Synthetic Approaches towards 4-Functionalized Estrone Derivatives

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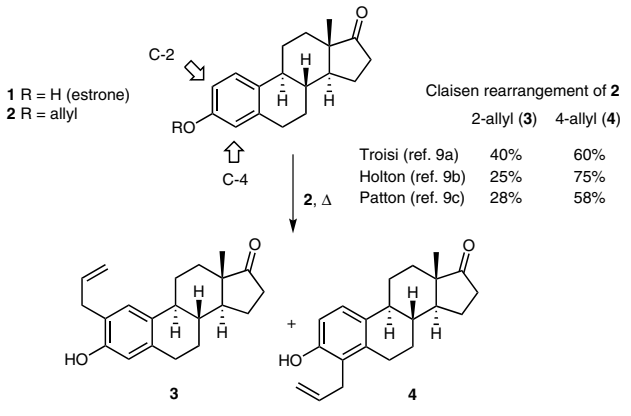
Abstract: Directed *ortho*-lithiation of estrone carbamate followed by reaction with electrophiles afforded 2-substituted estrone derivatives. Reductive cleavage of the carbamate group followed by O-allylation and Claisen rearrangement led to new 4-functionalized estrone derivatives.

Key words: carbanions, Claisen rearrangement, estrone, *ortho*-lithiation, steroids

Steroids are a biologically important class of natural compounds with a large range of pharmaceutical applications.[1,2] Specific functionalization of the tetracyclic core is still a key synthetic issue and current methods have been reviewed.[3–5]

Steroidal derivatives exert a wide range of biological actions. These include receptor agonists or antagonists of estrogens, androgens, corticoids, and inhibitors of steroidogenic enzymes.[6,7] Besides manual chemistry, combinatorial methods have also been pursued to generate compound libraries.[8]

As part of an ongoing research program we were interested in synthesizing new estrone derivatives functionalized at C-4. However, synthesis of these estrones is still not well explored. A common approach utilizes the Claisen rearrangement of estrone allyl ether (**2**).[9] The published results show that this method creates mixtures of 2-allyl- (**3**) and 4-allylestrone (**4**) (Scheme 1).



Scheme 1 Claisen rearrangement of estrone allyl ether (**2**)

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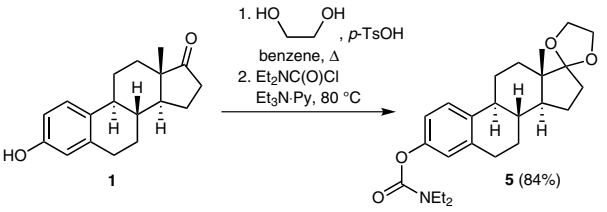
In this report we disclose our investigations on the selective synthesis of 4-substituted estrone derivatives by exploiting the *ortho*-directed lithiation of estrone carbamate **5**.[10]

For realizing this approach a robust protection of the 17-keto group was required, which we found to be the acetal functionality. Estrone (**1**) was protected under standard conditions and the resulting acetal was treated with diethylcarbamoyl chloride in pyridine in the presence of triethylamine. The desired carbamate **5** was obtained in 84% overall yield (Scheme 2). It is noteworthy that carbamoylation proceeded slowly without completion in the absence of triethylamine.

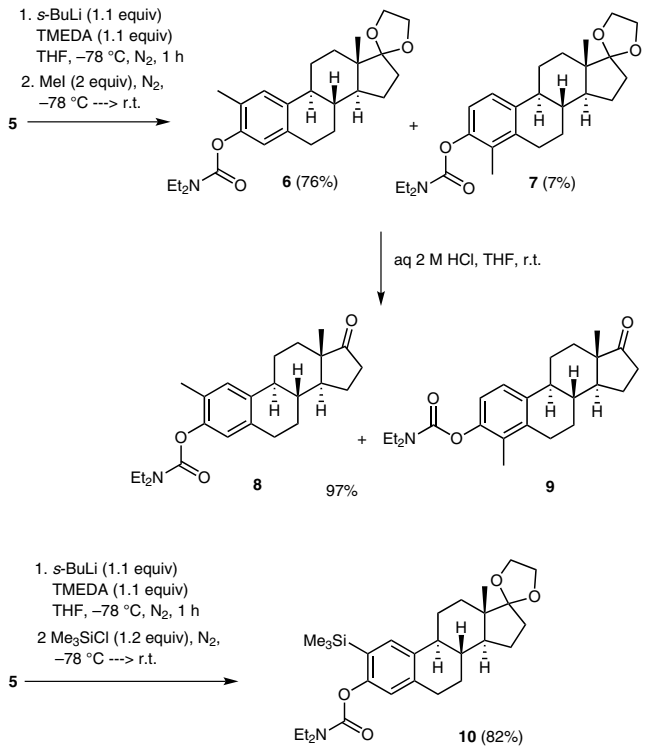


Scheme 2 Preparation of esterone 3-(*N*,*N*-diethyl)carbamate **5**

Treatment of carbamate **5** with *sec*-butyllithium in the presence of TMEDA (THF, –78 °C, 1 h) followed by trapping of the carbanion with electrophiles such as methyl iodide or trimethylsilyl chloride afforded the corresponding estrone derivatives **6** and its 4-isomer **7** (ratio = 10:1) as well as **10** in synthetically useful yields (Scheme 3). Clearly, substitution at C-2 is favored over functionalization at C-4, reflecting the preferred site of lithiation. It can be assumed that this preference is based on sterical grounds. The regioselectivity of *ortho*-lithiation observed for carbamate **5** correlates well with the results reported for *ortho*-metalation of estrone derivatives with the 3-methoxymethyl substituent as directing group.[11]

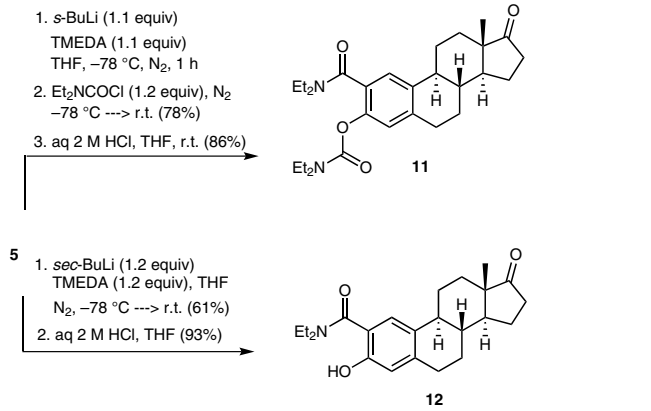
The methyl-substituted carbamates **6** and **7** could smoothly be deprotected for liberating the keto group at C-17 yielding estrone derivatives **8** and **9**.

