Areno-annelated estra-1,3,5(10),6,8,11,14,16-octaenes

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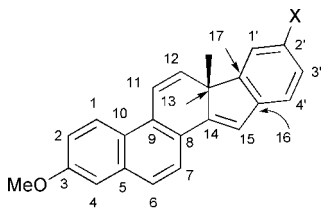
The novel areno-annelated estra-1,3,5(10),6,8,11,14,16-octaenes are synthesized in a simple, four-step protocol. The preparation includes a new areno-annelation of an α-bromo-δ-nitrodiene 3 incorporating a domino Heck–cyclisation–aromatisation sequence with the nitro functionality acting as a leaving group. The framework of the resulting areno-annelated estra-1,3,5(10),16-tetraenes can be dehydrogenated easily with DDQ to give the title compounds.

Estrone-derived molecules often show a strong interaction with the estradiol receptor ERα and can have estrogenic or antiestrogenic character. Synthetic estrogens have been used in hormone replacement therapy and have been targeted for the development of radioligands suitable for early detection of human estrogen-positive breast cancer. The influence of substitution in estradiols on the binding affinity towards ERα has already been studied to some degree.[1] Much less work has been carried out on the influence of structural changes within the framework of the steroids on the binding affinity.[2] In particular, the addition of insaturations within the frame should lead to a change in affinity due to a change in conformation, that is in the overall topology of the molecule. Thus, while estra-3,17β-diol is the natural estrogen *par excellence*, 17β-dihydroequilenin shows a weaker estrogenic character.[3] On the other hand, 17β-dihydroequilin[3] and some estra-1,3,5(10),6-tetraenes have shown a greater *in vitro* binding affinity to ERα than their saturated analogues, the corresponding estra-1,3,5(10)-trienes.[4] Thus, it is important to better assess the effect of the molecular shape and topology of estrone-derived molecules on their binding affinity to ERα, their estrogenity, and their carcinogenity. Within our ongoing research on estrone-based diagnostica for breast cancer the synthesis of the expanded estrones of type A with an annelated aromatic E-ring[5] and a totally dehydrogenated skeleton was targeted and will be described in the following.



A

For the E-ring annelation the introduction of a bromo functionality at C-17 and of a formyl group at C-16 was envisaged to facilitate a subsequent ring annelation at C-16/C-17.[6] 3-Methoxyestrone (**1**) can be transformed easily to 17-bromo-16-formylestra-1,3,5(10),16-tetraene[7] (**2**) by an Arnold–Vilsmeier reaction.[8] The C-16 formyl functionality can be derivatised by Wittig- and analogous olefination procedures. The C-17 bromo functionality lends itself to Heck-olefination with a number of different olefins such as alkyl acrylates, acrylonitrile and methylvinyl ketone. When elevated temperatures (90 °C) are used in this process, a mixture of compounds is formed. This is comprised of the 'open' trienes as the primarily formed Heck products, and a number of cyclisation products[9] all stemming from the triene but differing in the position of the newly formed double bonds within the E-ring.

When **2** is reacted with nitromethane under ultrasound,[10] the α-bromo-δ-nitrodiene **3** is produced. Only the *E*-isomer could be detected. **3** reacts under Heck conditions with alkenes such as acrylonitrile, styrene or alkyl acrylates to give the areno-annelated estra-1,3,5(10),16-tetraenes (*i.e.*, **4** and **5**, see Scheme 1) in one step. In most sequences previously published, which involve a Heck reaction to form a triene and a subsequent cyclisation of the triene to either a cyclohexadiene or an arene in the presence of an oxidant, the methods incorporate successive steps where the cyclisation/dehydrogenation procedure necessitates the use of high reaction temperatures. In the one-step domino-type[11] procedure shown here, the reaction temperatures are much lower. It is supposed that the nitro group activates the triene system formed by the Heck reaction for the subsequent cyclisation. The last step in the sequence, the formal elimination of 'HNO_2', may be either base-induced or may involve the expulsion of a nitrite[12,13] to form a π-allyl palladium complex with subsequent deprotonation of **8** (Scheme 2). Thus, the success of this novel *one-pot* areno-annelation lies in the nitro group acting both as the activator of the cyclisation reaction and as the leaving group. Experiments have been carried out both with $Pd(PPh_3)_4$ as catalyst and with $Pd(OAc)_2$ in the presence of tris(*o*-tolyl)phosphine as ligand. In all experiments triethylamine has been used as the base and reducing agent.

