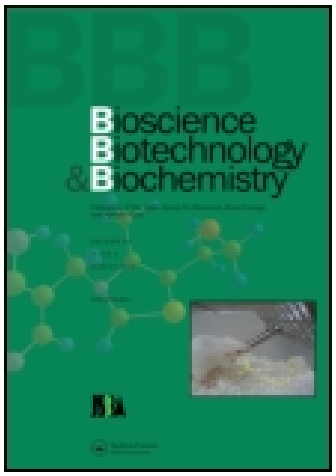

Bioscience, Biotechnology, and Biochemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/tbbb20

Syntheses of (14β,15β,16β,17α)- and (14β,15α,16α,17α)-1,3,5(10)-Estratriene-2,3,14,15, 16,17-hexaols, Possible Candidates for the Inagami—Tamura Endogenous Digitalis-like Factor, and Their Activity

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Published online: 12 Jun 2014.

To cite this article: Masayuki Sakakibara & Aki Ogawa Uchida (1996) Syntheses of (14β,15β,16β,17α)- and (14β,15α,16α,17α)-1,3,5(10)-Estratriene-2,3,14,15, 16,17-hexaols, Possible Candidates for the Inagami—Tamura Endogenous Digitalis-like Factor, and Their Activity, Bioscience, Biotechnology, and Biochemistry, 60:3, 405-410, DOI: 10.1271/bbb.60.405

To link to this article: http://dx.doi.org/10.1271/bbb.60.405

Biosci. Biotech. Biochem., **60** (3), 405–410, 1996

Syntheses of (14β,15β,16β,17α)- and (14β,15α,16α,17α)-1,3,5(10)-Estratriene-2,3,14,15,16,17-hexaols, Possible Candidates for the Inagami–Tamura Endogenous Digitalis-like Factor, and Their Activity

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Received August 14, 1995

Structures are proposed for the Inagami–Tamura endogenous digitalis-like factor (EDLF), and two possible candidates, (14β,15β,16β,17α)- and (14β,15α,16α,17α)-2,3,14,15,16,17-hexahydroxy-1,3,5(10)-estratrienes, were synthesized. Both compounds were potent in inducing a contractile response in isolated rat aorta and guinea pig left atrium.

Key words: endogenous digitalis-like factor; 14β-hydroxyestrogens; vasocontraction; hypertension; cardiotonic

EDLF is an unidentified substance which elevates the intracellular Ca^{2+} concentration through the inhibition of Na/K ATPase and subsequent Na/Ca exchange and, as a result, contracts cells.[1] Thus, the factor has been conceived as a pathogen of hypertension[2] when it works on vascular smooth muscles and as an endogenous cardiotonic substance[3] when it works on the heart. It also works on the kidney as a regulator of fluid volume and natriuresis.[4] The other profile of the factor has been conceived as a pathogen of cataracts, and two kinds of 19-norbufadienolides have been isolated from the lenses of cataract patients.[5] In the last case, however, it is controversial whether these compounds are really endogenous, since the presence of Na/K ATPase in the eye seems to indicate that real EDLF works to maintain the function of the eye through an unknown mechanism. The isolation and mass spectral characterization of ouabain from the plasma of hypertensive patients and its main production in adrenals have recently been reported[6] and it was suggested that two EDLFs named ODC-1 and -2 showed quite similar behavior by HPLC to that of ouabain and digoxin, respectively.[7] It seems, however, still controversial on the basis of the following evidence whether *the ouabain activity* was really endogenous. For example, it is known that the activity of digitalis derived from foods, especially from vegetables, is accumulated in the adrenals and gradually released into the blood.[8] In fact, the detection of ouabain levels in several vegetables by a radio-immunoassay (RIA) has been reported.[8] Furthermore, it has been said that the adrenals might not be the major source of plasma ouabain, because the total content of adrenal ouabain cannot maintain the plasma ouabain level.[9]

In 1987, Inagami and his co-workers reported by isolation of an EDLF with a molecular weight of 336 from bovine adrenals.[10] This molecular weight is considerably smaller than that of digitalis compounds, and it was suggested to involve a molecule lacking the lactonic moiety of digitalis compounds. The lactonic moiety had previously been thought to be essential for their cardiotonic activity. However, the molecular weight enabled us to attach more importance to the 14β-hydroxyl moiety rather than to the lactonic moiety. Among several plausible structures deduced to account for the molecular weight, one of the 14β-hydroxyestradiols possessing additional three hydroxyl groups seemed the most plausible. As is known, the metabolism of estrogens is directed to oxidation, and many catecholestrogens have been described.[11] Thus, we deduced that one of the additional hydroxyl groups would be located at the 2- or 4-position. Our deduction was supported by the results of Graves.[12] Later, we could determine that the hydroxyl group was at the 2-position on the basis of the results on an NMR study of the other EDLF (A. Goto, personal communication). Unfortunately, however, the positions and the stereochemistry of the residual hydroxyl groups have not yet been clarified. Thus, we decided to synthesize some of the plausible compounds and to evaluate them so that the probability of the proposed undefined structure could be confirmed and the structure could be elucidated. We report here the syntheses and results of the evaluation of two possible candidates, **1** and **2**, for the Inagami–Tamura EDLF.

Phenolic compound **3**[13] was quantitatively benzylated to give compound **4**. The ^{1}H- and ^{13}C-NMR spectra of **4** suggested the presence of two conformers in a ratio of about 3/2. Diphenyl ether bond-cleavage of **4** accompanied by hydrolysis afforded 2-benzyloxyestradiol **5**, which was benzylated to give dibenzyl ether **6** together with a considerable amount of its formyl ester **6′**. Thus, the mixture was treated with K_2CO_3 in aq. MeOH to afford **6** as a single product. Jones oxidation of **6** gave ketone **7** (59.2% yield) together with 6-oxo derivative **7′** (4.5% yield). In order to introduce a conjugate double bond to **7**, Saegusa oxidation was investigated under several conditions. Among them, the combination of TES enol ether **8** as a substrate and $Pd(OAc)_2$ coupled with $Cu(OAc)_2$ and O_2[14] gave the best results (M. Sakakibara and L. Baroche, unpublished

Abbreviations: EDLF, endogenous digitalis-like factor; RIA, radioimmunoassay; TID, theoretical ion distribution; *p*-TsOH, *p*-toluenesulfonic acid; PBA, peroxybenzoic acid; *m*-CPBA, *m*-chloroperoxybenzoic acid; DMF, dimethylformamide; THF, tetrahydrofuran; DMAP, 4-(*N*,*N*-dimethylamino)pyridine; NMO, *N*-methylmorpholine *N*-oxide; EtOAc, ethyl acetate; TES, triethylsilyl; LDA, lithium diisopropylamide; FDMS, field desorption mass spectrometry; FABMS, fast atom bombardment mass spectrometry.

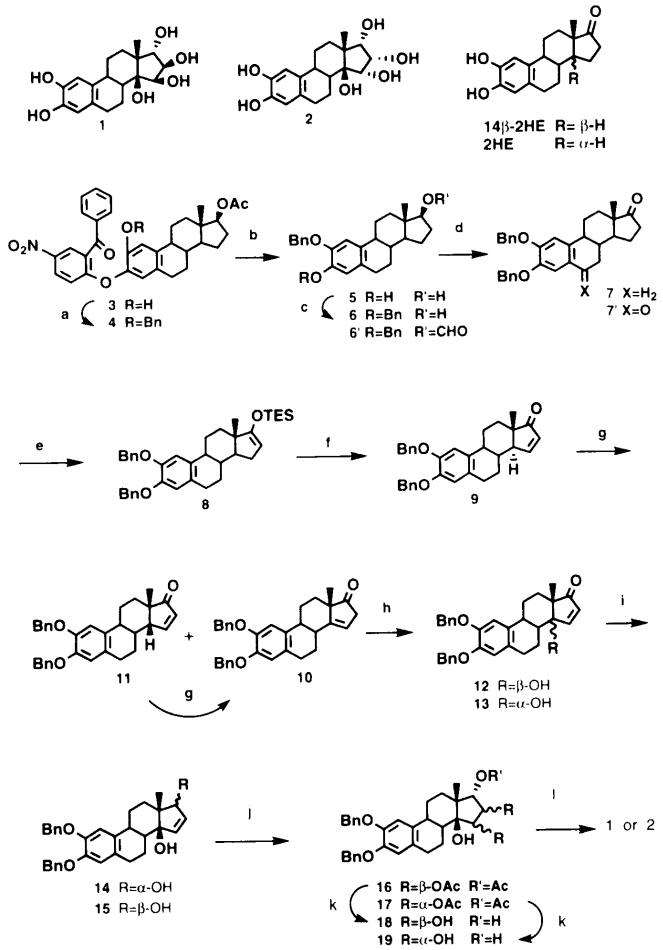

Fig. 1. Synthetic Scheme for **1** and **2**.

