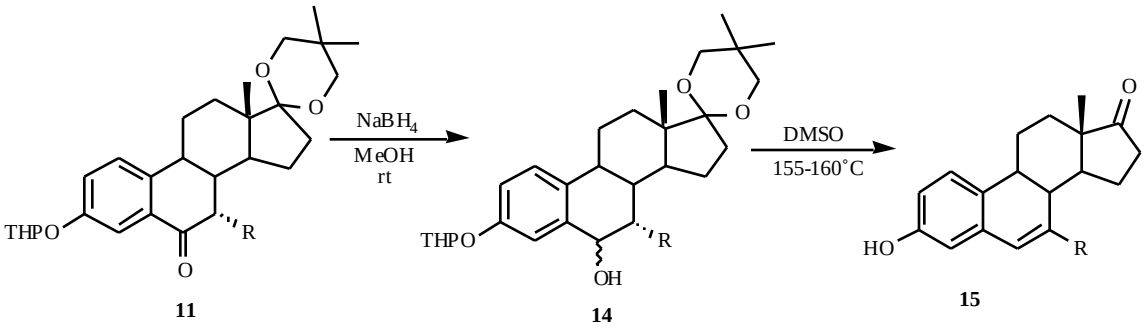
Thereafter, the benzoate protective group was removed (KOH, THF, MeOH) and the resulting estra-1,3,5(10)-trien-3-ol-6,17-dione 17,17-dimethyldioxane (**8**) was reacted with dihydropyran (DHP) (CH_2Cl_2, *p*-TsOH) to give **9**. **9** was transformed into its enolate (KOBu^t, THF, DME [5,7,8]), which was reacted with cyanoalkyl iodides **10** [12] and with *N*-butyl-*N*-methylamidoundecyl iodide (**12**) [12] to form 7α-substituted **11** and **13**, respectively (Schemes **2** and **3**). The 6-keto group in **11** and **13** was reduced with $NaBH_4$ in MeOH to afford mainly the 6α-hydroxy compounds **14** and **18** (Schemes **4** and **5**).



16 **17**

Fig. (2).

Performing a dehydration of **14** or **18** under acidic conditions (*p*-TsOH, benzene, reflux or Amberlyst 15, toluene, 80-90ºC) did not lead to the desired estra-1,3,5(10),6-tetraenes, where mostly oligomeric products were formed. This is due to an intermolecular reaction of the stabilized benzylic carbocation, most likely with the aromatic A ring. In the parent 3-*O*-THP-estra-1,3,5(10)

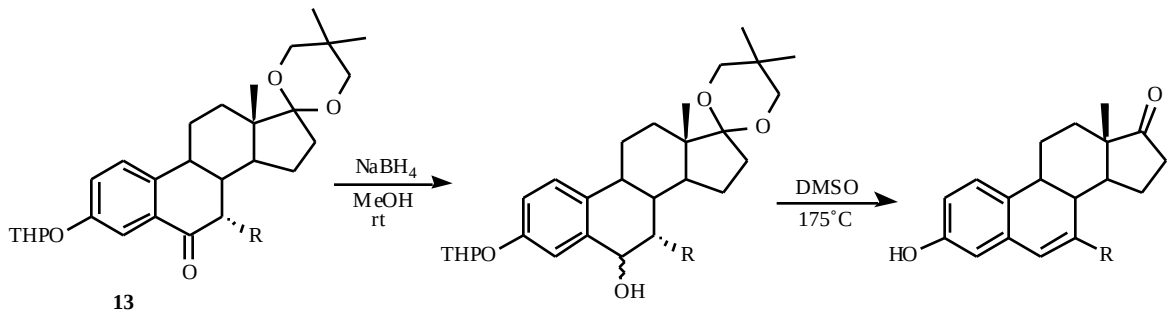


11 **14** **15**

11a - 14a [R = (CH$_2$)$_4$CN]: 99%
11b - 14b [R = (CH$_2$)$_5$CN]: 98%
11c - 14c [R = (CH$_2$)$_6$CN]: 85%

14a - 15a [R = (CH$_2$)$_4$CN]: 35%
14b - 15b [R = (CH$_2$)$_5$CN]: 32%
14c - 15c [R = (CH$_2$)$_6$CN]: 69%

