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Modification of α-Santonin. IV.[1] Epoxidation of Germacranolide-type Sesquiterpenes

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Epoxidation of germacranolide-type sesquiterpenes (**1**, **5**, **11**, **17**, **20**, and **34**) with *m*-chloroperbenzoic acid in dichloromethane or in a dichloromethane–aqueous sodium hydrogen carbonate biphasic system is described. 5-Hydroxy compounds (**11** and **20**) gave the corresponding epoxides (**7**, **21**, **22**, and **23**) with *m*-chloroperbenzoic acid in a dichloromethane–aqueous sodium hydrogen carbonate biphasic system, while these compounds afforded the cyclized products (**12**, **29** and **30**) with *m*-chloroperbenzoic acid in dichloromethane.

Keywords——α-santonin; sesquiterpenoid; germacranolide; epoxidation; oxidation; *m*-chloroperbenzoic acid; cyclization; configuration

The germacranes are a class of commonly occurring sesquiterpenes which have the cyclodecane ring system.[3,4] Some of their members are known as synthetic and biogenetic precursors of other important class of sesquiterpenes,[5,6] and others are noted by their pronounced cytotoxic and antitumor activities.[7] In the preceding papers,[1,8] we reported a novel method for the preparation of cyclodecanone intermediates which are useful for the synthesis of not only germacranolides but guaianolides, starting from α-santonin, and further reported the synthesis of dihydrocostunolide,[9] a typical germacranolide, isolated from costus root oil.

Now our interests are forcused on epoxidation of the synthetic cyclodecane intermediates (**1**, **5**, **11**, **17**, **20** and **34**) for the synthetic approach to the naturally occurring epoxy-germacranolides, heliangine and pyrethrosin, *etc.*, as well as the hydroxy-germacranolides such as artemorin and tamaulipin A which may be synthesized *via* the epoxy-germacrane intermediates.

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2) Location: *Hirosawa, Wako-shi, Saitama, 351, Japan.*
3) H. Yoshioka, T.J. Marby, and B.N. Timmermann, "Sesquiterpene Lactones," University of Tokyo Press, Tokyo, 1973, p. 7.
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5) Biogenetic studies: *a*) J.B. Hendrickson, *Tetrahedron*, **7**, 82 (1959); *b*) G. Rücker, *Ang. Chem.*, **85**, 895 (1973); *c*) G.A. Cordell, *Chem. Rev.*, **76**, 425 (1976).
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8) *a*) Y. Fujimoto, T. Shimizu, and T. Tatsuno, *Chem. Pharm. Bull.* (Tokyo), **24**, 365 (1976); *b*) *Idem*, *Tetrahedron Lett.*, **1976**, 2041.
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First, we examined epoxidation of the 5-keto compounds[1] (**1** and **5**) with *m*-chloroperbenzoic acid (MCPBA) in dichioromethane or in a dichloromethane–aqueous sodium hydrogen carbonate biphasic system.[10] When the compound **1** was treated with 1.2 equivalents of MCPBA at room temperature, the corresponding monoepoxide (**2**) [*m/e* 264(M^+)] was obtained in a high yield. The reaction of **5** with MCPBA similarly afforded the corresponding epoxide