Only a few precedents of a multiple introduction of double bonds within a steroidal framework are known in the literature.[14] Nevertheless, the total dehydrogenation of the steroidal framework of **4**, **5**, **9**, and **12** proceeded with greater ease than expected and subjecting these E-areno-annelated compounds to dichlorodicyanoquinone (DDQ) in refluxing benzene readily gave the areno-estra-1,3,5(10),6,8,11,14,16-octaenes **10**, **11**, **13** and **14** (Scheme 3). In **11**, **13** and **14** four double bonds were introduced into the steroidal frame; in **10**, which results from a Wittig-olefination–Heck reaction–cyclisation sequence in 45% overall yield, even five double bonds. It could be shown that the use of 5–7 equiv. of DDQ gave the best yields in the reaction. Although DDQ is known as a dehydrogenation agent,[15] this seems to be one of the few cases known of facile multiple dehydrogenation of a steroidal system with DDQ. That this is not the result of the existence

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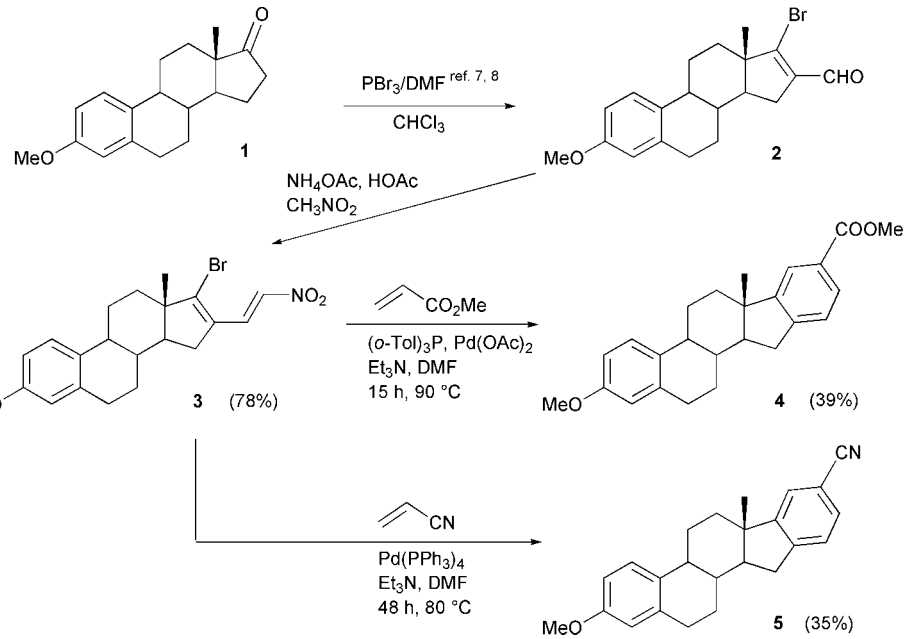
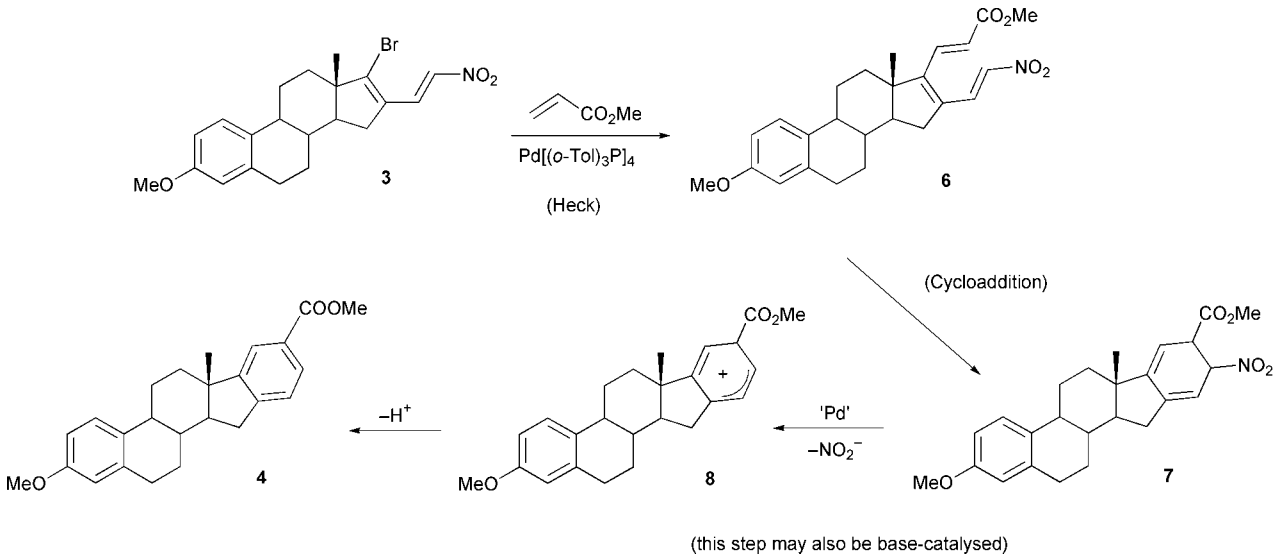
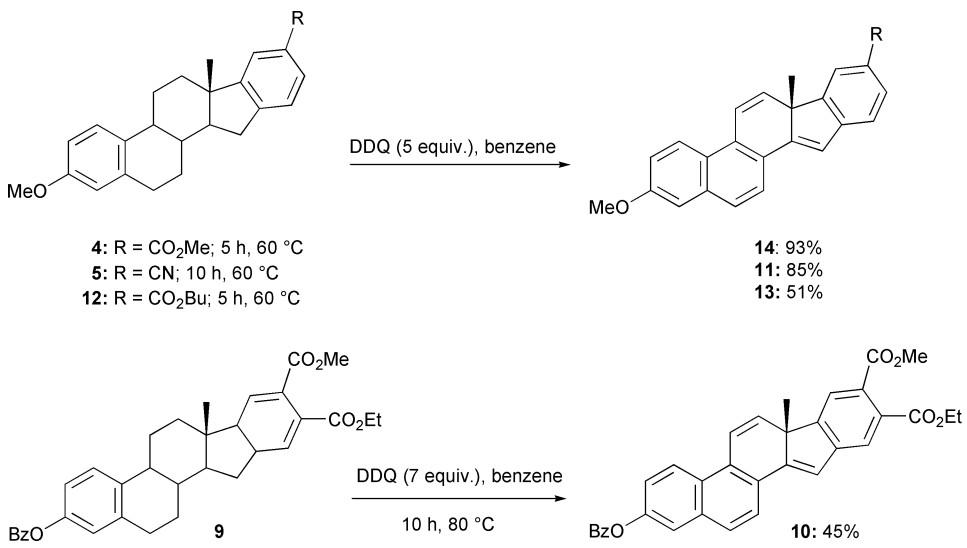