In a similar manner, the 2-position can exclusively be functionalized as amide, when the lithiated intermediate was reacted with diethylcarbamoyl chloride. Hydrolysis of the acetal group yielded estrone derivative **11** in good yield. Remarkably, when lithiation of **5** was initiated and the solution was allowed to warm to room temperature in the absence of an electrophile, estrone derivative **12** was



Scheme 3 Selective *ortho*-lithiation of esterone 3-(*N*,*N*-diethyl)carbamate **5** followed by electrophilic trapping

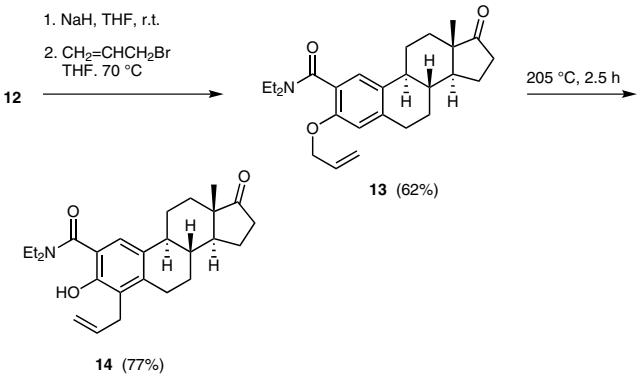
formed and isolated in good yield after acidic removal of the ketal group. This 1,3-migration of the carbamido group[12] resembles an anionic *ortho*-Fries rearrangement and exclusively furnishes the 2-substituted product **12** (Scheme 4).



Scheme 4 1,3-Migration of carbamido group of esterone 3-(*N*,*N*-diethyl)carbamate **5**

In essence, the *ortho*-lithiation strategy allows to modify C-2 in estrone. It can also serve to specifically introduce a substituent like the allyl group in the 4-position. For achieving this goal, the 2-position needs to be blocked first before C-4 can specifically be addressed. Indeed, it looked tempting to carry out a second directed *ortho*-lithiation/alkylation protocol starting from carbamate **10** for targeting the 4-alkylated estrone derivatives. Unfortunately, this approach did not provide 4-alkylation products under the common conditions. Instead, the 1,3-migration of the carbamido group was the prevailing process. Therefore, we pursued an alternative approach that is based on the Claisen rearrangement.

Our first attempt of O-allylation of estrone derivative **12** under standard conditions (allyl bromide, acetone, K_2CO_3, heat) failed. We assumed that H-bonding of the phenolic proton with the neighboring carboxamide group is responsible for this lack of reactivity. However, after metalation with sodium hydride in THF under refluxing conditions in the presence of an excess of allyl bromide, the targeted allyl ether **13** was isolated in 62% yield. It is noteworthy that no allylation in the α-position of the keto group took place. Upon heating, allyl ether **13** smoothly underwent Claisen rearrangement with migration of the allyl group to the only vacant *ortho*-position affording 2-(*N*,*N*-diethylcarboxamide)-4-allylestrone (**14**) in 77% yield (Scheme 5).

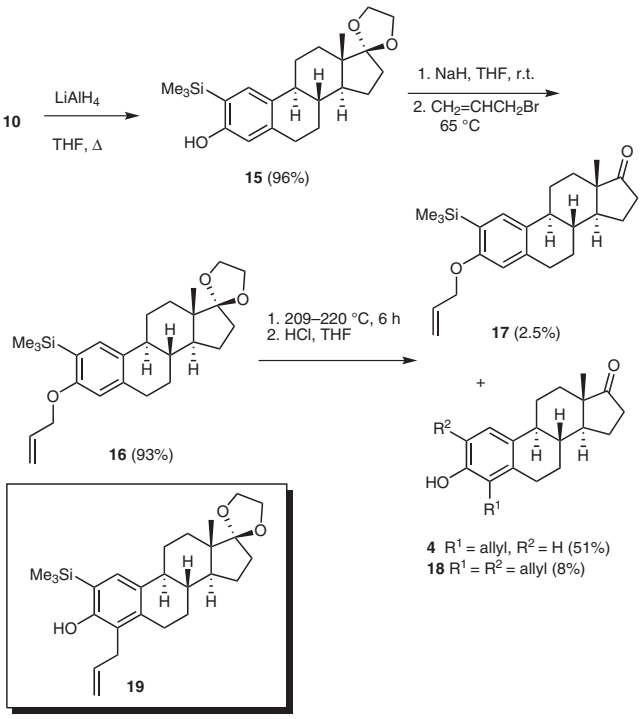


Scheme 5 Claisen rearrangement of allyl ether **13**

However, as the carbamido group at C-2 is not removable, we pursued to introduce a group at C2 that can be easily cleaved after functionalization of the 4-position. Thus, the silyl derivative **10** served as starting point (Scheme 6). First, the carbamate was removed under reductive conditions and this was followed by O-allylation to yield allyl ether **16**. With this precursor in hand, the Claisen rearrangement was performed at 209 °C raising the temperature to 220 °C after three hours.

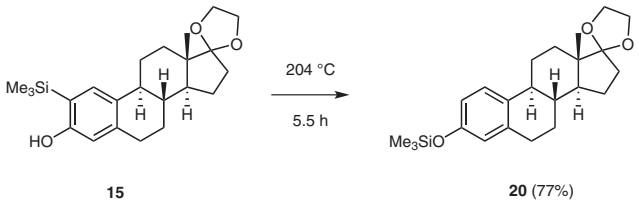
Thin layer chromatography revealed only one new spot very close to that of the starting material. However, NMR analysis of the crude product showed a mixture of products. After treatment under acidic conditions, three compounds, namely 4-allylestrone (**4**) (dominating product), **17**, and 2,4-diallylestrone (**18**) were isolated by flash chromatography on silica gel (Scheme 6).

For better understanding of these results, several additional experiments were carried out (data on reaction scheme not shown). Claisen rearrangement of silylated allyl ether **17** that still contains the keto group was performed at 204 °C and afforded the crude product revealing a few diagnostic signals (for 1-H_{arom} and 2-H_{arom} and the trimethylsilyl group) in the complex ^1H NMR spectrum.



Scheme 6 Claisen rearrangement of allyl ether **16**.

However, the phenolic hydroxyl group was not present. After acidic treatment of this crude product, pure 4-allylestrone (**4**) was isolated in 49% yield. When 2-silylated estrone ketal **15** was heated under the conditions of Claisen rearrangement (204 °C, 5.5 h), full conversion was achieved, and O-silylated estrone ketal **20** was isolated in 77% yield as a single product (Scheme 7).



Scheme 7 Thermal C → O migration of trimethylsilyl group

This thermal 1,3-migration of the trimethylsilyl group[13] can be considered as a protodesilylation[14] promoted by the acidic phenolic proton and trapping of the cleaved silyl species by the phenolate anion. O-Silylated estrone ketal **20** was prepared also directly through the silylation of estrone ketal with trimethylchlorosilane. Acidic treatment of estrone ketal **20** under the conditions used for the removal of the acetal protection (2 M HCl, THF, r.t., 2 h) gave estrone **1** in 95% isolated yield.

These findings allow us to rationalize the results described in Scheme 6. Indeed, the Claisen rearrangement of allyl ether **16** proceeded smoothly with the formation of the 4-allyl derivative **19**. Then, thermal C → O migration of the trimethylsilyl group occurs to yield the corresponding aryl silyl ether, which may react with a second *O*-allyl group in an intermolecular process to furnish the corresponding 2,4-diallyl derivative. During acidic removal of the acetal group also the aryl silyl ether group is cleaved which liberated the phenol functionality and gave the products **4**, **17**, and **18**.

In summary, directed *ortho*-lithiation of estrone carbamates followed by reaction with different electrophiles afford 2-substituted estrone derivatives in synthetically useful yields. 4-Substituted derivatives were obtained from these products after reductive cleavage of the carbamate group, O-allylation and Claisen rearrangement. These principal studies allow to specifically address functionalization of the 2- or 4-position in estrone (**1**).

