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REGIO- AND STEREOSELECTIVE INTRODUCTION OF 15β-HYDROXY GROUP AND SIDE CHAINS TO STEROIDS BY THE PALLADIUM-CATALYZED REACTION OF 1,3-DIENE MONOEPOXIDES WITH CARBONUCLEOPHILES

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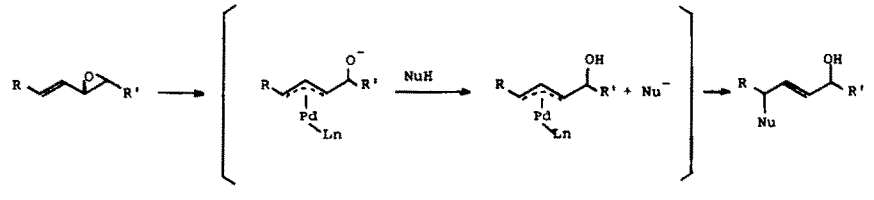
Abstract—The Pd-catalyzed reaction of 1,3-diene monoepoxides with carbonucleophiles is applied to the regio- and stereoselective introduction of 15β-hydroxy group and side chains to steroid nuclei. 3β-Hydroxyandrost-5-en-17-one (**15**) was converted to 15,16β-epoxy-$\Delta^{17(20)}$ isoheptylidene steroid **20** and ethylidene steroid **21**. The former was subjected to the Pd-catalyzed reaction with dimethyl malonate and then converted to 15β-hydroxycholesterol (**29**). Similarly, 15β-hydroxyisocholesterol (**32**) was obtained from the ethylidene steroid **21** using the Pd-catalyzed reaction of methyl 3-oxo-5-methylhexanoate (**24**) as a key reaction.

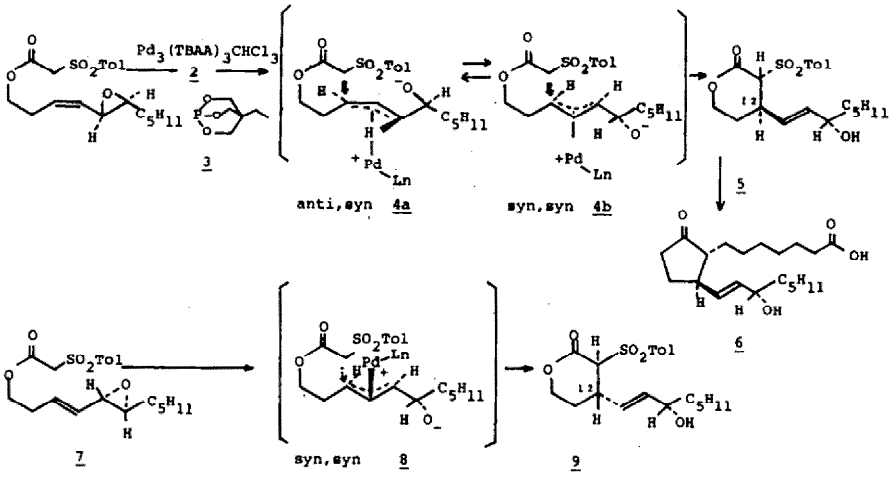
INTRODUCTION

Palladium-catalyzed displacement reaction of various allylic compounds via π-allylpalladium complexes with carbonucleophiles is an important and useful synthetic method, and has been studied extensively.[1,2] Allylic acetates are commonly used for the reaction. In our continuous effort to expand the usefulness of the π-allylpalladium chemistry in organic syntheses, we have found that allylic carbonates are more reactive than acetates and their reaction proceeds under neutral conditions.[3] Also we paid our attention to the possibility of forming π-allylpalladium complexes from 1,3-diene monoepoxides, because they can be regarded as allylic ethers. Simple allylic ethers are inactive for the Pd-catalyzed reaction, but we expected that allylic epoxides would be more reactive. The Pd-catalyzed ring opening reaction of various 1,3-diene monoepoxides has been reported by Noyori and co-workers,[4] which seems to proceed via the formation of π-allylpalladium complexes. We have confirmed that the Pd-catalyzed reaction of 1,3-diene monoepoxides with carbonucleophiles proceeds smoothly. Particularly the reaction is highly regioselective to give 1,4-adducts as main products[5,6] (Scheme 1). In addition, this reaction proceeds under neutral conditions, because alkoxide anion is generated by C—O bond cleavage and abstracts proton from nucleophiles. Thus the reaction can be carried out without addition of external bases.

The highly regioselective reaction of 1,3-diene monoepoxides is very useful for organic synthesis. We have synthesized the pheromone of the Monarch butterfly in short steps using the monoepoxide of isoprene.[5] Furthermore we found that the reaction is not only regioselective, but also stereoselective.[7] We have observed high stereo- and regioselectivity in the intramolecular nucleophilic displacement of the following 1,3-diene monoepoxides **1** and **7** (Scheme 2) at room temperature to give the 6-membered lactones **5** and **9**, without forming 8-membered lactones using the palladium complex **2**[8] and trimethylolpropane phosphite **3**. These two epoxides **1** and **7** are different only in their double bond configuration. The cyclization of **1** gave a mixture of δ-lactones **5** and **9** in a ratio of 92:8, while the reaction of **7** led to a mixture **5** and **9** in a ratio of 5:95. The lactones **5** and **9** are diastereomers, epimeric at C(12). The lactone **5** was converted to (±)-11-deoxyprostaglandin E_1 (**6**). These results and mechanistic consideration indicate that the cyclization of **7** proceeds with overall retention of the stereochemistry of the epoxides through the *syn, syn* Pd complex **8**, while the cyclization of **1** proceeds through



Scheme 1.



Scheme 2.

either Pd complex **4a** (*anti, syn*) or **4b** (*syn, syn*) derived from **4a** via π-allyl to σ-allyl interconversion and bond rotation. In these transformations, the initial ionization of the epoxides occurs with inversion of configuration, and the following cyclization also proceeds with inversion of the resultant π-allylpalladium complexes.

Encouraged by the high regio- and stereoselectivity, we have attempted the steroid side chain synthesis based on this reaction. Wicha and Kabat have carried out a partial synthesis of digitoxigenin applying the regioselective intramolecular reaction of steroidal 1,3-diene monoepoxide.[9] But the stereoselectivity is not a problem in their synthesis.

