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PAPER

The use of symmetry in enantioselective synthesis: Four pairs of chrysene enantiomers prepared from 19-nortestosterone†

Eva Stastna,[a] Nigam P. Rath[b] and Douglas F. Covey*[a]

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Expansion of the D-ring of 19-norsteroids with incorporation of the steroid C-18 methyl group into a newly formed six-membered ring provides easy access to the chrysene ring system. By taking advantage of the symmetry of the chrysene ring system and avoiding *meso* chrysene intermediates, four optically pure 2,8-difunctionalized (C-2 hydroxyl group and C-8 oxo group) hexadecahydrochrysene diastereomers, and their corresponding optically pure enantiomers were prepared from 19-nortestosterone. The eight chrysene stereoisomers are of interest as starting materials for preparing chrysene analogues of physiologically important neurosteroids.

Introduction

Some endogenous steroids in the androgen and pregnane classes and their analogues are known to be potent modulators of γ-aminobutyric acid type A ($GABA_A$) receptors.[1] Among the androgens, the non-naturally occurring enantiomers of androsterone and etiocholanolone, *ent*-androsterone and *ent*-etiocholanolone, were found to be better modulators of $GABA_A$ receptors than their natural enantiomers[2,3] (Chart 1).

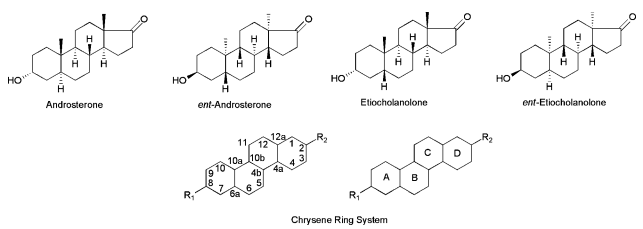
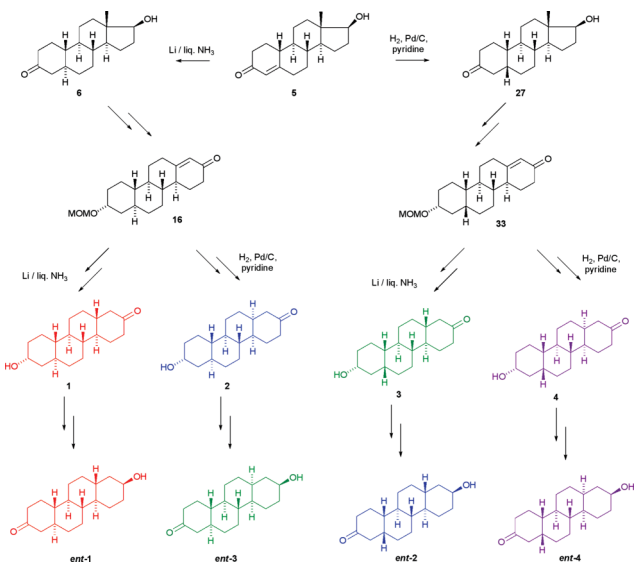


Chart 1

By contrast, the unnatural enantiomers of several other steroids in the pregnane class are not more active than their natural enantiomers.[4,5] Currently, the molecular basis for these enantioselectivity differences between the androgen and pregnane classes is not fully understood. One way to gain a further understanding of these previous enantioselectivity findings is to enlarge the steroid studies to include enantioselectivity studies in closely related ring systems. In this regard, the chrysene ring system substituted at the C-2 and C-8 positions is one such option (Chart 1). This is a particularly attractive ring system for an analogue enantioselectivity study because, as described herein, optically pure chrysene diastereomers differing in the configurations of their A,B and C,D ring fusions as well as their optically pure enantiomers can all be readily prepared from optically pure 19-nortestosterone. The synthetic strategy used to prepare diastereomers **1–4** and their corresponding enantiomers ***ent*-1**-***ent*-4** 19-nortestosterone (**5**) is outlined in Scheme 1.



Scheme 1 Stereochemical plan.

For chrysenes **1–4**, the appropriate choice of reaction conditions for reduction of the Δ^4-double bond of steroid **5** will establish the stereochemistry of the A,B ring fusion. Li/liquid NH_3 reduction

[a]*Department of Developmental Biology, Campus Box 8103, Washington University in St. Louis, School of Medicine, 660 S. Euclid Ave., St. Louis, MO, 63110, USA. E-mail: dcovey@wustl.edu; Fax: +1 314 362 7058; Tel: +1 314 362 1726*

[b]*Department of Chemistry and Biochemistry and Center for Nanoscience, University of Missouri St. Louis, One University Boulevard, St. Louis, 63121, USA*

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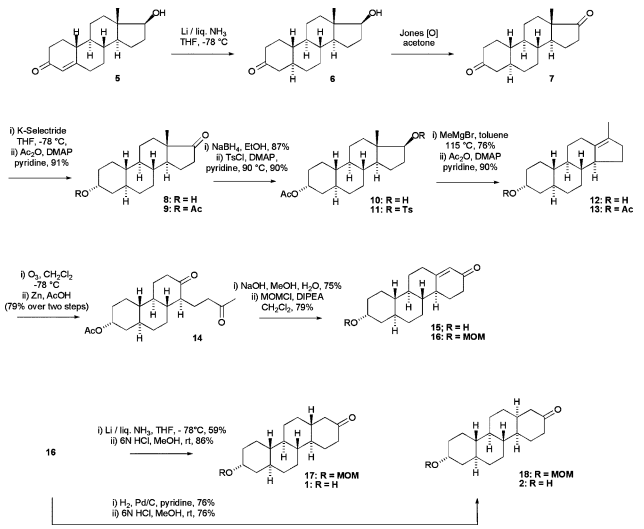
will lead ultimately to the *trans* A,B-ring fused chrysenes **1** and **2**, whereas Pd/C catalyzed hydrogenation in pyridine will lead ultimately to the *cis* A,B-ring fused chrysenes **3** and **4**. A series of reactions is then used to first convert the 3-oxo groups of steroids **6** and **27** into MOM-protected 3α-hydroxyl groups and then subsequently to expand the steroid five-membered D-ring into the six-membered D-ring of chrysene enones **16** and **33**. The double bond of these enones is then either reduced using Li/liquid NH_3 to give chrysenes **1** and **3** which have the *trans* C,D-ring fusion or reduced using Pd/C catalyzed hydrogenation in pyridine to give chrysenes **2** and **4** which have the *cis* C,D-ring fusion. The corresponding 2,8-diketones formed by oxidation of the hydroxyl groups of chrysenes **1** and **4** have a center of symmetry at the mid-point of the C-4b,C-10b bond and are therefore non-optically active *meso* structures. Because of this symmetry, we reasoned that chrysenes **1** and **4** could be converted to their corresponding enantiomers ***ent*-1** and ***ent*-4** by interchanging the positions of the hydroxyl (*axial* for chrysenes **1** and **2**, *equatorial* for chrysenes **3** and **4**) and oxo groups of these chrysenes as long as *meso* structures (*e.g.*, the 2,8-diketones or *diaxial*-2,8-diols) were avoided. We accomplished this by using protection/deprotection reactions in combination with oxidation/reduction reactions to switch the relative positions of the hydroxyl and oxo groups. The 2,8-diketones derived from chrysenes **2** and **3** do not have a center of symmetry and are not *meso* structures. Consequently, use of the same strategy to switch the relative positions of the hydroxyl and oxo groups does not lead to their corresponding enantiomers. However, this same chemistry will convert chrysene **2** to ***ent*-3**, the enantiomer of chrysene **3**, and chrysene **3** to ***ent*-2**, the enantiomer of chrysene **2**. Thus, we planned to convert chrysenes **1–4** to their corresponding enantiomers by simple procedures that preclude any degree of racemization of the previously established stereocenters at C-4a, C-4b, C-6a, C-10a, C-10b or C-12a.

Results and discussion

Synthesis of chrysenes 1 and 2

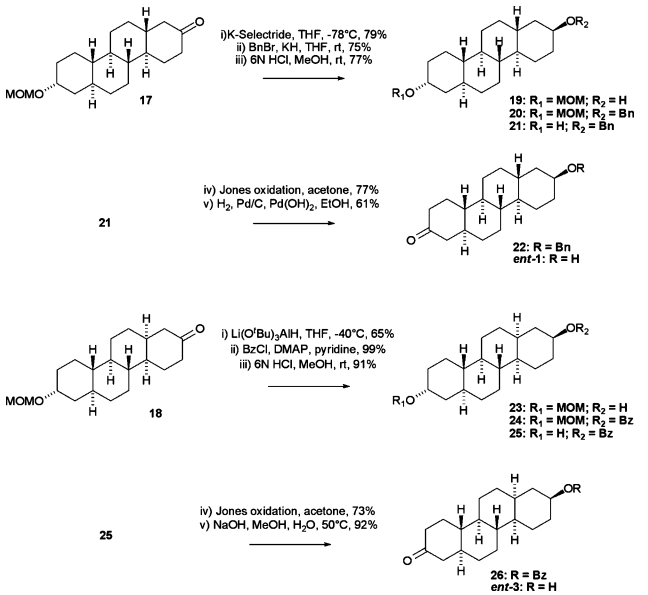
Commercially available 19-nor-testosterone (**5**) was converted by Li/liquid NH_3 reduction followed by Jones oxidation to (5α)-estrane-3,20-dione (**7**) in two steps in 63% overall yield[6] (Scheme 2). The 3-oxo group was then selectively reduced by K-Selectride in THF at −78 °C to afford the *axial*-3-alcohol derivative **8** in 55% yield. Treatment of compound **8** with acetic anhydride in pyridine in the presence of DMAP at room temperature gave the *axial*-3-acetate derivative **9** in 91% yield. $NaBH_4$ reduction of the 17-oxo group in EtOH gave the 17β-alcohol derivative **10** in 87% yield. Compound **10** was then treated with *p*-toluenesulfonyl chloride in the presence of DMAP in pyridine at 90 °C to give the 17β-tosylate **11** in 90% yield. The Kägi-Miescher rearrangement[7,8,9] (1,2 shift of the C-18 methyl group) was accomplished by following the modified procedure of Engel *et al.*[10] by refluxing of 17β-tosylate **11** in toluene with methylmagnesium bromide to afford the desired $\Delta^{13(17)}$-ene derivative **12** in 76% yield. The ^{1}H NMR spectrum of compound **12** displayed a singlet for the migrated methyl group at δ 1.61 and the ^{13}C NMR of the compound showed resonances at δ 136.8 and δ 127.8 for the $\Delta^{13(17)}$-double bond. Since the conditions of the Kägi-Miescher rearrangement led to deprotection of the 3-hydroxyl group, compound **12** was treated with acetic anhydride in pyridine in the presence of DMAP at room temperature to afford the 3-acetate derivative **13** in 90% yield. Compound **13** then gave upon ozonolysis in CH_2Cl_2 at −78 °C and subsequent reduction with Zn/AcOH of the intermediate cyclic ozonide, diketone **14** in 79% yield. Diketone **14** was then cyclized using aqueous NaOH in MeOH to the desired enone **15** in 75% yield. Since enone **15** was sparingly soluble in most solvents (*e.g.* hexanes, EtOAc), it was treated with MOMCl and *N*,*N*-diisopropylethylamine at room temperature overnight to afford the more soluble MOM derivative **16** in 79% yield. Reduction of the double bond of enone **16** with Li/liquid NH_3 gave chrysene **17** (79% yield) having the *trans* C,D-ring fusion, and reduction of this double bond with Pd/C in pyridine gave chrysene **18** (75%) having the *cis* C,D-ring fusion. Finally, the MOM groups of compounds **17** and **18** were removed using 6 N aqueous HCl in MeOH. Compounds **1** and **2** were prepared in 13 steps from 19-nortestosterone (**5**) in total yields of 4.5% and 4.6%, respectively.



