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SYNTHETIC STUDIES OF WITHANOLIDES. PART 3.[1] SOME APPROACHES FOR THE SIDE-CHAIN LACTONE SYNTHESIS BY MEANS OF γ-COUPLING OF LITHIUM DIENOLATES WITH THE STEROIDAL 22-ALDEHYDES.[2]

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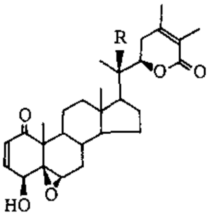
Abstract -- γ-Coupling of the lithium dienolates 5a-d with the steroidal 22-aldehydes 1-4 was investigated. Condensation of 5a with the (20R)-20-methoxymethyloxy-22-al 4 followed by lactonization gave the (20R,22R)-20-hydroxy-δ-lactone 13 which had the identical structure with withanolide D side-chain moiety, while the reaction of 5a with the 20-deoxy-22-al 1 gave the 22S-δ-lactone 6 which had the opposite stereochemistry at the 22-position to that of deoxywithaferin A. Attempts to invert the 22S-compounds 6 and 11 were unsuccessful. Lactonization of the 5,22,24-trienoic acid 14 gave predominantly the unsaturated γ-lactones.

The hydroxy group at the 22-position with R-configuration is characteristic of several biologically interesting steroids, such as ecdysones (22R-hydroxy group),[4] withanolides (22R-lactone),[5] and 23-deoxyantheridiol (22R-lactone).[6] Although several useful methods for the stereoselective introduction of 22R-hydroxy group have been already reported,[7a-f] less attention was paid to the synthesis of the 22R-δ-lactones.[8a-c] We reported that γ-coupling of lithium dienolates with steroidal 22-aldehydes gave directly the corresponding unsaturated δ-lactone having opposite configuration to natural δ-lactones at the 22-position.[9] In the course of the synthetic studies of withanolides, we have investigated the synthetic approaches to the side-chain lactone moieties of deoxywithaferin A and withanolide D, by γ-coupling reaction of dienolates from 2,3-dimethylbutenoic acid derivatives



R = H : deoxywithaferin A

R = OH : withanolide D

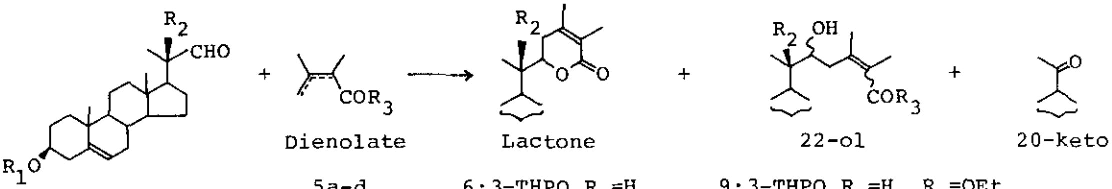
with 22-aldehydes 1-4.

Four 22-aldehydes were prepared as follows. Tetrahydropyranyl ether (1, R_1=THP, R_2=H) and acetate (2, R_1=Ac, R_2=H) of 3β-hydroxy-23,24-bisnorchol-5-en-22-al were synthesized according to the literature.[7f] The stereochemistry of 20-hydroxy group of 3β,20-dihydroxy-23,24-bisnorchol-5-en-22-al (3), prepared by the method of Lettre *et al.*,[10] was deduced as 20*R* by comparison of the NMR spectrum[11] with those of the corresponding (20*R*)- and (20*S*)-20-hydroxy-5,6-dihydro-22-al.[12] The 20*R*-configuration is desired for the synthesis of withanolide D side-chain moiety. The 20*R*-methoxymethyloxy(MOMO) derivative (4) was obtained by etherification with chloromethyl methyl ether on acetylated 3. Ethyl 2,3-dimethylbutenoate (5a), the methyl ester (5b), and the acid (5d) were prepared by the known method.[13] N,N-(1',5'-Pentanediyl)amide (5c) was obtained by chlorination of 5d with thionyl chloride followed by a reaction with piperidine. Although these four butenoic acid derivatives were mixtures of the α,β- and γ,δ-unsaturated isomers, they were used without further purification.