Recently, new steroids have been discovered which have a 15-hydroxy group such as oogoniol (**10**)[10] (steroidal sex hormone of the water mold) and pavoninin (**11**)[11] (shark repellent) (Fig. 1). We paid our attention to the possibility that the Pd-catalyzed regio- and stereoselective reaction of 15,16-epoxy-$\Delta^{17(20)}$-alkylidene steroids with carbonucleophiles is particularly useful for the stereoselective introduction of steroid side chains and a 15-hydroxy group. In this paper, we wish to report the stereoselective introduction of side chains and synthetic approach toward 15-hydroxy steroids based on the Pd-catalyzed reaction of 15,16-epoxy-$\Delta^{17(20)}$-alkylidene steroids **12** with various carbonucleophiles. A preliminary report has been published,[12] and the details of the studies are presented in this paper.

RESULTS

The reaction of 1,3-diene monoepoxide with organocuprates is known to undergo selective anti attack. But the reaction is not always regioselective, and sometimes a mixture of 1,2- and 1,4-adducts is obtained depending on the structure of ene oxides.[13] Indeed recent study by Marino,[14] on the introduction of side chains and a 15-hydroxy group to the steroid nucleus showed that the reaction of ethylidene epoxide **12** (R = Me) with lithium isohexylcyanocuprate proceeds regioselectively to give the 1,4-adduct **13** cleanly and in high yield by the anti S_N2' attack. On the other hand, the reaction of the isoheptylidene epoxide **12** (R = $(CH_2)_3CMe_2$) with lithium methylcuprate was not regioselective and resulted in the formation of equal amounts of the 1,2- and 1,4-adducts. The Pd-catalyzed reaction of 1,3-diene monoepoxide is different from the copper mediated reaction. We expected that the reaction of 1,3-diene monoepoxides **12** with carbonucleophiles should give 1,4-adducts **14** regioselectively with *syn* relationship of the entering nucleophile and the departing group of oxygen. This Pd-catalyzed S_N2,[15] S_N2',[16] and ScN'[17] reactions are valuable for the transfer of C—O chirality to that of a C atom of the newly formed C—C bond. We wanted to examine this concept within the context of the stereoselective construction of the natural C(20*R*) and unnatural C(20*S*) configuration in steroid side

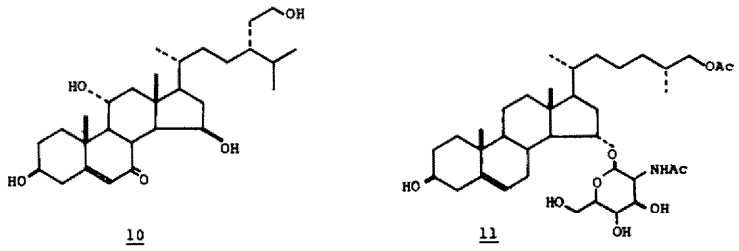
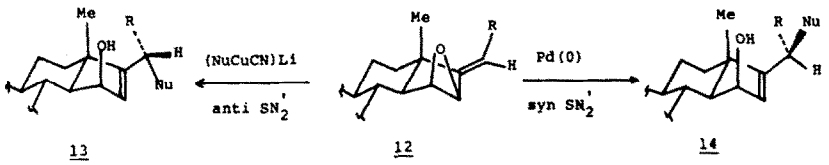


Fig. 1.



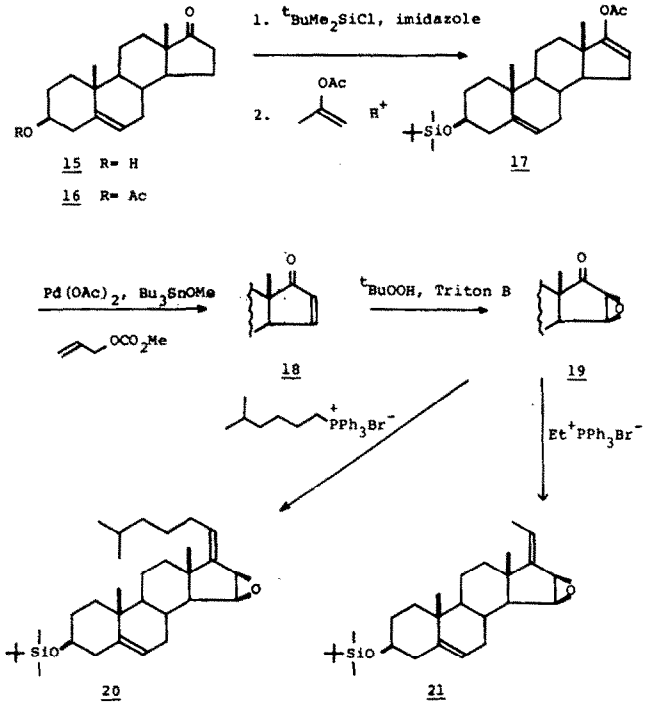
Scheme 3.

chains. Although most steroids have C(20*R*) configuration, steroids having C(20*S*) configuration have been proved to be useful in a number of biological studies.[18]

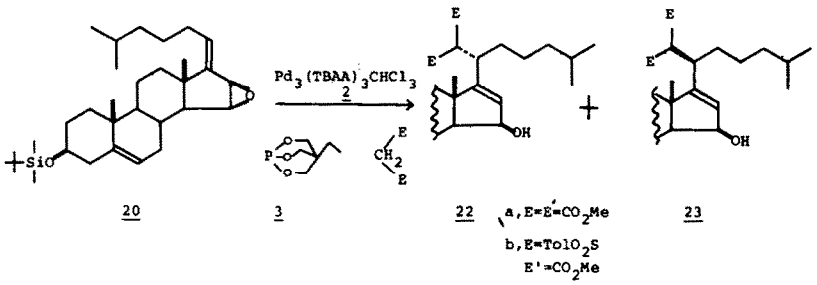
The alkylidene epoxides **20** and **21** were prepared by Marino[14] from 3β-acetoxyandrost-5-en-17-one (**16**). In their synthesis, 3β-t-butyldimethylsiloxyandrost-5,15-dien-17-one (**18**) was prepared from **16** by bromination–dehydrobromination after protection of the carbonyl group as ketal. However, we applied our new Pd-catalyzed synthetic method for enone from saturated ketones via their enol acetates[19] to the introduction of the double bond.

After silylation of the alcohol in **15** (t-BuMe$_2$SiCl–imidazole–DMF; 98% yield), the enol acetate **17** was prepared by transacetylation with isopropenyl acetate in 79% yield. Then the enol acetate **17** was refluxed with allyl methyl carbonate in CH_3CN by using $Pd(OAc)_2$ and tributyltin methoxide as the bimetallic catalysts to give the enone **18** in 89% yield after chromatography. The epoxidation of **18** with t-butylhydroperoxide in Triton B afforded selectively the β-epoxide **19**[20] in 77% yield. The subsequent Wittig reaction of the resultant epoxy ketone **19** with isoheptyl- and ethyltriphenylphosphonium bromides (n-BuLi in THF at −30°) afforded the desired epoxides **20** and **21** in 87 and 77% yields respectively. These epoxides are not stable and decomposed during column chromatographic purification. Therefore, they were purified by recrystallization.