NMR spectra were recorded on a Bruker Avance I 400 spectrometer at 400 MHz (^{1}H NMR) or 100 MHz (^{13}C NMR) in $CDCl_3$ using TMS as the internal standard. IR spectra were recorded on a Bruker Vektor 22 FT-IR spectrophotometer (GoldenGate ATR unit). Mass spectra were obtained at 70 eV with a type VG Autospec apparatus (Micromass). Optical rotations were measured on a PerkinElmer Polarimeter 241. Melting points were determined in open glass capillaries on an Electrothermal IA 9200 apparatus and are uncorrected. Analytical TLC was performed using precoated silica gel 60 F_{254} plates (Merck, Darmstadt), and the spots were visualized with UV light at 254 nm or with vanillin reagent. Flash column chromatography was performed on Merck silica gel 60 (230–400 mesh). Commercially available starting materials and reagents were purchased from Fluka, Acros, and Aldrich and used as received. All solvents were dried by conventional methods.

Estrone Ethylene Ketal 3-(*N*,*N*-Diethyl)carbamate 5

Estrone Ethylene Ketal: A mixture of estrone (**1**; 595 mg, 2.2 mmol), *p*-TsOH·H_2O (38 mg, 0.2 mmol), and ethylene glycol (2.78 g, 44.8 mmol) in anhyd benzene (15 mL) was stirred under refluxing conditions in a Dean–Stark device for 12 h. After cooling to r.t., the mixture was poured into H_2O (30 mL) and extracted with CH_2Cl_2 (2 × 30 mL). The combined organic extracts were washed with H_2O (30 mL) and dried (Na_2SO_4). Concentration and flash chromatography of the residue on silica gel (hexane–EtOAc, 2:1) afforded estrone ethylene ketal as a colorless solid; yield: 623 mg (2 mmol, 90%); mp 182–183 °C (Lit.[15] mp 180–181 °C); $[\alpha]_D^{25}$ +27.1 (*c* = 1.0, CH_2Cl_2) {Lit.[16] $[\alpha]_D^{25}$ +26.2 (*c* = 1.0, $CHCl_3$)}.

IR (ATR): 3297 cm^{-1} (OH).

^{1}H NMR ($CDCl_3$): δ = 0.88 (s, 3 H, CH_3), 1.22–1.64 (m, 6 H), 1.70–1.90 (m, 4 H), 1.97–2.07 (m, 1 H), 2.15–2.27 (m, 1 H), 2.28–2.34 (m, 1 H), 2.72–2.85 (m, 2 H), 3.87–3.99 (m, 4 H, OCH_2CH_2O), 4.91 (s, 1 H, OH), 6.56 (d, *J* = 2.7 Hz, 1 H_{arom}), 6.62 (dd, *J* = 8.5, 2.7 Hz, 1 H_{arom}), 7.15 (d, *J* = 8.5 Hz, 1 H_{arom}).

^{13}C NMR ($CDCl_3$): δ = 14.48, 22.48, 26.27, 27.05, 29.75, 30.86, 34.36, 39.15, 43.72, 46.30, 49.47, 64.72, 65.38, 112.76, 115.38, 119.65, 126.67, 132.88, 138.45, 153.45.

LRMS: *m*/*z* = 314 (M^+, 35%).

HRMS: *m*/*z* calcd for $C_{20}H_{26}O_3$ (M^+): 314.1882; found: 314.1888.

Carbamate ***5***: To a solution of the above estrone ethylene ketal (1.568 g, 4.99 mmol) in anhyd pyridine (20 mL) was added diethylcarbamoyl chloride (1.356 g, 10 mmol) and Et_3N (1.012 g, 10 mmol) in one portion. The mixture was stirred at 80 °C overnight and then cooled to r.t. H_2O (100 mL) was added, the mixture was stirred for 30 min, and extracted with EtOAc (100 mL). The aqueous phase was extracted with EtOAc (3 × 30 mL). The combined organic phases were washed with H_2O (40 mL), aq 1 M HCl (5 × 40 mL), brine (3 × 40 mL), and dried (Na_2SO_4). Concentration under vacuum and flash chromatography of the residue on silica gel (hexane–EtOAc, 3:1) gave carbamate **5** as a colorless solid; yield: 1.923

g (4.65 mmol, 93%); yield over two steps: 84%; mp 139–142 °C; $[\alpha]_D^{25}$ +20.8 (*c* = 1.0, CH_2Cl_2).

IR (ATR): 1713 cm^{-1} (C=O).

^1H NMR ($CDCl_3$): δ = 0.88 (s, 3 H, CH_3), 1.19 (t, *J* = 7.8 Hz, 3 H, CH_3), 1.23 (t, *J* = 7.8 Hz, 3 H, CH_3), 1.27–1.69 (m, 6 H), 1.70–1.91 (m, 4 H), 1.98–2.08 (m, 1 H), 2.20–2.38 (m, 2 H), 2.80–2.90 (m, 2 H), 3.32–3.46 (m, 4 H, CH_2NCH_2), 3.85–4.00 (m, 4 H, OCH_2CH_2O), 6.82 (d, *J* = 2.4 Hz, 1 H_{arom}), 6.87 (dd, *J* = 8.4, 2.4 Hz, 1 H_{arom}), 7.25 (d, *J* = 8.4 Hz, 1 H_{arom}).

^{13}C NMR ($CDCl_3$): δ = 13.52, 14.33, 14.42, 22.47, 26.12, 26.95, 29.64, 30.81, 34.33, 38.87, 41.93, 42.27, 43.92, 46.21, 49.49, 64.68, 65.35, 118.88, 119.51, 121.79, 126.25, 137.32, 138.06, 149.32, 154.64.

LRMS: *m*/*z* = 413 (M^+, 56%).

HRMS: *m*/*z* calcd for $C_{25}H_{35}NO_4$ (M^+): 413.2566; found: 413.2566.

Lithiation of Carbamate 5 Followed by Reaction with Electrophiles; General Procedure A

A solution of carbamate **5** (62 mg, 0.15 mmol) in THF (0.5 mL) was added via a syringe to a stirred solution of *s*-BuLi (127 μL of 1.3 M solution in cyclohexane, 0.165 mmol, 1.1 equiv) and TMEDA (25 μL, 0.165 mmol, 1.1 equiv) in THF (1 mL) at –78 °C under N_2 atmosphere. The resulting greenish solution was stirred at –78 °C for 1 h, treated dropwise via a syringe with a solution of an electrophile (0.18 mmol, 1.2 equiv) in THF (0.5 mL), stirred at this temperature for 1 h, and then the reaction mixture was allowed to warm to r.t. The mixture was hydrolyzed with sat. aq NH_4Cl (2 mL) and extracted with EtOAc (2 × 5 mL). The combined organic extracts were washed with brine (5 mL) and dried (Na_2SO_4). Concentration under reduced pressure und flash chromatography of the residue on the silica gel using hexane–EtOAc as an eluent afforded the products.

Cleavage of Ethylenedioxyketal Protecting Group; General Procedure B

A solution of estrone ketal derivative (0.5 mmol) in THF (6 mL) was treated with aq 2 M HCl (2.5 mL). The mixture was shaken at r.t. for 2.5 h, then sat. aq $NaHCO_3$ (ca. 5 mL) was added dropwise until pH ca. 8. The mixture was extracted with EtOAc (3 × 10 mL); the combined organic extracts were washed with H_2O (10 mL) and brine (10 mL), and dried (Na_2SO_4). Concentration under vacuum and flash chromatography of the residue on silica gel afforded the estrone derivative with free 17-keto group.