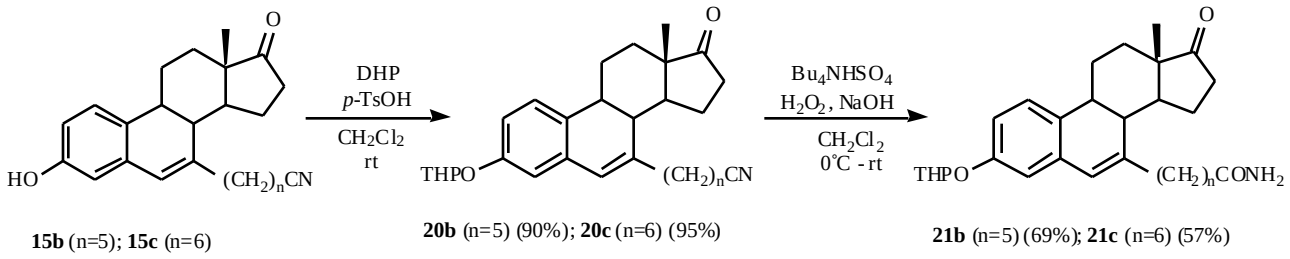
Scheme 4.



13
R = (CH$_2$)$_{10}$CON(Me)Bu

18 (81%) **19** (45%)

Scheme 5.



15b (n=5); **15c** (n=6)

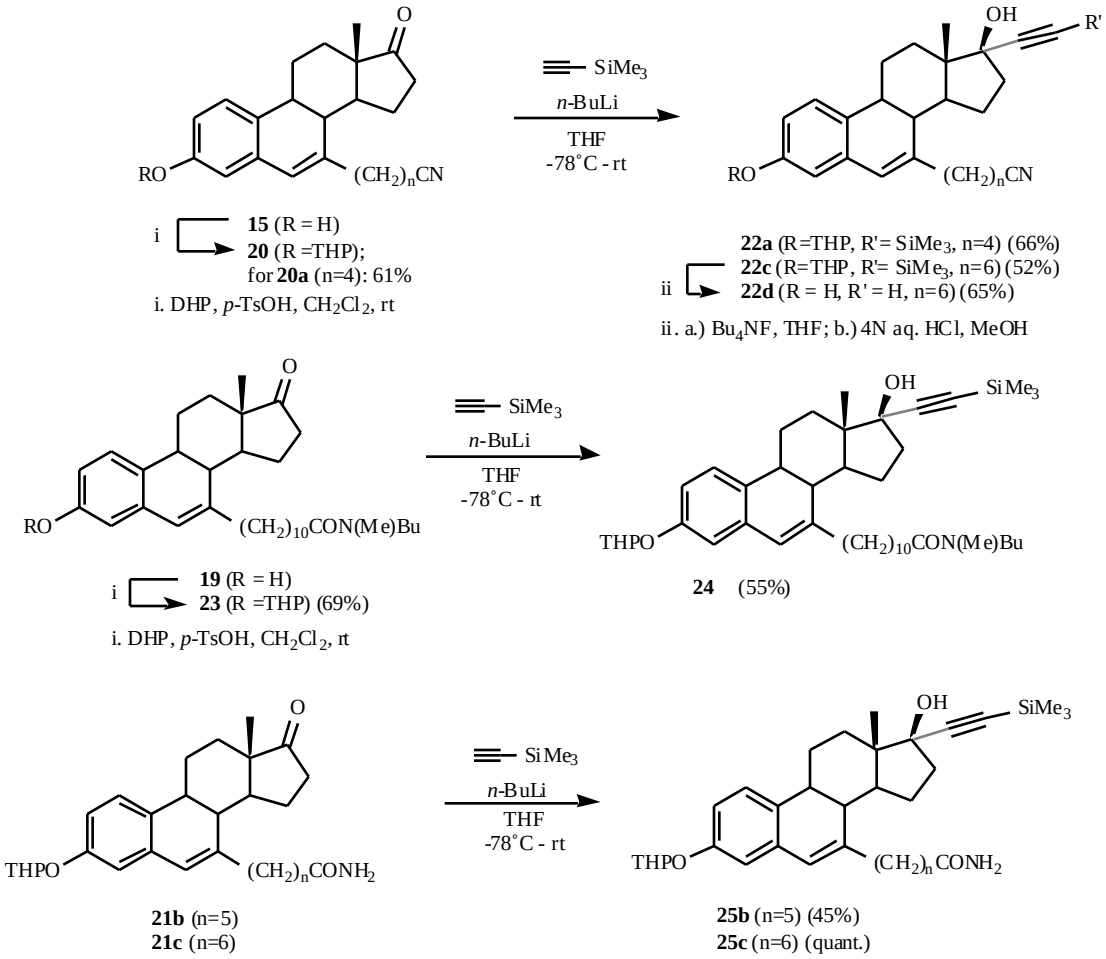
20b (n=5) (90%); **20c** (n=6) (95%)

21b (n=5) (69%); **21c** (n=6) (57%)

Scheme 6.

