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Stereochemistry of Electrophilic Reactions at the
Steroidal C-22 Double Bond*,¹⁾

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The stereoselectivity of three kinds of electrophilic reactions, *viz.* osmium tetroxide oxidation, bromohydrination and peracid epoxidation of 24-nor-5 α -chol-22-en-3 β -ol **4** was investigated by the analysis of the products. The conformations II and III are proposed as participating in the transition states in the course of these reactions. The stereochemistry of the Grignard reaction on the 22-aldehyde is also discussed.

There are a number of biologically interesting steroids containing an asymmetric carbon at the 22-position, *e.g.* ecdysones,³⁾ withanolides,⁴⁾ antheridiol,⁵⁾ gorgosterol⁶⁾ *etc.* For synthesis of those compounds, a stereoselective introduction of a functional group on C-22 position is a problem of primary importance. Two typical stereoselective reactions at the C-22 position are Grignard reaction on the 22-aldehyde and the electrophilic addition reaction to the Δ^{22} bond.⁷⁻¹¹⁾ The former reaction gives mainly [22S]-alcohol predicted by Cram's rule and the reaction of a stereoselective and regioselective iodoacetoxylation, as an example of the latter, has been reported.⁹⁾

During the course of our investigations, Poyser, *et al.*¹⁰⁾ have reported on stereochemical aspects of the electrophilic addition reaction to the Δ^{22} bond, which was applied to a synthesis of [22R]-hydroxycholesterol starting from a 24-nor-chol-22-ene derivative. Their results were interpreted on the hypothesis that the electrophile would approach the Δ^{22} system (in a conformation such that the Δ^{22} bond is eclipsed to the C-20 hydrogen) predominantly from the side of the 21-methyl group (Formula I). Considering the fact that this reaction model is not appropriate to account for all the results reported,^{7,8)} we have further investigated the stereochemistry of the reaction at the Δ^{22} bond.

24-Nor-5 α -chol-22-en-3 β -ol acetate **4a** was chosen as a simple 22-ene derivative, and was synthesized as follows. 3 β -Acetoxy-22,23-bisnor-5 α -cholanolic acid **1** obtained by catalytic hydrogenation of commercially available 22,23-bisnorcholenic acid was converted by treatment with ethyl chloroformate and triethylamine into the mixed anhydride, which was then reduced

* Dedicated to the memory of Prof. Eiji Ochiai.

- 1) This report is Part XXVIII in the series of "Studies on Steroids." Part XXVI: Y. Tanaka, H. Frank, H.F. DeLuca, N. Koizumi, and N. Ikekawa, *Biochemistry*, **14**, 3293 (1975). Part XXVII: Y. Tanaka, H.F. DeLuca, N. Ikekawa, M. Morisaki, and N. Koizumi, *Arch. Biochem. Biophys.*, in press.
- 2) Location: Meguro-ku, Tokyo.
- 3) K. Nakanishi, "The Chemistry of Natural Products 7," Butterworth, London, 1971, p. 167.
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- 10) J.P. Poyser, F.R. Hirtzbach, and G. Ourisson, *Tetrahedron*, **30**, 977 (1974); J.P. Poyser, F.R. Hirtzbach, and G. Ourisson, *J. Chem. Soc., Perkin I*, **1974**, 378; J.P. Poyser, and G. Ourisson, *ibid.*, **1974**, 2061.
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with a large excess of aqueous sodium borohydride¹²⁾ to give 22-alcohol **2** in high yield. When the reduction, however, was carried out with methanolic sodium borohydride, the mixture of 22-alcohol **2** and 22-acid **1** was obtained in approximately the same ratio. Collins oxidation¹³⁾ of **2** gave 22-aldehyde **3** and the subsequent Wittig reaction with methylene triphenylphosphorane yielded 22-ene derivative **4a** (40%, overall yield from **1**).

