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Synthesis of 7-ω-Amidoalkyl-substituted 6,7-Dehydroestra-3,17β-diols

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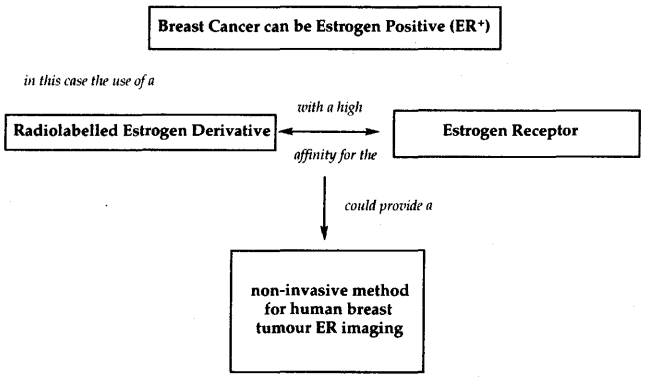
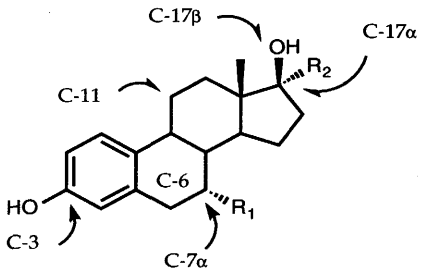
The entry to the novel C7-alkylsubstituted 6,7-dehydroestrones **10** by addition of C-nucleophiles on the enolate of suitably protected 6-ketoestrone derivative **3**, reduction of the 6-keto group in **7**, dehydration of 6-hydroxy group in **8** with a subsequent deprotection step is presented. An exemplary transformation of **10** to the 17α-iodoethynylestradiol **12** is shown.

Introduction

Breast cancer is a major disease and statistically afflicts one woman in eight in Western Europe and the United States and accounts for a significant number of deaths annually (Japan 7131 / Germany 18356 / USA 43644, all data is for 1994 on the basis of WHO database [www-dep.iarc.fr/cgi-bin/ggisql/who-cancer.idc]).[1] An important issue for a successful treatment of cancer is a sure diagnosis in its early stage. About 50 – 70% of the human breast tumours are estrogen receptor (Er_α) positive.[2] These tumour cells possess receptors for the estrogenic steroid hormones in concentrations much greater than in normal breast tissues or in non-target tissues.[3] The detection of these heightened concentrations of estrogen receptor can be a suitable tool for the diagnosis and also for the oriented therapy for breast cancer patients. For this purpose, a γ-emitting estrogen receptor-binding radioligand can be a potentially important tool in single-photon emission computerised tomography for the non-invasive detection and analysis of estrogen receptor-positive primary and metastatic breast tumours. Up to date, iodine [^{123}I],[4] fluorine [^{18}F][5], rhenium [^{186}Re][6] and technetium [^{99m}Tc][7] have been used as radiolabels. These are joined to organic structures that have estrogenic character and a high, selective binding affinity to the estrogen receptor Er_α.[8]



Most suitable are modified (*i.e.*, synthetic) estranes. It has been shown that a number of featural modifications in these estranes provide for more optimal, selective receptor binding. These are: a C-17α alkyl-, alkenyl-, or alkynyl-group retards the metabolic hydroxylation of C-16;[9] a hydroxy- or protected hydroxy-functionality at C-3 is mandatory[10] and a β-hydroxy group at C-17 is desirable.[10] It has been shown that additional substituents at C-11 or C-7α can alter the receptor binding characteristics of the ligand.[11] A long alkyl-chain with a polar group near its terminus is known to increase receptor binding in some cases.[12] As part of a study to determine the effect of unsaturation within the steroidal framework in the vicinity of C-7 and the effect of unsaturation in, *i.e.* rigidification of, the C-7 alkyl-chain, the synthesis of a number of C-7 amidoalkyl-substituted 6,7-dehydroestrones is shown below. Further transformation to the 17β-iodoethynyl derivatives is exemplified.



Results and Discussion

Two general synthetic routes to 7-substituted estranes can be envisaged. In the first case nortestosterone is the starting material. The key step in this synthesis is a

