

[Chem. Pharm. Bull.]
[32(4)1416—1422(1984)]

Structural Modification of Bioactive Compounds. I. Syntheses of Vitamin D Analogues I¹⁾

KATSUhide MATOBA,* KAKUYA KONDO, and TAKAO YAMAZAKI

*Faculty of Pharmaceutical Sciences, Toyama Medical & Pharmaceutical
University, Sugitani, Toyama 930-01, Japan*

(Received August 10, 1983)

Three vitamin D analogues, (25*R*)-9,10-seco-spirosta-5,7,10(19)-trien-3 β -ol (I), 17 β -(*N*-methyl-*N*-4-methylpentylamino)-9,10-seco-androsta-5,7,10(19)-trien-3 β -ol (II), and (20*S*)-20-isopentylamino-9,10-seco-pregna-5,7,10(19)-trien-3 β -ol (III), were prepared starting from diosgenin (IVa), 3 β -hydroxy-5-androsten-17-one (Va), and 3 β -hydroxy-5-pregnen-20-one (VIa), respectively, *via* the adducts of the corresponding 5,7-dienes and 4-phenyl-1,2,4-triazoline-3,5-dione.

Keywords—vitamin D; diosgenin; 3 β -hydroxy-5-androsten-17-one; 3 β -hydroxy-5-pregnen-20-one; 4-phenyl-1,2,4-triazoline-3,5-dione; photochemistry

Many structural analogues of natural and synthetic compounds having significant biological activities have been synthesized in order to examine structure–activity relationships and mechanisms of biological actions. From such a point of view, we intend to investigate the syntheses of structurally modified bioactive compounds, especially vitamin, amino acid, and steroid analogues in this series of studies. It is anticipated that vitamin D antagonists may be clinically useful for reducing the hypercalcemia associated with a variety of human disorders such as primary and tertiary hyperparathyroidism, vitamin D toxicity, idiopathic hypercalcemia of infancy, sarcoidosis, and hypercalcemia of malignancy. A few reports on vitamin D antagonists have appeared in the literature,²⁾ but none of them has been used as a medicine. We have now synthesized three kinds of vitamin D analogues, (25*R*)-9,10-seco-spirosta-5,7,10(19)-trien-3 β -ol (I), 17 β -(*N*-methyl-*N*-4-methylpentylamino)-9,10-seco-androst-5,7,10(19)-trien-3 β -ol (II), and (20*S*)-20-isopentylamino-9,10-seco-pregna-5,7,10(19)-trien-3 β -ol (III), starting from diosgenin (IVa), 3 β -hydroxy-5-androsten-17-one (Va), and 3 β -hydroxy-5-pregnen-20-one (VIa), respectively.

Diosgenin acetate (IVb) was brominated with *N*-bromosuccinimide (NBS, 1.1 mol eq) by refluxing in *n*-hexane for 15 min³⁾ to give the 7-bromide (VII) as a crystalline compound in a yield of 74.4%. Dehydrobromination of VII was carried out by refluxing in xylene for 90 min in the presence of γ -collidine⁴⁾ to give the crude 5,7-diene (VIII), which exhibits two multiplet signals at δ 5.40 and 5.56 ppm and has $\lambda_{\max}$ 293, 282, and 271 nm absorption in the ultraviolet (UV) spectrum, characteristic of a steroidal 5,7-diene system. To obtain the crystalline 5,7-diene (X), a solution of the crude dehydrobromination product in methylene chloride was treated with a small excess of 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD),⁵⁾ and the resulting adduct was purified by column chromatography on silica gel. The PTAD adduct (IX), mp 170–172 °C, exhibited AB type signals at δ 6.23 and 6.36 ppm (J = 8 Hz) due to the C₆ and C₇ protons, and a broad signal centered at around δ 7.45 ppm due to phenyl protons in the nuclear magnetic resonance (NMR) spectrum. Reduction of IX with lithium aluminum hydride (LAH) gave (25*R*)-spirosta-5,7-dien-3 β -ol (X) as a crystalline compound. This compound exhibited characteristic absorption maxima at 293, 281, and 271 nm in the UV spectrum.