The Pd-catalyzed reaction of **20** with several nucleophiles was carried out in order to introduce C(20) methyl group. The catalyst solution was prepared by mixing $Pd_3(TBAA)_3CHCl_3$ **2**[8] and three equivalents of the bicyclic phosphite **3** in THF for 30 min at room temperature under argon. When triphenylphosphine instead of **3** was used as the ligand, no reaction took place. To the catalyst solution, a mixture of the epoxide **20** and the nucleophile in THF was added dropwise at room temperature. The best result was obtained with dimethyl malonate (Table 1), and the 1,4-adduct **22a** was obtained in 83% yield in 2 hr. On the other hand, the reaction of sulfonylacetate was slow and the adduct **22b** was obtained in 73% yield after 20 hr. No reaction took place with disulfone. Further investigation of the adduct of dimethyl malonate revealed that the reaction proceeded with 100% regioselectivity, but



Scheme 4.



Scheme 5.

Table 1

Run	Nucleophile	Pd^0 (mol %)	Time (hr)	Ratio (22 : 23)	Yield (%)
1	$MeO_2C \frown CO_2Me$	5	2	95 : 5	83
2	$TolO_2S \frown CO_2Me$	10	20	—	73
3	$PhO_2S \frown SO_2Ph$	10	—	—	—

TBAA : tribenzylidene acetylacetone.

the stereoselectivity was not complete and the diester **22a** and its C(20)-isomer **23b** were obtained in a ratio of 95 : 5.

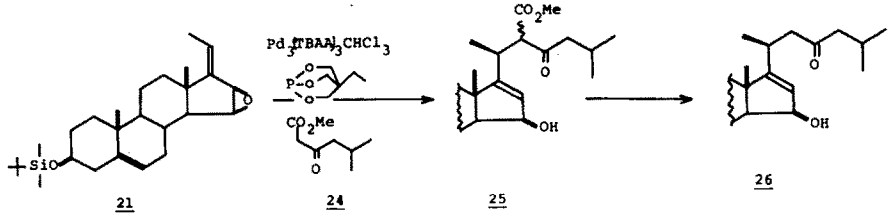
Similarly the epoxide **21** was allowed to react with the β-keto ester **24** (Scheme 6). The adduct **25** was obtained in 91% yield in 2 hr as a mixture of stereoisomers due to the methoxycarbonyl group. After demethoxycarbonylation with NaI in HMPA/H_2O at 180° to form **26** in 97% yield, the regio- and stereoselectivity of this Pd-catalyzed reaction was examined, and none of the regio- and stereoisomers of **26** were detected by ^{13}C-NMR and HPLC.

Then the stereochemistry at C(20) of the 1,4-adducts **22a** and **26** was determined by conversions to 3β-t-butyldimethylsiloxy-15β-hydroxycholesterol (**30**) and 3β-t-butyldimethylsiloxy-15β-hydroxyisocholesterol (**33**), respectively. The transformation of the diester **22a** into **30** was carried out in the following way (Scheme 7). Demethoxycarbonylation of **22a** (69% yield) and selective hydrogenation of Δ^{16}-double bond over PtO_2 at 40 atm of hydrogen afforded the alcohol **27** in 89% yield. After protection of the 15-hydroxy group with ethyl vinyl ether, the ester group was reduced to primary alcohol with diisobutylaluminum hydride and then oxidized to the aldehyde **28** with Collins reagent in 85% overall yield. Removal of the aldehyde group in **28** with $RhCl(PPh_3)_3$ in refluxing benzene[21] and hydrolysis of two protecting groups with *p*-toluenesulfonic acid in MeOH gave the diol **29** in 82% overall yield. The selective protection of 3-hydroxy group with t-butyldimethylsilyl chloride gave the known alcohol **30**[14] in 81% yield.

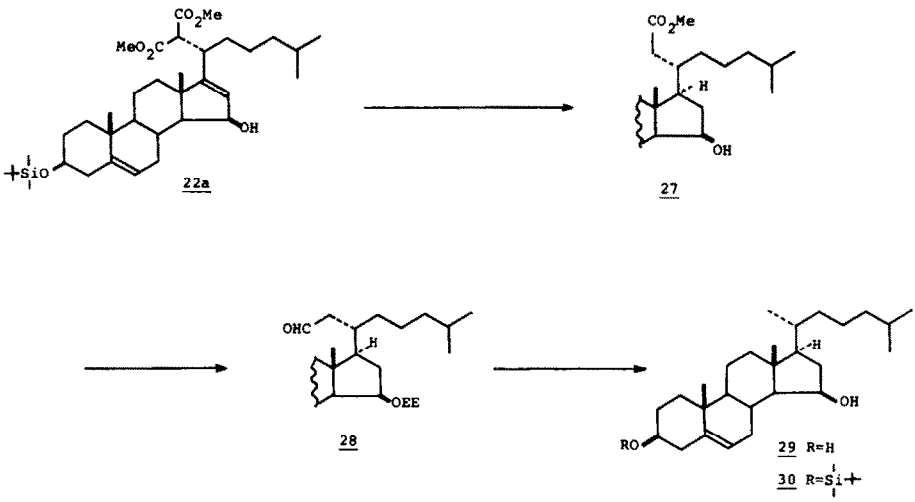
The conversion of the ketone **26** into **33** was carried out in the following way (Scheme 8). The Wolff–Kishner reduction gave the diol **31** in 68% yield. The selective hydrogenation of the Δ^{16}-double bond over PtO_2 and finally the silylation of 3-hydroxy group with t-butyldimethylsilyl chloride afforded the known alcohol **33**[14] in 75% overall yield. Comparison of the NMR spectra (360 MHz) of the two alcohols **30** and **33** nicely distinguishes the two isomers in the C(20)-methyl region. The chemical shift of C(20)-methyl of **30** was 0.93 and that of **33** was found to be 0.85. It is noteworthy that **33**, of the unnatural 20*S* chirality, has the more upfield shift than **30** of the natural 20*R* chirality for C(20)-methyl signal. Those chemical shifts of C(20)-methyl are in agreement with those previously reported.[14,22]

DISCUSSION

Stereocontrolled introductions of side chains at C(20) in (*Z*)-$\Delta^{17(20)}$- and 20(*S*)-acetyl-Δ^{16}-unsaturated steroids using stoichiometric and catalytic organopalladium, respectively, were reported by Trost[23] and Schwartz[24] independently. Mechanisms of these reactions were also well discussed. Now we have observed the high regio- and stereoselectivity (**22a** : **23a** = 95 : 5; Table 1) in the reaction of 1,3-diene



Scheme 6.



