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Synthesis of Steroid Intermediates via Alkylation of Dianion Derived from Acetoacetic Ester†

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Abstract—A synthetic route for A-ring aromatic steroid intermediates starting from alkylation of dianion derived from acetoacetic ester with *m*-methoxyphenylethyl bromide to form benzene ring connected to a linear six-carbon fragment is described. This unit, after chemical modifications to **5**, was condensed with 2-methylcyclopentan-1,3-dione (**6a**) to form prochiral trione, **7a**, a key synthetic intermediate in A-ring aromatic steroid. Microbial reduction of **7a** with *Schizosaccharomyces pombe* (NRRL Y-164) gave chiral (–)-**11** in 65% yield. Starting from 2,2-dimethylsuccinic acid, 2,4,4-trimethylcyclopentan-1,3-dione (**6a**) was prepared, which was condensed subsequently with **5** to form racemic **7b** trione intermediate. Asymmetric cyclization of **7b** in the presence of L-(–)-phenylalanine, followed by acidic cyclization led to regiospecific synthesis of 16,16-dimethyl tetracyclic steroid intermediate.

Introduction

For the past years, extensive synthetic effort has been directed towards the A-ring aromatic steroids because of their medicinal and commercial importance, and also for the display of new organic synthetic methodology.[1] The dianion generated from ethyl acetoacetate has been successfully γ-alkylated in high yields and the resulting products have been applied to the synthesis of a number of natural products.[2,3] In our laboratory, we have engaged in the preparation of chiral steroid intermediates by asymmetric cyclization[4] and microbiological reduction.[5] In the present report, we describe an alternative approach to the synthesis of A-ring aromatic steroid intermediates by alkylation of dianion derived from acetoacetic ester with *m*-methoxyphenylethyl bromide for the construction of an aromatic ring connected to a linear six carbon fragment. After modifications, this was condensed with a five-membered ring moiety to construct the required carbon member and as substrate for subsequent asymmetric cyclization and microbial reduction.

Results and Discussion

Alkylation of dianion derived from ethyl acetoacetate with 3-methoxylethyl bromide (**1**)[6] gave ethyl 6-*m*-methoxyphenyl-3-oxohexanoate (**2**) in 80% yield. Compound **2**, colorless liquid, showed in its mass spectrum a molecular ion at m/z 264, corresponding to a formula of $C_{15}H_{20}O_4$. A two-proton singlet at δ 3.38 (H-11) and absence of a -COCH$_3$ signal together with the presence of aromatic proton signals at δ 7.17 (t, H-1) and 6.73 (3H, m) in the ^{1}H-NMR spectrum of **2** is indication of the successful γ-alkylation of the ethyl acetoacetate by **1**. Subsequent chemical modification of **2** by: (1) formation of ethylenedioxy function for the protection of carbonyl group, (2) $LiAlH_4$ reduction of the carboxylate to primary carbinol, and (3) acidic carbonyl deprotection and dehydration, resulted in the formation of the α,β-unsaturated carbonyl function [H_E-12: δ 5.78 (dd, J = 10.5 and 1.4 Hz); H-11: δ 6.32 (dd, J = 17.6 and 10.5 Hz); H_Z-12: δ 6.15 (dd, J = 17.6 and 1.4 Hz)] in **5** with 76% overall yield. Condensation of **5** with **6a**[7] gave the known prochiral trione **7a**,[8] whose ^{13}C-NMR spectrum shows the signals of three carbonyl carbons at δ 209.8 (C-9), 215.7 (C-14 and C-17), in 80% yield. Heating of **7a** with *p*-TsOH at reflux in benzene solution gave crystalline tetracyclic product **8a**,[8] $\delta_{H\text{-}15}$ 5.85 (t, J = 2.5 Hz), for further structure confirmation. This present approach seems to be a simple and convenient alternative route for the synthesis of prochiral trione **7a** which is the key intermediate in the estrone synthesis of the Smith–Hughes approach.[9]

Microbial reduction of prochiral **7a** with *Schizosaccharomyces pombe* (NRRL Y-164)[5] gave monohydroxy products (+)-**11** and (–)-**12** in 65.0 and 9.1% yield, respectively. Compound (+)-**11**, colorless liquid with $[\alpha]_D$ + 42.8° (c = 7.28, MeOH), showed in its high resolution mass spectrum a molecular ion at m/z 318.1833, corresponding to a formula of $C_{19}H_{26}O_4$ (calcd 318.1832). Its IR absorption at 3480 cm^{-1} and a proton signal at δ 3.95 (t, J = 5.7 Hz, H-17) in its ^{1}H-NMR spectrum support the presence of a secondary hydroxyl group. Since (+)-**11** resisted Oppenauer oxidation while (–)-**12** was oxidized back to **7a**, it was assumed that the hydroxyl group in (+)-**11** must be situated on the five-membered ring while the (–)-**12** must be formed by reduction of the side-chain carbonyl group. This suggestion was supported by the fact that the proton signals at δ 3.95 (H-17) couple only to two protons' signal at δ 1.90 and 2.22 (H-16's) in the homo-COSY spectrum. Cyclization of

†Dedicated to Professor C. J. Sih on the occasion of his 60th birthday.

Key words—A-Ring aromatic steroids, dianion alkylation, asymmetric cyclization, microbial reduction.

(+)-**11** to (+)-**10a** was carried out with piperidine and glacial HOAc in 70% yield. Compound (+)-**10a** is a colorless liquid, $[\alpha]_D$ + 20° (c = 1.1, MeOH), showed in its high resolution mass spectrum a molecular ion at m/z 300.1724, corresponding to a formula of $C_{19}H_{26}O_3$ (calcd 300.1725). Its UV absorption maximum at 252.4 nm (log ε 3.98) and IR absorption at 1625 and 1585 cm^{-1} indicated the successful cyclization and presence of a substituted α,β-unsaturated carbonyl chromophore in the molecule.[10] The 2D NMR HMBC (^{1}H-detected multiple-bond heteronuclear multiple-quantum coherence) spectrum indicates the coupling of H-18 (δ 1.02) to a disubstituted olefinic carbon (s, δ 168.9, C-14), C-12 (t, δ 33.5), C-13 (s, δ 45.2) and C-17 (d, δ 80.8) supports the structure assigned for **10a**. This technique also facilitates the assignment of the rest of the carbons' and protons' chemical shifts in **10a** and the data are listed in the Experimental Section.

The structure of (+)-**10a** was further established by the following chemical approach. Asymmetric cyclization of **7a** with L-(−)-phenylalanine and $HClO_4$ gave (+)-**9a** with 79% e.e.[4] in 90% yield. The UV absorption maximum at λ 249.6 supports the successful formation of C ring. Sodium borohydride reduction of (+)-**9a** in MeOH[11] gave after purification a colorless liquid product with $[\alpha]_D$ + 19° (c = 0.94, MeOH) which was identical in every respect (UV, IR, NMR) to (+)-**10a**.

