Synthesis of Enantiopure Estrone via a Double Heck Reaction

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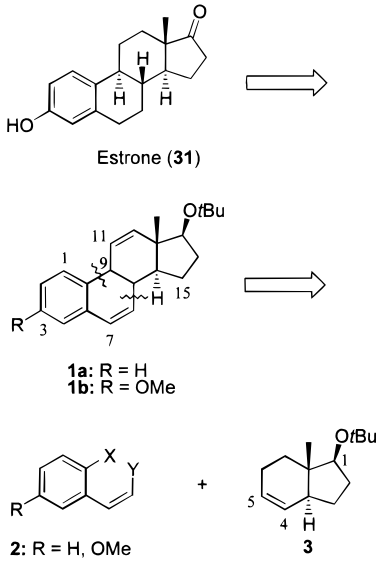
Abstract: An novel efficient catalytic approach to steroids by a double Heck reaction of the vinyl bromides **2** and the CD-building block **3** is presented. The new estrogen analogues **1a** and **1b** are formed via **23a** and **23b** in a highly regio- and stereoselective manner in good yields. They contain a *cis*-BC ring junction and two double bonds in the 6,7- and the 11,12-positions which can be functionalized in a selective way. Inter alia, homogeneous hydrogenation with $(PPh_3)_3RhCl$ to give **28** followed by hydrogenation with 1,4-cyclohexadiene in the presence of palladium affords the known estradiol derivative **29a** in 76% yield which can easily be transformed into estrone **31**.

The total synthesis of steroids represents an attractive research area due to their high biological activity and broad pharmacological applications.[1] Thus, several of the most applied pharmaceutical drugs in the United States contain estrogens[2] and millions of women use estradiol in oral contraceptives.[3] In past decades, several elegant approaches to steroids were developed employing new synthetic methodologies;[4] among them are the cationic polyolefinic cyclization,[5] the more recent transition metal mediated reactions of polyenynes,[6] and the thermally induced radical cyclization of enyne-allenes.[7] They all allow the construction of the steroidal skeleton in one step. However, the number of total syntheses of steroids is rather limited compared to the nearly numberless publications which deal with the partial synthesis of steroids and selective functionalizations of mostly every position of the steroidal tetracycle.[8]

In recent years, palladium-catalyzed bond forming processes have evolved as very powerful tools for constructing complex natural compounds.[9] The syntheses of morphine, calcitriol, CC-1065, paclitaxel, camptothecin, and cephalotaxine employing the Heck reaction demonstrate their broad potential.[10]

Here we describe a highly efficient total synthesis of enantiopure estrone **31** using two successive Heck reactions as key steps for constructing the steroidal skeleton (Scheme 1). In addition, new estradiol derivatives with the unusual *cis*-ring junction of the rings B and C containing $\Delta^{6,7}$- and $\Delta^{11,12}$-double bonds have been prepared.[11] The novel compounds might be of great interest for investigations of structure−binding affinity relationships with the estrone receptor.

Scheme 1. Retrosynthetic Analysis of Estrone



The key intermediate in our synthesis of estrone **31** is the tetracycle **1b** which was further transformed by selective

(1) For biological properties, see: Anstead, G. M.; Carlson, K. E.; Katzenellenbogen, J. A. *Steroids* **1997**, *62*, 268−303.

(2) Simonsen, L. L. P. *Pharm. Times* **1994**, *April*, 18−32.

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(7) Andemichael, Y. W.; Huang, Y.; Wang, K. K. *J. Org. Chem.* **1993**, *58*, 1651−1652.

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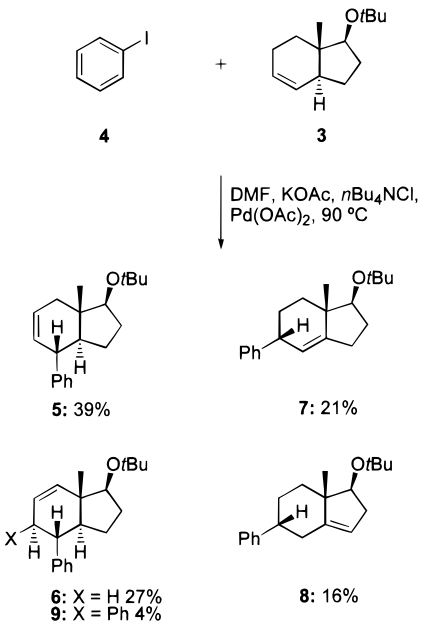
Scheme 2. Products of Arylation of **3** with **4**



hydrogenation. The retrosynthetic analysis of **1b** consists of a disconnection of the 7,8- and the 9,10-C−C bond in the steroid skeleton to give the doubly functionalized arene **2** and the chiral hydrindene **3** as potential starting material for the two successive Heck reactions. In this approach the steroid skeleton is derived from a ring A and a CD-building block which so far has not been used for the total synthesis of steroids.

However, several problems had to be faced in this project: (1) Cyclohexenes have already been used quite often in inter- and intramolecular Heck reactions, but they usually react rather sluggishly.[12] (2) In Heck reactions, the C−C bond formation usually takes place at the less-hindered position; thus, for the reaction of hydrinden **3** the formation of a mixture of regioisomers had to be expected. (3) The shielding of the upper face of **3** by the angular methyl group would clearly allow a stereoselective addition from the lower face. (4) A further problem on which we had to focus is the usually low selectivity of the formation of the double bond in Heck reactions. Thus, an isomerization of the primarily formed double bond is encountered quite often under Heck conditions. (5) Finally, nothing was known about the difference in reactivity of a vinyl halide and an aryl halide functionality being in the same molecule.

For the investigations on the rate as well as the diastereo- and regioselectivity of the Heck reaction with **3**, we performed several transformations with mono-functionalized iodo arenes (Scheme 2). The Heck reaction of **3** and iodo benzene **4** was performed under modified Jeffery conditions[13] to quantitatively provide a mixture of the four arylated compounds **5**, **6**, **7**, and **8** in a ratio of 2.4:1.7:1.3:1 which could be separated by crystallization and column chromatography. As expected, the reaction takes place with a low regioselectivity at C-4 and C-5, however with complete stereocontrol anti to the angular methyl group of **3**. The formation of the double bond isomers **6** and **8** can be explained by a readdition−elimination process of a H−Pd^{II}−I species to **5** and **7**. The reaction was also performed in the presence of silver carbonate to suppress the isomerization

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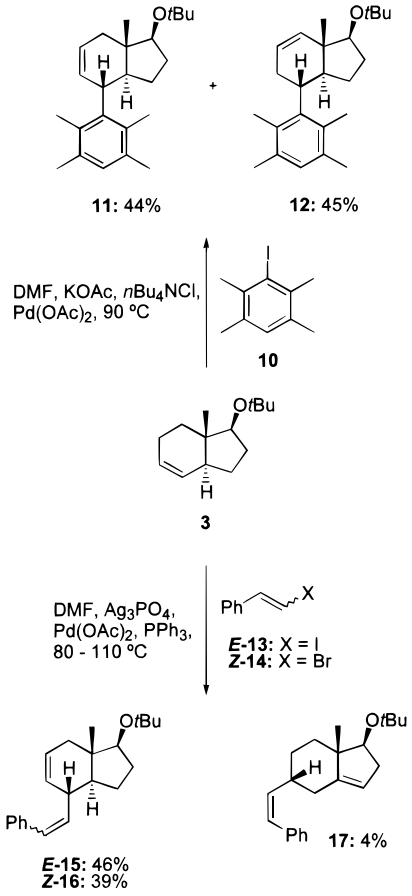
(13) Jeffery, T. *Tetrahedron Lett.* **1985**, *26*, 2667−2670.