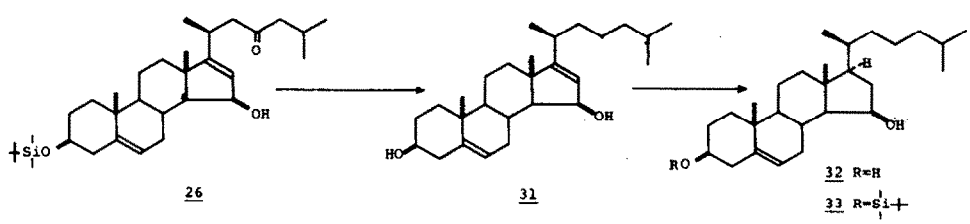
Scheme 7.

monoepoxide **20** with dimethyl malonate. This result can be rationalized as follows. The initial attack of Pd(0) to 1,3-diene monoepoxide **20** takes place from the opposite face of the epoxide, as observed in the π-allylpalladium alkylation with allyl acetate,[25] to form the most stable *syn* π-allylpalladium complex **34a**. The *syn–anti* isomerization involving π-allyl to σ-allyl interconversion and bond rotation would essentially be possible if either the epoxide or the olefin were in acyclic systems.[23] In the case of steroids, however, *syn–anti* isomerization (**34a** ⇌ **34b**) would be very slow and the concentration of **34b** would be low due to the unfavorable *anti* configuration of alkyl group and the location of the Pd on the congested β-face of the steroid in **34b**. Therefore the following attack of the carbonucleophile proceeds again from the opposite face of the *syn* π-allylpalladium complex **34a** with inversion of configuration to give the major product **22**. Thus the inversion at the oxidative addition and inversion at the alkylation of π-allylpalladium with nucleophiles lead to net retention of configuration as the major reaction course.

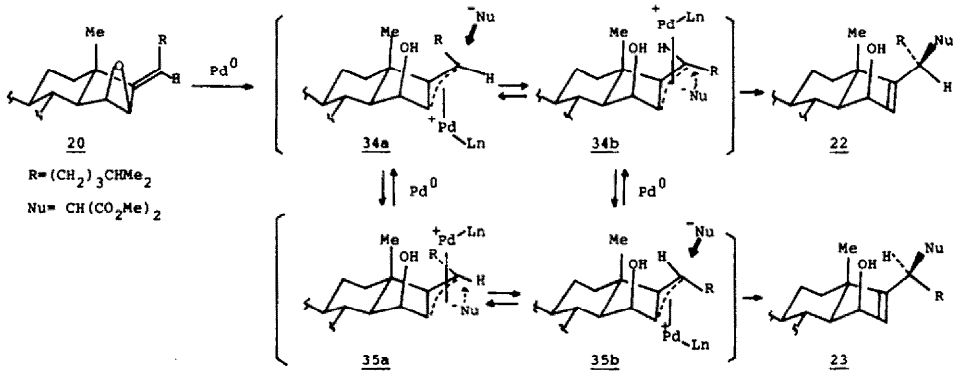
The formation of the minor product **23** can be rationalized as follows. Trost *et al.* explained[25,26] very rapid interconversion of *cis*-3-acetoxy-5-carbomethoxy-1-cyclohexene and its *trans*-isomer in the presence of Pd(0) by the internal transfer of the dissociated acetate anion from the same face of Pd. The Pd-catalyzed reaction of diene monoepoxide is different from the reaction of allyl acetate and this type of interconversion is impossible. One rational explanation for the isomerization of **34** to **35** is that Pd is displaced from the π-allylpalladium complex **34a** by Pd(0) species present in the reaction medium, as a strong nucleophile, with inversion of configuration. This metal–metal exchange is well known in other systems involving metal nucleophiles.[27] The less stable π-allylpalladium complex **35a** formed by metal–metal exchange may isomerize to the stable π-allylpalladium complex **35b** by π-allyl to σ-allyl interconversion. Then the displacement of π-allylpalladium complex **35b** with carbonucleophile proceeds from the opposite face with inversion of configuration to give the minor product **23**.

The regiochemical results observed for the products **22** and **23** can be understood in terms of steric effects. The 1,2-addition course of nucleophile to π-allylpalladium complexes **34a** and **35b** is blocked with the resulting hydroxy group, thereby the less crowded 1,4-addition course of nucleophile became dominant. This higher regioselectivity in the Pd-catalyzed ring opening reaction of 1,3-diene monoepoxide system is not dependent on the peculiarity of the structure.

The present studies reveal that the Pd-catalyzed regio- and stereoselective reaction of 15β,16β-epoxy-17(*E*)-alkylidene steroids with carbonucleophiles offers a very good method for the stereoselective introduction of steroid side chains with both 20*R* and 20*S* configuration and 15β-hydroxy group. These results indicate that the Pd-catalyzed ring opening of 1,3-diene monoepoxide gives the *syn* S_N2' alkylation product.



Scheme 8.



Scheme 9.

EXPERIMENTAL

IR spectra were recorded on JASCO IRA-2 spectrometer. IR data represent ν_{max} in cm^{-1}. EI-MS were recorded on a Hitachi M-80 mass spectrometer. High resolution mass spectra were recorded on a Jeol JMS-OISG-2 mass spectrometer. ^{1}H-NMR spectra were recorded on a Nicolet NT-360 spectrometer at 360 MHz, a Jeol FX-90Q spectrometer at 90 MHz and a Hitachi R-24A spectrometer at 60 MHz. TMS was used as a standard at 0.00 ppm for measurements in $CDCl_3$ or in CCl_4. ^{1}H-NMR data represent in ppm (multiplicity, J values in Hz, assignments). ^{13}C-NMR spectra were recorded on a Jeol FX-90Q spectrometer at 22.5 MHz. A signal for TMS was used as an internal standard. Optical rotations were measured with a Yanaco OR-50 polarimeter in 5 ml soln using a glass cell (l = 0.5 dm). Column chromatography was performed using silica gel (Kanto) 100/200 mesh. TLC was performed using Merck precoated TLC plate 60F 254 (silica gel). Preparative high performance liquid chromatography (HPLC) was performed on Nihonseimitsu NSLC-100 using silica gel (60–5 μm; 7.5 o.d. × 250 mm) column and RI-detector.