Scheme 1 E-Annulated estranes by the Arnold–Vilsmeer, nitro olefination, tandem Heck cycloaddition/aromatisation protocol.



Scheme 2 The route of the domino Heck cycloaddition/aromatisation reaction sequence.

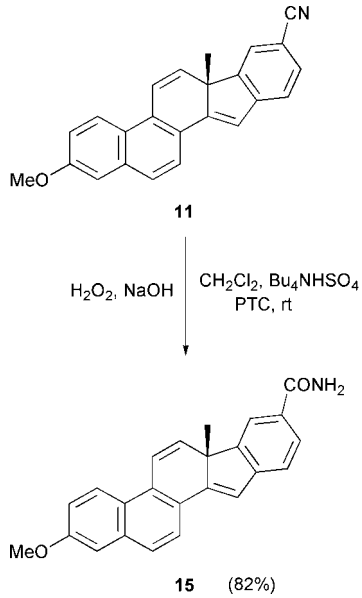


Scheme 3 Dehydrogenation of estranes.

of an unsaturation at C-16/C-17 can be seen in the fact that **2** and similar estra-1,3,5(10),16-tetraenes dehydrogenate only sluggishly under the same conditions (benzene, 80 °C, 2 h). Reaction of **2** itself or related compounds with DDQ in toluene at higher temperature (110 °C) results in the formation of a number of products.

The functional groups on the E-ring of the areno-estra-1,3,5(10),6,8,11,14,16-octaenes can be transformed with ease. Thus, the cyano group in **11** can be hydrolysed to the amido group (*i.e.*, to **15**) with H_2O_2/NaOH under PTC conditions (Scheme 4).[16] The double bonds within the frame of **11** are not epoxidised or hydroxylated under these conditions.

