[Chem. Pharm. Bull.
16(5) 814—818 (1968)]

UDC 547.92.07 : 581.19

Studies on C-nor-D-Homosteroids. VII.[1] Synthesis of Nitrogen-free Veratramine Derivatives

Hiroshi Mitsuhashi and Kazunori Shibata

Faculty of Pharmaceutical Sciences, Hokkaido University[2]

(Received May 23, 1967)

The conversion of hecogenin acetate to some C–nor–D–homopregnane derivatives and the synthesis of a nitrogen–free derivative of veratramine from hecogenin are described. These conversions provide final confirmation of the C–9 configuration of vetatramine and correlation with the normal steroids.

Since the original structure was proposed for jervine (1) and veratramine (11) by Fried, Wintersteiner, and co–workers,[3,4] further evidences for them have been added by many investigators. Acetoylsis of I gave a nitrogen–free compound[3] (IV) which was assigned a peculiar C–nor–D–homo skeletal structure. A previous communication[5] from this laboratory in 1961 reported the synthesis of this nitrogen–free derivative (IV) of jervine starting from hecogenin. On the basis of the known stereochemistry of hecogenin and the reactions used, the stereochemistry of jervine (1) at C–3, 8, 9, 10, and 14 was assigned.

The configuration of other asymmetric carbon atoms in jervine (I) has been assigned by Tsuda and Okuda[6] (C–25), and by Augustine.[7]

Wintersteiner obtained the 11–oxoveratramine derivative (III) by treating jervine O,N–diacetate with acetic anhydride/acetic acid and a catalytic amount of sulfuric acid, followed by catalytic hydrogenation of the 5—6 double bond with Palladium. III was also obtained by chromic acid oxidation of dihydroveratramine triacetate. From this correlation, the stereochemical relationship between jervine (I) and veratramine (II) was established.[8] The *trans* B/C ring juncture (9α) of jervine was suggested from these experiments, but there remained some ambiguity concerning the C–9 configuration of veratramine (II). House[9] has pointed out that *cis* form is more stable than the *trans* form in benzindanone (VI). In the correlation experiments,[8] jervine was treated with a rather strong acid to obtain an 11–oxoveratramine derivative. Some possiblity exists that the C–9 configuration may be changed from α to β (B/C *cis*) under these conditions. Aslo, 11–oxoveratramine is believed to be the biogenetic precursor of veratramine,[10] so a more stable 9β–configuration might be more favorable for veratramine (Chart 1).

Johnson and co–workers[11] proved the 9α–configuration of VIII by comparison of the NMR signal for the 19–methyl group with N–acetyl–11–oxoveratramine and synthetic com-

---

[1] Part VI: *Chem. Pharm. Bull.* (Tokyo), **14**, 809 (1966).
[2] Location: *Nishi–5–Chome, Kita–12–jo, Sapporo, Hokkaido.*
[3] J. Fried, O. Wintersteiner, M. Moore, B.M. Iselin, and A. Klingsberg, *J. Am. Chem. Soc.*, **73**, 2970 (1951); Ch. Tamm and O. Wintersteiner, *ibid.*, **74**, 3842 (1952).
[4] J. Fried and A. Klingsberg, *J. Am. Chem. Soc.*, **75**, 4929 (1953).
[5] H. Mitsuhashi and Y. Shimizu, *Tetrahedron Letters*, 777 (1961); *Tetrahedron*, **19**, 1027 (1963).
[6] S. Okuda, K. Tsuda, and H. Kataoka, *Chem. Ind.* (London), **1961**, 512.
[7] R.L. Augustine, *Chem. Ind.* (London), **1961**, 1448.
[8] O. Wintersteiner and N. Hosansky, *J. Am. Chem. Soc.*, **74**, 4474 (1952).
[9] H.O. House, V. Paraganian, R.S. Ro, and D.J. Wluka, *J. Am. Chem. Soc.*, **82**, 1457 (1960).
[10] L.F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N.Y., 1959, 876.
[11] P.W. Schiess, D.M. Bailey, and W.S. Johnson, *Tetrahedron Letters*, 549 (1963); D.M. Bailey, D.G. Hamon, and W.S. Johnson, *ibid.*, 555 (1963).