-trien-3,6,17β-triol, an acidic dehydration does lead to a small amount of estra-1,3,5(10),6-tetraen-3,17β-diol, that is to the dehydrated product, where the THP group has been cleaved. Isolatable side product in this case is a dimer, where the benzylic cation of one molecule reacts with one molecule of product. Similar reactions have been noted in the acidic dehydration of tetrahydronaphthols, eg. of **16** (Fig. **2**) [13], where again dimers, e.g. **17**, could be isolated. A transformation of the 6-hydroxy group in **14** to the corresponding tosylate or mesylate with subsequent base catalysed elimination does not succeed. Routes such as the direct transformation of the 6-keto derivatives to the corresponding tosylhydrazones with subsequent Shapiro reaction [5b], which had been developed successfully by the authors for steroids with short C-7 alkyl chains with terminal functionalities, which are also prone to oligomerize under acidic conditions, were deemed too laborious in the present case.

In 1962, V. J. Traynelis *et al*. [14] reported on a thermal dehydration of alcohols in DMSO. This very infrequently used reaction was utilized by H. J. Siemann *et al*. [15] in the dehydration of a 14,15-spirocyclopropane containing, albeit C7-unsubstituted 6-hydroxyestradiol derivative. Although the mechanism of this reaction is not clear, with V. J. Traynelis *et al*. giving some evidence for at least a partial cationic charge at C6 in the transition state, the experimental data suggests that no benzyl cation *per se* is involved. This led us to subject **14** to a thermolysis in DMSO at 150 – 160ºC. The C7-substituted estra-1,3,5(10),6-tetraen-3-ol-17-ones **15** could be isolated in fair yield (Scheme **4**). It must be noted that under the conditions



Scheme 7.

both the THP protective group at HO(C3) as well as the acetal at C17 are cleaved. Incompletely run reactions indicate that the THP at HO(C3) is the first to cleave before appreciable amounts of either olefin formation or acetal deprotection takes place. The reaction is very temperature dependent. Temperatures lower than 150ºC leads mainly only to the deprotection of **14**. Temperatures above 160ºC promote the oxidation of the benzylic alcohol to the corresponding 6-keto compounds. This latter reaction is also a side reaction in the temperature range of 150ºC – 160ºC, even when the reactions are carried out under inert atmosphere. The best result for the thermolytic dehydration of amide **18** was found at slightly higher temperatures (175ºC) (Scheme **5**).

The cyano function of the C7-side chain in **15** and analogous compounds can be elaborated further. Principally, the cyano group can be derivatised further to carboxylic acid, carbaldehyde or methylamine. In the present case, the cyano group in **20b** and **20c** was partially hydrolysed to form amides **21b** and **21c** (Scheme **6**) [16].

Finally, for the possibility of linking a radiolabel [^{123}I or ^{125}I] at a C17 substituent such as in the form of a 17-(2'-iodovinyl) group, **15**, **19** and **21** were transformed to the C7-substituted 17*a*-(ethynyl)-estra-1,3,5(10),6-tetraen-3,17β-diols **22**, **24**, and **25**. For this, **15** and **19** were reprotected with DHP to give 3-*O*-THP **20** and **23**. **20**, **21**, and **23** were then reacted with commercially available trimethylsilylacetylene (*n*-BuLi, THF [17]) to give the 17α-trimethylsilylethynyl substituted estra-1,3,5(10),6-tetraen-3,17β-diols **22**, **24**, and **25** (Scheme **7**). These compounds are stable enough to be stored over a prolonged time. Exemplary deprotection of **22c** to **22d** by reaction with *n*-Bu_4NF to cleave the trimethylsilyl group and subsequent treatment with 4N aq. HCl to cleave the 3-*O*-THP group was carried out with success without any noticable dehydrative elimination of the 17β-hydroxy function [18] (Scheme **7**).