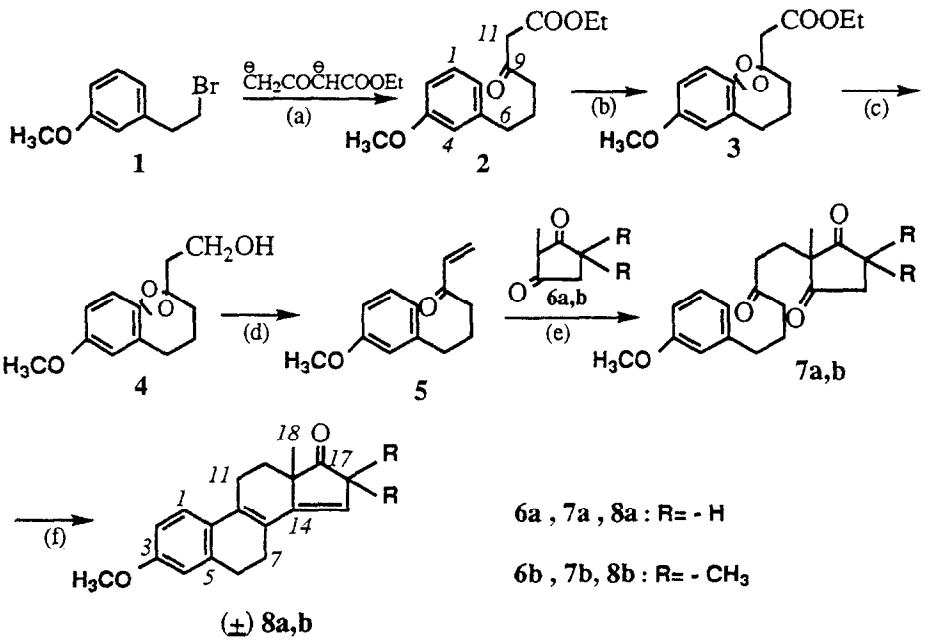


Figure 1. Synthesis of triones **7a,b**. (a) THF, NaH, *n*-BuLi, N_2, 0 °C, 80%; (b) HO-CH_2-CH_2-OH, *p*-TsOH, ϕ-H, reflux, 90; (c) THF, $LiAlH_4$, N_2, reflux, 95%; (d) HCl, H_3CCOCH_3, 90%; (e) THF, NEt_3, pH 8, 40 °C, **5**–**7d**; (f) *p*-TsOH, ϕ-H, reflux

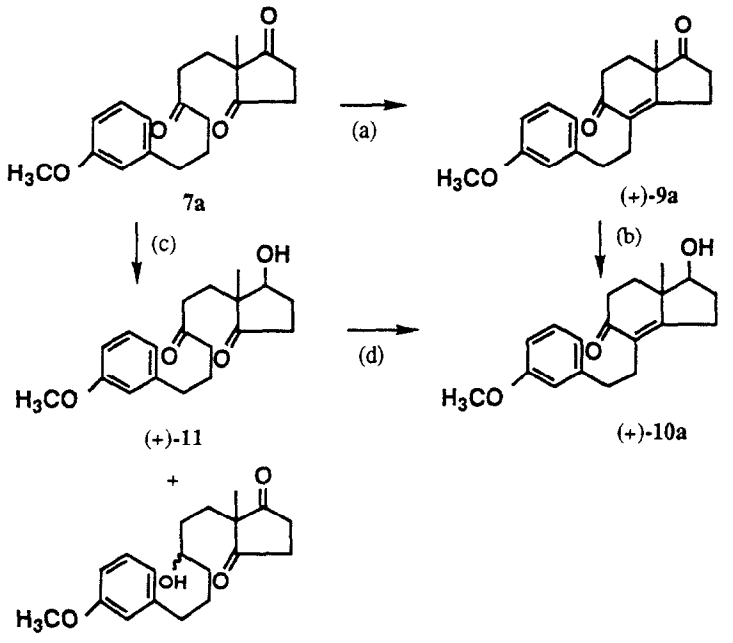


Figure 2. Asymmetric cyclization and microbial reduction of prochiral trione **7a**. (a) L-(−)-phenylalanine, $HClO_4$, reflux, 48 h, 90%; (b) $NaBH_4$, MeOH, 0 °C; (c) *Schizosaccharomyces pombe*(NRRL Y-164), **11**(65%), **12**(9.1%); (d) piperidine, HOAc, reflux, 9 h, 70%

Since the present approach to the synthesis of A-ring aromatic steroid intermediates is a high yield process, we applied it in the preparation of a 16,16-dimethyl derivative. Michael condensation of **5** with **6b**[5b] gave racemic **7b** as a colorless liquid in 70% yield. Asymmetric cyclization of (±)-**7b** in the presence of L-(–)-phenylalanine gave 44% of (+)-**9b** and recovered 55% of substrate. Twice recycling of recovered substrate led to a final yield of 48.5% of (+)-**9b** with $[\alpha]_D$ + 109° (c = 0.76, MeOH) and recovery of 44% (+)-**7b** with $[\alpha]_D$ + 5° (c = 1.0, MeOH). On the other hand, when (±)-**7b** was cyclized in the presence of D-(+)-phenylalanine, a 49% yield of (–)-**9b** with $[\alpha]_D$ –110° (c = 0.96, MeOH) was obtained and recovered 49% of (–)-**7b** with $[\alpha]_D$ –5° (c = 1.0, MeOH). When (–)-**7b** and (+)-**7b** were employed as the starting material in the asymmetric cyclization, (+)-**9b** with $[\alpha]_D$ + 125° (c = 0.85, MeOH) and (–)-**9b** with $[\alpha]_D$ –126° (c = 0.84, MeOH) were obtained, respectively.

The structure of **7b** was supported by the 2D NMR HMBC. This spectrum indicated that three methyl singlets (δ 1.11, 1.19 and 1.26) were three-bond coupled to C-17 signal (δ 215.7). This observation is possible only when C-13 is mono-methylated and C-16 is dimethylated, thus, confirming the structure of **7b**. This technique also allows the complete ^{13}C-NMR assignment of **7b**. The assignment for the active methylene carbons (C-8, δ 41.8; C-11, δ 36.8) and the benzylic carbon (C-6, δ 35.0) is made from their long range coupling to H-4 and H-10 (δ 6.70) (C-6), H-6 (δ 2.55) (C-8), H-7 (δ 1.85) (C-6 and C-8) and H-8 (δ 2.37) (C-6), respectively.

Compound (+)-**9b**, showed in its high resolution mass spectrum a molecular ion at m/z 326.1889, corresponding to a formula of $C_{21}H_{26}O_3$ (calcd 326.1882). Its UV absorption at 249 nm and IR absorption at 1667 cm^{-1} suggest formation of an α,β-unsaturated carbonyl chromophore.[10] Another IR absorption at 1747 cm^{-1} indicated a non-conjugated five-membered carbonyl group. Although structure **14** is possible as the product of the aldol condensation of **7b**, a HMBC spectrum which indicated that all three methyl singlets (δ 0.80, 1.18 and 1.18) were three-bond coupled to the signal of five-membered carbonyl carbon (C-17, δ 221.7) eliminated this alternative in which only the protons of a methyl group (H-18) would be coupled to C-17. This 2D NMR technique, which also allowed the complete ^{13}C-NMR assignment of **9b**, hence confirmed its structure as the sole product of the asymmetric cyclization.

