Syntheses of (20*R*)- and (20*S*)-1α,3β-Diacetoxypregna-5,7-dien-20-ol and 1α,3β-Diacetoxyandrosta-5,7-dien-17β-ol

Yoji TACHIBANA

Research Center, Nisshin Flour Milling Co., Ltd., Tsurugaoka, Ooimachi, Iruma-gun, Saitama 356, Japan.
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Syntheses of (20*R*)- and (20*S*)-1α,3β-diacetoxypregna-5,7-dien-20-ol (1 and 2), important synthetic intermediates for the preparation of 1α,25-dihydroxy-22-oxa-vitamin D_3 derivatives, were achieved starting from pregnenolone. Similar treatment of androst-5-ene-3β,17β-diol afforded 1α,3β-diacetoxyandrosta-5,7-dien-17β-ol.

Keywords 1α,25-dihydroxy-22-oxa-vitamin D_3; pregnenolone; androst-5-ene-3β,17β-diol; 1α,3β-diacetoxypregna-5,7-dien-20-ol; 1α,3β-diacetoxyandrosta-5,7-dien-17β-ol; 1α,25-dihydroxy-20-oxa-vitamin D_3

The active form of vitamin D_3, namely 1α,25-dihydroxyvitamin D_3 in addition to its traditional role in calcium homeostasis, plays a role in cellular differentiation.[1] This has led to increased interest in the possible use of vitamin D_3 and its analogues in the treatment of certain cancers and skin diseases.[2,3] Thus great efforts have been made to separate the various physiological activities. Along this line, Maruyama *et al.* synthesized 1α,25-dihydroxy-22-oxa-vitamin D_3,[4] which showed increased activity in causing differentiation of human myeloid leukemia cells (HL-60) into macrophages while having a markedly diminished calcium-immobilizing activity *in vivo* compared with 1α,25-dihydroxyvitamin D_3. They synthesized this active form of vitamin D_3 from 1α-hydroxyepiandrosterone[5] obtainable by microbiological 1α-hydroxylation of dehydroepiandrosterone.[6]

Creation of the correct natural configuration at C-20 in the side chain is an important problem. Further, preparation of the unnatural epimer is also attracting attention because steroids having unnatural configuration at C-20 show interesting biological activities different from those of natural epimers.[7] Employment of naturally occurring products which have the desired configuration would be a convenient approach. In addition, construction of the 5,7-diene in the steroid moiety is required for the syntheses of provitamin D derivatives (precursor of vitamin D). However, bromination and subsequent dehydrobromination of the 5-ene derivative to form the steroidal 5,7-diene moiety generally give a poor yield because of the formation of considerable amounts of the undesired 4,6-diene isomer.[8]

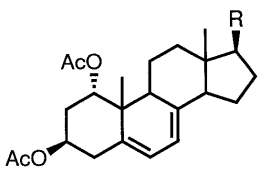
Here, we describe convenient syntheses of 1α-hydroxylated pregna-5,7-diene and androsta-5,7-diene derivatives (**1**—**4**), which can serve as steroidal synthons for the preparation of 1α,25-dihydroxy-22- and 20-oxa-vitamin D_3 derivatives,[9] starting from commercially available pregnenolone and androst-5-ene-3β,17β-diol.

The synthetic procedure is outlined in Chart 2. (20*R*)-Acetoxy pregna-1,4,6-trien-3-one (**5**),[10] readily available from pregnelone, was reacted with isopropenyl acetate in the presence of *p*-toluenesulfonic acid to obtain an enol acetate, 3,20*R*-diacetoxypregna-1,3,5,7-tetraene (**8**).[11] The reduction of the tetraene (**8**) with calcium borohydride and treatment of the resulting 5,7-diene with 4-phenyl-3*H*-1,2,4-triazolidine-3,5(4*H*)-dione (PTAD) gave the Diels–Alder cycloadduct (**11**).

The hydroxyl group of **11** was protected as a *tert*-butyldimethylsilyl ether derivative (**14**) to perform selective α-epoxidation.[12] The C-20 acetate of the silyl ether (**14**) was hydrolyzed on treatment with ethanolic potassium hydroxide to provide the C-20 alcohol (**17**). The hydroxyl group at C-20 of **17** was protected as a tetrahydropyranyl ether (THP) derivative on treatment with 3,4-dihydro-2*H*-pyran (DHP) under acidic conditions to distinguish it chemically from the hydroxyl groups at the C1 and C3 position in a later step. Each diastereomer of the THP ether (**20**) was clearly separable on silica-gel chromatography. The THP ether (**20**) was oxidized with excess *m*-chloroperbenzoic acid (*m*-CPBA) to produce the 1α,2α-epoxide (**23**) selectively. The orientation of the epoxide was confirmed by comparing the ^{1}H-NMR spectrum of **23** with those of the established 1α,2α-epoxide derivatives.[12] After the removal of the silyl group by treatment with tetrabutylammonium fluoride (Bu_4NF) tetrahydrofuran solution, the epoxy alcohol (**26**) was subjected to reduction with lithium aluminum hydride to afford the diol (**29**). The acetylation of **29** with acetic anhydride in pyridine and the subsequent cleavage of the THP group in ethanol under acidic conditions furnished the target compound, (20*R*)-1α,3β-diacetoxypregna-5,7-dien-20-ol (**1**).