2-Methylestrone Ketal Carbamate 6

The title compound was obtained as a colorless solid as the major product from **5** according to general procedure A using MeI as an electrophile; yield: 49 mg (76%); mp 145–148 °C.

IR (ATR): 1716 cm^{-1} (C=O).

^1H NMR ($CDCl_3$): δ = 0.87 (s, 3 H, CH_3), 1.13–1.28 (m, 6 H, 2 × CH_3), 1.29–1.67 (m, 6 H), 1.70–1.90 (m, 4 H), 2.00–2.10 (m, 1 H), 2.16 (s, 3 H, 2-CH_3), 2.20–2.38 (m, 2 H), 2.77–2.87 (m, 2 H), 3.34–3.47 (m, 4 H, CH_2NCH_2), 3.86–3.98 (m, 4 H, OCH_2CH_2O), 6.77 (s, 1 H_{arom}, H-4), 7.10 (s, 1 H_{arom}, H-1).

^{13}C NMR ($CDCl_3$): δ = 13.59, 14.42, 14.46, 16.26, 22.51, 26.18, 27.07, 29.25, 30.86, 34.36, 38.95, 41.96, 42.30, 43.92, 46.24, 49.55, 64.71, 65.38, 119.58, 122.17, 127.19, 128.00, 135.52, 137.48, 147.83, 154.40.

LRMS: *m*/*z* = 427 (M^+, 67%).

HRMS: *m*/*z* calcd for $C_{26}H_{37}NO_4$ (M^+): 427.2723; found: 427.2723.

Product **6** could not be separated chromatographically from the minor product, the 4-methylated carbamate **7**. The latter was identified based on diagnostic ^1H NMR signals of aromatic protons: δ = 6.86 (d, *J* = 8.6 Hz, 1 H_{arom}, H-2) and 7.16 (d, *J* = 8.6 Hz, 1 H_{arom}, H-1). All other signals overlapped with signals of the major product **6**. The estimated yield of compound **7** was 7%; the total yield of *ortho*-methylated carbamates **6** and **7** was 83%.

2-Methylestrone Carbamate 8

The title compound was obtained after deprotection of compound **6** according to general procedure B as a colorless solid; yield: 47 mg (97%); mp 169–172 °C.

IR (ATR): 1732, 1704 cm^{-1} (C=O).

^1H NMR ($CDCl_3$): δ = 0.90 (s, 3 H, CH_3), 1.20 (t, *J* = 7.0 Hz, 3 H, CH_2CH_3), 1.26 (t, *J* = 7.0 Hz, 3 H, CH_2CH_3), 1.38–1.68 (m, 6 H), 1.89–2.18 (m, 4 H), 2.16 (s, 3 H, 2-CH_3), 2.19–2.29 (m, 1 H), 2.35–2.42 (m, 1 H), 2.43–2.53 (m, 1 H), 2.86 (dd, *J* = 8.5, 3.8 Hz, 2 H, CH_2C=O), 3.39 (q, *J* = 7.0 Hz, 2 H, NCH_2CH_3), 3.44 (q, *J* = 7.0 Hz, 2 H, NCH_2CH_3), 6.79 (s, 1 H_{arom}, H-4), 7.11 (s, 1 H_{arom}, H-1).

^{13}C NMR ($CDCl_3$): δ = 13.58, 13.98, 14.40, 16.26, 21.74, 25.97, 26.63, 29.10, 31.73, 36.02, 38.28, 41.97, 42.33, 44.26, 48.12, 50.61, 122.27, 127.46, 128.02, 135.22, 136.78, 148.04, 154.34, 221.14.

LRMS: *m*/*z* = 383 (M^+, 59%).

HRMS: *m*/*z* calcd for $C_{24}H_{33}NO_3$ (M^+): 383.2460; found: 383.2464.

According to the ^1H NMR spectrum, compound **8** contained about 8% of the 4-methyl isomer **9**, which was not chromatographically separable from the major isomer **8**.

2-Trimethylsilylestrone Ketal Carbamate 10

The title compound was obtained as a colorless foam from **5** according to general procedure A using Me_3SiCl as an electrophile; yield: 120 mg (82%); mp 137–138 °C; $[\alpha]_D^{25}$ +23.5 (*c* = 1.0, CH_2Cl_2).

IR (ATR): 1714 cm^{-1} (C=O).

^1H NMR ($CDCl_3$): δ = 0.26 [s, 9 H, $Si(CH_3)_3$], 0.88 (s, 3 H, CH_3), 1.19 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3), 1.24 (t, *J* = 7.0 Hz, CH_2CH_3), 1.31–1.66 (m, 6 H), 1.71–1.90 (m, 4 H), 1.98–2.08 (m, 1 H), 2.22–2.40 (m, 2 H), 2.85 (dd, *J* = 8.3, 3.9 Hz, 2 H), 3.39 (q, *J* = 7.2 Hz, 2 H, NCH_2CH_3), 3.46 (q, *J* = 7.0 Hz, 2 H, NCH_2CH_3), 3.87–3.99 (m, 4 H, OCH_2CH_2O), 6.77 (s, 1 H_{arom}, H-4), 7.36 (s, 1 H_{arom}, H-1).

^{13}C NMR ($CDCl_3$): δ = –0.63, 13.46, 14.32, 14.46, 22.51, 26.10, 26.95, 29.68, 30.89, 34.36, 39.00, 41.65, 42.01, 44.05, 46.27, 49.56, 64.73, 65.40, 119.59, 122.28, 128.01, 131.98, 136.88, 139.78, 154.22, 154.77.

LRMS: *m*/*z* = 485 (M^+, 12%).

HRMS: *m*/*z* calcd for $C_{28}H_{43}NO_4Si$ (M^+): 485.2961; found: 485.2963.

2-Carbamoylated Estrone Carbamate 11

The title compound was prepared from **5** according to general procedure A using diethylcarbamoyl chloride as an electrophile.

Intermediate Ethylene Ketal: The intermediate ethylene ketal protected derivative was obtained as a colorless, glassy solid that softens at 70–80 °C; yield: 60 mg (78%); $[\alpha]_D^{22}$ +26.2 (*c* = 1.0, CH_2Cl_2).

IR (ATR): 1634, 1715 cm^{-1} (C=O).

^1H NMR ($CDCl_3$): δ = 0.87 (s, 3 H, CH_3), 1.04 (t, *J* = 7.1 Hz, 3 H, CH_3), 1.15 (t, *J* = 7.1 Hz, 3 H, CH_3), 1.19 (t, *J* = 7.0 Hz, 6 H, 2 × CH_3), 1.28–1.92 (m, 10 H), 1.97–2.07 (m, 1 H), 2.20–2.32 (m, 2 H), 2.80–2.88 (m, 2 H), 3.08–3.41 (m, 8 H, 4 × NCH_2), 3.83–3.97 (m, 4 H, OCH_2CH_2O), 6.90 (s, 1 H_{arom}, H-4), 7.14 (s, 1 H_{arom}, H-1).

^{13}C NMR ($CDCl_3$): δ = 12.86, 13.51, 14.12, 14.26, 14.44, 22.48, 26.14, 26.85, 29.53, 30.76, 34.34, 38.76, 38.78, 42.10, 42.28, 42.95, 43.83, 46.20, 49.47, 65.40, 67.71, 119.49, 123.11, 123.81, 127.82, 137.62, 138.86, 145.11, 153.97, 168.46.

LRMS: *m*/*z* = 512 (M^+, 67%).