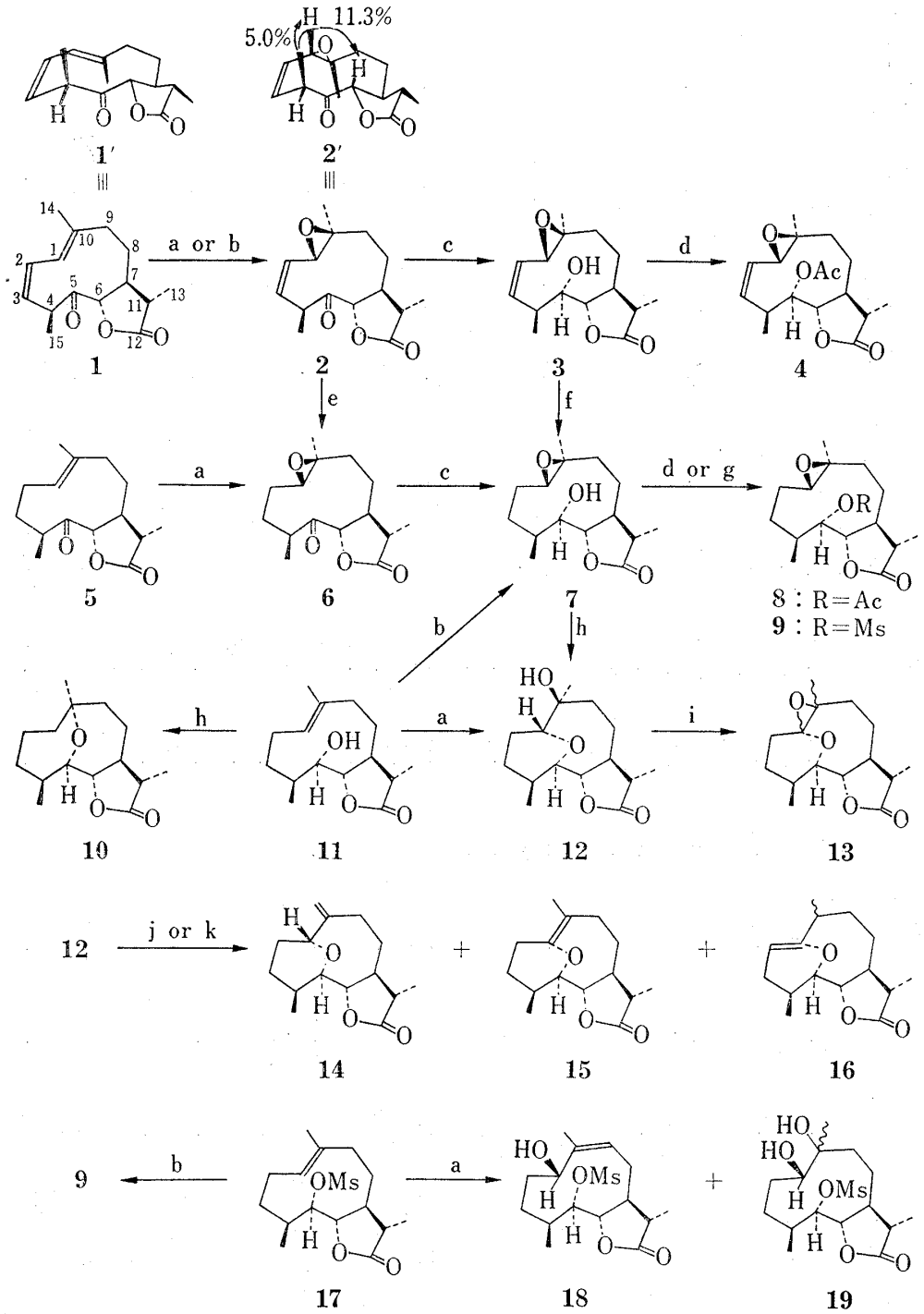

Chart 1

a) MCPBA in CH_2Cl_2, b) MCPBA in CH_2Cl_2–$NaHCO_3$–H_2O, c) $NaBH_4$, d) Ac_2O–pyridine (4-dimethylaminopyridine), e) H_2–PtO_2, f) H_2–Pd/C, g) CH_3SO_2Cl–pyridine, h) HCl, i) CrO_3–pyridine in CH_2Cl_2, j) $SOCl_2$–pyridine, k) Et_3N^+-$SO_2N^-CO_2Me$.

10) W.K. Anderson and T. Veysoglu, *J. Org. Chem.*, **38**, 2267 (1973).

TABLE I. Spectral Data of Oxidation Products and Dehydration Product of **12**

Compd. No.	GC–MS *m/e* (M^+)	IR (KBr) cm^{-1}	^{1}H-NMR spectral data ($CDCl_3$, δ) (Hz)								^{13}C-NMR spectral data ($CDCl_3$, δ) (Hz)					
			H-15	H-14	H-13	H-1	H-5	H-6	OH	$J_{5,6}$	C-1	C-5	C-6	C-10	C-12	
3	266	3430 1755	1.18 d (6.2)	1.27 s	1.42 d (6.0)	3.48 d (6.5)	3.53 dd (10.0) (1.0)	4.29 br. s	3.90 br. s	1.0						
7	268	3460 1762	1.08 d (6.0)	1.35 s	1.34 d (7.0)	2.98 dd (9.6) (3.2)	3.63 ddd (8.0) (5.5) (2.0)	4.50 dd (5.2) (2.0)	2.54 d (8.0)	2.0	63.4 d (168)	73.2 d (140)	87.6 d (146)	59.5 s	179.0 s	
12	268	3450 1750	1.00 d (6.0)	1.18 s	1.27 d (6.0)	3.68 dd (3.5) (3.5)	3.58 d (8.3)	4.20 dd (8.3) (8.3)	2.40 br. s	8.5	77.6* d (140)	78.0* d (143)	80.0 d (144)	75.1 s	178.5 s	
13	266	1780 1765(sh)	1.06 d (6.5)	1.31 s	1.28 d (6.0)	—	3.76 dd (9.0) (4.0)	4.38 dd (9.0) (9.0)		9.0	86.1 s	80.7* d	81.0* d	67.0 s	178.0 s	
14	250	1775 1640(w)	0.97 d (6.5)	5.05 br. s (2H)	1.27 d (5.5)	4.20 m	3.58 dd (9.5) (4.5)	4.41 dd (9.5) (9.5)		9.5	72.6 d	79.5 d	80.1 d	150.9 s	178.0 s	112.3 t (C-4)
15	250	1780 1770(sh) 1695(w) 1675(w)	0.99 d (7.0)	1.62 s	1.28 d (6.0)	—	3.77 dd (9.0) (4.5)	4.47 dd (9.0) (9.0)		9.0	145.2 s	83.4 d	80.5 d	117.4 s	178.1 s	
16	250	1783 1770(sh) 1670(w)	0.94 d (6.8)	1.06 d (6.4)	1.23 d (6.0)	—	3.09 d (8.2) (3.6)	4.23 d (8.2) (8.2)	4.67 m (H-2)	8.2	155.5 s	78.2* d	81.8* d		178.0 s	99.4 d (C-2)

* These assignments may be interchanged.

6 which was also obtained by hydrogenation of **2** over platinum. Configuration of the epoxy ring of **2** as well as of **6** could be assigned as shown in the structure **2** from the assumption that an oxygen atom must be added to an ethylene bond from the outside of the ten-membered ring.[6b] Furthermore, the conformation of **2** was confirmed as shown by structure **2'** by the intramolecular internuclear Overhauser effect (NOE) experiments.

Next, we examined epoxidation of the 5-hydroxy compound[1] (**11**). The reaction of **11** with MCPBA in dichloromethane gave a cyclic ether (**12**) which has an 11-oxadicyclo[5.3.1]-undecane system, in an almost quantitative yield. The structure of **12** was determined on the basis of its spectral data given in Table I and from the chemical evidences. The infrared (IR) spectrum of **12** [*m/e* 268(M^+)] showed the presence of a tertiary hydroxyl group (ν_{max}: 3450 cm^{-1}) which is not acetylated by the ordinary procedure (acetic anhydride–pyridine, room temperature, 24 hr). The proton nuclear magnetic resonance (PMR) spectrum of **12** indicates the presence of one tertiary methyl group (1.18 ppm) and two ether protons (3.63 and 3.70 ppm, each 1H). Moreover, this structure agrees with considerations based on the Dreiding model (**12**: ∠H-5—H-6=140°, **11**: ∠H-5—H-6=110°), where a large coupling constant (8.5 Hz obserbed) between the H-5 and the H-6 in **12** would be expected as compared with a small constant (2.0 Hz observed) in **11**. **12** was also obtained by the action of a catalytic amount of hydrochloric acid on **7** which was obtained by reduction of **6** with sodium borohydride or by hydrogenation of the alcohol (**3**) derived from **2**. These spectral data and reactions supported the structure **12**. Now, we examined whether the epoxy compound (**7**) was an intermediate of the reaction of **11** with MCPBA. On treatment of **7** with *m*-chlorobenzoic acid in dichloromethane (room temp., 1 day), the starting material was recovered and a detectable amount of **12** was not found in the reaction mixture. This result suggests that the epoxy-alcohol (**7**) was not the intermediate and the cyclized alcohol (**12**) was formed directly through the participation of the OH on the C-1 on oxidation reaction of **11** with MCPBA in dichloromethane. While the epoxy-alcohol (**7**) gave **12** by the action of hydrochloric acid, the enol (**11**) afforded the cyclized product (**10**) through the attack of the OH on the C-10 under the same conditions.