Scheme 3. Products of Arylation and Vinylation of **3** with **10**, **15**, and **16**



of the double bond;[14] however, we observed a similiar ratio of isomeric products. In addition, a small amount of the biphenylated compound **9** was formed probably due to the higher reactivity of an intermediate L_2Pd^+ species [**5** (37%), **6** (26%), **7** (8%), **8** (8%), **9** (4%)]. The phenyl group at C-5 in **9** is introduced *syn* to the angular methyl group due to the stronger directing properties of the phenyl group at C-4 which is introduced first.

Rather unexpectedly, the Heck reaction of the sterically highly hindered 3-iodotetramethylbenzene (**10**) with **3** under modified Jeffery conditions gave exclusively attack at C-4 with the formation of the two isomers **11** and **12** in a 1:1 ratio in 90% yield; the diastereoselectivity of this reaction again was >98% (Scheme 3). Also in this transformation, the use of a silver salt did not prevent the isomerization of the initially formed double bond. Thus, in the presence of silver phosphate **11** and **12** were obtained in a ratio of 1:2 and a yield of 74%.[15]

Next we performed Heck reactions of **3** with the halovinylarenes **13** or **14**,[16] to allow the introduction of two additional carbons to give **15** or **16** with selective C−C-bond formation at C-4 in 46% and 39% yield, respectively. Approximately 50% of **3** was recovered in each case and in addition 4% of **17** was isolated in the reaction of **14** and **3**. The lower yield in these transformations is probably due to the higher sensitivity of **15** and **16** compared to **4** and **10** (Scheme 3).

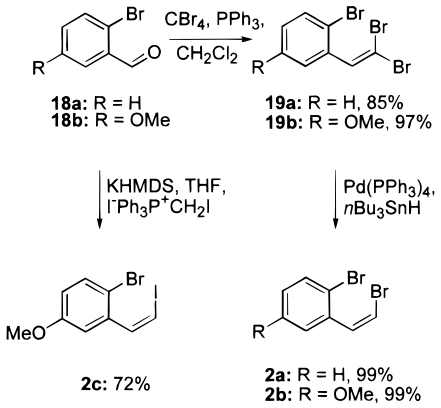
For the formation of ring B of the steroidal skeleton, a doubly functionalized arene with different reactivity of the two functions

(14) Conditions: 10 mol % $Pd(OAc)_2$, 22 mol % PPh_3, 2.5 equiv of Ag_2CO_3, 2.0 equiv of **4**, DMF, 110 °C, 60 h.

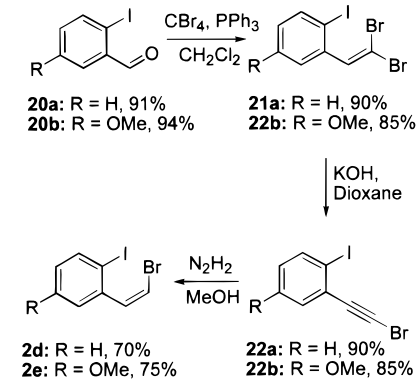
(15) Conditions: 5 mol % $Pd(OAc)_2$, 2.0 equiv of Ag_3PO_4, 2.0 equiv of **10**, DMF, 90 °C, 64 h.

(16) Albrecht, K.; de Meijere, A. *Chem. Ber.* **1994**, *127*, 2539−2541.

Scheme 4. Synthesis of Bromo Arenes



Scheme 5. Synthesis of Iodo Arenes



had to be used. We therefore prepared the five halogenated halovinylarenes **2a**−**e** according to Schemes 4 and 5. Compounds **2a** and **2b** were obtained in two steps from **18a** and **18b** by a Corey−Fuchs reaction[17] and a selective Pd-catalyzed replacement of one Br atom with *n*-Bu_3SnH in excellent yield.[18] The (*Z*)-configuration of the double bond in **2a**−**e** was confirmed by a coupling constant of $J = 8.0-8.3$ Hz by the signals of the two vinylic hydrogens in the ^1H NMR spectra.

The Heck reactions of **3** with the doubly functionalized compounds **2a**−**e** revealed that in general, vinyl iodides and vinyl bromides are more reactive than the bromo and iodo arenes. However, the difference in reactivity between the two functions in **2d** and **2e** proved to be insufficient to allow a highly chemoselective reaction. Furthermore, in the presence of silver salts, we observed an I/Br exchange at the arene moiety. On the other hand, the vinyl iodide **2c** appeared to be rather unstable in palladium-catalyzed reactions. Therefore, we used **2a** and **2b** in the double Heck reaction with **3** which proceeded in an astoundingly selective fashion with the nearly exclusive formation of **23a** and **23b**, respectively (Table 1, Scheme 6). Thus, no diastereomer, regioisomer, or double bond isomer of **23a** or **23b** was found. Under optimized conditions **23a** was obtained in 66% yield and **23b** in a slightly lower yield of 50% after chromatographic purification. In both cases approximately 30% of **3** could be recovered. Thus, on the basis of transformed **3**, the reaction of **2a** is nearly quantitative and that of **2b** shows a yield of about 80%. As byproducts in the different reactions, the butadiene **24a** was obtained in traces and the butadiene **24b** was isolated in variable yields of 5−10% being formed by a Pd-catalyzed homocoupling process of **2a** and **2b**, respectively.[19] This type of a Pd-catalyzed Ullmann coupling process was also performed with Zn as reducing agent, but formation of the butadienes could not be detected.[20] Using a 2-fold excess of **3**, the isolated yield of **23b** could be increased to 61%. Under these conditions, **24b** was also formed only in traces. The relative configuration of **23b** was determined by X-ray analysis.[21]

Interestingly, the transformations are highly sensitive toward the ratio of palladium and triphenylphosphane; with a ratio of 1:3 and higher, the Heck reaction is completely suppressed. Also noteworthy, the vinyl bromides **2a** and **2b** do not react until the alkene **3** is added to the mixture[22] and addition of water (10%) strongly accelerates the coupling.[23]

The highly selective formation of **23a** and **23b** needs some comment. The high stereoselectivity can easily be explained by shielding of the upper face of **3** by the angular methyl group, and the absence of double bond isomerization compared to the reaction with iodobenzene may be due to the milder reaction conditions. However, the high regioselectivity in the C−C-bond formation is difficult to understand. We assume that this might be due to a stereoelectronic effect which forces the attack of the palladium at C-5 from the α-face to allow a chair-like transition state with subsequent *syn* addition of the vinyl group at C-4 (structure **26**).[24]

A variety of different catalyst systems was employed for the intramolecular Heck reaction of **23a** and **23b** to give the estradiol derivatives **1a** and **1b** (Table 2). The best results were obtained using the recently described palladacycle **25** providing **1a** and **1b** in quantitative yield as single diastereomers with a *cis*-junction of the rings B and C as well as a $\Delta^{6,7}$- and a $\Delta^{11,12}$-C−C double bond. Also in this case, the addition of water leads to a increase of the reaction rate.[24] Compared to the transformation with $Pd(OAc)_2$ and PPh_3, the reaction is much cleaner in the presence of **25** and needs a shorter reaction time.

