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Steroids

Total Synthesis of (–)-C/D-*cis*-Dehydro-3-*O*-methyl-estradiols

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Dedicated to Professor Horst Kunz on the occasion of his 75th birthday

Abstract: A convergent synthesis of (–)-dehydro-3-*O*-methyl-C/D-*cis*-estradiol started from stereochemically defined substituted optically active 3-(2-arylethyl)-γ-butyrolactones. Regioselective bromination of the anisyl moiety, reductive ring opening of the iodolactone, and protecting-group changes led to a Weinreb amide. This then underwent an intramolecular Grignard reaction closing the B-ring to give a tetralone with defined configuration. Introduction of C-11 through an allyl Grignard addition and subsequent ring-closing metathesis gave a tetrahydro phenanthrene derivative. Oxidation of the side-chain alcohol resulted in the key aldehyde group, and a final samarium-diiodide-mediated reductive D-ring annulation resulted in the generation of the target dehydro-C/D-*cis*-estradiol derivatives with high stereoselectivity. Structure elucidation was carried out using NOEDS (nuclear Overhauser enhanced differential spectroscopy) analysis on the one hand, and conversion into known 3-*O*-methyl-13β-estradiols by double-bond hydrogenation on the other. Further efforts to use this estradiol synthetic strategy to generate more complex steroidal natural products and pharmaceutically interesting compounds are in progress.

Introduction

Compared to the better known C/D-*trans*-configured steroidal natural products and pharmaceutically important compounds, their congeners containing a C/D-*cis* ring junction are less widespread.[1] Focussing on C/D-*cis*-configured steroid natural products with high biological activity, cardiac glycosides of the cardenolide and bufadienolide families have been intensively investigated.[2] In addition, the marine-sponge-derived Xestobergsterols A–C and Contignasterol (Figure 1) show some antihistaminic properties.[3] Ritterazines A–M (highly active) as well as Aglaiaglabretol B and Breynceanothanolic acid (less active) have varying cytotoxic activities.[4]

(–)-C/D-*cis*-Estradiol has the basic tetracyclic framework with configurationally defined B/C and C/D ring junctions. The change from a C/D-*trans* to a C/D-*cis* configuration causes a structural change in the shape of the steroid that results in a significantly decreased affinity to the estrogen receptors, and a loss of the original biological activity.[5] C/D-*cis*-Estradiol and its derivatives have been discussed in the context of the investigation and development of new steroidal drugs, e.g., anti-cancer drugs, without standard steroid–receptor interactions:[6] While both Mifepristone (C/D-*trans*) and Onapristone (C/D-*cis*) show progesterone-receptor-blocking properties, only Onapristone also has a low antiglucocorticoide activity.[7]

Originally, 13α/14α-(–)-estrone (13-*epi*-*lumi*-estrone) was prepared by Butenandt by the one-step photochemical isomerisation of 13β/14α-(–)-estrone.[8] Several further syntheses of steroidal compounds used the same reaction to establish a C/D-*cis* ring junction.[9] Alternatively, reductions (Birch) and catalytic hydrogenations of olefin precursors allowed the establishment of a 13-methyl group and a 14-hydrogen with a *cis* configuration.[10,11]

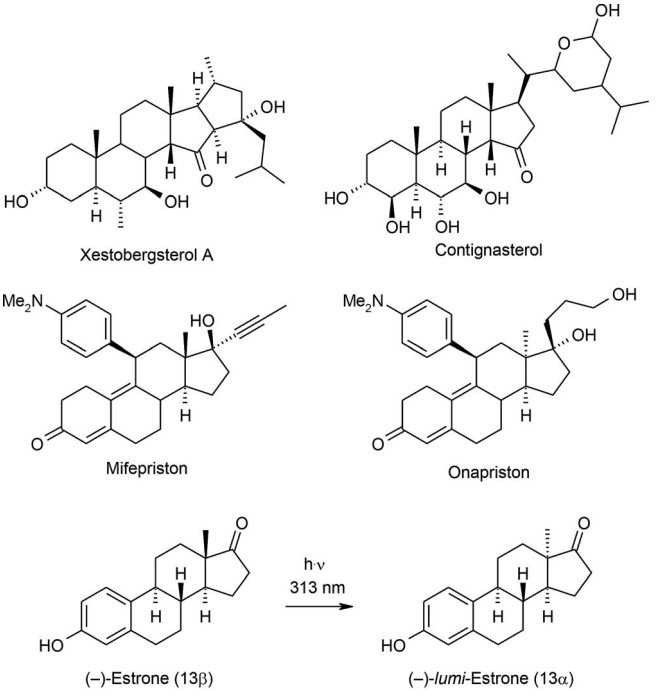

Figure 1. Selected biologically active steroids, synthesis of (–)-C/D-*cis*-estrone.

A long-term program in our group focusses on the syntheses of steroids with a C/D-*cis* ring junction. A brief retrosynthesis of

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an estradiol derivative **V** is outlined in Figure 2: Estradiol **V** should be generated from tetralone **VIII** by C-11 introduction and C/D-ring closure using a radical cascade cyclisation via diene **VI** or following a stepwise process via cyclohexadiene **VII**. Tetralone **VIII** can be obtained from lactone **IX** by intramolecular Grignard reaction (X = Br) or by Vilsmeier cyclisation (X = H) from amide **X**. Amide **X** (X^c represents an optically active pyrrolidine moiety operating as a chiral auxiliary) is the product of an auxiliary-directed zwitterionic ketene aza-Claisen rearrangement starting from (unsaturated) 4-arylbutanoic acid fluoride **XI** (A/B ring fragment) and *N*-allylpyrrolidine **XII** (C/D ring fragment) incorporating a trisubstituted olefin moiety. Allylamine **XII** and arylbutanoic/butenoic acid derivative **XI** can be synthesized by short reaction sequences as shown in Figure 3.

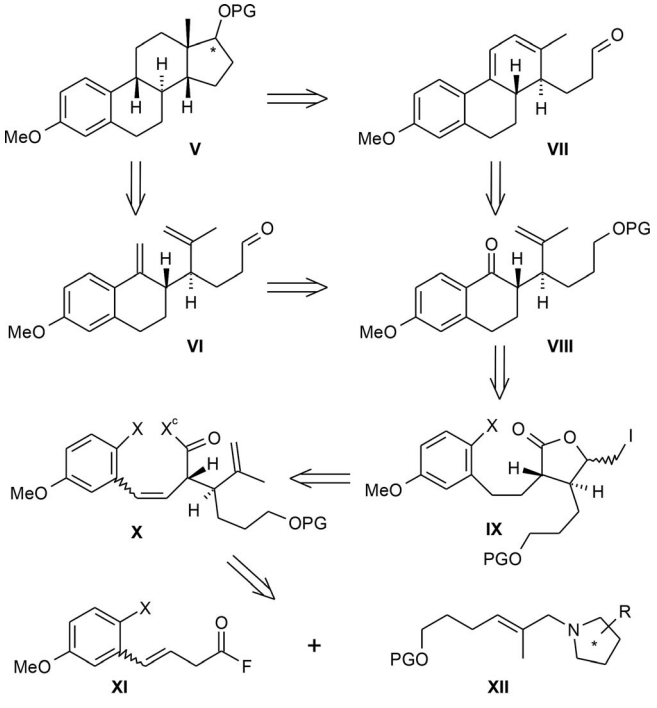


Figure 2. Retrosynthesis of (–)-C/D-*cis*-estradiol.

Following the convergent strategy, the synthesis of key intermediate lactam **8** started from *trans*-4-hydroxy-L-proline (**1**), 1,4-butanediol (**3**), and *m*-anisaldehyde (**6**) (Figure 3). An initial six-step sequence allowed us to convert *trans*-4-hydroxy-L-proline (**1**) into (2*S*,3*R*)-4-*tert*-butoxy-2-(phenoxymethyl)pyrrolidine (**2**) in about 28 % overall yield.[12] After generating allylic alcohol **4** (three steps, 81 % yield from butanediol **3**), it was activated as a mesylate. The mesylate was coupled with amine **2** using a palladium-catalysed reaction to give allylamine **5** (84 % yield). Chain-elongation of *m*-anisaldehyde **6** by Wittig olefination, and subsequent transformation of the acid intermediate delivered acid fluoride **7** (50 % yield). Then, a zwitterionic aza-Claisen rearrangement (aza-ketene Claisen rearrangement) using key compounds **5** and **7** enabled the assembly of a γ,δ-unsaturated amide in 92 % yield, with almost complete simple *anti*-diastereoselectivity and a high asymmetric induction of about 7.5:1.[13] Hydrogenation of the styryl olefin moiety (96 % yield)