Scheme 2 Synthesis of chrysenes **1** and **2**.

Synthesis of chrysenes *ent*-1 and *ent*-3

A reaction sequence which utilized protection/deprotection chemistry in combination with oxidation/reduction chemistry was used for the synthesis of compound ***ent*-1** from compound **17** (Scheme 3). The 2-oxo group of compound **17** was selectively reduced by K-Selectride in THF at −78 °C to afford the *axial*-alcohol **19** in 79% yield. Treatment of compound **19** with BnBr/KH in THF gave the benzyl derivative **20** in 75% yield. Acidic hydrolysis of compound **20** with aqueous HCl in MeOH gave compound **21** which was then subsequently oxidized with Jones reagent to compound **22** (77% yield in each step). Overnight hydrogenation of chrysene **22** using Pd/C in EtOAc did not lead to the desired product and only starting material was recovered. If EtOH was used instead of EtOAc as solvent, a mixture of desired compound ***ent*-1** and other side products were obtained. A characteristic broad multiplet at δ 3.59 ppm in the ^{1}H NMR spectrum of the major side product indicated that reduction of the oxo group had occurred when EtOH was the solvent. Finally, hydrogenation using a mixture of Pd/C and $Pd(OH)_2$ (4 : 1) in EtOH afforded the desired compound



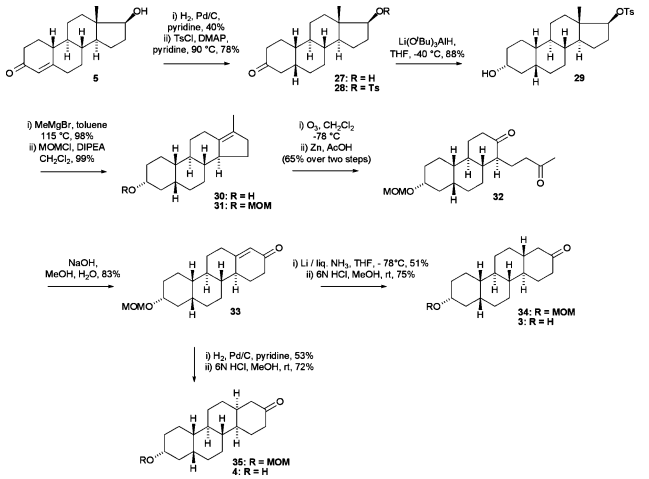
Scheme 3 Synthesis of chrysenes ***ent*-1** and ***ent*-3**.

***ent*-1** in 61% yield. Chrysene ***ent*-1** was prepared in 17 steps from 19-nortestosterone (**5**) in a total yield of 0.8%.

A benzoate ester instead of a benzyl ether protecting group was used for the synthesis of chrysene ***ent*-3** because of the difficulty encountered with removal of the benzyl ether protecting group in the synthesis of chrysene ***ent*-1**. Except for the changes in hydroxyl group protection/deprotection reactions, the synthetic strategy used to prepare compounds ***ent*-3** and ***ent*-1** were the same. Thus, the 2-oxo group of compound **18** was selectively reduced by lithium tri(*tert*-butoxy)aluminum hydride in THF at –40 °C to afford *equatorial*-alcohol **23** in 65% yield. The hydroxyl group stereochemical assignment was confirmed by ^{1}H-NMR which showed a resonance at δ 3.64 that was a multiplet ($W_{1/2}$ ~ 36 Hz) as expected for an *axial*-proton at C-2 in chrysene **23**. Treatment of compound **23** with benzoyl chloride in the presence of DMAP gave benzoate ester **24** in 99% yield. Acidic hydrolysis with aqueous HCl in MeOH gave compound **25** (91% yield) and a subsequent Jones oxidation gave intermediate **26** (73% yield). Basic hydrolysis using aqueous NaOH in MeOH at room temperature afforded the desired chrysene ***ent*-3** in 92% yield. Compound ***ent*-3** was prepared in 17 steps from 19-nortestosterone (**5**) in total yield of 2.7%. The increase in overall yield for the preparation of ***ent*-3** relative to the overall yield obtained for ***ent*-1** is largely due to the improved choice of the benzoate protecting group used for the synthesis of ***ent*-3**.

Synthesis of chrysenes 3 and 4

The experience gained in the synthesis of chrysenes **1** and **2** (Scheme 2) motivated us to modify the synthetic sequence to decrease the number of reactions needed to prepare chrysenes **3** and **4** (Scheme 4). Catalytic hydrogenation of 19-nor-testosterone (**5**) in pyridine using Pd/C gave (5β,17β)-17-hydroxyestrane-3-one (**27**, 40% yield). Tosylation of the 17-hydroxyl group gave compound **28**, and subsequent selective reduction of the 3-oxo group afforded intermediate **29** in yields of 78% and 88%, respectively. Kägi-Miescher rearrangement of compound **29** to

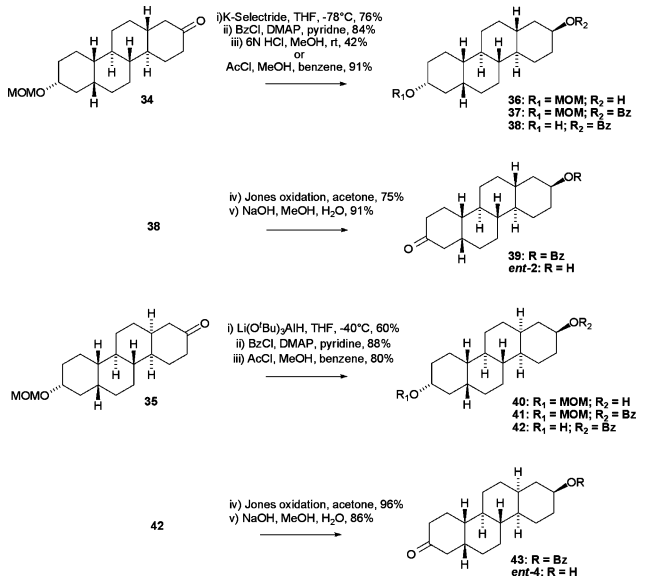


Scheme 4 Synthesis of chrysenes **3** and **4**.

the $\Delta^{13(17)}$-ene derivative **30** was carried out in 98% yield. This product's structure was confirmed by its ^{1}H NMR and ^{13}C NMR spectra which showed a resonance for the migrated 18-methyl group as a singlet at δ 1.60 in the ^{1}H NMR spectrum and resonances at δ 136.7 and δ 127.9 for the $\Delta^{13(17)}$-double bond in the ^{13}C NMR spectrum. To avoid potential solubility issues in the subsequent ozonolysis and D-ring closure reactions, compound **30** was first converted to MOM-derivative **31** (99%). Ozonolysis of compound **31** gave compound **32** in 65% yield, and ring closure of this product under basic conditions afforded compound **33** (83% yield). Reduction of the double bond of compound **33** using Li/liquid NH_3 gave product **34** (51%) which had the *trans* C,D ring fusion. Reduction of the double bond of compound **33** by catalytic hydrogenation using Pd/C in pyridine gave product **35** (53%) which had the *cis* C,D ring fusion. Finally, the MOM groups of compounds **34** and **35** were removed under acidic conditions using aqueous 6 N HCl in MeOH. Compound **3** and compound **4** were each prepared in 9 steps from 19-nortestosterone (**5**) in total yields of 5.5% and 6%, respectively.

Synthesis of chrysenes *ent*-2 and *ent*-4

Protecting groups used during the synthesis of compounds ***ent*-2** and ***ent*-4** were the methoxymethyl and benzoate ester groups (Scheme 5). The 2-oxo group of compound **34** was selectively reduced using K-Selectride to afford derivative **36** in 76% yield. Lithium tri(*tert*-butoxy)aluminum hydride reduction of compound **35** was used to obtain compound **40** in 60% yield. Treatment of compound **36** as well as compound **40** with benzoyl chloride in the presence of DMAP gave ester **37** in 84% yield and ester **41** in 88% yield, respectively. Overnight acidic hydrolysis of compound **37** with aqueous HCl (Method A) was very slow and afforded only a 42% yield of compound **38** (47% of starting material was recovered). Therefore, acetylchloride in MeOH (Method B) was used to carry out transesterification reactions to obtain compounds **38** and **42** in yields of 91% and 80%, respectively. Jones oxidation of compound **38** (75% yield) followed by basic hydrolysis of oxidation product **39** using aqueous NaOH in MeOH at 50 °C (92% yield) afforded chrysene ***ent*-2**. Similarly, compound ***ent*-4** was obtained by oxidation of compound **42** (96% yield) and hydrolysis of compound **43** (86% yield). Compound ***ent*-2**



Scheme 5 Synthesis of chrysenes ***ent*-2** and ***ent*-4**.

was prepared in 13 steps from 19-nortestosterone (**5**) in a total yield of 3%. Compound ***ent*-4** was prepared in 13 steps from 19-nortestosterone (**5**) in a total yield of 2.9%.

Summary

The enantiomeric relationship between chrysenes **1–4** and their corresponding enantiomers ***ent*-1**-***ent*-4** was confirmed by comparison of the physical and spectroscopic properties of the enantiomer pairs. Optical rotations and melting points are summarized in Table 1. Additional comparisons of IR and ^{1}H-NMR spectra for the enantiomer pairs can be made of this data as reported in the Experimental Section. The near zero values for the optical rotations of chrysenes **2** and **4** and their corresponding enantiomers made determinations of their optical purity by optical rotation measurements unreliable. Accordingly, the absolute configuration of compound ***ent*-2** was confirmed by an X-ray structure determination (Fig. 1) of the compound's 4-bromobenzoate ester

Table 1 Values of optical rotation and melting points for chrysenes **1–4** and their corresponding enantiomers

nat-Chrysenes			*ent*-Chrysenes		
1	$[\alpha]_D^{20}$ −25.65	183–184 °C	***ent*-1**	$[\alpha]_D^{20}$ +26.51	182–184 °C
2	$[\alpha]_D^{20}$ −0.92	158–161 °C	***ent*-2**	$[\alpha]_D^{20}$ −1.88	160–162 °C
3	$[\alpha]_D^{20}$ −28.37	161–163 °C	***ent*-3**	$[\alpha]_D^{20}$ +29.7	160–162 °C
4	$[\alpha]_D^{20}$ −1.67	181–183 °C	***ent*-4**	$[\alpha]_D^{20}$ +0.68	183–184 °C

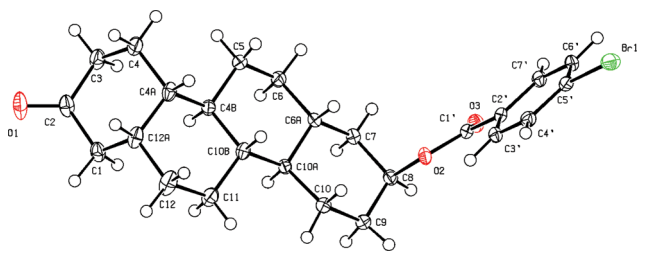


Fig. 1 Projection plot showing the absolute configuration of the benzoate derivative of chrysene ***ent*-2**.

derivative since its optical rotation as well as that of chrysene **2** were both negative.