HRMS: *m*/*z* calcd for $C_{30}H_{44}N_2O_5$ (M^+): 512.3250; found: 512.3251.

*Carbamate **11***: Deprotection of the above protected carbamate according to general procedure B gave the carbamate **11** as a colorless solid; yield: 47 mg (86%); mp 147–150 °C; $[\alpha]_D^{20}$ +78.7 (*c* = 1.1, CH_2Cl_2).

IR (ATR): 1732, 1704, 1633 cm^{-1} (C=O).

^1H NMR ($CDCl_3$): δ = 0.90 (s, 3 H, CH_3), 1.05 (t, *J* = 7.0 Hz, 3 H, CH_2CH_3), 1.16 (t, *J* = 7.0 Hz, 3 H, CH_2CH_3), 1.19 (t, *J* = 7.2 Hz, 6 H, 2 × CH_2CH_3), 1.38–1.65 (m, 6 H), 1.93–2.16 (m, 4 H), 2.20–2.40 (m, 2 H), 2.43–2.57 (m, 1 H), 2.91 (dd, *J* = 8.5, 3.8 Hz, CH_2C=O), 3.10–3.50 (m, 4 H, 2 × NCH_2), 3.35 (q, *J* = 7.0 Hz, 2 H, NCH_2CH_3), 3.37 (q, *J* = 7.0 Hz, 2 H, NCH_2CH_3), 6.93 (s, 1 H_{arom}, H-4), 7.14 (s, 1 H_{arom}, H-1).

^{13}C NMR ($CDCl_3$): δ = 12.88, 13.51, 13.96, 14.17, 14.26, 21.71, 25.91, 26.41, 29.38, 31.63, 35.98, 38.09, 38.84, 42.12, 42.31, 42.98, 44.15, 48.05, 50.55, 123.25, 123.83, 128.09, 136.93, 138.55, 145.35, 153.93, 168.26, 220.85.

LRMS: *m*/*z* = 468 (M^+, 20%).

HRMS: *m*/*z* calcd for $C_{28}H_{40}N_2O_4$ (M^+): 468.2988; found: 468.2978.

2-Carbamoylestrone (12)

Intermediate Ethylene Ketal Protected Derivative: Standard metalation of carbamate **5** (62 mg, 0.15 mmol) was conducted, followed by slow (2 h) warming of the reaction mixture to r.t. in the absence of any electrophile. After standard workup of the reaction mixture, the intermediate ethylene ketal protected derivative was isolated as a colorless foam; yield: 38 mg (61%); mp 110–113 °C; $[\alpha]_D^{20}$ +28.3 (*c* = 1.0, CH_2Cl_2).

IR (ATR): ~3120 (O–H, br), 1582 cm^{-1} (C=O).

^1H NMR ($CDCl_3$): δ = 0.89 (s, 3 H, CH_3), 1.28 (t, *J* = 7.1 Hz, 6 H, 2 × CH_2CH_3), 1.23–1.68 (m, 6 H), 1.72–1.90 (m, 4 H), 1.98–2.05 (m, 1 H), 2.15–2.28 (m, 2 H), 2.75–2.86 (m, 2 H), 3.48 (q, *J* = 7.1 Hz, 2 H, NCH_2CH_3), 3.55 (q, *J* = 7.1 Hz, 2 H, NCH_2CH_3), 3.83–3.99 (m, 4 H, OCH_2CH_2O), 6.70 (s, 1 H_{arom}, H-4), 7.18 (s, 1 H_{arom}, H-1), 9.66 (s, 1 H, OH).

^{13}C NMR ($CDCl_3$): δ = 13.62, 14.47, 22.48, 26.34, 26.93, 29.71, 30.77, 34.33, 39.05, 42.36, 43.51, 46.19, 49.44, 64.71, 65.40, 115.52, 117.52, 119.49, 124.38, 130.78, 142.11, 156.66, 172.06.

LRMS: *m*/*z* = 413 (M^+, 100%).

HRMS: *m*/*z* calcd for $C_{25}H_{35}NO_4$ (M^+): 413.2566; found: 413.2567.

2-Carbamoylestrone (12): Deprotection of the above intermediate ketal derivative (37 mg, 0.089 mmol) according to general procedure B gave 2-carbamoylestrone (**12**) as a colorless solid; yield: 30 mg (93%); mp 160–162 °C; $[\alpha]_D^{20}$ +129.5 (*c* = 1.5, CH_2Cl_2).

IR (ATR): ~3120 (O–H, br), 1733 (C=O), 1574 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.92 (s, 3 H, CH_3), 1.29 (t, *J* = 7.0 Hz, 6 H, 2 × CH_2CH_3), 1.35–1.65 (m, 5 H), 1.93–2.34 (m, 7 H), 2.45–2.57 (m, 1 H), 2.88 (dd, *J* = 8.5, 4.2 Hz, 2 H, CH_2C=O), 3.50 (q, *J* = 7.0 Hz, 2 H, NCH_2CH_3), 3.53 (q, *J* = 7.0 Hz, 2 H, NCH_2CH_3), 6.73 (s, 1 H_{arom}, H-4), 7.18 (s, 1 H_{arom}, H-1), 9.65 (s, 1 H, OH).

^{13}C NMR ($CDCl_3$): δ = 13.67, 13.98, 21.72, 26.10, 26.49, 29.57, 31.67, 35.99, 38.37, 42.36, 42.41, 43.86, 48.05, 50.53, 115.78, 117.65, 124.38, 130.11, 141.76, 156.86, 171.94, 220.83.

LRMS: *m*/*z* = 369 (M^+, 90%).

HRMS: *m*/*z* calcd for $C_{23}H_{31}NO_3$ (M^+): 369.2304; found: 369.2301.

Allyl Ether 13

To a solution of **12** (174 mg, 0.471 mmol) in anhyd THF (3 mL) was added NaH (24 mg, 1 mmol, 80% suspension in mineral oil). After stirring for 1 h at r.t., allyl bromide (121 mg, 1 mmol) was added, and the mixture was stirred at 70 °C overnight. The mixture was hydrolyzed with H_2O (3 mL), then aq 1 M HCl was added dropwise until pH ~4, and the mixture was extracted with EtOAc (10 mL). The aqueous layer was extracted with EtOAc (2 × 5 mL), the combined organic phases were washed with H_2O (5 mL), brine (5 mL), and dried (Na_2SO_4). Concentration under vacuum and flash chromatography of the residue on silica gel (hexane–EtOAc, 1:1) afforded allyl ether **13** as a colorless solid; yield: 120 mg (0.293 mmol, 62%); mp 176–177 °C; $[\alpha]_D^{20}$ +118.6 (*c* = 1.03, CH_2Cl_2).

IR (ATR): 1733, 1626 cm^{-1} (C=O).

^1H NMR ($CDCl_3$): δ = 0.90 (s, 3 H, CH_3), 1.03 (t, *J* = 7.1 Hz, 3 H, NCH_2CH_3), 1.23 (t, *J* = 7.1 Hz, 3 H, NCH_2CH_3), 1.35–1.70 (m, 6 H), 1.90–2.60 (m, 7 H), 2.88 (dd, *J* = 7.8, 3.4 Hz, 2 H, CH_2C=O), 3.18 (q, *J* = 7.1 Hz, 2 H, NCH_2CH_3), 3.30–3.80 (2 br s, 2 H, NCH_2CH_3), 4.50 (ddd, *J* = 4.1, 1.6, 1.6 Hz, 2 H, OCH_2CH=CH_2), 5.22 (ddt, *J* = 10.4, 1.6, 1.6 Hz, 1 H_{olef}), 5.36 (ddt, *J* = 17.3, 1.6, 1.6 Hz, 1 H_{olef}), 5.99 (ddt, *J* = 17.3, 10.4, 5.1 Hz, 1 H_{olef}), 6.59 (s, 1 H_{arom}, H-4), 7.11 (s, 1 H_{arom}, H-1).