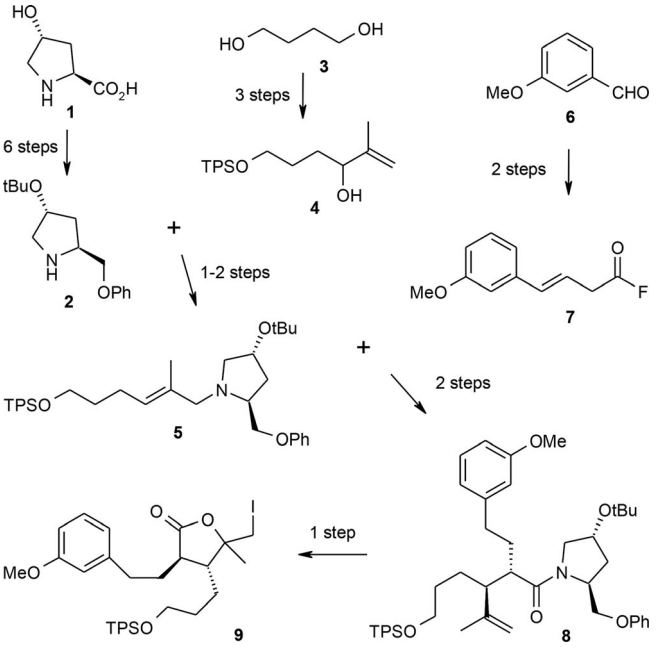


Figure 3. (–)-C/D-*cis*-estradiol: convergent synthesis of the key amide and lactone according to ref.[13] (TPS = *tert*-butyldiphenylsilyl).

gave amide **8** after separation of the minor diastereomers and careful structural elucidation. Finally, iodocyclisation delivered lactone **9** in 68 % yield. Furthermore, most of the chiral auxiliary (i.e., **2**) could be recovered after the aqueous work-up, which allows this material to be reused in another synthesis of allylamine **5**.

Results and Discussion

With the stereochemically defined substituted pyrrolidide **8** in hand, we first attempted to generate tetralone **14** through straightforward B-ring closure under Vilsmeier or Friedel–Crafts conditions. However, these reactions failed because of acid-induced side-reactions.[14] The in-situ-activated amide moiety preferentially underwent cyclisation involving the double bond to form lactones, leaving the aromatic core unaffected.[15] Therefore, a Grignard-type intramolecular acylation was considered. This required a suitably positioned halide within the aromatic ring. Treatment of iodolactone **9** with 1 equiv. of bromine in acetic acid should allow the introduction of the desired 4-bromide.[16] In our first attempts to carry out the bromination, we tried to maintain the TPS ether of the side-chain, but this gave only moderate yields. Using short reaction times (30 min) and low reactant concentrations (40 mol/L), pure α-iodomethyl diastereomer **9α** gave silyl ether **10aα** (α-iodomethyl group) in ca. 25 % yield; the corresponding acetate (i.e., **10bα**) was found to be the major product (50 % yield). The analogous reaction of iodolactone **9β** (β-iodomethyl group) gave silyl ether **10aβ** (β-iodomethyl group) in 23 % yield, and the corresponding acetate (i.e., **10bβ**) in ca. 54 % yield. A reaction time of 26 h was necessary to achieve complete consumption of the starting material. Because of the low stability of the silyl ether moiety under the reaction conditions, the exchange of this protecting

group for acetate could be enforced. Using a mixture of α- and β-iodomethyl lactones **9**, and running the bromination with a high reactant concentration (120 mmol/L), 4-bromide **10b** was isolated in a yield of ca. 88 % (mixture of **10bα/β**). The corresponding 2,4- and 2,6-dibromides were found as minor products (<5 %).[17] However, 2,4-dibromolactone **10eβ** crystallised, which allowed us to check the absolute and relative configuration of the stereogenic centres by X-ray analysis (Figure 4).[18] Reductive ring-opening of iodolactones **10** was achieved using zinc in acetic acid at 65 °C.[19] Acetate **10b** proved to have the optimal substitution pattern, and acid **11b** was obtained in almost quantitative yield. In contrast, TPS-protected lactone **10a** gave the corresponding TPS acid (i.e., **11a**) in about 56 % yield (Scheme 1).[20]

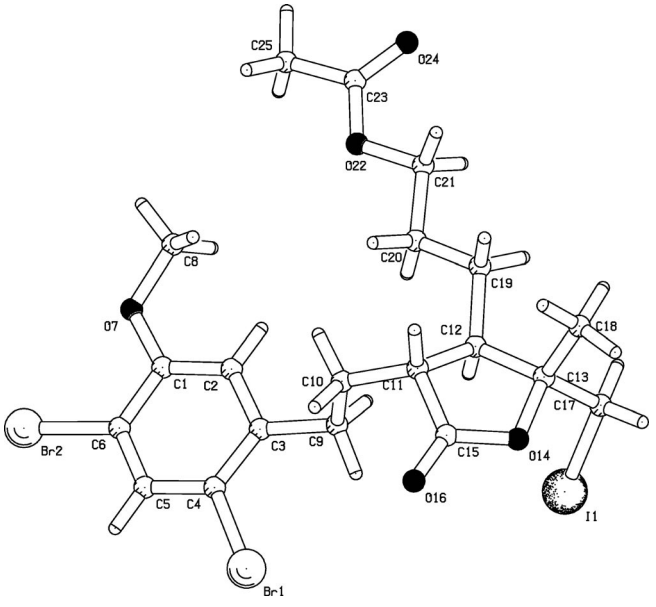
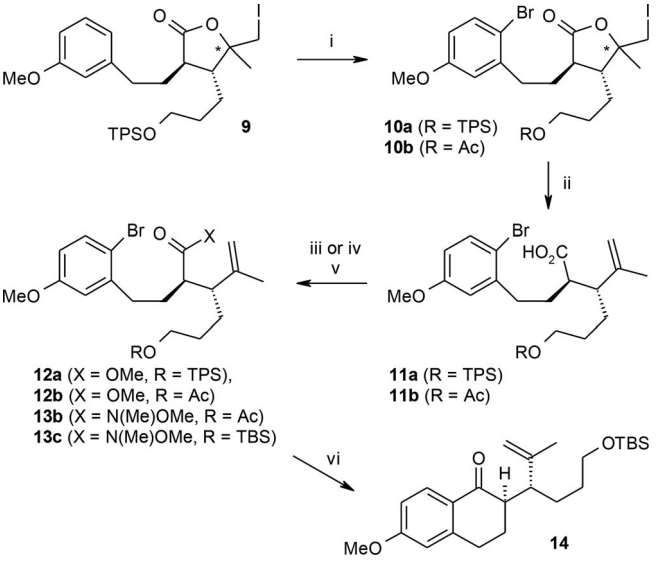


Figure 4. X-ray structure of dibromolactone **10eβ** (only selected hydrogens are shown).

Before B-ring closure, appropriate functionalisation of carboxylic acids **11** had to take place. Methyl ester formation using acidified methanol failed because of competing lactonisation.[15] Starting from TPS acid **11a**, esterification using EDCI [1-ethyl-3-(3-dimethylaminopropyl)carbodiimide] and DMAP [4-(dimethylamino)pyridine] gave a moderate 32 % yield of methyl ester **12a**. In contrast, reaction of acid **11b** with diazomethane delivered the corresponding methyl ester (i.e., **12b**) in 77 % yield.[21] With the aim of avoiding side-reactions during the Grignard ring-closure reaction, the side-chain acetate was replaced by a silyl ether. Initial Zemplén transesterification gave the corresponding alcohol in 97 % yield. However, subsequent TPS-ether formation turned out to be very slow, and only 25 % of ether **12a** (85 % based on recovered starting material) was obtained after 12 d.[22] Alternatively, treatment of acid **11b** with CDI (carbonyldiimidazole), DMAP, and *N*,*O*-dimethylhydroxylamine gave Weinreb amide **13b** in 75 % yield (Figure 5).[23,24] When amide **13b** was subjected to the sequence of Zemplén cleavage and TBS-ether (TBS = *tert*-butyldimethylsilyl) formation, silyl-protected amide **13c** was isolated in 97 % yield over two steps.[25] Finally, B-ring formation was carried out by treatment with *t*BuLi in THF.[26] Even though low temperatures and just 1 equiv. of *t*BuLi were used, the cyclisation of ester **12a** preferentially gave a alcohol product. This indicates a rapid *t*BuLi addition to an intermediate tetralone **14**.[27] In contrast, when halogen–metal exchange was applied to Weinreb amide **13c**, no subsequent addition of *t*BuLi to the C=O group was observed. After work-up using aqueous ammonium chloride, key tetralone **14** was isolated in nearly quantitative yield. Again, the material crystallised, which allowed us to prove by X-ray



Scheme 1. Synthesis of tetralone **14**. α/β determines the position of the iodomethyl group. Reagents and conditions: i) Br_2 (1 equiv.), AcOH, 23 °C, 1.5 h [from **9β**: **10aβ**: 22.7 %, **10bβ**: 53.9 %. from **9α**: **10aα**: 25.2 %, **10bα**: 50 %. from **9α/β**: **10aα/β** (R = TPS): 5 %, **10bα/β**: 88 %]; ii) Zn, AcOH, 65 °C, 24 h (from **10aβ**: **11a** 55.5 %; from **10bα/β**: **11b** 100 %); iii) CH_2N_2, Et_2O (**12b** 77 %); iv) CDI, CH_2Cl_2, 23 °C, 2 h, then HN(Me)OMe•HCl, CH_2Cl_2, reflux, 2 d (**13b**: 75 %); v) 1. NaOMe (cat.), MeOH, 23 °C, 12 h, 2. TPSCl, *i*Pr_2NEt, CH_2Cl_2, 23 °C, 12 d (**12a**: 48 % over two steps) or 2. TBSCl, imidazole, CH_2Cl_2, 23 °C, 2 d (**13c**: 96.5 % over two steps); vi) *t*BuLi, THF, –78 °C, 3.5 h [**14**: 100 % from **13c**; 0 % (TPS ether) from **12a**].