Conclusions

Because of the symmetry of the chrysene ring system we were able to develop efficient procedures for the preparation of four pairs of 2,8-disubstituted hexadecahyrochrysene enantiomers from 19-nortestosterone. These procedures provide each enantiomer in any pair of chrysene enantiomers in optically pure form. To our knowledge there are no previous reports in the literature of enantiospecific routes to these optically active 2,8-disubstituted hexadecahydrochrysenes. The successful development of the synthetic routes to the reported chrysenes makes these compounds available as starting materials for structure–activity studies of chrysene modulation of $GABA_A$ receptors and other ligand-gated ion channels known to be modulated by steroids.

Experimental

General

Solvents were either used as purchased or dried and purified by standard methodology. All extraction solvents were dried with anhydrous Na_2SO_4. Flash chromatography was performed using silica gel (32–63 μm) purchased from Scientific Adsorbents (Atlanta, GA). Melting points were determined on Kofler micro hot stage and are uncorrected. Infrared spectra were recorded as films on a NaCl plate on a Perkin–Elmer Spectrum One FT-IR spectrometer. Optical rotations were measured on a Perkin–Elmer Model 341 Polarimeter in the solvent indicated. NMR spectra were recorded on Varian NMR spectrometer in $CDCl_3$ at ambient temperature operating at 300 MHz (^{1}H) or 75 MHz (^{13}C). Chemical shifts are reported as δ values relative to internal chloroform ($\delta = 7.27$) for ^{1}H and chloroform ($\delta = 77.23$) for ^{13}C.

For the ^{1}H NMR spectra, only the chemical shifts associated with substituents are listed. The chemical shifts of the remaining steroid or chrysene envelope protons can be found in the spectra reported in the Supportive Information. Reactions were monitored by thin layer chromatography (TLC) with 250 μm precoated silica gel plates (Analtech). Elemental analyses were performed by M-H-W Laboratories (Phoenix, AZ).

Experimental section

(4a*R*, 4b*S*, 6a*S*, 8*R*, 10a*S*, 10b*R*, 12a*R*) - 8 - Hydroxy - hexadeca - hydro-chrysen-2-one (1). A solution of compound **17** (110 mg, 0.34 mmol) in MeOH (8 mL) was treated with 6 N HCl (1 mL) at room temperature. After 15 h, it was poured into water–ice and aqueous sat. $NaHCO_3$ was added to pH 8. The precipitated product was filtered off, dried at room temperature, and recrystallized from EtOAc/hexanes to afford desired alcohol **1** (82 mg, 86%): mp 183–184 °C (EtOAc/hexanes); $[\alpha]_D^{20}$ −25.65 (*c* 0.11 in $CHCl_3$). Found: C, 78.1; H, 10.3. Calc for $C_{18}H_{28}O_2$: C, 78.2; H, 10.2%. IR (ν_{max}/cm^{-1}) 3438, 2946, 2914, 2850, 1702. δ_H (300 MHz, $CDCl_3$) 4.1 (1H, bs). δ_C (75 MHz, $CDCl_3$) 212.3, 66.5, 48.8, 47.5, 46.9, 46.8, 46.4, 43.5, 41.5, 40.6, 35.7, 34.2, 33.7, 33.1, 30.5, 30.1, 29.4, 23.5.

(4a*S*, 4b*R*, 6a*R*, 8*S*, 10a*R*, 10b*S*, 12a*S*) - 8 - Hydroxy - hexadecahydro-chrysen-2-one (*ent*-1). Compound **22** (103 mg, 0.28 mmol) was dissolved in EtOH (50 mL). To this, 10% Pd/C (20 mg) and $Pd(OH)_2$ (5 mg) were added. The reaction mixture was hydrogenated (60 psi, H_2) for 3.5 h, then additional $Pd(OH)_2$ (5 mg) was added. After 2 h of hydrogenation, the reaction mixture was filtered through a short column of silica gel to remove the catalyst, washing with CH_2Cl_2. Solvents were removed under vacuo and the residue was purified by column chromatography on silica gel (5% EtOAc in CH_2Cl_2) to give compound ***ent*-1** (47 mg, 61%) as a white solid: mp 182–184 °C (EtOAc/hexanes), $[\alpha]_D^{20}$ +26.51 (*c* 0.23 in $CHCl_3$). Found: C, 78.0; H, 10.1. Calc for $C_{18}H_{28}O_2$ C, 78.2; H, 10.2%. IR (ν_{max}/cm^{-1}) 3437, 2914, 2850, 1702. δ_H (300 MHz, $CDCl_3$) 4.1 (1H, m); δ_C (75 MHz, $CDCl_3$) 212.3, 66.5, 48.8, 47.4, 46.96, 46.93, 46.45, 43.5, 41.5, 40.7, 35.7, 34.3, 33.8, 33.2, 30.5, 30.1, 29.4, 23.6.

(4a*R*, 4b*S*, 6a*S*, 8*R*, 10a*S*, 10b*R*, 12a*S*) - 8 - Hydroxy - hexadecahydro-chrysen-2-one (2). Compound **2** was prepared in the same manner as compound **1**. Starting from compound **18** (221 mg, 0.69 mmol), compound **2** (146 mg, 76%) was obtained as a white solid after column chromatography on silica gel (2% EtOAc in CH_2Cl_2): mp 158–161 °C (EtOAc/hexanes); $[\alpha]_D^{20}$ –0.92 (*c* 0.26 in $CHCl_3$). Found: C, 78.3; H, 10.1. Calc. for $C_{18}H_{28}O_2$ C, 78.2; H, 10.2%. IR (ν_{max}/cm^{-1}) 3401, 2914, 2857, 1706. δ_H (300 MHz, $CDCl_3$) 2.58 (1H, t, J = 13.5 Hz), 4.1 (1H, bs); δ_C (75 MHz, $CDCl_3$) 213.4, 66.4, 47.4, 47.3, 43.0, 40.7, 40.5, 38.1, 37.5, 36.7, 35.6, 33.8, 33.1, 30.8, 29.8, 27.5, 24.1, 23.5.

(4a*S*, 4b*R*, 6a*R*, 8*S*, 10a*R*, 10b*S*, 12a*R*) - 8 - Hydroxy - hexadecahydro-chrysen-2-one (*ent*-2). A solution of compound **39** (317 mg, 0.83 mmol) in MeOH (50 mL) and water (1 mL) was treated with NaOH (578 mg, 14.4 mmol) at 50 °C. After 1 h, TLC indicated 90% starting material remained. NaOH (400 mg, 10.0 mmol) was added again and the reaction mixture was heated at 50 °C. After 5 h, the solution was poured into water (100 mL) and extracted with CH_2Cl_2 (2 × 100 mL). The combined extracts were washed with brine and the solvent dried over anhydrous Na_2SO_4. After solvent evaporation, the oily residue was purified by column chromatography on silica gel (20% EtOAc in hexanes) to afford compound ***ent*-2** (210 mg, 91%) as a white solid: mp 160–162 °C (EtOAc/hexanes); $[\alpha]_D^{20}$ –1.88 (*c* 0.25 in $CHCl_3$). Found: C, 78.4; H, 10.2. Cacl. for $C_{18}H_{28}O_2$ C, 78.2; H, 10.2%. IR (ν_{max}/cm^{-1}) 3411, 2914, 2857, 2822. δ_H (300 MHz, $CDCl_3$) 4.09 (1H, m), 2.58 (1H, t, J = 13.8 Hz); δ_C (75 MHz, $CDCl_3$) 213.1, 66.4, 47.4, 47.2, 42.9, 40.7, 40.4, 38.0, 37.5, 36.6, 35.6, 33.7, 33.1, 30.8, 29.8, 27.4, 24.0, 23.5.

(4a*R*, 4b*S*, 6a*R*, 8*R*, 10a*S*, 10b*R*, 12a*R*) - 8 - Hydroxy - hexadecahydro-chrysen-2-one (3). Compound **3** was prepared in the same manner as compound **1**. Starting from compound **34** (156 mg, 0.48 mmol), compound **3** (100 mg, 75%) was obtained as a white solid after column chromatography on silica gel (20% EtOAc in hexanes): mp 161–163 °C (EtOAc/hexanes); $[\alpha]_D^{20}$ –28.37 (*c* 0.24 in $CHCl_3$). Found: C, 78.5; H, 10.0. Calc. for $C_{18}H_{28}O_2$ calcd. C, 78.2; H, 10.2%. IR (ν_{max}/cm^{-1}) 3409, 2916, 2862, 1714. δ_H (300 MHz, $CDCl_3$) 3.57 (1H, bm); δ_C (75 MHz, $CDCl_3$) 212.2, 71.8, 48.8, 47.3, 46.3, 43.4, 41.4, 40.4, 37.3, 36.3, 35.3, 34.2, 31.6, 30.5, 29.9, 29.4, 25.8, 25.3.

(4a*S*, 4b*R*, 6a*S*, 8*S*, 10a*R*, 10b*S*, 12a*S*) - 8 - Hydroxy - hexadecahydro-chrysen-2-one (*ent*-3). A solution of compound **26** (250 mg, 0.65 mmol) in MeOH (36 mL) and water (1 mL) was treated with NaOH (500 mg, 12.5 mmol) at 50 °C. After 1 h, the solution was poured into water (100 mL) and extracted with CH_2Cl_2 (2 × 100 mL). The combined extracts were washed with brine and solvent dried over anhydrous Na_2SO_4. After solvent evaporation, the oily residue was purified by column chromatography on silica gel (20% EtOAc in hexanes) to afford compound ***ent*-3** (168 mg, 92%) as a white solid: mp 160–162 °C (EtOAc/hexanes); $[\alpha]_D^{20}$ +29.7 (*c* 0.19 in $CHCl_3$). Found: C, 78.3; H, 10.5. Calc. for $C_{18}H_{28}O_2$ calcd. C, 78.2; H, 10.2%. IR (ν_{max}/cm^{-1}) 3410, 2916, 2862, 1714. δ_H (300 MHz, $CDCl_3$) 3.66 (1H, bm); δ_C (75 MHz, $CDCl_3$) 212.2, 71.8, 48.8, 47.3, 46.3, 43.5, 41.5, 40.4, 37.4, 36.3, 35.4, 34.2, 31.6, 30.5, 29.9, 29.5, 25.8, 25.3.

(4a*R*, 4b*S*, 6a*R*, 8*R*, 10a*S*, 10b*R*, 12a*S*) - 8 - Hydroxy - hexadecahydro-chrysen-2-one (4). Compound **4** was prepared in the same manner as compound **1**. Starting from compound **35** (149 mg, 0.46 mmol), compound **4** (93 mg, 72%) was obtained as a white solid after column chromatography on silica gel (20% EtOAc in hexanes): mp 181–183 °C (EtOAc/hexanes); $[\alpha]_D^{20}$ –1.67 (*c* 0.21 in $CHCl_3$). Found: C, 78.0; H, 10.1. Calc. for $C_{18}H_{28}O_2$ C, 78.2; H, 10.2%. IR (ν_{max}/cm^{-1}) 3464, 2929, 2907, 2857, 1697. δ_H (300 MHz, $CDCl_3$) 2.58 (1H, t, J = 14 Hz), 4.1 (1H, bs); δ_C (75 MHz, $CDCl_3$) 213.2, 71.8, 43.0, 40.4, 40.3, 38.2, 37.9, 37.7, 36.7, 36.3, 35.5, 31.6, 30.8, 29.9, 27.6, 25.8, 25.1, 24.2.