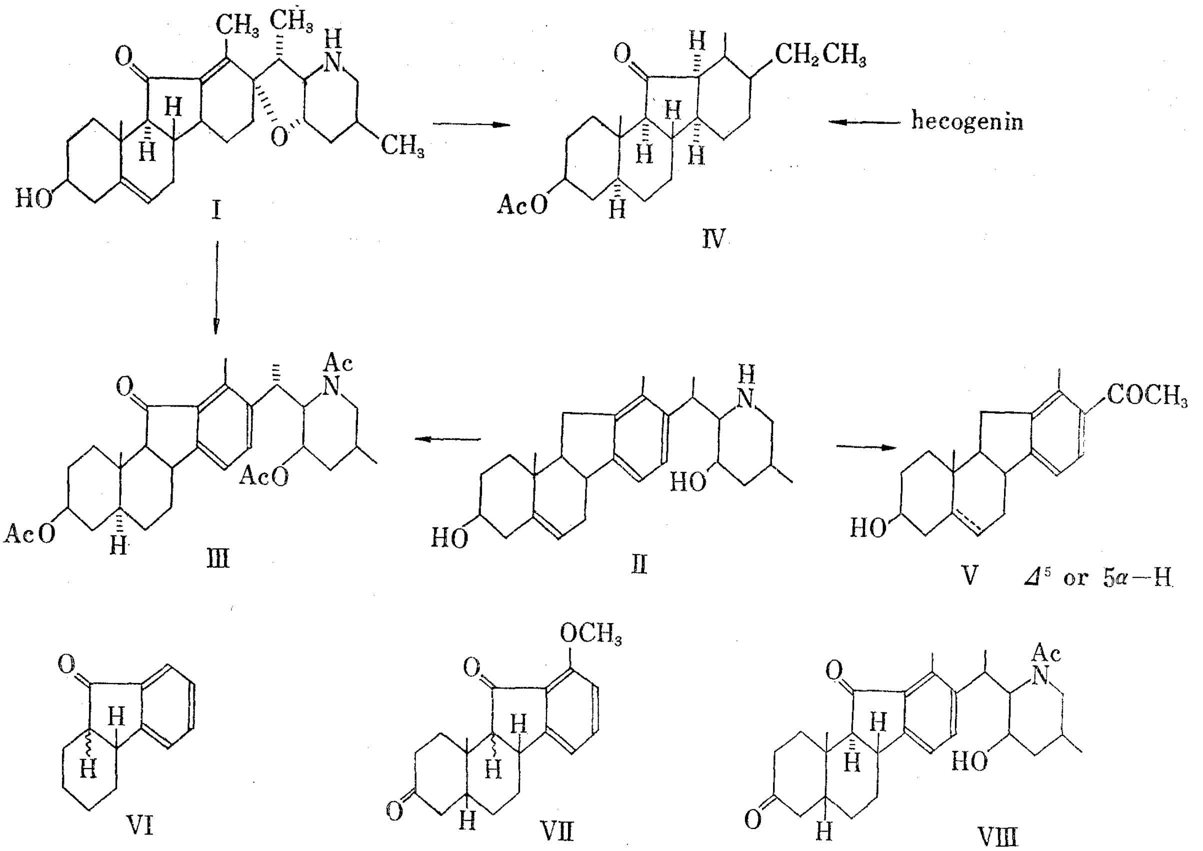

Chart 1

pounds (VII) with 9α- and 9β-configuration. Having thus established the B/C *trans* (9α) configuration of 11-oxoveratramine, the transformation of this compound to veratramine (II) by removal of the carbonyl group under conditions which preclude inversion at C-9 succeeded. Veratramine (II), therefore, has a B/C *trans* (9α) configuration. They also attempted a total synthesis of veratramine[12] starting from the compound (V) obtained by degradation of II as shown in Chart 2. As a synthetic proof for the structure of veratramine (II), we have been in search for a facile method for degradation and C-nor-D-homo conversion of hecogenin.