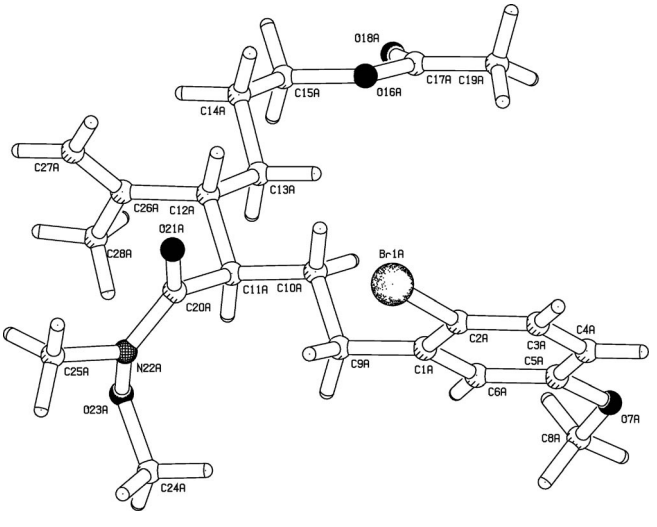


Figure 5. X-ray structure of Weinreb amide **13b** (only selected hydrogens are shown).

analysis that the stereogenic centres had remained unchanged (Scheme 1, Figure 6).[28]

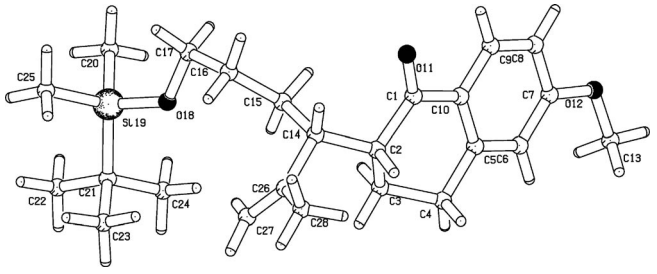
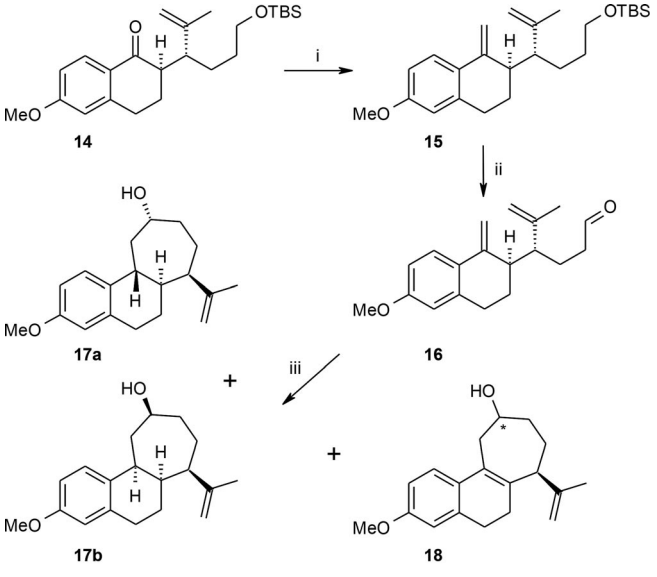


Figure 6. X-ray structure of tetralone **14** (only selected hydrogens are shown).

The first strategy to complete the steroid synthesis was based on a radical cascade process. Thus, the conversion of the keto group of tetralone **14** into an *exo*-methylene group was addressed. Various attempted methylenation reactions, including Peterson, Wittig, Lombardo, and Tebbe olefinations, failed or gave only disappointing yields of methylene tetraline **15**.[29] The best results were achieved by using the Petasis method.[30] Methylenation using the Schrock carbene gave the desired olefin (i.e., **15**) in 90 % yield. Then, the TBS group was removed with TBAF (tetrabutylammonium fluoride) solution in THF, and the resulting alcohol (86 %) was converted into the corresponding aldehyde (i.e., **16**). The choice of oxidation procedure proved to be crucial. Swern oxidation led to mixtures of chlorinated products, and in several runs the *exo*-methylene group isomerised to give a dihydronaphthalene moiety.[31] Under Ley's conditions [TPAP (tetrapropylammonium perruthenate), NMO (*N*-methylmorpholine *N*-oxide)], which are neutral and less electrophilic, aldehyde **16** was obtained in 59 % yield (Scheme 2).[32]

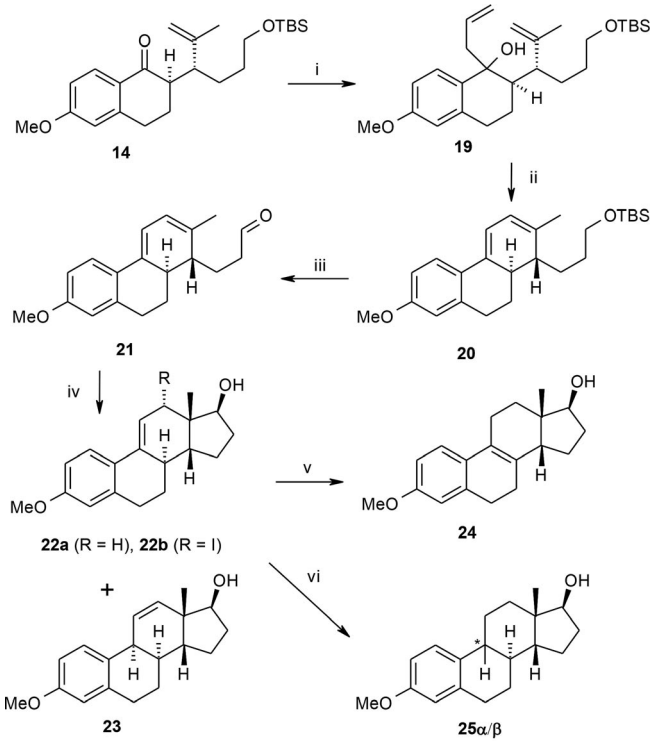


Scheme 2. SmI_2 cyclisation of exomethylenetetraline **16**. Reagents and conditions: i) Cp_2TiMe_2, PhMe, 65 °C, 20 h (**15**: 90 %); ii) 1. TBAF, THF, AcOH, 23 °C, 44 h; 2. TPAP (5 mol-%), NMO, CH_2Cl_2, MS (3 Å), 23 °C, 2 h (**16**: 51 % over two steps); iii) SmI_2, 5 % HMPA in THF, 23 °C, 1.5 h (**17a**: 4 %, mixture of **17b**/**18**: 18 %).

Aldehyde **16** served as the starting material for samarium-diiodide-induced reductive cyclisations.[33,34] Unfortunately, all attempts to form the steroid backbone by radical cascade reactions failed. Even though a wide variety of reaction conditions were tested, no initial 5-*exo*-*trig* ring closure occurred. In some experiments, especially in those where water was added, simple reduction of the aldehyde group of **16** occurred. When reactions were run in THF with HMPA (hexamethylphosphoramide) as a cosolvent, some 7-*endo*-*trig* cyclisations took place to form varying mixtures of tricycles **17a** (about 4 %) and a mixture of **17b**/**18** (about 19 %). The facile attack of the initially formed ketyl radical onto the sterically less hindered methylidenetetraline double bond predominated, delivering a stable intermediate benzyl radical.[35] Finally, a second SmI_2-induced reduction/protonation delivered diastereomers **17a** and **17b**, and trapping with iodine (from the SmI_2 preparation) and subsequent dehydroiodination gave alkene **18** (Scheme 2). Overall, steric shielding of the 5-*exo* olefin position by the methyl group, and low radical-stabilising ability of the isopropylidene moiety, were proposed as the reasons for the failure of the initial 5-*exo*-*trig* cyclisation.[36]