Four 2,3-dimethylbutenoic acid derivatives 5a-d reacted with lithium diisopropylamide(LDA)-hexamethylphosphoramide(HMPA) complex at -78° and the resulting dienolates were treated with 1-1/4 equivalent of four 22-aldehydes 1-4 in tetrahydrofuran(THF) at -78°. The results are summarized in Table 1. Reactions of the 20-deoxy-22-als 1 and 2 with dienolates of the esters 5a and 5b gave the δ-lactones 6 and 7 as major products and the 22-hydroxy esters 9 and 10 as minor ones, respectively. C-22 Protons of both lactones 6 and 7 showed characteristic couplings at δ 4.42 (dd, J=4 and 12 Hz) in their NMR spectra, whereas that of withaferin A appears at δ 4.40 in double triplet.[14a] This implied the lactones 6 and 7 had opposite configuration to natural δ-lactones. Moreover, the stereochemistry at C-22 of the lactone 6 was assigned by comparing the circular dichloism (CD) spectrum with those of naturally occurring δ-lactones. The CD curve of 6 gave a strong negative peak at 258 nm (Δε, -3.72) in contrast with positive curves of dihydrodeoxywithaferin A acetate (248 nm; Δε, +3.54)[14b] and parasorbic acid (260 nm),[15] supporting the stereochemistry (22S-) opposite to the natural δ-lactones. The structures of the minor products, the 22-hydroxy esters 9 and 10, were studied by NMR and mass spectrometry. Comparison of their 28-methyl(Me) signals (δ 2.02 and 1.99) with those of the corresponding lactones (δ 1.92 and 1.91) indicated that the esters have trans Δ^{24} bonds, but the configurations of 22-hydroxy groups remained obscure. These results suggest that the condensation follows the Cram's rule as an addition of Grignard reagents to the 22-aldehyde[7c] and that the coupling reaction occurs through the 'U'form[16] of the dienolates rather than the corresponding 'sickle'form, to give cis esters which afford the δ-lactones.

On the other hand, if the condensation of the dienolates with 20-hydroxy-22-als also follows Cram's rule (cyclic model), one might expect to obtain a stereochemi-

Table 1. Condensation of 22-Aldehydes 1-4 with Lithium Dienolates Derived from 5a-d



22-Aldehyde
1-4

5a-d

6: 3-THPO R$_2$=H
7: 3-AcO R$_2$=H
8: 3-AcO R$_2$=MOMO

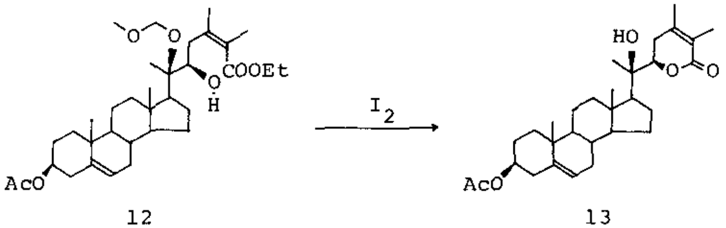
9: 3-THPO R$_2$=H R$_3$=OEt
10: 3-AcO R$_2$=H R$_3$=OMe
11: 3-AcO R$_2$=H R$_3$=$C_5H_{10}N$
12: 3-AcO R$_2$=MOMO R$_3$=OEt

22-Aldehyde			Dienolate			Reaction Condition	Product (yield %)		
	R$_1$	R$_2$		R$_3$	(Eq.)		Lactone	22-ol	20-keto
1	THP	H	5a	EtO	(3)	-78°, 2 hr	6(56)	9(22)	
2	Ac	H	5b	MeO	(3)	-78°, 3 hr	7(44)	10(16)	
2	Ac	H	5c	$C_5H_{10}N$	(1.5)	-78～-10°, 16 hr		11(59)	
3	H	OH	5a	EtO	(4)	-78°, 3 hr[a)]			(80)
3	H	OH	5d	HO	(4)	-78°, 3 hr			(84)
4	Ac	MOMO	5a	EtO	(4)	-78°, 3 hr		12(26)[b)]	
4	Ac	MOMO	5a	EtO	(4)	-78°, 2 hr[c)]		12(25)	(35)
4	Ac	MOMO	5a	EtO	(4)	-78～-35°, 8 hr	8(16)	12(44)	

a) Followed by stirring at room temperature, 19 hr. b) Recovered 4 (40% yield). c) Followed by stirring at room temperature, 2 hr.