Photochemical conditions suitable to convert X to previtamin D (XI), which was

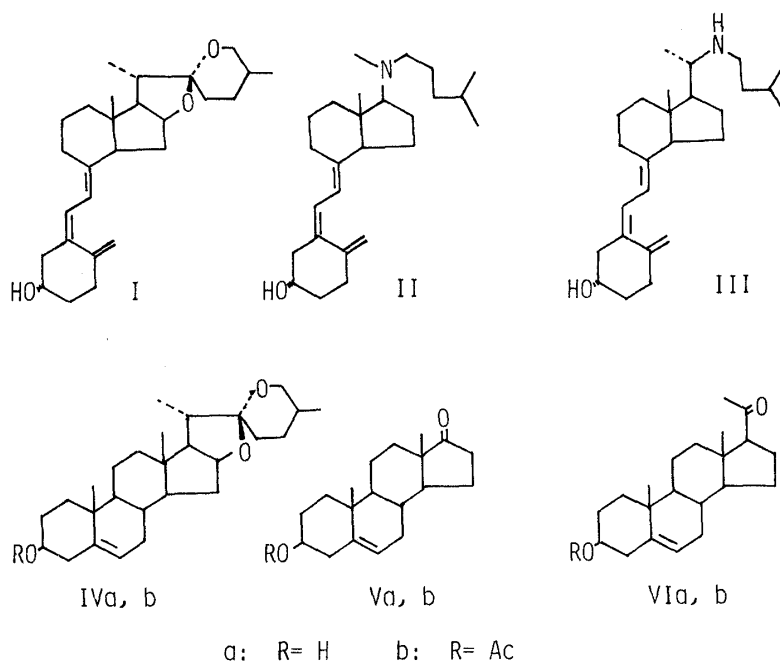


Chart 1

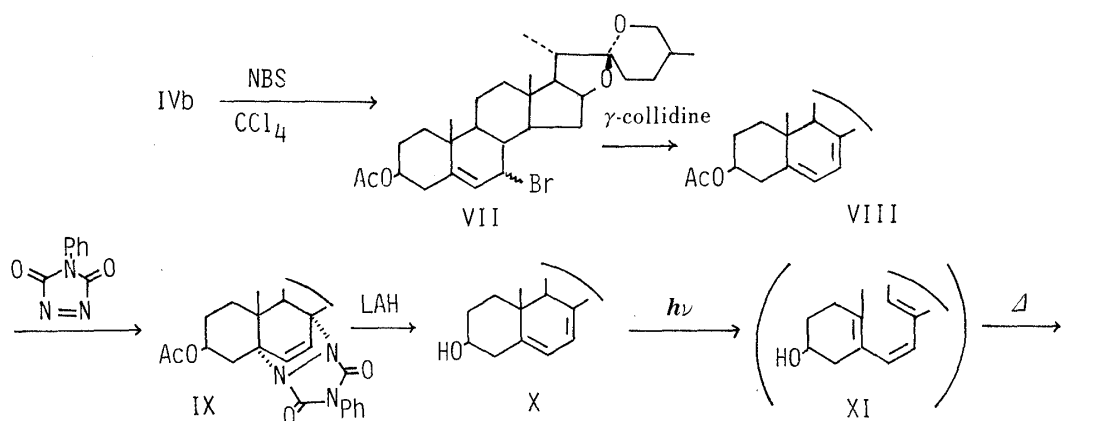


Chart 2

transformed into a vitamin D analogue (I) by refluxing for 1.5 h in benzene, were examined. On the basis of products analysis by high performance liquid chromatography (HPLC) and UV techniques, it was found that the best conditions were to irradiate X in absolute ether for 7 min using a quartz vessel and a high-pressure mercury lamp (200 W) with a Vycor glass filter under a nitrogen atmosphere at below 18 °C. The vitamin D analogue (I) after purification by silica gel column chromatography exhibited $\lambda_{\max}$ 262 nm and $\lambda_{\min}$ 227 nm, and two doublet signals due to exocyclic methylene protons appeared at δ 4.85 and 5.03 ppm.

We next turned our attention to synthesis of the 20-aza analogue of vitamin D (II) from 3 β -hydroxy-5-androsten-17-one (Va). According to the method reported in the literature,⁶⁾ the corresponding acetate (Vb) was converted to the 17 β -amino derivative (XIIa) by treatment with 4-methylpentylamine in the presence of *p*-toluenesulfonic acid in benzene followed by reduction with LAH in dioxane. Unfortunately conversion of XIIa into its N-methyl derivative (XIIb) under the reported conditions was unsuccessful. Therefore, 17 β -methylaminoandrost-5-en-3 β -ol (XIIc), which was prepared from Vb,⁷⁾ was treated with isocaproyl chloride in the presence of triethylamine in benzene to give the amide ester (XIId)