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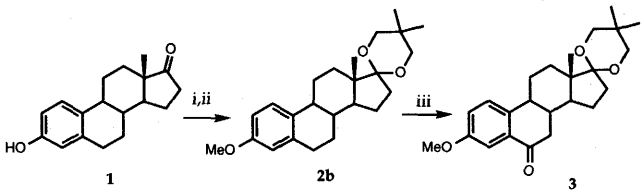
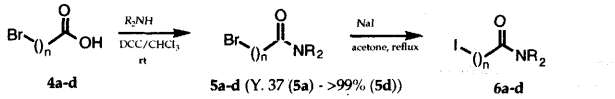
Homo Michael addition to an norandostan-4,6-dien-3-one.[13] After the addition, aromatisation of ring A and group-transformations in the side chain, both of which need elaborate protective group chemistry, are the major steps of concern. In our hand this route proved to be tedious. Another principle route takes advantage of readily available estrone **1**, in which the C-7 position needs to be activated for C-C bond formation. Estrone can be oxidized selectively to the corresponding 6-ketoestrone;[14] thus the 'activation' can be achieved in quite a straightforward way. Estrone is protected at the C-3 by methylation to give 3-*O*-methylestone **2a** and at C-17 by acetalisation with neopentylglycol (NPG) to give 3-*O*-methylestrone-17,17-dimethyldioxane **2b**. Oxidation of **2b** with PCC adsorbed on Celite provides the 6-keto-derivative **3**.[14b]



i. KOH/DMSO; MeI; ii. NPG, *p*-TsOH, benzene, Δ; iii. PCC-Celite

Scheme 1

C-7 substitution proceeds directly by reaction of a C-nucleophile to the enolate of **3**.[15] The α,ω-alkyl/arylamidoalkyliodides **6** can be synthesised by conventional methods from the commercially available bromoalkanecarboxylic acids by amidation using DCC[16] and subsequent nucleophilic exchange to the iodo-substituent analogous to a known procedure.[17]



4a-d

a: n = 5; b: n = 10

5a-d (Y. 37 (**5a**) - >99% (**5d**))

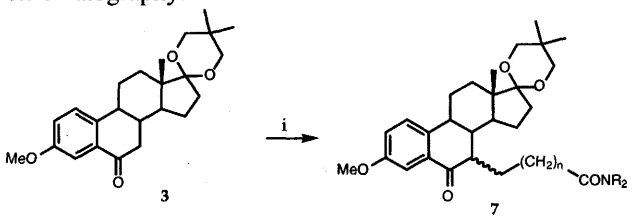
R = Bzl, Bu

6a-d

Y. 50 (**6a**) - 79% (**6c**)

Scheme 2

Reaction of **3** with KOBu^t in THF forms the dark red-colored enolate of **3**. Addition of the amidoiodoalkanes to the enolate at –78°C with subsequent warming to rt leads to a mixture of 7α and 7β-amidoalkylsubstituted estranes **7**. By far, the major isomer is the 7α-substituted estrone derivative; the isomers can be separated by column chromatography.

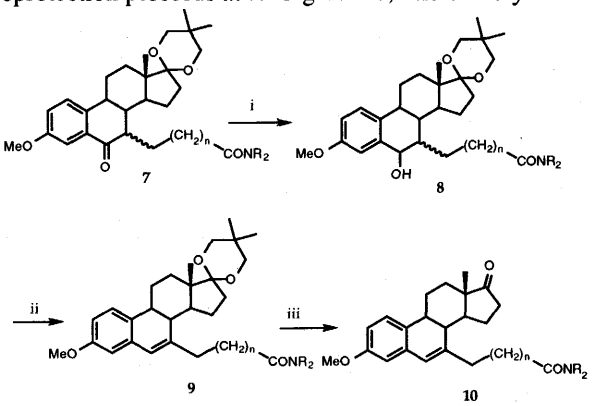


i. KOBu^t, THF, $R_2NCO(CH_2)_{(n+1)}I$

R = Bzl, Bu
n = 4, 9

Scheme 3

The 6-keto group in **7** can be reduced selectively in the presence of the terminal amido-function in the C-7 chain substituent by treating **7** with $NaBH_4$ in a mixture ether and methanol to give the 6-hydroxyestrane **8**. Acid-catalysed dehydration of **8** with *p*-toluenesulfonic acid in benzene leads to a mixture of **9** and **10**, which is not separated but subjected to complete deprotection at C-17 by acid-catalysed transacetalisation with acetone. *De facto*, only the solvent benzene is exchanged to acetone. The deprotection proceeds at rt to give **10**, exclusively.

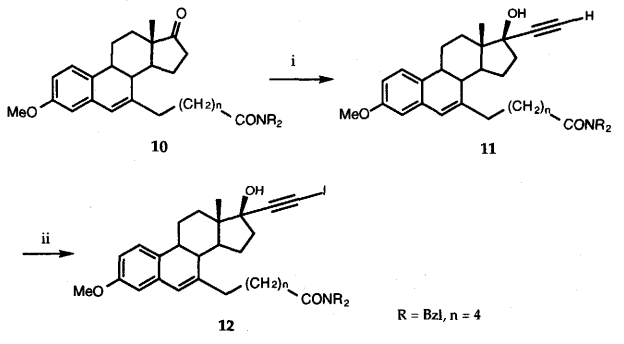


i. $NaBH_4$, Et_2O/MeOH; ii. *p*-TsOH, benzene, Δ; iii. *p*-TsOH, acetone, rt; R = Bzl, Bu *n* = 4, 9