cally identical structure with withanolide D side-chain δ-lactone. However, condensation of the (20R)-20-hydroxy-22-al 3 with lithium dienolates of 5a and 5d afforded no desired compound, but of both gave pregnenolone, which probably arose by elimination of 20-formyl group in the basic condition.[12] In order to prevent the elimination of the formyl group, the 20-hydroxy group was protected as methoxymethyl(MOM) ether. Treatment of the protected aldehyde 4 with dienolate of 5a at -78~-35° for 8 hr successfully gave the corresponding δ-lactone 8 (16% yield) and 22-hydroxy ester 12 (44% yield), though a similar treatment at an elevated temperature gave pregnenolone along with 12. The structures of the products were characterized by their spectral data and by the transformation into the object δ-lactone 13. The Δ^{24} bond of the hydroxy ester 12 seems to be cis geometry from comparison of the 28-Me signal (δ 1.92) with those of δ-lactones 6-8 (δ 1.90 ~ 1.92) and of trans esters 9 and 10 (δ 2.02 and 1.99). The configuration of C-22 carbon of 12 was determined as 22R by measurement of CD curve of the corresponding δ-lactone 13. This indicates that attack of the dienolate to the 20-MOMO-22-al proceeds through the 'U'form to provide the aldol products. The reluctance of 12 to form the lactone might result from the steric bulkiness of the MOMO group. Although 22-aldehydes reacted with Grignard reagents to give normal condensation products,[7c,12] treatment of 4 with isoamylmagnesium bromide provided mainly a reduced product. The above results suggest that the 20-formyl group is very hindered by the bulky MOMO group. In fact, removal of the 20-MOM group of 12 easily gave the corresponding 20-hydroxy δ-lactone as described in the next transformation.

The MOMO compound 12, when treated with iodine in THF, provided the desired δ-lactone 13 in one step in a high yield. Although detailed investigations have not

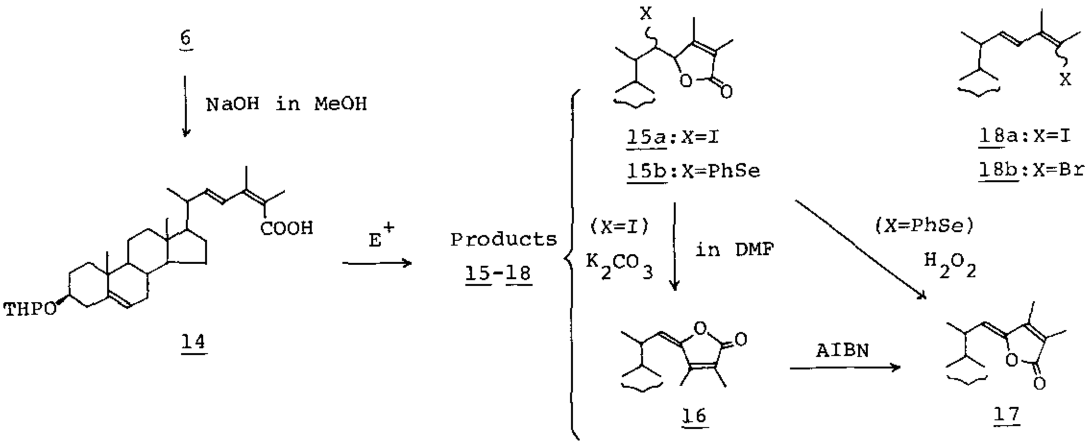


12 13

been made, we are not aware of such examples of the removal of MOM group by iodine so far. The stereochemistry of 13 was deduced by comparing NMR and CD spectral data with those of withanolide D. The proton signals of 18-Me, 21-Me, 22-H, 27-Me, and 28-Me of 13 showed a perfect agreement with those of withanolide D.[17] Furthermore, the configuration at C-22 was assigned to be R by a strong positive peak in the CD spectrum at 252 nm (Δε, +5.2), which is also a fair agreement with that of withanolide D acetate (254 nm; Δε, +3.72).[14b]