3β - t - Butyldimethylsiloxy - 17 - acetoxyandrosta - 5,16 - diene (**17**)

A mixture of 3β-t-butyldimethylsiloxyandrost-5-en-17-one (7.0 g, 17.4 mmol), prepared from **15** (5.0 g, 17.3 mmol), imidazole (4.7 g, 69.2 mmol) and t-BuMe_2SiCl (5.3 g, 34.7 mmol) in dry DMF, and a catalytic amount of *p*-toluenesulfonic acid in isopropenyl acetate (160 ml) was refluxed for 18 hr under N_2. To this soln was added K_2CO_3 at 0° and the mixture was stirred for 1 hr. The resulting soln was filtered through a short silica gel column and then the solvent was removed *in vacuo*. The residue was purified by column chromatography on silica gel with ether–hexane (1:20) to afford **17** (6.14 g, 79% yield): IR (KBr): 2920, 1770, 1620, 1460, 1380, 1210, 1090, 840, 770; ^{1}H-NMR (60 MHz, CCl_4): δ 0.90 (s, Si—CMe_3 and 13-Me), 1.03 (s, 10-Me), 2.15 (s, OCOMe), 5.4–5.6 (m, 6-H), 5.55–5.7 (m, 16-H) and the starting material (1.48 g, 21% yield).

3β - t - Butyldimethylsiloxyandrosta - 3,15 - dien - 17 - one (**18**)

To a soln of **17** (10.8 g, 24.3 mmol), allyl methyl carbonate (5.53 g, 48.6 mmol), and Bu_3SnOMe (2.26 ml, 7.3 mmol) in CH_3CN (300 ml) was added $Pd(OAc)_2$ (267 mg, 1.21 mmol) at 70° under argon. The mixture was refluxed for 2 hr, and then the soln was filtered through a short silica gel column. After removal of the solvent, the residue was chromatographed on silica gel with ether–hexane (1:15) to give **18** (8.63 g, 89% yield): m.p. 111–112° (petroleum ether); $[\alpha]_D^{25} = -111°$ (*c* = 0.656, $CHCl_3$); EI-MS 400 $[M]^+$, 385 $[M-Me]^+$, 343 $[M-t\text{-}Bu]^+$; IR (KBr): 2900, 1730, 1450, 1370, 1250, 1090, 830, 770; ^{1}H-NMR (90 MHz, $CDCl_3$): δ 0.09 (s, Si—Me_2), 0.89 (s, Si—CMe_3 and 13-Me), 1.08 (s, 13-Me), 3.2–3.6 (m, 3-H), 5.3–5.4 (m, 6-H), 6.03 (dd, 3.2, 6.0 Hz, 16-H), 7.48 (dd, 1.2, 6.0 Hz, 15-H).

3β - t - Butyldimethylsiloxy - 15β - 16β - epoxy - 5 - androsten - 17 - one (**19**)

To a mixture of t-butylhydroperoxide (70% in water) (1.12 g, 8.73 mmol) and trimethylbenzylammonium hydroxide (Triton-B) (40% in water) (1.83 g, 4.37 mmol) in THF (15 ml) was added a soln of **18** (1.17 g, 2.91 mmol) in THF (5 ml) at −20°. After the soln was stirred for 1 min, the mixture was poured into cold water and extracted with ether. The excess peroxide was quenched with sodium thiosulfate, and washed with NH_4Cl aq and brine, and dried over $MgSO_4$. After removal of the solvent *in vacuo*, the residue was purified by column chromatography on silica gel with ether–hexane (1:15) to give **19** (935 mg, 77% yield): IR (KBr): 2950, 1750, 1470, 1380, 1260, 1080, 900, 840, 780; ^{1}H-NMR (90 MHz, $CDCl_3$): 0.06 (s, Si—Me_2), 0.89 (s, Si—CMe_3), 1.05 (s, 13-Me), 1.16 (s, 10-Me), 3.26 (d, 3.6 Hz, 15-H), 3.78 (d, 3.6 Hz, 16-H), 5.2–5.4 (m, 6-H).

3β - t - Butyldimethylsiloxy - 15β - 16β - epoxy - cholesta - 5,17E(20) - diene (**20**)

To a suspension of the iso-heptyltriphenylphosphonium bromide (1.86 g, 4.21 mmol) in dry THF (10 ml) was added n-BuLi (1.6 N, 2.4 ml) at 0°. The color changed into red and the mixture was stirred for 1 hr at 0°. To this soln was added **19** (700 mg, 1.68 mmol) at −30°. After 1 hr, the resulting mixture was poured into NH_4Cl aq and extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was diluted with hot hexane (150 ml), and the mixture was cooled to 0°. After triphenylphosphine oxide crystallized out from hexane, the mixture was filtered. The filtrate was concentrated *in vacuo* and recrystallized from hexane to give **20** (724 mg, 87% yield): EI-MS: 498 $[M]^+$, 480 $[M-H_2O]^+$, 441 $[M-t\text{-}Bu]^+$; m.p. 135–136° (petroleum ether); $[\alpha]_D^{25} = -39.3°$ (*c* = 0.364, $CHCl_3$); IR (KBr): 2950, 1460, 1360, 1250, 1180, 1080, 900, 840, 780, 550; ^{1}H-NMR (90 MHz, $CDCl_3$): δ 0.06 (s, Si—Me_2), 0.86 (d, 6.0 Hz, 25-Me_2), 0.88 (s, Si—CMe_2), 1.05 (s, 13-Me), 1.14 (s, 10-Me), 3.48 (d, 3.6 Hz, 15-H), 5.25–5.45 (m, 16-H), 5.25–5.45 (m, 6-H), 5.58 (t, 7.5 Hz, 20-H); ^{13}C-NMR (22.5 MHz, $CDCl_3$): −4.5, 19.2, 21.0, 22.6, 22.9, 25.9, 27.9, 28.1, 28.3, 31.3, 32.1, 36.9, 37.3, 38.3, 38.7, 39.4, 42.9, 51.3, 57.1, 58.0, 59.1, 72.5, 120.3, 128.3, 142.1, 145.4.