The UV spectra of the estra-1,3,5(10)6,8,11,14,16-octaenes have been measured in acetonitrile (Fig. 1). For comparison the UV spectra of *trans*-stilbene, benzoic acid, methoxynaphthalene and 3-methoxy-estra-1,3,5(10)triene-17-one in acetonitrile have been included in the figure. The large bathochromic shift of the absorption bands exhibited by **10**, **13** and **14** in comparison to the molecules just named indicates that in the dehydrogenated areno-annelated estranes there is an appreciable conjugation of the π-systems, although the sp^3-hybridised carbon at C-14 with the angular methyl group



Scheme 4 Partial hydrolysis under PTC conditions.

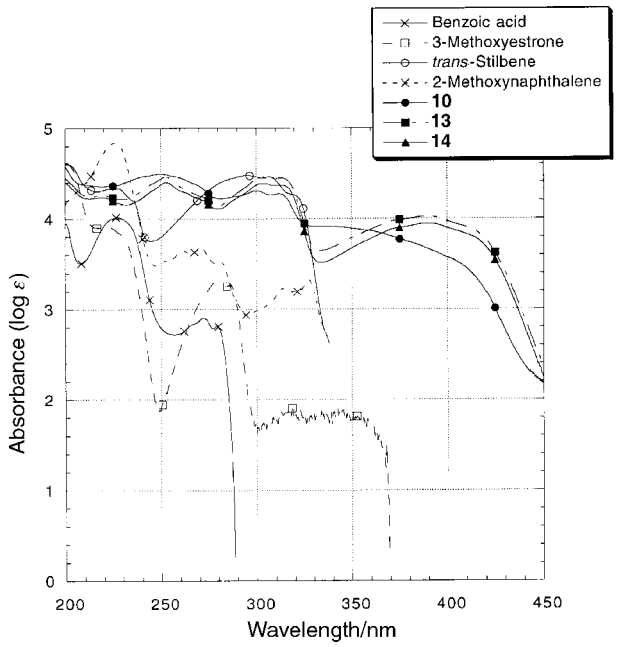


Fig. 1 UV spectra in acetonitrile.

forces the molecules to adopt a very shallow 'V' where planar rings A/B form one side and ring E the other side. The compounds are fluorescent in solution; thus **14** shows a fluorescence maximum at $\lambda = 442$ nm in acetonitrile (excitation at $\lambda = 368$ nm). The shift of the fluorescence maximum seems solvent independent $\lambda = 443$ nm in ethanol).

Studies on the binding affinity of these molecules and of C-7 substituted derivatives to the estrogen receptor ERα are underway, as are studies on the electro-optical properties of derivatives of these compounds with long-chain substituents at positions C-3 and C-2′, in view of the preparation of cholesteric fluorescent liquid crystals.

Experimental

General

Melting points were measured on a Yanaco microscopic hot-stage and are uncorrected. Infrared spectra were obtained with JASCO IR-700 and Nippon Denshi JIR-AQ2OM machines. ^{1}H and ^{13}C NMR spectra were recorded with a JEOL EX-270 (270 MHz [^{1}H], 67.8 MHz [^{13}C]) spectrometer or with a JOEL JNM-LA 395 (400 MHz [^{1}H], 100.4 MHz [^{13}C]) spectrometer. The chemical shifts are relative to TMS (solvent $CDCl_3$, unless otherwise noted). Assignments of ^{13}C signals were aided by DEPT measurements; (+) denotes primary and tertiary, (−) secondary and C_{quat} quaternary carbons. Mass spectra were obtained with a JMS-01-SG-2 spectrometer (EI, 70 eV). Column chromatography was carried out on Wakogel 300.