Although withanolide D side-chain moiety could be successfully obtained by condensation of the dienolate with the 20-MOMO-22-al as described above, a similar condensation with the 20-deoxy-22-al had provided the 22S-products which had the opposite stereochemistry to that of deoxywithaferin A. For the stereocontrolled introductions of a steroidal 22-hydroxy group, we have already reported several useful methods. In order to invert the 22S alcohols, we investigated two approaches; the electrophillic attack to the 22-double bond[7e,18] and the inversion of the mesylate of hydroxy group by potassium superoxide.[7f] For the application

Table 2. Attempts of Lactonization of Trienoic Acid 14 and Transformation of the Products 15-18.



Electrophile	Solv.	Condition	Product Yield % Lactone 15	 Enol 16	 Lactone 17	 Triene 18
$I_2\cdot K_2CO_3$	CH_3CN	r.t., 16 hr	35a)	trace		19a)
$I_2\cdot K_2CO_3$	DMF	r.t., 40 hr		67		
PhSeCl	THF	r.t., 3 hr	57a,b)			
Ph_2Se_2 d)	THF	-78°, 0.5 hr			44	
NBS	$CHCl_3$	-78°, 1/4 hr				20a,c)

a) Isolated as a stereoisomeric mixture. b) Containing the 3-OH compound 15′ (40% yield). c) A mixture of unidentified compounds (19% yield, $C_{33}H_{49}O_4Br$). d) Diphenyldiselenide was used instead of disulfide.[20b]

of these method, 5,22,24-trienoic acid 14 and 22-hydroxy amide 11 were prepared by isomerization of lactone 6 and coupling reaction of the 22-aldehyde 2 with the amide 5c, respectively.

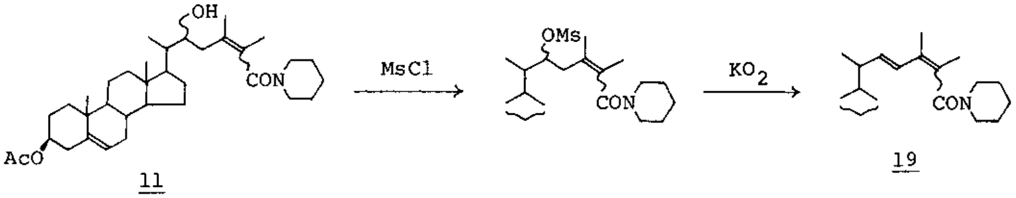
Treatment of δ-lactone 6 under hydrolytic condition with 15% methanolic sodium hydroxide gave no hydroxy acid but only the isomerized 5,22,24-trienoic acid 14. Then, halo-[19] and phenylselenolactonization[20a,b] of 14 were investigated under various conditions. The results are summarized in Table 2. Iodolactonization in the presence of potassium carbonate (K_2CO_3) in acetonitrile gave the iodo-γ-lactone 15a accompanied with the 25-iodotriene 18a, while a similar treatment in N,N-dimethylformamide(DMF) gave the enol γ-lactone 16 as the sole product. Treatment of 15a with K_2CO_3 in DMF gave 16. Selenolactonization with phenylselenenyl chloride gave the seleno-γ-lactone 15b, while treatment with diphenyl diselenide provided the enol γ-lactone 17. Oxidation of the selenolactone 15b with 30% aqueous hydrogen peroxide also gave the enol lactone 17. Moreover, 17 was obtained by isomerization of 16 in the presence of azobisisobutyronitrile(AIBN). Treatment of 14 with N-bromosuccinimide(NBS) gave the 25-bromotriene 18b along with a mixture of unidentified compounds. The lactones 15a, 15b, 16, and 17 were characterized as γ-lactones by their spectral data and elemental analyses. It was also comfirmed that the lactones (15a, 15b) and the halotrienes (18a, 18b) were mixtures of two stereoisomers by 18-Me, 22-, and 23-proton signals of their NMR data. As to the configuration of the 22-double bond, 16 and 17 are logically to have *Z*- and *E*-configuration,[21] *i.e.*, iodo- and selenolactonization are known to proceed *via trans* addition to produce 15a and 15b, so that *trans* dehydroiodation of 15a with K_2CO_3 must give the *Z*-configuration product 16 and that *syn*-elimination of phenylselenenyl group of 15b with hydrogen peroxide must give the *E*-configuration product 17. These assumptions are supported by the NMR data of the products; the 22-proton signal of 16 appeared at a lower field (δ 5.54) than that of 17 (δ 5.00). Molecular models of 16 and 17 indicate that the 28-Me group of 16 has a strong steric interaction with the C-16 and C-21 groups in *cis* position while that of 17 has no such interaction. The easiness of the isomerization of 16 into 17 would be interpreted by these steric differences. Although the formation of 25-halotrienes 18a and 18b must include an elimination of the carboxyl group, it is not clear whether the decarboxylation proceeds through a halonium intermediate or a radical intermediate.[22]