In a similar manner, (20*S*)-1α,3β-diacetoxypregna-5,7-dien-20-ol (**2**) and, 1α,3β-diacetoxyandrosta-5,7-dien-17β-ol (**3**) were synthesized. The oxidation of **3** gave 1α,3β-diacetoxyandrosta-5,7-dien-17-one (**4**).

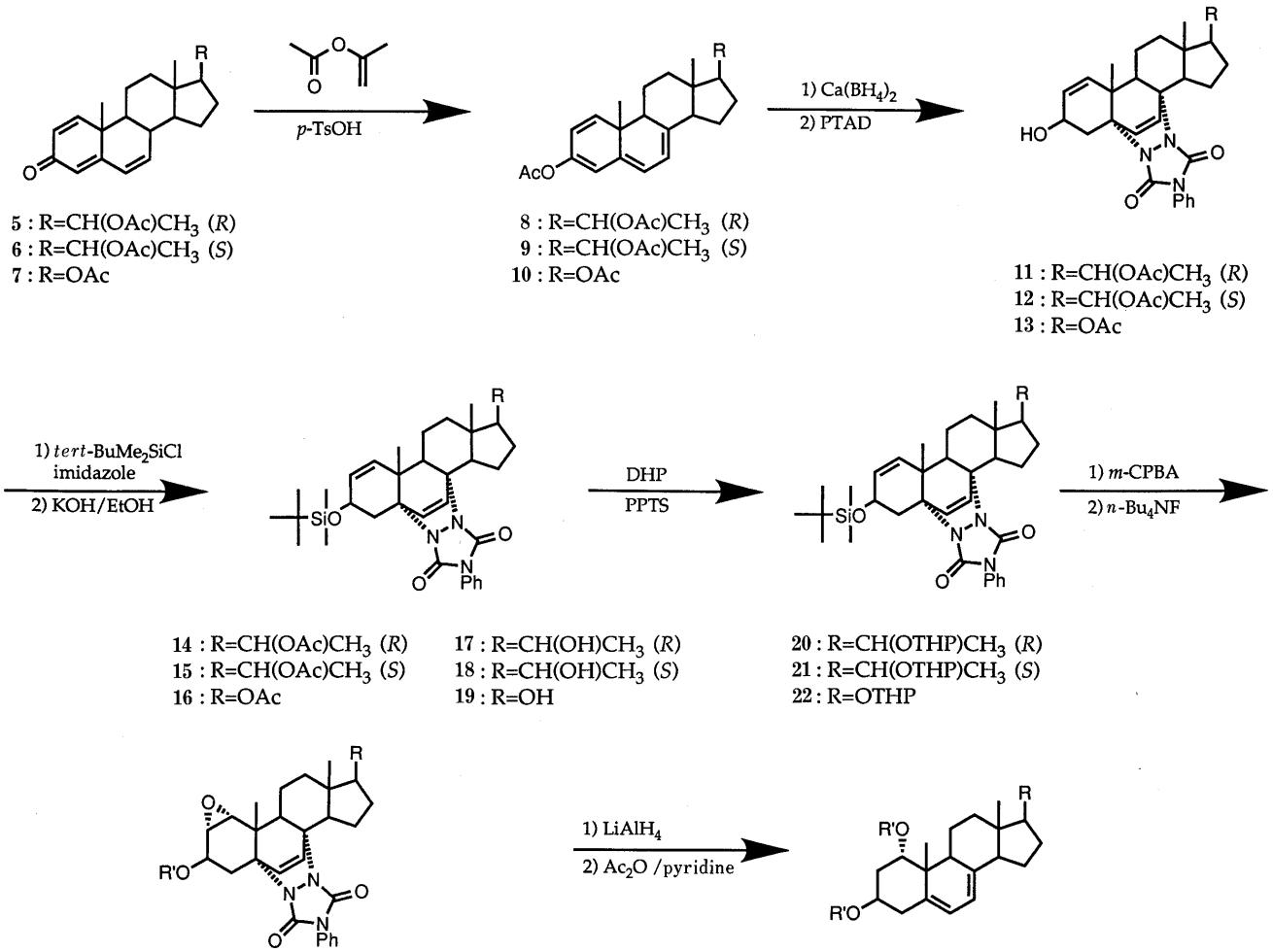
The methodology described in this paper represents a versatile and convenient synthetic strategy for the preparation of 1α-hydroxylated analogues of provitamin D modified in the side chain.



1 : R=CH(OH)CH_3 (*R*)
2 : R=CH(OH)CH_3 (*S*)
3 : R=OH
4 : R=O

(Ac=$COCH_3$)

Chart 1



5 : R=CH(OAc)CH_3 (*R*)
6 : R=CH(OAc)CH_3 (*S*)
7 : R=OAc

8 : R=CH(OAc)CH_3 (*R*)
9 : R=CH(OAc)CH_3 (*S*)
10 : R=OAc

11 : R=CH(OAc)CH_3 (*R*)
12 : R=CH(OAc)CH_3 (*S*)
13 : R=OAc

14 : R=CH(OAc)CH_3 (*R*)
15 : R=CH(OAc)CH_3 (*S*)
16 : R=OAc

17 : R=CH(OH)CH_3 (*R*)
18 : R=CH(OH)CH_3 (*S*)
19 : R=OH

20 : R=CH(OTHP)CH_3 (*R*)
21 : R=CH(OTHP)CH_3 (*S*)
22 : R=OTHP

23 : R=CH(OTHP)CH_3 (*R*)
R'=*tert*-$BuMe_2Si$
24 : R=CH(OTHP)CH_3 (*S*)
R'=*tert*-$BuMe_2Si$
25 : R=OTHP
R'=*tert*-$BuMe_2Si$