Scheme 4

As mentioned above, for protection of C-16 against fast metabolic hydroxylation, it is crucial that C-17 carries a sterically demanding C-17β-substituent. This may be an alkyl, an alkenyl- or alkynyl-group. This site may also be used to attach the label. For this purpose the introduction of either an iodovinyl- or an iodoethynyl-substituent seems expedient. An iodoalkyl group is too labile, both *in vitro* and *in vivo*, to be considered. While the authors have introduced both an *E*- and a *Z*-iodovinyl moiety in the parent 6,7-dehydroestrone system,[18,19] here an example of the introduction of an iodoethynyl group is presented.

10 can be reacted to **11** with lithium acetylide ethylenediamine complex in dry DMSO at rt. **11** is stable for long periods of time and should be the chosen structure for storage for later radiolabelling experiments. Cold iodination proceeds via an iodine-morpholine complex to give **12**. **12** deiodinates after some weeks and cannot be stored for an indefinite length of time.



i. LiC≡CH·EDA, DMSO; ii. I_2-Morpholine, $CHCl_3$

R = Bzl, n = 4

Scheme 5

Experimental

General. IR spectra were recorded on a JASCO IR-700 spectrometer (KBr pellets or NaCl plates [designated as *neat*). ^{1}H NMR spectra were measured on a JEOL EX-270 (270 MHz), a JEOL JNM-LA 395 (400 MHz), and a JEOL JNM-LA 600 (600 MHz) spectrometer. ^{13}C NMR spectra were measured on a JEOL EX-270 (67.9 MHz) and a JEOL 395 (100.4 MHz) spectrometer. Assignments of ^{13}C signals were aided by DEPT (= Distortionless Enhancement by Polarisation Transfer) measurements; (+) denotes primary and tertiary, (-) secondary, and (C_{quat}) quaternary carbon atoms; * denotes that the C-17 (C=O) has not been measured as it was outside the chosen chemical shift range; Mass spectra were taken on a JEOL-01-SG-2 machine at 70 eV using a direct inlet system. Wakogel C-300 was used as silica gel in all column chromatographic separations.

3-Methoxy-6-oxoestrone-17,17-(2'-[5',5'-dimethyl-1',3'-dioxane]) (**3**), *N,N*-dibutyl α,ω-iodopentanamide (**6a**), *N,N*-dibenzyl α,ω-iodopentanamide (**6b**), *N,N*-dibutyl α,ω-iododecanamide (**6c**), and *N,N*-dibenzyl α,ω-iododecanamide (**6d**) were prepared analogous to literature procedures.[14b,16,17]

7α-(*N,N*-Dibenzylcarbamidopentyl)-3-*O*-methyl-6-oxoestrone-17,17-(2'-[5',5'-dimethyl-1',3'-dioxane]) (7aα-NBzl$_2$) - General Procedure A. – To a solution of **3** (300mg, 0.78 mmol) in dry THF (0.9 mL) and DME (12 mL) was added at 0C and under argon KOBu^t (120 mg, 0.90 mmol). The resulting dark-red solution was stirred for 1h at rt. Thereafter the mixture was cooled to –78°C and **6b** (378 mg, 0.90 mmol) was added via syringe. The solution was stirred for 20h, during which it was allowed to warm to rt. The solution lightened in color noticably and an appreciable amount of precipitate (KI) formed. Then water (20 mL) was added and the mixture was extracted with ethyl acetate (2 x 20 mL). The combined organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel (eluant toluene/ethyl acetate 9:1) to give **7aα-NBzl$_2$** (120 mg, 23%) as colorless crystals, mp. 53-65°C; R_f 0.24; IR (KBr) 3466, 2942, 2862, 1680, 1650, 1494, 1454, 1286, 1105, 1031, 732, 699 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.74 (s, 3H, CH_3), 0.83 (s, 3H, CH_3), 1.17 (s, 3H, CH_3), 1.21 - 2.71 (m, 22H), 3.77 – 3.81 (m, 4H), 3.82 (s, 3H, OCH_3); 4.41 (s, 2H), 4.48 (s, 2H), 7.05 – 7.39 (m, 12H), 7.51 (d, 1H, *J* 3.0 Hz); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 13.78, 21.98, 22.25, 22.51, 23.65, 25.23, 26.51, 26.84, 27.21, 29.29, 29.44, 30.36, 33.12, 37.28, 42.74, 42.82, 47.31, 47.99, 48.79, 55.41, 70.69, 72.59, 108.36, 109.86, 121.45, 125.28, 126.34, 127.31, 128.21, 128.55, 128.91, 132.09, 136.56, 137.49, 139.00, 158.03, 173.61, 201.35; MS (FAB, 3-nitrobenzyl alcohol) *m/z* (678, MH$^+$); HRMS (FAB) Found 678.4157. Calcd for $C_{44}H_{56}O_5N$: 678.4158.