in a yield of 67.5%. It exhibited $\nu_{\max}$ 1730 and 1640 cm^{-1} in the infrared (IR) spectrum due to ester and amide functions, respectively. The NMR spectrum of XIId exhibited two pairs of singlets at δ 0.68, 0.75 and 2.91, 2.86 ppm in the ratio of 2:1 due to the C_{18} - and N-methyl protons, respectively. The phenomenon could be attributed to the two rotational isomers of the amide group. This consideration was supported by the NMR spectrum of XIIf obtained by reduction of XIId with LAH; the C_{18} and N-methyl protons each appeared as a single singlet at δ 0.81 and 2.22 ppm, respectively. The amide ester, XIId, was brominated with NBS in carbon tetrachloride, then dehydrobrominated with γ -collidine in xylene and the crude product was converted to its PTAD adduct (XIII) in an overall yield of 31.5%. In the NMR spectrum of XIII, signals due to the rotational isomers of the amide group were observed in the ratio of 3:1. Anisotropy of neighboring substitutions⁸⁾ affected the C_3 - and C_{14} -protons at δ 5.50 and 3.29 ppm, respectively, whereas in XIId, the C_3 -proton appeared at δ 4.5—4.7 ppm and no signals attributable to C_{14} -proton were seen below δ 3.0 ppm. Unmasking of XIII yielded the amino alcohol (XIV) in 41.4% yield.

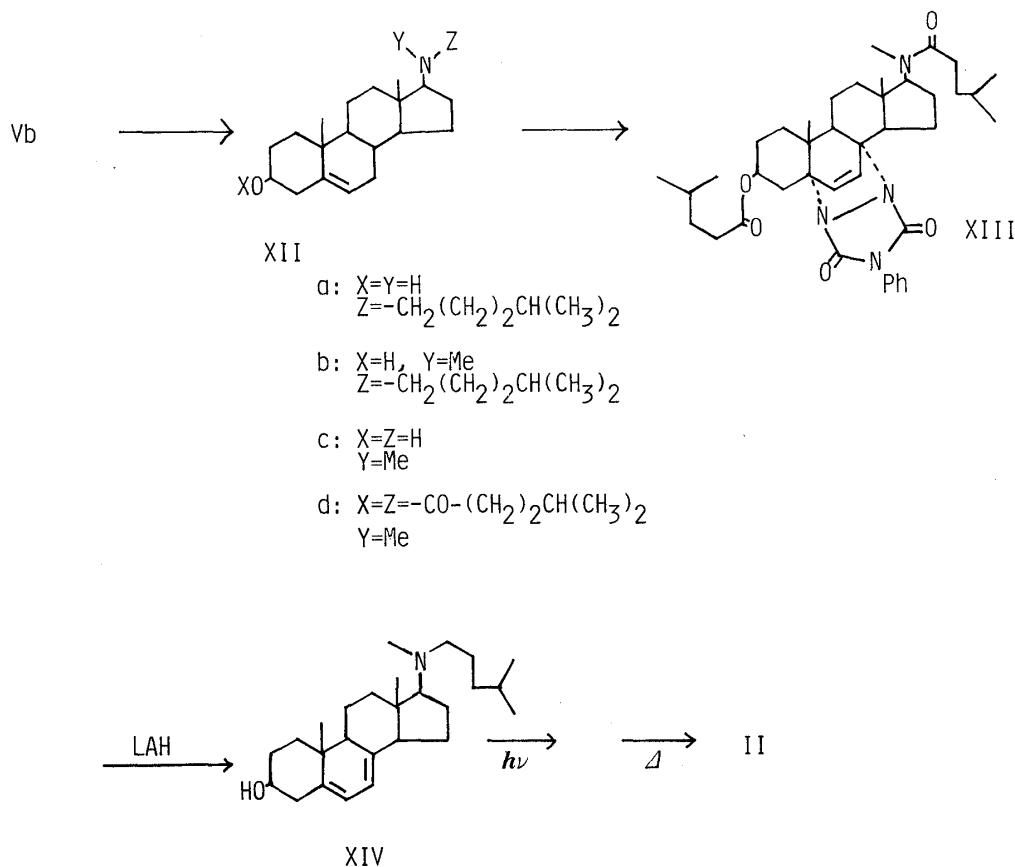
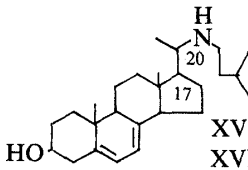
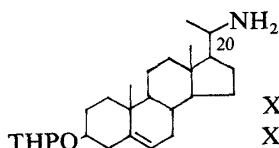


Chart 3

As the 5,7-diene (XIV) was insoluble in ether, the photochemical conditions used for X could not be applied. The best result was obtained by irradiation with a 200 W mercury lamp in a quartz vessel in benzene below 22 °C under an argon atmosphere, followed by refluxing for 1.5 h to give II in 36.1% yield, after chromatography on silica gel. The UV and NMR spectra of II showed the characteristic features of vitamin D.