(4a*S*, 4b*R*, 6a*S*, 8*S*, 10a*R*, 10b*S*, 12a*R*) - 8 - Hydroxy - hexadecahydro-chrysen-2-one (*ent*-4). Compound ***ent*-4** was prepared in the same manner as compound ***ent*-3**. Starting from compound **43** (270 mg, 0.71 mmol), compound ***ent*-4** (170 mg, 86%) was obtained as a white solid after column chromatography on silica gel (20% EtOAc in hexanes): mp 183–184 °C (EtOAc/hexanes); $[\alpha]_D^{20}$ +0.68 (*c* 0.29 in $CHCl_3$). IR (ν_{max}/cm^{-1}) 3466, 2907, 2857, 1697, 1067. δ_H (300 MHz, $CDCl_3$) 2.57 (1H, t, J = 13.8 Hz), 3.66 (1H, bm); δ_C (75 MHz, $CDCl_3$) 213.0, 71.8, 43.0, 40.5, 40.4, 38.2, 38.0, 37.8, 36.6, 36.4, 35.5, 31.6, 30.8, 29.9, 27.6, 25.8, 25.1, 24.2. HRMS (FAB) m/z Cacld for $C_{18}H_{29}O_2$ $[M]^+$ 277.2168, found: 277.2170.

(5α)-Estrane-3,17-dione (7). Compound **7** was prepared in two steps from 19-nortestosterone (**5**) according to the literature[11,12] as a white solid: mp 99–100 °C (EtOAc/hexanes). Found: C, 79.0; H, 9.8. Calc. for $C_{18}H_{26}O_2$ C, 78.8; H, 9.55%. δ_H (300 MHz, $CDCl_3$) 0.90 (3H, s); δ_C (75 MHz, $CDCl_3$) 221.0, 211.4, 50.6, 48.7, 48.1, 48.0, 45.9, 43.8, 41.4, 40.7, 36.0, 33.9, 31.7, 30.7, 29.7, 25.6, 21.8, 14.0.

(3α,5α)-3-Hydroxyestran-17-one (8). Compound **8** was prepared according to the literature[13] as a white solid: mp 160–161 °C (EtOAc/$CHCl_3$). Found: C, 78.4; H, 9.9. Calc for $C_{18}H_{28}O_2$ C, 78.2; H, 10.2%. δ_H (300 MHz, $CDCl_3$) 0.82 (3H, s), 2.34–2.43 (1H, m), 4.03 (1H, bm); δ_C (75 MHz, $CDCl_3$) 221.6, 66.2, 50.7, 48.3, 47.9, 47.0, 40.8, 40.6, 36.0, 35.9, 33.5, 33.0, 31.6, 29.9, 24.9, 23.7, 21.7, 13.9.

(3α,5α)-3-(Acetyloxy)estran-17-one (9). 4-Dimethylaminopyridine (114 mg, 0.9 mmol) and acetic anhydride (4.2 mL, 44.7 mmol) were added to a solution of steroid **8** (2.6 g, 9.4 mmol) in pyridine (25 mL). After 2 h at room temperature, the reaction mixture was poured into ice–water, stirred for 2 h, and then

extracted with EtOAc (3 × 70 mL). Combined extracts were washed with an aqueous solution of $KHCO_3$, brine, and dried over anhydrous Na_2SO_4. After solvent evaporation, the oily residue was purified by column chromatography on silica gel (15% EtOAc in hexanes) to give compound **9** (2.74 g, 91%) as a white solid: mp 96–98 °C (Et_2O/hexanes). Found: C, 75.6; H, 9.3. Calc. for $C_{20}H_{30}O_3$ C, 75.4; H, 9.5%. δ_H (300 MHz, $CDCl_3$) 0.85 (3H, s), 2.01 (3H, s), 5.02 (1H, bm); δ_C (75 MHz, $CDCl_3$) 221.4, 170.7, 69.9, 50.8, 48.3, 48.0, 46.7, 40.9, 37.7, 36.9, 35.9, 33.4, 31.7, 30.2, 29.8, 25.0, 24.5, 21.7, 21.6, 13.9.

(3α,5α,17β)-Estrane-3,17,diol 3-acetate (10). Compound **9** (10 g, 31.4 mmol) was dissolved in EtOH (400 mL) and cooled in an ice-bath. $NaBH_4$ (1.2 g, 31.7 mmol) was added in small portions to a stirred solution. After 1.5 h, the reaction mixture was poured into a solution of brine (500 mL) and AcOH (7 mL) and stirred for 1h. The precipitate was filtered off, dissolved in CH_2Cl_2 (400 mL), and washed with brine. Solvent was dried over anhydrous Na_2SO_4 and evaporated. Column chromatography on silica gel (10% EtOAc in CH_2Cl_2) gave compound **10** (8.7 g, 87%) as a white solid: mp 219–221 °C ($CHCl_3$/hexanes); $[\alpha]_D^{20}$ +28.67 (*c* 0.75 in $CHCl_3$). Found: C, 75.2; H, 9.9. Calc. for $C_{20}H_{32}O_3$ C, 75.0; H, 10.1%. IR (ν_{max}/cm^{-1}) 3436, 2933, 2951, 2899, 2857, 2840, 1698. δ_H (300 MHz, $CDCl_3$) 0.74 (3H, s), 2.04 (3H, s), 3.63 (1H, t, J = 8.5 Hz), 5.03 (1H, bm); δ_C (75 MHz, $CDCl_3$) 170.9, 82.2, 70.2, 50.4, 48.3, 46.8, 43.3, 41.5, 37.8, 37.0, 36.9, 33.6, 30.7 (2 × C), 30.3, 25.4, 24.6, 23.4, 21.7, 11.7.

(3α,5α,17β)-Estrane-3,17,diol 3-acetate, 17-tosylate (11). A solution of compound **10** (8.7 g, 31.4 mmol), 4-dimethylaminopyridine (330 mg, 2.7 mmol), and *p*-TsCl (7.5 g, 39.3 mmol) in anhydrous pyridine (75 mL) was heated at 90 °C overnight. Then, 4-dimethylaminopyridine (60 mg, 0.49 mmol) and *p*-TsCl (1.3 g, 6.82 mmol) were added and the reaction mixture was heated another 24 h. The reaction mixture was poured into ice–water, extracted with CH_2Cl_2 (2 × 300 mL). The combined extracts were washed with aqueous HCl, aqueous $KHCO_3$, brine, and dried over anhydrous Na_2SO_4. After solvent evaporation, the oily residue was purified by column chromatography on silica gel (5% EtOAc in CH_2Cl_2) to give compound **11** (11.6 g, 90%) as a white solid: mp 114–115 °C (CH_2Cl_2/hexanes); $[\alpha]_D^{20}$ +10.49 (*c* 0.51 in $CHCl_3$). Found: C, 68.4; H, 8.2; S, 6.8. Calc. for $C_{27}H_{38}O_5S$ C, 68.3; H, 8.1; S, 6.8%. IR (ν_{max}/cm^{-1}) 3306, 2919, 2861, 1732, 1598, 1445, 1361, 1176. δ_H (300 MHz, $CDCl_3$) 0.74 (3H, s), 2.04 (3H, s), 2.44 (1H, s), 4.27 (1H, m), 5.02 (1H, bm), 7.32 (2H, m), 7.78 (2H, d, J = 8.4 Hz); δ_C (75 MHz, $CDCl_3$) 170.8, 144.5, 134.6, 129.8, 128.0, 90.3, 70.0, 49.4, 48.1, 46.7, 43.3, 41.1, 37.7, 36.9, 36.3, 34.5, 30.5, 30.2, 27.8, 25.1, 24.5, 23.3, 21.8, 21.7, 11.9.

(3α,5α)-17-methylgon-13(17)-en-3-ol (12). Compound **11** (550 mg, 1.17 mmol) was dissolved in anhydrous toluene (8 mL) and heated to 100 °C. Methylmagnesium bromide (3.0 M in Et_2O, 2 mL, 6 mmol) was added to the stirring hot solution under an N_2 atmosphere dropwise as a white precipitate appeared. The reaction mixture was heated for 2 h at 115 °C. The flask was cooled, a few pieces of crushed ice were added, and the pH of the solution was adjusted to pH 2 by dropwise addition of 2 N aqueous H_2SO_4. The toluene layer was separated and the aqueous layer was extracted with EtOAc (80 mL). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4 and the solvents evaporated. Column chromatography on silica gel (5% EtOAc in CH_2Cl_2) gave compound **12** (230 mg, 76%) as a white solid: mp 125–128 °C (CH_2Cl_2/hexanes); $[\alpha]_D^{20}$ +4.30 (*c* 0.62 in $CHCl_3$). Found: C, 82.9; H, 11.0. Calc for $C_{18}H_{28}O$ C, 83.0; H, 10.8%. IR (ν_{max}/cm^{-1}) 3350, 2920, 2848, 1595. δ_H (300 MHz, $CDCl_3$) 1.61 (3H, s), 2.47–2.57 (1H, m), 4.08 (1H, m). δ_C (75 MHz, $CDCl_3$) 136.8, 127.8, 66.7, 52.9, 51.3, 47.3, 46.4, 40.9, 37.4, 36.0, 33.8, 33.3, 31.5, 29.8, 28.2, 25.6, 23.9, 13.6.

(3α,5α)-3-(Acetyloxy)-17-methylgon-13(17)-ene (13). Compound **13** was prepared in the same manner as compound **9**. Starting from compound **12** (6.9 g, 26.5 mmol), compound **13** (7.23 g, 90%) was obtained as a white solid after column chromatography on silica gel (10% EtOAc in hexanes): mp 103–104 °C (Et_2O/hexanes); $[\alpha]_D^{20}$ +6.41 (*c* 0.88 in $CHCl_3$). Found: C, 79.5; H, 10.0. Calc. for $C_{20}H_{30}O_2$ C, 79.4; H, 10.0%. IR (ν_{max}/cm^{-1}) 3351, 2917, 2847, 1734, 1597. δ_H (300 MHz, $CDCl_3$) 1.61 (3H, s), 2.06 (3H, s), 5.0 (1H, bs). δ_C (75 MHz, $CDCl_3$) 170.9, 136.7, 127.9, 70.2, 53.0, 51.2, 46.9, 46.3, 37.8, 37.4, 36.8, 33.6, 31.4, 30.4, 29.8, 28.2, 25.6, 24.6, 21.7, 13.6.

Acetic acid (1*S*,4a*R*,4b*S*,7*R*,8a*S*,10a*R*)-7-oxo-8-(3-oxo-butyl)-tetradecahydro-phenanthren-2-yl ester (14). A solution of compound **13** (4 g, 13.2 mmol) in CH_2Cl_2 (100 mL) was treated with ozone at −78 °C until a blue color persisted (*ca.* 30 min). Oxygen was passed through the solution for 30 min until the blue color disappeared. AcOH (50 mL) was added and the CH_2Cl_2 was evaporated under vacuum without heating. Then, AcOH (50 mL) and Zn dust (8.6 g, 130 mmol) were added and the reaction mixture was stirred at room temperature for 1h. Zn dust was filtered off through cotton, washing with CH_2Cl_2 (100 mL). The Zn dust was stirred with EtOAc (200 mL) for 1 h. The solids were filtered off, the combined solvents were evaporated and the product was purified by a column chromatography on silica gel (15% EtOAc in hexanes) to give compound **14** (3.5 g, 79%) as a white solid: mp 71–73 °C (Et_2O/hexanes); $[\alpha]_D^{20}$ +22.92 (*c* 1.65 in $CHCl_3$). Found: C, 72.0; H, 8.9. Calc. for $C_{20}H_{30}O_4$ C, 71.8; H, 9.0%. IR (ν_{max}/cm^{-1}) 3404, 2917, 2938, 2861, 1732, 1711, 1228, 1249. δ_H (300 MHz, $CDCl_3$) 2.04 (3H, s), 2.11 (3H, s), 5.04 (1H, m); δ_C (75 MHz, $CDCl_3$) 212.7, 209.3, 170.8, 69.8, 54.2, 47.9, 46.6, 46.2, 41.8, 41.1, 37.3, 36.2, 33.4, 31.2, 30.7, 30.1, 24.5, 21.6, 19.5.