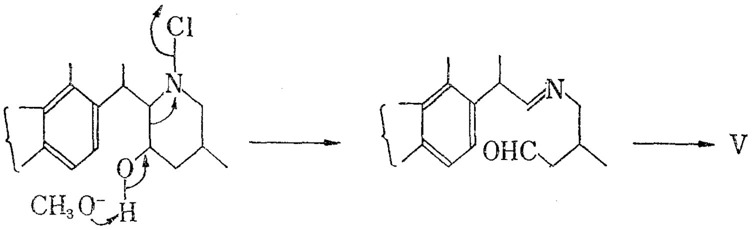

Chart 2

There have been several methods reported for the conversion of normal steroids to C-nor-D-homosteroids,[13] but most of these methods are unsuitable for obtaining compound V. Generally it is rather difficult to find selective reactivity between the oxygen groups attached to 3, 12, and 20 in pregnane derivatives. It was planned to obtain the starting material

---

[12] R.W. Franck and W.S. Johnson, *Tetrahedron Letters*, 545 (1963); R.W. Franck, G.P. Rizzi, and W.S. Johnson, *Steroids*, **4**, 463 (1964).

[13] H. Mitsuhashi, K. Shibata, T. Sato, and Y. Shimizu, *Chem. Pharm. Bull.* (Tokyo), **12**, 1 (1964); H. Mitsuhashi and N. Kawahara, *Tetrahedron*, **21**, 1215 (1965).

which possess a 12–keto or 12β–OH groups. Hecogenin was converted to pseudohecogenin (IX) by the usual method, then subsequent peracid oxidation[14] gave 20–hydroxyhecogenin (XI). Acetylation of XI gave XII and sodium borohydride reduction of XII yielded 5α–siprostane–3β,12ξ,20α–triol 3–monoacetate (XIII) which possessed a free tertiary OH group and was proved to be a mixture of 12α (minor) and 12β (major) epimers by thin–layer chromatography.

This 3,12,20–triol 3–acetate (XIII) was oxidized to 5α–pregn–16–ene–3β,12β–diol–20–one