Finally we shall describe the synthesis of the 22-aza analogue of vitamin D (III). Pregnenolone acetate (Vib) was converted to the PTAD adduct (XV) *via* three steps in a usual manner in an overall yield of 30.0%. XV, mp 181—183 °C, showed AB type signals at δ 6.24 and 6.41 ppm due to the C_6 - and C_7 -vinylic protons and a broad signal centered at around

TABLE I

			
XVIa:	17 β , 20S	XVIIa:	20S
XVIb:	17 β , 20R	XVIIb:	20R
XVIc:	17 α , 20S		
XVI d:	17 α , 20R		

	Polarity on Al ₂ O ₃	Chemical shift	
		C ₁₈ -Me	C ₂₁ -Me
XVIIa	Less polar	0.67 ppm	1.13 ppm
XVIa	Less polar	0.63 ppm	1.11 ppm
XVIIb	More polar	0.77 ppm	1.02 ppm
XVIb, c, d	More polar	0.65, 0.70, 0.76 ppm (3 : 1 : 1)	1.00 ppm

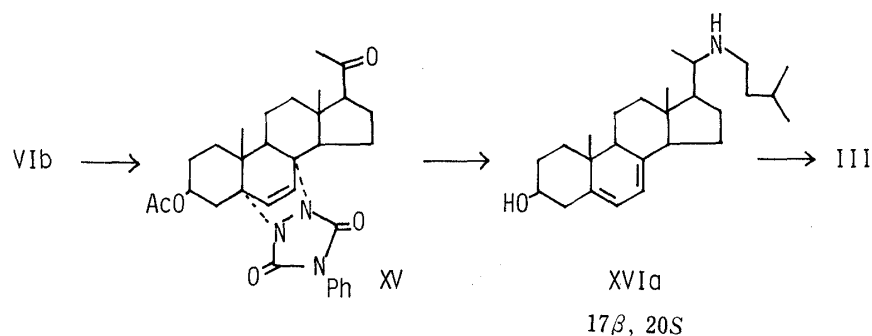


Chart 4

δ 7.40 ppm due to the aromatic protons. XV was treated with isoamylamine in absolute benzene in the presence of a catalytic amount of *p*-toluenesulfonic acid followed by reduction with sodium borohydride to give the crude 22-aza compound, a stereoisomeric mixture at C₁₇ and C₂₀. This was derivatized into the perchlorate, which was then reduced with LAH in dioxane. The crude product was chromatographed on alumina to give the less polar fraction (5.5%) containing the 17 β ,20S isomer (XVIa) and the more polar fraction (4.9%) containing a mixture of the 17 β ,20R, 17 α ,20S, and 17 α ,20R isomers (XVIb, XVIc, and XVI d, respectively). The stereochemical assignments of these isomers were based on analogy with the behavior of the reference compound, (20S)- and (20R)-aminopregnan-3 β -ol tetrahydropyranyl (THP) ethers (XVII),⁹⁾ as shown in Table I.

Formation of the isomers at the C₁₇-position (XVIc and d) can be attributed to imine and enamine tautomerization. The direct reduction of the isoamylimine derivative of XV with LAH gave isomerically pure XVIa and 3 β -hydroxy-5,7-pregnadien-20-one in yields of 12.7 and 3.4%, respectively. It may be that the enamine tautomer of the starting material was inert to reduction with LAH and was hydrolyzed to the 20-ketone during work-up.

To convert XVIa into the vitamin D analogue, III, a benzene solution of XVI was irradiated with a 200 W mercury lamp for 10 min and then refluxed for 1.5 h. Compound III was isolated by column chromatography on silica gel in a yield of 21.5%, and showed the expected spectral properties (see, Experimental).

The biological assay of these synthetic vitamin D analogues, I, II, and III, is in progress.

Experimental

All melting points are uncorrected. IR spectra were determined by using a JASCO IRA-1 diffraction grating spectrometer; absorption data are given in cm^{-1} . NMR spectra were recorded on JEOL PMX-60 and Varian XL-200 spectrometers with tetramethylsilane (TMS) as an internal standard. The chemical shifts and coupling constants (J) are given in δ and Hz, respectively. Mass spectra (MS) were measured with a JEOL JMS D-200 (70 eV, direct inlet system) spectrometer. UV spectra were obtained in MeOH with a Hitachi 200-10 spectrometer, and absorption maxima are given in nm. HPLC was done on a Waters 244 instrument with radial pack A and B (8 m/m $\times$ 10 cm) for reverse and normal phase separation, respectively. The velocity of the solvent in HPLC was 2 ml/min. Specific rotation ($[\alpha]_D$) were obtained in CHCl_3 with a JASCO DIP-4 polarimeter. All solvents were removed by evaporation under reduced pressure after drying of the solution over anhyd. MgSO_4 .