(4a*S*,4b*R*,6a*S*,8*R*,10a*S*,10b*R*)-8-Hydroxy-4,4a,4b,5,6,6a,7,8,-9,10,10a,10b,11,12-tetradecahydro-3*H*-chrysen-2-one (15). A solution of NaOH (10% w/v in MeOH/water (9 : 1), 30 mL) was added to a solution of compound **14** (3.5 g, 10.5 mmol) in MeOH (100 mL) and the mixture was stirred for 1 h at 40 °C. A few pieces if crushed ice were added and the pH was adjusted to pH 1 by adding aqueous 1 N HCl. Solids were filtered off, washed several times with water and dried overnight at room temperature to give **15** (2.16 g, 75%) as a yellow solid, which was then crystallized from MeOH/$CHCl_3$ to afford white crystals. The aqueous phase was extracted with CH_2Cl_2 (2 × 100 mL), the organic extract was washed with brine, dried over anhydrous Na_2SO_4, and the solvent evaporated to afford additional, but slightly impure, oily product **15** (570 mg, 19%). Crystalline product **15** had: mp 250–251 °C (MeOH/$CHCl_3$), $[\alpha]_D^{20}$ −14.73 (*c* 0.27 in $CHCl_3$). Found: C, 78.6; H, 9.6. Calc. for $C_{18}H_{26}O_2$ C, 78.8; H, 9.55%. IR (ν_{max}/cm^{-1}) 3403, 2928, 2856, 1648, 1611. δ_H (300 MHz, $CDCl_3$) 4.12 (1H, m), 5.83

(1H, s); δ_C (75 MHz, $CDCl_3$) 200.3, 167.2, 124.3, 66.5, 48.9, 47.2, 46.4, 43.1, 40.5, 36.7, 35.8, 35.5, 33.6, 33.1, 30.5, 30.0, 26.4, 23.7.

(4a*S*, 4b*R*, 6a*S*, 8*R*, 10a*S*, 10b*R*) - 8 - Methoxymethoxy - 4, 4a,-4b,5,6,6a,7,8,9,10,10a,10b,11,12-tetradecahydro-3*H*-chrysen-2-one (16). *N*,*N*-Diisopropylethylamine (0.52 mL, 2.9 mmol) was added to a solution of compound **15** (410 mg, 1.49 mmol) in dry CH_2Cl_2 (40 mL). The solution was cooled to 0 °C, MOMCl (0.22 mL, 2.8 mmol) was added and the mixture was stirred under Ar at room temperature. After 30 h, CH_2Cl_2 (50 mL) was added and the organic layer was washed with the aqueous HCl (5%), aqueous $NaHCO_3$, and brine. Solvent was dried over anhydrous Na_2SO_4 and evaporated. Column chromatography on silica gel (10% EtOAc in hexanes) gave compound **16** (380 mg, 79%) as a white solid: mp 64–65 °C (EtOAc/hexanes); $[\alpha]_D^{20}$ −19.46 (*c* 0.35 in $CHCl_3$). Found: C, 75.15; H, 9.5. Calc. for $C_{20}H_{30}O_3$ C, 75.4; H, 9.5%. IR (ν_{max}/cm^{-1}) 3332, 2915, 2858, 1673, 1621, 1045. δ_H (300 MHz, $CDCl_3$) 3.35 (3H, s), 3.86 (1H, bm), 4.64 (2H, s), 5.79 (1H, s). δ_C (75 MHz, $CDCl_3$) 200.2, 167.1, 124.2, 94.7, 71.4, 55.3, 48.9, 46.9, 46.3, 43.0, 38.3, 36.6, 36.0, 35.7, 33.6, 30.4 (2 × C), 29.9, 26.3, 24.2.

(4a*R*,4b*S*,6a*S*,8*R*,10a*S*,10b*R*,12a*R*)-8-Methoxymethoxy-hexahydro-chrysen-2-one (17). Anhydrous NH_3 (10 mL) was condensed with a gas condenser into a three-neck flask containing Li metal (18 mg, 2.6 mmol) at −78 °C. Then, anhydrous THF (12 mL) was added and the resulting blue solution was stirred for 0.5 h. A solution of compound **16** (168 mg, 0.53 mmol) in dry THF (6 mL) was added dropwise to the vigorously stirred solution. After 3 h of stirring, the reaction color was discharged by careful addition of solid NH_4Cl in portions and left overnight while the NH_3 evaporated. The reaction was then acidified with aqueous 1 N HCl up to pH <7 and the product was extracted with EtOAc (2 × 50 mL). The combined organic phases were washed with sat. aqueous $NaHCO_3$, brine, dried with anhydrous Na_2SO_4, and the solvent evaporated. Purification by prep-TLC (4 plates, 40% EtOAc/hexanes) afforded ketone **17** (110 mg, 59%) as a white solid: mp 103–105 °C (hexanes), $[\alpha]_D^{20}$ −32.09 (*c* 0.21 in $CHCl_3$). Found: C, 75.1; H, 10.2. Calc. for $C_{20}H_{32}O_3$ C, 75.0; H, 10.0%. IR (ν_{max}/cm^{-1}) 3368, 2952, 2910, 2848, 2836, 1721, 1042. δ_H (300 MHz, $CDCl_3$) 3.37 (3H, s), 3.87 (1H, bm), 4.66 (2H, s); δ_C (75 MHz, $CDCl_3$) 211.9, 94.7, 71.4, 55.2, 48.7, 47.2, 46.8, 46.8, 46.3, 43.4, 41.4, 38.4, 36.1, 34.2, 33.7, 30.43, 30.40, 29.9, 29.3, 24.1.

(4a*R*,4b*S*,6a*S*,8*R*,10a*S*,10b*R*,12a*S*)-8-Methoxymethoxy-hexadecahydro-chrysen-2-one (18). A solution of compound **16** (200 mg, 0.63 mmol) in pyridine (25 ml) was hydrogenated in the presence of Pd/C (5%, 30 mg) at 60 psi. After 12 h, the catalyst was filtered through a short column of silica gel, washing with CH_2Cl_2. The solvent was removed *in vacuo* to yield a white solid. Column chromatography on silica gel (2% EtOAc in CH_2Cl_2) gave compound **18** (153 mg, 76%) as a white solid: mp 94–96 °C (hexanes), $[\alpha]_D^{20}$ −6.66 (*c* 0.195 in $CHCl_3$). Found: C, 75.1; H, 10.0. Calc. for $C_{20}H_{32}O_3$ C, 75.0; H, 10.1%. IR (ν_{max}/cm^{-1}) 2909, 2856, 2823, 1710, 1034. δ_H (300 MHz, $CDCl_3$) 2.58 (1H, t, J = 13.5 Hz), 3.37 (3H, s), 3.87 (1H, bs), 4.66 (2H, s); δ_C (75 MHz, CDCl) 213.3, 94.8, 71.5, 55.3, 47.3, 47.3, 43.0, 40.5, 38.6, 38.1, 37.5, 36.7, 36.3, 33.8, 30.9, 30.5, 29.8, 27.5, 24.1, 24.1.

(2*S*,4a*R*,4b*S*,6a*S*,8*R*,10a*S*,10b*R*,12a*R*)-8-Methoxymethoxy-octadecahydro-chrysen-2-ol (19). Compound **19** was prepared in the same manner as compound **8**. Starting from compound **17** (538 mg, 1.67 mmol), compound **19** (429 mg, 79%) was obtained as a white solid after column chromatography on silica gel (10% EtOAc in hexanes): mp 141–142 °C (EtOAc/hexanes); $[\alpha]_D^{20}$ −5.59 (*c* 0.22 in $CHCl_3$). Found: C, 74.2; H, 10.7. Calc. for $C_{20}H_{34}O_3$ C, 74.5; H, 10.6%. IR (ν_{max}/cm^{-1}) 3293, 2915, 2848, 1050. δ_H (300 MHz, $CDCl_3$) 3.37 (3H, s), 3.88 (1H, bm), 4.09 (1H, m), 4.67 (2H, s); δ_C (75 MHz, $CDCl_3$) 94.8, 71.7, 66.7, 55.3, 47.7, 47.6, 47.3 (2 × C), 40.8, 38.6, 36.4, 35.8, 34.1, 34.0, 33.2, 30.6, 29.6 (2 × C), 24.2, 23.6.

(2*S*,4a*R*,4b*S*,6a*S*,8*R*,10a*S*,10b*R*,12a*R*)-2-Benzyloxy-8-methoxymethoxy-octadecahydro-chrysene (20). KH (106 mg, 30% suspension in mineral oil, 0.82 mmol) was added to a solution of compound **19** (75 mg, 0.23 mmol) in dry THF (12 mL). After 60 min reflux under an N_2 atmosphere, the mixture was allowed to attain room temperature. Then, BnBr (0.1 mL, 0.82 mmol) was added and the resulting mixture was stirred at room temperature. After 3 h, the reaction mixture was carefully quenched with MeOH (2 mL), extracted with CH_2Cl_2 (50 mL). The organic phase was washed with brine and dried over anhydrous Na_2SO_4. Column chromatography on silica gel (2% EtOAc in CH_2Cl_2) gave compound **20** (72 mg, 75%) as a white solid: mp 95–97 °C (hexanes), $[\alpha]_D^{20}$ −2.85 (*c* 0.31 in $CHCl_3$). Found: C, 78.9; H, 9.45. Calc. for $C_{27}H_{40}O_3$ C, 78.6; H, 9.7%. IR (ν_{max}/cm^{-1}) 3368, 2903, 2847, 1605, 1496, 1099, 1049. δ_H (300 MHz, $CDCl_3$) 3.38 (3H, s), 3.69 (1H, bm), 3.88 (1H, m), 4.5 (2H, d, J = 3.3 Hz), 4.67 (2H, s), 7.28–7.36 (5H, m); δ_H (75 MHz, $CDCl_3$) 139.7, 128.5 (2 × C), 127.5 (2 × C), 127.4, 94.8, 73.3, 71.7, 69.8, 55.4, 47.8, 47.6, 47.3, 47.3, 38.6, 38.2, 36.4, 36.3, 34.1, 31.2, 30.6, 29.9, 29.6 (2 × C), 24.2, 24.1.