^{13}C NMR ($CDCl_3$): δ = 13.03, 13.99, 14.23, 21.72, 26.62, 29.86, 31.67, 35,99, 38.37, 38.89, 42.93, 44.03, 48.12, 50.54, 69.34, 112.92, 117.08, 125.29, 132.65, 133.35, 138.33, 152.28, 169.16, 220.87.

LRMS: *m*/*z* = 409 (M^+, 70%).

HRMS: *m*/*z* calcd for $C_{26}H_{35}NO_3$ (M^+): 409.2617; found: 409.2614.

2-(*N*,*N*-Diethylcarboxamide)-4-allylestrone (14)

Allyl ether **13** (98 mg, 0.239 mmol) was heated at 205 °C under N_2 atmosphere for 2.5 h. Purification by flash chromatography on silica gel (hexane–EtOAc, 2:1) afforded the title compound **14** as a colorless foam; yield: 75 mg (0.183 mmol, 77%); mp 46–52 °C ('caramelization' in the form of transparent glassy drops, no meniscus); $[\alpha]_D^{20}$ +108.0 (*c* = 1.0, CH_2Cl_2).

IR (ATR): 3074 (O–H, br), 1737, 1624 (C=O), 1581 cm^{-1} (C=C).

^1H NMR ($CDCl_3$): δ = 0.91 (s, 3 H, CH_3), 1.29 (t, *J* = 7.1 Hz, 6 H, 2 × NCH_2CH_3), 1.32–1.58 (m, 5 H), 1.90–2.34 (m, 7 H), 2.41–2.51 (m, 1 H), 2.66–2.78 (m, 1 H), 2.89–2.98 (m, 1 H), 3.38–3.48 (m 2 H, $ArCH_2CH$=), 3.52 (q, *J* = 7.1 Hz, 4 H, 2 × NCH_2CH_3), 4.97 (ddt, *J* = 17.3, 1.7, 1.7 Hz, 1 H_{olef}), 5.00 (ddt, *J* = 10.2, 1.5, 1.4 Hz, 1 H_{olef}), 5.94 (ddt, *J* = 17.3, 10.2, 6.1 Hz, 1 H_{olef}), 7.12 (s, 1 H_{arom}, H-1), 9.87 (s, 1 H, OH).

^{13}C NMR ($CDCl_3$): δ = 13.65, 13.94, 21.69, 26.32, 26.67, 26.74, 30.12, 31.70, 36.02, 37.71, 42.37, 44.19, 47.97, 50.57, 114.82, 115.28, 122.36, 126.11, 129.97, 135.85, 139.93, 154.79, 172.45, 220.93.

LRMS: *m*/*z* = 409 (M^+, 100%).

HRMS: *m*/*z* calcd for $C_{26}H_{35}NO_3$ (M^+): 409.2617; found: 409.2614.

2-Trimethylsilylestrone Ketal 15

A solution of 2-trimethylsilyl carbamate **10** (595 mg, 1.225 mmol) in anhyd THF (5 mL) was added at 0 °C to a stirred suspension of $LiAlH_4$ (232 mg, 6.125 mmol) in anhyd THF (7 mL) under N_2. After stirring under refluxing conditions for 22 h, the mixture was cooled to r.t. and treated with H_2O (232 μL), 15% aq NaOH (232 μL), and H_2O (696 μL). After stirring for 10 min, the precipitate formed was filtered off and washed on the filter with THF (5 mL) and EtOAc (4 × 5 mL). The combined organic phases were dried (Na_2SO_4). Concentration under vacuum and flash chromatography of the residue on silica gel (hexane–EtOAc, 3.5:1) afforded 2-trimethylsilyl estrone ketal **15** as a colorless solid; yield: 457 mg (1.182 mmol, 96%); mp 101–103 °C; $[\alpha]_D^{20}$ +33.3 (*c* = 1.0, CH_2Cl_2).

IR (ATR): 3416 cm^{-1} (O–H).

^1H NMR ($CDCl_3$): δ = 0.30 [s, 9 H, $Si(CH_3)_3$], 0.88 (s, 3 H, CH_3), 1.23–1.67 (m, 6 H), 1.70–1.90 (m, 4 H), 1.97–2.07 (m, 1 H), 2.15–2.27 (m, 1 H), 2.30–2.40 (m, 1 H), 2.72–2.87 (m, 2 H), 3.87–3.99 (m, 4 H, OCH_2CH_2O), 4.67(s, 1 H, OH), 6.42 (s, 1 H_{arom}, H-4), 7.29 (s, 1 H_{arom}, H-1).

^{13}C NMR ($CDCl_3$): δ = –0.68, 14.48, 22.52, 26.28, 27.03, 29.74, 30.91, 34.38, 39.33, 43.84, 46.33, 49.50, 64.74, 65.40, 114.70, 119.62, 122.33, 132.38, 132.41, 139.95, 158.37.

LRMS: *m*/*z* = 386 (M^+, 35%).

HRMS: *m*/*z* calcd for $C_{23}H_{34}O_3Si$ (M^+): 386.2277; found 386.2280.

Allyl Ether 16

To a solution of 2-trimehylsilylestrone ketal **15** (435 mg, 1.125 mmol) in anhyd THF (5 mL) was added NaH (54 mg, 2.25 mmol, 80% suspension in mineral oil). After stirring for 1 h at r.t., allyl bromide (272 mg, 2.25 mmol) was added, and the mixture was stirred at 60 °C overnight. The mixture was hydrolyzed with sat. aq NH_4Cl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine (25 mL) and dried (Na_2SO_4). Concentration under vacuum and flash chromatography of the residue on silica gel (hexane–EtOAc, 3.5:1) afforded allyl ether **16** as a colorless adhesive foam that softens at 100–105 °C; yield: 448 mg (1.05 mmol, 93%); $[\alpha]_D^{25}$ +25.9 (*c* = 1.0, CH_2Cl_2).

IR (ATR): 1596 cm^{-1} (C=C).

^1H NMR ($CDCl_3$): δ = 0.27 [s, 9 H, $Si(CH_3)_3$], 0.88 (s, 3 H, CH_3), 1.25–1.70 (m, 6 H), 1.70–1.90 (m, 4 H), 1.95–2.08 (m, 1 H), 2.20–2.28 (m, 1 H), 2.30–2.40 (m, 1 H), 2.77–2.90 (m, 2 H), 3.86–3.98 (m, 4 H, OCH_2CH_2O), 4.50 (ddd, *J* = 5.0, 1.4, 1.4 Hz, 2 H, $OCH_2CH{=}CH_2$), 5.25 (ddt, *J* = 10.3, 1.4, 1.4 Hz, 1 H_{olef}), 5.40 (ddt, *J* = 17.2, 1.4, 1.4 Hz, 1 H_{olef}), 6.06 (ddt, *J* = 17.2, 10.3, 5.0 Hz, 1 H_{olef}), 6.54 (s, 1 H_{arom}, H-4), 7.32 (s, 1 H_{arom}, H-1).