a: BnCl, Na_2CO_3/DMF (99.6%); **b**: KOH/EtOH (>68.3%); **c**: i) BnCl, Na_2CO_3/DMF (88.0%); ii) K_2CO_3/aq. MeOH; **d**: Jones reagent (56.5%); **e**: TESOTf, Et_3N/CH_2Cl_2 (93.0%); **f**: $Pd(OAc)_2$, $Cu(OAc)_2$, O_2/MeCM (71.9%); **g**: *p*-TsOH/C_6H_6 (59.0%); **h**: (i) PBA/CH_2Cl_2, C_6H_6, (ii) Na_2CO_3/*t*-BuOH, H_2O (88.2%); **i**: $NaBH_4$, $CeCl_3$/MeOH, THF (**14**: 82.7%, **15**: 10.8%); **j**: (i) OsO_4, NMO/aq. acetone, (ii) Ac_2O/Py, DMAP (**16**: 68.3%; **17**: 19.1%); **k**: Na_2CO_3/aq. MeOH, THF (**18**: 98.9%; **19**: 87.6%); **1**: H_2, 5% Pd $BaSO_4$/EtOAc (quant. yield).

results). Enone **9** thus obtained was briefly treated with *p*-TsOH in refluxing benzene to give unconjugate enone **10** accompanied with conjugate 14β-enone **11**, which was convertible into **10** under the same conditions. In our case, the reaction time of 15 min used by Johnson *et al.*[15] made the yield of **10** decrease and predominantly gave **11**. Enolization of **9** with LDA or *tert*-BuOK and subsequent aqueous quenching resulted only in the recovery of **9**. The formation of a silyldienolether from **9** with TES triflate and triethylamine and subsequent quenching with 30% $HClO_4$ resulted mainly in the recovery of **9** accompanied by a small amount of **10**. Epoxidation of **10** with PBA[16] and subsequent treatment with Na_2CO_3 resulted in the almost completely stereoselective formation of 14β-enonol **12**. When *m*-CPBA was used instead of PBA, the stereoselectivity decreased to $\alpha/\beta = 1/4$–$1/5$. The stereochemical assignments of **12** and its 14α-isomer **13** were made by comparing the chemical shifts of their angular methyl carbons[17]; *i.e.*, their chemical shifts were δ 20.1 and 22.9 ppm, respectively. The fact that the difference between both values was less than expected seems to be derived from the contribution of steric interaction with the 14β-hydroxyl group in **12** and with the 15-methine moiety in **13** to up-

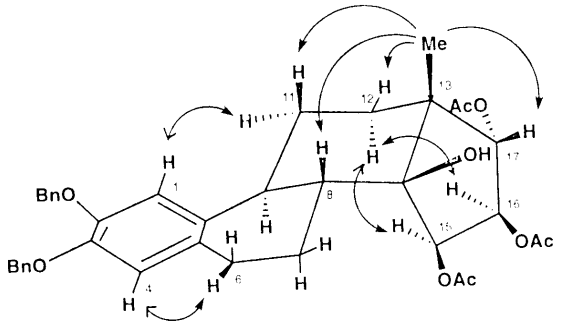

Fig. 2. Probable Stereochemistry of **16**.

Arrows indicate the presence of NOE differences between the designated protons.

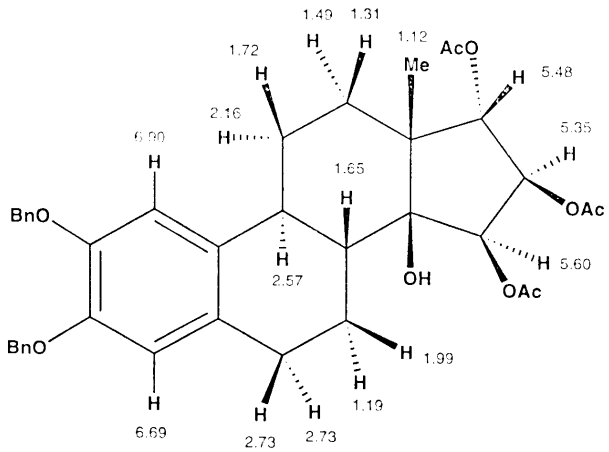

Fig. 3. Assignment of Protons on the Steroidal Skeleton of **16**.

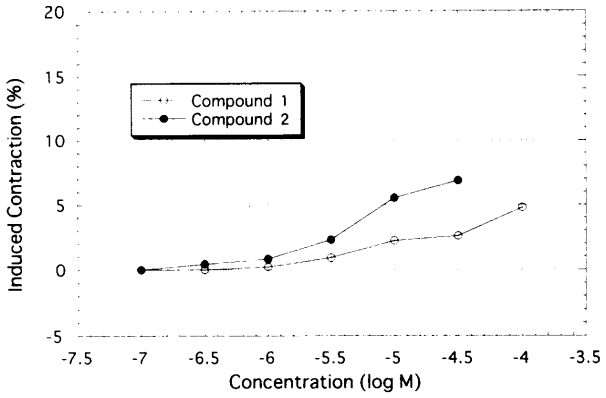

Fig. 4. Contractile Response of Isolated Rat Aorta Induced by **1** and **2**.

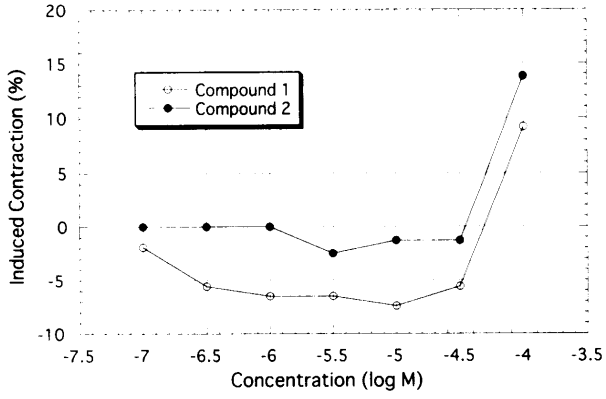

Fig. 5. Contractile Response of Isolated Guinea Pig Left Atrium Induced by **1** and **2**.

shifting being comparable. In this connection, 2-hydroxy-14β-isoestrone (14β-2HE) and 2-hydroxyestrone (2HE) showed the signals at δ 18.8 and 13.9 ppm, respectively. Enonol **12** was reduced with $NaBH_4$–$CeCl_3$[18] to give 17α- and 17β-alcohols **14** and **15** in the ratio of 23/3. The stereochemistry of both alcohols was confirmed by NOE experiments on the 16-olefinic, 17-oxymethine, and 18-methyl protons of **15**. Major alcohol **14** was dihydroxylated with catalytic OsO_4 and then acetylated to give triacetates **16** and **17** in 68.3% and 19.1% yields, respectively. The stereochemistry of **16** was established by NOE and H-COSY experiments, and all protons attached to the B, C, and D-rings were assigned as shown in Figs. 2 and 3, respectively. Both triacetates **16** and **17** were hydrolyzed separately to give tetraols **18** and **19**, respectively. Both tetraols **18** and **19** were then hydrogenolyzed separately to afford target molecules **1** and **2**, respectively. Negative FABMS data for **1** and **2** gave ordinary $(M-H)^-$, while neither FDMS nor positive FABMS gave any peak. It is interesting that the positive FABMS data for all the measured intermediates gave M^+, since this is usually said to give $(M+H)^+$.

Compounds **1** and **2** were evaluated with isolated rat aorta[19] and isolated guinea pig left atrium.[20] Both compounds induced a contractile response in isolated rat aorta dose-dependently in the concentration range of 10^{-6}–10^{-4} M, and in isolated guinea pig left atrium at a concentration of 10^{-4} M as shown in Figs. 4 and 5. The observation of a contractile response in the isolated tissues induced by **1** or **2**, although their effects were unsatisfactory both in concentration and strength, suggests that the structures of **1** and **2** were satisfactory *sine qua non* for EDLF; that is, the proposed structure was fundamentally probable. However, the unsatisfactory effects of **1** and **2** both in concentration and strength imply that **1** and **2** included some incorrect sub-structures, possibly in respect of the location and stereochemistry of undefined hydroxyl groups. Further studies on the structure of EDLF are in progress.

Experimental

All melting point (mp) values are uncorrected. IR spectra were determined with a JEOL Diamond-20 FT-IR spectrophotometer, while ^{1}H-NMR and ^{13}C-NMR spectra were recorded with a JEOL JNM-A500 FT NMR spectrometer. Chemical shifts for ^{1}H-NMR are expressed in ppm downfield from TMS as an internal standard, and those for ^{13}C-NMR are expressed in ppm based on the signal of $CDCl_3$ at 77.0 ppm, unless otherwise noted. Mass spectra were measured with a JEOL JMS-SX/SX 102A tandem mass spectrometer, ion modes being noted. Specific rotation values were determined with a JASCO DIP-140 digital polarimeter, and elemental analyses were carried out with a Perkin-Elmer 240C elemental analyzer.