The formation of **1b** from **3** and **2b** was also carried out as a domino reaction without isolation of **23b** using catalyst **25**.[25] However, so far the yield (35%) is slightly lower than found for the two-step transformation.[26]

For the synthesis of estrone it was necessary to hydrogenate the two olefinic double bonds and isomerize the stereogenic center C-9 in **1b** to provide a *trans*-ring junction of the rings B and C (Scheme 7).[27] Hydrogenation of **1b** using Pd/C in acetic acid under a hydrogen atmosphere of 3 bar provided a separable mixture of **29a** and **29b** in a ratio of 1:2, obtained in almost quatitative yield. The formation of **29a** might be explained by an intermediate isomerization of the $\Delta^{11,12}$- to the $\Delta^{9,11}$-double

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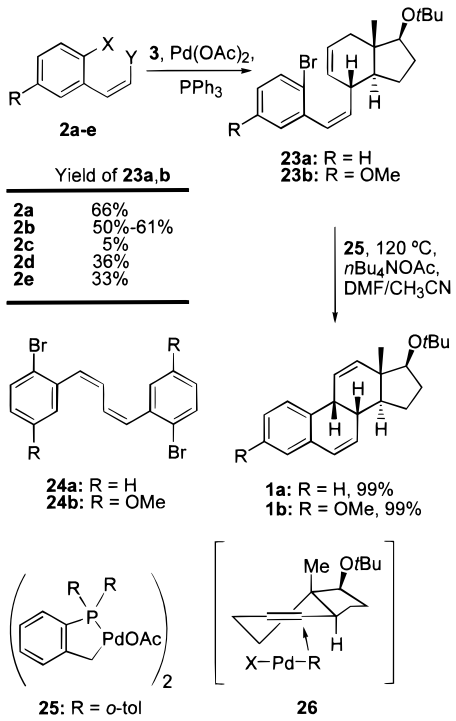
(20) Jutand, A.; Mosleh, A. *Synlett* **1993**, 568−570.
(21) Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-101100 (**25b**) and CCDC-101054 (**27**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax (+44) 1223 336−033; e-mail deposit@ccdc.cam. ac.uk).
(22) Herrmann, W. A.; Brossmer, Ch.; Öfele, K.; Reisinger, C. P.; Priermeier, T.; Beller, M.; Fischer, H. *Angew. Chem.* **1995**, *107*, 1989−1992; *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1844−1846; *Chem. Eur. J.* **1997**, *3*, 1357−1364.
(23) Jeffery, T. *Tetrahedron Lett.* **1994**, *35*, 3051−3054.
(24) Whiting, D. A. *J. Chem. Soc., Chem. Commun.* **1987**, 510−511.
(25) (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115−136. (b) Tietze, L. F.; Beifuss, U. *Angew. Chem.* **1993**, *105*, 137−170; *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131−163.
(26) Conditions: 2.5 mol % *trans*-di-(μ-acetato)bis[*o*-(di-*o*-tolylphosphino)benzyl]dipalladium(II), 2.5 equiv of *n*-Bu_4NOAc, DMF/CH_3CN/H_2O (1:1:0.2), 168 h, 60 °C, 30% of **2** could be recovered.
(27) Johnstone, R. A. W.; Wilby, A. H.; Entwistle, I. D. *Chem. Rev.* **1985**, *85*, 129−170.

Table 1. Conditions for Heck Reaction of **2a**−**e** and **3**

entry	substrate	catalyst	solvent	additive	product yield [%]
1	**2a**	10 mol % $Pd(OAc)_2$, 22 mol % PPh_3, 60 °C, 60 h	DMF/CH_3CN	*n*-Bu_4NOAc; 2.0 equiv of **2a**	66
2	**2b**	10 mol % $Pd(OAc)_2$, 25 mol % PPh_3, 75 °C, 7 h	$DMF/CH_3CN/H_2O$	*n*-Bu_4NOAc	50
3	**2b**	10 mol % $Pd(OAc)_2$, 20 mol % PPh_3, 80 °C, 7 h	$DMF/CH_3CN/H_2O$	*n*-Bu_4NOAc; 2.0 equiv of **3**	61
4	**2c**	10 mol % $Pd(OAc)_2$, 70 °C, 4 h	$DMF/CH_3CN/H_2O$	*n*-Bu_4NOAc	<5
5	**2d**	5 mol % $Pd[PPh_3]_4$, 120 °C, 69 h	DMF	Ag_3PO_4	36
6	**2e**	5 mol % $Pd[PPh_3]_4$, 80 °C, 68 h	DMF	Ag_3PO_4	33

Scheme 6. Products of Coupling Reactions of **2a**−**e** with **3**



bond which is known to give a *trans*-B/C-ring junction on hydrogenation to provide the thermodynamically more stable all-*trans* configuration of the steroidal skeleton. Using Pd/C without any source of hydrogen **1b** is transformed into the unsaturated equilenin derivative **27** in excellent yield.

The diene **1b**, however, could also be transformed highly selectively into **29b** in 97% yield using platinum as catalyst in the hydrogenation. As expected, no isomerization was observed. The homogeneous hydrogenation employing the Wilkinson catalyst allowed the selective hydrogenation of the more accessible $\Delta^{6,7}$-double bond of **1b**; thus, in the presence of 10 mol % $(PPh_3)_3RhCl$ in methanol/ethyl acetate at ambient hydrogen pressure and room temperature for 4 h the alkene **28** was obtained in 94% yield. The reaction takes place without changing the configuration at C-8 and C-9 which was confirmed by an X-ray analysis of **28**.[21] The $\Delta^{11,12}$-double bond is much less reactive under homogeneous catalysis; thus, even under 55 bar of hydrogen pressure for 4 h only 30% of **29b** together with 70% of **28** was obtained. Estradiol derivatives with a $\Delta^{11,12}$-double bond have been isolated from the urine of pregnant women.[28]

The synthesis of the known estradiol derivative **29a** which can easily be transformed into estrone **31** using known procedures was finally accomplished in good yield by hydrogenation of **28** in the presence of palladium and a large excess of 1,4-cyclohexadiene as a source of a hydrogen. Using 0.6 equiv of palladium in ethanol for 48 h at 100 °C, **29a** was obtained in 76% yield. In addition 24% of the equilenin derivative **30** was found. Using a smaller concentration of palladium (0.07 equiv), 24% of **29a** and 68% of **30** were isolated. The formation of **30** results from an aromatization of the B-ring by migration of the double bond and dehydrogenation due to the low concentration of active hydrogen.[29] The formation of **29a** from **28** can be explained as already mentioned by an isomerization of the $\Delta^{11,12}$- to the $\Delta^{9,11}$-double bond followed by hydrogenation. All spectroscopic properties of **29a** were identical with those reported.[30]