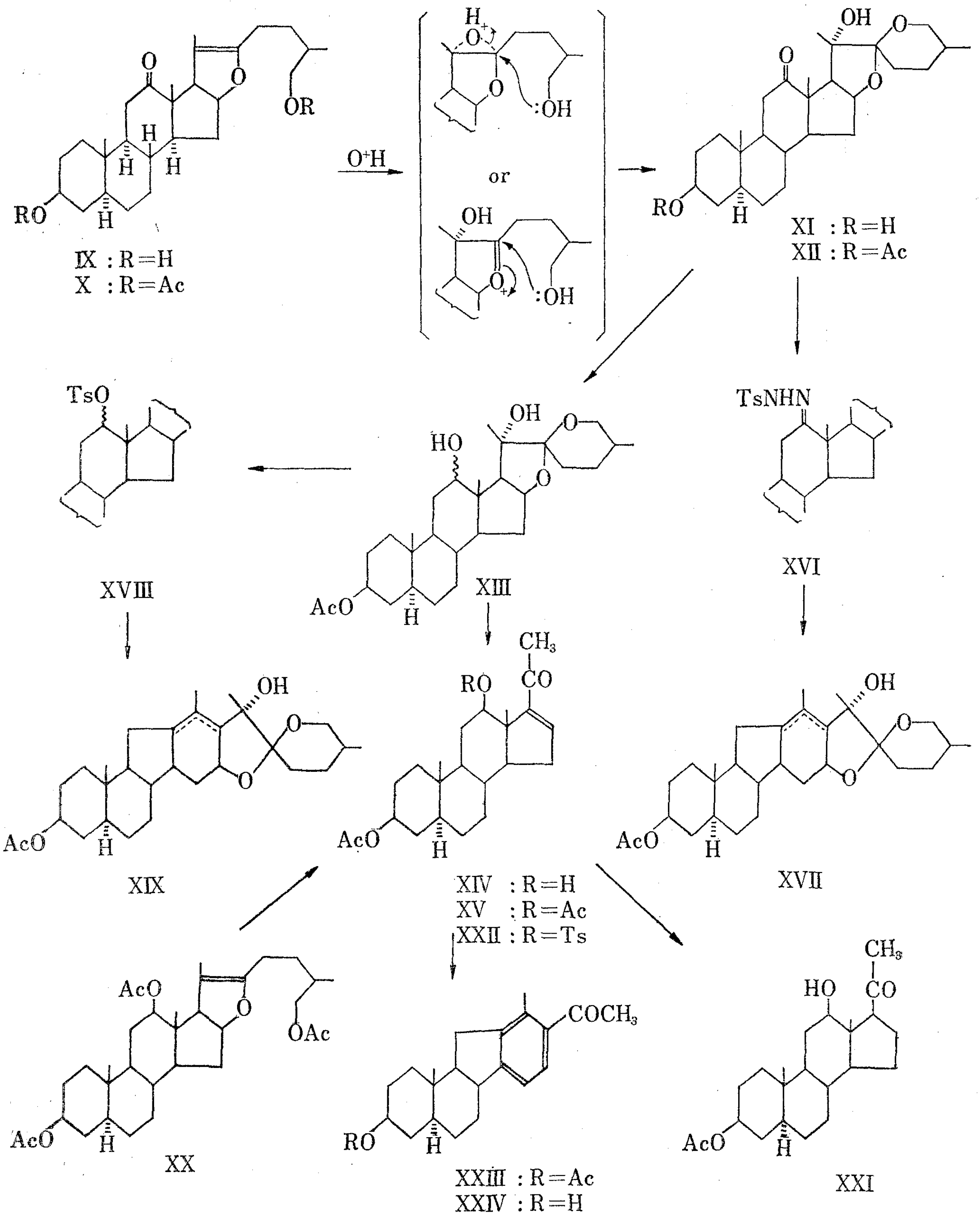

Chart 3

---

[14] R.K. Callow and V.H.T. James, *Chem. Ind.* (London), **1965**, 112.

3-monoacetate (XIV) by lead tetraacetate in 90% acetic acid.[15] Acetylation of XIV gave the diacetate (XV), and the identity of this compound was comfirmed by comparison with 5α-pregn-16-ene-3β,12β-diol-20-one 3,12-diacetate[16] obtained by chromic acid oxidation of pseudo-rockogenin triacetate (XX). This indicates that XIII is a mixture of 12α- and 12β-epimers, but the product (XIV) by oxidation with lead tetraacetate is only the 12β-OH compound (Chart 3).

The tosylhydrozone (XVI), obtained on treatment of 20α-hydroxyhecogenin (XI) with tosylhydrazine in AcOH, was heated in ethylene glycol with Na (Bamford-Stevens reaction). Acetylation of the product obtained with Ac_2O/pyridine gave XVII. The NMR spectrum of XVII exhibited a 3-proton singlet at $\delta=1.70$ ppm which shows that the 18-CH_3 is a vinyl methyl. This indicates that during the Bamford-Stevens reaction, a C/D ring rearrangement had occurred.

Treatment of 20α-hydroxyrockogenin 3-monoacetate (XIII) with tosyl chloride in pyridine gave the 12-tosylate (XVIII). Refluxing of the 12-tosylate (XVIII) with pyridine for several hours resulted in the formation of a compound (XIX) which exhibited NMR absorption of 18-CH_3 group very similar to that of XVII. Both XVII and XIX showed very similar properties, but the relative strength of the IR absorptions appearing at 1270 and 1240 cm^{-1} was reversed in the two compounds. It is not clear if the difference in the IR spectrum is due to a different spiroketal ring conformation or different position of the double bond (Δ^{12-13} or Δ^{13-17}) in each compound.

Treatment of XIV with tosyl chloride in pyridine at 50—60° for several days gave the tosylate derivative (XXII). The 12-tosylate (XXII) was refluxed in pyridine for 5—6 hours and then hydrolyzed with 5% methanolic potassium hyroxide. Recrystallization of the product from methanol-water yielded a crystalline compound (XXIV), mp 170—175°, λ_{max}^{EtOH} 259 mμ (ε 13600); ν_{max}^{Nujol} 1670, 1597 cm^{-1}; NMR, 2 protons as doublets at $\delta=6.94$ and 7.50 ppm ($J=7.5$ cps).

This compound (XXIV) was completely identical with the degradation product (V) prepared from veratramine, by mixed melting point and comparison of IR spectra.[17] By this comparison the B/C ring juncture of veratramine is thus proved to be *trans* (9α).

Experimental

20α-Hydroxyhecogenin (XI, R=H)——A solution of 0.2 g of pseudohecogenin (IX) in 10 ml of dioxane was treated with 0.135 g of monoperphthalic acid in ether. The mixture was kept at room temperature for 42 hr and dliuted with H_2O. The solid product was collected, washed with 5% $FeSO_4$ and H_2O, and crystallized, twice from EtOAc, giving 20α-hydroxyhecogenin (XI) mp 238—242°, yield 73%; $[\alpha]_D$ +11.1° ($c=1.08$, EtOH); IR ν_{max}^{Nujol} cm^{-1}: 3530, 3460, 1698, 1065, 923, 903, 866. *Anal.* Calcd. for $C_{27}H_{42}O_5$: C, 72.61; H, 9.48. Found: C, 72.85; H, 9.27.