(17β)-17-Acetoxy-3-(2'-benzoyl-4'-nitrophenyloxy)-2-benzyloxy-1,3,5(10)-estratriene (**4**). A mixture of phenolic compound **3** (11.10 g, 20.0 mmol), Na_2CO_3 (8.48 g, 80 mmol), benzyl chloride (7.60 g, 60 mmol), and DMF (200 ml) was stirred at 100–120°C for 5 h and then poured into crushed ice. The resulting mixture was extracted three times with ether. The combined extracts were successively washed with two portions of 1 N KOH and two portions of brine, dried over anhydrous $MgSO_4$, and evaporated to give a crude product (16.10 g), which was purified by silica gel (480 g) column chromatography (60 mmϕ × 340 mm) using a mixed solvent (hexane–EtOAc = 7:2 and 7:3) as the eluent to give a yellow amorphous powder (12.86 g, 99.6% yield), mp 90°C; $[\alpha]_D^{23}$ +27.8° (*c* 1.0, $CHCl_3$). Several attempts at crystallization were unsuccessful. ν_{max} (Nujol) cm^{-1}: 1730, 1665, 1610, 1595, 1580, 1518, 1500. NMR δ_H ($CDCl_3$): 0.79 (s, 3 × 0.4H), 0.81 (s, 3 × 0.6H), 1.2–1.9 (m), 2.03 (s, 3 × 0.6H), 2.04 (s, 3 × 0.4H), 2.08–2.24 (m, 3H), 2.70 (d, *J* = 4.0 Hz, 0.4H), 2.72 (d, *J* = 5.5 Hz, 0.4H), 2.79 (d, *J* = 4.0 Hz, 0.6H), 2.81 (d, *J* = 5.5 Hz, 0.6H), 4.65 (t, *J* = 8.5 Hz, 0.6H), 4.67 (t, *J* = 8.5 Hz, 0.4H), 4.90 (d, *J* = 11.5 Hz, 1H), 4.93 (d, *J* = 11.5 Hz, 1H), 6.70 (s, 0.6H), 6.72 (s, 0.4H), 6.79 (d, *J* = 9.0 Hz, 0.6H), 6.80 (d, *J* = 9.0 Hz, 0.4H), 6.90 (s, 0.4H), 6.93 (s, 0.6H), 7.09 (m, 2H), 7.2–7.3 (m, 4H), 7.35 (m, 1H), 7.47 (m, 1H), 7.75 (m, 2H), 8.19 (dd, *J* = 1.5 and 9.0 Hz, 0.4H), and the other 8.19 (dd, *J* = 1.5 and 9.0 Hz, 0.6H), 8.28 (d, *J* = 3.0 Hz, 0.6H), and the other 8.28 (d, *J* = 3.0 Hz, 0.4H). NMR δ_C ($CDCl_3$): a complex spectrum including characteristic signals at 12.0, 21.2, 23.2, 27.5, 36.7, 38.2, 42.8, 43.7, 44.2, 49.7, 70.7, 193.7, 212.7. Positive FABMS *m/z*: 645.2728 (observed); 645.2727 (TID for $C_{40}H_{39}O_7N$). Elemental analysis: satisfactory data could not be obtained.

(17β)-2-Benzyloxy-1,3,5(10)-estratriene-3,17-diol (**5**). A mixture of **4** (67.24 g, 0.1 mol) and 6% ethanolic KOH (1700 ml) was stirred at refluxing temperature under an argon atmosphere for 2 h and then evaporated to give a dark reddish syrup. This syrup was dissolved in water and extracted with ether three times. The combined extracts were washed with water, dried over anhydrous Na_2SO_4, and evaporated to give a crystalline residue, which was filtered and washed with ether to give crystals (19.70 g, 62.8% yield). A second crop (1.73 g, 5.5% yield) was obtained from the mother liquor. Recrystallization from $CHCl_3$–MeOH gave colorless fine crystals, mp 196–197°C (sinter at 185°C); $[\alpha]_D^{23}$ +59.8° (*c* 1.0, $CHCl_3$). ν_{max} (Nujol) cm^{-1}: 3500, 3400, 3300, 3150, 1605, 1510. NMR δ_H ($CDCl_3$): 0.77 (s, 3H), 1.18 (dt, *J* = 7.5 and 11.5 Hz, 1H), 1.27 (dt, *J* = 4.0 and 13.0 Hz, 1H), 1.30 (ddd, *J* = 7.0, 12.0, and 23.0 Hz, 1H), 1.36 (ddd, *J* = 5.5, 12.0, and 23.5 Hz, 1H), 1.38–1.53 (m, 3H), 1.58 (s, 1H), 1.69 (dddd, *J* = 3.0, 7.0, 9.0, and 12.5 Hz, 1H), 1.86 (ddt, *J* = 2.5, 6.0, and 12.5 Hz, 1H), 1.93 (dt, *J* = 3.0 and 12.5 Hz, 1H), 2.11 (ddt, *J* = 6.0, 9.5, and 13.0 Hz, 1H), 2.18 (dd, *J* = 4.0 and 11.5 Hz, 1H), 2.25 (ddd, *J* = 4.0, 7.0, and 13.0 Hz, 1H), 2.74 (dd, *J* = 6.0 and 16.5 Hz, 1H), 2.80 (ddd, *J* = 6.0, 11.5, and 16.5 Hz, 1H), 3.72 (dt, *J* = 5.5 and 8.5 Hz, 1H), 5.06 (s, 2H), 5.48 (s, 1H), 6.65 (s, 1H), 6.90 (s, 1H), 7.34–7.43 (m, 5H). NMR δ_C ($CDCl_3$): 11.0, 23.1, 26.4, 27.4, 29.2, 30.6, 36.7, 38.8, 43.3, 44.1, 50.1, 71.2, 81.9, 111.8, 112.6, 127.8 (×2), 128.0, 128.3, 128.7 (×2), 133.7, 136.6, 143.7, 143.8. FDMS *m/z*: 378 (M^+). Positive FABMS *m/z*: 378.2202 (observed); 378.2194 (TID for $C_{25}H_{30}O_3$). Elemental analysis. Found: C, 79.80; H, 7.77%. Calcd. for $C_{25}H_{30}O_3$: C, 79.33; H, 7.99%.

(17β)-2,3-Dibenzyloxy-1,3,5(10)-estratrien-17-ol (**6**). A mixture of **5** (21.43 g, 0.057 mol), Na_2CO_3 (24.0 g, 0.227 mol), benzyl chloride (21.5 g, 19.5 ml, 0.170 mol), and DMF (450 ml) was stirred at 100–120°C for 20 h, poured into water, and extracted with ether three times. The combined extracts were successively washed with two portions of 1 N KOH and two portions of water, dried over anhydrous Na_2SO_4, and evaporated to give an orange syrup (35.14 g). Column chromatography of a small portion (0.6 g) of the mixture with silica gel (24 g) in hexane–EtOAc (7:1) gave **6** (224 mg) and its formyl ester **6'** (158 mg). ν_{max} (KBr) cm^{-1}: 1720, 1610, 1505. NMR δ_H ($CDCl_3$): 0.84 (s, 3H), 1.23–1.48 (m, 6H), 1.60 (m, 1H), 1.75 (m, 1H), 1.87 (m, 2H), 2.17 (m, 2H), 2.24 (ddt, *J* = 6.0, 9.0, and 13.5 Hz, 1H), 2.75 (m, 2H), 4.78 (t, *J* = 8.0 Hz, 1H), 5.11 (s, 4H), 6.67 (s, 1H), 6.89 (s, 1H), 7.29 (t, *J* = 7.5 Hz, 1H), 7.30 (t, *J* = 7.5 Hz, 1H), 7.35 (t, *J* = 7.5 Hz, 2H), 7.36 (t, *J* = 7.5 Hz, 2H), 7.44 (d, *J* = 7.5 Hz, 4H), 8.10 (s, 1H). FDMS *m/z*: 496 (M^+).

A solution of the residual mixture and K_2CO_3 (15 g) in MeOH–H_2O (4:1, 500 ml) was stirred at refluxing temperature for 1 h and then evaporated. The residue thus obtained was partitioned between EtOAc and water, and the aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with water, dried over anhydrous Na_2SO_4, and evaporated to give a yellow crystalline residue (36.57 g). Ether was added to the residue, and filtration gave pale yellow crystals (19.22 g, 72.4% yield). The mother liquor gave second and third crops (4.09 g, 15.0%). Recrystallization from hexane–EtOAc gave colorless fine needles of **6**, mp 82°C (sinter at 78°C). $[\alpha]_D^{23}$ +59.2° (*c* 0.8, $CHCl_3$). ν_{max} (KBr) cm^{-1}: 3400, 3050, 3020, 2900, 2850, 1602, 1500, 1450. NMR δ_H ($CDCl_3$): 0.75 (s, 3H), 1.15 (dt, *J* = 7.0 and 11.5 Hz, 1H), 1.25 (dt, *J* = 3.0 and 12.0 Hz, 1H), 1.27 (dd, *J* = 6.0 and 12.0 Hz, 1H), 1.35 (ddd, *J* = 6.5, 12.0, and 23.5 Hz, 1H), 1.40 (dd, *J* = 4.0 and 12.0 Hz, 1H), 1.45 (ddd, *J* = 4.0, 8.0, and 13.0 Hz, 1H), 1.46 (ddt, *J* = 5.0, 8.0, and 23.5 Hz, 1H), 1.67 (dddd, *J* = 3.0, 7.0, 9.0, and 12.0 Hz, 1H), 1.83 (ddt, *J* = 2.5, 6.0, and 12.0 Hz, 1H), 1.91 (ddd, *J* = 2.5, 4.0, and 12.0 Hz, 1H), 2.09 (ddd, *J* = 6.0, 9.0, and 19.0 Hz, 1H), 2.16 (m, 2H), 2.71 (ddd, *J* = 2.0, 6.0, and 16.0 Hz, 1H), 2.76 (ddd, *J* = 6.0, 12.0, and 16.0 Hz, 1H), 3.70 (t, *J* = 8.5 Hz, 1H), 5.09 (s, 4H), 6.89 (s, 1H), 7.03 (s, 1H), 7.272 (t, *J* = 7.0 Hz, 1H), 7.276 (t, *J* = 7.0 Hz, 1H), 7.329 (t, *J* = 7.0 Hz, 2H), 7.334 (t, *J* = 7.0 Hz, 2H), 7.43