(*N,N*-Dibutylcarbamidopentyl)-3-*O*-methyl-6-oxoestrone-17,17-(2'-[5',5'-dimethyl-1',3'-dioxane]) (7aα-NBu$_2$). – **3** (330 mg, 0.86 mmol) in THF (1.0 mL) and DME (12 mL) was reacted successively with KOBu^t (111 mg, 1.0 mmol) and **6a** (349 mg, 1.0 mmol) according to general procedure A. Column chromatography on silica gel (eluant: toluene/ethyl acetate 9:1) yielded **7aα-NBu$_2$** (151 mg, 29%) as an oil; R_f 0.35; IR (KBr) 3010, 2956, 2866, 1675, 1622, 1495, 1466, 1216, 1104, 754, 668 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.66 (s, 3H, CH_3), 0.75 (s, 3H, CH_3), 0.79 – 0.91 (m, 6H), 1.09 (m, 3H), 1.14 – 2.40 (m, 29H), 2.60 – 2.68 (m, 1H), 3.09 (t, 2H, *J* 7.6 Hz), 3.20 (t, 2H, *J* 7.6 Hz), 3.29 – 3.62 (m, 4H), 3.76 (s, 3H, OCH_3), 7.00 (d, 1H, *J* 2.6, 8.6 Hz), 7.25 (d, 1H, *J* 8.6 Hz), 7.44 (d, 1H, *J* 3.0 Hz); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 13.85, 13.89, 20.09, 20.25, 21.99, 22.26, 22.52, 23.66, 25.28, 25.32, 26.54, 26.86, 27.26, 29.31, 29.51, 29.94, 30.35, 31.25, 31.48, 32.92, 37.30, 42.80, 42.84, 45.59, 47.09, 47.33, 48.84, 55.42, 70.69, 72.60, 108.30, 109.94, 121.38, 127.24, 132.15, 139.03, 158.06, 172.47, 201.33; MS (FAB, 3-nitrobenzyl alcohol) *m/z* (%) 610 (MH$^+$). HRMS Found 610.4473. Calcd for $C_{38}H_{60}O_5N$: 610.4471.

(*N,N*-Dibutylcarbamidodecyl)-3-*O*-methyl-6-oxoestrone-17,17-(2'-[5',5'-dimethyl-1',3'-dioxane]) (7bα-NBu$_2$). – **3** (530 mg, 1.4 mmol) in THF (1.6 mL) and DME (10 mL) was reacted successively with KOBu^t (178 mg, 1.6 mmol) and **6c** (671 mg, 1.6 mmol) according to general procedure A. Column chromatography on silica gel (eluant toluene/ethyl acetate 15:1 – 10:1 – 7:1) yielded **7bα-NBu$_2$** (303 mg, 32%) as an oil, R_f 0.33 (eluant ratio 9:1]; IR (neat) 3434, 3052, 2930, 2858, 1679, 1630, 1494, 1466, 1265, 1105, 740 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ = 0.74 (s, 3H, CH_3), 0.83 (s, 3H, CH_3), 0.92 (t, 3H, *J* 7.3 Hz), 0.95 (t, 3H, *J* 7.3 Hz), 1.17 (s, 3H, CH_3), 1.18 – 2.76 (40H, m), 3.21 (t, 2H, *J* 7.7 Hz), 3.30 (t, 2H, *J* 7.3 Hz), 3.40 (t, 2H, *J* 10.6 Hz), 3.48 (d, 1H, *J* 10.8 Hz), 3.69 (d, 1H, *J* 10.8 Hz), 3.84 (s, 3H, OCH_3), 7.08 (dd, 1H, *J* 2.9, 8.6), 7.33 (1H, d, *J* 8.6 Hz), 7.53 (d, 1H, *J* 2.9 Hz); ^{13}C NMR (150.8 MHz, $CDCl_3$) δ 13.78, 13.86, 13.91, 20.10, 20.26, 22.01, 22.26, 22.52, 23.81, 25.52, 26.55, 26.91, 27.40, 29.33, 29.47, 2949, 29.51, 29.56, 29.71, 29.94, 30.36, 31.28, 33.14, 37.31, 42.81, 42.89, 45.58, 47.35, 47.71, 48.84, 55.41, 70.73, 72.59, 108.34, 109.94, 121.34, 127.21, 132.19, 139.00, 158.06, 172.64, 201.36; MS (70 eV) *m/z* (%) 679 (M$^+$, 62), 141 (100). HRMS Found 679.5184. Calcd for $C_{43}H_{69}O_5N$ 679.5176.