26 : R=CH(OTHP)CH_3 (*R*)
R'=H
27 : R=CH(OTHP)CH_3 (*S*)
R'=H
28 : R=OTHP
R'=H

29 : R=CH(OTHP)CH_3 (*R*)
R'=H
30 : R=CH(OTHP)CH_3 (*S*)
R'=H
31 : R=OTHP
R'=H

32 : R=CH(OTHP)CH_3 (*R*)
R'=Ac
33 : R=CH(OTHP)CH_3 (*S*)
R'=Ac
34 : R=OTHP
R'=Ac

Chart 2

Experimental

Melting points are uncorrected. UV spectra are taken on a Hitachi 320 spectrometer. ^{1}H-NMR spectra were recorded in $CDCl_3$ on a JEOL FX200 spectrometer with TMS as an internal standard. Mass spectra were measured on a Hitachi M-80 mass spectrometer. IR spectra were recorded on a Jasco IR-810 spectrometer. Solvents were dried over anhydrous sodium sulfate and removed under reduced pressure.

(20*R*)-Acetoxypregna-1,4,6-trien-3-one (5) A dioxane solution (500 ml) of (20*R*)-pregn-5-ene-3β,20-diol (25.0 g, 69.2 mmol) and 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (75.0 g, 330 mol) was refluxed for 16 h. The solution was filtered to remove the hydroquinone formed. The filtrate was concentrated and the residue was extracted with ethyl acetate. The solution was washed with 10% KOH solution and brine, and evaporated. The residue was purified by silica gel chromatography (chloroform–ethyl acetate, 95 : 5, v/v). The product (15.6 g, 43.2 mmol) was allowed to react with acetic anhydride (15 ml, 147.0 mmol) in pyridine (50 ml) at 90°C for 1 h. The solution was extracted with ethyl acetate, washed with $NaHCO_3$ solution and brine, and chromatographed on silica gel (chloroform) to give **5** (14.3 g, 51%). mp 162—163 °C (methanol) MS *m/z*: 355 (M^+). ^{1}H-NMR δ: 5.97—7.09 (5H, m, 1-H, 2-H, 4-H, 6-H, 7-H), 4.86 (1H, m, 20-H), 2.00 (3H, s, $COCH_3$), 1.17 (3H, d, J=6.0 Hz, 21-CH_3), 1.14 (3H, s, 19-CH_3), 0.76 (3H, s, 18-CH_3). IR (Nujol): 1720, 1660, 1610, 1580, 1240, 890 cm^{-1}. *Anal.* Calcd for $C_{23}H_{30}O_3$: C, 77.91; H, 8.55. Found: C, 77.96; H, 8.53.

(20*S*)-Acetoxypregna-1,4,6-trien-3-one (6) In the same manner, (20*S*)-pregn-5-ene-3β,20-diol (10.0 g) was converted into **6** (oil) (4.1 g, 37%). ^{1}H-NMR δ: 5.97—7.09 (5H, m, 1-H, 2-H, 4-H, 6-H, 7-H), 4.91 (1H, m, 20-H), 2.01 (3H, s, $COCH_3$), 1.23 (3H, d, J=8.0 Hz, 21-CH_3), 1.18 (3H, s, 19-CH_3), 0.80 (3H, s, 18-CH_3).

(20*R*)-3,20-Diacetoxypregna-1,3,5,7-tetraene (8) A solution of the trienone (**5**) (14.3 g, 40.3 mmol) and isopropenyl acetate (150 ml) in butyl acetate (150 ml) was heated under reflux for 10 h. The solution was washed with $NaHCO_3$ solution and brine. Evaporation of the solvent left a solid, which was recrystallized from methanol to afford **8** (7.1 g, 44%). mp 159—160 °C. MS *m/z*: 397 (M^+). ^{1}H-NMR δ: 5.63—5.97 (5H, m, 1-H, 2-H, 4-H, 6-H, 7-H), 4.89 (1H, m, 20-H), 2.06, 2.17 (6H, s, $COCH_3$), 1.17 (3H, d, J=6.0 Hz, 21-CH_3), 0.77 (3H, s, 19-CH_3), 0.60 (3H, s, 18-CH_3). IR (Nujol): 1770, 1730, 1255, 1200 cm^{-1}. *Anal.* Calcd for $C_{25}H_{32}O_4$: C, 75.71; H, 8.15. Found: C, 75.62; H, 8.14.

(20*S*)-3,20-Diacetoxypregna-1,3,5,7-tetraene (9) In the same manner, the trienone (**6**) (4.1 g) was converted into **9** (1.6 g, 35%). mp 148—149 °C (methanol). ^{1}H-NMR δ: 5.65—6.00 (5H, m, 1-H, 2-H, 4-H, 6-H, 7-H), 4.89 (1H, m, 20-H), 2.00, 2.17 (6H, s, $COCH_3$), 1.23 (3H, d, J=8.0 Hz, 21-CH_3), 0.77 (3H, s, 19-CH_3), 0.63 (3H, s, 18-CH_3). IR (Nujol): 1750, 1725, 1240, 1210 cm^{-1}.