The failure of the attempted radical cascade reaction required a change of strategy, and we now focussed on a stepwise closure of C-ring and D-ring. Starting from key tetralone **14**, allylmagnesium chloride addition delivered alcohol **19** in 96 % yield as a mixture of diastereomers. Then, a ring-closing metathesis using Grubbs (I) catalyst (2.5 mol-%) resulted in the formation of the C-ring.[29a,37] The resulting tertiary benzylic alcohol underwent immediate dehydration to give 1,3-tetrahydronaphthalene **20** in 94 % yield. Since the cyclohexadiene moiety in **20** was highly susceptible to dehydrogenation, all subsequent reactions required careful exclusion of oxygen and avoidance of strongly oxidising conditions. TBAF-mediated cleavage of the TBS ether gave an intermediate alcohol (80 % yield). Again, the choice of conditions for the subsequent oxidation proved to be crucial. Swern oxidation caused an immediate aromatisation of the C-ring moiety, and no cyclohexadienyl aldehyde **21** was isolated.[31,38] In contrast, carefully monitored oxidation using TPAP/NMO (Ley's conditions) gave aldehyde **21** in 78.4 % yield (63 % over two steps; Scheme 3).[32]

When aldehyde **21** was subjected to SmI_2-mediated reductive cyclisation conditions, the D-ring closure to generate dehydro-13β-estradiol derivatives took place.[3,39] Treatment of **21** with freshly prepared SmI_2 solution in THF/HMPA delivered a mixture of regioisomeric $\Delta^{9(11)}$ olefin **22a** (14.2 %) and $\Delta^{11(12)}$ olefin **23** (10.5 %). In addition, $\Delta^{9(11)}$ iodide **22b** was obtained in 10.6 % yield. Upon standing (preferentially in $CDCl_3$), $\Delta^{9(11)}$ isomer **22a** underwent slow double-bond isomerisation to form $\Delta^{8(9)}$-dehydro-13β-estradiol derivative **24** (mixtures of **22a** and **24** were obtained).[40] All isomers were separated by column chromatography and preparative HPLC. The relative configuration of the new stereogenic centres in **22** and **23** was proved by NOEDS (nuclear Overhauser enhanced differential spectroscopy) analysis. This indicated that this key step, installing C-13 and C-17 of the steroid backbone, proceeded with a high diastereoselectivity (remote stereocontrol, 1,2-asymmetric induction).[41] In this series, the lack of a sterically unhindered terminal alkene and the increased radical-acceptor properties of the aryl butadiene subunit represented the driving force to



Scheme 3. Synthesis of (–)-C/D-*cis*-3-*O*-methylestradiols. Reagents and conditions: i) $H_2C{=}CHCH_2MgCl$, THF, –78 °C to –20 °C, 4 h (**19**: 96 %); ii) Grubbs (I) catalyst (2 × 2.5 mol-%), CH_2Cl_2, reflux, 22 h + 24 h (**20**: 94 %); iii) 1. TBAF, THF, AcOH, 23 °C, 42 h, 2. TPAP (5 mol-%), NMO, CH_2Cl_2, MS (3 Å), 23 °C, 2 h (**21**: 63 % over two steps); iv) SmI_2, 5 % HMPA in THF, –40 °C to –20 °C, 1.5 h (**22a**: 8.2 %, **22b**: 10.6 %, **23**: 10.5 %); v) $CDCl_3$ (cat. H^+) 23 °C (2:3 mixture of **22a** and **24**: 6 %); vi) 1,4-cyclohexadiene, Pd/C (5 %), EtOH, 23 °C, 2 d (**25α**: 86 %, **25β**: 14 %).

start the crucial 5-*exo-trig* cyclisation. However, the overall yield of the ring closure (about 35 % overall) still requires optimisation. Analysis of literature precedent revealed that reductive five-membered ring annulation reactions between an aldehyde and a cyclohexadiene (without an angular methyl group) have been described through Ni-catalysed hydrosilylation (40–60 % yield).[42] SmI_2-induced 5-*exo-trig* cyclisations involving sterically congested olefins always required α,β-unsaturated carbonyl systems as radical acceptors, and yields of up to 60–70 % have been reported for selected examples.[43]

For analytical purposes, completion of the 3-*O*-methylestradiol synthesis required the removal of the C-ring double bond. Catalytic hydrogenation of $\Delta^{9(11)}$-dehydroestradiol **22a** with cyclohexadiene/Pd/C in methanol gave an 86:14 mixture of (–)-10-*epi*-C/D-*cis*-estradiol (–)-**25α** and (–)-C/D-*cis*-estradiol (–)-**25β** in quantitative yield.[44] The analytical data of the target molecules were found to be consistent with those published in the literature, proving the general applicability of the strategy (Scheme 3).[45]

The stereochemical outcome of the SmI_2-induced reductive cyclisation can be rationalised as follows. After the first SmI_2-mediated reduction of aldehyde **21**, the resulting ketyl radical **a** undergoes 5-*exo-trig* addition to the sterically more shielded methyl-substituted terminus of the cyclohexadiene moiety. This ring-closing reaction goes through an envelope-shaped transition state with a quasi-*cis* arrangement of 14-CH, the adjacent 13-C-methyl group, and the oxygen, to give the C/D-*cis* ring junction with 14-CH and 13-CMe in a β configuration in **b**. The resulting cinnamyl radical mesomers (i.e., **b1** and **b2**) were trapped by a second equivalent of SmI_2 to form the corresponding cinnamyl anion (i.e., **c1** and **c2**), which finally underwent α-protonation at C-12 to give $\Delta^{9(11)}$-dehydroestradiol derivative **22a**, and at C-10 to give $\Delta^{11(12)}$-dehydroestradiol derivative **23** (*cis* relative to 9-CH), respectively. NOEDS analyses of dehydroestradiols **22a** and **23** always showed contacts between 18-Me and 14-CH, as well as between 8-CH and 17-CH, which allowed us to assign the relative configurations of the new stereogenic centres. Alternatively, trapping with iodine delivered α-12-iodide $\Delta^{9(11)}$-dehydroestradiol derivative **22b** (with the iodide *trans* to the 13-CMe group). Here, NOEDS contacts of *cis* 18-Me/14-CH/12-CH groups, as well as *cis* 8-CH/17-CH groups, provided conclusive evidence. Finally, hydrogenation of $\Delta^{9(11)}$-dehydroestradiol **22a** gave a mixture of 3-*O*-methylestradiols **25**. Literature data published for major diastereomer **25α** (both enantiomers) were found to be incomplete. However, the published data and measured data for **25α** were consistent. In contrast, a complete set of data for *ent*-**25β** was published by Schönecker et al. The data obtained for minor diastereomer **25β** were in excellent agreement with these literature data, which confirms the correct assignment of both the relative and absolute configurations of all the stereogenic centres of the 3-*O*-methylestradiols (Figure 7).

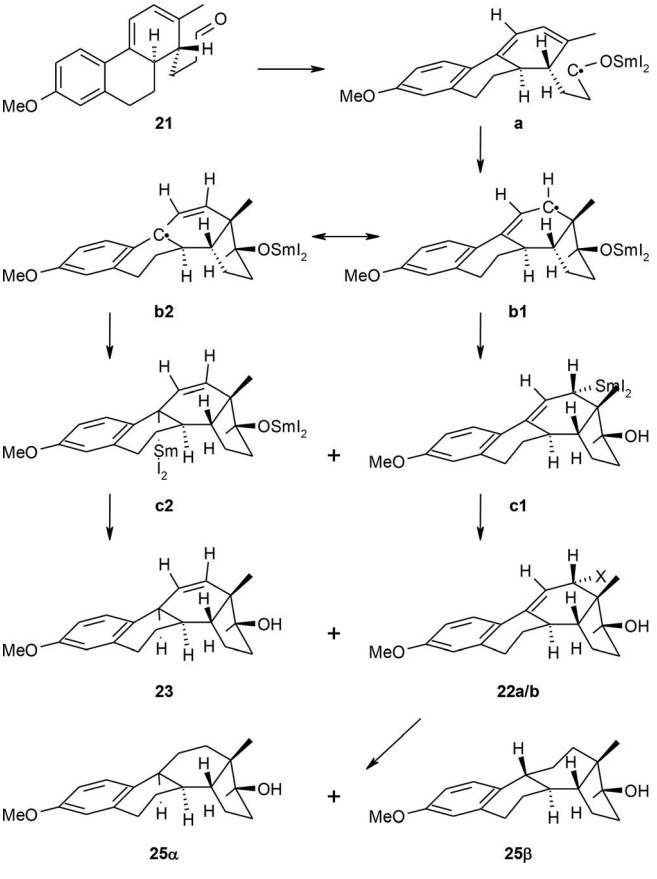


Figure 7. Stereoselectivity of C/D-ring closure and final hydrogenation starting from dihydrophenanthrene **21**.