(d, J=7.0 Hz, 4H). NMR δ_C ($CDCl_3$): 11.0, 23.1, 26.4, 27.3, 29.2, 30.7, 36.8, 38.7, 43.3, 44.2, 50.1, 71.5, 72.1, 81.9, 108.2, 113.6, 115.6, 115.7, 127.3 (×2), 127.5 (×2), 127.7 (×2), 128.4 (×2), 130.0, 133.3, 137.6, 137.7, 147.0, 147.3. FDMS m/z: 468 (M^+). Positive FABMS m/z: 468.2624 (observed); 468.2664 (TID for $C_{32}H_{36}O_3$). Elemental analysis. Found: C, 82.70; H, 7.99%. Calcd. for $C_{32}H_{36}O_3$: C, 82.01; H, 7.74%.

2,3-Dibenzyloxy-1,3,5(10)-estratrien-17-one (**7**). Jones reagent (1.4 ml) was added dropwise to a stirred solution of **6** (4.68 g, 10 mmol) in acetone (120 ml) in an ice bath. Three minutes after adding the reagent, 2-propanol (2 ml) was added to the reaction mixture, which was stirred for an additional 5 min, diluted with water, and extracted three times with ether. The combined extracts were washed with water, dried over anhydrous Na_2SO_4, and evaporated to give a pale yellow gummy material (4.37 g). Chromatography with a column (46 mmϕ × 320 mm) of silica gel (262 g), eluting with hexane–EtOAc (7 : 1–7 : 2), gave colorless crystals of **7** (2.63 g, 56.5% yield) and pinkish crystals of 6-oxo derivative **7′** (0.65 g, 13.5% yield). Recrystallization of **7** from hexane–EtOAc gave colorless crystals, mp 128°C; $[\alpha]_D^{20}$ +109.7° (c 1.16, $CHCl_3$). ν_{max} (KBr) cm^{-1}: 1740, 1605, 1510. NMR δ_H ($CDCl_3$): 0.90 (s, 3H), 1.40 (ddd, J=6.5, 11.5, and 24.0 Hz, 1H), 1.46 (dd, J=9.0 and 10.5 Hz, 1H), and the other 1.46 (m, 1H), 1.49 (ddd, J=7.0, 12.5, and 23.0 Hz, 1H), 1.56 (ddd, J=2.5, 12.0, and 19.0 Hz, 1H), 1.61 (ddd, J=9.0, 12.0, and 23.0 Hz, 1H), 1.94 (dd, J=2.5 and 9.0 Hz, 1H), 1.98 (ddt, J=2.5, 5.5, and 12.5 Hz, 1H), 2.04 (ddd, J=5.5, 8.5, and 12.0 Hz, 1H), 2.13 (dt, J=9.0 and 19.0 Hz, 1H), 2.22 (m, 1H), 2.24 (m, 1H), 2.50 (dd, J=9.0 and 19.0 Hz, 1H), 2.78 (ddd, J=2.5, 6.5, and 16.5 Hz, 1H), 2.83 (ddd, J=5.5, 11.5, and 16.5 Hz, 1H), 5.11 (s, 4H), 6.69 (s, 1H), 6.90 (s, 1H), 7.30 (m, 2H), 7.35 (m, 4H), 7.45 (d, J=8.0 Hz, 4H). NMR δ_C ($CDCl_3$): 13.9, 21.6, 26.0, 26.6, 29.0, 31.6, 35.9, 38.2, 44.2, 48.0, 50.4, 71.5, 72.0, 113.4, 115.6, 127.3 (×2), 127.5 (×2), 127.7 (×2), 128.5 (×2), 129.7, 132.7, 137.5, 137.6, 147.0, 147.5, 166.2, 187.2, 220.8. FDMS m/z: 466 (M^+). Elemental analysis. Found: C, 82.17; H, 7.38%. Calcd. for $C_{32}H_{34}O_3$: C, 82.37; H, 7.35%. Positive FABMS m/z: 466.2480 (observed); 466.2508 (TID for $C_{32}H_{34}O_3$). Recrystallization of **7′** from ether–hexane–EtOAc gave colorless plates, mp 202–203°C; $[\alpha]_D^{20}$ +65.9° (c 1.14, $CHCl_3$). ν_{max} (KBr) cm^{-1}: 3028, 2951, 2935, 2910, 2891, 2860, 1734, 1670, 1599, 1508, 1468, 1281. NMR δ_H ($CDCl_3$): 0.91 (s, 3H), 1.50–1.68 (m, 4H), 1.98–2.12 (m, 3H), 2.17 (dt, J=9.0 and 19.0 Hz, 1H), 2.26 (dd, J=13.0 and 16.5 Hz, 1H), 2.34 (m, 1H), 2.52 (dd, J=11.5 and 22.0 Hz, 1H) and the other 2.52 (dd, J=9.0 and 19.0 Hz, 1H), 2.79 (dd, J=3.5 and 16.5 Hz, 1H), 5.20 (s, 2H), 5.24 (s, 2H), 6.92 (s, 1H), 7.29–7.40 (m, 6H), 7.45 (d, J=7.0 Hz, 2H), 7.47 (d, J=7.0 Hz, 2H), 7.68 (s, 1H). NMR δ_C ($CDCl_3$): 13.6, 21.3, 25.1, 31.2, 35.7, 39.6, 42.8, 43.0, 47.6, 50.2, 70.8, 70.9, 110.1, 111.7, 126.0, 127.1 (×2), 127.3 (×2), 127.9, 128.1, 128.5 (×2), 128.6 (×2), 136.4, 136.7, 141.3, 147.4, 153.5, 196.1, 219.8. FDMS m/z: 480 (M^+). Positive FABMS m/z: 480.2271 (observed); 480.2301 (TID for $C_{32}H_{32}O_4$).

2,3-Dibenzyloxy-17-triethylsilyloxy-1,3,5(10),16-estratetraene (**8**). Triethylamine (9.9 ml, 80 mmol) and then TES triflate (7.7 ml, 34.1 mmol) were added to a stirred solution of **7** (1.86 g, 4.0 mmol) in dry CH_2Cl_2 (120 ml) at −78°C. The mixture was stirred for 2 h more, while being warmed to 5°C. The reaction mixture was then diluted with ether, successively washed with saturated $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, and evaporated to give an oily residue (6.09 g). Isolation of **8** by chromatography with a column (50 mmϕ × 250 mm) of silica gel (240 g), using hexane–EtOAc (7 : 1) as the eluent, gave a pale yellowish gum (2.16 g, 93.0% yield). NMR δ_H ($CDCl_3$): 0.71 (m, 6H), 0.88 (s, 3H), 1.01 (m, 9H), 1.37 (m, 1H), 1.48 (m, 1H), 1.56 (m, 3H), 1.81 (m, 1H), 1.90 (m, 2H), 2.08 (m, 1H), 2.21 (m, 2H), 2.78 (m, 2H), 4.48 (s, 1H), 5.13 (s, 4H), 6.70 (s, 1H), 6.91 (s, 1H), 7.36 (m, 6H), 7.46 (m, 4H). FDMS m/z: 580 (M^+). This material was immediately used for the next reaction, while crude **8** was used for the next reaction in all the other runs.