3,17β-Diacetoxyandrosta-1,3,5,7-tetraene (10) In the same manner as described above, the trienone[13] (**7**) (6.5 g, 19.5 mmol) was converted to **10** (3.8 g, 52%). mp 160—161 °C (methanol). MS *m/z*: 369 (M^+), 309

($M^+ - CH_3COOH$), 249 ($309 - CH_3COOH$). ^{1}H-NMR δ: 5.57—6.04 (5H, m, 1-H, 2-H, 4-H, 6-H, 7-H), 4.75 (1H, m, 17-H), 2.06, 2.20 (6H, s, $COCH_3$), 0.91 (3H, s, 19-CH_3), 0.76 (3H, s, 18-CH_3). IR (Nujol): 1770, 1740, 1645, 1250, 1200 cm^{-1}. *Anal.* Calcd for $C_{23}H_{28}O_4$: C, 74.96; H, 7.67. Found: C, 74.98; H, 7.67.

(20*R*)-Acetoxy-5α,8α-(4-phenyl-3,5-dioxo-1,2,4-triazolidine-1,2-diyl)-pregna-1,6-dien-3β-ol (11) An ethanol solution (300 ml) of $NaBH_4$ (20 g, 526 mmol) was added dropwise to a solution of $CaCl_2$ (40 g (350 mmol) in 400 ml of methanol) at 0——5 °C, and the mixture was kept at the same temperature for 1 h. An ether solution (300 ml) of **8** (7.1 g, 17.9 mmol) was added dropwise to the calcium borohydride solution at −10——15 °C. The mixture was stirred at the same temperature for 3 h and then at room temperature overnight. Next, 50% acetic acid was added at below 0 °C to give a clear solution. This solution was extracted with ethyl acetate, and the extract was washed with $NaHCO_3$ solution and brine. Then PTAD was added portionwise until a faint pink color persisted. The solution was concentrated and the residue was purified by silica gel chromatography (chloroform–ethyl acetate, 9 : 1, v/v) to give **11** (amorphous solid) (6.7 g, 71%). MS *m/z*: 357 ($M^+ - 175$). ^{1}H-NMR δ: 7.37 (5H, m, C_6H_5), 6.29, 6.43 (2H, ABq, J=8.0 Hz, 6-H, 7-H), 5.86 (2H, s, 1-H, 2-H), 5.03 (1H, t, 20-H), 2.04 (3H, s, $COCH_3$), 1.17 (3H, d, J=6.0 Hz, 21-CH_3), 0.91 (3H, 19-CH_3), 0.77 (3H, s, 18-CH_3). IR (Nujol): 3420, 1745, 1700, 1240 cm^{-1}.

(20*S*)-Acetoxy-5α,8α-(4-phenyl-3,5-dioxo-1,2,4-triazolidine-1,2-diyl)-pregna-1,6-dien-3β-ol (12) In the same manner as described above, the diacetate (**9**) (1.6 g) was converted into **12** (amorphous solid) (1.6 g, 75%). ^{1}H-NMR δ: 7.44 (5H, m, C_6H_5), 6.26, 6.43 (2H, ABq, J=8.0 Hz, 6-H, 7-H), 5.71 (2H, s, 1-H, 2-H), 4.97 (2H, m, 3-H, 20-H), 2.00 (3H, s, $COCH_3$), 1.24 (3H, d, J=8.0 Hz, 21-CH_3), 1.01 (3H, s, 19-CH_3), 0.80 (3H, s, 18-CH_3).

17β-Acetoxy-5α,8α-(4-phenyl-3,5-dioxo-1,2,4-triazolidine-1,2-diyl)-androsta-1,6-dien-3β-ol (13) In the same manner as described for **11**, the diacetate (**10**) (3.8 g) was converted into **13** (amorphous solid) (4.2 g, 80%). MS *m/z*: 329 ($M^+ - 175$). ^{1}H-NMR δ: 7.40 (5H, m, C_6H_5), 6.29, 6.43 (2H, ABq, J=8.0 Hz, 6-H, 7-H), 5.71 (2H, s, 1-H, 2-H), 5.00 (1H, t, 3-H), 4.76 (1H, t, 17-H), 2.04 (3H, s, $COCH_3$), 1.06 (3H, s, 19-CH_3), 0.90 (3H, s, 18-CH_3).

(20*R*)-Acetoxy-3β-(*tert*-butyldimethylsililoxy)-5α,8α-(4-phenyl-3,5-dioxo-1,2,4-triazolidine-1,2-diyl)pregna-1,6-diene (14) *tert*-Butylidimethylsilyl chloride (3.5 g, 23.2 mmol) and imidazole (3.5 g, 51.4 mmol) were added to a *N*,*N*-dimethylformamide (DMF) solution (20 ml) of **11** (6.7 g, 12.6 mmol). The mixture was warmed at 40 °C for 1 h and extracted with ether. The solution was washed with brine and evaporated to produce **14** as an amorphous solid (7.0 g, 86%). MS *m/z*: 471 ($M^+ - 175$). ^{1}H-NMR δ: 7.37 (5H, m, C_6H_5), 6.26, 6.41 (2H, ABq, J=8.0 Hz, 6-H, 7-H), 5.66 (2H, s, 1-H, 2-H), 4.93 (1H, m, 3-H), 4.84 (1H, m, 20-H), 2.03 (3H, s, $COCH_3$), 1.17 (3H, d, J=6.0 Hz, 21-CH_3), 1.07 (3H, s, 19-CH_3), 0.90 (9H, s, *tert*-Bu), 0.77 (3H, s, 18-CH_3), 0.09, 0.10 (6H, s, Si–CH_3).