The stereoselectivity of three kinds of electrophilic reactions on the double bond of **4a** was investigated by the analysis of the 22-epimeric epoxides derived from the reaction products. Osmium tetroxide oxidation of **4a** provided 22,23-diol **5**.¹⁴⁾ Five developments on thin-layer chromatography (TLC) with a mobile phase of benzene-ether (3:1) revealed the presence of two epimers, the less polar one being the major component which could be isolated by recrystallization. The circular dichroism (CD) spectrum of the corresponding dibenzoate **6**¹⁵⁾ showed a positive Cotton effect at 235 nm ($\Delta\epsilon=1.2$) and a negative one at 222 nm ($\Delta\epsilon=0.7$), suggesting that the major diol had the *S*-configuration at 22-position and also that the free rotation of the 22—23 single bond of **6** would be restricted to a considerable extent. Treatment of the diol **5a** with 1.3 mole equivalent of *p*-toluenesulfonyl chloride gave 23-monotosylate **7**, which was converted into epoxy acetate **8a** by refluxing with anhydrous potassium carbonate in methanol for 5 min., whereas further reflux resulted in the epoxy alcohol **9a**.

Epoxidation of **4a** with *m*-chloroperbenzoic acid gave the epimeric mixture of epoxy acetates **8**. The third epoxidation could be effected by bromohydrination with *N*-bromosuccinimide in aqueous glyme, followed by treatment with potassium carbonate.

The epimeric epoxy benzoate **10a** and **10b** were found to be effectively separated on high pressure liquid chromatography using Zorbax SIL column. The stereoselectivity of three kinds of electrophilic reactions could be conveniently determined by means of this technique. The benzoate **4b** was therefore subjected to the electrophilic reactions and the products were directly converted to the epoxides in the same manner as described above. Thus, the ratio of the amounts of less polar epoxide **10a** and the more polar one **10b** was found as follows: 6:1 for the cyclization product from the diol obtained by osmium tetroxide oxidation, 1:2 for direct epoxidation and 9:1 for cyclization of bromohydrins. Taking account of the result of CD measurement of the dibenzoate **6**, it can be determined that the less polar epoxide **8a** had 22-*S* configuration and the more polar one **8b** had 22-*R*.

To obtain further confirmation on the configuration of the epoxide, the 22-alcohol obtained by the Grignard reaction of 22-aldehyde **11** with methyl magnesium iodide was compared with the lithium aluminum hydride reduction product of the epoxide. Recrystallization of 22-alcohol **12** prepared by the Grignard reaction afforded the pure major component **12b**, whose configuration at C-22 was determined as *S* by a modified Horeau method.¹⁶⁾ Gas-liquid chromatography (GLC) analysis of the 3,22-ditrimethylsilyl ether **14** derived from the crude tetrahydropyranyl (THP) ether **12**, using a glass capillary column, revealed the presence of 4:1 mixture of two epimeric alcohols **12**, the major component of which has shorter retention time.

Lithium aluminum hydride reduction was carried out on the 3-THP ether **15**, which was derived from the mixture of epoxy acetates **8**. The 22-alcohol **12** was obtained by the regioselective attack of hydride at C-23 position. GLC analysis of the trimethylsilyl ether **14** of

12) K. Ishizumi, K. Koga, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **16**, 492 (1968).

13) R. Ratcliffe and R. Rodehorst, *J. Org. Chem.*, **35**, 4000 (1970).

14) Compound number without a or b indicates the epimeric mixture.

15) H. Harada and K. Nakanishi, *J. Am. Chem. Soc.*, **91**, 3989 (1969).

16) C.J.W. Brooks and J.D. Gilbert, *J. Chem. Soc. Chem. Comm.*, **1973**, 194.

Chart 1

stereoselectivity should be the same as the peracid epoxidation. However, the result of osmium tetroxide oxidation in our present experiments suggested that the transition state of the reaction on the Δ^{22} bond would have other conformations as far as the reaction follows the Curtin-Hammett principle.

We wish to propose other conformations which explain the stereoselectivity of the reactions on the Δ^{22} bond in terms of the postulate that in the transition state all staggered forms will be more stable than the eclipsed ones. The conformations II and III can be proposed as the stable formulae among six possible conformations. Four other staggered conformations have a large steric interaction between the steroid nucleus, especially C-16 β -H, and the electrophile or C-23-methylene group.