The structure **12** was further confirmed by its transformation to the dehydrated products (**14**, **15**, and **16**) [*m/e* 250 (M^+) for all] with thionyl chloride–pyridine (0°, 25 min) or (carboxysulfamoyl)triethylammonium hydroxide inner salt methyl ester[11] (80°, 5 hr). Oxidation of **12** with chromic anhydride-pyridine complex in dichloromethane[12] (room temp., 1 hr) unexpectively afforded an epoxide (**13**) as a major product, which was also obtained by oxidation of **15** with MCPBA in the two-phase system[10] or by oxidation with chromic anhydride-pyridine complex. The structure of **13** [*m/e* 266(M^+)] was confirmed by its ^{13}C-nuclear magnetic resonance (CMR) spectrum which showed two singlet signals assigned to the C-10 and the C-1 at 67.0 and 86.1 ppm, respectively. When **11** was treated with MCPBA in the dichloromethane–aqueous sodium hydrogen carbonate biphasic system[10] (room temp., 10 min), the corresponding epoxide (**7**) was obtained in 90.8% yield and a detectable amount of **12** was not found in the reaction mixture.

On the other hand, the reaction of the 5-mesyloxy compound[1] (**17**) with MCPBA in dichloromethane (room temp., 24 hr) gave an enol (**18**) as a major product, together with a small amount of diol (**19**) which must be derived from its *m*-chlorobenzoate. By the two-phase epoxidation procedure, **17** gave the corresponding epoxide (**9**) quantitatively which was also obtained by mesylation of **7** with methanesulfonyl chloride–pyridine (room temp., 2 hr).

Next, we examined the reaction of the 1,3-dien-5-ol derivative[1] (**20**) with MCPBA. When **20** was treated with 1.2 equivalents of MCPBA in the dichloromethane–aqueous sodium

11) E.M. Burgess, H.R. Penton, Jr., and E.A. Taylor, *J. Org. Chem.*, **38**, 26 (1973).
12) R. Ratcliffe and R. Rodehorst, *J. Org. Chem.*, **35**, 4000 (1970).

TABLE II. Spectral Data of Oxidation Products and Their Derivatives

Compd. No.	GC–MS *m/e* (M^+)	IR (KBr) cm^{-1}	^{1}H-NMR spectral data ($CDCl_3$, δ) (Hz)										^{13}C-NMR spectral data ($CDCl_3$, δ) (Hz)						
			H-15	H-14	H-13	H-1	H-2	H-3	H-5	H-6	OH or Ac	$J_{5,6}$	C-1	C-2	C-3	C-4	C-5	C-6	C-12
21	266	3460 1760	1.86 br. s	1.13 br. s	1.38 d (6.5)	2.7[a]	4.53 m	5.45 dq (5.0) (2.0)	4.53 br. s	4.14 dd (8.5) (2.0)	2.90 br. s (OH)	2.0	65.0 d (164)	54.8 d (184)	128.5 d (160)	135.6 s	73.4 d (144)	83.2 d (149)	179.1 s
22	266	3550 1770	1.43 s	1.05 d (6.5)	1.29 d (7.0)	5.33 dd (11.0) (9.0)	5.71 dd (11.0) (4.5)	3.62 dd (4.5) (1.5)	4.28 d (2.0)	4.25 dd (8.5) (2.0)		2.0							
23	282	3450 1775	1.43 s	1.20 br. s	1.37 d (6.5)	2.8[a]	3.60 dd (6.5) (4.5)	2.78 d (6.5)	4.49 d (2.0)	4.31 dd (8.0) (2.0)	2.70 br. s (OH)	2.0	61.4 d (168)	55.8 d (184)	63.1 d (178)	60.1 s	70.3 d (144)	81.7 d (144)	178.2 s
24	308	1770 1750	1.93 s	1.17 br. s	1.42 d (6.5)	2.6[a]	4.00 ddq (5.0) (5.0) (1.0)	5.45 dd (5.0) (2.0)	5.50 d (2.5)	4.19 dd (8.5) (2.5)	2.12 s (Ac)	2.5	65.0 d (168)	54.3 d (176)	128.5 d (160)	134.2 s	74.1 d (160)	80.4 d (148)	177.8[b] s
27	264	1790[c] 1720	2.05 br. s	1.12 br. s	1.37 d (6.5)		3.66 m	5.58 m	—	4.66 d (9.0)									
29	266	3480 3380 1780 1760 (sh)	1.86 br. s	0.91 d (6.0)	1.23 d (6.0)	3.65 dd (9.0) (6.0)	5.15 m	5.53 ddq (1.6) (1.6) (1.6)	4.53 m	4.12 dd (9.0) (7.5)		7.5	76.1 d (140)	87.7 d (152)	120.9 d (169)	140.4 s	90.2 d (152)	86.5 d (148)	178.6 s
30	282	3330 1760	1.36 s	0.93 d (6.0)	1.27 d (6.0)	4.17—4.70 m (4H) C_1,C_2,C_3 and C_4-H			4.02 br. s		3.27 br. s (OH)		78.0* d (160)	79.2* d (160)	83.0* d (158)	75.8 s	84.0* d (160)	84.2* d (155)	179.4 s
31	308	1765 1738	1.89 br. s	0.85 d (6.0)	1.28 d (6.5)	4.89 dd (6.0) (6.0)	5.10 m	5.42 m	4.57 dd (8.0) (2.0)	4.13 dd (8.0) (8.0)	2.06 s (Ac)	8.0							
32	264	1770 1715	1.90 br. s	0.99 d (6.0)	1.28 d (6.0)	—	5.05 ddq (2.0) (2.0) (2.0)	5.39 m	4.72 m	4.37 dd (8.0) (8.0)		8.0							

a) Chemical shift of H-1 was presumed by selective proton-decoupling on ^{13}C-NMR spectrum. *b*) 167.6 (s, Ac). *c*) In $CHCl_3$.
* These assignments may be interchanged.