2,3-Dibenzyloxy-1,3,5(10),15-estratetraen-17-one (**9**). A mixture of crude **8** that had been prepared from 6.63 g of **7**, $Pd(OAc)_2$ (1.0 g), $Cu(OAc)_2$ (2.0 g), and dry acetonitrile (160 ml) was stirred at 50°C under an oxygen atmosphere for 17 h. The resulting crystals were dissolved in EtOAc. The mixture thus obtained was passed through a short column of silica gel (200 g), and the column being washed with EtOAc until **9** could no longer be detected by TLC. The eluate and the washings were combined and evaporated to give a crystalline residue (10.1 g), chromatographic separation with a column of silica gel (600 g), giving **9** (4.75 g, 71.9% yield) accompanied by the recovery of **7** (1.20 g, 18.1%). Recrystallization of **9** from hexane–EtOAc–acetone gave fine colorless needles, mp 116–118°C; $[\alpha]_D^{23}$ −14.9° (c 1.0, $CHCl_3$). ν_{max} (KBr) cm^{-1}: 3064, 3030, 2931, 2893, 2862, 1703, 1606, 1508, 1454. NMR δ_H ($CDCl_3$): 1.10 (s, 3H), 1.49 (dd, J=7.5 and 12.0 Hz, 1H), 1.65 (ddt, J=1.5, 4.0, and 12.5 Hz, 1H), 1.72 (dd, J=4.0 and 12.5 Hz, 1H), 1.79 (ddt, J=2.5, 10.0, and 12.0 Hz, 1H), 2.00 (dd, J=4.0 and 12.0 Hz, 1H), 2.17 (ddt, J=2.5, 6.0, and 12.0 Hz, 1H), 2.31 (m, 2H), 2.49 (dt, J=2.5 and 11.5 Hz, 1H), 2.86 (m, 2H), 5.12 (s, 4H), 6.08 (dd, J=3.0 and 6.0 Hz, 1H), 6.70 (s, 1H), 6.90 (s, 1H), 7.30 (m, 2H), 7.36 (m, 4H), 7.45 (d, J=7.0 Hz, 4H), 7.62 (dd, J=1.5 and 6.0 Hz, 1H). NMR δ_C ($CDCl_3$): 21.0, 25.5, 26.7, 28.7, 29.2, 35.5, 45.3, 51.4, 56.1, 71.4, 72.0, 113.1, 115.6, 127.3 (×3), 127.4, 127.7, 128.4 (×4), 129.4, 131.9, 132.5, 137.5, 137.6, 147.0, 147.5, 158.1 (×2), 212.9. FDMS m/z: 464 (M^+). Positive FABMS m/z: 464.2377 (observed); 464.2352 (TID for $C_{32}H_{32}O_3$). Elemental analysis. Found: C, 82.25; H, 7.03%. Calcd. for $C_{32}H_{32}O_3$: C, 82.73; H, 6.94%.

2,3-Dibenzyloxy-1,3,5(10),14-estratetraen-17-one (**10**). A mixture of **9** (3.17 g, 0.0068 mol), *p*-TsOH·H_2O (1.35 g, 7.1 mmol) and benzene (140 ml) was stirred at refluxing temperature for 4 min in an oil bath preheated to 110°C. After cooling, the mixture was washed with aqueous $NaHCO_3$, dried over anhydrous K_2CO_3, and evaporated to afford a reddish gummy material. Chromatography with a column (60 mmϕ × 235 mm) of silica gel (332 g), using hexane–EtOAc (10 : 1) as the eluent, gave a pale yellow gum of **10** (1.87 g, 59.0% yield) accompanied by a pale yellow gum of conjugate 14β-enone **11** (0.96 g, 30.3% yield). Physical data for **10**. $[\alpha]_D^{23}$ +66.1° (c 1.05, $CHCl_3$). ν_{max} (KBr) cm^{-1}: 3062, 3032, 2929, 2862, 1740, 1709, 1650, 1606, 1508. NMR δ_H ($CDCl_3$): 1.15 (s, 3H), 1.44 (ddd, J=4.0, 13.0, and 13.0 Hz, 1H), 1.56 (dddd, J=3.0, 4.0, 11.0, and 23.0 Hz, 1H), 1.68 (ddd, J=6.0, 11.5, and 23.0 Hz, 1H), 1.90 (dt, J=3.0 and 13.0 Hz, 1H), 2.12 (ddd, J=1.5, 6.0, and 13.0 Hz, 1H), 2.17 (dd, J=11.5 and 13.0 Hz, 1H), 2.21 (dd, J=11.0 and 13.0 Hz, 1H), 2.29 (ddd, J=3.0, 6.0, and 13.0 Hz, 1H), 2.85 (ddd, J=6.0, 16.0, and 23.0 Hz, 1H), 2.86 (dt, J=6.0 and 13.0 Hz, 1H), 2.90 (dt, J=1.5 and 23.0 Hz, 1H), 3.05 (ddd, J=1.5, 3.0, and 23.0 Hz, 1H), 5.11 (s, 2H), 5.12 (s, 2H), 5.60 (dd, J=1.5 and 3.0 Hz, 1H), 6.71 (s, 1H), 6.89 (s, 1H), 7.30 (d, J=7.0 Hz, 1H), 7.31 (d, J=7.0 Hz, 1H), 7.35 (t, J=7.0 Hz, 2H), 7.36 (t, J=7.0 Hz, 2H), 7.44 (d, J=7.0 Hz, 2H), 7.45 (d, J=7.0 Hz, 2H). NMR δ_C ($CDCl_3$): 20.1, 24.9, 26.6, 29.0, 33.3, 38.8, 41.5, 44.8, 50.9, 71.4, 72.0, 113.2, 113.6, 115.7, 127.3 (×2), 127.38, 127.44 (×2), 127.7 (×2), 128.4 (×3), 129.7, 132.2, 137.5, 137.6, 147.1, 147.6, 152.4, 222.2. FDMS m/z 464 (M^+). Elemental analysis: satisfactory data could not be obtained. Positive FABMS m/z: 464.2348 (observed); 464.2352 (TID for $C_{32}H_{32}O_3$). Physical data for **11**. $[\alpha]_D^{20}$ +73.4° (c 1.11, $CHCl_3$). ν_{max} (KBr) cm^{-1}: 3062, 3032, 2980, 2929, 2866, 1705, 1668, 1497, 1473, 1450; NMR δ_H ($CDCl_3$): 1.13 (s, 3H), 1.33 (dddd, J=6.0, 7.5, 10.0, and 13.5 Hz, 1H), 1.56 (ddd, J=6.0, 8.0, and 14.0 Hz, 1H), 1.63 (ddd, J=5.0, 13.0, and 25.0 Hz, 1H), 1.77 (ddd, J=6.0, 7.5, and 13.5 Hz, 1H), 1.90 (m, 2H), 2.05 (ddt, J=6.0, 7.5, and 13.0 Hz, 1H), 2.21 (dt, J=7.0 and 10.5 Hz, 1H), 2.72 (br. dd, J=4.0 and 16.0 Hz, 1H), 2.81 (m, 2H), 5.06 (s, 2H), 5.09 (s, 2H), 6.19 (dd, J=2.5 and 5.5 Hz, 1H), 6.62 (s, 1H), 6.72 (s, 1H), 7.26 (t, J=7.5 Hz, 1H), 7.28 (t, J=7.5 Hz, 1H), 7.32 (t, J=7.5 Hz, 2H), 7.34 (t, J=7.5 Hz, 2H), 7.40 (d, J=7.5 Hz, 2H), 7.42 (d, J=7.5 Hz, 2H), 7.58 (dd, J=2.5 and 6.0 Hz, 1H). NMR δ_C ($CDCl_3$): 22.3, 27.5, 27.6, 29.9, 31.2, 35.6, 37.9, 47.7, 54.7, 71.4, 71.7, 114.2, 115.2, 127.3 (×2), 127.4 (×2), 127.7 (×2), 128.4 (×3), 129.2, 132.8 (×2), 133.3, 137.5, 147.3 (×2), 162.0 (×2), 214.6. FDMS m/z: 464 (M^+). Positive FABMS m/z: 464.2318 (observed); 464.2352 (TID for $C_{32}H_{32}O_3$).

(14β)-2,3-Dibenzyloxy-1,3,5(10),15-estratetraene-17-on-14-ol (**12**). A solution of 0.04 M PBA in benzene (50 ml, 2.0 mmol) was added to a stirred solution of **10** (358 mg, 1.0 mmol) in dry CH_2Cl_2 (35 ml), stirring then being continued for 3 days. The reaction mixture was evaporated, and the residue thus obtained was dissolved in hexane–ether (1 : 1) and passed through a column of alumina (10 g). The eluent was evaporated to afford a pale yellow crystalline residue, into which *tert*-BuOH (10 ml) and 20% aq. Na_2CO_3 (15 ml) were added. The mixture was stirred at refluxing temperature for 1 h and after being cooled, was extracted twice with ether. The extracts were combined, washed with water, dried over anhydrous K_2CO_3, and evaporated to afford a crystalline residue, which was washed with a small amount of EtOAc to give colorless crystals of **12** (330 mg, 88.2% yield) as a single product. Recrystallization from hexane–EtOAc gave colorless plates, mp 166.0–166.5°C; $[\alpha]_D^{23}$ +165.8° (c 1.0, $CHCl_3$). ν_{max} (KBr) cm^{-1}: 3311, 2929, 1680, 1608, 1508. NMR δ_H ($CDCl_3$): 1.10 (s, 3H), 1.33 (ddd, J=5.0, 10.0, and 13.0 Hz, 1H), 1.38 (dt, J=6.0 and 12.0 Hz, 1H), 1.67 (dt, J=8.0 and 14.0 Hz, 1H), 1.78 (s, 1H), 1.86 (ddd, J=2.5, 12.0, and 12.0 Hz, 1H), 1.87 (ddd, J=4.5, 7.0, and 14.0 Hz, 1H), 2.12 (ddd, J=8.0, 13.0, and 16.0 Hz, 1H), 2.17 (dt, J=8.0 and 11.0 Hz, 1H), 2.39 (ddt, J=2.5, 5.0, and 10.0 Hz, 1H), 2.71 (ddd, J=2.5, 5.0, and