(20*S*)-Acetoxy-3β-(*tert*-butyldimethylsilyloxy)-5α,8α-(4-phenyl-3,5-dioxo-1,2,4-triazolidine-1,2-diyl)pregna-1,6-diene (15) In the same manner as described for **14**, **12** (1.7 g) was converted into **15** (1.0 g, 52%). mp 196—198 °C (methanol). ^{1}H-NMR δ: 7.37 (5H, m, C_6H_5), 6.26, 6.43 (2H, ABq, J=8.0 Hz, 6-H, 7-H), 5.66 (2H, s, 1-H, 2-H), 4.99 (2H, m, 3-H, 20-H), 2.00 (3H, s, $COCH_3$), 1.22 (3H, d, J=8.0 Hz, 21-CH_3), 1.10 (3H, s, 19-CH_3), 0.91 (9H, s, *tert*-Bu), 0.80 (3H, s, 18-CH_3), 0.09, 0.10 (6H, s, Si–CH_3). IR (Nujol): 1750, 1700, 1260, 1045 cm^{-1}. *Anal.* Calcd for $C_{37}H_{51}N_3O_5$ Si: C, 68.79; H, 7.97; N, 6.51. Found: C, 68.88; H, 7.96; N, 6.41.

17β-Acetoxy-3β-(*tert*-butyldimethylsilyloxy)-5α,8α-(4-phenyl-3,5-dioxo-1,2,4-triazolidine-1,2-diyl)androsta-1,6-diene (16) In the same manner as described for **14**, **13** (4.2 g, 8.3 mmol) was converted into **16** (4.0 g, 78%). mp 205—206 °C (ethanol). MS *m/z*: 443 ($M^+ - 175$). ^{1}H-NMR δ: 7.41 (5H, m, C_6H_5), 6.28, 6.41 (2H, ABq, J=8.0 Hz, 6-H, 7-H), 5.70 (2H, s, 1-H, 2-H), 4.98 (1H, m, 3-H), 4.76 (1H, m, 17-H), 2.03 (3H, s, $COCH_3$), 1.06 (3H, s, 19-CH_3), 0.90 (12H, s, *tert*-Bu, 18-CH_3), 0.09, 0.10 (6H, s, Si–CH_3). IR (Nujol): 1755, 1705, 1690, 1240, 1055 cm^{-1}. *Anal.* Calcd for $C_{35}H_{47}O_5N_3Si$; C, 68.02; H, 7.68; N, 6.80. Found: C, 68.24; H, 7.65; N, 6.77.

(20*R*)-3β-(*tert*-Butyldimethylsilyloxy)-5α,8α-(4-phenyl-3,5-dioxo-1,2,4-triazolidine-1,2-diyl)pregna-1,6-dien-20-ol (17) An ethanolic potassium hydroxide solution (KOH 4.0 g (71.4 mmol) in 50 ml of ethanol) was added to an ethanol solution (30 ml) of **14** (7.0 g, 10.8 mmol). The mixture was stirred at room temperature for 30 min. Water was added and the whole was extracted with ethyl acetate. The solution was washed with brine, dried and evaporated to afford **17** (5.7 g, 87%). mp 203—205 °C (isopropyl ether). MS *m/z*: 429 ($M^+ - 175$). ^{1}H-NMR δ: 7.37 (5H, m, C_6H_5), 6.26, 6.43 (2H, ABq, J=8.0 Hz, 6-H, 7-H), 5.69 (2H, s, 1-H, 2-H), 4.97 (1H, t, 3-H), 3.70 (1H, m, 20-H), 1.14 (3H, d, J=6.0 Hz, 21-CH_3), 1.09 (3H, s, 19-CH_3), 0.89 (12H, m, *tert*-Bu, 18-CH_3), 0.09, 0.10 (6H, s, Si–CH_3). IR (Nujol): 3510, 3425, 1755, 1700, 1500, 1260, 1040 cm^{-1}. *Anal.* Calcd for $C_{35}H_{49}N_3O_4Si$: C, 69.60; H, 8.19; N, 6.96. Found: C, 69.49; H, 8.20; N, 6.94.

(20*S*)-3β-(*tert*-Butyldimethylsilyloxy)-5α,8α-(4-phenyl-3,5-dioxo-1,2,4-triazolidine-1,2-diyl)pregna-1,6-dien-20-ol (18) In the same manner as described for **17**, **15** (1.0 g) was converted into **18** (930 mg, 99%). ^{1}H-NMR δ: 7.37 (5H, m, C_6H_5), 6.26, 6.43 (2H, ABq, J=8.0 Hz, 6-H, 7-H), 5.66 (2H, s, 1-H, 2-H), 4.99 (1H, m, 3-H), 3.77, (1H, m, 20-H), 1.23 (3H, d, J=6.0 Hz, 21-CH_3), 1.08 (3H, s, 19-CH_3), 0.90 (9H, s, *tert*-Bu), 0.80 (3H, s, 18-CH_3), 0.09, 0.10 (6H, s, Si–CH_3). IR (Nujol): 3400, 1760, 1705, 1500, 1260, 1070 cm^{-1}.