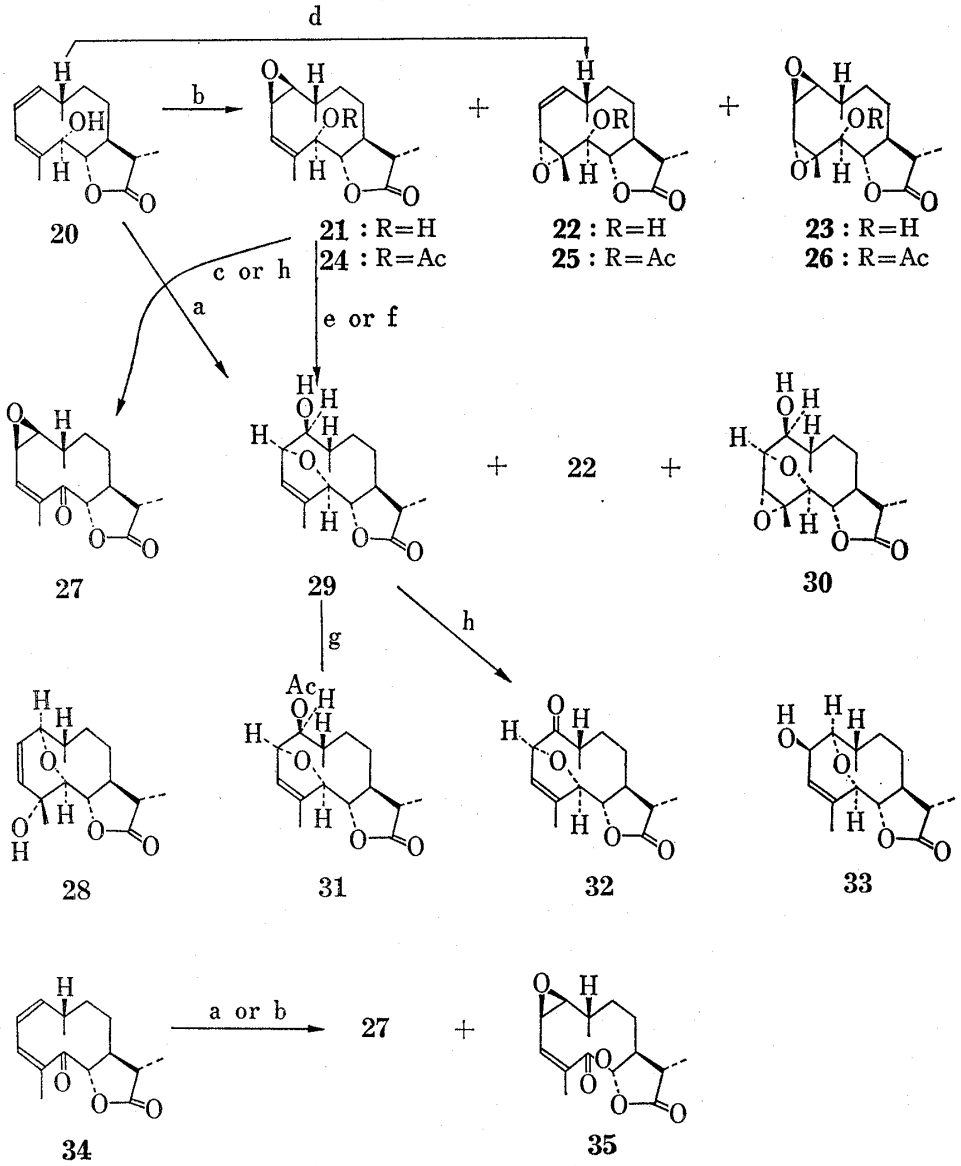

Chart 2

a) MCPBA in CH_2Cl_2, b) MCPBA in $NaHCO_3$–H_2O–CH_2Cl_2, c) MnO_2, d) *t*-BuOOH–VO $(acac)_2$, e) HCl, f) *m*-chlorobenzoic acid, g) Ac_2O–pyridine, h) CrO_3–pyridine–CH_2Cl_2.

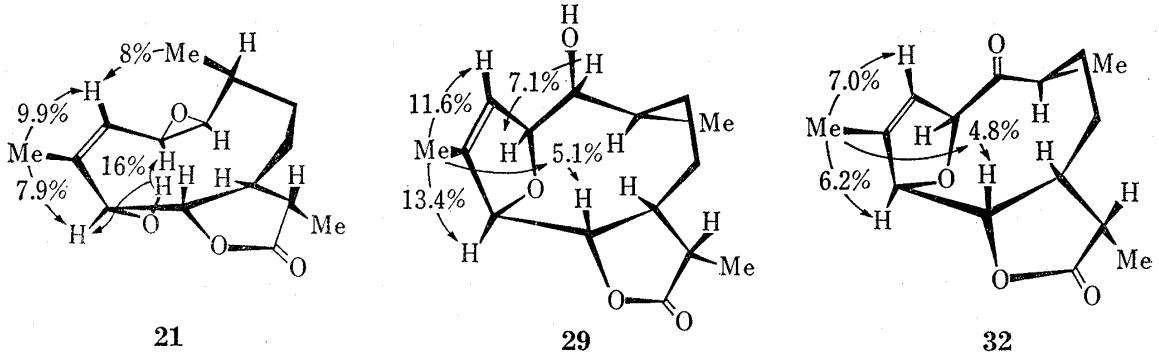

Fig. 1. Conformation and NOE Values of Compounds **21**, **29** and **32**

Arrows indicate the observation of positive NOEs.