7-Bromo-(25R)-spirosta-5-en-3 β -ol Acetate (VII)—NBS (1.72 g, 9.7 mmol) was added in one portion to an *n*-hexane solution (48 ml) of (25R)spirost-5-en-3 β -ol acetate (IVb, 4.12 g, 9.0 mmol). The mixture was refluxed for 15 min and then cooled at 15 °C. The precipitate was filtered off and the filtrate was concentrated. The residue was recrystallized from *n*-hexane to give VII in 74.4% yield. mp 140–143 °C. NMR (CDCl_3): 2.03 (3H, s), 3.10 (2H, d, $J=4$), 4.3–4.7 (3H, m), 5.70 (1H, d, $J=4$). Anal. Calcd for $\text{C}_{29}\text{H}_{43}\text{BrO}_4$: C, 65.04; H, 8.09. Found: C, 65.06; H, 7.81.

(25R)-Spirosta-5,7-dien-3 β -ol Acetate (VIII)—A xylene solution (107 ml) of VII (1.80 g, 1.9 mmol) and γ -collidine (25.3 ml) was refluxed for 1.5 h and then cooled at room temperature and diluted with Et_2O . The mixture was washed with 10% HCl, sat. NaHCO_3 , and brine. The residue obtained after removal of the solvent was recrystallized from AcOEt. mp 157–160 °C (yellow needles). HPLC (5% AcOEt–*n*-hexane) t_R 8.40 min. UV, λ_{max} : 293, 282, 271. NMR (CDCl_3): 2.04 (3H, s), 3.44 (2H, d, $J=4$), 4.50 (2H, br s), 5.40, 5.56 (each 1H, m). Anal. Calcd for $\text{C}_{29}\text{H}_{42}\text{O}_4$: C, 76.61; H, 9.31. Found: C, 76.51; H, 9.28.

Adduct of VIII and PTAD (IX)—PTAD was added portionwise at room temperature to a CH_2Cl_2 solution of crude VIII until the red color of PTAD no longer disappeared, and the mixture was stirred for a further 1 h. The solvent was removed, and the residue was fractionated through an SiO_2 column. IX was eluted with benzene and recrystallized from Et_2O –*n*-hexane to give a white sand. mp 170–172 °C. The yield from VII was 50.3%. UV, λ_{max} (ϵ): 256 (16000), 212 (31200). NMR (CDCl_3): 2.03 (3H, s), 3.40 (2H, s like), 4.50 (1H, br s), 5.47 (1H, br s), 6.23 and 6.36 (each 1H, d, $J=8$), 7.43 (5H, br s). Anal. Calcd for $\text{C}_{37}\text{H}_{47}\text{N}_3\text{O}_6$: C, 70.56; H, 7.52; N, 6.67. Found: C, 70.95; H, 7.95; N, 6.57.

(25R)-Spirosta-5,7-dien-3 β -ol (X)—A tetrahydrofuran (THF) solution (50 ml) of IX (0.65 g, 1.02 mmol) was added dropwise to a suspension of LAH (0.64 g, 16.8 mmol) in THF under an Ar atmosphere with ice-cooling. After being stirred for 30 min at room temperature, the mixture was refluxed for 1 h. The complex was destroyed with sat. Na_2SO_4 aq. solution under ice-cooling, and then the inorganic material was removed by filtration. The filtrate was concentrated to give crude X as a crystalline material, which was recrystallized from MeOH. The yield of X was 54.5%. X: mp 148–150 °C (white granules). HPLC (20% AcOEt–*n*-hexane) t_R 7.75 min. UV (MeOH), λ_{max} (ϵ): 293 (7100), 281 (11800), 271 (11600). NMR (CDCl_3): 1.85 (3H, s), 3.30–3.50 (2H, m), 3.64 (1H, br s), 4.52 (1H, q, $J=4$), 5.41 and 5.56 (each 1H, m). Anal. Calcd for $\text{C}_{27}\text{H}_{40}\text{O}_3 + 1/3\text{H}_2\text{O}$: C, 77.47; H, 9.79. Found: C, 77.36; H, 9.91.

(25R)-9,10-Seco-spirosta-5,7,10(19)-trien-3 β -ol (I)—After N_2 gas had been bubbled for 30 min into a solution of X (111.8 mg, 0.27 mmol) in abs. Et_2O (250 ml), the solution was irradiated with a high-pressure mercury lamp (200 W) for 10 min using a Vycor filter at a temperature below 19 °C. A benzene solution of the residue obtained after removal of Et_2O was refluxed for 1.5 h and concentrated. The crude product was fractionated by SiO_2 column chromatography. Compound I was obtained from the 5% AcOEt–benzene eluate as a white amorphous compound softening at about 90 °C. The yield from X was 28%. I: HPLC (5% aq. MeOH) t_R 5.46 min. UV (MeOH), λ_{max} : 262, λ_{min} : 227. NMR (CDCl_3): 3.50 (3H, br s), 4.00 (2H, br s), 4.50 (1H, br s), 4.85 (1H, br s), 5.03 (1H, br s), 6.05 and 6.24 (each 1H, d, $J=12$). MS, m/e (%): 412 (M^+ , 30), 379 (15), 138 (80), 118 (100). High resolution MS, Calcd for $\text{C}_{27}\text{H}_{40}\text{O}_3$: 412.2975. Found: 412.2964. $[\alpha]_D^{23} -32.4^\circ$ ($c=0.42$).