Finally we attempted the configurational inversion of 22-hydroxy group. Since *it was impossible to obtain the 22S-hydroxy acid by hydrolyzing the lactone 6 as* mentioned above, an alternative method was investigated to prepare 22S-hydroxy compound. Condensation of the amide 5c with 22-aldehyde 2 in a similar manner

Table 3. Physical and Spectral Data.

Comp	Mp °C	NMR$^{b)}$	δ ppm(J Hz)				Found
No	(solv)$^{a)}$	18-Me	19-Me	22-H	27- and 28-Me$^{c)}$		Anal:C%, H% or Mass
4	102-103(M)	0.78	1.37	9.74(s)	-	-	403.28542$^{d)}$
6	185-188(M)	0.68	1.05	4.42(4,12)	1.92	1.92	408.31186$^{e)}$
7	210-212(M)	0.69	1.05	4.42(4,12)	1.91	1.91	408.31155$^{f)}$
8	106-108(M)	0.85	1.38	4.25(4,12)	1.90	1.90	468.32040$^{g)}$
9	129-132(E)	0.71	1.03	3.72(m)	1.92	2.02	75.69, 10.14
10	218-220(M)	0.70	1.00	*	1.91	1.99	440.32249$^{g)}$
11$^{h)}$	173-175(M)	0.69$^{i)}$	1.02	3.92(m)	1.83	1.83	493.38820$^{g)}$
12	192-195(M)	0.88	1.40	4.28(4,12)	1.92	1.92	469.32813$^{j)}$
13	217-218(M)	0.86	1.28	4.23(4,12)	1.92	1.92	424.29816$^{g)}$
WD$^{k)}$	-	0.85	1.27	4.25(5,12)	1.91	1.91	-
14	167-169(A)	0.65	1.00	5.67(8,15)	1.85	1.85	408.30785$^{e)}$
15a$^{h)}$	179-181(M)	[0.74 0.70	* *	4.14(2,6) 4.36(2,6)	1.83 1.90	2.22 1.90]	62.43, 7.75
15b$^{h)}$	170-173(A)	[0.66 *	1.08 *	3.40(4) 3.38(4)	1.83 1.82	1.86 1.87]	70.55, 8.08$^{l)}$
16	191-193(M)	0.74	1.02	5.54(11)	1.90	2.24	424.29866$^{m)}$
17	190-192(M)	0.74	1.00	5.00(10)	1.89	2.00	424.29089$^{m)}$
18a$^{h)}$	131-134(A)	[0.74 0.69	1.04 *	5.55(8,15) 5.61(8,15)	1.94 *	2.64 *]	65.12, 8.46
18b$^{h)}$	103-107(M)	[0.71 *	1.01 *	6.05(8,15)$^{n)}$ 6.05(8,15)$^{n)}$	1.79 *	2.38 *]	70.37, 9.08
19	135-137(A)	0.69	1.02	5.47(8,15)	1.76	1.87	535.39076$^{f)}$