16.0 Hz, 1H), 2.75 (ddd, J = 4.0, 12.0, and 16.0 Hz, 1H), 5.05 (d, J = 12.0 Hz, 1H), 5.08 (d, J = 12.0 Hz, 1H), 5.10 (s, 2H), 6.27 (d, J = 6.0 Hz, 1H), 6.63 (s, 1H), 6.69 (s, 1H), 7.29 (d, J = 8.0 Hz, 1H), 7.30 (d, J = 8.0 Hz, 1H), 7.34 (t, J = 8.0 Hz, 4H), 7.36 (d, J = 6.0 Hz, 1H), 7.41 (d, J = 8.0 Hz, 2H), 7.43 (d, J = 8.0 Hz, 2H). NMR δ_C ($CDCl_3$): 20.1, 23.9, 27.3, 28.8, 29.7, 34.9, 44.9, 52.9, 71.4, 71.7, 83.5, 114.3, 115.0, 127.3 (×2), 127.4 (×2), 127.7 (×2), 128.4 (×4), 129.1, 132.9, 133.1, 137.4, 137.5, 147.2, 147.4, 160.1, 211.1. FDMS m/z: 480 (M^+). Elemental analysis. Found: C, 79.91; H, 6.82%. Calcd. for $C_{32}H_{32}O_4$: C, 79.97; H, 6.71%. Positive FABMS m/z: 480.2270 (observed); 480.2310 (TID for $C_{32}H_{32}O_4$).

When *m*-CPBA was used instead of PBA for the epoxidation process just described, a mixture of **12** and **13** was obtained, both products being separable by column chromatography. Recrystallization of minor product **13** from hexane EtOAc gave colorless crystals, mp 80 C; $[\alpha]_D^{28}$ +70.3 (c 0.535, $CHCl_3$). ν_{max} (KBr) cm^{-1}: 3421, 2929, 1716, 1606, 1506. NMR δ_H ($CDCl_3$): 1.14 (s, 3H), 1.36 (s, 1H), 1.60 (ddd, J = 5.0, 12.0, and 24.0 Hz, 1H), 1.78 (m, 2H), 1.98 (m, 2H), 2.22 (dd, J = 5.0 and 13.0 Hz, 1H), 2.27 (m, 1H), 2.85 (m, 2H), 3.04 (dt, J = 5.0 and 11.0 Hz, 1H), 5.11 (s, 2H), 5.12 (s, 2H), 6.15 (d, J = 6.0 Hz, 1H), 6.64 (s, 1H), 6.70 (s, 1H), 7.30 (m, 2H), 7.35 (m, 4H), 7.45 (d, J = 7.0 Hz, 4H), 7.73 (d, J = 6.0 Hz, 1H). NMR δ_C ($CDCl_3$): 22.9, 23.6, 24.2, 24.6, 29.0, 36.8, 37.8, 54.6, 71.5, 72.0, 82.2, 113.5, 115.5, 127.4 (×2), 127.5 (×2), 127.7, 127.8, 128.5 (×4), 129.2, 133.8, 134.0, 137.5, 137.6, 147.1, 147.3, 157.8, 211.7. FDMS m/z: 480 (M^+). Positive FABMS m/z: 480.2342 (observed); 480.2301 (TID for $C_{32}H_{32}O_4$). Elemental analysis. Found: C, 80.25; H, 6.85%. Calcd. for $C_{32}H_{32}O_4$: C, 79.97; H, 6.71%.

(14β,17α)-2,3-Dibenzyloxy-1,3,5(10),15-estratetraene-14,17-diol (**14**). To a stirred solution of **12** (139 mg, 0.3 mmol) and $CeCl_3 \cdot 7H_2O$ (112 mg, 0.3 mmol) in MeOH (2 ml) and THF (2 ml) was added $NaBH_4$ (11.3 mg, 0.3 mmol). Ten minutes later, additional $CeCl_3 \cdot 7H_2O$ (56 mg, 0.15 mmol) and $NaBH_4$ (6 mg, 0.15 mmol) were added. Fifty minutes after this, the reaction mixture was poured into water and extracted three times with EtOAc. The combined extracts were washed twice with brine, dried over anhydrous Na_2SO_4, and evaporated to afford a colorless gum (144 mg). Preparative TLC, developing with hexane EtOAc (1:1) gave major product **14** (115 mg, 82.7% yield) and minor **15** (15 mg, 10.8% yield) as a colorless gum. Crystallization of **14** from $CHCl_3$ gave colorless crystals, mp 62–64 C; $[\alpha]_D^{20}$ +50.8° (c 0.93, $CHCl_3$). Spectral data for **14**. ν_{max} (KBr) cm^{-1}: 3402, 3062, 3032, 2931, 2862, 1606, 1508, 1454, 1437. NMR δ_H ($CDCl_3$): 1.22 (s, 3H), 1.29 (ddd, J = 2.5, 13.0, and 26.0 Hz, 1H), 1.51 (m, 3H), 1.57 (s, 2H), 1.65 (ddd, J = 2.5, 3.0, and 13.0 Hz, 1H), 2.10 (ddd, J = 3.0, 6.0, and 13.0 Hz, 1H), 2.25 (m, 2H), 2.77 (m, 2H), 4.81 (br.s, $W_{1/2}$ = 9.0 Hz, 1H), 5.11 (s, 2H), the other 5.11 (s, 2H), 6.00 (d, J = 5.5 Hz, 1H), 6.06 (dd, J = 2.0 and 5.5 Hz, 1H), 6.68 (s, 1H), 6.89 (s, 1H), 7.30 (d, J = 7.0 Hz, 1H), 7.31 (d, J = 7.0 Hz, 1H), 7.34 (t, J = 7.0 Hz, 2H), 7.36 (t, J = 7.0 Hz, 2H), 7.44 (d, J = 7.0 Hz, 2H), 7.45 (d, J = 7.0 Hz, 2H). NMR δ_C ($CDCl_3$): 16.1, 23.0, 27.0, 29.9, 31.8, 40.4, 44.5, 49.8, 71.3, 72.0, 84.3, 85.9, 114.2, 115.3, 127.3 (×3), 127.4 (×2), 127.7 (×2), 128.4 (×3), 130.1, 132.3, 133.6, 137.4, 137.6, 139.4, 147.0, 147.4. FDMS m/z 482 (M^+). Elemental analysis: satisfactory results could not be obtained. Positive FABMS m/z 482.2492 (observed); 482.2457 (TID for $C_{32}H_{34}O_4$). Crystallization of **15** from $CHCl_3$ hexane gave colorless crystals, mp 135–136.5 C; $[\alpha]_D^{20}$ +116.3° (c 0.435, $CHCl_3$). Spectral data of **15**. ν_{max} (KBr) cm^{-1}: 3494, 3400 (sh), 3086, 3062, 3032, 2999, 2924, 2926, 2862, 1606, 1508. NMR δ_H ($CDCl_3$): 1.17 (s, 3H), 1.28 (ddd, J = 2.5, 13.0, and 14.0 Hz, 1H), 1.36 (ddd, J = 3.0, 13.0, and 26.0 Hz, 1H), 1.46 (ddd, J = 6.0, 12.0, and 24.0 Hz, 1H), 1.60 (dd, J = 5.0 and 13.0 Hz, 1H), 1.62 (s, 1H), 1.62 (dd, J = 2.5 and 24.0 Hz, 1H), 1.95 (br s, 1H), 2.04 (ddd, J = 3.0, 3.0, and 13.0 Hz, 1H), 2.21 (br. t, J = 11.0 Hz, 1H), 2.29 (dddd, J = 2.5, 2.5, 5.0, and 12.0 Hz, 1H), 2.77 (dt, J = 4.0 and 16.0 Hz, 1H), 2.78 (ddd, J = 5.0, 16.0, and 26.0 Hz, 1H), 4.00 (d, J = 2.5 Hz, 1H), 5.09 (s, 2H), 5.11 (s, 2H), 6.19 (dd, J = 2.5 and 6.0 Hz, 1H), 6.22 (d, J = 6.0 Hz, 1H), 6.68 (s, 1H), 6.85 (s, 1H), 7.29 (d, J = 7.0 Hz, 1H), 7.30 (d, J = 8.0 Hz, 1H), 7.34 (t, J = 8.0 Hz, 2H), 7.36 (t, J = 7.0 Hz, 2H), 7.43 (d, J = 8.0 Hz, 2H), 7.44 (d, J = 7.0 Hz, 2H). NMR δ_C($CDCl_3$): 14.3, 23.2, 27.8, 30.0, 36.2, 39.6, 43.6, 46.8, 71.3, 72.0, 83.7, 86.0, 114.2, 115.3, 127.3 (×2), 127.4 (×2), 127.7 (×2), 128.4 (×2), the other 128.4 (×2), 130.2, 132.2, 136.9, 137.4, 137.6, 138.5, 147.0, 147.4. FDMS m/z: 482 (M^+). Elemental analysis: satisfactory results were not obtained. Positive FABMS m/z: 482.2422 (observed); 482.2457 (TID for $C_{32}H_{34}O_4$).