(2*S*,4a*R*,4b*S*,6a*S*,8*R*,10a*S*,10b*R*,12a*R*)-8-Benzyloxy-octahydro-chrysen-2-ol (21). Compound **21** was prepared in the same manner as compound **1**. Starting from compound **20** (450 mg, 1.09 mmol), compound **21** (310 mg, 77%) was obtained as a white solid after column chromatography on silica gel (10% EtOAc in hexanes): mp 156–158 °C (EtOAc/hexanes); $[\alpha]_D^{20}$ −1.42 (*c* 0.15 in $CHCl_3$). Found: C, 81.4; H, 9.8. Calc. for $C_{25}H_{36}O_2$ C, 81.5; H, 9.85%. IR (ν_{max}/cm^{-1}) 3271, 2916, 2850, 1595, 1094, 730, 694. δ_H (300 MHz, $CDCl_3$) 3.62 (1H, t, J = 2.7 Hz), 4.01 (1H, t, J = 2.7 Hz), 4.43 (2H, dd, J_1 = 12 Hz, J_2 = 15.3 Hz), 4.5 (2H, d, J = 3.3 Hz), 7.19–7.3 (5H, m); δ_C (75 MHz, $CDCl_3$) 139.7, 128.5 (2 × C), 127.6 (2 × C), 127.4, 73.3, 69.8, 66.7, 47.8, 47.7, 47.3, 47.2, 40.8, 38.2, 36.3, 35.8, 34.1, 34.0, 33.2, 29.9, 29.64, 29.67, 27.1, 23.6.

(4a*S*, 4b*R*, 6a*R*, 8*S*, 10a*R*, 10b*S*, 12a*S*) - 8 - Benzyloxy - hexadecahydro-chrysen-2-one (22). Jones reagent was added dropwise to a solution of compound **21** (320 mg, 0.87 mmol) in acetone (20 mL) at 0 °C until an orange color persisted. The course of the reaction was checked by TLC. Then, 2-propanol was added dropwise until the reaction mixture turned green. After 30 min, the reaction mixture was poured into water–ice. The product was extracted with EtOAc (2 × 50 mL) and the water phase was partially evaporated (1/3) and extracted with EtOAc (50 mL). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and the solvent was evaporated. Column chromatography on silica gel (10% EtOAc in hexanes) gave compound **22** (247 mg, 77%) as a white solid: mp 109–110 °C (Et_2O); $[\alpha]_D^{20}$ +17.88 (*c* 0.34 in $CHCl_3$). Found: C, 82.0; H, 9.3.

Calc. for $C_{25}H_{34}O_2$ C, 81.9; H, 9.35%. IR (ν_{max}/cm^{-1}) 3407, 2948, 2913, 2847, 1715, 1096, 1068. δ_H (300 MHz, $CDCl_3$) 3.60 (1H, bm), 4.41 (2H, dd, J = 12 Hz, J = 15.9 Hz), 7.17–7.26 (5H, m); δ_C (75 MHz, $CDCl_3$) 212.3, 139.6, 128.5 (2 × C), 127.5 (2 × C), 127.4, 73.1, 69.8, 48.8, 47.5, 46.94, 46.97, 46.5, 43.5, 41.5, 38.1, 36.2, 34.3, 33.9, 30.5, 30.1, 29.9, 29.4, 24.1.

(2*S*,4a*R*,4b*S*,6a*S*,8*R*,10a*S*,10b*R*,12a*S*)-8-Methoxymethoxy-octahexahydro-chrysen-2-ol (23). Lithium tri(*tert*-butoxy)-aluminum hydride (1 M solution in THF, 4.8 mL) was added dropwise to a cooled solution (–40 °C) of compound **18** (860 mg, 2.68 mmol) in anhydrous THF (200 mL) under an N_2 atmosphere. After 2 h at –40 °C, aqueous 1 N HCl (50 mL) was carefully added and the mixture was allowed to attain room temperature. The product was extracted with CH_2Cl_2 (2 × 150 mL), combined extracts were washed with sat. aqueous $NaHCO_3$, brine, dried over anhydrous Na_2SO_4. After solvent evaporation, the residue was purified by column chromatography on silica gel (10% EtOAc in hexanes) to afford compound **23** (570 mg, 65%) as a white solid: mp 118–119 °C (EtOAc/hexanes), $[\alpha]_D^{20}$ –4.0 (*c* 0.15 in $CHCl_3$); IR (ν_{max}/cm^{-1}) 3306, 2915, 2864, 1049. δ_H (300 MHz, $CDCl_3$) 3.37 (3H, s), 3.64 (1H, bm), 3.87 (1H, bs), 4.66 (2H, s). δ_C (75 MHz, $CDCl_3$) 94.8, 72.1, 71.6, 55.4, 47.7, 47.5, 40.6, 38.6, 37.6, 36.5, 36.4, 35.5, 34.0, 31.8, 30.6, 30.0, 29.7, 25.8, 24.8, 24.2. HRMS (FAB) *m*/*z* Calcd for $C_{20}H_{34}O_3$ $[M]^+$ 332.2508, found: 332.2495.

Benzoic acid (2*S*, 4a*R*, 4b*S*, 6a*S*, 8*R*, 10a*S*, 10b*R*, 12a*S*) - 8 - methoxymethoxy-octadecahydro-chrysen-2-yl ester (24). A solution of compound **23** (520 mg, 1.61 mmol) and 4-dimethylaminopyridine (10 mg, 0.01 mmol) in dry pyridine (45 mL) was cooled in an ice-bath. Then, BzCl (0.9 mL, 8.06 mmol) was added dropwise while stirring. After 15 h at room temperature, the reaction mixture was poured into water and extracted with CH_2Cl_2 (2 × 150 mL). The combined extracts were washed with aqueous HCl, sat. aqueous $NaHCO_3$, brine, and dried over anhydrous Na_2SO_4. After solvent evaporation, the oily residue was purified by column chromatography on silica gel (10% EtOAc in hexanes) to afford compound **24** (683 mg, 99%)as a white solid: $[\alpha]_D^{20}$ –15.85 (*c* 0.2 in $CHCl_3$); IR (ν_{max}/cm^{-1}) 2915, 2867, 1715, 1275, 1039. δ_H (300 MHz, $CDCl_3$) 3.38 (3H, s), 3.88 (1H, bs), 4.67 (2H, s), 5.01 (1H, bm), 7.41–7.46 (2H, m), 7.52–7.57 (1H, m), 8.03–8.06 (2H, m); δ_C (75 MHz, $CDCl_3$) 166.3, 132.8, 131.1, 129.7 (2 × C), 128.4 (2 × C), 94.8, 75.22, 71.6, 55.3, 47.6, 47.5, 40.6, 38.7, 37.6, 36.3, 35.4, 34.0, 32.5, 31.6, 30.6, 29.7, 26.2, 25.7, 24.7, 24.2. HRMS (FAB) *m*/*z* Calcd for $C_{27}H_{38}O_4Na$ $[M + Na]^+$ 449.2668, found: 449.2664.

Benzoic acid (2*S*, 4a*R*, 4b*S*, 6a*S*, 8*R*, 10a*S*, 10b*R*, 12a*S*) - 8 - Hydroxy-octadecahydro-chrysen-2-yl ester (25). Compound **25** was prepared in the similar fashion as compound **1**, wherein MeOH (60 mL) and 6 N HCl (4 mL) were used to carry out the hydrolysis. Starting from compound **24** (550 mg, 1.28 mmol), compound **25** (450 mg, 91%) was obtained as a white solid after column chromatography on silica gel (10% EtOAc in hexanes): mp 164–166 °C (EtOAc/hexanes); $[\alpha]_D^{20}$ –17.81 (*c* 0.16 in $CHCl_3$). Found: C, 78.6; H, 8.8. Calc. for $C_{25}H_{34}O_3$ C, 78.5; H, 9.0%. IR (ν_{max}/cm^{-1}) 3364, 2913, 2865, 1715,1275, 772. δ_H (300 MHz, $CDCl_3$) 4.1 (1H, bs), 5.01 (1H, bm), 7.41–7.46 (2H, m), 7.52–7.58 (1H, m), 8.04–8.07 (2H, m); δ_C (75 MHz, $CDCl_3$) 166.3, 132.8, 131.1, 129.7 (2 × C), 128.4 (2 × C), 75.2, 66.6, 47.61, 47.58, 40.8, 40.6, 37.6, 35.7, 35.4, 33.9, 33.2, 32.5, 31.6, 29.7, 26.2, 25.6, 24.7, 23.6.

Benzoic acid (4a*S*, 4b*R*, 6a*S*, 8*S*, 10a*R*, 10b*S*, 12a*S*) - 8 - Oxo - octadecahydro-chrysen-2-yl ester (26). Compound **26** was prepared in the same manner as compound **22**. Starting from compound **25** (400 mg, 1.04 mmol), compound **26** (289 mg, 73%) was obtained as a solidified foam after column chromatography on silica gel (10% EtOAc in hexanes): $[\alpha]_D^{20}$ +1.3 (*c* 0.16 in $CHCl_3$); IR (ν_{max}/cm^{-1}) 2914, 2866, 1714, 1274. δ_H (300 MHz, $CDCl_3$) 5.02 (1H, bm), 7.41–7.47 (2H, m), 7.53–7.59 (1H, m), 8.04–8.07 (2H, m). δ_C (75 MHz, $CDCl_3$) 212.0, 166.3, 132.9, 131.1, 129.7 (2 × C), 128.5 (2 × C), 74.9, 48.8, 47.3, 46.3, 43.4, 41.5, 40.4, 37.4, 35.3, 34.2, 32.4, 31.5, 30.5, 29.5, 26.2, 25.7, 25.3. HRMS (EI) *m*/*z* Calcd for $C_{25}H_{32}O_3$ $[M]^+$ 380.2351, found: 380.2355.

(5β,17β)-17-Hydroxyestran-3-one (27). Compound **27** was prepared in the same manner as compound **18**. Starting from compound **5** (6 g, 21.8 mmol), pure 5β-isomer **27** (2.39 g, 40%) and a mixture of 5β/5α-isomers (95 : 5, 1.98 g, 33%) were obtained after column chromatography on silica gel (15% EtOAc in hexanes): mp 105–106 °C (EtOAc, hexanes). δ_H (300 MHz, $CDCl_3$) 0.77 (3H, s), 2.57 (1H, t, J = 13.9 Hz), 3.66 (1H, t, J = 8.4 Hz); δ_C (75 MHz, $CDCl_3$) 213.2, 82.1, 50.2, 43.4, 43.1, 41.7, 39.9, 38.6, 38.5, 36.8, 36.6, 30.68, 30.72, 27.9, 25.7, 25.2, 23.4, 11.3. HRMS (FAB) *m*/*z* Calcd for $C_{18}H_{29}O_2$ $[M + H]^+$ 277.2168, found: 277.2168.

(5β,17β)-17-hydroxyestran-3-one 17-tosylate (28). Compound **28** was prepared in the same manner as compound **11**. Starting from compound **27** (5.8 g, 20.1 mmol), compound **28** (7.03 g, 78%) was obtained after column chromatography on silica gel (10% EtOAc in hexanes): mp 130–132 °C (EtOAc/hexanes); $[\alpha]_D^{20}$ +7.49 (*c* 0.25 in $CHCl_3$). Found: C, 69.6; H, 8.25; S, 7.3. Calc. for $C_{25}H_{34}O_4S$ C, 69.4; H, 8.4; S, 7.4%. IR (ν_{max}/cm^{-1}) 3400, 2920, 2871, 1708, 1357, 1175. δ_H (300 MHz, $CDCl_3$) 0.83 (3H, s), 2.45 (3H, s), 2.53 (1H, t, J = 14 Hz), 4.28 (1H, t, J = 9 Hz), 7.31–7.35 (2H, m), 7.77–7.79 (2H, m); δ_C (75 MHz, $CDCl_3$) 212.8, 144.6, 134.4, 129.8 (2 × C), 128.0 (2 × C), 90.0, 49.2, 43.4, 43.0, 41.3, 39.8, 38.4, 38.3, 36.5, 36.3, 30.6, 27.87, 27.82, 25.3, 25.0, 23.3, 21.8, 11.9.