a) Recrystallization solvent: M; methanol, E; ethanol, A; ethyl acetate. b) The marks * indicate that the signals could not be assigned. c) The signals may be reversed. d) M^+-CHO e) M^+-$C_5H_{10}O_2$(2-hydroxytetrahydropyran). f) M^+. g) M^+-CH_3COOH. h) An isomeric mixture. i) Another signal 0.72. j) M^+-CH_3COOH-OC_2H_5. k) Withanolide D, ref. 17. l) As a mixture of the corresponding 3-OH derivatives. m) M^+-C_5H_8O(dihydropyran). n) 23-H(δ 6.54 and 6.25, both J=15 Hz) gave the 22-hydroxy amide 11 in 59% yield without lactonization. NMR spectral data indicated that 11 was a mixture of the stereoisomers, *i.e.*, the C-18 proton signals appeared at δ 0.69 and 0.72 as two singlets in the ratio 1:2. By the reaction of mesyl chloride, 11 could be transformed into mesylate. Treatment of the mesylate



with potassium superoxide afforded no desired C-22 substitution product but only the elimination product 19. The elimination predominates probably because the allylic 23-hydrogen is fairly acidic compared with those of 22-hydroxycholesterol 3-THP ethers.[7f]

Experimental

M.p.s. are uncorrected. The NMR spectra were run on a JEOL-JNM-4H-100 in $CDCl_3$ with tetramethylsilane as an internal standard and mass spectra were recorded on a Hitachi M-80 mass spectrometer. Optical rotations were taken for ethanol solution on a JASCO-DIP-S polarimeter. The physical and spectral data are summarized in Table 3, unless stated. The data of elemental analyses and high resolution mass spectra were in good agreement with their calculated values. Column chromatography was performed using silica gel (Wakogel C-200). Organic extracts were dried over magnesium sulphate. The usual work-up refers to dilution with water, extraction with an organic solvent, washing to neutrality, drying, filtration, and evaporation under vacuum.

N,N-(1',5'-Pentanediyl)-2,3-dimethylbutenamide (5c) --- Thionyl chloride (17 ml) was added to acid 5d (15 g, 0.13 mol) and the mixture was stirred for 1 hr at 40-50°. Reduced distillation gave the acid chloride (14.2 g, bp 65-68°/36 mmHg). The acid chloride (14.2 g) was added slowly to a solution of piperidine (15 ml) and N,N-dimethylaniline (18 ml) in THF (20 ml) and the mixture was stirred for 2 hr. After the usual work-up (ether for extraction), the residue was distilled to give the amide 5c (10.4 g, 43.7%), bp 94-95°/4 mmHg. NMR; δ 1.25(3H, d, J=6 Hz), 1.1-1.3(9H), 3.3-3.6(5H), 4.85(2H): Mass; M^+=181.

(20R)-3β-Acetyloxy-20-methoxymethyloxy-23,24-bisnorchol-5-en-22-al (4) --- A mixture of 3β,20-dihydroxy-22-al 3 (492 mg, 1.42 mmol) and acetic anhydride (2 ml) in pyridine (6 ml) was stirred at room temperature for 4 hr. The usual work-up (ether for extraction) gave a crude 3-acetate (494 mg). The acetate (410 mg, 1.1 mmol) in dioxane (8 ml) was treated with N,N-diethylcyclohexylamine (2 ml) and chloromethyl methyl ether at 80° for 2 hr. After addition of 2N hydrochloric acid, the usual work-up (ether for extraction) gave a crude product, which recrystallized from methanol to afford the 20-MOM ether 4 (344 mg, 75%).

Condensation of 23,24-Bisnorchol-5-en-22-als 1-4 with Dienolates of 5a-d --- A solution of 5a-d (1 mmol) in THF (1 ml) and HMPA (0.2 ml) was added at -78° under argon to a solution of LDA (1 mmol) in THF (2 ml) and the mixture had been stirred at -78° for 1 hr. Then a solution of 22-aldehydes (1-1/4 eq.) in THF (2 ml) was added to this enolate at -78° and the resulting mixture had been stirred under the conditions described in Table 1. 2N-Hydrochloric acid was added to this reaction mixture at -78° and warmed up to room temperature. After the usual work-up, (ethyl acetate for extraction), the crude product was chromatographed on silica gel to give the condensation products 6-12. Yields and product distributions are summarized in Table 1.