Conclusion

A novel highly efficient strategy for the preparation of new types of estrogen derivatives has been developed with two stereoselective Heck reactions as the key steps which provide a general and selective access to the steroidal skeleton. Furthermore, the obtained products **1a** and **1b** with two double bonds in the 6,7- and the 11,12-positions might be used as starting materials for the synthesis of numerous novel highly functionalized steroids. Hydrogenation of **1b** allows the selective formation of the known estradiol derivative **29a** which can be transformed into estrone **31**.[30d]

Scheme 7. Selective Hydrogenation and Dehydrogenation of **1b**

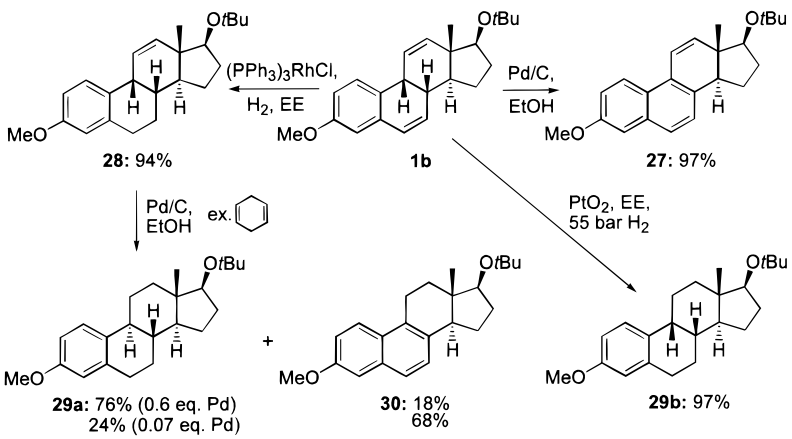


Table 2. Conditions for Intramolecular Heck Reactions to **1a**,**b**

entry	substrate	catalyst	solvent	additive	product yield [%]
1	**23a**	16 mol % $Pd(OAc)_2$, 34 mol % PPh_3, 60 °C, 60 h	$DMF/CH_3CN/H_2O$	*n*-Bu_4NOAc	68%
2	**23a**	12 mol % $Pd(OAc)_2$, 24 mol % PPh_3, 115 °C, 60 h	DMF	Ag_3PO_4	85%
3	**23a**	2.5 mol % **25**, 115 °C, 4.5 h	$DMF/CH_3CN/H_2O$	*n*-Bu_4NOAc	99%
4	**23b**	13 mol % $Pd(OAc)_2$, 27 mol % PPh_3, 115 °C, 60 h	DMF	Ag_3PO_4	63%
5	**23b**	2.5 mol % **25**, 115 °C, 4.5 h	$DMF/CH_3CN/H_2O$	*n*-Bu_4NOAc	99%

Experimental Section

Instrumentation. Multiplicities of ^{13}C NMR peaks were determined with the APT pulse sequence. Mass spectra were measured at 70 eV. UV/vis spectra [λ_{max}, nm, log ϵ) were taken in CH_3CN. IR spectra were recorded as KBr pellets or as films. Melting points are corrected.

Materials. All reactions were performed in oven-dried glassware in an atmosphere of nitrogen or argon unless otherwise noted. Solvents were dried and distilled prior to use and degassed by pump and freeze methodology. TLC chromatography was performed on precoated silica gel SIL G/UV_{254} plates (Machery, Nagel & Co.), and silica gel 32−63 (0.032−0.064 mm) (Machery, Nagel & Co.) was used for column chromatography.

The starting materials 3-*tert*-butoxy-3a-methyl-2,3,3a,4,5,7a-hexahydro-1*H*-indene (**3**),[31] 3-iodotetramethylbenzene (**10**),[32] ((*E*)-(2-iodoethenyl)benzene (**13**),[33] ((*Z*)-(2-bromoethenyl)benzene (**14**),[34] and 2-bromo-5-methoxybenzaldehyde (**18b**)[35] were prepared according to published procedures.

1-Bromo-2-(2,2-dibromovinyl)benzene (19a). To a solution of CBr_4 (3.58 g, 10.8 mmol) in CH_2Cl_2 (20 mL) was added a solution of PPh_3 (5.67 g, 21.6 mmol) in CH_2Cl_2 (20 mL) at 0 °C. The mixture was stirred for 30 min, and then a solution of **18a** (1.00 g, 5.40 mmol) in CH_2Cl_2 (20 mL) was added. The reaction mixture was allowed to warm to room temperature with continued stirring. After 2 h the mixture was poured in petroleum ether (200 mL), filtered, and concentrated in vacuo. Purification by column chomatography provided **19a** (1.57 g, 4.61 mmol, 85%) as yellow oil: R_f 0.57 (petroleum ether); UV (CH_3CN) λ_{max} (log ϵ) 206.0 (4.314), 250.5 (3.942); IR (film) 3060, 1604; ^1H NMR (200 MHz, $CDCl_3$) δ 7.21 (dt, J = 7.4, 1.2 Hz, 1 H), 7.34 (dt, J = 7.4, 1.2 Hz, 1 H), 7.51 (s, 1 H), 7.59 (dd, J = 8.0, 1.2 Hz, 1 H), 7.59 (dd, J = 8.0, 1.2 Hz, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 92.83, 123.0, 127.1, 129.8, 130.3, 132.5, 136.0, 136.6; MS (70 eV, EI) *m*/*z* (%) 339.9 (72) [M^+], 261.0 (100) [M^+ − HBr], 180.0 (87) [M^+ − HBr − Br], 101.1 (46) [M^+ − HBr − Br − Br]; EI HRMS *m*/*e* 337.7941, $C_8H_5Br_3$ requires 337.7940.

(*Z*)-1-Bromo-2-(2-bromovinyl)benzene (2a). To a degassed solution of **19a** (868 mg, 2.55 mmol) in anhydrous toluene (15 mL) and $Pd(PPh_3)_4$ (4 mol %, 118 mg) was added *n*-Bu_3SnH (778 mg, 2.67 mmol, 0.72 mL), and the mixture was stirred for 1 h at room temperature. The reaction mixture was poured in petroleum ether (100 mL), washed with water (30 mL), brine (30 mL), and dried over $MgSO_4$. Concentration in vacuo and purification by column chromatography provided **2a** (661 mg, 99%) as yellow oil: R_f 0.44 (petroleum ether); UV (CH_3CN) λ_{max} (log ϵ) 206.5 (4.284), 247.0 (3.924); IR (film) 3070, 1618; ^1H NMR (300 MHz, $CDCl_3$) δ 6.75 (d, J = 8.0 Hz, 1 H), 7.17 (dt, J = 7.5, 1.5 Hz, 1 H), 7.20 (d, J = 8.0 Hz, 1 H), 7.33 (dt, J = 7.5, 1.5 Hz, 1 H), 7.59 (dd, J = 8.0, 1.5 Hz, 1 H), 7.76 (dd, J = 7.5, 1.5 Hz, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 109.3, 123.7, 126.8, 129.6, 130.5, 132.3, 132.6, 135.1; MS (70 eV, EI) *m*/*z* (%) 259.9 (28) [M^+], 181.0 (100) [M^+ − HBr], 102.0 (78) [M^+ − HBr − Br]; EI HRMS *m*/*e* 259.8836, $C_8H_6Br_2$ requires 259.8836.