From the above results, it was concluded that a pair of enantiomeric products was obtained from the asymmetric cyclization of (±)-**7b**, respectively. The optical purity of the product obtained in this asymmetric cyclization is 87% ee, however, the optically pure form was obtained from cyclization of (–)-**7b** and (+)-**7b**, respectively. It was observed that (+)-**9b** resisted $NaBH_4$ (0 °C, MeOH) reduction[11] and under forced conditions, it led to the reduction of the six-membered α,β-unsaturated carbonyl chromophore with formation of a pair of epimeric alcohols. This chemical evidence also points out that the compound with two methyl groups adjacent to the C-17

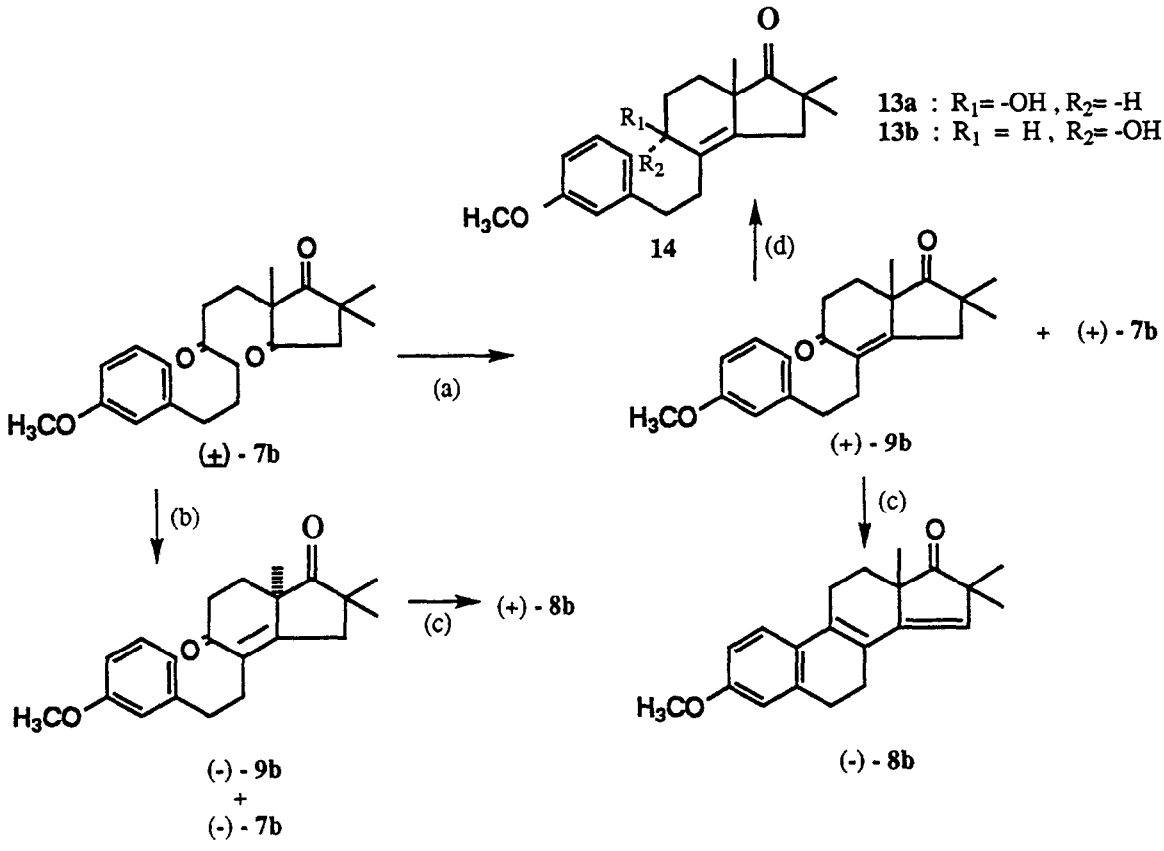
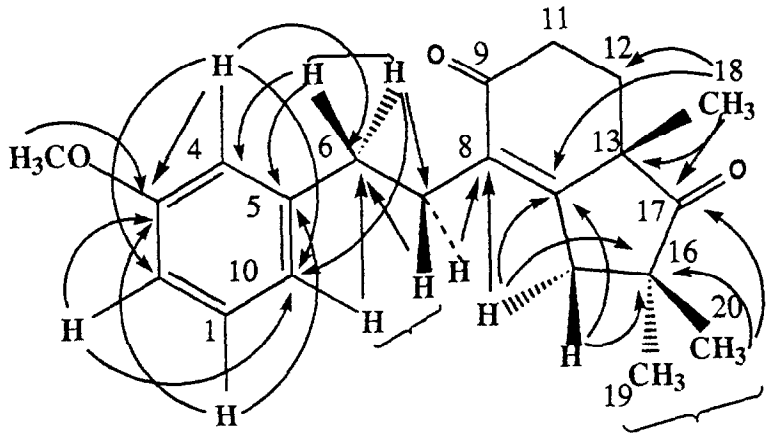


Figure 3. Asymmetric cyclization of racemic trione **7b**. (a) L-(-)-Phenylalanine, $HClO_4$, CH_3CN, reflux 96 h; (b) D-(+)-phenylalanine, $HClO_4$, CH_3CN, reflux 96 h; (c) CH_3SO_3H, ϕ-H, reflux 0.5 h; (d) $NaBH_4$, MeOH, 10 °C, 0.5 h



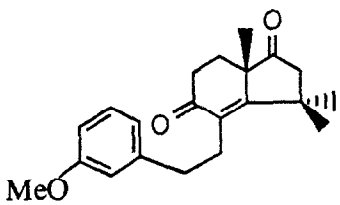


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Figure 4. HMBC of **9b**

carbonyl function is the likely product. This speculation was unambiguously settled by acidic cyclization of the bicyclic compounds to form tetracyclic products. When (+)-**9b** was heated at reflux in benzene with methanesulfonic acid, a crystalline tetracyclic product, (–)-**8b**, (m.p. 176–178 °C), $[\alpha]_D$ –16.9° (c = 0.16, MeOH), its high resolution mass spectrum showed a molecular ion at m/z 308.1713, corresponding to a formula of $C_{21}H_{24}O_2$ (calcd 308.1776), was isolated in 60% yield. Same treatment of (–)-**9b** gave (+)-**8b** (m.p. 176–178 °C), $[\alpha]_D$ + 17° (c = 0.1, MeOH), its high resolution mass spectrum showed a molecular ion at m/z 308.1693, which was isolated in 60% yield. It was also noticed that when (±)-**7b** was heated at reflux with catalytic amount of *p*-TsOH in benzene, racemic **8b** (m.p. 176–178 °C) was also obtained as the sole product in 70% yield. Thus, in this report, we also present a convenient regiospecific approach to the preparation of 16,16-dimethylsteroid intermediates.

Experimental Section

Melting points measured on a Buchi 510 melting point apparatus were uncorrected. Optical rotations were measured on a JASCO DIP-300 Digital Polarimeter and Circular Dichroism on a JASCO J-720 Spectropolarimeter. Proton and carbon nuclear magnetic resonance spectra were obtained with Bruker AC-80, AM-300 and AMX-400 spectrometers. The 2D NMR spectra were recorded with Bruker's standard pulse programs. IR spectra were recorded on a Perkin–Elmer 1760-X Infrared FT spectrometer. The UV spectra were recorded on Hitachi 150-20 spectrophotometer. Eims were recorded on a Finnigan Mat 4500 series GC/MS and JEOL JMS-HX 110 mass spectrometer. Normal phase silica gel used for column chromatography were Merck 7734 (70–230 mesh) and 9385 (230–400 mesh); TLC plates of Merck 573 (Si 60 with F254, 0.25 mm) were purchased from E. Merck, A.G., Darmstadt, Germany.