The preference between the conformations II and III will be determined by the difference of the effective molecular size between electrophile and C-23-methylene group. The effective molecular size of osmium tetroxide may be larger than that of methylene, whereas that of peracid in epoxidation may be smaller. A similar situation has been recognized in the electrophilic reactions of methylene cyclohexane derivatives **16**.¹⁷⁾ The most stable transition state in osmium tetroxide oxidation should be the conformation II, while that in peracid epoxy-

17) G. Berti, "Topics in Stereochemistry 7," John Wiley and Sons, New York, 1973, p. 194.

dation is the conformation III. Yanuka *et al.*⁷⁾ obtained mainly the 22-S bromide in α -bromination of 24-nor-cholanal. This result can be interpreted in terms of the conformations II and III. The most stable transition state is the conformation II, as the size of bromine ion should be larger than that of the C-23 functional group. In the bromohydrin reaction, the rate-determining step is not formation of bromonium ion, but rather a step of the attack of hydroxide anion on a bromonium ion. The conformation V is thus more stable than the conformation IV which has severe steric interaction between the incoming hydroxide anion and the C-16-hydrogens.

Taking into account the rate-determining step and the effective molecular sizes, the stereoselectivity of the electrophilic reactions on the Δ^{22} bond can be interpreted on the basis of conformations II and III. Furthermore, these models seem to be applicable to elucidate the stereoselectivity of the nucleophilic reactions on the 22-aldehyde. As the analogues of II and III, VI and VII can be proposed for the conformations of the transition state of these reactions. The preference between VI and VII will also be determined by the difference of the effective molecular sizes between nucleophile and O-metal (*e.g.* Li, MgX *etc.*) group. With saturated alkyl Grignard reagents, the 22-aldehyde will therefore react mainly *via* the conformation VI, giving predominantly Cram's rule product (22S-hydroxycompound). Attack of acetylenic Grignard reagent will proceed to provide preferentially anti Cram's rule product¹⁸⁾ *via* the conformation VII, as the relative size of the linear acetylenic group will be smaller than that of O-MgX group.

It was found that nuclear magnetic resonance (NMR) spectrum of 22-alcohol 2 clearly showed the ABX type signals due to the C-22-protons which were assigned as pro *R* proton (3.34 ppm, $J=7.5, 10.0$ Hz) and pro *S* proton (3.65 ppm, $J=2.5, 10.0$ Hz) in the most stable conformation (VIII). These signals also suggested the highly restricted rotation about C-20-22

18) H. Mori and K. Shibata, *Chem. Pharm. Bull.* (Tokyo), **17**, 1969 (1970); W. Sucrow, P.P. Calderia, and M. Slopianka, *Chem. Ber.*, **106**, 2236 (1973).

Chart 3

single bond. Thus, the stereoselectivity of lithium aluminum deuteride reduction can be elucidated by NMR spectrum. The 22-alcohol obtained by this reduction at -78° was converted into the 22-acetate **18** followed by hydrolysis of THP group. The resulting 3-alcohol **19** was oxidized by Jones' reagent to the 3-keto-22-acetate **20**. The NMR spectrum of this keto-acetate **20** showed the 22-protons at 3.75 ppm and 4.06 ppm, having a peak area ratio of 5:6. The result indicates the product ratio of 6:5 corresponding to 22*R*-acetate **20a** and 22*S*-acetate **20b**. This stereoselectivity would be interpreted in terms of the difference of the effective molecular size between deuteride (small) and O-Li (large); 22*R* (**20a**) from conformation VII and 22*S* (**20b**) from conformation VI.

Highly stereoselective epoxidation using alkaline hydrogen peroxide¹⁹ and cyclopropanation with sulfoxonium ylide²⁰ on a steroidal 22-en-24-one system

are interesting examples of nucleophilic reactions at the 22-position. However, the rate-determining step of these reactions may not be the attack of nucleophile on the C-22 position. Further, the stereoselectivity at the C-22 position of these reactions may be affected by several factors. The reaction model of the Grignard reaction with a 22-aldehyde would, therefore, be inapplicable.