2-(2,2′-Dibromoethenyl)-4-methoxybromobenzene (19b). To a suspension of CBr_4 (99.50 g, 300 mmol) and Zn (19.62 g, 300 mmol) in CH_2Cl_2 (1000 mL) was added a solution of PPh_3 (78.69 g, 300 mmol) in CH_2Cl_2 (200 mL) at room temperature. After 30 min, a solution of **18b** (32.24 g, 150 mmol) in CH_2Cl_2 (150 mL) was added, and the mixture was stirred for 1.5 h. The mixture was diluted with petroleum ether (2000 mL), filtered, and concentrated under reduced pressure. Purification by column filtration (petroleum ether) afforded **19b** (54.10 g, 97%) as white solid: mp 46.9 °C (MeOH); UV (CH_3CN) λ_{max} (log ϵ) 202.0 (4.335), 294.0 (3.392); IR (KBr) 3020, 2962, 2832, 1594; ^1H NMR (200 MHz, $CDCl_3$) δ 3.80 (s, 3 H), 6.77 (dd, J = 8.8, 3.2 Hz, 1 H), 7.15 (d, J = 3.2 Hz, 1 H), 7.45 (d, J = 8.8 Hz, 1 H), 7.48 (s, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 55.54, 92.84, 113.4, 115.6, 115.9, 133.1, 136.4, 136.5, 158.4; MS (70 eV, EI) *m*/*z* (%) 370.0 (100) [M^+], 291.0 (25) [M^+ − Br], 210.1 (75) [M^+ − 2 × Br]. Anal. Calcd for $C_9H_7OBr_3$ (370.7): C, 29.13; H, 1.88; Br, 64.66. Found: C, 29.53; H, 1.89; Br, 64.32.

(*Z*)-1-Bromo-2-(2-bromovinyl)-4-methoxybenzene (2b).[36] To a degassed solution of **19b** (2.68 g, 7.23 mmol) in anhydrous toluene (40 mL) and $Pd(PPh_3)_4$ (4 mol %, 334 mg) was added *n*-Bu_3SnH (7.59 mmol, 2.21 g, 2.04 mL), and the mixture was stirred for 1 h at room temperature. The reaction mixture was poured in petroleum ether (100 mL), washed with water (30 mL) and brine (50 mL), and dried over $MgSO_4$. Concentration in vacuo and purification by column chromatography provided **2b** (2.06 g, 98%) as yellow oil: R_f 0.05 (pentane); bp 78 °C (0.01 mbar); UV (CH_3CN) λ_{max} (log ϵ) 202.5 (4.295), 297.0 (3.279); IR (film) 3002, 2932, 2832, 1590; ^1H NMR (200 MHz, $CDCl_3$) δ 3.81 (s, 3 H), 6.57 (d, J = 8.1 Hz, 1 H), 6.76 (dd, J = 8.7, 3.0 Hz, 1 H), 7.18 (d, J = 8.1 Hz, 1 H), 7.36 (d, J = 3.0 Hz, 1 H), 7.47 (d, J = 8.7 Hz, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 55.50, 109.2, 114.2, 115.6, 115.8, 132.1, 133.1, 135.6, 158.2; MS (70 eV, EI) *m*/*z* (%) 292.1 (100) [M^+], 211.1 (62) [M^+ − HBr], 132.1 (84) [M^+ − HBr − Br]. Anal. Calcd for $C_9H_8OBr_2$ (291.8): C, 37.01; H, 2.74. Found: C, 37.05; H, 2.81.

(3*R*,3a*S*,7*S*,7a*S*)-(−)-3-*tert*-Butoxy-3a-methyl-7-(*Z*)-[2-(2-bromophenyl)vinyl]-2,3,3a,4,7,7a-hexahydro-1*H*-indene (23a). To a degassed solution of **3** (208 mg, 1.0 mmol) and **2a** (524 mg, 2.0 mmol) in DMF (5 mL) were added $Pd(OAc)_2$ (10 mol %, 23 mg), PPh_3 (20 mol %, 52 mg), and silver phosphate (836 mg, 2.0 mmol). The mixture was stirred for 60 h at 120 °C. The mixture was then cooled to room temperature and diluted with ether (20 mL) and water (20 mL). The organic layer was washed with brine (15 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification by column chromatography afforded 257 mg of **23a** (66%) as colorless oil: R_f 0.23 (petroleum ether/CH_2Cl_2 = 10:1); [α] −23.3 (c = 0.45, $CHCl_3$); UV (CH_3CN) λ_{max} (log ϵ) 195.5 (4.395); IR (film) 3052, 2970; ^1H NMR (300 MHz, $CDCl_3$) δ 0.63 (s, 3 H),

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1.13 (s, 9 H), 1.15−1.20 (m, 1 H), 1.22−1.40 (m, 2 H), 1.52−1.70 (m, 1 H), 1.76−1.88 (m_c, 2 H), 1.98 (dddd, J = 17.3, 4.9, 1.9, 1.7 Hz, 1 H), 2.82−3.00 (m, 1 H), 3.48 (dd, J = 8.5, 8.1 Hz, 1 H), 5.46 (dd, J = 11.0, 10.7 Hz, 1 H), 5.40−5.50 (m, 1 H), 5.69 (dddd, J = 9.5, 4.6, 2.4, 2.2 Hz, 1 H), 6.47 (d, J = 11.0 Hz, 1 H), 7.04−7.20 (m, 1 H), 7.22−7.34 (m, 2 H), 7.57 (d, J = 7.8 Hz, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 11.48, 24.71, 28.75, 30.44, 38.74, 38.76, 41.21, 46.31, 72.23, 80.63, 123.9, 126.9, 127.4, 128.3, 128.9, 129.3, 130.6, 132.5, 136.3, 137.8; MS (70 eV, EI) *m*/*z* (%) 388.0 (5) [M^+], 210.1 (46) [$M^+ - C_4H_9^+ - Br - C_3H_5^+$], 105.1 (32) [$C_8H_9^+$], 91.0 (46) [$C_7H_7^+$], 57.0 (100) [$C_4H_9^+$], 41.0 (19) [$C_3H_5^+$]. Anal. Calcd for $C_{22}H_{29}OBr$ (389.4): C, 68.05; H, 7.21. Found: C, 68.20; H, 7.25.