hydrogen carbonate biphasic system (room temp., 5 hr), 1,2β-epoxide (**21**) [*m/e* 266(M^+)], 3,4α-epoxide (**22**) [*m/e* 266 (M^+)], and 1,2β-3,4α-diepoxide (**23**) [*m/e* 282 (M^+)] were obtained in 46.0, 14.9, and 9.2% yields, respectively, together with 18% of the starting material. The treatment of **20** with excess MCPBA afforded **23** as a major product. The structures of these compounds were determined on the basis of their spectral data given in Table II and from their chemical conversions. The CMR spectrum of **21** showed signals due to the epoxide ring-carbon at 54.8 ppm ($J_{C-2,H-2}$=184 Hz) and 65.0 ppm ($J_{C-1,H-1}$=164 Hz) with large coupling constants. The PMR spectrum of **21** showed a multiplet signal due to the H-2 at 4.53 ppm. By acetylation or oxidation of **21**, the signals due to the H-2 of **24** and **27** were observed at higher fields (4.00 and 3.66 ppm, respectively) than that in **21**. These results reveal that the H-2 and OH in **21** lie spatially close, and from considerations using the Dreiding model, steric proximity of the H-2 and the OH is only possible when the C-2 and the C-5 are in the *R*-configuration. In fact, the steric proximity of the H-2 and the OH, as well as the conformation of **21**, was proved by the NOE experiments on **21**, shown in Fig. 1. The PMR spectrum of **21** showed a broad singlet signal due to the H-14 at 1.13 ppm. This may be attributed to the long range coupling between the H-14 and the H-1, the H-9. The 3,4-epoxide ring in **22** was assigned to be in an α-configuration by the fact that **22** was also obtained by the reaction of **20** with *t*-butyl hydroperoxide–vanadyl acetylacetonate in refluxing benzene.[13] In 1976, Teranishi *et al.*[14] reported a novel transformation of cyclic 2,4-dienols to 1,5-oxy-3-en-2-ols using *t*-butyl hydroperoxide–vanadyl acetylacetonate. However, the compouned (**20**) did not afford an enol (**28**) under similar reaction conditions.

The reaction of **20** with 2.0 equivalents of MCPBA in dichloromethane afforded the cyclized products (**29**) and (**30**) in 45.5 and 34.0% yields, respectively, together with small amounts of the starting material and **22**. The structure of **29** was determined on the basis of its spectral data given in Table II and from the chemical evidences. The IR spectrum of **29** indicated the presence of a secondary hydroxyl group (ν_{max}: 3480 cm^{-1}) which is acetylated easily by the ordinary procedure (acetic anhydride–pyridine, room temp., 5 hr) to give **31**. The CMR spectrum of **29** showed four doublet signals due to $-\overset{H}{\underset{|}{C}}-O-$ group at 76.1 ($J_{C-1,H-1}$=140 Hz), 86.5 ($J_{C-6,H-6}$=148 Hz), 87.7 ($J_{C-2,H-2}$=152 Hz), and 90.2 ppm ($J_{C-5,H-5}$ =152 Hz). The PMR spectrum of **29** indicated the presence of one vinyl methyl (1.90 ppm), one vinyl proton (5.61 ppm), and four protons attached to the carbon atom bearing the oxygen atom (3.65, 4.12, 4.53, and 5.12 ppm). The coupling constant between the H-5 and the H-6 in **29** was large (8.0 Hz) compared with that in the epoxy-alchohol (**21**) (2.0 Hz). **29** was also obtained quantitatively from **21** by the action of 1 N hydrochloric acid or *m*-chlorobenzoic acid in methanol. From the above spectral data and the reaction, the structure **33** was also presumed to be the structure of the oxidation product obtained by the reaction of **20** with MCPBA in dichloromethane. However, the structure **33** was denied from the spectral data of its acetate and oxidation product. The proton signal assigned to the H-1 (3.65 ppm) in the cyclized alcohol shifted to a lower field (4.89 ppm) in the acetoxy compound (**31**). The oxidation product (**32**) of the cyclized alcohol did not show the presence of α,β-unsaturated carbonyl group in its IR and ultraviolet (UV) spectra. Thus, the structure of the cyclized alcohol was confirmed as **29**. Figure 1 shows the conformations of **29** and **32** on the basis of the NOE experiments.

When the 1,3-dien-5-one derivative[1] (**34**) was treated with 2.0 equivalents of MCPBA in the two-phase system or in dichloromethane at room temperature, 1,2-epoxide (**27**) and its Baeyer–Villigar oxidation product (**35**) were obtained, and a large amount of the starting material was recovered. On the other hand, treatment of **34** with a large excess of MCPBA

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14) T. Itoh, K. Jitsukawa, K. Kaneda, and S. Teranishi, *Tetrahedron Lett.*, **1976**, 3157.

in the presence of disodium hydrogen phosphate in dichloromethane (reflux, 4 days) gave **35** as a major product, with small amounts of the starting material and **27**. In the PMR spectrum of **35** [*m/e* 280 (M^+)], the doublet signal due to the H-6 was observed in a lower field by 0.61 ppm compared with that in **27** (5.58 ppm). The CMR spectrum of **35** showed two doublet signals due to the epoxide ring-carbon at 57.5 ppm ($J_{C-2,H-2}$=176 Hz) and 64.4 ppm ($J_{C-1,H-1}$=164 Hz). From these spectral data, the structure of **35** was assigned to that shown in Chart 2.

These results revealed that the reaction of the 5-hydroxygermacrane-type compounds (**11** and **20**) with MCPBA in the two-phase system gave the corresponding epoxides, but that the reaction in dichloromethane afforded the cyclized products.