Conclusions

A new synthesis of optically active C/D-*cis*-3-*O*-methylestradiol diastereomers has been completed. Starting from 1,4-butanediol (**3**), *m*-anisole (**6**), and selected enantiopure pyrrolidine derivatives **2**, an auxiliary-directed convergent sequence developed earlier allowed the generation of configurationally defined iodolactones **9** as suitable starting materials. Then, a six-step sequence of bromination, protecting-group transformations, and intramolecular Grignard addition to close the B-ring delivered key tetralone **14** in high yield. Introduction of the missing C-11 atom was achieved through a Petasis olefination (→ **15**) or by an allyl Grignard reagent addition (→ **19**). A first attempt to use a radical cyclisation cascade to install the C- and D-rings in a single step from tetraline **15** failed. A competing 7-*endo-trig* ring closure involving the sterically less hindered styryl olefin moiety and delivering tricycles **17** and **18** was favoured over the originally planned initial 5-*exo-trig* cyclisation involving an unactivated isopropylidene double bond as the starting step. A stepwise closure of the C- and D-rings allowed the generation of the desired steroidal framework. Ring-closing metathesis and accompanying dehydration (→ **20**), protecting-group removal, and carefully controlled oxidation of the primary alcohol gave **21**, containing an aryl cyclohexadiene moiety with improved radical-acceptor properties. SmI_2-mediated reductive radical cyclisation diastereoselectively gave dehydroestradiols with a C/D-*cis* ring junction as a mixture of olefin regioisomers **22** and **23**, showcasing the applicability of this late key step. The relative configuration of the newly formed stereogenic centres was proved by NOEDS analysis. Furthermore, hydrogenation of the double bond of cyclohexene **22** gave a mixture of 3-*O*-methylestradiols **25α** (major) and **25β** (minor), and the data of these compounds matched with those published in the literature for (+)-3-*O*-methyl-9-*epi*-13β-estradiol (major) and (+)-3-*O*-methyl-9-*epi*-13β-estradiol and (–)-3-*O*-methyl-13β-estradiol (enantiomer, minor). Further work using and optimising this strategy to synthesise new steroidal natural products and pharmaceutically important compounds with other substitution patterns is in progress.

Experimental Section

General Remarks: Reaction solvents were dried by standard procedures before use when necessary. All reactions including moisture- or air-sensitive reagents were carried out under an argon atmosphere. ^{1}H, ^{13}C, and 2D (COSY, HSQC, HMBC, NOESY) NMR spectra were recorded at room temperature with a Bruker ARX400, AV400, or AV600 spectrometer in $CDCl_3$ using the signal of residual $CHCl_3$ as an internal standard. The additional signals from the amide's rotamers are given in square brackets. IR spectra were recorded with a Jasco FT/IR-400 plus spectrometer. High-resolution mass spectra (HRMS) were recorded with a Waters Q Tof Ultima 3 Micromass spectrometer. Optical rotations were recorded with a Perkin–Elmer P 241 polarimeter. Column chromatography was carried out on MN silica gel 60M from Macherey–Nagel (grain size: 0.040–0.063 mm). The progress of reactions was monitored by thin-layer chromatography (TLC) on aluminium sheets pre-coated with silica gel 60 F254 silica gel from Merck. HPLC: t_R = peak retention time, k = retention factor = $(t_R - t_0)/t_0$.

Monobromination of Iodolactones 9 (α,β-Iodomethyl Group): Iodolactones **9** (8.02 g, 11.96 mmol, 1.0 equiv.) in AcOH (100 mL) were treated dropwise with bromine (1.91 g, 0.61 mL, 11.96 mmol, 1 equiv.). The mixture was stirred for 1.5 h at room temperature. Then, the AcOH was removed in vacuo, and the residue was dissolved in CH_2Cl_2. The remaining bromine was destroyed with $Na_2S_2O_3$ solution (10 % aq.). The aqueous layer was extracted with CH_2Cl_2 (3 ×), the organic phase was dried ($MgSO_4$), and the solvents were removed in vacuo. The crude product was purified by column chromatography (gradient EtOAc/petroleum ether, 1:10–1:4) to give TPS ethers **10a** (α,β-iodomethyl group; 454 mg, 0.61 mmol, 5.1 %) as a clear colourless oil, and acetates **10b** (α,β-iodomethyl group; 5.81 g, 10.5 mmol, 87.8 %) as a clear colourless oil. For spectroscopic data, see the Supporting Information.

Reductive Ring-Opening of Iodolactones 10b (α,β-Iodomethyl Group): Iodolactones **10b** (5.97 g, 10.79 mmol, α,β-iodomethyl group) in AcOH (40 mL) were treated portionwise with zinc (7.05 g, 107.9 mmol, 10 equiv.). The mixture was stirred for 24 h at 65 °C. The mixture was then cooled to 23 °C, and excess HCl (1 M aq.) was added. The mixture was extracted with Et_2O (5 ×). The organic layers were dried ($MgSO_4$), and the solvents were removed in vacuo. The residue was purified by column chromatography (EtOAc/hexanes, 1:2) to give acid **11b** (4.68 g, 10.79 mmol, nearly 100 %) as a clear colourless oil.

(2*R*,3*R*)-3-(3-Acetoxypropyl)-2-[2-(2-bromo-5-methoxyphenyl)-ethyl]-4-methyl-4-pentenoic Acid (11b): R_f = 0.25 (EtOAc/petroleum ether, 1:2). $[\alpha]_D^{22}$ = 14.0 (c = 1.01, CH_2Cl_2). IR: $\tilde{\nu}$ = 3084 (b), 2937 (s), 2855 (s), 1735 (b), 1705 (b), 1595 (m), 1572 (m), 1472 (s), 1366 (m), 1279 (s), 1240 (b), 1164 (s), 1050 (s), 896 (m), 812 (w) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.30–1.38 (m, 1 H, 4-H), 1.41–1.64 (m, 2 H, 5-H), 1.54–1.64 (m, 1 H, 4-H), 1.66 (s, 3 H, 17-H), 1.81–1.95 (m, 2 H, 7-H), 2.03 (s, 3 H, 20-H), 2.33 (m, 1 H, 3-H), 2.50 (td, $^3J_{H,H}$ = 3.9, $^3J_{H,H}$ = 9.9 Hz, 1 H, 2-H), 2.66 (ddd, $^3J_{H,H}$ = 6.3, $^3J_{H,H}$ = 10.2, $^2J_{H,H}$ = 13.4 Hz, 1 H, 8-H), 2.74 (ddd, $^3J_{H,H}$ = 5.8, $^3J_{H,H}$ = 10.4, $^2J_{H,H}$ = 13.4 Hz, 1 H, 8-H), 3.76 (s, 3 H, 15-H), 4.02 (m, 2 H, 6-H), 4.77 (s, 1 H, 18-H), 4.85 (s, 1 H, 18-H), 6.63 (dd, $^3J_{H,H}$ = 8.7, $^4J_{H,H}$ = 3.0 Hz, 1 H, 12-H), 6.77 (d, $^4J_{H,H}$ = 3.0 Hz, 1 H, 10-H), 7.39 (d, $^3J_{H,H}$ = 8.7 Hz, 1 H, 13-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.73 (C-17), 20.95 (C-20), 25.51 (C-4), 26.20 (C-5), 29.64 (C-7), 34.48 (C-8), 48.98, 49.14 (C-3, C-2), 55.38 (C-15), 64.30 (C-6), 113.39 (C-12), 114.31 (C-18), 114.62 (C-14), 116.04 (C-10), 133.29 (C-13), 141.68 (C-9), 144.28 (C-16), 158.88 (C-11), 171.22 (C-19), 180.77 (C-1) ppm. HRMS (ESI): calcd. for $C_{20}H_{27}O_5{}^{23}NaBr$ 449.0940; found 449.0926.

(*R*)-3,4-Dihydro-2-[(*R*)-6-*tert*-butyldimethylsiloxy-2-methylhex-1-en-3-yl]-6-methoxynaphthalen-1(2*H*)-one (14): Under Ar, a solution of TBS Weinreb amide **13c** (3.05 g, 5.621 mmol) in dry THF (150 mL) was cooled to –78 °C. Then, *tert*-butyllithium (1.9 M in pentane; 3.9 mL, 7.41 mmol, 1.3 equiv.) was added dropwise over 30 min while stirring at –78 °C. After 3 h, the reaction was quenched by the addition of saturated aq. NH_4Cl. The mixture was warmed to room temperature, then the aqueous layer was extracted with Et_2O (4 ×). The organic phases were dried ($MgSO_4$), and the solvents were removed in vacuo. The crude material was purified by column chromatography (gradient EtOAc/petroleum ether, 1:20–1:10) to give tetralone **14** (2.22 g, 5.61 mmol, 100 %) as a colourless oil, which crystallised at –18 °C. R_f = 0.51 (EtOAc/petroleum ether, 1:4), m.p. 37 °C. $[\alpha]_D^{21}$ = –9.9 (c = 1.27, CH_2Cl_2). IR: $\tilde{\nu}$ = 2962 (w), 2931 (s), 2856 (s), 1675 (s), 1600 (m), 1494 (s), 1462 (m), 1350 (m), 1270 (s), 1250 (s), 1098 (s), 1030 (w), 892 (m), 836 (s), 774 (s), 668 (w) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, COSY): δ = 0.01 (s, 6 H, 19-H), 0.87 (s, 9 H, 21-H), 1.34–1.59 (m, 4 H, 15-H, 16-H), 1.75 (s, 3 H, 18-H), 1.93 (dtd,