20α-Hydroxyhecogenin (XI) was acetylated with mixture of Ac_2O and pyridine (1:2) to give the 3-monoacetate (XII, R=Ac), mp 237—249.5°; $[\alpha]_D$ −9.15° ($c=1.42$, $CHCl_3$); IR ν_{max}^{Nujol} cm^{-1}: 3570, 1740, 1710, 1250, 1065, 923, 905, 870. *Anal.* Calcd. for $C_{29}H_{44}O_6$: C, 71.28; H, 9.08. Found: C, 71.48; H, 9.14.

5α-Spirostane-3β,12ξ-,20α-triol 3-Monoacetate (XIII)——20α-Hydroxyhecogenin 3-monoacetate (4 g) was dissolved in dioxane (80 ml) and CH_3CN (100 ml), and the solution was treated with $NaBH_4$ (1 g) in 50% CH_3CN (10 ml) at room temperature for 96 hr. The excess reagent was destroyed with AcOH, and H_2O was added. The precipitated crystals were collected, washed with H_2O, dried, and recrystallized from MeOH to white needles (3.7 g), mp 226—228°; $[\alpha]_D$ −53.8° ($c=1.15$, EtOH); IR ν_{max}^{Nujol} cm^{-1}: 3400, 1740, 1240. *Anal.* Calcd. for $C_{29}H_{46}O_6$: C, 70.98; H, 9.45. Found: C, 71.40; H, 9.55.

5α-Pregn-16-ene-3β,12β-diol-20-one 3-Monoacetate (XIV)——Lead tetraacetate (0.8 g) was added with stirring to a solution of 5α-spirostanne-3β,12ξ,20α-triol 3-monoacetate (0.5 g) in 90% AcOH (40 ml). The

---

15) H. Mitsuhashi, K. Shibata, and N. Uehara, *Chem. Pharm. Bull.* (Tokyo), **14**, 301 (1966).

16) R.K. Callow and V.H.T. James, *J. Chem. Soc.*,**1956**, 4744. R. Tscheshe, G. Brügmann, H.W. Marquardt, and H. Machleidt, *Ann.*, **648**, 185 (1961).

17) T. Masamune and M. Takasugi, private communication.

reaction mixture was maintained at 60—65° for 2 hr and benzene was added in order to remove water by azeotropic destillation.

The remaining mixture was refluxed for 2 hr. AcOH was distilled off, the residue was extracted with CH_2Cl_2, washed with 5% $NaHCO_3$, and dried. The solvent was removed by distillation and the residue was crystallized from ether to white needles (0.16 g), mp 220—224.5°; $[\alpha]_D$ 0° (c=0.97, EtOH); UV $\lambda_{\max}^{\mathrm{EtOH}}$ 243 mμ (ε 8900); IR $\nu_{\max}^{\mathrm{Nujol}}$ cm^{-1}: 3400, 1740, 1640, 1585, 1245; NMR (ppm): 0.85 (C_{18}– and C_{19}–Me), 2.00 (acetate), 2.36 ($COCH_3$), 6.98 (C_{16}–H). *Anal.* Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.59; H, 8.91.

The 12β–hydroxyl group in XIV (50 mg) is moderately resistant to acylation. A solution of XIV in equal volumes of pyridine and Ac_2O was heated on boiling water bath for 16 hr but the yield of diacetate (XV) was only 17.3 mg. The diacetate formed white needles (from MeOH), mp 134—137°, identical with an authentic sample prepared from pseudorockogenin diacetate.

20α-Hydroxyhecogenin 12-Tosylhydrozone (XVI)——To a solution of 2 g of 20α–hydroxyhecogenin in 60 ml of AcOH was added 2 g of tosylhydrazine with stirring. After standing 2 hr at room temperature, the crystals precipitated out were collected, washed with ether, and recrystallized from CH_2Cl_2–MeOH, mp 230—232° (2.1 g); IR $\nu_{\max}^{\mathrm{Nujol}}$ cm^{-1}: 3550, 3350, 3100, 1640, 1600, 1165.