The chemical transformation of these compounds into the natural products is now in progress.

Experimental

All melting points were determined on a Yanagimoto Micromelting Point apparatus and were uncorrected. IR spectra (cm^{-1}) of crystallized compounds were recorded using a KBr disk on Hitachi EPI-G2 spectrophotometer. PMR spectra (δ, 100 and 60 MHz) and CMR spectra were measured in $CDCl_3$ containing 1% tetramethylsilane as an internal standard with Varian HA-100, JEOL PMX-60, and JEOL FX-100 spectrometer. Mass (MS) spectra were recorded with Hitachi RMU-6M spectrometer. High-pressure liquid chromatography (HPLC) were performed on Hitachi liquid chromatograph Model 635A. Silica gel GF_{254} was used for preparative thin-layer chromatography (TLC) and silica gel 60 was used for column chromatography.

Reaction of Germacrane-type Compounds with *m*-Chloroperbenzoic Acid——General Procedure: (A) MCPBA was added to a stirred solution of germacrane-type compound in CH_2Cl_2, and the mixture was stirred at room temperature for the time shown in Table III. The solvent was evaporated under reduced pressure and the residue was dissolved in AcOEt. Then the solution was washed with 1 N Na_2CO_3 and saturated NaCl solution, and dried over $MgSO_4$. When the residue obtained by evaporation of the solvent was a

Table III. Oxidation of Germacranolide with MCPBA

Compd. No.	Procedures	MCPBA molar ratio	Time (hr)	Product No.	Yield (%)
1	A	1.2	2	**2**	95
	B	1.2	5	**2**	95
5	A	1.2	1	**6**	65
11	A	1.2	0.25	**12**	99
	B	1.2	0.2	**7**	90.8
17	A	1.3	24	**18**	64
				19	18
	B	1.2	2	**9**	99
20	A	2.0	8	**29**	45.5(47.8)[a]
				22	1.6(1.7)
				30	34.0(35.7)
				20	5.0
	B	1.2	5	**21**	46.0(56.0)[a]
				22	14.9(18.0)
				23	9.2(11.0)
				20	18.0
34	A	2.0	24	**27**	20.8(29.9)[a]
				35	25.0(35.9)
				34	30.2
	B	2.0	48	**27**	21.2(28.3)[a]
				35	24.3(32.7)
				34	25.5
		2.0[b]	96	**35**	44.0

a) Yield based on deduction of the starting material.
b) **34** was treated with *m*-chloroperbenzoic acid in the presence of 3.0 equivalents of $Na_2HPO_4 \cdot 12H_2O$ in CH_2Cl_2 (reflux).

mixture of products, it was separated by preparative TLC. The product was purified by recrystallization to afford the analytical sample.

(B) MCPBA was added to a stirred mixture of germacrane-type compound in 2- or 3-fold excess of 1 N $NaHCO_3$ and CH_2Cl_2. The reaction mixture was treated in the same manner as above to afford the product.

2——mp 176—178°, colorless needles from $CHCl_3$–ether. *Anal.* Calcd. for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.03; H, 7.60. MS *m/e*: 264 (M^+). IR (cm^{-1}): 1770, 1720. PMR ($CDCl_3$, δ): 1.24 (3H, d, J=6.0 Hz, H-13), 1.29 (3H, s, H-14), 1.37 (3H, d, J=6.5 Hz, H-15), 3.57 (1H, d, J=4.8 Hz, H-1), 3.78 (1H, ddq, J=5.2, 2.8, 6.5 Hz, H-4), 4.82 (1H, d, J=4.0 Hz, H-6), 5.55 (1H, dd, J=11.0, 5.2 Hz, H-3), 5.72 (1H, ddd, J=11.0, 4.8, 2.8 Hz, H-2).

6——mp 107.5—108°, colorless prisms from ether–petr. ether. *Anal.* Calcd. for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found: C, 67.32; H, 8.27. MS *m/e*: 266 (M^+). IR (cm^{-1}): 1775, 1760 (shoulder), 1710. PMR ($CDCl_3$, δ): 1.29 (3H, d, J=7.0 Hz, H-13 or H-15), 1.32 (3H, s, H-14), 1.34 (3H, d, J=6.5 Hz, H-13 or H-15), 4.77 (1H, d, J=7.5 Hz, H-6).

7——mp 194—195°, colorless prisms from ether, colorless needles from AcOEt. *Anal.* Calcd. for $C_{15}H_{24}O_4$: C, 67.13; H, 9.02. Found: C, 67.19; H, 9.00. Table I.

9——mp 170—171°, colorless prisms from AcOEt–ether. *Anal.* Calcd. for $C_{16}H_{26}O_6S$: C, 55.48; H, 7.57. Found: C, 55.36; H, 7.52. IR (cm^{-1}): 1780 (shoulder), 1768. PMR ($CDCl_3$, δ): 1.12 (3H, d, J=6.0 Hz, H-15), 1.27 (3H, d, J=6.5 Hz, H-13), 1.42 (3H, s, H-14), 2.85 (1H, dd, J=8.0, 1.0 Hz, H-1), 3.11 (3H, s, CH_3SO_2), 4.47 (1H, dd, J=9.0, 2.0 Hz, H-6), 4.90 (1H, d, J=2.0 Hz, H-5).

Oxidation Product (12)——mp 128—129°, colorless needles from ether–petr. ether. *Anal.* Calcd. for $C_{15}H_{24}O_4$: C, 67.13; H, 9.02. Found: C, 67.08; H, 8.99. Table I.