(1*S*,3a*S*,4*S*,7a*S*)-(−)-4-[2-(2-Bromo-5-methoxyphenyl)vinyl]-1-*tert*-butoxy-7a-methyl-2,3,3a,4,7,7a-hexahydro-1*H*-indene (23b). To a degassed solution of **3** (208 mg, 1.0 mmol), **2b** (292 mg, 1.0 mmol), and *n*-Bu_4NOAc (2.5 mmol, 754 mg) in DMF/CH_3CN/H_2O (1:1:0.2, 10 mL) were added at 50 °C $Pd(OAc)_2$ (10 mol %, 23 mg) and PPh_3 (25 mol %, 66 mg). The mixture was stirred for 8 h at 70 °C. The mixture was then cooled to room temperature and diluted with ether (50 mL) and water (50 mL). The organic layer was washed with water (2 × 50 mL) and brine (30 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification by column chromatography afforded **23b** (210 mg, 50%) as colorless oil. Recrystallization from methanol yielded white needles: R_f 0.27 (petroleum ether/CH_2Cl_2 = 3:1); mp 85.4 °C (MeOH); [α] −60.4 (c = 0.5, $CHCl_3$); UV (CH_3CN) λ_{max} (log ϵ) 201.0 (4.403), 289.0 (3.422); IR (KBr) 3012, 2970, 2836; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.66 (s, 3 H), 1.13 (s, 9 H), 1.15−1.22 (m, 1 H), 1.30−1.44 (m, 2 H), 1.63−1.71 (m, 1 H), 1.80−1.90 (m, 2 H), 2.00 (dddd, J = 17.1, 5.4, 1.8, 1.8 Hz, 1 H), 2.97 (m_c, 1 H), 3.49 (t, J = 8.4 Hz, 1 H), 3.78 (s, 3 H), 5.45 (dd, J = 11.2, 10.7 Hz, 1 H), 5.45 (m_c, 1 H), 5.69 (dddd, J = 9.8, 4.6, 2.3, 2.3 Hz, 1 H), 6.45 (d, J = 11.2 Hz, 1 H), 6.69 (dd, J = 8.7, 3.0 Hz, 1 H), 6.82 (d, J = 3.0 Hz, 1 H), 7.45 (d, J = 8.7 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.45, 24.78, 28.73, 30.49, 38.77, 41.22, 46.31, 55.42, 72.22, 80.60, 114.4, 114.5, 115.9, 127.5, 128.8, 129.3, 133.0, 136.4, 138.5, 158.4; MS (70 eV, EI) *m*/*z* (%) 418.1 (32) [M^+], 265.1 (100) [$M^+ - OC_4H_9^+ - Br$], 105.0 (43) [$C_8H_9^+$], 91.0 (20) [$C_7H_7^+$], 57.0 (92) [$C_4H_9^+$]. Anal. Calcd for $C_{23}H_{31}O_2Br$ (419.4): C, 65.87; H, 7.45; Br, 19.05. Found: C, 65.95; H, 7.45; Br, 18.95.

1,4-Bis[2-bromo-5-methoxyphenyl]-1,3-butadiene (24b). R_f 0.28 (petroleum ether/CH_2Cl_2 = 3:1); mp 157.0 °C (ether); UV (CH_3CN) λ_{max} (log ϵ) 192.5 (4.404), 222.0 (4.339), 332.0 (4.136); IR (KBr) 2934; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.84 (s, 6 H), 6.71 (dd, J = 8.8, 3.3 Hz, 2 H), 7.00 (m_c, A_2B_2−signal, 4 H), 7.16 (d, J = 3.3 Hz, 2 H), 7.45 (d, J = 8.8 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.53, 111.2, 114.8, 115.6, 131.5, 132.4, 133.7, 137.3, 159.0; MS (70 eV, EI) *m*/*z* (%) 423.9 (29) [M^+], 343.0 (21) [$M^+ - Br$], 264.1 (100) [$M^+ - 2 \times Br$], 249.1 (12) [$M^+ - 2 \times Br - CH_3$]. Anal. Calcd for $C_{18}H_{16}O_2Br_2$ (424.13): C, 50.97; H, 3.80. Found: C, 51.21; H, 3.98.

(−)-17β-*tert*-Butoxy-9β-estra-1,3,5(10),6,11(12)-pentaene (1a). To a carefully degassed solution of **23a** (157 mg, 0.40 mmol) and *n*-Bu_4NOAc (302 mg, 1.00 mmol) in DMF/CH_3CN/H_2O (1:1:0.2, 5 mL) was added *trans*-di-(μ-acetato)bis[*o*-di-*o*-tolylphosphino)benzyl]dipalladium-(II) (**25**) (7.5 mg, 2.0 mol %) at 50 °C. The mixture was stirred for 4.5 h at 115 °C. After cooling to room temperature, the mixture was diluted with ether (100 mL) and washed with water (30 mL) and brine (30 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification by column chromatography afforded **1a** (123 mg, 99%) as colorless oil: R_f 0.29 (petroleum ether/CH_2Cl_2 = 10:1); [α] −173.4 (c = 0.5, $CHCl_3$); UV (CH_3CN) λ_{max} (log ϵ) 213.0 (4.362), 219.0 (4.351), 225.5 (4.221), 264.0 (3.866), 271.5 (3.846); IR (film) 2970, 1082; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.90 (s, 3 H), 1.13 (s, 9 H), 1.39−1.58 (m, 3 H), 1.78 (ddd, J = 12.1, 11.9, 6.6 Hz, 1 H), 1.83−1.91 (m, 1 H), 2.69 (ddd, J = 11.9, 6.6, 6.1 Hz, 1 H), 3.48 (dd, J = 6.7, 6.6 Hz, 1 H), 3.77 (dd, J = 6.6, 5.0 Hz, 1 H), 5.90 (dd, J = 9.6, 6.1 Hz, 1 H), 6.09 (d, J = 10.1 Hz, 1 H), 6.17 (dd, J = 10.1, 5.0 Hz, 1 H), 6.40 (d, J = 9.6 Hz, 1 H), 6.99 (dd, J = 7.1, 1.6 Hz, 1 H), 7.11−7.19 (m, 2 H), 7.30 (d, J = 7.4 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.87, 22.75, 28.65, 31.74, 33.75, 37.92, 41.45, 44.73, 72.30, 76.21, 125.2, 126.1, 126.6, 126.67, 126.69, 127.2, 130.0, 132.8, 136.1, 137.3; MS (70 eV, EI) *m*/*z* (%) 308.2 (7) [M^+], 251.2 (43) [$M^+ - C_4H_9^+$], 233.1 (100) [$M^+ - C_4H_9^+ - H_2O$], 57.1 (41) [$C_4H_9^+$], 41.1 (15) [$C_3H_5^+$]; EI HRMS *m*/*e* 308.2140, $C_{22}H_{28}O$ requires 308.2140.