All of the solvents and inorganic chemicals were reagent grade. 2,2-Dimethyl succinic acid, D-(+)-phenylalanine and *m*-methoxyphenyl acetic acid were purchased from Sigma Chemical Co., St Louis, MO, U.S.A. L-(–)-Phenylalanine, *p*-toluenesulfonic acid, methanesulfonic acid, lithium aluminum hydride, sodium hydride, sodium borohydride and *n*-butyl lithium were purchased from E. Merck, A. G. Nutrient broth was obtained from Difco Laboratories, Detroit, MI, U.S.A. The microorganism, *Schizosaccharomyces pombe* (NRRL Y-164) was maintained on an agar slant (Maltose 4%, Proteose peptone-#3 1.5% and Agar 3%) at 26 °C for 11 days before being transferred to broth medium.

*Ethyl 6-*m*-methoxyphenyl-3-oxo-hexanoate (2)*

Sodium hydride (0.14 g, 5.83 mmol) was dissolved in THF (40 mL) at –15 °C (ice/salt). To this solution, ethyl acetoacetate (0.65 g, 5.00 mmol) was added dropwise followed by *n*-BuLi (3.1 mL, 5.00 mmol). After 20 min of stirring, **1** (1.0 g, 4.63 mmol) was added and reacted for 30 min. Then the ice-bath was removed and the reaction mixture was stirred for a further 30 min. Reaction was terminated by addition of 1N HCl and the pH of the mixture adjusted to 6, then extracted with $CHCl_3$. The combined $CHCl_3$ extract was dried over Na_2SO_4 then evaporated *in vacuo* to give 1.09 g of oily residue. Purification of the residue over silica gel (100 g) gave **2** (0.98 g, 80%) as clear oil. **2**: IR ν_{max} (film, cm^{-1}) 1747 (C=O), 1718 (-COOEt), 1602 and 1585 (aromatic); UV λ_{max} (MeOH, log ε) 278.0 (3.21) and 272 nm (3.27); EIMS m/z (rel. int. %) 264 (M^+; 8), 246 (13), 177 (17), 134 (100), 121 (19), 91 (18); ^{1}H-NMR δ ($CDCl_3$) 7.17 (t, *J* = 7.6 Hz, H-1), 6.73 (m, H-2, -4 and -10), 4.16 (q, O–$C\underline{H}_2$–CH_3, *J* = 7.1 Hz), 3.77 (s, 3-$OC\underline{H}_3$), 3.38 (2H, s, H-11), 2.59 (t, *J* = 7.2 Hz, H-6), 1.90 (quintet, *J* = 7.2 Hz, H-7), 2.52 (t, *J* = 7.2 Hz, H-8), and 1.21 (t, OCH_2–$C\underline{H}_3$, J = 7.1 Hz); ^{13}C-NMR δ ($CDCl_3$, m) 129.2 (d, C-1), 111.2 (d, C-2), 159.6 (s, C-3), 114.1 (d, C-4), 142.9 (s, C-5), 35.0 (t, C-6), 24.6 (t, C-7), 41.9 (t, C-8), 202.4 (s, C-9), 120.7 (d, C-10), 49.2 (t, C-11), 167.0 (s, C-12), 61.2 (t, $CO_2\underline{C}H_2CH_3$) and 13.9 (q, $-CO_2CH_2\underline{C}H_3$).

*3,3-Ethylenedioxy-6-(*m*-methoxyphenyl) hexanoate (3)*

To a solution of **2** (1.0 g, 3.79 mmol) in benzene (50 mL), $HOCH_2CH_2OH$ (0.47 g, 7.57 mmol) a catalytic

amount of *p*-TsOH was added and the mixture was heated at reflux for 2.5 h with a Dean–Stark water separator attached. The reaction mixture was washed with 10% $NaHCO_3$ and the benzene layer was dried over Na_2SO_4 and evaporated to dryness *in vacuo* to give a yellowish oily residue. The residue was purified over silica gel (100 g) and eluted with $CHCl_3$–benzene (8:92) to give **3** (1.05 g, 90%) as colorless liquid. **3**: IR ν_{max} (film, cm^{-1}) 1734 (-COOEt), 1602 and 1585 (aromatic); UV λ_{max} (MeOH, log ε) 278 (3.21) and 272 nm (3.25); EIMS m/z (%) 308 (M^+; 24), 246 (27), 221 (39), 159 (57), 134 (100), 117 (14), 99 (16); ^{1}H-NMR δ ($CDCl_3$) 7.17 (t, *J* = 7.2 Hz, H-1), 6.72 (m, H-2, -4 and H-10), 4.11 (q, *J* = 7.1 Hz, O–C<u>H</u>$_2$–CH_3), 3.95 (m, 9-O–C<u>H</u>$_2$–C<u>H</u>$_2$–O-), 3.77 (s, 3-OCH_3), 2.62 (s, H–11), 2.58 (t, *J* = 7.5 Hz, H-6), 1.88–1.65 (4H, m, H-7 and H-8), 1.22 (t, *J* = 7.1 Hz, OCH_2-C<u>H</u>$_3$).

3,3-Ethylenedioxy-6-(m-methoxyphenyl) hexanol (4)

A mixture of **3** (1.0 g, 3.24 mmol) and $LiAlH_4$ (0.12 g, 3.24 mmol) in THF (55 mL) was heated at reflux under N_2 for 2h. Excess $LiAlH_4$ was decomposed with ice–water and the reaction mixture was acidified with 10% H_2SO_4, and extracted with $CHCl_3$. The combined $CHCl_3$ extract was washed with 10% $NaHCO_3$, dried over Na_2SO_4 and evaporated to dryness *in vacuo* to give yellowish oily residue. The residue was purified over silica gel (100 g) and eluted with $CHCl_3$–Me_2CO (8:2) to give **4** (0.82 g, 95%) as colorless liquid. **4**: IR ν_{max} (film, cm^{-1}) 3367 (-OH), 2940, 1602 and 1585 (aromatic); UV λ_{max} (MeOH, log ε) 277.2 (3.20) and 271.2 nm (3.24); EIMS m/z (%) 266 (M^+, 12), 221 (10), 134 (48), 117 (100), 99 (86), 91 (47); ^{1}H-NMR δ ($CDCl_3$) 7.18 (t, *J* = 7.8 Hz, H-1), 6.73 (3H, m, H-2, -4 and H-10), 3.94 (m, 9-O–C<u>H</u>$_2$–C<u>H</u>$_2$–O-), 3.78 (s, 3-OCH_3), 3.71 (m, H-12), 2.58 (m, H-6), 1.90 (t, *J* = 5.7 Hz, H-11), 1.67 (4H, m, H-7 and H-8).