^{13}C NMR ($CDCl_3$): δ = –0.64, 14.49, 22.51, 26.25, 27.12, 30.28, 30.94, 34.39, 39.35, 43.90, 46.35, 49.51, 64.74, 65.40, 68.77, 111.01, 116.98, 119.61, 125.09, 132.26, 132.27, 133.84, 139.64, 161.41.

LRMS: *m*/*z* = 426 (M^+, 47%).

HRMS: *m*/*z* calcd for $C_{26}H_{38}O_3Si$ (M^+): 426.2590; found: 426.2589.

Claisen Rearrangement of Allyl Ether 16

Allyl ether **16** (416 mg, 0.975 mmol) was heated at 209 °C for 3 h and then at 220 °C for 3 h under N_2. TLC analyses of the crude product revealed only one spot, and the corresponding fraction was isolated after flash chromatography on silica gel (hexane–EtOAc, 95:5) as an adhesive colorless solid (297 mg). According to ^1H NMR analysis, this fraction contained a mixture of compounds. A portion of this fraction (280 mg) was dissolved in THF (7 mL), aq 2 M HCl (2.6 mL) was added, and the mixture was shaken at r.t. for 3 h. After workup according to general procedure B, flash chromatography on silica gel (hexane–EtOAc, 3:1) afforded compounds **17** (9 mg, 0.023 mmol, 2.5%), 4-allylestrone (**4**; 153 mg, 0.493 mmol, 51%), and 2,4-diallylestrone (**18**; 27 mg, 0.077 mmol, 8%).

4-Allylestrone (4)

Colorless solid; mp 129–131 °C (Lit.[9c] mp 131–132 °C); $[\alpha]_D^{25}$ +118.1 (*c* = 1.0, CH_2Cl_2) {Lit.[9b] $[\alpha]_D^{25}$ +115.3 (*c* = 1.0, 1,4-dioxane)}.

IR (ATR): 3351 (O–H), 1720 (C=O), 1636 cm^{-1} (C=C).

^1H NMR ($CDCl_3$): δ = 0.90 (s, 3 H, CH_3), 1.20–1.70 (m, 6 H), 1.90–2.50 (m, 7 H), 2.70–2.95 (m, 2 H), 3.42 (ddd, *J* = 5.8, 1.5, 1.5 Hz, 2 H, $ArCH_2$), 4.86 (s, 1 H, OH), 5.03 (ddt, *J* = 17.1, 1.7, 1.7 Hz, 1 H_{olef}), 5.06 (ddt, *J* = 10.6, 1.6, 1.6 Hz, 1 H_{olef}), 5.96 (ddt, *J* = 17.1, 10.6, 5.8 Hz, 1 H_{olef}), 6.67 (d, *J* = 8.4 Hz, 1 H_{arom}, H-4), 7.10 (d, *J* = 8.4 Hz, 1 H_{arom}, H-1).

^{13}C NMR ($CDCl_3$): δ = 13.27, 21.71, 26.32, 26.84, 26.86, 30.28, 31.75, 36.06, 37.73, 44.51, 48.09, 50.58, 113.24, 115.49, 123.45, 124.55, 132.73, 135.69, 136.33, 152.14, 221.30.

LRMS: *m*/*z* = 310 (M^+, 100%).

HRMS: *m*/*z* calcd for $C_{21}H_{26}O_2$ (M^+): 310.1933; found: 310.1935.

2,4-Diallylestrone (18)

White solid; mp 117–119 °C (Lit.[9c] mp 121.5–122 °C); $[\alpha]_D^{20}$ +107.0 (*c* = 0.5, CH_2Cl_2).

IR (ATR): 3407 (OH), 1721 (C=O), 1636 cm^{-1} (C=C).

^1H NMR ($CDCl_3$): δ = 0.90 (s, 3 H, CH_3), 1.20–1.70 (m, 6 H), 1.90–2.54 (m, 7 H), 2.68–2.94 (m, 2 H), 3.35–3.47 (m, 4 H, 2 × $ArCH_2$), 4.95–5.07 (m, 3 H, 2 × H_{olef} and OH), 5.13–5.23 (m, 2 H, 2 × H_{olef}), 5.90–6.07 (m, 2 H, 2 × H_{olef}), 6.98 (s, 1 H_{arom}, H-1).

^{13}C NMR ($CDCl_3$): δ = 13.98, 21.71, 26.37, 26.79, 26.90, 30.50, 31.77, 36.01, 36.06, 37.82, 44.48, 48.08, 50.60, 115.42, 116.69, 122.68,124.01, 125.54, 132.42, 134.51, 135.88, 136.92, 150.91, 221,24.

LRMS: *m*/*z* 350 (M^+, 100%).

HRMS: *m*/*z* calcd for $C_{24}H_{30}O_2$ (M^+): 350.2246; found: 350.2247.

2-Trimethylsilylestrone Allyl Ether 17

2-Trimethylsilylestrone: To a solution of 2-trimethylsilylestrone ketal **15** (250 mg, 0.65 mmol) in THF (7 mL) was added aq 2 M HCl (2 mL), and the mixture was shaken at r.t. for 2 h. After workup according to general procedure B and flash chromatography of the crude product on silica gel (hexane–EtOAc, 3:1), 2-trimethylsilylestrone was obtained as a colorless solid (186 mg, 0.543 mmol, 84%); mp 207–209 °C; $[\alpha]_D^{20}$ +147.8 (*c* = 1.0, CH_2Cl_2).

IR (ATR): 3275 (O–H), 1717 cm^{-1} (C=O).

^1H NMR ($CDCl_3$): δ = 0.30 [s, 9 H, $Si(CH_3)_3$], 0.91 (s, 3 H, CH_3), 1.35–1.65 (m, 6 H), 1.94–2.20 (m, 4 H), 2.20–2.30 (m, 1 H), 2.40–2.55 (m, 2 H), 2.82–2.92 (m, 2 H), 4.84 (s, 1 H, OH), 6.45 (s, 1 H_{arom}, H-4), 7.29 (s, 1 H_{arom}, H-1).

^{13}C NMR ($CDCl_3$): δ = –0.70, 14.00, 21.74, 26.06, 26.60, 29.59, 31.74, 36.04, 38.64, 44.20, 48.19, 50.54, 114.73, 122.67, 131.67, 132.37, 139.60, 158.60, 221.36.

LRMS: *m*/*z* = 342 (M^+, 100%).

HRMS: *m*/*z* calcd for $C_{21}H_{30}O_2Si$ (M^+): 342.2015; found: 342.2013.

*2-Trimethylsilylestrone Allyl Ether **17***: NaH (24 mg, 1 mmol, 80% suspension in mineral oil) was added to a solution of 2-trimethylsilylestrone (173 mg, 0.505 mmol) in anhyd THF (3 mL). After stirring for 1 h at r.t., allyl bromide (122 mg, 1 mmol) was added, and the mixture was stirred at 65 °C overnight. After cooling to r.t., the mixture was hydrolyzed with sat. aq NH_4Cl (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine (15 mL) and dried (Na_2SO_4). Concentration under vacuum and flash chromatography of the residue on silica gel (hexane–EtOAc, 3:1) afforded **17** as a colorless solid (142 mg, 0.371 mmol, 73%); mp 145–147 °C; $[\alpha]_D^{20}$ +125.4 (*c* = 1.0, CH_2Cl_2).

IR (ATR): 1736 (C=O), 1595 cm^{-1} (C=C).