Experimental

Melting points were determined on a hot stage microscope and are uncorrected. Optical rotations were taken for chloroform solution on a JASCO-DIP-S polarimeter. ^1H NMR spectra were run on a JEOL JNM-4H-100 spectrometer, with ^2H -chloroform as solvent and with tetramethylsilane (TMS) as internal reference. Column chromatography was normally effected with Wako silica gel C-200. Organic solvent extracts of aqueous solution were dried over MgSO_4 . "The usual work-up" refers to dilution with water, extraction with organic solvent which is indicated in the parenthesis, washing to neutrality, drying, filtration and evaporation under vacuum. Ether refers to diethyl ether and THF to tetrahydrofuran. The following abbreviations apply to NMR data: s=singlet; d=doublet; dd=double doublet; t=triplet; m=multiplet.

23,24-Bisnor-5 α -cholane-3 β ,22-diol 3-Acetate (2)—22,23-Bisnor-5 α -cholanolic acid (**1**) (390 mg, 1 mm) in THF (5 ml) was treated with ethyl chloroformate (130 mg, 1.2 mm) and triethylamine (120 mg, 1.2 mm) at 0° for 20 min. To this mixture was added a solution of sodium borohydride (380 mg, 10 mm) in water (2 ml) at 0° , and this solution was stirred at 0° for 2 hr. The usual work-up (ether) afforded the crystalline alcohol **2** (390 mg), mp (MeOH) $172-173^\circ$, $[\alpha]_D^{20} -9^\circ$ (c , 2.0), δ : 0.66 (3H, s, 18-Me), 0.82 (3H, s, 19-Me), 1.03 (3H, d, $J=6$ Hz, 21-Me), 2.01 (3H, s, CH_3CO), 3.34 (1H, dd, $J=7.5, 10$ Hz, 22-H), 3.65 (1H, dd, $J=2.5, 10$ Hz, 22-H), 4.70 (1H, m, 3 α H). *Anal.* Calcd. for $\text{C}_{24}\text{H}_{40}\text{O}_3$: C, 76.55; H, 10.71. Found: C, 76.78; H, 10.75.

24-Nor-5 α -chol-22-en-3 β -ol Acetate (4a) from 2—The 22-alcohol **2** (700 mg, 1.87 mm) in dichloromethane (14 ml) was treated with chromium trioxide (1.125 g, 11.25 mm) and pyridine (1.82 ml, 22.5 mm) at room temp. for 30 min. The usual work-up (ether) provided the crystalline aldehyde **3** (500 mg, 71.4%).

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The aldehyde **3** in THF (2.4 ml) was added at room temp. to the ether solution (10 ml) of methylene triphenylphosphorane, which was prepared by treatment of methyl triphenylphosphonium bromide (667 mg, 1.76 mm) with *n* BuLi-hexane (0.7–8N, 2.1 ml, 1.7 mm) at room temp. for 30 min. The solution was left at 120° for 18 hr in sealed tube. Filtration and evaporation afforded the crude olefin (454 mg). The usual acetylation and chromatography on silica (17 g), eluting with benzene, gave the olefin acetate **4a** (295 mg, 60%), mp (MeOH) 111–113°, $[\alpha]_D -10^\circ$ (*c*, 2.0), δ : 0.66 (3H, s, 18-Me), 0.82 (3H, s, 19-Me), 1.02 (3H, d, *J*=6 Hz, 21-Me), 2.01 (3H, s, CH₃CO), 4.70 (m, 3 α -H), 4.78 (dd, *J*=9.8, 5 Hz, 23-H), 4.86 (dd, *J*=17.5, 5 Hz, 23-H), 5.65 (1H, m, *J*=9.8, 17.5, 8 Hz, 22-H). *Anal.* Calcd. for C₂₅H₄₀O₂: C, 80.59; H, 10.82. Found: C, 80.67; H, 10.83.