6-(m-Methoxyphenyl) hex-1-en-3-one (5)

To a solution of **4** (0.50 g, 1.88 mmol) in acetone (60 mL) and cooled with an ice-bath, conc. HCl (1.0 mL, 33.30 mmol) was added dropwise with stirring. After 30 min, the ice-bath was removed and the reaction mixture was stirred at r.t. for 4 h, then distilled H_2O (60 mL) was added to terminate the reaction. The mixture was extracted with $CHCl_3$, and the combined $CHCl_3$ extract was washed with 10% $NaHCO_3$, dried with Na_2SO_4, evaporated down to dryness *in vacuo* to give yellowish oily residue. The residue was purified over silica gel (60 g) and eluted with EtOAc–*n*-hexane (3:97) to give **5** (0.35g, 90%) as colorless liquid. **5**: IR ν_{max} (film, cm^{-1}) 2839 (C=C), 1677 (C=C–<u>C</u>O-), 1604 and 1585 (aromatic); UV λ_{max} (MeOH, log ε) 278.8 (3.26), 272.4 (3.30) and 222.0 nm (3.83); EIMS m/z (%) 205 ($(M + 1)^+$, 3), 204 (M^+; 2), 177 (4), 135 (100), 134 (62), 122 (30), 91 (33); ^{1}H-NMR δ ($CDCl_3$) 7.18 (dd, *J* = 7.4 and 7.8 Hz, H-1), 6.73 (3H, m, H-2, -4 and H-10), 6.32 (dd, *J* = 17.6, 10.5 Hz, H-11), 6.15 (dd, *J* = 17.6, 1.4 Hz, H_Z-12), 5.78 (dd, *J* = 10.5, 1.4 Hz, H_E-12), 3.77 (s, 3-OCH_3), 2.58 (4H, m, H-6 and H-8), and 1.94 (quintet, *J* = 7.3 Hz, H-7).

2-(6-m-Methoxyphenyl-3-oxohexyl)-2-methylcyclopenta-1,3-dione (7a)

To a solution of **5** (1.14 g, 5.59 mmol) in THF (50 mL), **6a** (0.75 g, 6.70 mmol) was added and stirred to effect solution. The pH of the mixture was adjusted to 8.0 with 3% NEt_3 in THF and maintained at 40 °C for 5 days. Water (50 mL) was added to the reaction mixture and extracted with benzene (50 mL x 3). The combined benzene extract was washed with 1N HCl, dried over Na_2SO_4 and evaporated to dryness *in vacuo* to give yellowish oily residue. The residue was purified over silica gel (150 g) and eluted with EtOAc–benzene (9:91) to give **7a** (1.33 g, 75%) as a colorless liquid. **7a**: IR ν_{max} (film, cm^{-1}) 1765 and 1720 (C=O), 1600 and 1585 (aromatic), 1260, 1160, 1140, (lit.[8], film, 1767, 1718, 1600, 1250, 1150, 1140 cm^{-1}); UV λ_{max} (MeOH, log ε) 278.8 (3.26), 272.4 nm (3.30); EIMS m/z (%) 316.2 (M^+; 99), 298.2 (3), 177 (4), 134 (100), 121 (22), 91 (26); HREIMS m/z 316.1678 (calcd for $C_{19}H_{24}O_4$ 316.1675); ^{1}H-NMR δ ($CDCl_3$) 7.17 (t, *J* = 7.8 Hz, H-1), 6.73–6.68 (m, H-2, -4 and -10), 3.77 (s, 3-OC<u>H</u>$_3$), 2.78 (4H, m, H-15's and H-16's), 2.54 (t, *J* = 7.4 Hz, 6-H), 2.35 (4H, m, H-8 and -11), 1.836 (4H, m, H-7 and -12), 1.07 (s, H-18) (lit.[8], $CDCl_3$, 7.20, 6.76, 3.80, 2.88, 2.72, 2.50, 1.90, 1.10); ^{13}C-NMR δ ($CDCl_3$, m) 129.3 (d, C-1), 111.3 (d, C-2), 159.6 (s, C-3), 114.2 (d, C-4), 143.1 (s, C-5), 35.0 (t, C-6), 24.9 (t, C-7), 42.0 (t, C-8), 209.8 (s, C-9), 120.8 (d, C-10), 36.5 (t, C-11), 27.9 (t, C-12), 55.2 (s, C-13), 215.7 (s, C-14 and C-17), 34.7 (t, C-15 and C-16), 19.1 (q, C-18), 55.2 (q, 3-OMe).

(±)-3-Methoxyestra-1,3,5(10),8(9),14-pentaen-17-one ((±)-8a)

Catalytic amount of TsOH (30 mg) was added to a solution of **7a** (0.10 g, 0.32 mmol) in benzene (50 mL) and heated at reflux for 30 min with a Dean–Stark water separator attached. After cooling, aqueous 10% $NaHCO_3$ (20 mL) was added and the benzene layer was separated, dried with Na_2SO_4 and evaporated to dryness *in vacuo* to give a solid residue. The residue was purified over silica gel (100 g) and eluted with EtOAc–*n*-hexane (3:97) to give **8a** as white solid material. Recrystallization with methanol gave **8a** (58 mg, 65%), m.p. 113.5–115 °C (lit.[8] 113–115 °C); IR ν_{max} (KBr, cm^{-1}) 2875, 1740 (C=O), 1602 and 1585 (aromatic), 1035 (lit.[8], 1745, 1600, 1040, 800 cm^{-1}); UV λ_{max} (MeOH, log ε) 310.8 (4.55), 232.4 nm (4.21); EIMS m/z (%) 280 (M^+; 49), 252 (100), 237 (41), 223 (17), 165 (33), 149 (41), 126 (20), 111 (33); ^{1}H-NMR δ ($CDCl_3$) 7.24 (d, *J* = 8.0 Hz, H-1), 6.75–6.71 (2H, m, H-2 and H-4), 5.85 (t, *J* = 2.5 Hz, H-15), 3.80 (s, 3-OCH_3), 3.30 (br d, *J* = 23.5 Hz, H-16), 2.91 (dd, *J* = 23.5, 3.1 Hz, H-16), 2.78 (2H, t, *J* = 7.1 Hz), 2.64–2.56 (2H, m), 2.32 (1H, m), 2.02 (1H, m), 1.12 (s, H-18) (lit.[8], $CDCl_3$, 7.40, 6.88, 6.00, 3.92, 1.10 ppm).