18——mp 222—223°, colorless prisms from AcOEt. *Anal.* Calcd. for $C_{16}H_{26}O_6S$: C, 55.48; H, 7.57. Found: C, 55.40; H, 7.57. IR (cm^{-1}): 3460, 1760, 1360, 1335, 1170. PMR ($CDCl_3$, δ): 1.17 (3H, d, J=6.0 Hz, H-15), 1.28 (3H, d, J=7.5 Hz, H-13), 1.76 (3H, s, H-14), 3.03 (3H, s, CH_3SO_2), 4.5—5.1 (3H, m, H-1, H-5, H-6), 5.47 (1H, m, H-9). PMR (D_3CCOCD_3, δ): 1.07 (3H, d, J=6.0 Hz, H-15), 1.22 (3H, d, J=6.5 Hz, H-13), 1.72 (3H, s, H-14), 3.04 (3H, s, CH_3SO_2), 3.72 (1H, d, J=4.0 Hz, OH), 4.63 (1H, dd, J=11.5, 2.0 Hz. H-6), 4.82 (1H, dd, J=10.0, 2.0, H-5), 4.89 (1H, m, H-1), 5.56 (1H, m, H-9).

19——mp 220—221.5°, colorless prisms from AcOEt–ether. IR (cm^{-1}): 3480, 1780, 1775 (shoulder), 1340, 1170. PMR (D_3CCOCD_3, δ): 1.12 (3H, d, J=6.0 Hz, H-15), 1.27 (3H, d, J=6.5 Hz, H-13), 1.27 (3H, s, H-14), 3.06 (3H, s, CH_3SO_2), 3.70 (1H, dd, J=11.0, 6.0 Hz, H-1), 4.71 (1H, dd, J=12.0, 2.0, H-6), 4.97 (1H, dd, J=10.0, 2.0 Hz, H-5).

21——mp 175—176°, colorless prisms from ether–petr. ether or AcOEt. *Anal.* Calcd. for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found: C, 67.61; H, 8.32. Table II.

22——160—162°, colorless needles from ether–petr. ether. *Anal.* Calcd. for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found: C, 67.61; H, 8.31. Table II.

1,2β-3,4α-Diepoxy-5α-hydroxy-7,10α(H),6,11β(H)-germacran-6,12-olide (23)——mp 168—170°, colorless prisms from ether–petr. ether. *Anal.* Calcd. for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 63.84; H, 7.83. Table II.

27——Colorless oil. UV λ_{max}^{MeOH}: 202, 230 nm. Table II.

Oxidation Product (29)——mp 159—160°, colorless needles from ether–petr. ether. *Anal.* Calcd. for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found: C, 67.61; H, 8.32. Table II.

Oxidation Product (30)——mp 228—229°, colorless prisms from AcOEt. *Anal.* Calcd. for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 63.68; H, 7.79. Table II.

Baeyer–Villigar Oxidation Product (35)——mp 146—147°, colorless needles from ether. *Anal.* Calcd. for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 64.18; H, 7.20. MS *m/e*: 280 (M^+). IR (cm^{-1}): 1795, 1725, PMR ($CDCl_3$, δ): 1.24 (3H, broad s, H-14), 1.30 (3H, d, J=6.0 Hz, H-13), 1.99 (3H, s, H-15), 2.92 (1H, dd, J=8.5, 4.0 Hz, H-1), 3.87 (1H, m, H-2), 6.19 (1H, d, J=7.5 Hz, H-6), 6.43 (1H, m, H-3).

Reduction of 2 with $NaBH_4$——The ketone (2) (26.4 mg, 0.1 mmol) in MeOH (10 ml) was treated with $NaBH_4$ (7.5 mg, 0.2 mmol) for 24 hr at room temperature. MeOH was evaporated to dryness, the residue was mixed with H_2O, and extracted with AcOEt. Evaporation of the solvent afforded 27 mg of a solid, which was purified by recrystallization from $CHCl_3$–ether–hexane to give the analytical sample of 3 as colorless prisms, mp 236—238°, 24 mg (90.3%). *Anal.* Calcd. for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found: C, 67.32; H, 8.51. PMR ($CDCl_3$, δ): 1.18 (3H, d, J=6.2 Hz, H-15), 1.27 (3H, s, H-14), 1.42 (3H, d, J=6.0 Hz, H-13), 2.73 (1H, m, H-4), 3.90 (1H, broad s, OH), 3.48 (1H, d, J=6.5 Hz, H-1), 3.53 (1H, dd, J=10.0, 1.0 Hz, H-5), 4.29 (1H, broad s, H-6), 5.46 (1H, dd, J=10.0, 6.5 Hz, H-2), 5.60 (1H, dd, J=10.0, 5.5 Hz, H-3). Table I.

Acetylation of 3——To a stirred solution of 3 (13.3 mg, 0.05 mmol), 4-dimethylaminopyridine (1 mg), and pyridine (0.1 ml) in $CHCl_3$ (1 ml), Ac_2O (10 μl, 0.1 mmol) was added at 0° and the whole solution was stirred for 5 hr at room temperature. The solvent evaporated under reduced pressure and the residue was extracted with AcOEt. The organic layer was washed successively with 2 N HCl, $NaHCO_3$, and saturated NaCl solution, and dried over $MgSO_4$. Evaporation of the solvent afforded 15 mg (97.5%) of the acetate (4) as a solid, which was recrystallized from ether–pentane, colorless prisms, mp 135—137°. IR (cm^{-1}): 1755, 1740. PMR ($CDCl_3$, δ): 1.16 (3H, d, J=7.0 Hz, H-15), 1.33 (3H, s, H-14), 1.42 (3H, d, J=6.0 Hz, H-13),

2.13 (3H, s, CH_3CO), 2.84 (1H, m, H-4), 3.53 (1H, m, H-1), 4.33 (1H, m, H-6), 5.05 (1H, dd, J=7.5, 2.0 Hz, H-5), 5.8—5.87 (2H, m, H-2, H-3).

Hydrogenation of 2——A mixture of **2** (13.2 mg, 0.05 mmol) and PtO_2 catalyst (1 mg) in AcOEt (1 ml) was hydrogenated at ordinary temperature and pressure. After uptake of *ca.* 1.2 ml of H_2, the catalyst was filtered off and then the solvent was evaporated to dryness. The resulting solid was purified by preparative TLC (developed with benzene–AcOEt=5: 2) to afford 12 mg (90.3%) of **6**. This compound was identical with the sample obtained by epoxidation of **5** with MCPBA in TLC, GLC, HPLC, and IR and PMR spectra.