Reaction of 20-MOMO-22-al 4 with iso-Amylmagnesium Bromide --- Compound 4 (86 mg, 0.2 mmol) in THF (1 ml) was added at 0° to a solution of isoamylmagnesium bromide in THF (2 ml), prepared from magnesium (26 mg, 1.1 mmol) and isoamylbromide (150 mg, 1.1 mmol). After stirring for 1.5 hr at room temperature, aq. NH_4Cl solution was added to the reaction mixture. Usual work-up (ether for extraction) gave a crude product. Acetylation of the crude product with acetic anhydride in pyridine followed by purification by column chromatography gave 20-MOMO-23,24-bisnorchol-5-en-3,22-diol diacetate (39 mg, 40%), mp(methanol) 98-100°. NMR; δ 0.83(18-Me), 1.02(19-Me), 1.38(21-Me), 3.35(OMe), 4.05(s, 2H, 22-H), 4.68 and 4.80(OCH_2O). Mass; Found: M^+-CH_3COOH = 416.30057.

(20R,22R)-3β-Acetyloxy-20,22-dihydroxy-24-methylcholesta-5,24-dien-26-oic Acid δ-Lactone (13) --- The 22-hydroxy ester 12 (157 mg, 0.27 mmol) was treated with iodine (220 mg) in THF (8 ml) at 50-60° for 16 hr. After addition of 2N aq. $Na_2S_2O_3$ solution, the usual work-up (ether for extraction) gave a crude product, which was chromatographed on silica gel to give the pure lactone 13 (109 mg, 83%).

3β-Tetrahydropyran-2'-yloxy-24-methylcholesta-5,22,24-trienoic Acid (14) --- Suspension of lactone 6 (306 mg, 0.6 mmol) and sodium hydroxide (625 mg) in methanol (15 ml) was refluxed for 15 hr. After the solvent was evaporated, the residue was dissolved in dichloromethane and acidified with 2N hydrochloric acid. The usual work-up gave a crude product which was chromatographed on silica gel to give the acid 14 (198 mg, 65%).

Lactonization of Acid 14 --- Materials used as follows. Iodolactonization; 14 (0.3 mmol), K_2CO_3(1.5 mmol), iodine(0.75 mmol), and solvent(15 ml, CH_3CN or DMF). Selenolactonization; 14(0.3 mmol), phenylselenenyl chloride(0.33 mmol), and THF (6 ml): Acid 14(0.3 mmol), diphenyl diselenide(0.54 mmol), lead tetraacetate(0.54 mmol), trifluoroacetic acid(4.8 mmol) and THF(5 ml). Bromolactonization; 14(0.3 mmol) in chloroform (9 ml) and NBS(0.3 mmol) in acetone. Reaction conditions are shown in Table 2. After the usual work-up, the crude products were separated by column chromatography or plc.

Transformation of γ-Lactones 15a, 15b, and 16 --- a) A mixture of iodolactone 15a (12 mg) and K_2CO_3 (14 mg) in DMF (1 ml) was stirred for 18 hr at room temperature. The usual work-up (ethyl acetate for extraction) gave the enol lactone 16 (6 mg). b) Selenolactone 15b (12 mg) was stirred in THF (0.2 ml) containing six drops of 30% aq. hydrogen peroxide at room temperature for 1 hr. The usual work-up gave the enol lactone 17 (8 mg). c) A solution of enol lactone 16 (12 mg) and AIBN (1 mg) in THF (0.3 ml) was refluxed for 4.5 hr. The usual work-up gave the isomerized enol lactone 17 (10 mg).

Attempt for Inversion of 22-Hydroxy Amide 11 by Potassium Superoxide --- 22-Hydroxy amide 11 (230 mg, 0.4 mmol) was treated with mesyl chloride (0.7 ml) in pyridine (3 ml) for 2.5 hr at room temperature. The usual work-up gave a crude mesylate (267 mg). To a solution of the mesylate (58 mg, 0.09 mmol) in dimethyl sulfoxide(1.5 ml)-dimethylformamide(1.5 ml) was added dicyclohexyl-18-crown-6 (137 mg, 0.36 mmol) and potassium superoxide (26 mg, 0.36 mmol). After stirring for 23 hr at 0° and for 30hr at room temperature, the solution was extracted with ether. The usual work-up gave a crude product (199 mg), which was chromatographed on silica gel to give the elimination product 19 (38 mg, 48%).

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