(+)-3-Methoxy-9,10-secoestra-1,3,5(10),8-tetraene-9,17-dione ((+)-9a)

Compound **7a** (187 mg, 0.59 mmol) and L-(–)-phenylalanine (122 mg, 0.74 mmol) were dissolved in

CH_3CN (4.5 mL) containing 1N $HClO_4$ (0.5 mL). The mixture was heated at reflux under N_2 for 48 h. After cooling, the reaction was filtered and the solid residue washed with $CHCl_3$. The filtrate and $CHCl_3$ washing were combined and washed with 10% Na_2CO_3 and H_2O. After drying over Na_2SO_4, the organic solvent was evaporated to dryness *in vacuo* to give oily residue. The residue was purified over silica gel (25 g) and eluted with EtOAc–benzene (9:91) to afford (+)-**9a** (176 mg, 90%); $[\alpha]_D$ = +181° (c = 0.8, MeOH; 79% ee);[4] IR ν_{max} (film, cm^{-1}) 1746 (C=O), 1663 (C=C–CO), 1601 and 1584 (aromatic), 1261, 1163; UV λ_{max} (MeOH, log ε) 249.6 (3.93), and 280 nm (sh. 3.37); EIMS m/z (%) 298 (M^+; 88), 270 (4), 177 (7), 164 (100), 149 (23), 121 (86), 91 (57); HREIMS m/z 298.1571 (calcd for $C_{19}H_{22}O_3$ 298.15696); ^{1}H-NMR δ ($CDCl_3$) 7.11 (t, *J* = 7.8 Hz), 6.67 (m, H-2 and H-10), 6.60 (t, *J* = 1.9 Hz, H-4), 3.73 (s, 3-OCH_3), 2.64 (t, *J* = 6.4 Hz, H-6), 2.50 (m, H-7's), 2.45 (m, H-11's), 2.00 and 1.70 (m, H-12's), 2.15 and 2.45 (m, H-15's), 1.95 and 2.55 (m, H-16's), 1.14 (s, H-18); ^{13}C-NMR δ ($CDCl_3$, m) 129.1 (d, C-1), 111.0 (d, C-2), 159.5 (s, C-3), 114.9 (d, C-4), 143.1 (s, C-5), 34.7 (t, C-6), 27.3 (t, C-7), 132.5 (s, C-8), 197.4 (s, C-9), 121.4 (d, C-10), 33.0 (t, C-11), 28.8 (t, C-12), 48.8 (s, C-13), 164.2 (s, C-14), 24.3 (t, C-15), 35.5 (t, C-16), 217.4 (s, C-17), 21.0 (q, C-18) and 55.0 (q, 3-OMe), assigned from homo- and hetero-COSY.

Microbiological reduction of ***7a***

Schizosaccharomyces pombe (NRRL Y-164) was grown in 1.6 L of Nutrient broth–Dextrose medium (Nutrient broth 1.6% and Dextrose 4%) contained in four 2-L Erlenmyer flasks at 24–26 °C on a rotary shaker (250 rpm, 1-in stroke). **7a** (0.37 g) dissolved in 8 mL *N,N*-dimethylformamide was distributed evenly among the flasks, and the incubation was continued for 72 h. The culture broth was acidified with HOAc to a pH of 3.0 and was extracted with $CHCl_3$ (650 mL x 3). The combined $CHCl_3$ layer was dried over Na_2SO_4 and evaporated to dryness *in vacuo* to give yellow oily residue (0.94 g). The residue was taken up with $CHCl_3$ and chromatographed over silica gel (100 g). In the fractions eluted with $CHCl_3$–Me_2CO (99:1), (–)-**12** (33.8 mg, 9.1%) was obtained, and in the fractions eluted with $CHCl_3$–Me_2CO (95:5), (+)-**11** (242 mg, 65%) was obtained. (+)-**11**: colorless liquid, $[\alpha]_D$ + 42.8° (c = 7.28, MeOH); IR ν_{max} (film, cm^{-1}) 3480 (-OH), 1738 and 1710 (C=O), 1600 and 1585 (aromatic), 1220; UV λ_{max} (MeOH, log ε) 278.8 (3.10), and 272.4 nm (3.14); EIMS m/z (%) 318 (M^+; 17), 300 (4), 184 (9), 177 (14), 169 (16), 134 (100), 121 (27), 113 (17), 91 (16); HREIMS m/z 318.1833 (calcd for $C_{19}H_{26}O_4$ 318.18318); ^{1}H-NMR δ ($CDCl_3$) 7.16 (t, *J* = 7.7 Hz, H-1), 6.70 (m, H-2 and H-10), 6.67 (br s, H-4), 3.95 (t, *J* = 5.7 Hz, H-17), 3.76 (s, 3-OCH3), 2.55 (t, *J* = 7.4 Hz, H-6), 1.90 (m, H-7), 2.40 (4H, m, H-8's and H-11's), 1.66 and 1.75 (m, H-12), 2.10 and 2.40 (m, H-15's), 1.90 and 2.22 (m, H-16's), 0.93 (s, H-18); ^{13}C-NMR δ ($CDCl_3$, m) 129.3 (d, C-1), 111.2 (d, C-2), 159.6 (s, C-3), 114.2 (d, C-4), 143.0 (s, C-5), 35.0 (t, C-6), 25.0 (t, C-7), 41.9 (t, C-8), 211.0 (s, C-9), 120.8 (d, C-10), 37.3 (t, C-11), 27.8 (t, C-12), 52.5 (s, C-13), 220.0 (s, C-14), 34.8 (t, C-15), 27.1 (t, C-16), 75.7 (d, C-17), 14.8 (q, C-18) and 55.1 (q, 3-OMe), assigned from homo- and hetero-COSY.

(–)-**12** colorless liquid, $[\alpha]_D$ –27.9° (c = 0.53, MeOH); IR ν_{max} (film, cm^{-1}) 3450 (-OH), 1735 (C=O), 1600 and 1585 (aromatic), 1260; UV λ_{max} (MeOH, log ε) 278 (3.10), and 272.4 nm (3.13); EIMS m/z (%) 318 (M^+; 7), 300 (6), 184 (13), 177 (8), 169 (2), 134 (100), 121 (18), 114 (21), 91 (12); ^{1}H-NMR δ ($CDCl_3$) 7.17 (t, *J* = 7.8 Hz, H-1), 6.71 (3H, m, H-2, -4 and -10), 4.21 (m, H-9), 3.77 (s, 3-OCH_3), 2.55 (t, *J* = 7.4 Hz, H-6), 2.32 (2H, m) and 1.90 (2H, m) (H-15's and H-16's), 1.90 (2H, m), 1.73–1.48 (6H, m), 1.23 (s, H-18).

*(+)-3-Methoxy-9,10-secoestra-1,3,5(10),8-tetraene-17β-hydroxy-9-one ((+)-**10a**)*

To a solution of (+)-**11** (72.8 mg, 0.24 mmol) in benzene (70 mL) was added piperidine (4 mL, 0.04 mol) and glacial HOAc (5 mL, 87 mmol). The mixture was heated at reflux for 9 h with a Dean–Stark water separator attached. After cooling, it was washed with 1N HCl, 10% Na_2CO_3 and 5% HOAc, dried over Na_2SO_4 and evaporated to dryness *in vacuo* to give yellowish oily residue. The residue was purified over silica gel (50 g) eluted with $CHCl_3$–EtOAc mixture to give (+)-**10a** (47 mg, 68.5%): colorless liquid, $[\alpha]_D$ + 20° (c = 1.1, MeOH), IR ν_{max} (film, cm^{-1}) 3392 (-OH), 1625 (CO–C=C), 1585, 1450, 1259; UV λ_{max} (MeOH, log ε) 252.4 (3.98), 220.4 (3.98) and 280 nm (sh. 3.42); EIMS m/z (%) 300 (M^+; 29), 179 (11), 166 (18), 147 (12), 133 (21), 121 (100), 107 (17), 91 (43); HREIMS m/z 300.1725 (calcd for $C_{19}H_{24}O_3$ 300.17253); ^{1}H-NMR δ ($CDCl_3$) 7.13 (t, *J* = 7.8 Hz, H-1), 6.67 (3H, m, H-2, -4 and -10), 3.76 (s, 3-OCH_3), 3.67 (dd, *J* = 7.2 and 10.4 Hz, H-17), 2.58 (t, *J* = 7.1 Hz, H-6), 2.49–1.63 (10H, m), 1.02 (s, H-18); ^{13}C-NMR δ ($CDCl_3$, m) 129.1 (d, C-1), 111.0 (d, C-2), 159.5 (s, C-3), 114.6 (d, C-4), 143.6 (s, C-5), 33.9 (t, C-6), 27.8 (t, C-7), 132.3 (s, C-8), 198.2 (s, C-9), 121.3 (d, C-10), 34.5 (t, C-11), 33.5 (t, C-12), 45.2 (s, C-13), 168.9 (s, C-14), 25.0 (t, C-15), 29.4 (t, C-16), 80.8 (d, C-17), 15.2 (q, C-18) and 55.2 (q, 3-OMe), assigned from HMBC.