NOE experiments on **15**. Irradiation at δ 4.00 for the 17-oxymethine proton showed an NOE difference at δ 6.19 for the 16-olefinic proton but not at δ 1.17 for the angular methyl proton.

(14β,15β,16β,17α)-15,16,17-Triacetoxy-2,3-dibenzyloxy-1,3,5(10)-estratrien-14-ol (**16**) *and (14β,15α,16α,17α)-15,16,17-triacetoxy-2,3-dibenzyloxy-1,3,5(10)-estratrien-14-ol* (**17**). To a solution of **14** (107 mg, 0.22 mmol) in acetone (7 ml), a solution of OsO_4 (7 mg, 0.03 mmol) in *tert*-BuOH (70 μl), *N*-methylmorpholine *N*-oxide (110 mg, 0.94 mmol), and water (184 μl) were successively added. The mixture was stirred for 4 days in an argon atmosphere. One hour after $NaHSO_3$ (1 g) and K_2CO_3 (200 mg) had been added to the stirred mixture, it was evaporated to afford a dark residue, which was extracted five times with EtOAc. The combined extracts were dried over anhydrous Na_2SO_4 and evaporated to afford a dark greenish residue (114 mg). To this residue were added dry pyridine (5 ml), acetic anhydride (1 ml) and DMAP (100 mg). The mixture was stirred for 17 h, poured into dilute HCl, and extracted three times with EtOAc. The combined extracts were successively washed with water, saturated aqueous $CuSO_4$ twice, water, saturated $NaHCO_3$, and brine three times, dried over anhydrous $MgSO_4$, and evaporated to afford a crystalline residue. Preparative TLC of the residue gave colorless crystals of **16** (96 mg, 68.3% yield) as the major product and a colorless gum of **17** (27 mg, 19.1% yield) as a less-polar minor product. Recrystallization of **16** from hot $CHCl_3$ hexane gave colorless crystals, mp 227–228 C; $[\alpha]_D^{19}$ +27.0 (c 1.065, $CHCl_3$). ν_{max} (KBr) cm^{-1}: 3454, 2966, 2924, 2858, 1734, 1605, 1516, 1369, 1261, 1241, 1217. NMR δ_H ($CDCl_3$): 1.10 (s, 3H), 1.19 (ddt, J = 8.0, 10.0, and 12.0 Hz, 1H), 1.31 (dddd, J = 3.5, 13.0, 14.0, and 14.0 Hz, 1H), 1.49 (dt, J = 3.5 and 14.0 Hz, 1H), 1.65 (dt, J = 1.0 and 12.0 Hz, 1H), 1.72 (ddd, J = 3.0, 3.5, and 14.0 Hz, 1H), 1.99 (dm, J = 12.0 Hz, 1H), 2.06 (s, 3H), 2.08 (s, 3H), 2.09 (s, 3H), 2.16 (dddd, J = 3.0, 3.0, 3.5, and 14.0 Hz, 1H), 2.57 (ddd, J = 3.0, 12.0, and 13.0 Hz, 1H), 2.73 (dd, J = 3.0 and 8.0 Hz, 1H), and the other 2.73 (m, 1H), 2.77 (br.s, 1H), 5.11 (s, 2H), and the other 5.11 (s, 2H), 5.35 (dd, J = 5.5 and 8.5 Hz, 1H), 5.48 (d, J = 5.5 Hz, 1H), 5.60 (d, J = 8.5 Hz, 1H), 6.64 (s, 1H), 6.85 (s, 1H), 7.29 (d, J = 7.5 Hz, 1H), 7.31 (d, J = 7.5 Hz, 1H), 7.35 (t, J = 7.5 Hz, 2H), 7.36 (t, J = 7.5 Hz, 2H), 7.43 (d, J = 7.5 Hz, 4H). NMR δ_C ($CDCl_3$): 16.4, 20.5, 20.6, 20.9, 22.0, 26.1, 30.1, 30.5, 39.4, 43.5, 44.4, 69.0, 71.3, 72.1, 73.1, 80.6, 84.5, 114.0, 115.3, 127.3 (×2), 127.4 (×2), 127.7, 127.8, 128.5 (×4), 129.4, 131.7, 137.4, 137.5, 147.1, 147.5, 168.6, 169.9, 170.6. FDMS m/z: 642 (M^+). Elemental analysis. Found: C, 71.36; H, 6.74%. Calcd. for $C_{38}H_{42}O_9$: C, 71.01; H, 6.59%. Positive FABMS m/z: 642.2834 (observed); 642.2828 (TID for $C_{38}H_{42}O_9$).

Several attempts to crystallize **17** were unsuccessful; $[\alpha]_D^{19}$ +23.1 (c 1.015, $CHCl_3$). ν_{max} (KBr) cm^{-1}: 3452, 2937, 2870, 1745, 1610, 1504, 1375, 1234. NMR δ_H ($CDCl_3$): 1.12 (s, 3H), 1.33 (ddd, J = 3.0, 13.0, and 26.0 Hz, 1H), 1.43 (ddd, J = 7.0, 12.0, and 23.0 Hz, 1H), 1.51 (dt, J = 1.0 and 12.0 Hz, 1H), 1.60 (m, 2H), 2.01 (s, 3H), 2.06 (s, 3H), 2.07 (s, 3H), 2.19 (m, 2H), 2.77 (m, 2H), 2.90 (dt, J = 4.0 and 12.0 Hz, 1H), 5.11 (s, 2H), 5.12 (s, 2H), 5.27 (d, J = 8.0 Hz, 1H), 5.28 (d, J = 6.0 Hz, 1H), 5.59 (dd, J = 6.0 and 8.0 Hz, 1H), 6.69 (s, 1H), 6.90 (s, 1H), 7.31 (d, J = 7.5 Hz, 2H), 7.36 (t, J = 7.5 Hz, 4H), 7.45 (d, J = 7.5 Hz, 4H). NMR δ_C ($CDCl_3$): 18.5, 20.3, 20.5, 20.9, 22.6, 25.1, 28.7, 29.8, 38.7, 45.2, 46.7, 68.7, 71.3, 72.1, 77.5, 78.6, 81.0, 113.5, 115.3, 127.3 (×2), 127.4 (×2), 127.8 (×2), 128.5 (×4), 129.5, 133.1, 137.4, 137.6, 147.0, 147.5, 168.9, 169.0, 170.1. FDMS m/z: 642 (M^+). Elemental analysis: satisfactory results could not be obtained. Positive FABMS m/z: 642.2824 (observed); 642.2829 (TID for $C_{38}H_{42}O_9$).

(14β,15β,16β,17α)-2,3-Dibenzyloxy-1,3,5(10)-estratriene-14,15,16,17-tetraol (**18**). A mixture of **16** (44 mg, 0.068 mmol), Na_2CO_3 (100 mg, a large mol excess), MeOH (4 ml), water (1 ml) and THF (1 ml) was stirred for 18 h and then evaporated. The residue thus obtained was partitioned between water and EtOAc, the aqueous layer being extracted twice with EtOAc. The combined organic layers were washed twice with brine, dried over anhydrous Na_2SO_4, and evaporated to afford a colorless gum (35 mg, 98.9% yield), which was crystallized from $CHCl_3$ hexane EtOAc to give colorless crystals, mp 159–160 C; $[\alpha]_D^{19.5}$ +45.6° (c 0.835, $CHCl_3$). ν_{max} (KBr) cm^{-1}: 3452, 3030, 2939, 2861, 1608, 1506, 1456. NMR δ_H ($CDCl_3$): 1.04 (s, 3H), 1.16 (ddt, J = 2.0, 12.0, and 13.0 Hz, 1H), 1.25 (ddt, J = 1.0, 13.0, and 13.0 Hz, 1H), 1.37 (ddt, J = 8.0, 10.0, and 12.0 Hz, 1H), 1.52 (t, J = 12.0 Hz, 1H), 1.65 (dd, J = 2.0 and 12.0 Hz, 1H), 2.02 (dd, J = 2.0 and 12.0 Hz, 1H), 2.08 (dd, J = 3.0 and 13.0 Hz, 1H), 2.39 (dt, J = 2.0 and 12.0 Hz, 1H), 2.68 (d, J = 10.0 Hz, 1H), 2.69 (d, J = 8.0 Hz, 1H), 3.18 (br.s, $W_{1/2}$ = 27 Hz, 1H), 3.96 (d, J = 6.0 Hz, 1H), 4.03 (dd, J = 6.0 and 9.0 Hz, 1H), 4.18 (d, J = 9.0 Hz, 1H), 5.02 (s, 2H), 5.04 (s, 2H), 6.60 (s, 1H), 6.83 (s, 1H), 7.23 (d, J = 7.0 Hz, 1H), 7.25 (d, J = 7.0 Hz, 1H), 7.28 (t, J = 7.0 Hz, 2H), 7.29 (t, J = 7.0 Hz, 2H), 7.37 (d, J = 7.0 Hz, 4H). NMR δ_C ($CDCl_3$): 16.8, 22.4, 25.9, 29.8 and the other 29.8, 39.6, 43.9 and the other 43.9, 67.2, 71.3, 72.1, 74.6, 80.2, 86.4, 113.9, 115.3, 127.3 (×2), 127.5 (×2), 127.7 (×2), 128.4 (×4), 129.9, 132.1, 137.5, 146.9, 147.5. FDMS m/z: 516

(M^+). Positive FABMS *m/z*: 516.2510 (observed); 516.2512 (TID for $C_{32}H_{36}O_6$). Elemental analysis. Found: C, 74.46; H, 7.14%. Calcd. for $C_{32}H_{36}O_6$: C, 74.39; H, 7.02%.