3β-(*tert*-Butyldimethylsilyloxy)-5α,8α-(4-phenyl-3,5-dioxo-1,2,4-triazolidine-1,2-diyl)androsta-1,6-dien-17β-ol (19) In the same manner as described for **17**, **16** (4.0 g) was converted into **19** (amorphous solid) (3.4 g, 90%). MS *m/z*: 401 ($M^+ - 175$), 383 ($401 - H_2O$). ^{1}H-NMR δ: 7.40 (5H, m, C_6H_5), 6.24, 6.46 (2H, ABq, J=8.0 Hz, 6-H, 7-H), 5.69 (2H, s, 1-H, 2-H), 4.94 (1H, t, 3-H), 3.76 (1H, m, 17-H), 1.07 (3H, s, 19-CH_3), 0.90 (9H, s, *tert*-Bu), 0.88 (3H, s, 18-CH_3), 0.10, 0.11 (6H, s, Si–CH_3).

(20*R*)-3β-(*tert*-Butyldimethylsilyloxy)-5α,8α-(4-phenyl-3,5-dioxo-1,2,4-triazolidine-1,2-diyl)-20-tetrahydropyranyloxypregna-1,6-diene (20) A dichloromethane solution (100 ml) of **17** (5.7 g, 9.4 mmol), 3,4-dihydro-2*H*-pyran (3.0 g, 35.7 mmol) and pyridinium *p*-toluenesulfonate (300 mg, 1.2 mmol) was stirred for 3 h at room temperature. The solvent was removed and the residue was extracted with ether. The ether solution was washed with brine, dried and concentrated to give the diastereomeric mixture as an amorphous solid (4.98 g, 75%). The crude product was chromatographed on silica gel (chloroform–hexane, 1 : 2, v/v) to afford a less polar product (2.3 g) and a more polar product (2.1 g). Less polar product: mp 196—198 °C (chloroform–ether). MS *m/z*: 513 ($M^+ - 175$). ^{1}H-NMR δ: 7.37 (5H, m, C_6H_5), 6.26, 6.44 (2H, ABq, J=8.0 Hz, 6-H, 7-H). 5.66 (2H, s, 1-H, 2-H), 4.97 (1H, t, 3-H), 4.60 (1H, s, CH(THP)), 3.90 (2H, m, CH_2(THP), 20-H), 3.57 (1H, m, CH_2(THP)), 1.07 (6H, m, 21-CH_3, 19-CH_3), 0.90 (12H, s, *tert*-Bu, 18-CH_3), 0.09, 0.10 (6H, s, Si–CH_3). IR (Nujol): 1755, 1710, 1400, 1255, 1030 cm^{-1}. *Anal.* Calcd for $C_{40}H_{57}N_3O_5Si$: C, 69.82; H, 8.37; N, 6.11. More polar product: mp 188—190 °C (ether–hexane). ^{1}H-NMR δ: 7.37 (5H, m, C_6H_5), 6.26, 6.44 (2H, ABq, J=8.0 Hz, 6-H, 7-H), 5.67 (2H, m, 1-H, 2-H), 4.97 (1H, t, 3-H), 4.60 (1H, s, CH(THP)), 3.90 (2H, m, CH_2(THP), 20-H), 3.58 (1H, m, CH_2(THP)), 1.22 (3H, d, J=6.0 Hz, 21-CH_3), 1.08 (3H, s, 19-CH_3), 0.90 (9H, s, *tert*-Bu), 0.80 (3H, s, 18-CH_3), 0.09, 0.10 (6H, s, Si–CH_3).

(20*S*)-3β-(*tert*-Butyldimethylsilyloxy)-5α,8α-(4-phenyl-3,5-dioxo-1,2,4-triazolidine-1,2-diyl)-20-tetrahydropyranyloxypregna-1,6-diene (21) In the same manner as described for **20**, **18** (930 mg) was converted into **21** (oil) (960 mg, 91%). ^{1}H-NMR δ: 7.38 (5H, m, C_6H_5), 6.26, 6.43 (2H, ABq, J=8.0 Hz, 6-H, 7-H), 5.66 (2H, s, 1-H, 2-H), 4.94 (1H, m, 3-H), 4.63, 4.70 (1H, s, CH(THP)), 3.91 (2H, m, 20-H, CH_2(THP)), 3.51 (1H, m, CH_2(THP)), 1.14, 1.29 (3H, dd, J_1=J_2=6.0 Hz, 21-CH_3), 1.09 (3H, s, 19-CH_3), 0.90 (9H, s, *tert*-Bu), 0.77, 0.83 (3H, s, 18-CH_3), 0.90, 0.10 (6H, s, Si–CH_3). IR (Nujol): 1760, 1710, 1500, 1070 cm^{-1}.

3β-(*tert*-Butyldimethylsilyloxy)-5α,8α-(4-phenyl-3,5-dioxo-1,2,4-triazolidine-1,2-diyl)-17β-tetrahydropyranyloxyandrosta-1,6-diene (22) In the same manner as described for **20**, **19** (3.4 g) was converted into **22** (oil) (3.6 g, 92%). MS *m/z*: 485 ($M^+ - 175$), 401 ($485 - THP$). ^{1}H-NMR δ: 7.40 (5H, m, C_6H_5), 6.26, 6.44 (2H, ABq, J=8.0 Hz, 6-H, 7-H), 5.66 (2H, s, 1-H, 2-H), 4.94 (1H, t, 3-H), 4.57 (1H, s, CH(THP)), 3.80 (2H, m, CH_2(THP), 17-H), 3.49 (1H, m, CH_2(THP)), 1.06 (3H, s, 19-CH_3), 0.90 (12H, s, *tert*-Bu, 18-CH_3), 0.09, 0.10 (6H, s, Si–CH_3).