*$NaBH_4$ Reduction of (+)-**9a***

(+)-**9a** (24 mg, 0.08 mmol) dissolved in MeOH (20 mL) in an ice-bath was reduced with $NaBH_4$ (30 mg, 0.65 mmol). After 20 min, 6% ammonia water was added to make a pH of 9. Distilled H_2O (40 mL) was added and the mixture extracted with $CHCl_3$ (50 mL x 3). Evaporation of the $CHCl_3$ extract gave an oily residue. The residue was purified over silica gel (20 g), elution with $CHCl_3$–Me_2CO (9:1) gave (+)-**10a** (20 mg, 82.8%): colorless liquid, $[\alpha]_D$ + 19° (c = 0.94, MeOH); HREIMS m/z 300.1724 (calcd for $C_{19}H_{24}O_3$, 300.1725).

*2(-6-*m*-Methoxyphenyl-3-oxohexyl)-2,4,4-trimethyl-cyclopenta-1,3-dione (±)-**7b***

Compound **5** (1.80 g, 8.82 mmol) and **6b** (1.36 g, 9.70 mmol) in THF (50 mL) was reacted as mentioned above for 7 days. Work-up and purification of the product

obtained with silica gel (200 g) and elution with EtOAc–benzene (5:95) gave (±)-**7b** (2.1 g, 70%) as colorless liquid. (±)-**7b**: IR (film) ν_{max} cm^{-1} 1726, 1719, 1602, 1584, 1260; UV λ_{max} (MeOH) (log ε) 278 (3.15) and 272 nm (3.19); EIMS m/z (rel. int. %) 344 (M^+; 16), 326 (3), 210 (4), 141 (13), 134 (100), 121 (14), 91 (9), 69 (16); ^{1}H-NMR δ ($CDCl_3$) 7.17 (t, J = 7.8 Hz, H-1), 6.70 (m, H-2, -4, -10), 2.55 (t, J = 7.4 Hz, H-6's), 1.85 (m, H-7's and H-12's), 2.37 (m, H-8's and H-11's), 2.57 and 2.69 (H-15's, J = 18.0 Hz), 1.11 (s, H-18), 1.19 and 1.26 (s, H-19 and -20), 3.77 (s, 3-OMe), assigned from HMBC.

(+)-3-Methoxy-9,10-secoestra-1,3,5(10),8-tetraene-16, 16-dimethyl-9,17-dione ((+)-9b)

(a) A mixture of (±)-**7b** (0.55 g, 1.60 mmol), L-(–)-phenylalanine (0.33 g, 2.00 mmol) and 1N $HClO_4$ (1 mL) in CH_3CN (9 mL) was heated at reflux for 96 h. After cooling, L-(–)-phenylalanine was filtered and washed with $CHCl_3$. The combined organic layer was washed with 10% Na_2SO_4 and H_2O, dried over Na_2SO_4 and evaporated to dryness *in vacuo* to give an oily residue. The residue was chromatographed over 100 g silica gel and eluted with EtOAc–benzene (5:95) to obtain (+)-**9b** (0.23 g, 44%), $[\alpha]_D$ + 109° (c = 0.75, MeOH), as colorless oil and recovered (±)-**7b** (0.303 g, 55%). Recycling of the recovered (±)-**7b** twice led to the overall yield of (+)-**9b** (0.254 g, 48.5%) and recovered (+)-**7b** (0.242 g, 44%). (+)-**7b**: colorless liquid, $[\alpha]_D$ + 5° (c = 1.0, MeOH); CD (MeOH) $[\theta]_{295}$ +1060°, $[\theta]_{234}$ –960°, $[\theta]_{221}$ –1860°, $[\theta]_{212}$ –2060°, other small negative Cotton effect (CE) at λ 271, 260, 251 nm and small positive CE at λ 276 (sh), 266 and 255 nm; ^{13}C-NMR δ ($CDCl_3$) 129.3 (d, C-1), 111.2 (d, C-2), 159.6 (s, C-3), 114.1 (d, C-4), 143.1 (s, C-5), 35.0 (t, C-6), 25.0 (t, C-7), 41.8 (t, C-8), 208.8 (s, C-9), 120.8 (d, C-10), 36.8 (t, C-11), 28.5 (t, C-12), 54.5 (s, C-13), 215.7 (s, C-14), 50.4 (t, C-15), 46.3 (s, C-16), 220.3 (s, C-17), 19.5 (q, C-18), 24.9 and 26.5 (q, C-19 and C-20), 55.0 (q, 3-OMe), assigned from HMBC: HREIMS m/z 344.1999 (calcd for $C_{21}H_{28}O_4$ 344.1987).

(b) When (–)-**7b** (0.15 g, 0.44 mmol), L-(–)-phenylalanine (0.09 g, 0.55 mmol) and 1N $HClO_4$ (0.5 mL) in CH_3CN (4.5 mL) were reacted as mentioned above, work-up of the reaction mixture gave (+)-**9b** (0.09 g, 60%) as a colorless liquid; $[\alpha]_D$ + 125° (c = 0.85, MeOH); CD (MeOH) $[\theta]_{370}$ 0°, $[\theta]_{309}$ +9,600°, $[\theta]_{278}$ 0°, $[\theta]_{256}$ –22,800°, $[\theta]_{238}$ 0°, $[\theta]_{225}$ +10,200°; IR (film) ν_{max} cm^{-1} 1747, 1667, 1602, 1585; UV λ_{max} (MeOH) (log ε) 280 (sh, 3.47) and 249 nm (4.02); HREIMS m/z 326.1889 (calcd for $C_{21}H_{26}O_3$ 326.1882); EIMS m/z (rel. int. %) 326 (M^+; 45), 311 (10), 269 (5), 192 (100), 177 (23), 135 (16), 121 (34), 107 (7), 91 (22); ^{1}H-NMR δ ($CDCl_3$) 7.10 (t, J = 7.9 Hz, H-1), 6.69 (m, H-2, -4, -10), 2.73 and 2.60 (m, H-6's), 2.63 and 2.50 (m, H-7's), 2.07 (br d, J = 13.4 Hz, H-12β), 1.75 (dt, J = 6.5, 13.4, 13.4 Hz, H-12α), 2.50 and 2.20 (AB q, H-15's, J_{AB} = 16.2 Hz), 1.18 (s, H-18), 1.18 and 0.80 (s, H-19 and H-20), 3.75 (s, 3-OMe), assigned from HMBC; ^{13}C-NMR ($CDCl_3$) 129.3 (d, C-1), 111.0 (d, C-2), 159.6 (s, C-3), 114.9 (d, C-4), 143.2 (s, C-5), 34.9 (t, C-6), 27.5 (t, C-7), 133.0 (s, C-8), 197.4 (s, C-9), 121.3 (d, C-10), 33.2 (t, C-11), 30.3 (t, C-12), 46.9 (s, C-13), 162.9 (s, C-14), 41.1 (t, C-15), 48.6 (s, C-16), 221.7 (s, C-17), 21.2 (q, C-18), 24.7 and 25.6 (q, C-19, C-20), 55.2 (q, 3-OMe), assigned from HMBC.