3β - t - Butyldimethylsiloxy - 15β,16β - epoxypregna - 5,17(E)(20) - diene (**21**)

Compound **21** was prepared from **19** (2.5 g, 6.0 mmol), ethyltriphenylphosphonium bromide (8.91 g, 24.0 mmol), and

BuLi (1.6 N, 13.4 ml) by the same procedure as above. The crude product was recrystallized from petroleum ether to give **21** (1.98 g, 77% yield): EI-MS: 428 $[M]^+$, 413 $[M-Me]^+$, 371 $[M-t\text{-}Bu]^+$; m.p. 178–179.5° (petroleum ether); $[\alpha]_D^{25} = -55.1°$ ($c = 0.668$, $CHCl_3$); IR (KBr): 2950, 1460, 1380, 1250, 1080, 900, 840, 780; ^{1}H-NMR (90 MHz, $CDCl_3$): δ 0.06 (s, Si—Me_2), 0.89 (s, Si—CMe_2), 1.04 (s, 13-Me), 1.14 (s, 10-Me), 1.76 (d, 7.2 Hz, 21-H), 3.47 (d, 3.4 Hz, 15-H), 3.59 (d, 3.4 Hz, 16-H), 5.3–5.45 (m, 6-H), 5.70 (q, 7.2 Hz, 20-H); ^{13}C-NMR (22.5 MHz, $CDCl_3$): −4.6, 13.5, 18.2, 19.2, 21.0, 22.4, 25.9, 28.3, 31.3, 32.1, 36.9, 37.3, 38.1, 39.5, 42.9, 51.3, 57.1, 57.9, 58.9, 72.5, 120.3, 121.7, 142.1, 146.4.

Alkylation of the 1,3-*diene monoxide* **20** *with dimethyl malonate*

A mixture of **2** (25.5 mg, 0.017 mmol) and **3** (24.3 mg, 0.15 mmol) in dry THF (2 ml) was stirred for 30 min at room temp under argon. To the soln was added a soln of **20** (500 mg, 1.00 mmol) and dimethyl malonate (529 mg, 4.01 mmol) in dry THF (4 ml) at room temp. The mixture was stirred for 2 hr at the same temp and filtered through a short florisil column. The solvent was removed *in vacuo*. The residue was chromatographed on silica gel with ether–hexane (1:10) to give **22a** (525 mg, 83% yield) and isomer **23a** (28 mg, 4.4% yield).

Compound **22a**. $R_f = 0.28$ (ether–hexane, 1:1); EI-MS: 630 $[M]^+$, 612 $[M-H_2O]^+$, 573 $[M-t\text{-}Bu]^+$, 555 $[M-t\text{-}Bu-H_2O]^+$, 481 $[M-CHCO_2Me$ or $(t\text{-}BuSiMe_2)]^+$, 349 $[M-H_2O-CH_2CO_2Me-t\text{-}BuSiMe_2OH]^+$; $[\alpha]_D^{25} = -81.6°$ ($c = 0.674$, $CHCl_3$); IR (neat): 3450, 2950, 2230, 1730, 1430, 1250, 1150, 1090, 910, 830, 730; ^{1}H-NMR (90 MHz, $CDCl_3$): δ 0.06 (s, Si—Me_2), 0.84 (d, 7.0 Hz, 25-Me_2), 0.89 (H, s, Si—CMe_3), 1.06 (s, 13-Me), 1.14 (s, 10-Me), 2.8–3.1 (m, 20-H), 3.68 (6H, s, OCOMe), 4.3–4.5 (m, 15-H), 5.2–5.4 (m, 6-H), 5.55–5.65 (m, 16-H); ^{13}C-NMR (22.5 MHz, $CDCl_3$): −4.5, 18.2, 19.2, 20.6, 22.5, 22.7, 23.1, 24.3, 26.0, 27.6, 27.7, 30.8, 31.1, 32.1, 35.0, 37.0, 37.3, 39.0, 42.9, 47.4, 51.0, 52.0, 52.3, 55.7, 59.9, 72.6, 73.3, 120.7, 127.3, 141.9, 159.8, 168.6, 168.8.

C(20)-*Isomer* **23a**. $R_f = 0.13$ (ether–hexane, 1:1); IR (Nujol): 3400, 2900, 1740, 1460, 1380, 1250, 1100, 830, 770; ^{1}H-NMR (90 MHz, $CDCl_3$): δ 0.06 (s, Si—Me_2), 0.88 (s, Si—CMe_3), 1.05 (s, 13-Me), 1.12 (s, 10-Me), 2.65 (br d, 7.5 Hz, 20-H), 3.64 (d, 7.5 Hz, 21-H), 3.72 (6H, s, OCOMe), 4.3–4.5 (m, 15-H), 5.25–5.4 (m, 6-H), 5.4–5.5 (m, 16-H).

Alkylation of the 1,3-*diene monoxide* **20** *with methyl* p-*toluenesulfonylacetate*

The reaction of **20** (250 mg, 0.50 mmol) and methyl *p*-toluenesulfonylacetate (572 mg, 2.51 mmol) proceeded using $Pd_3(TBAA)_3CHCl_3$ (25.5 mg, 0.011 mmol) and **3** (24.3 mg, 0.15 mmol) by the same procedure as above. The reaction took 20 hr to give **22b** (267 mg, 73% yield): IR (KBr): 3500, 2930, 1740, 1600, 1460, 1330, 1150, 1080, 830, 770, 710, 580, 510; ^{1}H-NMR (90 MHz, $CDCl_3$): δ 0.08 (s, Si—Me_2), 0.84 (d, 7.5 Hz, 25-Me_2), 0.88 (s, Si—CMe_3), 1.06 (s, 13-Me), 1.10 (s, 10-Me), 2.46 (s, Ph—Me), 3.60, 3.70 (3H, s, OCOMe), 4.25–4.5 (m, 15-H), 5.2–5.4 (m, 6-H), 5.5–5.6 (m, 16-H), 7.34 (2H, br d, 8.0 Hz, Ph—H), 7.76, 7.83 (2H, br d, 8.0 Hz, Ph—H).

Alkylation of the 1,3-*diene monoxide* **21** *with methyl* 3-*oxo*-5-*methylhexanoate* (**24**)

To a mixture of $Pd_3(TBAA)_3CHCl_3$ (29.8 mg, 0.020 mmol) and **3** (28.4 mg, 0.18 mmol) in dry THF (2 ml) was added a soln of **21** (500 mg, 1.17 mmol) and **24** (554 mg, 3.51 mmol) in dry THF (5 ml) at room temp. The mixture was stirred for 2 hr at the same temp. After the usual work-up, the residue was chromatographed on silica gel with ether–hexane (1:5) to give **25** (625 mg, 91% yield): IR (Nujol): 3350, 2900, 1740, 1710, 1460, 1370, 1250, 1090, 830, 770, 730; ^{1}H-NMR (90 MHz, $CDCl_3$): δ 0.07 (s, Si—Me_2), 0.90 (s, Si—CMe_3), 1.08 (s, 13-Me), 1.17 (s, 10-Me), 3.60, 3.72 (3H, s, OCOMe), 4.3–4.5 (m, 15-H), 5.2–5.4 (m, 6-H), 5.5–5.7 (m, 16-H).