(−)-17β-*tert*-Butoxy-3-methoxy-9β-estra-1,3,5(10),6,11(12)-pentaene (1b). To a carefully degassed solution of **23b** (182 mg, 0.43 mmol) and *n*-Bu_4NOAc (327 mg, 1.09 mmol) in DMF/CH_3CN/H_2O (1:1:0.2, 5 mL) was added *trans*-di-(μ-acetato)bis[*o*-di-*o*-tolylphosphino)benzyl]dipalladium(II) (**25**) (8.1 mg, 2.0 mol %) at 50 °C. The mixture was stirred for 4.5 h at 115 °C. After cooling to room temperature, the mixture was diluted with ether (100 mL) and washed with water (30 mL) and brine (30 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification by column chromatography afforded **1b** (145 mg, 99%) as a colorless solid: R_f 0.28 (petroleum ether/ CH_2Cl_2 = 3:1); mp 65.4 °C (MeOH); [α] −149.0 (c = 0.5, $CHCl_3$); UV (CH_3CN) λ_{max} (log ϵ) 228.5 (4.425), 256.0 (3.699), 265.5 (3.734), 275.5 (3.654), 302.5 (3.405), 313.0 (3.353); IR (KBr) 3032, 3014, 2972, 2834, 1390; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (s, 3 H), 1.11 (s, 9 H), 1.35−1.50 (m, 3 H), 1.65−1.75 (m, 1 H), 1.81−1.92 (m, 1 H), 2.64 (ddd, J = 11.7, 6.7, 6.4 Hz, 1 H), 3.46 (dd, J = 6.5, 6.4 Hz, 1 H), 3.67 (dd, J = 6.4, 4.5 Hz, 1 H), 3.77 (s, 3 H), 5.90 (dd, J = 9.8, 6.7 Hz, 1 H), 6.03 (d, J = 9.9 Hz, 1 H), 6.11 (dd, J = 9.9, 4.5 Hz, 1 H), 6.32 (d, J = 9.8 Hz, 1 H), 6.54 (d, J = 2.8 Hz, 1 H), 6.68 (dd, J = 8.3, 2.8 Hz, 1 H), 7.17 (d, J = 8.3 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.93, 22.80, 28.71, 31.82, 34.00, 37.15, 41.46, 44.80, 55.21, 72.35, 76.29, 112.05, 112.12, 125.5, 126.7, 127.7, 129.5, 131.0, 134.0, 135.9, 158.0; MS (70 eV, EI) *m*/*z* (%) 338.4 (25) [M^+], 281.0 (50) [$M^+ - C_4H_9^+$], 263.0 (100) [$M^+ - C_4H_9^+ - H_2O$], 57.1 (41) [$C_4H_9^+$], 41.0 (16) [$C_3H_5^+$]. Anal. Calcd for $C_{23}H_{30}O_2$ (338.5): C, 81.61; H, 8.93. Found: C, 81.52; H, 8.93.

(+)-17β-*tert*-Butoxy-3-methoxyestra-1,3,5(10),6,8(9),11-hexaene (27). A suspension of Pd/C (5%) and **1b** (75 mg, 0.22 mmol) in ethanol (4 mL) was stirred under a inert atmosphere at 80 °C for 3.5 d. After cooling, the reaction mixture was diluted with ether (10 mL). The catalyst was removed by filtration through a short pad of silica gel. Evaporation of the solvent and purification by column chromatography afforded 72 mg (97%) of **27** as colorless solid: R_f 0.26 (petroleum ether/CH_2Cl_2 = 3:1); mp 98.0 °C (EtOH); [α] +43.4 (c = 0.5, $CHCl_3$); UV (CH_3CN) λ_{max} (log ϵ) 201.0 (4.307), 239.5 (4.650), 286.5 (3.649), 300.0 (3.737), 313.0 (3.777), 338.5 (3.451), 354.0 (3.456); IR (KBr) 2968, 2874, 1626, 1556, 1382, 1360, 1086; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.66 (s, 3 H), 1.26 (s, 9 H), 1.70−1.78 (m_c, 1 H), 1.82−2.10 (m, 2 H), 2.20−2.30 (m_c, 1 H), 3.00 (dd, J = 12.0, 8.0 Hz, 1 H), 3.92 (s, 3 H), 3.98 (dd, J = 7.6, 7.5 Hz, 1 H), 6.46 (d, J = 10.0 Hz, 1 H), 7.10−7.14 (m_c, 2 H), 7.16 (dd, J = 8.5, 3.0 Hz, 1 H), 7.23 (d, J = 10.0 Hz, 1 H), 7.62 (d, J = 9.5 Hz, 1 H), 8.02 (d, J = 9.5 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.53, 21.75, 28.82, 32.45, 44.91, 46.00, 55.24, 72.58, 75.63, 106.3, 118.7, 122.1, 124.2, 124.24, 125.1, 125.9, 129.5, 133.5, 133.7, 139.4, 156.6; MS (70 eV, EI) *m*/*z* (%) 336.4 (50) [M^+], 261.3 (86) [$M^+ - C_4H_9^+ - H_2O$], 91.1 (12) [$C_7H_7^+$], 57.0 (18) [$C_4H_9^+$]; EI HRMS *m*/*e* 336.2089, $C_{23}H_{28}O_2$ requires 336.2089.

(−)-17β-*tert*-Butoxy-3-methoxy-9β-estra-1,3,5(10),11(12)-tetraene (28). A solution of **1b** (100 mg, 0.30 mmol) and $(PPh_3)_3RhCl$ (10 mol %, 27 mg) in methanol/ethyl acetate (1:1, 8 mL) was shaken at room temperature for 4 h under H_2 atmosphere (3 bar). The mixture was filtered and concentrated in vacuo. Purification by column chromatography afforded 95 mg of **28** (94%) as colorless solid: R_f 0.28 (petroleum ether/CH_2Cl_2 = 3:1); mp 60.9 °C (MeOH); [α] −37.8 (c = 0.5, $CHCl_3$); UV (CH_3CN) λ_{max} (log ϵ) 200.5 (4.585), 272.5 (3.685); IR (KBr): 2972, 2870, 1608; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (s, 3 H), 1.11 (s, 9 H), 1.41 (ddd, J = 23.6, 10.7, 5.7 Hz, 1 H), 1.46−1.54 (m, 2 H), 1.62 (dddd, J = 8.6, 8.6, 5.7, 2.0 Hz, 1 H), 1.70 (dddd, J = 8.8, 8.6, 4.4, 4.3 Hz, 1 H), 1.81 (tdd, J = 13.4, 4.8, 4.6 Hz, 1 H), 1.93 (dddd, J = 13.5, 9.4, 9.4, 6.2 Hz, 1 H), 2.34 (m_c, 1 H), 2.53 (ddd, J = 16.0, 4.4, 4.3 Hz, 1 H), 2.75 (ddd, J = 16.0, 11.7, 4.3 Hz, 1 H), 3.47 (m_c, 1 H), 3.47 (dd, J = 7.4, 7.1 Hz, 1 H), 3.77 (s, 3 H), 5.94 (dd, J = 9.9, 3.7 Hz, 1 H), 5.98 (dd, J = 9.9, 0.9 Hz, 1 H), 6.61 (d, J = 2.8 Hz, 1 H), 6.74 (dd, J = 8.6, 2.8 Hz, 1 H), 7.22 (d, J = 8.6 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.94, 22.91, 25.29, 26.20, 28.71, 31.48, 31.86, 38.67, 42.30, 44.53, 55.15, 72.30, 76.76, 112.1, 113.3, 128.6, 129.0, 131.5, 135.4, 138.6, 157.0; MS (70 eV, EI) *m*/*z* (%) 340.4 (56) [M^+], 283.3 (69) [$M^+ - C_4H_9^+$], 265.3 (51) [$M^+ -$

$C_4H_9^+ - H_2O$], 57.1 (41) [$C_4H_9^+$], 41.0 (9) [$C_3H_5^+$]. Anal. Calcd for $C_{23}H_{32}O_2$ (340.5): C, 81.13; H, 9.47. Found: C, 80.86; H, 9.17.