Syntheses

17-Bromo-3-methoxy-16-*E*-(β-nitroethenyl)estra-1,3,5(10),16-tetraene (3). A mixture of 17-bromo-16-formyl-3-methoxyestra-1,3,5(10),16-tetraene (**2**) (375 mg, 1.0 mmol), ammonium acetate (167 mg, 2.17 mmol) and acetic acid (157 mg, 2.62 mmol) in nitromethane (0.65 mL) was heated at 65 °C for 6 h under sonication. Thereafter, the solution was poured into CH_2Cl_2 (60 mL) and washed with water (3 × 40 mL). The organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel (hexane–ether 3 : 1) to give **3** (327 mg, 79%) as yellow needles; mp 218–219 °C (hexane–ether 1 : 1). IR (KBr) *ν* 2924, 1618, 1520, 1334, 1253, 1040, 952, 675 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) *δ* 0.94 (s, 3H, CH_3), 1.02–2.93 (m, 13H), 3.78 (s, 3H, OCH_3), 6.65 (s, 1H), 6.73 (d, 1H, ^3J 8.5 Hz), 7.13 (d, 1H, ^3J 13.4 Hz), 7.24 (d, 1H, ^3J 8.5 Hz), 7.93 (d, 1H, ^3J 13.4 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$, DEPT 90, DEPT 135) *δ* 15.6 (+, CH_3), 26.1 (−), 27.2 (−), 29.5 (−), 31.2 (−), 34.5 (−), 37.5 (+, CH), 44.1 (+, CH), 51.6 (C_{quat}), 53.5 (+, OCH_3), 55.2 (+, CH), 111.6 (+, CH), 113.9 (+, CH), 126.0 (+, CH), 131.9 (C_{quat}), 132.3 (C_{quat}), 133.2 (+, CH), 137.6 (C_{quat}), 138.4 (+, CH), 151.6 (C_{quat}), 157.7 (C_{quat}); MS (FAB, 3-nitrobenzyl alcohol) *m/z* (%) 419 ([^{81}BrM]$^+$, 11), 417 ([^{79}BrM]$^+$, 10). HRMS found: 417.0944; calc. for $C_{21}H_{24}O_3N^{79}Br$: 417.0940. Anal. calc. for $C_{21}H_{24}O_3NBr$ (418.33): C, 60.29; H, 5.78; N, 3.35; found: C, 60.31; H, 5.86; N, 3.28%.

General procedure for the E-ring annelation of 3. *Procedure A [use of P(o-tol)$_3$ as catalyst]*. In a screw-cap high-pressure flask, a deareated solution of **3** (126 mg, 0.3 mmol), triethylamine (0.30 mL, 212 mg, 2.1 mmol), methyl acrylate (0.43 mL, 413 mg, 4.8 mmol), $Pd(OAc)_2$ (30 mg, 0.09 mmol) and tri-*o*-tolylphosphine (182 mg, 0.6 mmol) in DMF (4.5 mL) was heated for 68 h at 90 °C. Thereafter, the cooled solution was poured into water (100 mL) and extracted with ether (3 × 100 mL). The organic phase was washed with water (100 mL), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel (hexane–ether 5 : 1) to give **4** (44.2 mg, 39%) as a colorless solid; mp 163–164 °C (hexane–ether 5 : 1). ^{1}H NMR (270 MHz, $CDCl_3$) *δ* 0.96 (s, 3H, CH_3), 1.01–2.91 (m, 13H), 3.74 (s,

3H, OCH_3), 3.76 (s, 3H, OCH_3), 6.63 (s, 1H), 6.68 (d, 1H, ^3J 8.4 Hz), 7.22 (d, 1H, ^3J 8.4 Hz), 7.31 (d, 1H, ^3J 7.6 Hz), 7.78 (s, 1H), 7.81 (d, 1H, ^3J 7.6 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$, DEPT 90, DEPT 135) δ 19.5 (+, CH_3), 26.9 (−), 28.3 (+, CH_3), 30.1 (−), 32.6 (−), 35.4 (−), 38.2 (+, CH), 44.8 (+, CH), 45.9 (C_{quat}), 52.2 (+, CH), 55.5 (+, CH_3), 57.0 (+, CH), 111.7 (+, CH), 114.1 (+, CH), 122.2 (+, CH), 125.3 (+, CH), 126.4 (+, CH), 128.1 (+, CH), 128.9 (C_{quat}), 133.1 (C_{quat}), 138.3 (C_{quat}), 149.2 (C_{quat}), 155.5 (C_{quat}), 158.0 (C_{quat}), 167.7 (C_{quat}, C=O); MS (FAB, 3-nitrobenzyl alcohol) *m*/z (%) 377 ([MH]$^+$, 14), 376 (M$^+$, 15). HRMS found: 377.2111; calc. for $C_{25}H_{29}O_3$: 377.2117 ([MH]$^+$, FAB).