3β - *t* - *Butyldimethylsiloxy* - 15β - *hydroxy* - 20 - *isocholesta* - 5,16 - *dien* - 23 - *one* (**26**)

A mixture of **25** (230 mg, 0.39 mmol) and NaI (116 mg, 0.78 mmol) in HMPA–H_2O (16:1, 2.5 ml) was heated at 180° for 15 min. The mixture was diluted with ether, washed with H_2O several times, and dried. After removal of the solvent, the residue was chromatographed on silica gel with ether–hexane (1:5) to give **26** (201 mg, 97% yield): HPLC retention time (14.5–16.5 min, 4.3 ml/min, 1% isopropyl alcohol in hexane); EI-MS: 528 $[M]^+$, 510 $[M-H_2O]^+$, 471 $[M-t\text{-}Bu]^+$; $[\alpha]_D^{25} = -84.9°$ ($c = 1.178$, $CHCl_3$); IR (KBr): 3450, 2950, 1720, 1460, 1370, 1260, 1100, 840, 780, 670; ^{1}H-NMR (90 MHz, $CDCl_3$): δ 0.06 (s, Si—Me_2), 0.89 (s, Si—CMe_3), 0.90 (d, 6.2 Hz, 25-Me_2), 1.07 (s, 13-Me), 1.11 (d, 7.7 Hz, 20-Me), 1.16 (s, 10-Me), 3.2–3.6 (m, 3-H), 4.44 (dd, 2.7, 4.7 Hz, 15-H), 5.2–5.4 (m, 6-H), 5.57 (d, 2.7 Hz, 16-H); ^{13}C-NMR (22.5 MHz, $CDCl_3$): −4.6, 18.2, 19.2, 20.6, 21.1, 22.5, 23.4, 24.5, 25.9, 27.3, 27.5, 30.8, 32.0, 35.1, 36.9, 37.3, 42.9, 47.4, 50.4, 51.1, 52.4, 59.9, 72.5, 73.3, 120.7, 124.0, 141.8, 165.7, 209.4.

3β - *t* - *Butyldimethylsiloxy* - 15β - *hydroxy* - 21 - *methoxycarbonyl* - *cholesta* - 5 - *ene* (**27**)

Similar treatment of **22a** (749 mg, 1.19 mmol) as above afforded 3β - t - butyldimethylsiloxy - 15β - hydroxy - 21 - methoxycarbonyl - cholesta - 5,16 - diene as an oil (473 mg, 69% yield): IR (Nujol): 3450, 2930, 1740, 1460, 1370, 1250, 1160, 1090, 830, 770; ^{1}H-NMR (90 MHz, $CDCl_3$): δ 0.06 (s, Si—Me_2), 0.85 (d, J = 6.8 Hz, 25-Me_2), 0.88 (s, Si—CMe_3), 1.07 (s, 13-Me), 1.14 (s, 10-Me), 3.3–3.7 (m, 3-H), 3.63 (s, OCOMe), 4.44 (dd, 3.0, 4.5 Hz, 15-H), 5.2–5.4 (m, 6-H), 5.58 (d, 3.0 Hz, 16-H). The above ester (155 mg, 0.27 mmol) was hydrogenated in EtOAc (3 ml) with PtO_2 (30 mg) under 40 atm of H_2 for 5 hr. Column chromatography on silica gel with ether–hexane (1:10) gave the ester **27** as an oil (138 mg, 89% yield): EI-MS: 574 $[M]^+$, 517 $[M-t\text{-}Bu]^+$, 499 $[M-t\text{-}Bu-H_2O]^+$; $[\alpha]_D^{25} = -37.8°$ ($c = 0.576$, $CHCl_3$); IR (Nujol): 3450, 2930, 1740, 1460, 1380, 1250, 1090, 830, 770; NMR (90 MHz, $CDCl_3$) 0.06 (s, Si—Me_2), 0.85 (d, 6.5 Hz, 25-Me_2), 0.88 (s, Si—CMe_3), 0.96 (s, 13-Me), 1.02 (s, 10-Me), 3.3–3.6 (m, 3-H), 3.64 (s, OCOMe), 4.18 (br t, 7 Hz, 15-H), 5.2–5.4 (m, 6-H).

3β - *t* - *Butyldimethylsiloxy* - 15β - (1 - *ethoxy*-)*ethoxy* - 21 - *formylcholest* - 5 - *ene* (**28**)

To a soln of **27** (173 mg, 0.30 mmol) and a catalytic amount of *p*-toluenesulfonic acid in dry CH_2Cl_2 (5 ml) was added ethyl vinyl ether (0.5 ml, 5.2 mmol) at 0°. The mixture was stirred for 1 hr and poured into $NaHCO_3$ aq. After extraction of the mixture with ether, the organic layer was washed with brine and dried over $MgSO_4$. The solvent was removed *in vacuo* to give the crude mixture of 3β-t-butyldimethylsiloxy-15β - (1 - ethoxy) - ethoxy - 21 - methoxycarbonyl - cholest - 5-ene, which was used without further purification.

To the above ether in dry THF (10 ml) was added a soln of i-Bu_2AlH in toluene (1.2 N, 0.5 ml) at −40°. After the mixture was stirred for 30 min at −40°, cold 3 N HCl was added dropwise carefully. The resulting mixture was extracted with ether and washed with $NaHCO_3$ aq and brine. The organic layer was dried over $MgSO_4$. Evaporation of the solvent *in vacuo* afforded the crude mixture of 3β-t-butyldimethylsiloxy-15β - (1 - ethoxy) - ethoxy - 21 - hydroxymethylcholest - 5 - ene, which was used without further purification.

To a soln of pyridine (470 mg, 6 mmol) in CH_2Cl_2 (6 ml) was added CrO_3 (300 mg, 3 mmol) carefully over 10 min at 0°. After 20 min, the soln was warmed to room temp and to this soln was added the above crude alcohol. The stirring was continued for 1 hr and the mixture was diluted with hexane and filtered through a short celite column. The filtrate was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel with ether–hexane (1:10) to give **28** (161 mg, 85% overall yield from **27**): IR (KBr): 2950, 1730, 1460, 1380, 1260, 1100, 910, 840, 780, 740; ^{1}H-NMR (60 MHz) 0.85 (d, 6 Hz, 25-Me_2), 0.90 (s, Si—CMe_3), 1.02 (s, 10-Me), 5.1–5.4 (m, 6-H), 9.87 (br s, CHO).

3β,15β-*Dihydroxycholest*-5-*ene* (**29**)

To a soln of **28** (161 mg, 0.26 mmol) in dry benzene (7 ml) was added dropwise over 1 hr under reflux a soln of $RhCl(PPh_3)_3$

(278 mg, 0.30 mmol) in dry benzene (7 ml). After the mixture was stirred for an additional 1 hr, the mixture was filtered through a short florisil column. The filtrate was concentrated to give the 21-deformyl product which was used without further purification.