(3α,5α,17β)-estrane-3,17-diol 17-tosylate (29). Compound **29** was prepared in the same manner as compound **23**. Starting from compound **28** (6.94 g, 16.1 mmol), compound **29** (6.19 g, 88%) was obtained as a white solid after column chromatography on silica gel (20% EtOAc in hexanes): mp 174–176 °C (EtOAc/hexanes); $[\alpha]_D^{20}$ +7.89 (*c* 0.38 in $CHCl_3$). Found: C, 69.6; H, 8.25; S, 7.3. Calc. for $C_{25}H_{36}O_4S$ C, 69.4; H, 8.4; S, 7.4%. IR (ν_{max}/cm^{-1}) 3418, 2923, 2861, 1644, 1356, 1175. δ_H (300 MHz, $CDCl_3$) 0.77 (3H, s), 2.44 (3H, s), 3.60 (1H, bm), 4.23 (1H, t, J = 8 Hz), 7.33 (2H, d, J = 8.4 Hz), 7.78 (2H, d, J = 8.7 Hz); δ_C (75 MHz, $CDCl_3$) 144.5, 134.3, 129.8 (2 × C), 127.9 (2 × C), 90.3, 71.7, 49.2, 43.3, 41.6, 39.9, 384, 36.4, 36.3, 35.6, 31.4, 29.7, 27.8, 26.1, 25.7, 25.0, 23.3, 21.8, 11.9.

(3α,5β)-17-methylgon-13(17)-en-3-ol (30). Compound **30** was prepared in the same manner as compound **12**. Starting from compound **29** (2.9 g, 6.7 mmol), compound **30** (1.71 g, 98%) was obtained as a white solid after column chromatography on silica

gel (20% EtOAc in hexanes): mp 130–131 °C (EtOAc/hexanes); $[\alpha]_D^{20}$ −7.05 (*c* 0.105 in $CHCl_3$). Found: C, 83.0; H, 10.7. Calc. for $C_{18}H_{28}O$ C, 83.0; H, 10.8%. IR (ν_{max}/cm^{-1}) 3368, 2923, 2861, 1638, 1068, 1034. δ_H (300 MHz, $CDCl_3$) 1.60 (3H, s), 2.48–2.55 (1H, m), 3.64 (1H, bm); δ_C (75 MHz, $CDCl_3$) 136.7, 127.9, 72.0, 52.8, 51.6, 40.2, 37.4, 36.8, 36.5, 35.8, 31.6, 30.1, 30.1, 28.2, 26.6, 26.1, 25.7, 13.6.

(3α,5β)-3-Methoxymethoxy-17-methylgon-13(17)-ene (31). Compound **31** was prepared in the same manner as compound **16**. Starting from compound **30** (5.28 g, 20.2 mmol), compound **31** (6.11 g, 99%) was obtained as an oily material after column chromatography on silica gel (5% EtOAc in hexanes). Compound **31** had: $[\alpha]_D^{20}$ +1.35 (*c* 0.17 in $CHCl_3$); IR (ν_{max}/cm^{-1}) 2926, 2865, 1454, 1444, 1043. δ_H (300 MHz, $CDCl_3$) 1.60 (3H, s), 2.48–2.55 (1H, m), 3.38 (3H, s), 3.56 (1H, bm), 4.70 (2H, s); δ_C (75 MHz, $CDCl_3$) 136.7, 127.9, 94.7, 77.01, 55.3, 52.8, 51.6, 40.4, 37.4, 36.8, 35.8, 33.6, 31.7, 30.1, 28.2, 27.3, 26.5, 26.2, 25.7, 13.6. HRMS (FAB) *m/z* Calcd for $C_{20}H_{32}O_2Na$ $[M + Na]^+$ 327.2300, found: 327.2297.

(1*S*, 4a*R*, 4b*S*, 7*R*, 8a*R*, 10a*R*) - 7 - Methoxymethoxy - 1 - (3 - oxo-butyl)-dodecahydro-phenanthren-2-one (32). Compound **32** was prepared in the same manner as compound **14**. Starting from compound **31** (6.11 g, 20.06 mmol), compound **32** (4.43 g, 65%) was obtained as an oily material after column chromatography on silica gel (10% EtOAc in hexanes): $[\alpha]_D^{20}$ +22.6 (*c* 0.29 in $CHCl_3$); IR (ν_{max}/cm^{-1}) 2935, 2869, 1711, 1041. δ_H (300 MHz, $CDCl_3$) 2.10 (3H, s), 3.36 (3H, s), 3.56 (1H, bm), 4.68 (2H, s); δ_C (75 MHz, $CDCl_3$) 212.7, 209.2, 94.7, 76.6, 55.3, 54.1, 48.4, 42.0, 41.1, 40.3, 36.9, 35.0, 33.4, 31.6, 31.0, 30.0, 27.1, 26.7, 26.0, 19.5. HRMS (FAB) *m/z* Calcd for $C_{20}H_{33}O_4$ $[M + H]^+$ 337.2379, found: 337.2376.

(4a*S*, 4b*R*, 6a*R*, 8R, 10a*S*, 10b*R*) - 8 - Methoxymethoxy - 4, 4a, 4b, - 5, 6, 6a, 7, 8, 9, 10, 10a, 11, 12-tetradecahydro-3*H*-chrysen-2-one (33). Compound **32** was prepared in the same manner as compound **15**. Starting from compound **32** (4.37 g, 12.9 mmol), compound **33** (3.45 g, 83%) was obtained as an low melting solid after column chromatography on silica gel (20% EtOAc in hexanes): mp <65 °C (hexanes); $[\alpha]_D^{20}$ −13.77 (*c* 0.39 in $CHCl_3$). Found: C, 75.5; H, 9.4. Calc. for $C_{20}H_{30}O_3$ C, 75.4; H, 9.5%. IR (ν_{max}/cm^{-1}) 3382, 2931, 2865, 1671, 1040. δ_H (300 MHz, $CDCl_3$) 3.36 (3H, s), 3.56 (1H, bm), 4.68 (2H, s), 5.81 (1H, bs); δ_C (75 MHz, $CDCl_3$) 200.1, 166.9, 124.3, 94.7, 76.7, 55.3, 49.3, 42.9, 40.3, 36.8, 36.6, 35.7, 35.1, 33.5, 31.5, 30.2, 27.2, 26.4, 25.8, 25.6.

(4a*R*, 4b*S*, 6a*R*, 8*R*, 10a*S*, 10b*R*, 12a*R*) - 8 - Methoxymethoxy - hexadecahydro-chrysen-2-one (34). Compound **34** was prepared in the same manner as compound **17**. Starting from compound **33** (500 mg, 1.57 mmol), compound **34** (260 mg, 51%) and starting material **33** (140 mg, 28%) were obtained as white solids after column chromatography on silica gel (20% EtOAc in hexanes). Compound **34** had: mp 83–84 °C (hexanes); $[\alpha]_D^{20}$ −19.9 (*c* 0.31 in $CHCl_3$). Found: C, 75.2; H, 10.0. Calc. for $C_{20}H_{32}O_3$ C, 75.0; H, 10.1%. IR (ν_{max}/cm^{-1}) 2931, 2910, 2862, 1717, 1035. δ_H (300 MHz, $CDCl_3$) 3.36 (3H, s), 3.54 (1H, bm), 4.68 (2H, s); δ_C (75 MHz, $CDCl_3$) 212.1, 94.7, 76.8, 55.3, 48.8, 47.3, 46.3, 43.4, 41.4, 40.6, 37.3, 35.4, 34.2, 33.5, 31.6, 30.5, 29.4, 27.1, 25.8, 25.3.

(4a*R*, 4b*S*, 6a*R*, 8*R*, 10a*S*, 10b*R*, 12a*S*) - 8 - Methoxymethoxy - hexadecahydro-chrysen-2-one (35). Compound **35** was prepared in the same manner as compound **18**. Starting from compound **33** (400 mg, 1.25 mmol), *cis*-isomer **35** (214 mg, 53%), *trans*-isomer **34** (99 mg, 24%) and a mixture of **34** and **35** (1 : 1, 52 mg, 13%) were obtained after column chromatography on silica gel (10% EtOAc in hexanes): mp 102–103 °C (ether/hexanes); $[\alpha]_D^{20}$ +6.06 (*c* 0.21 in $CHCl_3$). Found: C, 75.1; H, 9.9. Calc. for $C_{20}H_{32}O_3$ C, 75.0; H, 10.1%. IR (ν_{max}/cm^{-1}) 2925, 2869, 2849, 1712, 1039. δ_H (300 MHz, $CDCl_3$) 2.58 (1H, t, J = 13.8 Hz), 3.37 (3H, s), 3.56 (1H, bm), 4.69 (2H, s); δ_C (75 MHz, $CDCl_3$) 213.1, 94.7, 76.8, 55.3, 43.0, 40.6, 40.3, 38.1, 37.9, 37.7, 36.6, 35.4, 33.5, 31.6, 30.8, 27.6, 27.1, 25.8, 25.0, 24.2.

(2*S*, 4a*R*, 4b*S*, 6a*R*, 8*R*, 10a*S*, 10b*R*, 12a*R*) - 8 - Methoxymethoxy - octadecahydro-chrysen-2-ol (36). Compound **36** was prepared in the same manner as compound **8**. Starting from compound **34** (860 mg, 2.68 mmol), compound **36** (660 mg, 76%) was obtained as a white solid after chromatography on silica gel (15% EtOAc in hexanes): mp 150–151 °C (Et_2O); $[\alpha]_D^{20}$ +4.7 (*c* 0.27 in $CHCl_3$). Found: C, 74.6; H, 10.8. Calc. for $C_{20}H_{34}O_3$ C, 74.5; H, 10.6%. IR (ν_{max}/cm^{-1}) 3275, 2914, 2866, 2845. δ_H (300 MHz, $CDCl_3$) 3.37 (3H, s), 3.54 (1H, bm), 4.07 (1H, bs), 4.69 (2H, s); δ_C (75 MHz, $CDCl_3$) 94.7, 76.8, 66.6, 55.3, 47.7, 47.6, 40.8 (2 × C), 37.5, 35.8, 35.5, 33.9, 33.6, 33.2, 31.8, 29.7, 27.1, 25.8, 24.7, 23.6.

Benzoic acid (2*S*, 4a*R*, 4b*S*, 6a*R*, 8*R*, 10a*S*, 10b*R*, 12a*R*) - 8 - methoxymethoxy-octadecahydro-chrysen-2-yl ester (37). Compound **37** was prepared in the same manner as compound **24**. Starting from compound **36** (610 mg, 1.89 mmol), compound **37** (680 mg, 84%) was obtained as a white solid after column chromatography on silica gel (10% EtOAc in hexanes): mp 130–131 °C (Et_2O/hexanes); $[\alpha]_D^{20}$ +5.52 (*c* 0.39 in $CHCl_3$). Found: C, 76.25; H, 9.1. Calc. for $C_{27}H_{38}O_4$ C, 76.0; H, 9.0%. IR (ν_{max}/cm^{-1}) 2930, 2865, 1715, 1450, 1275, 1040, 714. δ_H (300 MHz, $CDCl_3$) 3.38 (3H, s), 3.56 (1H, bm), 4.70 (2H, s), 5.31 (1H, m), 7.42–7.47 (2H, m), 7.53–7.59 (1H, m), 8.04–8.08 (2H, m); δ_C (75 MHz, $CDCl_3$) 166.1, 132.8, 1631.3, 129.7 (2 × C), 128.5 (2 × C), 94.7, 77.0, 70.7, 55.3, 47.6, 47.2, 40.8, 37.9, 37.5, 36.9, 35.5, 33.8, 33.6, 31.8, 30.5, 29.6, 27.1, 25.8, 24.7, 24.5.