^1H NMR ($CDCl_3$): δ = 0.27 [s, 9 H, $Si(CH_3)_3$], 0.91 (s, 3 H, CH_3), 1.20–1.70 (m, 6 H), 1.92–2.34 (m, 5 H), 2.40–2.60 (m, 2 H), 2.84–2.97 (m, 2 H),), 4.51 (ddd, *J* = 5.1, 1.4, 1.4 Hz, 2 H, $OCH_2CH{=}CH_2$), 5.25 (ddt, *J* = 10.4, 1.4, 1.4 Hz, 1 H_{olef}), 5.40 (ddt, *J* = 17.1, 1.4, 1.4 Hz, 1 H_{olef}), 6.06 (ddt, *J* = 17.1, 10.4, 5.1 Hz, 1 H_{olef}), 6.55 (s, 1 H_{arom}, H-4), 7.32 (s, 1 H_{arom}, H-1).

^{13}C NMR ($CDCl_3$): δ = –0.66, 14.02, 21.74, 26.04, 26.69, 30.14, 31.78, 36.04, 38.67, 44.26, 48.20, 50.55, 68.79, 111.01, 117.07, 125.42, 131.60, 132.26, 133.75, 139.34, 161.56, 221.20.

LRMS: *m*/*z* = 382 (M^+, 100%).

HRMS: *m*/*z* calcd for $C_{24}H_{34}O_2Si$ (M^+): 382.2328; found: 382.2326.

Thermal Transformation of 2-Trimethylsilylestrone Allyl Ether 17

2-Trimethylsilylestrone allyl ether **17** (111 mg, 0.290 mmol) was heated at 204 °C for 6 h under N_2. The crude mixture was taken up in CCl_4 (1 mL), trifluoroacetic acid (1 mL) was added, and the mixture was shaken at r.t. overnight. Dilution with EtOAc (10 mL), washing with sat. aq $NaHCO_3$ (5 mL) and brine (5 mL), drying (Na_2SO_4), concentration under vacuum and flash chromatography of the residue on silica gel (hexane–EtOAc, 3:1) afforded 4-al-

lylestrone (**4**; 44 mg, 0.142 mmol, 49%). For characterization, see above.

Thermal Rearrangement of 2-Trimethylsilylestrone Ketal 15

2-Trimethylsilylestrone ketal **15** (72 mg, 0.186 mmol) was heated at 204 °C for 5.5 h under N_2. Flash chromatography of the crude product on silica gel (hexane–EtOAc, 95:5) afforded *O*-trimethylsilylestrone ketal **20** as a colorless solid (55 mg, 0.142 mmol, 77%); mp 93–96 °C. For characterization, see below.

***O*-Trimethylsilylestrone Ketal 20**

Esterone Ethylene Ketal: Amberlyst 15 (dry, 100 mg) was added to a solution of estrone (**1**; 270 mg, 1 mmol), ethylene glycol (1.241 g, 20 mmol), and trimethyl orthoformate (1.061 g, 10 mmol) in anhyd toluene (17 mL) and anhyd MeCN (17 mL), and the mixture was stirred overnight at r.t. Filtration, concentration of the filtrate under vacuum, and flash chromatography of the residue on silica gel (hexane–EtOAc, 3:1) afforded estrone ethylene ketal as a colorless solid; yield: 311 mg (0.989 mmol, 99%); mp 181–182 °C. For characterization, see above.

*O-Trimethylsilylestrone Ketal **20***: A solution of Me_3SiCl (130 mg, 1.2 mmol) in anhyd CH_2Cl_2 (1 mL) was added to a solution of estrone ethylene ketal (317 mg, 1.01 mmol), imidazole (89 mg, 1.3 mmol) and *N*,*N*-dimethylaminopyridine (61 mg, 0.5 mmol) in anhyd CH_2Cl_2 (10 mL). The mixture was stirred for 3 h at r.t. and then concentrated under vacuum to give a white slurry, which was suspended in the eluent (hexane–EtOAc, 9:1) and loaded on the top of the chromatographic column filled with silica gel. Flash chromatography (hexane–EtOAc, 9:1) afforded *O*-trimethylsilyl estrone ketal **20** as a colorless solid; yield: 360 mg (0.931 mmol, 92%); mp 93–96 °C; $[\alpha]_D^{23}$ +25.0 (*c* = 1.0, CH_2Cl_2).

^{1}H NMR ($CDCl_3$): δ = 0.25 [s, 9 H, $Si(CH_3)_3$], 0.88 (s, 3 H, CH_3), 1.25–1.67 (m, 6 H), 1.70–1.90 (m, 4 H), 1.97–2.08 (m, 1 H), 2.18–2.35 (m, 2 H), 2.73–2.89 (m, 2 H), 3.84–4.00 (m, 4 H, OCH_2CH_2O), 6.56 (d, *J* = 2.4 Hz, 1 H_{arom}, H-4), 6.62 (dd, *J* = 8.4, 2.4 Hz, 1 H_{arom}, H-2), 7.13 (d, *J* = 8.4 Hz, 1 H_{arom}, H-1).

^{13}C NMR ($CDCl_3$): δ = 0.42, 14.50, 22.51, 26.20, 27.14, 29.78, 30.91, 34.39, 39.12, 43.82, 46.32, 49.55, 64.73, 65.39, 117.29, 119.61, 120.10, 126.33, 133.51, 138.11, 152.96.

LRMS: *m*/*z* = 386 (M^+, 57%).

HRMS: *m*/*z* calcd for $C_{23}H_{34}O_3Si$ (M^+): 386.2277; found: 386.2279.

Acidic Treatment of *O*-Trimethylsilylestrone Ketal 20

Aq 2 M HCl (0.75 mL) was added to a solution of *O*-trimethylsilylestrone ketal **20** (91 mg, 0.235 mmol) in THF (2.5 mL). After shaking for 2 h, the mixture was worked up according to general procedure B. Flash chromatography of the crude product on silica gel (hexane–EtOAc, 2:1) afforded estrone (**1**) as a colorless solid; yield: 60 mg (0.222 mmol, 95%); mp 254–256 °C (Lit.[17] mp 255–256 °C); $[\alpha]_D^{22}$ +162.8 (*c* = 1.0, 1,4-dioxane) {Lit.[18] $[\alpha]_D^{20}$ +163.6 (*c* = 0.486, 1,4-dioxane)}.

IR (ATR): 3340 (O–H) 1716 cm^{-1} (C=O).

^{1}H NMR ($CDCl_3$): δ = 0.91 (s, 3 H, CH_3), 1.30–1.65 (m, 6 H), 1.94–2.19 (m, 4 H), 2.20–2.29 (m, 1 H), 2.37–2.40 (m, 1 H), 2.47–2.54 (m, 1 H), 2.85–2.90 (m, 2 H), 4.86 (s, 1 H, OH), 6.58 (d, *J* = 2.7 Hz, 1 H_{arom}, H-4), 6.64 (dd, *J* = 8.4, 2.7 Hz, 1 H_{arom}, H-2), 7.15 (d, *J* = 8.4 Hz, 1 H_{arom}, H-1).

^{13}C NMR ($CDCl_3$): δ = 13.99, 21.73, 26.06, 26.63, 29.61, 31.70, 36.03, 38.48, 44.09, 48.18, 50.54, 112.96, 115.42, 126.67, 132.21, 138.19, 153.65, 221.34.

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{23}O_2$ $(M + H)^+$: 271.1698; found: 271.1697.

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