(+)-17*β*-*tert*-Butoxy-3-methoxyestra-1,3,5(10)-triene (29a). A suspension of **28** (51 mg, 0.15 mmol), 1,4-cyclohexadien (15 mmol, 1.41 mL), and Pd/C (5%, 0.60 equiv of Pd, 191 mg) in ethanol (8.0 mL) was stirred for 48 h at 100 °C. After cooling, the reaction mixture was diluted with ether (10 mL). The catalyst was removed by filtration through a short pad of silica gel. Evaporation of the solvent and purification by column chromatography afforded 39 mg (76%) of **29a** as colorless solid and 9 mg of **30**: R_f 0.32 (petroleum ether/*tert*-butyl methyl ether = 40:1); mp 92.6 °C (MeOH); (lit.[30d] 90−92 °C); [α] +59.2 (c = 0.5, $CHCl_3$; lit:[30d] + 62.2 c = 1.0, $CHCl_3$); UV (CH_3CN) λ_{max} (log ϵ) 200.0 (4.645), 279.0 (3.314), 286.5 (3.277); IR (KBr) 2972, 2864; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.76 (s, 3 H), 1.16 (s, 9 H), 1.16−1.43 (m, 5 H), 1.45−1.54 (m, 2 H), 1.63−1.69 (m, 1 H), 1.86−1.97 (m, 3 H), 2.18 (ddd, J = 11.5, 11.5, 4.0 Hz, 1 H), 2.25−2.30 (m_c, 1 H), 2.85 (dd, J = 8.0, 7.5 Hz, 2 H), 3.45 (t, J = 7.9 Hz, 1 H), 3.78 (s, 3 H), 6.63 (d, J = 2.7 Hz, 1 H), 6.71 (dd, J = 8.6, 2.7 Hz, 1 H), 7.22 (d, J = 8.6 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.61, 23.51, 26.41, 27.29, 28.77, 29.90, 31.24, 37.27, 38.77, 42.78, 44.14, 50.05, 55.19, 72.18, 80.86, 111.4, 113.8, 126.3, 132.9, 138.1, 157.4; MS (70 eV, EI) *m*/*z* (%) 342.3 (100) [M^+], 286.2 (74) [$M^+ - C_4H_9^+$], 267.2 (29) [$M^+ - C_4H_9^+ - H_2O$], 57.1 (25) [$C_4H_9^+$]; EI HRMS *m*/*e* 342.2558, $C_{23}H_{34}O_2$ requires 342.2559.

(−)-17*β*-*tert*-Butoxy-3-methoxy-9*β*-estra-1,3,5(10)-triene (29b). A suspension of **1b** (30 mg, 0.09 mmol) and PtO_2 (10 mol %, 20.4 mg) in ethyl acetate (5 mL) was subjected to 55 bar of hydrogen pressure at room temperature for 12 h. The catalyst was removed by filtration through a short pad of silica gel. Evaporation of the solvent gave **29b** (30 mg, 97%) as colorless oil: R_f 0.35 (petroleum ether/*tert*-butyl methyl ether = 40:1); [α] −10.6 (c = 0.5, $CHCl_3$); UV (CH_3CN) λ_{max} (log ϵ) 200.5 nm (4.610), 279.5 (3.318), 287.0 (3.291); IR (KBr) 2972, 2872; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.83 (s, 3 H), 0.93 (ddd, J = 12.8, 5.0, 3.7 Hz, 1 H), 1.07 (s, 9 H), 1.22−1.26 (m, 1 H), 1.29−1.35 (m, 1 H), 1.36−1.45 (m_c, 1 H), 1.51 (dt, J = 12.8, 3.4 Hz, 1 H), 1.55−1.62 (m_c, 1 H), 1.74−1.84 (m_c, 3 H), 1.93 (ddt, J = 14.6, 5.0, 3.8 Hz, 1 H), 2.04 (ddd, J = 11.9, 8.1, 3.8 Hz, 1 H), 2.29 (ddd, J = 14.6, 5.6, 3.1 Hz, 1 H), 2.63 (dt, J = 8.5, 3.6 Hz, 1 H), 2.75−2.82 (m_c, 1 H), 2.94 (s_{br}, 1 H), 3.25 (dd, J = 8.8, 7.4 Hz, 1 H), 3.79 (s, 3 H), 6.63 (d, J = 2.8 Hz, 1 H), 6.73 (dd, J = 8.5, 2.8 Hz, 1 H), 7.28 (d, J = 8.5 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.23, 23.54, 24.59, 25.41, 26.04, 28.72, 30.64, 32.90, 34.04, 37.37, 41.38, 42.73, 55.08, 72.12, 80.90, 111.8, 113.7, 127.4, 130.7, 139.0, 157.0; MS (70 eV, EI) *m*/*z* (%) 342.3 (79) [M^+], 286.2 (100) [$M^+ - C_4H_9^+$], 267.2 (56) [$M^+ - C_4H_9^+ - H_2O$], 57.1 (29) [$C_4H_9^+$]; EI HRMS *m*/*e* 342.2558, $C_{23}H_{34}O_2$ requires 342.2559.

(+)-17*β*-*tert*-Butoxy-3-methoxyestra-1,3,5(10),6,8(9)-pentaene (30). A suspension of **28** (41 mg, 0.12 mmol), 1,4-cyclohexadiene (12 mmol, 1.13 mL), and Pd/C (5%, 7 mol % Pd, 18 mg) in ethanol (4.0 mL) was stirred for 48 h at 100 °C. After cooling, the reaction mixture was diluted with ether (10 mL). The catalyst was removed by filtration through a short pad of silica gel. Evaporation of the solvent and purification by column chromatography afforded 28 mg (68%) of **30** as colorless solid and 10 mg (24%) of **29a**: R_f 0.28 (petroleum ether/*tert*-butyl methyl ether = 40:1); [α] +5.4 (c = 0.5, $CHCl_3$); UV (CH_3CN) λ_{max} (log ϵ) 229.5 (4.667), 259.0 (3.728), 277.5 (3.651), 288.0 (3.487), 302.5 (2.986), 323.0 (3.181), 338.0 (3.262); IR (KBr) 2964, 1624, 1084; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.70 (s, 3 H), 1.20 (s, 9 H), 1.50−1.82 (m, 4 H), 2.08−2.23 (m, 2 H), 2.65−2.80 (m_c, 1 H), 3.23 (t, J = 8.2 Hz, 2 H), 3.64 (t, J = 7.5 Hz, 1 H), 3.90 (s, 3 H), 7.08−7.22 (m, 3 H), 7.57 (d, J = 8.3 Hz, 1 H), 7.88 (d, J = 8.5 Hz, 1 H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 10.78, 23.90, 24.51, 28.76, 31.90, 34.35, 42.42, 46.25, 55.23, 72.34, 79.92, 106.5, 118.2, 124.8, 124.9, 125.3, 127.4, 130.8, 133.1, 134.4, 156.5; MS (70 eV, EI) *m*/*z* (%) 338.2 (100) [M^+], 281.1 (41) [$M^+ - C_4H_9^+$], 263.1 (61) [$M^+ - C_4H_9^+ - H_2O$]; EI HRMS *m*/*e* 338.2245, $C_{23}H_{30}O_2$ requires 338.2246.

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Supporting Information Available: Experimental procedures with NMR assignments for the compounds **5**−**9**, **11**−**12**, **15**−**17**, **20**−**22**, and **2c**−**e** (12 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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