In conclusion, a number of 7-cyanoalkyl and 7-amidoalkylsubstituted estra-1,3,5(10),6-tetraen-3-ol-17-ones **15** and **19** and 17α-ethynylestra-1,3,5(10),16-diols **22**, **24**, and **25** were synthesized as precursors to radiolabelled estra-1,3,5(10),6-tetraen-3,17β-diols. Further reactions to the iodovinyl derivatives are currently underway. This transformation, which has been carried out successfully with the parent compound [2], involves a hydrostannylation of the ethynyl group and a subsequent electrophilic substitution of the vinylstannane by radiolabelled iodine [Na^{125}I or Na^{123}I, chloroamine-T]. *In vivo* biodistribution studies in immature female mice of the radiolabelled compounds and *in vitro* estrogen receptor ERα binding affinity assays of both the compounds presented here [19] and the radiolabelled compounds will follow shortly.

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[18] For a report on the acid sensitivity of the 17β-hydroxy group in 17α-ethnyl-estra-3,17β-diol derivatives, see: Wang, J.; Watanabe, M.; Mataka, S.; Thiemann, T.; Ribeiro Morais, G.; Roleira, F.; Tavares da Silva, E.; Melo e Silva, C. *Zeitschr. f. Naturforschg., Sect. B* **2003**, *58b*, 799-804.

[19] Representative procedures to and data of the compounds: 7α-(*N*-butyl-*N*-methylundecanamide)-3-*O*-tetrahydropyranyl-6-oxoestra-1,3,5(10)-triene-3-ol- 17-one-17,17-dimethyldioxane (**13**).-To a

solution of **9** (1.41 g, 3.12 mmol)) in anhydrous THF (3.3 mL) and anhydrous DME (27 mL) was added potassium *tert*-butoxide (507 mg, 4.51 mmol) under inert atmosphere at 0 ºC. After 1 h, 11-iodo-(*N*-butyl-*N*-methyl)undecanamide (**12**, 1.52 g, 3.98 mmol) was added at 0 ºC and the reaction mixture was stirred at rt for 10 h. Thereafter, water (100 mL) was added and the mixture was extracted with ether (2 x 100 mL). The organic phase was dried over Na_2SO_4, filtered and the solvent evaporated to dryness. The resulting crude was separated by column chromatography on silica gel (*n*-hexane/ethyl acetate 4:1→2:1) affording **22** (1.09 g, 49%) as a gel. IR (neat) ν 2930, 2858, 1679, 1640, 1491, 1468, 1107, 1038, 1022, 968, 811 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.73 (s, 3H), 0.82 (s, 3H), 0.92-0.97 (m, 3H), 1.16 (s, 3H), 1.23-1.69 (m, 33H), 1.86-2.08 (m, 5H), 2.27-2.47 (m, 3H), 2.68-2.77 (m, 1H), 2.90 (s, 3H), 2.96 (s, 3H), 3.22-3.50 (m, 3H), 3.56-3.73 (m, 3H), 3.84-3.95 (m, 1H), 5.40 (m, 1H), 7.21 (dd, 1H, ^4J 2.7 Hz ^3J 8.6 Hz), 7.32 (d, 1H, ^3J 8.6 Hz), 7.68 (d, 1H, ^4J 2.7 Hz); ^{13}C NMR ($CDCl_3$, 67.8 MHz)* δ 13.71, 13.82, 18.74, 18.81, 19.90, 20.01, 21.94, 22.21, 22.46, 25.08, 25.11, 25.46, 26.47, 26.86, 27.35, 29.28, 29.36, 29.43, 29.50, 29.67, 30.20, 30.26, 30.30, 30.60, 32.94, 33.16, 33.60, 35.25, 37.27, 42.63, 42.71, 42.86, 47.29, 47.32, 48.77, 48.84, 49.70, 62.08, 62.19, 70.68, 72.54, 96.24, 96.49, 108.31, 114.52, 122.20, 127.01, 127.04, 132.28, 132.32, 139.67, 139.69, 155.36, 155.45, 172.81, 172.93, 201.02; MS (FAB^+, 3-nitrobenzyl alcohol) *m/z* 85 (53), 625 (100), 707 (M^+, 4); HRMS Found 707.5132; calcd for $C_{44}H_{69}O_6N$ (M^+) 707.5125. *The chiral centre of the THP group cannot be controlled and thus the compounds are formed as diastereoisomers, which is reflected in the ^{13}C NMR data.