$^3J_{H,H}$ = 4.4, $^3J_{H,H}$ = 10.2, $^2J_{H,H}$ = 10.3 Hz, 1 H, 7-H), 2.11 (ddd, $^3J_{H,H}$ = 4.5, $^3J_{H,H}$ = 10.0, $^2J_{H,H}$ = 14.3 Hz, 1 H, 7-H), 2.49 (dt, $^3J_{H,H}$ = 4.5, $^3J_{H,H}$ = 10.3 Hz, 1 H, 8-H), 2.85 (m, 2 H, 6-H, 14-H), 2.96 (td, $^3J_{H,H}$ = 5.0, $^2J_{H,H}$ = 16.7 Hz, 1 H, 6-H), 3.50–3.62 (m, 2 H, 17-H), 3.84 (s, 3 H, 11-H), 4.64 (s, 1 H, 12-H), 4.87 (s, 1 H, 12-H), 6.66 (d, $^4J_{H,H}$ = 2.7 Hz, 1 H, 4-H), 6.80 (dd, $^4J_{H,H}$ = 2.5, $^3J_{H,H}$ = 8.7 Hz, 1 H, 2-H), 7.97 (d, $^3J_{H,H}$ = 8.7 Hz, 1 H, 1-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, HSQC, HMBC): δ = –5.31 (C-19), 18.27 (C-20), 21.65 (C-18), 23.87 (C-7), 24.85 (C-15), 25.92 (C-21), 28.63 (C-6), 31.09 (C-16), 44.00 (C-14), 49.99 (C-8), 55.33 (C-11), 63.16 (C-17), 111.80 (C-12), 112.31 (C-4), 112.98 (C-2), 126.54 (C-10), 129.87 (C-1), 145.57 (C-13), 146.17 (C-5), 163.20 (C-3), 198.21 (C-9) ppm. HRMS (ESI): calcd. for $C_{24}H_{38}O_3Si^{23}Na$ 425.2488; found 425.2496.

(2*R*)-1-Allyl-1,2,3,4-tetrahydro-2-[(*R*)-6-*tert*-butyldimethylsiloxy-2-methylhex-1-en-3-yl]-6-methoxynaphthalen-1-ol (19): Under Ar, a solution of tetralone **14** (1.0 g, 2.484 mmol) in THF (125 mL) was cooled to –78 °C. Allylmagnesium chloride (1.7 M in THF; 2.4 mL, 4.08 mmol, 1.6 equiv.) was added dropwise over 20 min. Then, the mixture was stirred for 4 h over which time it was allowed to warm up to –20 °C. The mixture was then recooled to –78 °C, and the reaction was quenched by the addition of saturated aq. NH_4Cl. The aqueous layer was extracted with Et_2O (4 ×), the organic phases were dried ($MgSO_4$), and the solvents were removed in vacuo. The crude material was purified by column chromatography (gradient EtOAc/petroleum ether, 1:20–1:10) to give allyl alcohol **19** (1.06 g, 2.39 mmol, 96.3 %) as a colourless oil (presumably an inseparable mixture of diastereomers). R_f = 0.33 (EtOAc/petroleum ether, 1:10). $[\alpha]_D^{21}$ = 56.8 (*c* = 1.05, CH_2Cl_2). IR: $\tilde{\nu}$ = 3532 (b), 2954 (s), 2927 (s), 2856 (s), 1636 (w), 1608 (m), 1498 (s), 1472 (m), 1438 (w), 1254 (s), 1094 (b, s), 1040 (b, m), 1004 (m), 911 (m), 836 (s), 808 (m), 774 (s), 733 (m), 664 (w) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, COSY): δ = 0.04 (s, 6 H, 20-H), 0.89 (s, 9 H, 22-H), 1.20–1.46 (m, 3 H, 15-H, 16-H), 1.68–1.74 (m, 1 H, 16-H), 1.76 (s, 3 H, 18-H), 1.79–1.87 (m, 1 H, 7-H), 1.95–2.05 (m, 1 H, 7-H), 2.09 (m, 1 H, 8-H), 2.33 (ddd, $^3J_{H,H}$ = 3.4, $^3J_{H,H}$ = 8.0, $^3J_{H,H}$ = 11.3 Hz, 1 H, 14-H), 2.54 (t, $^3J_{H,H}$ = 6.9 Hz, 2 H, 11-H), 2.64 (td, $^3J_{H,H}$ = 5.9, $^2J_{H,H}$ = 18.0 Hz, 1 H, 6-H), 2.78 (ddd, $^3J_{H,H}$ = 6.1, $^3J_{H,H}$ = 9.6, $^2J_{H,H}$ = 17.2 Hz, 1 H, 6-H), 3.02 (s, 1 H, O-H), 3.57 (t, $^3J_{H,H}$ = 6.1 Hz, 2 H, 17-H), 3.79 (s, 3 H, 19-H), 4.63 (s, 1 H, 12-H), 4.79 (s, 1 H, 12-H), 5.02 (d, $^3J_{H,H}$ = 17.0 Hz, 1 H, 24-H), 5.03 (d, $^3J_{H,H}$ = 10.5 Hz, 1 H, 24-H), 5.75 (dddd, $^3J_{H,H}$ = 6.5, $^3J_{H,H}$ = 7.8, $^3J_{H,H}$ = 10.8, $^3J_{H,H}$ = 16.8 Hz, 1 H, 23-H), 6.58 (d, $^4J_{H,H}$ = 2.7 Hz, 1 H, 4-H), 6.76 (dd, $^4J_{H,H}$ = 2.7, $^3J_{H,H}$ = 8.7 Hz, 1 H, 2-H), 7.50 (d, $^3J_{H,H}$ = 8.7 Hz, 1 H, 1-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, HSQC, HMBC): δ = –5.29 (C-20), 18.30 (C-21), 19.17 (C-18), 21.29 (C-7), 25.54 (C-16), 25.94 (C-22), 26.39 (C-6), 30.33 (C-15), 41.70 (C-14), 44.74 (C-8), 48.35 (C-11), 55.05 (C-19), 63.04 (C-17), 76.42 (C-9), 112.12 (C-2), 112.63, 112.66 (C-4, C-12), 117.30 (C-24), 127.61 (C-1), 134.50 (C-23), 135.35 (C-10), 137.32 (C-5), 150.82 (C-13), 158.09 (C-3) ppm. HRMS (ESI): calcd. for $C_{27}H_{44}O_3Si^{23}Na$ 467.2957; found 467.2958.

1-*tert*-Butyldimethylsilyl-3-[(1*R*,10a*R*)-1,9,10,10a-tetrahydro-7-methoxy-2-methylphenanthren-1-yl]propan-1-ol (20): Under Ar, allyl alcohol **19** (240 mg, 0.539 mmol) and Grubbs (I) catalyst [benzylidene bis(tricyclohexylphosphine) ruthenium dichloride; 11 mg, 0.0135 mmol, 0.025 equiv.] in CH_2Cl_2 (30 mL) were heated to reflux for 22 h. Then, a second portion of Grubbs (I) catalyst (11 mg, 0.0135 mmol, 0.025 equiv.) was added, and heating was continued for 24 h. The mixture was then cooled, and the solvents were removed in vacuo. The crude material was purified by column chromatography (EtOAc/petroleum ether, 1:20) to give tetrahydrophenanthrene **20** (202 mg, 0.507 mmol, 94 %) as a colourless glass-like oil that solidified upon storing at –18 °C (very susceptible to oxidation). R_f = 0.56 (EtOAc/petroleum ether, 1:10), m.p. 35 °C. $[\alpha]_D^{26}$ = 216.6 (*c* = 1.03, CH_2Cl_2). IR: $\tilde{\nu}$ = 3026 (w), 2929 (s), 2855 (s), 1607 (s), 1570 (w), 1495 (s), 1471 (m), 1443 (w), 1260 (m), 1251 (s), 1232 (s), 1096 (b, s), 1052 (w), 960 (m), 833 (s, b), 812 (s), 774 (s), 715 (w), 660 (w) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, COSY): δ = 0.08 (s, 6 H, 20-H), 0.92 (s, 9 H, 22-H), 1.43–1.80 (m, 5 H, 7-H, 15-H, 16-H), 1.86 (s, 3 H, 18-H), 2.11 (m, 1 H, 7-H), 2.25 (br. d, $^3J_{H,H}$ = 15.8 Hz, 1 H, 14-H), 2.50 (br. t, $^3J_{H,H}$ = 14.1 Hz, 1 H, 8-H), 2.80 (dd, $^3J_{H,H}$ = 3.3, $^3J_{H,H}$ = 8.4 Hz, 2 H, 6-H), 3.66 (m, 2 H, 17-H), 3.80 (s, 3 H, 19-H), 5.87 (d, $^3J_{H,H}$ = 5.6 Hz, 1 H, 12-H), 6.32 (dd, $^4J_{H,H}$ = 2.4, $^3J_{H,H}$ = 5.8 Hz, 1 H, 11-H), 6.61 (d, $^4J_{H,H}$ = 2.6 Hz, 1 H, 4-H), 6.73 (dd, $^4J_{H,H}$ = 2.6, $^3J_{H,H}$ = 8.8 Hz, 1 H, 2-H), 7.57 (d, $^3J_{H,H}$ = 8.8 Hz, 1 H, 1-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, HSQC, HMBC): δ = –5.31 (C-20), 18.33 (C-21), 21.11 (C-18), 24.91 (C-15), 25.95 (C-22), 28.06 (C-16), 29.01 (C-7), 30.93 (C-6), 38.63 (C-8), 43.19 (C-14), 55.19 (C-19), 63.56 (C-17), 112.77, 112.99 (C-2, C-4), 114.75 (C-11), 122.14 (C-12), 124.45 (C-1), 127.53 (C-10), 133.35 (C-9), 137.88 (C-13), 138.41 (C-5), 158.28 (C-3) ppm. MS (FD, 5 kV/8 mA/min): *m/z* (%) = 396.267 (100) $[M - H_2]^+$, 397.268 $[M - H]^+$, 398.256 (9) $[M]^+$. HRMS (ESI): calcd. for $C_{25}H_{39}O_2Si$ $[M + H]^+$ 399.2719; found 399.2716. In several runs, some of the initial cyclohexenol product was isolated. This intermediate undergoes elimination of H_2O on standing. For some data for the cyclohexenol intermediate see the Supporting Information.