7α-(*N,N*-Dibenzylcarbamidopentyl)-6-hydroxy-3-*O*-methyl-estrone-17,17-(5',5'-dimethyl-1',3'-dioxane) (8a-NBzl$_2$) – General Procedure B. – To a solution of **7aα-NBzl$_2$** (109 mg, 0.16 mmol) in methanol (1mL) and ether (0.5 mL) was added $NaBH_4$ (28 mg, 0.74 mmol) at 0°C. The resulting mixture was stirred for 1h at 0°C and for 5h at rt. Thereafter water (2

mL) was added and the mixture was extracted with ether (3 x 10 mL). The organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel (eluant: toluene/ethyl acetate 9:2) to give **8a-NBzl$_2$** (63 mg, 58%) as a colorless solid, mp 63 – 74°C; R_f 0.18; IR (KBr) 3438, 2946, 1637, 1495, 1455, 1107, 732 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.73 (s, 3H, CH_3), 0.83 (s, 3H, CH_3), 1.16 (s, 3H, CH_3), 1.21 – 2.44 (m, 23H), 3.37 – 3.85 (m, 4H), 3.79 (s, 3H, OCH_3), 4.42 (s, 2H), 4.58 (s, 2H), 4.90 (s, 1H), 6.76 (dd, 1H, *J* 2.6, 8.6 Hz), 7.10 – 7.39 (m, 12H); ^{13}C NMR (67.9 MHz, $CDCl_3$, DEPT) δ 13.96, 22.00, 22.48, 22.81, 23.04, 25.11, 26.97, 27.06, 29.54, 30.01, 30.35, 30.93, 33.08, 38.35, 40.58, 41.42, 43.74, 47.53, 48.03, 49.85, 55.19, 70.68, 72.58, 74.27, 108.48, 111.41, 123.52, 126.33, 126.77, 127.31, 127.55, 128.25, 128.54, 128.90, 131.81, 136.55, 137.47, 140.14, 157.99, 173.73; MS (70 eV) *m/z* (%) 678 (M^+), 662 (M^+-H_2O); HRMS Found 662.4203. Calcd for $C_{44}H_{56}O_4N$ (M^+-H_2O) 662.4209.

7α-(*N*,*N*-Dibutylcarbamidopentyl)-6-hydroxy-3-*O*-methyl-estrone-17,17-(2'-[5',5'-dimethyl-1',3'-dioxane]) (8a-NBu$_2$). – **7aα-NBu$_2$** (140 mg, 0.23 mmol) in MeOH (1 mL) and ether (1 mL) was reacted with $NaBH_4$ (28 mg, 0.74 mmol) according to general procedure B (3h, rt). Column chromatography on silica gel (eluant: toluene/ethyl acetate 3:1 – 3:2) gave **8a-NBu$_2$** (101 mg, 72%) as a colorless oil; R_f 0.15; IR (KBr) 3402, 2954, 2864, 1621, 1494, 1467, 1215, 1105, 756 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.74 (s, 3H, CH_3), 0.83 (s, 3H, CH_3), 0.85 – 0.96 (m, 6H), 1.16 (s, 3H, CH_3), 1.22 - 2.39 (m, 31H), 3.18 (t, 2H, *J* 7.6 Hz), 3.28 (t, 2H, *J* 7.4 Hz), 3.38 – 3.70 (m, 4H), 3.81 (s, 3H, OCH_3), 4.91 (s, 1H), 6.76 (dd, 1H, *J* 2.6, 8.6 Hz), 7.18 (d, 1H, *J* 8.2 Hz), 7.22 (d, 1H, *J* 2.3 Hz); ^{13}C NMR (67.9 MHz, $CDCl_3$, DEPT 90, DEPT 135) δ 13.89 (+ CH_3), 20.25 (-), 22.01 (+, CH_3), 22.50 (+, CH_3), 22.81 (-), 23.04 (-), 25.16 (-), 25.25 (-), 26.97 (-), 27.06 (-), 29.54 (-), 29.92 (-), 30.10 (-), 30.35 (-), 31.00 (-), 31.23 (-), 32.92 (-), 33.03 (-), 38.33 (+, CH), 40.56 (+, CH), 41.42 (+, CH), 43.74 (+, CH), 45.61 (-), 47.53 (-), 55.20 (+, OCH3), 55.31 (C_{quat}), 70.69 (+, CH), 72.58 (-), 74.31 (-), 108.25 (C_{quat}), 108.50 C_{quat}), 111.02 (+, CH), 113.23 (+,CH), 126.79 (+, CH), 140.18 (C_{quat}), 157.99 (C_{quat}), 172.63 (C_{quat}, C=O); MS (FAB, 3-nitrobenzyl alcohol) *m/z* (%) 594 (MH^+). HRMS Found 594.4528. Calcd for $C_{38}H_{60}O_4N$ 594.4522.