7α-(5'-Cyanopentyl)-3-*O*-tetrahydropyranyl-estra-1,3,5(10)-triene-3,6-diol-17-one 17,17-dimethyldioxane (**14b**).-To a solution of **11b** (861 mg, 1.57 mmol) in ether (8 mL) and methanol (32 mL) was added $NaBH_4$ (850 mg, 22 mmol) at 0ºC. The reaction mixture was stirred at rt for 1 h. Thereafter, the solvent was evaporated and water (100 mL) was added. The aqueous phase was extracted with ether (2 x 100 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered and the solvent evaporated to dryness. The crude was crystallized in ether/*n*-hexane providing **14b** (851 mg, 98 %) as a mixture of the 6α and 6β-hydroxy-derivatives as a colorless solid; IR (NaCl) ν 3458, 2928, 2860, 2244 (CN), 1646, 1107 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.73 (s, 3H), 0.83 (s, 3H), 1.16 (s, 3H), 1.27-2.01 (m, 23H), 2.26-2.33 (m, 6H), 3.40-3.52 (m, 2H), 3.56-3.70 (m, 3H), 3.84-3.94 (m, 1H), 4.92 (b, 1H), 5.39-5.46 (m, 1H), 6.91 (dd, 1H, ^3J 8.37 Hz ^4J 2.4 Hz); 7.17 (d, 1H, ^3J 8.37 Hz), 7.29 (d, 1H, ^4J 2.4 Hz); ^{13}C NMR ($CDCl_3$, 67.8 MHz)* δ 13.97, 14.08, 17.05, 18.86, 18.78, 22.02, 22.51, 22.63, 22.92, 23.05, 25.27, 27.04, 29.42, 29.58, 30.37, 30.46, 31.56, 38.47, 40.72, 40.78, 41.39, 43.79, 47.57, 62.01, 62.09, 70.76, 72.62, 74.21, 74.23, 96.10, 96.63, 108.48, 114.08, 114.45, 115.25, 119.85, 126.82, 132.78, 132.92, 139.98, 155.50, 155.64; MS (FAB^+, 3-nitrobenzyl alcohol) *m/z* (%) 85 (15), 450 (8), 467 (5), 552 (MH^+, 2.5); HRMS Found 552.3687, calcd for $C_{34}H_{50}O_5N$ (MH^+) 552.3689. *The chiral centre of the THP group cannot be controlled and thus the compounds are formed as diastereoisomers, which is reflected in the ^{13}C NMR data.

7-(6'-Cyanohexyl)-estra-1,3,5(10),6-tetraene-17-one-3-ol **(15c)**.-A solution of **14c** (694 mg, 1.22 mmol) in DMSO (14 mL) was heated at 155-160 ºC for 2 h. Thereafter, water (50 mL) was added and the mixture was extracted with ether (3 x 50 mL). The organic phase was dried over anhydrous $MgSO_4$ and filtered. The filtrate was evaporated and the crude was submitted to column chromatographic on silica gel (ethyl acetate/*n*-hexane 1:1) to provide **15c** (289 mg, 63 %) as an oil. IR (NaCl) ν 3386, 2922, 2862, 2248, 1723, 1605, 1501, 1372, 1273, 1074, 912, 733 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.92 (s, 3H), 1.26-2.52 (m, 23H), 5.13 (s, 1H, OH), 6.20 (d, 1H), 6.54 (d, 1H, ^4J 2.7 Hz), 6.63 (dd, 1H, ^4J 2.7 Hz ^3J 8.1 Hz), 7.12 (d, 1H, ^3J 8.1 Hz); ^{13}C NMR ($CDCl_3$. 67.8 MHz) δ 14.03, 17.12, 24.10, 25.28, 25.50, 28.37, 28.64, 28.73, 30.73, 35.47, 36.00, 41.63, 41.78, 47.41, 49.64, 111.99, 112.79, 119.69, 124.44, 124.60, 130.66, 135.68, 145.75, 154.35, 220.34; MS (FAB^+, 3-nitrobenzyl alcohol) *m/z* 377 (4.28), 378 (MH^+, 2.18); HRMS Found 377.2356, calcd for $C_{25}H_{31}O_2N$ (M^+) 377.2355.