3-[(1*R*,10a*R*)-7-Methoxy-2-methyl-1,9,10,10a-tetrahydrophenanthren-1-yl]propanal (21): Ley oxidation: Alcohol **20a** (173 mg, 0.605 mmol) was dissolved in CH_2Cl_2 (15 mL) in a flame-dried flask in the presence of molecular sieves (3 Å) under Ar. *N*-Methylmorpholine *N*-oxide (NMO; 128 mg, 1.089 mmol, 1.8 equiv.) and tetrapropyl ammonium perruthenate (TPAP; 10.6 mg, 0.0302 mmol, 0.05 equiv.) were added, and the mixture was stirred at 23 °C for 1 h. The molecular sieves were removed by filtration, and the filtrate was diluted with CH_2Cl_2, and washed with saturated aq. $Na_2S_2O_3$. The aqueous layer was extracted with CH_2Cl_2 (3 ×). The organic phases were washed with brine [reextraction of the aqueous layer with CH_2Cl_2 (3 ×)], and dried ($MgSO_4$), and the solvent was removed in vacuo. The crude product was purified by column chromatography (EtOAc/petroleum ether, 1:4) to give aldehyde **21** (135 mg, 0.475 mmol, 78.4 %) as a clear colourless oil. R_f = 0.59 (EtOAc/petroleum ether, 1:2). $[\alpha]_D^{27}$ = 220.0 (*c* = 0.96, CH_2Cl_2). IR: $\tilde{\nu}$ = 2931 (s), 2834 (s), 2722 (w), 1720 (s), 1606 (s), 1496 (s), 1466 (m), 1443 (m), 1270 (m), 1233 (s), 1162 (m), 1047 (s), 834 (m), 812 (s) cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$, COSY): δ = 1.56 (m, 1 H, 7-H), 1.82 (s, 3 H, 18-H), 1.95 (ddd, $^3J_{H,H}$ = 5.3, $^3J_{H,H}$ = 10.2, $^2J_{H,H}$ = 14.7 Hz, 1 H, 15-H), 2.03 (m, 1 H, 7-H), 2.11 (ddt, $^3J_{H,H}$ = 4.1, $^3J_{H,H}$ = 10.9, $^2J_{H,H}$ = 14.8 Hz, 1 H, 15-H), 2.36 (m, 1 H, 14-H), 2.38 (m, 1 H, 8-H), 2.44 (m, 1 H, 16-H), 2.57 (br. dd, $^3J_{H,H}$ = 5.7, $^3J_{H,H}$ = 10.9, $^2J_{H,H}$ = 17.6 Hz, 1 H, 16-H), 2.81 (m, 2 H, 6-H), 3.79 (s, 3 H, 19-H), 5.89 (br. d, $^3J_{H,H}$ = 5.8 Hz, 1 H, 12-H), 6.27 (br. d, $^3J_{H,H}$ = 5.7 Hz, 1 H, 11-H), 6.60 (d, $^4J_{H,H}$ = 2.6 Hz, 1 H, 4-H), 6.73 (dd, $^4J_{H,H}$ = 2.6, $^3J_{H,H}$ = 8.8 Hz, 1 H, 2-H), 7.54 (d, $^3J_{H,H}$ = 8.8 Hz, 1 H, 1-H), 9.84 (s, 1 H, 17-H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$, HSQC): δ = 21.11 (C-18), 21.35 (C-15), 29.50 (C-7), 30.76 (C-6), 38.81 (C-8), 39.62 (C-16), 42.76 (C-14), 55.20 (C-19), 112.84 (C-2), 112.97 (C-4), 114.61 (C-11), 122.80 (C-12), 124.53 (C-1), 127.36 (C-10), 133.34 (C-5), 135.58 (C-13), 138.18 (C-9), 158.41 (C-3), 202.28 (C-17) ppm. HRMS (ESI): calcd. for $C_{19}H_{22}O_2^{23}Na$ $[M + Na]^+$ 305.1517; found 305.1515.

(8α,13β,14β,17β)-3-Methoxyestra-1,3,5(10),9(11)-tetraen-17-ol (22a), (8α,14β)-12-Iodo-3-methoxyestra-1,3,5(10),9(11)-tetraen-17-ol (22b), (8α,9α,13β,14β,17β)-3-Methoxyestra-1,3,5-(10),11(12)-tetraen-17-ol (23), and (14β)-3-Methoxyestra-1,3,5(10),8(9)-tetraen-17-ol (24): A solution of aldehyde **21** (35 mg, 0.124 mmol) in THF (4 mL) and HMPA (0.25 mL) was degassed by freezing the mixture (–196 °C), removing the gas in

vacuo, and refilling with Ar (3 ×). Then, a freshly prepared SmI_2 solution (excess, volume not determined) was added by cannula with stirring at –40 °C over about 30 min until the blue colour of unreacted SmI_2 remained for several minutes, and no reactant was detected by means of TLC control. The mixture was stirred for a further 1 h at –20 °C, then the mixture was diluted with CH_2Cl_2 (30 mL), and quenched with HCl (1 N aq.; 30 mL). The aqueous layer was extracted with CH_2Cl_2 (3 ×), the organic phases were dried ($MgSO_4$), and the solvents were removed in vacuo. The crude product was purified by column chromatography (EtOAc/petroleum ether, 1:4) and preparative HPLC (Nucleosil 50-5, ID = 32 × 238 mm, diethyl ether/hexane, 15:85, 48 mL/min, 47 bar) to give alcohol **23** (3.7 mg, 0.013 mmol, 10.5 %) as a clear colourless oil, alcohol **22a** (2.9 mg, 0.0102 mmol, 8.2 %) as a clear colourless oil, alcohol **22b** (5.4 mg, 0.0132 mmol, 10.6 %) as a clear colourless oil, and a mixture of alcohols **22a** and **24** (2.1 mg, 7.38 µmol, 6.0 %) as a clear colourless oil (this latter fraction was formed from the product mixture after column chromatography after standing in $CDCl_3$ for NMR spectroscopic measurements).