7α-(*N*,*N*-Dibutylcarbamidodecyl)-6-hydroxy-3-*O*-methyl-estrone-17,17-(2'-[5',5'-dimethyl-1',3'-dioxane]) (8b-NBu$_2$). – **7bα-NBu$_2$** (260 mg, 0.40 mmol) in MeOH (1.5 mL) and ether (1.5 mL) was reacted with $NaBH_4$ (45 mg, 1.2 mmol) according to general procedure B (4h, rt). Column chromatography on silica gel (eluant: toluene/ethyl acetate 7:1 – 4:1) gave **8b-NBu$_2$** (201 mg, 72%) as colorless oil, R_f 0.24 (eluant ratio 7:1); IR (KBr) 3418, 2926, 2856, 1626, 1495, 1466, 1242, 1142, 1110, 1039, 754 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.66 (s, 3H, CH_3), 0.76 (s, 3H, CH_3), 0.81 – 0.90 (m, 6H), 1.09 – 2.37 (m, 42H), 3.13 (t, 2H, *J* 7.6 Hz), 3.22 (t, 2H, *J* 7.6 Hz), 3.29 – 3.43 (m, 4H), 3.61 (d, 1H, *J* 11.2 Hz), 3.72 (s, 3H, OCH_3), 4.83 (s, 1H, OH), 6.68 (dd, 1H, *J* 2.3, 8.4 Hz), 7.10 (d, 1H, *J* 8.6 Hz), 7.15 (d, 1H, *J* 2.3 Hz); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 13.79, 13.86, 13.91, 20.04, 20.18, 21.96, 22.43, 22.99, 23.04, 25.45, 26.94, 27.01, 29.38, 29.51, 29.85, 30.30, 30.42, 31.20, 31.43, 33.08, 38.26, 40.74, 41.21, 43.69, 45.54, 47.46, 55.11, 70.62, 72.51, 74.20, 108.46, 111.09, 113.05, 126.69, 131.81, 140.25, 157.90, 172.65; MS (FAB, 3-nitrobenzyl alcohol) 664 (MH^+-H_2O, 82). HRMS Found 664.5311. Calcd for $C_{43}H_{70}O_4N$ 664.5305.

7-(*N*,*N*-Dibenzylcarbamidopentyl)-3-*O*-methyl-6,7-dehydroestrone (10a-NBzl$_2$) – General Procedure C. – A solution of **8a-NBzl$_2$** (60 mg, 0.09 mmol), *para* toluenesulfonic acid (*p*-TsOH) (14 mg, 0.08 mmol) in benzene (3 mL) was heated under reflux for 2h. Thereafter, benzene was evaporated *in vacuo*. To the residue was given acetone (3 mL). The resulting solution was stirred at rt for 20h. Then the solvent was evaporated *in vacuo*, and 5w% aq. Na_2CO_3 solution (3 mL) was added and the mixture was extracted with ether (5 mL). The organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel (eluant: toluene/ethyl acetate 9:2) to give **10a-NBzl$_2$** (36 mg, 71%) as a colorless solid, R_f 0.31; IR (KBr) 3006, 2932, 1738, 1640, 1497, 1453, 1268, 1216, 752 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.91 (s, 3H, CH_3), 1.26 – 2.57 (m, 21H), 3.79 (s, 3H, OCH_3), 4.46 (s, 2H), 4.61 (s, 2H), 6.22 (s, 1H), 6.59 (1H, d, *J* 2.6 Hz), 6.70 (dd, 1H, *J* 2.6, 8.3 Hz), 7.14 – 7.40 (m, 11H); ^{13}C NMR (67.9 MHz, $CDCl_3$, DEPT) δ 14.03, 24.13, 25.35, 25.50, 28.54, 29.40, 30.76, 33.19, 35.51, 36.05, 41.36, 41.78, 47.42, 48.16, 49.16, 49.92, 55.29, 110.30, 110.69, 124.42, 124.51, 126.32, 127.38, 127.62, 128.28, 128.59, 130.76, 135.56, 136.60, 137.48, 145.96, 158.31, 173.49*; MS (FAB, 3-nitrobenzyl alcohol) *m/z* (%) 576 (MH^+). HRMS Found 576.3484. Calcd for $C_{39}H_{46}O_3N$: 576.3478.