Procedure B [*use of Pd(PPh$_3$)$_4$ as catalyst*]. A deaerated solution of **3** (200 mg, 0.48 mmol), triethylamine (250 mg, 350 μL) $Pd(PPh_3)_4$ (35 mg, 0.03 mmol) and acrylonitrile (760 mg, 950 μL) in DMF (20 mL) was heated in a screw-cap high-pressure tube at 80 °C for 48 h. Thereafter, the solution was poured into water (150 mL) and extracted with chloroform (3 × 50 mL). The combined organic phases were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel (hexane–ether 5 : 1) to give **5** (58 mg, 35%) as a pale yellow solid; mp 173–174 °C. IR (KBr) *v* 2924, 2850, 2222, 1610, 1501, 1257, 1046 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (s, 3H, CH_3), 1.49–2.92 (m, 13H), 3.79 (s, 3H, OCH_3), 6.66 (d, 1H, ^4J 2.6 Hz), 6.74 (dd, 1H, ^3J 8.4, ^4J 2.6 Hz), 7.24 (d, 1H, ^3J 8.4 Hz), 7.33 (d, 1H, ^3J 7.5 Hz), 7.38 (d, 1H, ^4J 1.2 Hz), 7.44 (dd, 1H, ^3J 7.5, ^4J 1.2 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$, DEPT 90, DEPT 135) δ 19.2 (+, CH_3), 26.3 (−), 27.8 (−), 29.6 (−), 32.4 (−), 34.7 (−), 37.6 (+, CH), 44.2 (+, CH), 45.8 (C_{quat}), 55.2 (+, CH), 56.2 (+, OCH_3), 109.8 (C_{quat}), 111.5 (+, CH), 113.9 (+, CH), 119.6 (C_{quat}, CN), 124.4 (+, CH), 125.8 (+, CH), 126.1 (+, CH), 130.4 (+, CH), 132.2 (C_{quat}), 137.7 (C_{quat}), 148.6 (C_{quat}), 155.5 (C_{quat}), 157.5 (C_{quat}); MS (70 eV) *m*/z (%) 343 (M$^+$, 100), 173 (36), 160 (34). HRMS found: 343.1940; calc. for $C_{24}H_{25}ON$: 343.1936.

General procedure for areno-annelated estra-1,3,5(10),16-tetraenes: 3-methoxy-2′-methoxycarbonylbenzoestra-1,3,5(10),6,8,11,14,16-octaene (14). A mixture of **4** (8.0 mg, 21.2 × 10^{-3} mmol) and DDQ (24.0 mg, 0.11 mmol) in benzene (0.5 mL) was heated at 60 °C for 5 h. Thereafter, the solvent was evaporated *in vacuo* and the residue was subjected to column chromatography on silica gel (hexane–ether 3 : 1) to give **14** (7.3 mg, 93%) as a yellow solid; mp 198–200 °C. IR (KBr) *v* 2924, 1717, 1620, 1290, 1245, 1105, 1034 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.48 (s, 3H, CH_3), 3.94 (s, 6H, OCH_3, $COOCH_3$), 6.76 (d, 1H, *J* 9.6 Hz), 6.86 (s, 1H), 7.14 (s, 1H), 7.15 (d, 1H, *J* 9.6 Hz), 7.23 (d, 1H, *J* 9.2 Hz), 7.39 (d, 1H, *J* 7.9 Hz), 7.68 (s, 1H), 7.77 (s, 1H), 7.99 (d, 1H, *J* 7.9 Hz), 8.07 (d, 1H, *J* 9.2 Hz), 8.11 (s, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 28.3 (+, CH_3), 52.0, 54.0, 55.4, 106.8, 119.1, 121.4, 122.3, 122.4, 123.7, 124.3, 125.1, 125.8, 126.5, 127.1, 129.0, 129.3, 135.5, 136.7, 147.9, 150.0, 157.7, 159.1, 167.6 (C=O); UV (CH_3CN) λ_{max} (log ε) 253 (4.47), 304 (4.46), 390 nm (4.02); MS (70 eV) *m*/z (%) 368 (M$^+$, 100), 353 ([M − CH_3]$^+$, 54). HRMS found: 368.1411; calc. for $C_{25}H_{20}O_3$: 368.1412.