Conversion of XVI to XVII——A solution of 2 g of XVI in 40 ml of ethylene glycol containing 0.9 g of Na was heated in nitrogen atmosphere at 170—175°. Nitrogen gas evolved vigorously, but evolution soon ceased, and the mixture was kept for 20 min at 170° and then poured into ice water. One g out of 2.4 g of the residue was chromatographed on 30 g of Al_2O_3 from which the desired compound was eluted with benzene and crystallized from (iso–Pr)$_2$O 0.72 g of cyrstals, mp 162—179°, in 51% yield. A solution of 0.7 g of these crystals in 20 ml of pyridine and 10 ml of Ac_2O was heated for 30 min. The reaction mixture was treated in the usual manner and gave 0.45 g of XVII, mp 183—189°. *Anal.* Calcd. for $C_{29}H_{44}O_5$: C, 73.69; H, 9.38. Found: C, 73.66; H, 9.28.

Conversion of XIII to XIX——To a solution of 1 g of 20α–hydroxyrockogenin 3–monoacetate (XIII) in 15 ml of pyridine was added 1 g of tosyl chloride at 0°. After being left overnight at room temperature, the reaction mixture was heated for 8 hr. The reaction mixture was poured into ice water and the precipirated product filtered off. The residue was recrystallized twice from MeOH to 0.1 g of XIX, mp 180—186°. *Anal.* Calcd. for $C_{29}H_{44}O_5$: C, 73.69; H, 9.38. Found: C, 73.84; H, 9.44.

5α-Pregnane-3β,12β-diol-20-one 3-Monoacetate (XXI)——A solution of 0.1 g of XIV in 15 ml of EtOAc was shaken with 0.1 g of 5% Pd–C in H_2O at atmospheric pressure and room temperature for 4.5 hr. The catalyst was removed and the filtrate was evaporated under reduced pressure. The residue was crystallized from ether to give XXI, mp 148.5—152.2°; IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 3480, 1740, 1695, 1255, 1030; ORD in $CHCl_3$: first extremum $[\phi]$ −1806.5 (303 mμ), second extremum +1730.5 (262); in MeOH: first extremum +2823 (309), second extremum −2338.3 (764).

Solvolysis of 5α-Pregn-16-ene-3β,12β-diol-20-one 3-Monoacetate 12-Tosylate (XXII)——i) To a solution of 0.5 g of XIV in 5 ml of pyridine was added 1 g of tosyl cholride at 0°. After being left 96 hr at 50—60°, the reaction mixture was poured into ice water and the product extracted with ether. Ethereal solution was washed with dil. HCl and H_2O, and dried. Evaporation of the solvent gave the crude tosylate. Recrystallization from MeOH gave 180 mg of the tosylate (XXII), mp 110—116.5°. IR $\nu_{\max}^{\mathrm{Nujol}}$ cm^{-1}: 1740, 1680, 1600, 1240, 1180, 1170, 1020, 930, 900, 880, 850, 820, 670, no hydroxyl absorption.

ii) To a solution of 6.6 g of the 12β–ol (XIV) in 70 ml. of pyridine was added 14 g of tolyl chorlide and the solution heated in Nitrogen atmopshere at 60° for 48 hr. Further 3.0 g of tosyl chloride was added to the reaction mixture and kept for 22 hr. The progress of the reaction was checked by thin–layer chromatography and, after completion of the reaction, the mixture was refluxed for 6 hr. Pyridine was evaporated under a reduced pressure. The mixture was extracted with ether and ethereal solution was washed with HCl solution, dil. $NaHCO_3$, and H_2O, dried, and evaporated. The residue was hydrolyzed with 70 ml of 5%–MeOH·KOH for 30 min. The product was extracted with CH_2Cl_2. The product was worked up in the usual manner to give 5.3 g of residue. This residue was chromatographed on 150 g of Al_2O_3, from which the desired compound was eluated with benzene:EtOAc (9:1) and crystallized from MeOH–H_2O to 1.88 g of (XXIV), mp 170—175.5°. $\lambda_{\max}^{\mathrm{EtOH}}$: 259 m$\mu$ (ε 13.600), $[\alpha]_D$ +42.7°(c=1.12; $CHCl_3$). *Anal.* Calcd. for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.78; H, 9.09.

Acknowledgement We thank Prof. N. Masamune, Hokkaido University, and Dr. K. Takeda, Director of Shionogi Laboratory, for the kind donation of the starting material. Thanks are also due to Mrs. Toma and Miss A. Maeda for the elemantal analysis.