7-(*N*,*N*-Dibutylcarbamidopentyl)-3-*O*-methyl-6,7-dehydroestrone (10a-NBu$_2$). – A solution of **8a-NBu$_2$** (100 mg, 0.16 mmol), *p*-TsOH (35 mg, 0.20 mmol) in benzene (3.5 mL) were refluxed for 3h. Then the solvent was exchanged for acetone (3 mL) and the mixture was reacted according to general procedure C (12h). Column chromatography on silica gel (eluant: toluene/ethyl acetate 2:1) gave **10a-NBu$_2$** (50 mg, 62%) as a colorless oil; R_f 0.45; IR (neat) 3016, 2934, 1737, 1623, 1215, 754 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) 0.89 – 1.00 (m, 6H), 0.91 (s, 3H, CH_3), 1.26 – 2.55 (m, 29H), 3.21 (t, 2H, *J* 7.6 Hz), 3.30 (t, 2H, *J* 7.6 Hz), 3.80 (s, 3H, OCH3), 6.25 (bs, 1H), 6.61 (d, 1H, *J* 2.6 Hz), 6.71 (dd, 1H, *J* 2.6,

8.3 Hz), 7.17 (d, 1H, *J* 8.3 Hz); ^{13}C NMR (67.9 MHz, $CDCl_3$, DEPT 90, DEPT 135) δ 13.82 (+, CH_3), 13.98 (+, CH_3), 20.07 (-), 20.22 (-), 24.08 (-), 25.37 (-), 25.44 (-), 28.55 (-), 29.44 (-), 29.89 (-), 30.69 (-), 31.20 (-), 33.01 (-), 35.45 (-), 35.63(-), 41.58 (+, CH), 41.71 (+, CH), 45.57 (-), 47.35 (+, CH), 47.66 (-), 49.56 (C_{quat}), 55.22 (+, OCH_3), 110.62 (+, CH), 111.19 (+, CH), 130.71 (C_{quat}), 124.39 (+, CH), 135.53 (C_{quat}), 146.02 (C_{quat}), 158.24 (C_{quat}), 172.29 (C_{quat}, C=O(NR_2)*; MS (FAB, 3-nitrobenzyl alcohol) *m/z* (%) 508 (MH^+). HRMS Found 508.3790. Calcd for $C_{33}H_{50}O_3N$ (MH^+): 508.3791.

7-(*N*,*N*-Dibutylcarbamidodecyl)-3-*O*-methyl-6,7-dehydroestrone (10b-NBu$_2$). – A solution of **8b-NBu$_2$** (200 mg, 0.29 mmol), *p*-TsOH (51 mg, 0.29 mmol) in benzene (5 mL) was refluxed for 2h. Thereafter the solvent was exchanged for acetone (5 mL). The resulting mixture was reacted according to general procedure C (18h). Column chromatography on silica gel (eluant: ether/hexane 3:2) gave **10b-NBu$_2$** (103 mg, 62%) as a colorless oil; R_f 0.44; IR (neat) 3004, 2928, 2854, 1738, 1632, 1465, 1215, 754 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 – 0.97 (m, 6H), 0.92 (s, 3H, CH_3), 1.25 – 1.65 (m, 25H), 1.77 – 1.99 (m, 6H), 2.12 – 2.57 (m, 9H), 3.21 (t, 2H, *J* 7.7 Hz), 3.30 (t, 2H, *J* 7.7 Hz), 3.79 (s, 3H, OCH_3), 6.24 (bs, 1H), 6.61 (d, 1H, *J* 2.6 Hz), 6.70 (dd, 1H, *J* 8.4, 2.6 Hz), 7.17 (1H, d, *J* 8.4Hz); ^{13}C NMR (100.4 MHz, $CDCl_3$, DEPT 90, DEPT 135) δ 13.86 (+, CH_3), 14.00 (+, CH_3), 20.06 (-), 20.22 (-), 24.10 (-), 25.46 (-), 28.79 (-), 29.44 (-), 29.49 (-), 29.57 (-), 29.62 (-), 29.66 (-), 29.90 (-), 30.75 (-), 31.24 (-), 33.11 (-), 35.46 (-), 36.27 (-), 41.63 (+, CH), 41.76 (+, CH), 45.56 (-), 47.41 (-), 47.67 (+, CH), 49.56 (C_{quat}), 55.22 (+, OCH_3), 110.63 (+, CH), 111.19 (+, CH), 124.37 (+, CH), 130.73 (C_{quat}), 135.61 (C_{quat}), 146.26 (C_{quat}t), 158.27 (C_{quat}), 172.58 (C_{quat}, (C=O)NR_2), 220.16 (C_{quat}, C=O); MS (70 eV) *m/z* (%) 577. HRMS Found 577.4500. Calcd for $C_{38}H_{59}O_3N$: 577.4495.