Benzoic acid (2*S*, 4a*R*, 4b*S*, 6a*R*, 8*R*, 10a*S*, 10b*R*, 12a*R*) - 8 - hydroxy-octadecahydro-chrysen-2-yl ester (38). *Method A*: Compound **38** was prepared in the same manner as compound **1**. Starting from compound **37** (600 mg, 1.4 mmol), compound **38** (228 mg, 42%) and starting material **37** (286 mg, 47%) were obtained after column chromatography on silica gel (20% EtOAc in hexanes). *Method B*: To a solution of compound **37** (286 mg, 0.67 mmol) in MeOH (18 mL) and benzene (6 mL) was added dropwise AcCl (0.8 mL, 11.2 mmol) at 0 °C and the reaction mixture was allowed to stir overnight at room temperature. Then, a few pieces of crushed ice were added and the pH was adjusted with sat. aqueous $NaHCO_3$ to pH 6. The product was extracted with CH_2Cl_2 (2 × 80 mL) and the combined extracts were washed with brine and dried over anhydrous Na_2SO_4. After solvent evaporation, the residue was purified by a column chromatography (20% EtOAc/hexanes) to afford compound **38** (233 mg, 91%): mp 196–198 °C (EtOAc); $[\alpha]_D^{20}$ −0.92 (*c* 0.24 in $CHCl_3$). Found: C, 78.3; H, 9.0. Calc. for $C_{25}H_{34}O_3$ C, 78.5; H, 9.0%. IR (ν_{max}/cm^{-1}) 3377, 2922, 2862, 1714, 1450, 1275, 713. δ_H (300 MHz, $CDCl_3$)

3.65 (1H, m), 5.32 (1H, m), 7.42–7.48 (2H, m), 7.53–7.59 (1H, m), 8.04–8.07 (2H, m); δ_C (75 MHz, $CDCl_3$) 166.1, 132.8, 131.4, 129.7 (2 × C), 128.5 (2 × C), 72.0, 70.7, 47.7, 47.3, 40.7, 37.9, 37.6, 36.9, 36.5, 35.5, 33.8, 31.8, 30.5, 30.1, 29.7, 25.8, 24.8, 24.6.

Benzoic acid (4a*S*, 4b*R*, 6a*R*, 8*S*, 10a*R*, 10b*S*, 12a*R*) - 8 - Oxo - octadecahydro-chrysen-2-yl ester (39). Compound **39** was prepared in the same manner as compound **22**. Starting from compound **38** (447 mg, 1.16 mmol), compound **39** (335 mg, 75%) was obtained as a white solid after column chromatography on silica gel (15% EtOAc in hexanes): mp 115–117 °C (EtOAc); $[\alpha]_D^{20}$ +1.84 (*c* 0.39 in $CHCl_3$). Found: C, 78.8; H, 8.6. Calc. for $C_{25}H_{32}O_3$ C, 78.9; H, 8.5%. IR (ν_{max}/cm^{-1}) 2916, 2862, 1712, 1274. δ_H (300 MHz, $CDCl_3$) δ 2.60 (1H, t, J = 13.8 Hz), 5.33 (1H, m), 7.43–7.49 (2H, m), 7.54–7.59 (1H, m), 8.05–8.09 (2H, m); δ_C (75 MHz, $CDCl_3$) 212.9, 166.1, 132.9, 131.3, 129.7 (2 × C), 128.5 (2 × C), 70.5, 47.3, 47.3, 43.0, 40.5, 38.1, 37.9, 37.5, 36.9, 36.7, 33.7, 30.9, 30.5, 29.8, 27.6, 24.5, 24.1.

(2*S*, 4a*R*, 4b*S*, 6a*R*, 8*R*, 10a*S*, 10b*R*, 12a*S*) - 8 - Methoxymethoxy - octadecahydro-chrysen-2-ol (40). Compound **40** was prepared in the same manner as compound **23**. Starting from compound **35** (264 mg, 0.823 mmol), compound **40** (160 mg, 60%) and starting material **35** (42 mg, 16%) were obtained as white solids after column chromatography on silica gel (15% EtOAc in hexanes). Compound **40** had: mp 151–152 °C (Et_2O); $[\alpha]_D^{20}$ +6.75 (*c* 0.24 in $CHCl_3$). Found: C, 74.4; H, 10.6. Calc. for $C_{20}H_{34}O_3$ C, 74.5; H, 10.6%. IR (ν_{max}/cm^{-1}) 3272, 2934, 2911, 2869, 2845, 1058. δ_H (300 MHz, $CDCl_3$) 3.37 (3H, s), 3.52–3.65 (2H, m), 4.68 (2H, s); δ_C (75 MHz, $CDCl_3$) 94.7, 76.8, 71.9, 55.3, 40.6, 40.4, 38.0 (2 × C), 36.4, 35.6, 35.5, 33.6, 31.8, 31.7, 29.9, 27.1, 25.9, 25.8, 24.9 (2 × C).

Benzoic acid (2*S*, 4a*R*, 4b*S*, 6a*R*, 8*R*, 10a*S*, 10b*R*, 12a*S*) - 8 - Methoxymethoxy-octadecahydro-chrysen-2-yl ester (41). Compound **41** was prepared in the same manner as compound **24**. Starting from compound **40** (480 mg, 1.48 mmol), compound **41** (560 mg, 88%) was obtained as a white solid after column chromatography on silica gel (5% EtOAc in hexanes): mp 126–128 °C (EtOAc/hexanes); $[\alpha]_D^{20}$ −8.71 (*c* 0.28 in $CHCl_3$). Found: C, 76.1; H, 8.8. Calc. for $C_{27}H_{38}O_4$ C, 76.0; H, 9.0%. IR (ν_{max}/cm^{-1}) 2932, 2869, 1719, 1450, 1273, 1044, 712. δ_H (300 MHz, $CDCl_3$) 3.38 (3H, s), 3.55 (1H, m), 4.70 (2H, s), 5.00 (1H, m), 7.40–7.46 (2H, m), 7.52–7.57 (1H, m), 8.03–8.07 (2H, m); δ_C (75 MHz, $CDCl_3$) 166.3, 132.8, 131.2, 129.7 (2 × C), 128.4 (2 × C), 94.8, 76.8, 75.1, 55.3, 40.7, 40.5, 38.10, 38.07, 35.6, 35.5, 33.6, 32.5, 31.8, 31.6, 27.2, 26.2, 25.9, 25.7, 24.95, 24.91.

Benzoic acid (2*S*, 4a*R*, 4b*S*, 6a*R*, 8*R*, 10a*S*, 10b*R*, 12a*S*) - 8 - Hydroxy-octadecahydro-chrysen-2-yl ester (42). Compound **42** was prepared in the same manner as compound **38** by *Method B*. Starting from compound **41** (530 mg, 1.24 mmol), compound **42** (380 mg, 80%) was obtained as a white solid after column chromatography on silica gel (25% EtOAc in hexanes): mp 173–174 °C (EtOAc); $[\alpha]_D^{20}$ −15.15 (*c* 0.2 in $CHCl_3$). Found: C, 78.7; H, 8.9. Calc. for $C_{25}H_{34}O_3$ C, 78.5; H, 9.0%. IR (ν_{max}/cm^{-1}) 3292, 2917, 2867, 1714, 1451, 1275, 711. δ_H (300 MHz, $CDCl_3$) 3.65 (1H, m), 5.00 (1H, m), 7.40–7.46 (2H, m), 7.52–7.57 (1H, m), 8.04–8.07 (2H, m); δ_C (75 MHz, $CDCl_3$) 166.3, 132.8, 131.2, 129.7 (2 × C), 128.4 (2 × C), 75.2, 71.9, 40.5, 38.1 (2 × C), 36.5, 35.6, 35.5, 32.5, 31.7, 31.6, 30.0, 26.2, 25.9, 25.7, 24.98, 24.92.

Benzoic acid (4a*S*, 4b*R*, 6a*S*, 8*S*, 10a*R*, 10b*S*, 12a*R*) - 8 - Oxo - octadecahydro-chrysen-2-yl ester (43). Compound **43** was prepared in the same manner as compound **22**. Starting from compound **42** (357 mg, 0.93 mmol), compound **43** (342 mg, 96%) was obtained as a white solid after column chromatography on silica gel (15% EtOAc in hexanes): mp 116–117 °C (hexanes), $[\alpha]_D^{20}$ −16.3 (*c* 0.24 in $CHCl_3$). Found: C, 79.0; H, 8.4. Calc. for $C_{25}H_{32}O_3$ C, 78.9; H, 8.5%. IR (ν_{max}/cm^{-1}) 2916, 2868, 1711, 1274. δ_H (300 MHz, $CDCl_3$) 2.60 (1H, t, J = 13.8 Hz), 5.02 (1H, bm), 7.41–7.46 (2H, m), 7.52–7.58 (1H, m), 8.04–8.08 (2H, m); δ_C (75 MHz, $CDCl_3$) 212.8, 166.2, 132.9, 131.1, 129.7 (2 × C), 128.4 (2 × C), 74.9, 43.0, 40.5, 40.4, 38.2, 38.0, 37.8, 36.6, 35.4, 32.4, 31.5, 30.8, 27.6, 26.2, 25.7, 25.1, 24.3.

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Notes and references

1 D. Belelli and J. J. Lambert, *Nat. Rev. Neurosci.*, 2005, **6**, 565.
2 B. W. Katona, K. Krishnan, Z. Y. Cai, B. D. Manion, A. Benz, A. Taylor, A. S. Evers, C. F. Zorumski, S. Mennerick and D. F. Covey, *Eur. J. Med. Chem.*, 2008, **43**, 107.
3 P. Li, J. Bracamontes, B. W. Katona, D. F. Covey, J. H. Steinbach and G. Akk, *Mol. Pharmacol.*, 2007, **71**, 1582.
4 D. F. Covey, D. Nathan, M. Kalkbrenner, K. R. Nilsson, Y. Hu, C. F. Zorumski and A. S. Evers, *J. Pharmacol. Exp. Ther.*, 2000, **293**, 1009.
5 L. L. Wittmer, Y. Hu, M. Kalkbrenner, A. S. Evers, CH. F. Zorumski and D. F. Covey, *Mol. Pharmacol.*, 1996, **50**, 1581.
6 A. Bowers, H. J. Ringold and E. Denot, *J. Am. Chem. Soc.*, 1958, **80**, 6115.
7 K. A. Parker and W. S. Johnson, *J. Am. Chem. Soc.*, 1974, **96**, 2556.
8 O. S. Madaeva, *Zh. Obshch. Khim.*, 1955, **25**, 1427.
9 W. J. Rodewald and J. W. Morzycki, *Polish J. Chem.*, 1978, **52**, 2361.
10 CH. R. Engel, P. Lachance, J. Capitaine, J. Zee, D. Mukhetjee and Y. Mérand, *J. Org. Chem.*, 1983, **48**, 1954.
11 D. Menberu, N. Van Phuoc, P. K. D. Onan and W. Le Quesne, *J. Org. Chem.*, 1992, **57**, 2100.
12 W. E. Farnsworth, *Steroids*, 1966, **8**, 825.
13 Y. Hu, CH. F. Zorumski and D. F. Covey, *J. Med. Chem.*, 1993, **36**, 3956.