3-Methoxy-2′-cyanobenzoestra-1,3,5(10),6,8,11,14,16-octaene (11). Analogously, a mixture of **5** (30 mg, 8.7 × 10^{-2} mmol) and DDQ (99 mg, 43.6 × 10^{-2} mmol) in benzene (1 mL) (60 °C, 10 h) gave after work-up **11** (25 mg, 85%) as a pale yellow solid. IR (KBr) *v* 2924, 2845, 2214 (CN), 857, 825, 784, 738 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.47 (s, 3H, CH_3), 3.95 (s, 3H, OCH_3), 6.69 (d, 1H, ^3J 8.5 Hz), 6.85 (s, 1H), 7.15–7.30 (m, 3H), 7.41 (d, 1H, ^3J 7.2 Hz), 7.57 (d, 1H, ^3J 7.2 Hz), 7.60–7.75 (m, 3H), 8.06 (d, 1H, ^3J 9.3 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$, DEPT 90, DEPT 135) δ 28.3 (+, CH_3), 54.2 (C_{quat}), 55.4 (+, OCH_3), 106.8 (+, CH), 107.9 (C_{quat}), 119.3 (+, CH), 122.1 (+, CH), 122.7 (+, CH), 123.0 (C_{quat}), 123.6 (+, CH), 123.8 (+, CH), 124.0 (C_{quat}), 124.6 (+, CH), 125.1 (+, CH), 125.4 (C_{quat}), 127.3 (+, CH), 128.8 (C_{quat}), 131.8 (+, CH), 135.6 (C_{quat}), 135.8 (+, CH), 143.5 (C_{quat}), 147.9 (C_{quat}), 150.6 (C_{quat}), 157.8 (C_{quat}); MS (70 eV) *m*/z (%) 335 (M$^+$, 100), 320 ([M − CH_3]$^+$, 63), 277 (44). HRMS found: 335.1315; calc. for $C_{24}H_{17}ON$: 335.1310.

Partial hydrolysis of 11 to 3-methoxy-2′-aminocarboxylbenzoestra-1,3,5(10),6,8,11,14,16-octaene (15). To **11** (20 mg, 0.06 mmol) and tetra-n-butylammonium hydrogensulfate (41 mg, 0.12 mmol) in CH_2Cl_2 (2 mL) were added successively aq. H_2O_2 (0.4 mL, 35 wt%) and 20 wt% aq. NaOH (0.32 mL). The resulting solution was stirred at 0 °C for 1 h, thereafter at rt for 3 h. Then the reaction mixture was poured into water and extracted with chloroform. The organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel (toluene–ethyl acetate 1 : 1) to give **15** (17 mg, 82%) as a pale yellow solid. IR (KBr) *v* 3358, 2924, 2854, 1660, 1615, 1382, 1036, 941, 855, 759, 735 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.41 (s, 3H, CH_3), 3.88 (s, 3H, OCH_3), 5.52–6.20 (br d, 2H), 6.79 (s, 1H), 6.69 (1H, ^3J 9.5 Hz), 7.07–7.20 (m, 3H), 7.32 (d, 1H, ^3J 7.5 Hz), 7.61 (m, 3H), 7.91 (s, 1H), 7.99 (d, 1H, ^3J 9.3 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$, DEPT 90, DEPT 135) δ 28.4 (+, CH_3), 54.0 (C_{quat}), 55.4 (+, OCH_3), 106.9 (+, CH), 112.8 (C_{quat}), 119.1 (+, CH), 120.9 (+, CH), 121.4 (+, CH), 122.4 (+, CH), 122.6 (C_{quat}), 123.7 (+, CH), 124.1 (+, CH), 125.1 (+, CH), 125.6 (C_{quat}), 126.5 (+, CH), 127.1 (+, CH), 128.7 (C_{quat}), 129.3 (C_{quat}), 135.3 (C_{quat}), 136.6 (+, CH), 136.8 (C_{quat}), 147.4 (C_{quat}), 155.7 (C_{quat}), 169.6 (C_{quat}); MS (70 eV) *m*/z (%) 353 (M$^+$, 100), 335 ([M − H_2O]$^+$, 61), 320 (32), 309 (24), 277 (25), 105 (88). HRMS found: 353.1417; calc. for $C_{24}H_{19}O_2N$: 353.1416.

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