17 β -(N-Methyl N-4-methylpentanoylamino)-5-androsten-3 β -yl 4-methylpentanoate (XIId)—A benzene solution (15 ml) of isocaproyl chloride (3.3 g, 24.5 mmol) was added to a warmed mixture of *N*-methyl-17 β -aminoandrost-5-en-3 β -ol (XIId, 2.1 g, 6.9 mmol), Et_3N (4.5 ml), and benzene (41.6 ml). The mixture was refluxed for 30 min. The cooled mixture was washed with 10% HCl, 10% Na_2CO_3 , and brine, and the organic solvent was removed to give white needles (from acetone). The yield was 67.5%. mp 162–164 °C. IR (KBr): $\nu_{\text{C=O}}$ 1730, 1640. NMR (CDCl_3): 0.68 and 0.75 (2:1, 3H, each s), 0.88 (12H, q, $J=4$, 2), 0.98 (3H, s), 2.86 and 2.91 (1:2, 3H, each s), 4.5–4.7 (2H, m), 5.40 (1H, s, like). $[\alpha]_D^{23} -94.5^\circ$ ($c=0.53$). Anal. Calcd for $\text{C}_{32}\text{H}_{53}\text{NO}_3$: C, 76.90; H, 10.69; N, 2.80. Found: C, 76.98; H, 10.92; N, 2.94.

17 β -(N-Methyl N-4-methylpentylamino)-5-androsten-3 β -ol (XIIa)—A dioxane solution (20 ml) of XIId (285.6 mg, 0.57 mmol) was added to a solution (20 ml) of LAH (216.6 mg, 5.7 mmol) under ice-cooling and stirring. The mixture was stirred at room temperature for 20 min and refluxed for 5 h. After the complex had been destroyed

by addition of 10% aq. NaOH solution, the reaction mixture was dried over MgSO_4 and filtered. The filtrate was concentrated to give a viscous oily compound, which was triturated with acetone. The white powder was recrystallized from aq. acetone. mp 126.5–129 °C. The yield was 78.9%. NMR (CDCl_3): 0.81 (3H, s), 0.87 (6H, d, $J=6$), 1.00 (3H, s), 2.22 (3H, s), 3.44–3.63 (1H, m), 5.36 (1H, d, $J=4$). $[\alpha]_D^{24} -60.1^\circ$ ($c=0.40$). MS, m/e (%): 387 (M^+ , 10), 369 (60), 354 (50), 154 (100). Anal. Calcd for $\text{C}_{26}\text{H}_{45}\text{NO}$: C, 80.56; H, 11.70; N, 3.61. Found: C, 80.56; H, 11.64; N, 3.90.

PTAD Adduct from XIId (XIII)—NBS (0.25 g, 1.4 mmol) was added in one portion to a refluxing CCl_4 solution (28 ml) of XIId (653.7 mg, 1.3 mmol) and benzoyl peroxide (cat. amount). The mixture was further refluxed for 20 min, then filtered after cooling. The filtrate was concentrated to give a brown-yellow oily compound. The crude 7-bromo derivative was treated with γ -collidine (10.5 ml) in xylene (42.9 ml) in a manner similar to that used for the preparation of IX from VII to give crude XIII, which was fractionated through an SiO_2 column. XIII was eluted with 5% AcOEt–benzene and recrystallized from Et_2O – n -hexane. mp 183–185 °C. The yield was 31.5% from XIId. UV, λ_{max} : 256. IR (KBr): $\nu_{\text{C=O}}$ 1750, 1700, 1630. NMR (CDCl_3): 2.94 and 3.00 (1:3, 3H, each s), 3.29 (1H, dd, $J=16, 4$), 4.76 (1H, t, $J=8$), 5.49 (1H, m), 6.27 and 6.41 (each 1H, d, $J=8$), 7.48 (5H, s). Anal. Calcd for $\text{C}_{40}\text{H}_{56}\text{N}_4\text{O}_5$: C, 71.39; H, 8.39; N, 8.33. Found: C, 71.25; H, 8.30; N, 8.32.

17 β -(*N*-Methyl-*N*-4-methylpentylamino)-5,7-androstadien-3 β -ol (XIV)—In a manner similar to that used in the preparation of X from IX, XIII (1.4 g, 2.1 mmol) in THF (105 ml) was treated with LAH (1.32 g, 34.7 mmol) in THF (105 ml) under an Ar atmosphere. The crude product was purified by SiO_2 column chromatography. XIV was obtained as a yellow oily compound from the CHCl_3 eluant. The yield was 41.4%. UV, λ_{max} : 292, 281, 271. IR (CHCl_3): ν_{OH} 3400, $\nu_{\text{C=C}}$ 1600. NMR (CDCl_3): 0.77 (3H, s), 0.93 (6H, d, $J=6$), 2.30 (3H, s), 3.56 (1H, br s), 5.41 and 5.66 (each 1H, d, $J=6$). MS, m/e (%): 385 (M^+ , 22), 154 (100).