7-(6'-Cyanohexyl)-17α-ethynylestra-1,3,5(10),6-tetraene-3,17β-diols **(22d)** To a solution of **22c** (65 mg, 0.11 mmol) in THF (1.5 mL) was added tetra-*n*-butyl ammonium fluoride (0.17 mL of a solution 1M in THF) at -10ºC and the reaction mixture was stirred at rt for 1 h. Thereafter, ether (20 mL) was added and the mixture was poured into a separatory funnel containing ice (25 g). The phases were separated and the aqueous phase was extracted with ether (2 x 25 mL). The organic phase was dried over $MgSO_4$, filtered and the filtrate evaporated. The resulting crude was dissolved in MeOH (1 mL) and a few drops of 4 N aq. sol. HCl were added. The reaction mixture was stirred at rt for 20 min. Thereafter, aq. 10w% $NaHCO_3$ (20 mL) was added and the resulting mixture was extracted with AcOEt (3 x 20 mL). The organic phase was dried over anhydrous $MgSO_4$, filtered and the crude resulting from the evaporation of the filtrate was submitted to column chromatographic separation on silica gel (ether/*n*-hexane/chloroform 1:1:1) to afford **22d** (29 mg, 65%). mp: 80-82 ºC, IR (KBr) ν 3412, 3250, 2930, 2315, 2230, 1612, 1498, 1455, 1058, 878 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.87 (s, 3H), 1.27-2.38 (m, 24H), 2.61 (s, 1H), 4.65 (s, 1H), 6.15 (s, 1H), 6.52 (d, 1H, ^4J 2.7 Hz), 6.64 (dd, 1H, ^4J 2.7 Hz ^3J 8.1 Hz), 7.13 (d, 1H, ^3J 8.1 Hz); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 12.69, 17.15, 24.45, 25.34, 26.68, 28.29, 28.70, 28.83, 31.64, 35.82, 38.39, 41.28, 42.75, 45.97, 48.61, 74.32, 78.84, 87.11, 111.78, 112.49, 119.76, 123.50, 124.60, 131.48, 135.97, 147.08, 154.05; MS (FAB^+, 3-nitrobenzyl alcohol) *m/z* 403 (M^+, 0.48); HRMS Found 403.2515, calcd for $C_{27}H_{33}O_2N$ (M^+) 403.2511.

7-(6'-Carboxamidohexyl)-3-*O*-tetrahydropyranyl-17α-trimethylsilylethynylestra-1,3,5(10),6-tetraene-3,17β-diol (**25c**).-To a solution of trimethylsilylacetylene (0.2 mL, 1.41 mmol) in anhydrous THF (4 mL) was added *n*-butyllithium (0.7 mL, solution 1.6 M in *n*-hexane) at -78 ºC under an argon atmosphere. After 30 min, the reaction mixture was allowed to stand at 0 ºC for another 30 min and a solution of **21c** (184 mg, 0.38 mmol) in anhydrous THF (5 mL) was added at -78 ºC. The reaction mixture was stirred at rt for 30 min. Thereafter, the solvent was removed, ethyl acetate (50 mL) was added, and the mixture was extracted with aq. NH_4Cl (50 mL). The organic phase was washed with water (50 mL), dried over anhydrous Na_2SO_4, and filtered. The solvent was evaporated, providing **25c** (220 mg) in quantitative yield. IR (KBr) ν 3422, 2934, 2856, 2154, 1667, 1607, 1576, 1250, 842 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.17 (s, 9H), 0.85 (s, 3H), 1.25-2.23 (m, 31H), 3.55-3.59 (m, 1H), 3.86-3.93 (m, 1H), 5.39 (m, 2H), 6.19 (s, 1H), 6.74 (d, 1H, ^4J 2.5 Hz), 6.84 (dd, 1H, ^4J 2.5 Hz ^3J 8.1 Hz), 7.17 (d, 1H, ^3J 8.1 Hz); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 0.00 (3C), 12.71, 14.15, 18.77, 24.45, 25.23, 25.43, 26.59, 28.66, 29.24, 29.33, 30.39, 31.72, 35.89, 38.33, 41.53, 42.66, 46.19, 48.69, 60.35, 61.95, 79.03, 90.32, 96.44, 109.14, 112.98, 113.92, 123.91, 124.30, 133.00, 136.00, 146.89, 146.95, 155.61, 171.05; MS (FAB^+, 3-nitrobenzyl alcohol) *m/z* 73 (100), 85 (84), 395 (47), 476 (8), 577 (M^+, 0.75); HRMS Found 577.3585, calcd for $C_{35}H_{51}O_4NSi$ (M^+) 577.3587.