24-Nor-5 α -cholane-3 β ,22,23-triol 3-Acetate (5)—The olefin acetate **4a** (565 mg, 1.53 mm) in dry ether (15 ml) was stirred with osmium tetroxide (434 mg, 1.74 mm) at room temp. for 24 hr. After evaporation of ether, the residue was treated with sodium bisulfate (1 g) in aqueous pyridine (25 ml) at room temp. for 3 hr. The usual work-up (ether) afforded the crude diol which was chromatographed on silica (24 g) (benzene-acetone, 10:1) to yield the glycol **5** (380 mg, 62%), mp (acetone) 215–216°, $[\alpha]_D +9^\circ$ (*c*, 2.0), δ : 0.65 (3H, s, 18-Me), 0.82 (3H, s, 19-Me), 0.93 (3H, d, *J*=6 Hz, 21-Me), 2.01 (3H, s, CH₃CO), 3.50 (2H, m, 23-H₂), 3.75 (1H, m, 22-H), 4.70 (1H, m, 3 α -H). *Anal.* Calcd. for C₂₅H₄₂O₄: C, 73.85; H, 10.41. Found: C, 73.94; H, 10.54.

3 β -Acetoxy-24-nor-5 α -cholan-22(S),23-diol 23-*p*-Toluenesulfonate (7)—22,23-Glycol **5a** (150 mg, 0.38 mm) in pyridine (2 ml) was stirred with *p*-toluenesulfonyl chloride (92 mg, 0.49 mm) at 0° for 20 hr. The usual work-up (ether) gave the crude tosylate (197 mg). Chromatography on silica (7 g), eluting with benzene, gave the 23-monotosylate **7** (176 mg, 87%), mp (MeOH) 80–82°, $[\alpha]_D +33^\circ$ (*c*, 2.0), δ : 0.63 (3H, s, 18-Me), 0.81 (s, 19-Me), 0.89 (d, *J*=6 Hz, 21-Me), 2.01 (3H, s, CH₃CO), 2.45 (3H, s, CH₃-C₆H₅), 3.85–4.30 (3H, m, 22-H, 23-H₂), 4.70 (1H, m, 3 α -H), 7.35, 7.80 (4H, aromatic-H). *Anal.* Calcd. for C₃₂H₄₈O₆S: C, 68.54; H, 8.62. Found: C, 68.07; H, 8.58.

22(S)-22,23-Epoxy-24-nor-5 α -cholan-3 β -ol Acetate (8a)—a) 23-Monotosylate **7** (150 mg, 0.27 mm) in methanol (6 ml) was refluxed with anhydrous potassium carbonate (30 mg) for 10 min. The usual work-up (ether) afforded the crystalline epoxide **8a** (106 mg, 99%), mp (MeOH) 146–148°, $[\alpha]_D -3^\circ$ (*c*, 2.0), δ : 0.65 (3H, s, 18-Me), 0.82 (3H, s, 19-Me), 0.95 (d, *J*=5 Hz, 21-Me), 2.01 (3H, s, CH₃CO), 2.40 (1H, m), 2.70 (2H, m), 4.70 (1H, m, 3 α -H). *Anal.* Calcd. for C₂₈H₄₀O₃: C, 77.27; H, 10.38. Found: C, 77.41; H, 10.43.

b) The olefin acetate **4a** (155 mg, 0.416 mm) in glyme (4.2 ml) was treated with N-bromosuccinimide (150 mg, 0.82 mm) and water (0.8 ml) at room temp. for 4 hr. The usual work-up (ether) provided the crude bromohydrin (3 spots on TLC, 187 mg), which was converted by refluxing with anhydrous potassium carbonate (50 mg) into the 22,23-epoxide **8a** (155 mg). Chromatography on silica (6 g), eluting with benzene-hexane (2:1) afforded the epoxide **8a** (80 mg, 50%), mp (MeOH) 149–151°, $[\alpha]_D -1^\circ$ (*c*, 2.0), δ : 0.65 (3H, s, 18-Me), 0.82 (3H, s, 19-Me), 0.95 (d, *J*=5 Hz, 21-Me), 2.01 (3H, s, CH₃CO), 2.40 (1H, m), 2.70 (2H, m), 4.70 (1H, m, 3 α -H). *Anal.* Calcd. for C₂₈H₄₀O₃: C, 77.27; H, 10.38. Found: C, 77.70; H, 10.58.