Data for **23**: R_f = 0.61 (EtOAc/petroleum ether, 1:2). HPLC: k = 11.0, t_R = 12 min. $[\alpha]_D^{28}$ = 59.3 (c = 0.10, CH_2Cl_2). IR: $\tilde{\nu}$ = 3408 (b, OH), 2927 (s), 2869 (s), 1735 (w), 1715 (w), 1608 (s), 1499 (s), 1457 (s), 1255 (s), 1234 (m), 1154 (w), 1092 (w), 1039 (s), 799 (w), 668 (w) cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$, COSY, NOESY): δ = 1.09 (s, 3 H, 18-H), 1.60–1.67 (m, 3 H, 7-H, 15-H, 16-H), 1.80–1.86 (m, 4 H, 7-H, 14-H, 16-H, 15-H), 2.02 (m, 1 H, 8-H), 2.72–2.76 (m, 2 H, 6-H), 3.40 (m, 1 H, 9-H), 3.73 (m, 1 H, 17-H), 3.78 (s, 3 H, 19-H), 5.51 (dd, $^3J_{H,H}$ = 2.7, $^3J_{H,H}$ = 10.2 Hz, 1 H, 12-H), 5.94 (dd, $^3J_{H,H}$ = 2.7, $^3J_{H,H}$ = 10.2 Hz, 1 H, 11-H), 6.61 (d, $^4J_{H,H}$ = 2.5 Hz, 1 H, 4-H), 6.75 (dd, $^4J_{H,H}$ = 2.7, $^3J_{H,H}$ = 8.5 Hz, 1 H, 2-H), 7.13 (d, $^3J_{H,H}$ = 8.4 Hz, 1 H, 1-H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$, HSQC, HMBC): δ = 26.49, 26.68 (C-15, C-16), 27.02 (C-18), 29.81 (C-6), 32.03 (C-7), 35.53 (C-9), 37.75 (C-8), 44.68 (C-13), 46.28 (C-14), 55.21 (C-19), 81.68 (C-17), 112.37 (C-4), 113.12 (C-2), 128.80 (C-12), 129.87 (C-1), 132.36 (C-10), 134.44 (C-11), 138.13 (C-5), 157.46 (C-3) ppm. HRMS (ESI): calcd. for $C_{19}H_{25}O_2$ 285.1855; found 285.1856.

Data for **22a**: R_f = 0.54 (EtOAc/petroleum ether, 1:2). HPLC: k = 12.4, t_R = 13.5 min. $[\alpha]_D^{24}$ = –33.2 (c = 0.19, CH_2Cl_2). IR: $\tilde{\nu}$ = 3403 (b, OH), 2924 (s), 2853 (s), 1738 (w), 1606 (s), 1571 (w), 1497 (s), 1464 (s), 1279 (s), 1257 (s), 1232 (s), 1162 (m), 1076 (m), 1036 (s), 812 (m), 716 (w) cm^{-1}. ^1H NMR (600 MHz, CD_2Cl_2, COSY, NOESY): δ = 0.94 (s, 3 H, 18-H), 1.38–1.45 (m, 2 H, 7-H, 15-H), 1.51–1.59 (m, 2 H, 14-H, 16-H), 1.92 (tdd, $^3J_{H,H}$ = 2.1, $^3J_{H,H}$ = 4.1, $^3J_{H,H}$ = 9.5 Hz, 1 H, 8-H), 2.03 (ddd, $^3J_{H,H}$ = 4.3, $^3J_{H,H}$ = 8.9, $^2J_{H,H}$ = 12.4 Hz, 1 H, 7-H), 2.05–2.11 (m, 4 H, 12-H, 15-H, 16-H), 2.77 (m, 2 H, 6-H), 3.76 (s, 3 H, 19-H), 3.87 (t, $^3J_{H,H}$ = 6.6 Hz, 1 H, 17-H), 6.14 (dt, $^4J_{H,H}$ = 3.6, $^3J_{H,H}$ = 7.0 Hz, 1 H, 11-H), 6.60 (d, $^4J_{H,H}$ = 2.6 Hz, 1 H, 4-H), 6.69 (dd, $^4J_{H,H}$ = 2.7, $^3J_{H,H}$ = 8.7 Hz, 1 H, 2-H), 7.47 (d, $^3J_{H,H}$ = 8.7 Hz, 1 H, 1-H) ppm. ^{13}C NMR (151 MHz, CD_2Cl_2, HSQC, HMBC): δ = 22.43 (C-18), 28.55 (C-15), 30.06 (C-7), 31.06 (C-6), 32.04 (C-16), 34.82 (C-12), 40.38 (C-8), 44.08 (C-13), 49.36 (C-14), 55.65 (C-19), 80.18 (C-17), 112.90 (C-2), 113.38 (C-4), 117.93 (C-11), 125.13 (C-1), 128.69 (C-10), 136.05 (C-9), 138.64 (C-5), 158.84 (C-3) ppm. HRMS (ESI): calcd. for $C_{19}H_{25}O_2$ 285.1855; found 285.1846.

Data for **22b**: R_f = 0.46 (EtOAc/petroleum ether, 1:2). HPLC: k = 13.4, t_R = 14.5 min. $[\alpha]_D^{24}$ = –40.5 (c = 0.36, CH_2Cl_2). IR: $\tilde{\nu}$ = 3449 (b, OH), 2924 (s), 2853 (s), 1724 (w), 1606 (s), 1497 (s), 1464 (s), 1377 (m), 1276 (s), 1255 (s), 1233 (s), 1164 (w), 1073 (m), 1054 (s), 1036 (s), 953 (m), 890 (m), 811 (m), 713 (m) cm^{-1}. ^1H NMR (600 MHz, CD_2Cl_2, COSY, NOESY): δ = 1.13 (s, 3 H, 18-H), 1.30–1.41 (m, 1 H, 7-H), 1.47 (ddd, $^3J_{H,H}$ = 3.2, $^3J_{H,H}$ = 9.7, $^2J_{H,H}$ = 13.1 Hz, 1 H, 15-H), 1.55 (m, 1 H, 14-H), 1.60–1.67 (m, 1 H, 16-H), 2.86 (t, $^3J_{H,H}$ = 10.9 Hz, 1 H, 8-H), 2.05–2.16 (m, 2 H, 15-H, 7-H), 2.32 (ddd, $^3J_{H,H}$ = 8.2, $^3J_{H,H}$ = 12.9, $^2J_{H,H}$ = 19.4 Hz, 1 H, 16-H), 2.86–2.90 (m, 2 H, 6-H), 3.14 (br. s, 1 H, 12-H), 3.74 (s, 3 H, 19-H), 4.56 (dd, $^3J_{H,H}$ = 6.8, $^3J_{H,H}$ = 15.0 Hz, 1 H, 17-H), 5.98 (s, 1 H, 11-H), 6.60 (m, 2 H, 2-H, 4-H), 7.42 (d, $^3J_{H,H}$ = 9.5 Hz, 1 H, 1-H) ppm. ^{13}C NMR (151 MHz, CD_2Cl_2, HSQC, HMBC): δ = 20.55 (C-18), 26.25 (C-15), 30.69, 30.94 (C-6, C-7), 32.12 (C-16), 39.48 (C-8), 41.09 (C-12), 45.73 (C-14), 51.33 (C-13), 55.65 (C-19), 73.69 (C-17), 113.04, 113.46 (C-2, C-4), 120.63 (C-11), 125.41 (C-1), 128.67 (C-9), 134.60 (C-10), 137.91 (C-5), 159.02 (C-3) ppm. MS (FD, 5 kV/8 mA/min): m/z (%) = 284.1 (100) $[M - I]^+$. MS (ESI): m/z (%) = 433.28 (3.6) $[M + Na]^+$, 305.23 (4.5) $[M - HI + Na]^+$.

Data for **24**: R_f = 0.54 (EtOAc/petroleum ether, 1:2). HPLC: k = 8.4, t_R = 9.4 min. $[\alpha]_D^{28}$ = 38.4 (c = 0.38, CH_2Cl_2). IR: $\tilde{\nu}$ = 3442 (b, OH), 2926 (s), 2875 (s), 2831 (m), 1725 (w), 1606 (s), 1572 (w), 1498 (s), 1465 (s), 1430 (m), 1375 (w), 1304 (w), 1250 (s), 1163 (s), 1087 (m), 1037 (s), 863 (w), 812 (m) cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$, COSY): δ = 1.00 (s, 3 H, 18-H), 1.41–1.54 (m, 3 H, 12-H, 15-H), 1.61–1.66 (m, 1 H, 16-H), 2.06–2.13 (m, 1 H, 7-H), 2.15–2.20 (m, 1 H, 16-H), 2.21–2.30 (m, 3 H, 7-H, 14-H, 15-H), 2.33–2.43 (m, 2 H, 11-H), 2.72 (m, 2 H, 6-H), 3.80 (s, 3 H, 19-H), 3.83 (dd, $^3J_{H,H}$ = 6.8, $^3J_{H,H}$ = 10.7 Hz, 1 H, 17-H), 6.69 (d, $^4J_{H,H}$ = 2.5 Hz, 1 H, 4-H), 6.72 (dd, $^4J_{H,H}$ = 2.7, $^3J_{H,H}$ = 8.4 Hz, 1 H, 2-H), 7.12 (d, $^3J_{H,H}$ = 8.4 Hz, 1 H, 1-H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$, HSQC, HMBC, NOESY): δ = 18.42 (C-18), 22.27 (C-11), 28.34 (C-7), 28.91 (C-6), 29.26 (C-12), 29.63 (C-15), 32.29 (C-16), 43.63 (C-13), 48.08 (C-14), 55.26 (C-19), 80.74 (C-17), 110.81 (C-2), 113.38 (C-4), 122.78 (C-1), 123.77 (C-9), 129.44 (C-10), 134.56 (C-8), 137.03 (C-5), 157.74 (C-3) ppm. HRMS (ESI): calcd. for $C_{19}H_{25}O_2$ 285.1855; found 285.1851.

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