17 β -(*N*-Methyl-*N*-4-methylpentylamino)-9,10-seco-androsta-5,7,10(19)-trien-3 β -ol (II)—Ar gas was passed through a benzene solution (250 ml) of XIV (114.4 mg, 0.3 mmol) for 30 min, then the solution was irradiated for 10 min with a 200 W high pressure mercury lamp. The temperature was held below 22 °C during this reaction. The benzene solution was refluxed for 1.5 h and concentrated. The residue was fractionated through an SiO_2 column, and II was obtained as a yellow oily compound from the 10% AcOEt–benzene eluate. The yield of II from XIV was 36.1%. HPLC (CHCl_3): t_R 6.11 min. UV, λ_{max} : 261, λ_{min} : 228. NMR (CDCl_3): 0.68 (3H, s), 0.89 (6H, d, $J=6$), 3.98 (1H, br s), 4.92 (1H, s like), 5.04 (1H, s like), 6.06 and 6.26 (each 1H, d, $J=12$). MS, m/e (%): 385 (M^+ , 15), 154 (100). High resolution MS, Calcd for $\text{C}_{26}\text{H}_{43}\text{NO}$: 385.3342. Found: 385.3289. $[\alpha]_D^{23} +10.9$ ($c=0.29$).

PTAD Adduct of 3 β -Acetoxy-5,7-pregnadien-20-one (XV)—In a manner similar to that used for the preparation of XIII from XIId, XV was synthesized from pregn-5-en-3 β -ol-20-one acetate (Vb, 2.5 g, 7.0 mmol) and NBS (1.37 g, 7.7 mmol) followed by dehydrobromination and adduct formation with PTAD. The crude XV was purified through an SiO_2 column. XV was eluted with 5% AcOEt–benzene and recrystallized from aq. MeOH. mp 181–183 °C (white needles). The yield was 30.0%. UV, λ_{max} : 256. NMR (CDCl_3): 0.79 (3H, s), 1.00 (3H, s), 2.03 (3H, s), 2.17 (3H, s), 5.37–5.54 (1H, m), 6.26 and 6.41 (each 1H, d, $J=8$), 7.40 (5H, s). MS, m/e (%): 531 (M^+ , 30), 467 (70), 296 (100). Anal. Calcd for $\text{C}_{31}\text{H}_{37}\text{N}_3\text{O}_5$: C, 70.03; H, 7.02; N, 7.90. Found: C, 69.78; H, 6.90; N, 8.08.

(20*S*)-20-Isopentylamino-5,7-pregnadien-3 β -ol (XVIa)—1) A benzene solution (50 ml) of XV (2.8 g, 5.26 mmol), isoamylamine (2.3 g, 26.3 mmol), and *p*-TsOH (0.2 g) was refluxed overnight using an apparatus equipped with a Dean–Stark water separator filled with molecular sieves 3A. After being cooled, the mixture was washed with brine and concentrated. NaBH_4 (0.6 g, 15.8 mmol) was added portionwise to a methanolic solution (50 ml) of the brownish residue under ice-cooling. The mixture was stirred for 2 h at room temperature, then 10% AcOH was added and the mixture was concentrated. The residue was extracted with CHCl_3 and the organic layer was washed with brine and concentrated to give an oily substance. Aq. HClO_4 (60%, 20 drops) was added to a methanolic solution of this product. After evaporation of the MeOH, the crystalline compound was washed with benzene to remove nonbasic compounds. The residue was dissolved in AcOEt and the solution was dried over anhyd. MgSO_4 . The crude perchlorate was obtained after removal of AcOEt as pale green crystals (2.34 g). A dioxane solution of the crude perchlorate was added to a suspension of LAH (2.45 g, 64.5 mmol) in dioxane (174 ml) under an Ar atmosphere with stirring. After being stirred for 30 min at room temperature, the mixture was refluxed for 5 h. The reaction mixture was worked up in the usual manner, and the crude product was purified through an Al_2O_3 column. XVIb—d and XVIa were eluted with benzene and 5% CHCl_3 –benzene, respectively. XVIa: mp 144–147 °C (colorless needles from Et_2O – n -hexane). The yield of XVIa from XV was 5.5%. UV, λ_{max} : 293, 281, 271. NMR (CDCl_3): 0.63 (3H, s), 0.88 (3H, s), 0.92 (6H, d, $J=5$), 1.11 (3H, d, $J=6$), 3.64 (1H, m), 5.42 (1H, m), 5.58 (1H, m). MS m/e (%): 385 (M^+ , 15), 370 (18), 114 (100). Anal. Calcd for $\text{C}_{26}\text{H}_{43}\text{NO}$: C, 80.98; H, 11.24; N, 3.63. Found: C, 81.04; H, 11.59; N, 3.63. XVIb—d: mp 118–128 °C (yellow granules from Et_2O – n -hexane). The yield of XVIb—d from XV was 4.9%. UV, λ_{max} : 293, 281, 271. NMR (CDCl_3): 0.65, 0.70, and 0.76 (*ca.* 3:1:1, 3H, each s), 0.87 and 0.88 (3H, each s), 0.91, 0.92, and 0.94 (6H, each s, like), 1.00 (3H, d, $J=6$), 3.63 (1H, m), 5.40 (1H, m), 5.58 (1H, m). MS, m/e (%): 385 (M^+ , 35), 370 (38), 114 (100). Anal. Calcd for $\text{C}_{26}\text{H}_{43}\text{NO}$: C, 80.98; H, 11.24; N, 3.63. Found: C, 80.57; H, 11.24; N, 3.72.