(–)-3-Methoxy-9,10-secoestra-1,3,5(10),8-tetraene-16,16-dimethyl-9,17-dione ((–)-9b)

(a) A mixture of (±)-**7b** (0.55 g, 1.6 mmol), D-(+)-phenylalanine (0.33 g, 2 mmol) and 1N $HClO_4$ (1 mL) in CH_3CN (9 mL) was reacted and work-up of the reaction mixture gave (–)-**9b** (0.23 g, 44 %), $[\alpha]_D$ –110° (c = 0.96, MeOH) as a colorless oil and recovered (±)-**7b** (0.30 g, 55 %). Recycling of the recovered (±)-**7b** twice led to the overall yield of (–)-**9b** (0.25 g, 49%) and recovered (–)-**7b** (0.27 g, 49%); CD curve is the mirror image of that of (+)-**7b**; HREIMS m/z 344.1992 (calcd for $C_{21}H_{28}O_4$ 344.1987).

(b) When (+)-**7b** (0.15 g, 0.44 mmol), D-(+)-phenylalanine (0.33 g, 2 mmol) and 1N $HClO_4$ (1 mL) in CH_3CN (4.5 mL) were reacted, work-up of the reaction mixture gave (–)-**9b** (0.09 g, 60%), as a colorless liquid; $[\alpha]_D$ = –126° (c = 0.84, MeOH); CD curve is the mirror image of that of (+)-**9b**; HREIMS m/z 326.1878 (calcd for $C_{21}H_{26}O_3$ 326.1882).

16,16-Dimethyl-3-methoxyestra-1,3,5(10),8(9),14-pentaen-17-one

(a) (–)-8b. To a benzene solution of (+)-**9b** (40 mg, 0.12 mmol), a catalytic amount of CH_3SO_3H (10 mg) was added and the mixture was heated at reflux for 30 min with a Dean–Stark water separator attached. The benzene solution was washed with 10% $NaHCO_3$, dried over Na_2SO_4 and evaporated to dryness *in vacuo* to give a yellowish residue. The residue was purified over silica gel (50 g) eluted with *n*-hexane–benzene (4:6) mixture to give (–)-**8b** (22 mg, 60%) as a colorless solid. Recrystallization from MeOH gave m.p. 176–178 °C, $[\alpha]_D$ = –169° (c = 0.16, MeOH); CD (MeOH) $[\theta]_{345}$ 0°, $[\theta]_{323}$ –12,000°, $[\theta]_{313}$ 0°, $[\theta]_{297}$ +26,800°, $[\theta]_{268}$ +0°, $[\theta]_{260}$ –6,000°, $[\theta]_{232}$ –46,900°; IR (KBr) ν_{max} cm^{-1} 2865, 1743, 1600, 1245; UV λ_{max} (MeOH) (log ε) 311.6 nm (4.54); HREIMS m/z 308.1713 (calcd for $C_{21}H_{24}O_2$ 308.1776); EIMS m/z (rel. int. %) 308 (M^+; 70), 293 (100), 280 (37), 265 (28), 248 (6), 234 (12), 220 (8), 208 (11), 177 (16), 165 (18), 152 (10), 140 (12), 128 (10); ^{1}H-NMR δ ($CDCl_3$) 7.22 (d, J = 9.3 Hz, H-1), 6.79–6.68 (m, H-2, H-4), 5.75 (s, H-15), 3.79 (s, 3-OMe), 1.27, 1.17 and 1.12 (s, H-18, -19 and -20)

(b) (+)-8b. A benzene solution of (–)-**9b** (30 mg, 0.09 mmol) and CH_3SO_3H (10 mg) was reacted as mentioned above. Work-up of the reaction mixture gave (+)-**8b** (16 mg, 60%); m.p. 176–178 °C, $[\alpha]_D$ +17° (c = 0.1, MeOH); HREIMS m/z 308.1693 (calcd for $C_{21}H_{24}O_2$ 308.1776).

(c) (±)-8b. To a solution of (±)-**7b** (80 mg, 0.23 mmol) in benzene (50 mL), a catalytic amount of *p*-TsOH (10 mg) was added and the mixture was heated at reflux for 30

min with a Dean–Stark water separator attached. Work-up of the reaction mixture gave (±)-**8b** (50 mg, 70%) as a white solid. Recrystallization from MeOH gave m.p. 176–178 °C.

$NaBH_4$ Reduction of (+)-9b

To a solution of (+)-**9b** (21 mg, 0.064 mmol) in MeOH (20 mL) in an ice-bath, $NaBH_4$ was added (29 mg, 0.64 mmol) and the mixture was stirred for 30 min. Work-up of the reaction mixture gave an oily residue. The residue was chromatographed over silica gel (40 g) and eluted with Me_2CO–$CHCl_3$ mixture stepwise from 5 to 10% and during this process, **13a** (12.6 mg, 59.6%) and **13b** (8.5 mg, 40.2%) were obtained.

13b. Colorless liquid; IR ν_{max} (film, cm^{-1}) 3455 (-OH), 1738 (C=O), 1602 and 1585; UV λ_{max} (MeOH, log ε) 279.2 (3.27) and 272.8 nm (3.30); EIMS m/z (%) 328 (M^+; 4), 311 (2), 207 (6), 122 (100), 121 (13); ^{1}H-NMR δ ($CDCl_3$) 7.18 (t, J = 7.4 Hz, H-1), 6.73 (3H, m, H-2, -4, -10), 4.27 (t, J = 8.2 Hz, H-9), 3.77 (s, 3-OCH_3), 2.75–2.36 (6H, m, H-6's, -7'd and -15's), 2.10 (1H, m), 1.76 (2H, t), 1.65 (1H, t), 1.18 (3H, s), 1.13 (3H, s), 0.79 (3H, s).

13a. Colorless liquid; IR ν_{max} (film, cm^{-1}) 3456 (OH), 1739 (C=O), 1602 and 1585; UV λ_{max} (MeOH, log ε) 279.2 (3.26), 272.8 nm (3.29); EIMS m/z (%) 328 (M^+; 14), 311 (18), 310 (8), 281 (17), 207 (29), 122 (100), 121 (13); ^{1}H-NMR δ ($CDCl_3$) 7.10 (t, J = 7.4 Hz, H-1), 6.70 (3H, m, H-2, -4, -10), 3.76 (s, 3-OCH_3), 3.32 (1H, bm, H-9), 2.68–2.35 (6H, m), 2.10 (1H, s), 2.06–1.91 (1H, m), 1.78 (2H, m), 1.11 (3H, s), 1.03 (3H, s), 0.91 (3H, s).

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