22,23-Epoxy-24-nor-5 α -cholan-3 β -ol Acetate (8)—The olefin acetate **4a** (214 mg, 0.575 mm) in chloroform (11.5 ml) was stirred with *m*-chloroperbenzoic acid (180 mg, 0.75 mm) at room temp. for 8 hr. The usual work-up (chloroform) gave the 22,23-epoxide **8** (220 mg), δ : 0.65 (3H, s, 18-Me), 0.82 (3H, s, 19-Me), 2.01 (3H, s, CH₃CO), 2.40–2.85 (3H, m, 22-H, 23-H), 4.70 (1H, m, 3 α -H).

22(ξ),23-Epoxy-24-nor-5 α -cholan-3 β -ol Benzoate (10)—a) Using Osmium Tetroxide: The olefin benzoate **4b** (30 mg, 0.069 mm) in ether (3 ml) was treated with osmium tetroxide at room temp. for 20 hr. Reduction of osmate by the similar method described above afforded the crude diol (22 mg). This diol was converted by treatment with *p*-toluenesulfonyl chloride (12.3 mg, 0.065 mm) and pyridine (0.5 ml) into monotosylate (26 mg) and then cyclized by treatment with anhydrous potassium carbonate (10 mg) in methanol (2 ml) and THF (0.2 ml) into the 22,23-epoxybenzoate **10** (22 mg) which showed homogeneity on TLC (benzene).

b) Using N-Bromosuccinimide in Aqueous Glyme: The olefin benzoate **4b** (90 mg, 0.203 mm) in glyme (14 ml) was treated with N-bromosuccinimide (154 mg, 0.845 mm) and water (0.7 ml) at room temp. for 4 hr. The usual work-up (dichloromethane) provided the crude bromohydrin (three spots on TLC), part of which (24 mg) was cyclized by the usual way into the 22,23-epoxybenzoate **10** (16 mg).

c) Using *m*-Chloroperbenzoic Acid: The olefin benzoate **4b** (13 mg, 0.03 mm) in chloroform (1 ml) was treated with *m*-chloroperbenzoic acid (9.3 mg, 0.04 mm) at room temp. for 20 hr. The usual work-up (chloroform) gave the 22,23-epoxybenzoate **10** (13 mg).

3 β -Tetrahydropyranyloxy-24-nor-5 α -cholan-22-ol (12)—a) Grignard Reaction with the 22-Aldehyde **11**: Magnesium (32 mg, 1.33 mm) in dry ether (0.5 ml) was reacted with methyl iodide (200 mg, 1.41 mm) at room temp. for 1 hr. To this solution was added the 22-aldehyde **11** (116 mg, 0.28 mm) in dry ether (1.8 ml) at room temp. This reaction mixture was stirred overnight. The usual work-up (ether) provided the 22-alcohol **12** (112 mg). Recrystallization (2 times) from methanol effected the pure (>97%) 22S-alcohol **12a**, mp 177–179°, δ : 0.66 (3H, s, 18-Me), 0.80 (3H, 19-Me), 0.90 (3H, d, *J*=6 Hz, 21-Me), 1.16 (3H, d, *J*=7 Hz, 23-Me), 3.3–4.1 (4H, m), 4.70 (1H, m).

b) Lithium Aluminum Hydride Reduction of the 22(S)23-Epoxy: Epoxy acetate (30 mg, 0.077 mm) in 2% methanolic sodium hydroxide (2 ml) was stirred at room temp. for 20 min. The usual work-up (ether) afforded the crystalline epoxyalcohol **9a** (27 mg), mp (MeOH) 159–161°, δ : 0.66 (3H, s, 18-Me), 0.81 (3H, s,

19-Me), 0.95 (d, $J=6$ Hz, 21-Me), 2.40 (1H, m), 2.70 (2H, m), 3.60 (1H, m, 3 α -H). *Anal.* Calcd. for $C_{25}H_{38}O_2 \cdot H_2O$: C, 75.77; H, 11.06. Found: C, 76.52; H, 11.08.