2) The imine obtained from XV (630 mg, 1.18 mmol) and isoamylamine (513.3 mg, 5.9 mmol) in a manner similar to that described above in 1) was dissolved in dioxane (62 ml). The dioxane solution was added dropwise to a suspension of LAH (867 mg, 22.8 mmol) in dioxane (62 ml) with stirring under an Ar atmosphere. The mixture was

worked up in the usual manner, and the crude product was purified through an Al_2O_3 column. Pregna-5,7-dien-3 β -ol-20-one (XVIII) and XVIa were eluted with benzene and 3% CHCl_3 -benzene, respectively. XVIII: mp 174–177 °C (white granules from Et_2O -*n*-hexane). The yield of XVIII from XV was 3.4%. UV, λ_{max} : 293, 281, 271. IR (KBr): ν_{OH} 3500, $\nu_{\text{C=O}}$ 1680. MS, m/e (%): 314 (M^+ , 50), 281 (80), 255 (60). The yield of XVIa from XV was 12.7%. The physical data were identical with those given for XVIa in 1).

20-Amino-5-pregnen-3 β -ol THP Ether (XVII)—XVII was obtained according to the literature.⁹⁾ The mixture of XVII was fractionated through an Al_2O_3 column, and 20*R*-XVII (XVIIb) and 20*S*-XVII (XVIIa) were eluted with 10% CHCl_3 -*n*-hexane and 20% CHCl_3 -*n*-hexane, respectively. XVIIa: mp 120–124 °C (white granules from *n*-hexane, lit.⁹⁾ mp 117–119 °C). The yield was 17.0% NMR (CDCl_3): 0.67 (3H, s), 1.00 (3H, s), 1.13 (3H, d, $J=6$), 4.73 (1H, br s), 5.38 (1H, br s). XVIIb: mp 163–166 °C (white needles from *n*-hexane, lit.⁹⁾ mp 156–159 °C). The yield was 23.0%. NMR (CDCl_3): 0.77 (3H, s), 1.02 (3H, d, $J=6$), 1.03 (3H, s), 4.73 (1H, br s), 5.38 (1H, br s).

(20*S*)-20-Isopentylamino-9,10-seco-pregna-5,7,10(19)-trien-3 β -ol (III)—In a manner similar to that used for the preparation of II from XIV, XVIa (142.6 mg, 0.37 mmol) was irradiated in benzene below 25 °C for 10 min followed by refluxing for 1.5 h. The crude product was purified through an SiO_2 column using CHCl_3 as an eluant. The yield was 21.5%. UV, λ_{max} : 265, λ_{min} : 228. NMR (CDCl_3): 0.62 (3H, s), 0.87 (6H, d, $J=6$), 1.06 (3H, d, $J=6$), 3.90 (1H, m), 4.80 (1H, br s), 5.04 (1H, br s), 6.03 (1H, d, $J=12$), 6.21 (1H, d, $J=12$). MS, m/e (%): 385 (M^+ , 25), 370 (20), 114 (100). High resolution MS, Calcd for $\text{C}_{26}\text{H}_{43}\text{NO}$: 385.3342. Found: 385.3315. $[\alpha]_{\text{D}}^{22} + 54.2^\circ$ ($c=1.54$).

Acknowledgement The authors are grateful to Prof. C. Kaneko, Faculty of Pharmaceutical Sciences, Kanazawa University, and Dr. S. Hirokami of our faculty for their invaluable advice and encouragement. Thanks are also due to Messrs. M. Morikoshi and M. Ogawa for the high resolution MS measurements and the elemental analyses.

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