A soln of the above crude product in MeOH (10 ml) and CH_2Cl_2 (1 ml) was treated with a catalytic amount of *p*-toluenesulfonic acid at 0° for 2 hr, and poured into $NaHCO_3$ aq. The usual work-up and chromatography on silica gel with ether–hexane (1:2) gave **29** (82.5 mg, 82% overall yield from **28**); EI-MS: 402 $[M]^+$, 384 $[M-H_2O]^+$, 351 $[M-2H_2O-Me]^+$; IR (KBr): 3240, 2900, 1460, 1380, 1040, 960, 840, 800; ^{1}H-NMR (90 MHz, $CDCl_3$): δ 0.85 (d, 7 Hz, 25-Me_2), 0.93 (d, 7 Hz, 20-Me), 0.95 (s, 13-Me), 1.03 (s, 10-Me), 3.5 (br, 3-H), 4.3 (bt, 15-H), 5.5 (br, 6-H).

3β - t - Butyldimethylsiloxy - 15β - hydroxycholest - 5 - ene (**30**)

To a soln of **29** (39 mg, 0.10 mmol) and imidazole (17 mg, 0.25 mmol) in dry DMF (2 ml) was added t-BuMe_2SiCl (19 mg, 0.13 mmol) at −20°. The mixture was stirred for 2 hr at this temp. After the usual work-up, the residue was purified by preparative silica gel HPLC (4.5 ml/min, 2% EtOAc in hexane) to give **30** (42 mg, 81% yield): HPLC retention time 18–21 min; EI-MS: 516 $[M]^+$, 459 $(M-t\text{-}Bu)^+$, high resolution mass spectrum, calc for $C_{33}H_{60}O_2Si$, *m/e* = 516.4359, found *m/e* = 516.4352; m.p. 147–149° (petroleum ether), $[\alpha]_D^{25} = -54.2$ (*c* = 0.251, $CHCl_3$); IR (KBr): 3400, 2900, 1460, 1385, 1255, 1090, 890, 870, 840, 775; ^{1}H-NMR (360 MHz, $CDCl_3$): δ 0.06 (s, Si—Me_2), 0.87 (d, 7 Hz, 25-Me_2), 0.89 (s, Si—CMe_3), 0.93 (d, J = 7 Hz, 20-Me), 0.95 (s, 13-Me), 1.03 (s, 10-Me), 1.33 (ddd, 2, 10, 15 Hz, 16-H), 2.40 (dt, 8, 15 Hz, 16-H), 3.49 (tt, 5, 11 Hz, 3-H), 4.18 (br t, 7 Hz, 15-H), 5.34 (br d, 5 Hz, 6-H).

3β - t - Butyldimethylsiloxy - 15β - hydroxy - 20 - isocholest - 5,16 - diene (**31**)

To a soln of **26** (158 mg, 0.30 mmol) in ethylene glycol (10 ml) was added 80% hydrazine hydrate (5 ml) and the mixture was stirred for 2 hr at 100°. The mixture was cooled to room temp and to this soln was added KOH (2 g). The resulting mixture was heated to 150° for 1 hr, then the condenser was removed and the temp was increased to 200°. After excess hydrazine and water boiled off, the condenser was replaced and the bath temp was maintained at 200° for 6 hr. The mixture was cooled and poured into water and extracted with ether. After the usual work-up the residue was chromatographed on silica gel to give **31** with ether–hexane (1:2) (82 mg, 68% yield): EI-MS: 400 $[M]^+$, 382 $[M-H_2O]^+$, 287 $[M-C_8H_{17}]^+$; m.p. 151–152° (ether–hexane): $[\alpha]_D^{25} = -108.4°$ (*c* = 0.387, $CHCl_3$); IR (KBr): 3230, 2910, 1450, 1370, 1040; ^{1}H-NMR (90 MHz, $CDCl_3$): δ 0.84 (d, 6.0 Hz, 25-Me_2), 1.08 (s, 13-Me), 1.11 (d, J = 6.5 Hz, 20-Me), 1.15 (s, 10-Me), 3.4–3.8 (m, 3-H), 4.47 (dd, 2.7, 4.7 Hz, 15-H), 5.2–5.4 (m, 6-H), 5.52 (d, 2.7 Hz, 16-H).

3β - t - Butyldimethylsiloxy - 15β - hydroxycholest - 5 - ene (**33**)

Compound **31** (60 mg, 0.15 mmol) was hydrogenated in EtOAc (3 ml) with PtO_2 (10 mg) under 30 atm of H_2 for 1 hr to give **32**; HPLC retention time (7.7–8.2 min, 4 ml/min, 5% isopropyl alcohol in hexane); IR (KBr): 3300, 2900, 1460, 1375, 1045, 1015, 960, 930; ^{1}H-NMR (90 MHz, $CDCl_3$): δ 0.87 (d, 6 Hz, 20-Me), 0.88 (d, 7 Hz, 25-Me_2), 0.95 (s, 13-Me), 1.04 (s, 10-Me), 3.4–3.8 (m, 3-H), 4.16 (br t, 6 Hz, 15-H), 5.3–5.5 (m, 6-H).

To a soln of **32** (50 mg, 0.12 mmol) and imidazole (24.5 mg, 0.36 mmol) in dry DMF (10 ml) was added t-BuMe_2SiCl (27.1 mg, 0.18 mmol) at −20°. The mixture was stirred for 2 hr at this temp. After the usual work-up, the residue was purified by preparative silica gel HPLC (4.5 ml/min, 2% EtOAc in hexane) to afford **33** (58 mg, 76% overall yield from **31**); HPLC retention time 23.5–26.5 min; EI-MS: 516 $[M]^+$, 459 $[M-t\text{-}Bu]^+$, 441 $[M-t\text{-}Bu-H_2O]^+$; IR (KBr): 3550, 2950, 1450, 1385, 1250, 1080, 890, 840, 775; ^{1}H-NMR (360 MHz, $CDCl_3$): δ 0.06 (s, Si—Me_2), 0.85 (d, 7 Hz, 20-Me), 0.88 (d, 7 Hz, 25-Me_2), 0.90 (s, Si—CMe_3), 0.95 (s, 13-Me), 1.04 (s, 10-Me), 1.35 (ddd, 2, 10, 15 Hz, 16-H), 2.37 (dt, 8, 15 Hz, 16-H), 3.49 (tt, 5, 11 Hz, 3-H), 4.18 (ddd, 2.5, 8 Hz, 15-H), 5.34 (br d, 5 Hz, 6-H).

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