(14β,15α,16α,17α)-2,3-Dibenzyloxy-1,3,5(10)-estratriene-14,15,16,17-tetraol (**19**). A mixture of **17** (27 mg, 0.042 mmol), Na_2CO_3 (100 mg, a large mol excess), MeOH (4 ml), water (1 ml) and THF (1 ml) was stirred at 50–60 C for 2 h and then evaporated. The residue thus obtained was partitioned between water and EtOAc, the aqueous layer being extracted three times with EtOAc. The combined organic layers were washed three times with brine, dried over anhydrous Na_2SO_4, and evaporated to give colorless crystals (19 mg, 87.6% yield). Recrystallization from hexane–EtOAc gave colorless crystals, mp 168 C (sinter at 161 C); $[\alpha]_D^{19.5}$ +52.8° (*c* 0.22, $CHCl_3$). ν_{max} (KBr) cm^{-1}: 3479, 3450, 3420, 3064, 3032, 2933, 2868, 1606, 1506, 1454, 1331, 1277, 1241, 1219. NMR δ_H ($CDCl_3$ as the solvent and $CHCl_3$ at 7.24 ppm as the internal standard): 1.08 (s, 3H), 1.13 (s, 1H), 1.28 (dddd, J=3.0, 12.0, 13.0, and 13.0 Hz, 1H), 1.46 (dt, J=2.0 and 12.0 Hz, 1H), 1.55 (m, 1H), 1.75 (dt, J=3.0 and 13.0 Hz, 1H), 1.90 (dddd, J=6.0, 12.0, 12.0, and 12.0 Hz, 1H), 2.14 (dddd, J=3.0, 3.0, 3.0, and 13.0 Hz, 1H), 2.20 (d, J=7.5 Hz, 1H), 2.20 (dddd, J=2.0, 2.0, 6.0, and 12.0 Hz, 1H), 2.75 (ddd, J=6.0, 12.0, and 16.5 Hz, 1H), 2.83 (ddd, J=2.0, 6.5, and 16.5 Hz, 1H), 2.99 (d, J=4.0 Hz, 1H), 3.08 (d, J=5.0 Hz, 1H), 3.26 (ddd, J=3.0, 12.0, and 12.0 Hz, 1H), 4.09 (dd, J=4.0 and 7.0 Hz, 1H), 4.11 (t, J=7.5 Hz, 1H), 4.31 (dt, J=5.0 and 7.5 Hz, 1H), 5.09 (s, 4H), 6.67 (s, 1H), 6.86 (s, 1H), 7.28 (d, J=7.5 Hz, 1H), the other 7.28 (d, J=7.5 Hz, 1H), 7.32 (t, J=7.0 Hz, 2H), 7.33 (t, J=7.5 Hz, 2H), 7.42 (d, J=7.5 Hz, 4H). NMR δ_C ($CDCl_3$): 18.8, 22.6, 25.2, 28.4, 29.9, 38.2, 45.6, 46.4, 69.0, 71.5, 72.1, 77.6, 79.1, 82.0, 113.4, 115.6, 127.4 (×3), 127.5 (×3), 127.7 (×2), 128.4 (×3), 129.6, 134.1, 137.6, 147.0, 147.2. FDMS *m/z*: 516 (M^+). Positive FABMS *m/z*: 516.2461 (observed); 516.2512 (TID for $C_{32}H_{36}O_6$). Elemental analysis. Found: C, 74.78; H, 7.28%. Calcd. for $C_{32}H_{36}O_6$: C, 74.39; H, 7.02%.

(14β,15β,16β,17α)-1,3,5(10)-Estratriene-2,3,14,15,16,17-hexaol (**1**). A suspension of 5% Pd $BaSO_4$ (45 mg) in EtOAc (3 ml) was added to a solution of **18** (24 mg, 0.046 mmol) in EtOAc (2 ml). The mixture was stirred in an H_2 atmosphere for 3 days and filtrated. The filtrate thus obtained was evaporated to afford crystals (17 mg, quantitative yield), mp 145 C (sinter at 125 C); $[\alpha]_D^{20}$ +63.3 (*c* 0.37, MeOH). ν_{max} (KBr) cm^{-1}: 3392, 2962, 2926, 2864, 1606, 1519, 1456, 1373, 1282, 1261, 1086. NMR δ_H (d_6-acetone): 0.92 (s, 3H), 1.11 (dddd, J=2.5, 12.0, 12.0, and 12.0 Hz, 1H), 1.16 (ddd, J=4.0, 14.0, and 24.0 Hz, 1H), 1.27 (ddd, J=6.0, 12.0, and 24.0 Hz, 1H), 1.35 (dt, J=2.0 and 12.0 Hz, 1H), 1.53 (dt, J=3.0 and 14.0 Hz, 1H), 1.96 (ddt, J=2.0 and 12.0 Hz, 1H), 2.01 (ddd, J=5.0, 12.0, and 16.0 Hz, 1H), 2.33 (dt, J=2.0 and 12.0 Hz, 1H), 2.49 (ddd, J=5.0, 12.0, and 16.0 Hz, 1H), 2.56 (ddd, J=2.0, 6.0, and 16.0 Hz, 1H), 3.26 (br. s, 1H), 3.44 (dd, J=7.0 and 14.0 Hz, 1H), and the other 3.44 (ddd, J=5.0, 18.0, and 24.0 Hz, 1H), 3.49 (br. s, 1H), 3.77 (d, J=6.0 Hz, 1H), 3.85 (br. s, 1H), 3.90 (dd, J=6.0 and 8.5 Hz, 1H), 4.12 (d, J=8.5 Hz, 1H), 6.38 (s, 1H), 6.64 (s, 1H), 7.4 (br. s, 2H). Statisfactory elemental analytical data could not be obtained. Negative FABMS *m/z*: 335.1494 (observed); 335.1495 (TID for $C_{18}H_{23}O_6$).

(14β,15α,16α,17α)-1,3,5(10)-Estratriene-2,3,14,15,16,17-hexaol (**2**). A suspension of 5% Pd $BaSO_4$ (20 mg) in EtOAc (1 ml) was added to a solution of **19** (10 mg, 0.019 mmol) in EtOAc (1 ml). The mixture was stirred in an H_2 atmosphere for 3 days and then filtered. The filtrate thus obtained was evaporated to afford crystals (8 mg, quantitative yield), mp 121 C (sinter at 102 C); $[\alpha]_D^{20}$ +61.0 (*c* 0.36, MeOH). ν_{max} (KBr) cm^{-1}: 3392, 2960, 2927, 2862, 1605, 1520, 1456. NMR δ_H (d_6-acetone): 0.94 (s, 3H), 1.07–1.24 (m, 2H), 1.38 (dt, J=2.0 and 12.0 Hz, 1H), 1.70 (dt, J=3.5 and 13.0 Hz, 1H), 1.74 (dddd, J=6.0, 12.0, 12.0, and 12.0 Hz, 1H), 1.96 (m, 1H), 2.01 (ddd, J=4.0, 10.0, and 13.0 Hz, 1H), 2.18 (ddt, J=2.5, 6.0, and 12.0 Hz, 1H), 2.53 (ddd, J=6.0, 12.0, and 16.0 Hz, 1H), 2.60 (ddd, J=2.0, 6.0, and 16.0 Hz, 1H), 3.10 (s, 1H), 3.16 (dt, J=3.5 and 12.0 Hz, 1H), 3.66 (d, J=7.5 Hz, 1H), 3.76 (d, J=4.0 Hz, 1H), 3.89 (t, J=7.5 Hz, 1H), 3.95 (dd, J=4.0 and 7.0 Hz, 1H), 4.08 (ddd, J=5.0, 7.0, and 7.5 Hz, 1H), 4.19 (d, J=5.0 Hz, 1H), 6.37 (s, 1H), 6.61 (s, 1H), 7.28 (s, 1H), 7.29 (s, 1H). Negative FABMS *m/z*: 335.1522 (observed); 335.1495 (TID for $C_{18}H_{23}O_6$).

Acknowledgments. We appreciate the help of Professor Tadashi Inagami and Dr. Masaaki Tamura of Vanderbilt University, and of Dr. Atsuo Goto of Tokyo University by their kind and suggestive communication. We thank Miss Tomoko Kashiwabara, Mrs. Yoko Miyata, and Miss Ikuko Murakami for their aggressive work on a biological evaluation of the synthesized compounds.

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