The epoxyalcohol **9a** (7 mg, 0.02 mm) in dichloromethane (0.5 ml) was treated with dihydropyran and *p*-toluenesulfonic acid at room temp. for 30 min. The usual work-up gave the tetrahydropyranyloxyepoxide **15a** (12.7 mg). Reduction of this epoxide **15a** (12.7 mg) with lithium aluminum hydride (10 mg) in refluxing THF (1 ml) provided the 22-alcohol **12a** (10.6 mg), δ : 0.66 (3H, s, 18-Me), 0.80 (3H, s, 19-Me), 0.90 (3H, d, $J=6$ Hz, 21-Me), 1.02 (3H, d, $J=6$ Hz, 23-Me), 3.30–4.10 (4H, m), 4.70 (1H, m).

22-D-3-Oxo-23,24-bisnor-5 α -cholan-22-ol Acetate (20)—The 22-aldehyde **11** (100 mg, 0.24 mm) in THF (1.5 ml) was added to the suspension of lithium aluminum deuteride (40 mg, 0.95 mm) in THF (1.5 ml) at -78° , and this mixture was stirred for 2 hr at -78° . The usual work-up (ether) afforded the 22D-22-alcohol **17** (88 mg). This crude product was acetylated by a usual way and then the resulting acetate was treated with 3N HCl solution (2 drops) in methanol (1.8 ml) for 30 min. The usual work-up (ether) gave the crude 3 β -alcohol (70 mg). The crude 3 β -alcohol **19** in acetone (1 ml) was oxidized with Jones' reagent for 10 min at room temp. The usual work-up (ether) provided the crude ketone **20** (59 mg), δ : 0.70 (3H, s, 18-Me), 1.00 (d, $J=6$ Hz, 21-Me), 1.01 (s, 19-Me), 2.03 (3H, s, CH_3CO), 3.75 (d, $J=7.5$ Hz), 4.06 (d, $J=2.5$ Hz).

Modified Horeau Analysis of 22S-Alcohol (12b)—22S-Alcohol **12b** was treated with ($\pm$)- α -phenylbutyric anhydride (1.2 μ l) and pyridine (14.8 μ l) at room temp. over night. To this reaction mixture was added (+)- α -phenylethylamine (3 μ l). After 15 min, the reaction mixture was directly analyzed by GLC using glass capillary column²¹; OV-17, 20 m $\times$ 0.25 mm, column temp. 210° . The peak high ratio of the diastereomeric amide was 1.2 (t_R 6.6 min): 1 (t_R 7.3 min).

High Pressure Liquid Chromatographic Analysis of 22,23-Epoxy Benzoate (10)—Dupont-Shimadzu high pressure liquid chromatograph Model 830 was employed. Zorbax SIL, 25 cm $\times$ 0.21 mm i.d., was used with a solvent of hexane- CH_2Cl_2 (2:1); pressure 60 atm. The retention times were 10.7 min for 22S-epoxy benzoate **10b** and 11.9 min for 22R-epoxy benzoate **10b**.

Gas Chromatographic Analysis of 3,22-diTMS Ether (14)—3 β -Tetrahydropyranyloxy alcohol (2 mg) **12** was treated with 2N HCl solution in methanol for 30 min. After the usual work-up, the resulting diol **13** was converted with large excess of trimethylsilylimidazole into diTMS ether **14**, which was directly analyzed by GLC using glass capillary column; OV-17, 20 m $\times$ 0.25 mm, column temp. 260° .²¹ The retention times were 8.3 min for 22S-diTMS **14b** and 9.3 min for 22R-diTMS **14a**.

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