7-(*N*,*N*-Dibenzylcarbamidopentyl)-17α-ethynyl-3-*O*-methyl-6,7-dehydroestra-3,17β-diol (11). – Under argon and at rt was added in multiple portions lithium acetylide ethylene diamine complex (53 mg, 0.58 mmol) to a solution of **10a-NBu$_2$** (34 mg, 0.06 mmol) in dry DMSO (1.5 mL). The resulting mixture was stirred for 20h. Thereafter, 5w% aq. HCl (1 mL) was added and the resulting mixture was extracted with ethyl acetate (3 x 3 mL). The organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel (eluant: ether/hexane 2:1) to give **11** (20 mg, 50%) as a colorless solid; R_f 0.50; IR (KBr) 3370 (bs, OH), 3302 (C≡CH), 2932, 2864, 1638, 1497, 1452, 1267, 1216, 1037, 752 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ = 0.86 (s, 3H, CH_3,), 1.23 – 2.48 (m, 22H), 2.59 (s, 1H), 3.79 (s, 3H, OCH_3), 4.46 (s, 2H), 4.61 (s, 2H), 6.18 (s, 1H), 6.59 (d, 1H, J 2.6 Hz), 6.70 (dd, 1H, *J* 2.6, 8.6 Hz), 7.14 – 7.40 (m, 11H); ^{13}C NMR (67.9 MHz, $CDCl_3$, DEPT 90, DEPT 135) δ = 12.69 (+, CH_3), 24.47 (-), 25.43 (-), 25.71 (-), 26.67 (-), 28.41 (-), 29.51 (-), 31.64 (-), 33.24 (-), 38.40 (-), 41.28 (+, CH), 42.78 (+, CH), 45.98 (+, CH), 48.14 (C_{quat}), 48.61 (-), 49.92 (-), 55.27 (+, OCH_3), 74.28 (C_{qua}t), 78.81 (C_{quat}), 87.17 (C≡CH), 110.49 (+, CH), 111.14 (+, CH), 123.57 (+, CH), 124.36 (+, CH), 126.34 (+, CH), 127.38 (+, CH), 127.60 (+, CH), 128.28 (+, CH), 128.59 (+, CH), 128.96 (+, CH), 131.41 (C_{quat}), 135.79 (C_{quat}), 136.60 (C_{quat}), 137.50 (Cquat), 147.15 (C_{quat}), 158.18 (C_{quat}), 173.60 (C_{quat}, C=O). MS (FAB, 3-nitrobenzyl alcohol) *m/z* (%) 602 (MH^+). HRMS Found: 602.3626. Calcd for $C_{41}H_{48}O_3N$: 602.3634.

7-(*N*,*N*-Dibenzylcarbamidopentyl)-17α-iodoethynyl-3-*O*-methyl-6,7-dehydroestra-3,17β-diol (12). – Iodine (4 mg, 0.03 mmol) was dissolved under stirring in CH_2Cl_2 (0.5 mL) and MeOH (0.5 mL). Morpholine (12 µL, 12 mg, 0.14 mmol) was added to the solution. After 30 min. **11** (20 mg, 0.03 mmol) was added and stirring at rt was continued for 4 d. Thereafter, the solvent was evaporated. The residue was dissolved in ethyl acetate (2 mL) and the resulting solution was washed with water (2 x 1 mL). The organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Column chromatography on silica gel (eluant: ether/hexane 2:1) gave **12** (6 mg, 30%) as an oil; R_f0.40; IR (KBr) 3396, 3010, 2930, 2862, 1632, 1453, 1267, 1216, 756 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ = 0.85 (s, 3H, CH_3), 1.86 – 2.48 (m, 22H), 3.79 (s, 3H, OCH_3), 4.46 (s, 2H), 4.62 (s, 2H), 6.18 (s, 1H), 6.59 (d, 1H, *J* 2.76 Hz), 6.70 (dd, 1H, *J* 2.8, 8.4 Hz), 7.15 – 7.40 (m, 11H); ^{13}C NMR (67.9 MHz, $CDCl_3$, DEPT) δ = 12.78 (+, CH_3), 15.29 (-), 25.48 (-), 26.72 (-), 28.37 (-), 29.52 (-), 29.70 (-), 31.91 (-), 33.26 (-), 35.74 (-), 38.38 (-), 41.22 (+, CH), 42.80 (+, CH), 46.18 (+, CH), 48.14 (-), 49.20 (-), 49.95 (C_{quat}), 55.29 (+, OCH_3), 80.71 (C≡CI), 97.73 (C≡CI), 110.51 (+, CH), 111.16 (+, CH), 123.56 (+, CH), 124.36 (+, CH), 126.36 (+, CH), 127.40 (+, CH), 127.62 (+, CH), 128.32 (+, CH), 128,60 (+, CH), 128.96 (+, CH), 131.35 (C_{quat}), 135.78 (C_{qua}t), 136.64 (C_{quat}), 137.54 (C_{quat}), 147.10 (C_{quat}), 158.20 (C_{quat}), 173.62 (C_{quat}, C=O); MS (FAB, 3-nitrobenzyl alcohol) *m/z* (%) 728 (MH^+). HRMS Found: 728.2585. Calcd for $C_{41}H_{47}O_3NI$ (MH^+) 728.2601.

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