(20*R*)-1α,2α-Epoxy-5α,8α-(4-phenyl-3,5-dioxo-1,2,4-triazolidine-1,2-diyl)-20-tetrahydropyranyloxypregn-6-en-3β-ol (26) A chloroform solution (100 ml) of **20** (4.4 g, 6.4 mmol), and *m*-CPBA (8.0 g, 46.4 mmol) was stirred at room temperature overnight. The solution was washed with 10% K_2CO_3 solution and brine, and evaporated to yield **23** as an oil. The crude product **23** (4.4 g) was dissolved in tetrahydrofuran (50 ml). To this solution, 20 ml of 1 M (1 mol/dm^3) Bu_4NF in tetrahydrofuran was added. The mixture was stirred for 3 h at room temperature, then extracted with ethyl acetate. The extract was washed with brine and evaporated, and the residue was chromatographed on silica gel. Elution

with chloroform–ethyl acetate (9 : 1, v/v) afforded **26** (oil) (2.8 g, 78%). MS *m/z*: 414 ($M^+ - 175$). ^{1}H-NMR δ: 7.41 (5H, m, C_6H_5), 6.20, 6.44 (2H, ABq, J=8.0 Hz, 6-H, 7-H), 5.03 (1H, t, 3-H), 4.65 (1H, s, CH(THP)), 3.51—3.89 (3H, m, 20-H, CH_2(THP)), 1.23 (3H, d, J=6.0 Hz, 21-CH_3), 1.06 (3H, s, 19-CH_3), 0.83 (3H, s, 18-CH_3). IR (Nujol): 3350, 1755, 1680, 1025 cm^{-1}.

(20*S*)-1α,2α-Epoxy-5α,8α-(4-phenyl-3,5-dioxo-1,2,4-triazolidine-1,2-diyl)-20-tetrahydropyranyloxypregn-6-en-3β-ol (27) In the same manner as described for **26**, **21** (960 mg) was converted into **27** (oil) (650 mg, 79%). ^{1}H-NMR δ: 7.38 (5H, m, C_6H_5), 6.19, 6.39 (2H, ABq, J=8.0 Hz, 6-H, 7-H), 4.99 (1H, m, 3-H), 4.60, 4.67 (1H, s, CH(THP)), 3.43—3.97 (3H, m, CH_2(THP), 20-H), 1.14, 1.29 (3H, dd, $J_1 = J_2$=6.0 Hz, 21-CH_3), 1.09 (3H, s, 19-CH_3), 0.77, 0.84 (3H, s, 18-CH_3). IR (Nujol): 3340, 1755, 1680, 1020 cm^{-1}.

1α,2α-Epoxy-5α,8α-(4-phenyl-3,5-dioxo-1,2,4-triazolidine-1,2-diyl)-17β-tetrahydropyranyloxyandrost-6-en-3β-ol (28) In the same manner as described for **26**, **23** (3.5 g) was converted into **28** (oil) (2.0 g, 70%). MS *m/z*: 387 ($M^+ - 175$). ^{1}H-NMR δ: 7.41 (5H, m, C_6H_5), 6.23, 6.47 (2H, ABq, J=8.0 Hz, 6-H, 7-H), 5.03 (1H, t, 3-H), 4.63 (1H, s, CH(THP)), 3.83 (2H, m, CH_2(THP), 17-H), 3.51 (1H, m, CH_2(THP)), 3.23 (2H, m, 1-H, 2-H), 1.09 (3H, s, 19-CH_3), 0.93, 0.94 (3H, s, 18-CH_3).

(20*R*)-1α,3β-Diacetoxy-20-tetrahydropyranyloxypregna-5,7-diene (32) A tetrahydrofuran solution (80 ml) of **26** (2.8 g, 4.8 mmol) was added to a tetrahydrofuran solution (40 ml) of $LiAlH_4$ (4.0 g, 10.5 mmol) at room temperature. The mixture was refluxed for 1 h. After decomposition of the excess $LiAlH_4$ by adding water, the solution was filtered through Celite. The filtrate was extracted with chloroform, washed with brine, dried and concentrated to afford **29**. The crude **29** (1.2 g, 2.9 mmol) was dissolved in pyridine (10 ml), and acetic anhydride (2 ml, 19.6 mmol) was added. The mixture was heated at 90 °C for 1 h and extracted with ethyl acetate. The solution was washed with $NaHCO_3$ solution and brine, and evaporated to give **32** (oil) (900 mg, 36%). MS *m/z*: 441 ($M^+ - CH_3COOH$). ^{1}H-NMR δ: 5.40, 5.70 (2H, m, 6-H, 7-H), 5.03 (2H, m, 1-H, 3-H), 4.70 (1H, s, CH(THP)), 3.89 (2H, m, 20-H, CH_2(THP)), 3.51 (1H, m, CH_3(THP)), 2.03, 2.10 (6H, s, $COCH_3$), 1.17 (3H, d, J=6.0 Hz, 21-CH_3), 0.99 (3H, s, 19-CH_3), 0.80 (3H, s, 18-CH_3).

(20*S*)-1α,3β-Diacetoxy-20-tetrahydropyranyloxypregna-5,7-diene (33) In the same manner as described for **32**, **27** (650 mg) was converted into **33** (oil) (320 mg, 58%). ^{1}H-NMR δ: 5.37, 5.63 (2H, m, 6-H, 7-H), 5.00 (2H, m, 1-H, 3-H), 4.57, 4.67 (1H, s, CH(THP)), 3.46—4.09 (3H, m, CH_2(THP), 20-H), 2.03, 2.09 (6H, s, $COCH_3$), 1.14, 1.29 (3H, dd, $J_1 = J_2$=6.0 Hz, 21-CH_3), 1.00 (3H, s, 19-CH_3), 0.62 (3H, s, 18-CH_3).

1α,3β-Diacetoxy-17β-tetrahydropyranyloxyandrosta-5,7-diene (34) In the same manner as described for **32**, **28** (2.0 g) was converted into **34** (oil) (1.0 g, 62%). MS *m/z*: 413 ($M^+ - CH_3COOH$). ^{1}H-NMR δ: 5.40, 5.67 (2H, m, 6-H, 7-H), 4.98 (2H, m, 1-H, 3-H), 4.63 (1H, s, CH(THP)), 3.87 (1H, m, CH_2(THP)), 3.74 (1H, m, 17-H), 3.49 (1H, m, CH_2(THP)), 2.03, 2.08 (6H, s, $COCH_3$), 1.03 (3H, s, 19-CH_3), 0.71, 0.73 (3H, s, 18-CH_3).

(20*R*)-1α,3β-Diacetoxypregna-5,7-dien-20-ol (1) An ethanol solution (20 ml) of **32** (900 mg, 1.8 mmol) and pyridinium *p*-toluenesulfonate (200 mg, 0.8 mmol) was heated at 40 °C for 3 h. The mixture was extracted with ethyl acetate, washed with brine, and evaporated. The residue was purified by silica gel chromatography. Elution with chloroform–ethyl acetate (9 : 1, v/v) provided **1** (620 mg, 82%). mp 188—189 °C (ether). MS *m/z*: 357 ($M^+ - CH_3COOH$). UV: λ_{max} 282 nm (ε=11500, ethanol). ^{1}H-NMR δ: 5.37, 5.70 (2H, m, 6-H, 7-H), 4.99 (2H, m, 1-H, 3-H), 3.73 (1H, m, 20-H), 2.03, 2.08 (6H, s, $COCH_3$), 1.16 (3H, d, J=6.0 Hz, 21-CH_3), 1.01 (3H, s, 19-CH_3), 0.69 (3H, s, 18-CH_3). IR (Nujol): 3500, 1740, 1720, 1260, 1240, 1025 cm^{-1}. *Anal.* Calcd for $C_{25}H_{36}O_5$: C, 72.07; H, 8.73. Found: C, 71.94; H, 8.76.

(20*S*)-1α,3β-Diacetoxypregna-5,7-dien-20-ol (2) In the same manner as described for **1**, **33** (320 mg) was converted into **2** (oil) (213 mg, 80%). ^{1}H-NMR δ: 5.39, 5.64 (2H, m, 6-H, 7-H), 4.94 (2H, m, 1-H, 3-H), 3.69 (1H, s, 20-H), 2.03, 2.06 (6H,s, $COCH_3$) 1.24 (3H, d, J=6.1 Hz, 21-CH_3), 1.00 (3H, s, 19-CH_3), 0.62 (3H, s, 18-CH_3). UV: λ_{max} 282 nm (ε=11000, ethanol). IR (Nujol): 3400, 1740, 1720, 1600, 1245, 1030 cm^{-1}.

1α,3β-Diacetoxyandrosta-5,7-dien-17β-ol (3) In the same manner as described for **1**, **34** (1.0 g) was converted into **3** (660 mg, 80%). mp 174—175 °C (ether–hexane). MS *m/z*: 329 ($M^+ - CH_3COOH$), 269 ($329 - CH_3COOH$). UV: λ_{max} 282 nm (ε=11500, ethanol). ^{1}H-NMR δ: 5.43, 5.68 (2H, m, 6-H, 7-H), 5.01 (2H, m, 1-H, 3-H), 3.77 (1H, m, 17-H), 2.03, 2.08 (6H, s, $COCH_3$), 1.00 (3H, s, 19-CH_3), 0.69 (3H, s, 18-CH_3). IR (Nujol): 3440, 1740, 1720, 1025 cm^{-1}. *Anal.* Calcd for $C_{23}H_{32}O_5$: C, 71.09; H, 8.32. Found: C, 71.17; H, 8.38.

1α,3β-Diacetoxyandrosta-5,7-dien-17-one (4) A dichloromethane solution (10 ml) of **3** (300 mg, 0.77 mmol) and pyridinium chlorochromate (500 mg, 2.0 mmol) was stirred at room temperature for 1 h. The solution was filtered and the filtrate was evaporated. The residue was chromatographed on silica gel (chloroform–hexane, 4 : 1, v/v) to afford **4** (195 mg, 65%). mp 220—222 °C (ether). MS *m/z*: 327 ($M^+ - CH_3COOH$). ^{1}H-NMR δ: 5.57, 5.71 (2H, m, 6-H, 7-H), 5.00 (2H, m, 1-H, 3-H), 2.04, 2.09 (6H, s, $COCH_3$), 1.03 (3H, s, 19-CH_3), 0.81 (3H, s, 18-CH_3). IR (Nujol): 1745, 1720, 1675, 1240, 1025 cm^{-1}. *Anal.* Calcd for $C_{23}H_{30}O_5$: C, 71.46; H, 7.84. Found: C, 71.20; H, 7.54.

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