Reduction of 6 with $NaBH_4$——$NaBH_4$ (3.8 mg, 0.1 mmol) was added to a stirred solution of **6** (53.4 mg, 0.2 mmol) in MeOH (2 ml) at room temperature. After 30 min, MeOH was evaporated at reduced pressure, the residue was mixed with H_2O, and extracted with AcOEt. Evaporation of the solvent afforded crude alcohol (**7**) which was recrystallized from ether as colorless prisms, mp 194—195°; 49 mg (91.3%). This compound was identical with the sample obtained by epoxidation of **11** with MCPBA.

Hydrogenation of 3——A solution of **3** (13.3 mg, 0.05 mmol) in AcOEt (1 ml) was hydrogenated over 10% Pd-C catalyst (2 mg) at room temperature and atmospheric pressure. After uptake of *ca.* 1.2 ml of H_2, the mixture was filtered and the filtrate was evaporated to give 13 mg (97%) of **7** as a colorless solid. This compound was identical with the sample obtained by epoxidation of **11** with MCPBA.

Acetylation of 5——A mixture of the alcohol (**5**) (6.7 mg, 0.025 mmol), 4-dimethylaminopyridine (1 mg), pyridine (0.1 ml), and Ac_2O (10 μl, 0.1 mmol) in $CHCl_3$ (1 ml) was stirred for 5 hr at room temperature. The reaction mixture was worked up in the same manner as **3** to afford 7.6 mg (97.8%) of the acetate (**8**) as a solid which was recrystallized from ether–pentane to give colorless prisms, mp 170—172°. MS *m/e*: 310 (M^+), IR (cm^{-1}): 1775 (shoulder), 1765, 1740. PMR ($CDCl_3$, δ): 1.08 (3H, d, J=6.5 Hz, H-15), 1.27 (3H, d, J=6.5 Hz, H-13), 1.44 (3H, s, H-14), 2.12 (3H, s, CH_3CO), 2.88 (1H, dd, J=8.0, 1.0 Hz, H-1), 4.26 (1H, dd, J=8.0, 2.2 Hz, H-6), 5.06 (1H, dd, J=2.2, 2.2 Hz, H-5).

Mesylation of 7——To a stirred solution of **7** (13.4 mg, 0.05 mmol) and pyridine (0.1 ml) in $CHCl_3$ (1 ml), 13.7 mg (0.06 mmol) of CH_3SO_2Cl was added. After 24 hr, usual treatment afforded 17 mg (98%) of **9** as a solid which was recrystallized from AcOEt–ether to colorless prisms, mp 170—171°. This compound was identical with the sample obtained by epoxidation of **17** with MCPBA.

Cyclization Reaction of Epoxy-alcohol (7)——A solution of **7** (6.7 mg) and 2 N HCl (10 μl) in CH_2Cl_2 (1 ml) was stirred for 6 hr at room temperature. After evaporation of the solvent, the residue was neutralized with 1 N $NaHCO_3$ and extracted with AcOEt. Evaporation of the solvent afforded 6.7 mg (100%) of the cyclized product (**12**) as colorless crystals, mp 128—129°. This product was identical with the compound obtained by oxidation of **11** with MCPBA.

Cyclization Reaction of Enol (11)——A solution of **11** (25.5 mg, 0.1 mmol) and 2 N HCl (0.1 ml) in THF (2 ml) was stirred for 10 days at room temperature. The same treatment as **7** gave a colorless solid, which was submitted to the preparative TLC with benzene–AcOEt (5: 2) as a developing solvent to afford 19 mg (75.5%) of **10**. Recrystallization from petr. ether gave colorless plates, mp 103—104°. *Anal.* Calcd. for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.33; H, 9.61. MS *m/e*: 252 (M^+). IR (cm^{-1}): 1755. PMR ($CDCl_3$, δ); 0.97 (3H, d, J=7.0 Hz, H-15), 1.22 (3H, s, H-14), 1.25 (3H, d, J=6.0 Hz, H-13), 3.72 (1H, dd, J=9.0, 3.0 Hz, H-5), 4.37 (1H, dd, J=9.0, 9.0 Hz, H-6), CMR ($CDCl_3$, δ): 79.1 (s, C-10), 81.4, 82.4 (each d, C-5, C-6).

Oxidation of 12 with CrO_3-Pyridine Complex——CrO_3 (150 mg, 1.5 mmol) was added in one portion to a stirred solution of dry pyridine (237 mg, 3 mmol) in 4 ml of CH_2Cl_2 under nitrogen. The solution was stirred for 15 min at room temperature, and then the alcohol (**12**) (26.8 mg, 0.1 mmol) was added in one portion. The mixture was further stirred for 1 hr at room temperature, then CH_2Cl_2 solution was decanted, and the tarry deposit was washed with CH_2Cl_2. The combined organic solution was washed successively with 1 N NaOH, 2 N HCl, 1 N $NaHCO_3$, and saturated NaCl, and dried over $MgSO_4$. Evaporation of the solvent afforded a solid which was separated by HPLC (elution with AcOEt–hexane=1: 1). In order of elution, 3 mg (11.3%) of colorless oil {MS *m/e*: 266 (M^+), IR ($CHCl_3$, cm^{-1}): 1770, 1705}, 10 mg (37.6%) of epoxide (**13**), 4 mg (17%) of the starting material (**12**), and 3 mg (10.6%) of colorless oil {MS *m/e*: 282 (M^+), IR ($CHCl_3$, cm^{-1}): 3450, 1770, 1740, 1710} were obtained. **13** was recrystallized from ether as colorless needles, mp 193—195°. Table I.

Dehydration of 12 with $SOCl_2$——$SOCl_2$ (28.4 mg, 0.24 mmol) was added to a stirred solution of **12** (53.6 mg, 0.2 mmol) and pyridine (0.1 ml) in $CHCl_3$ (1 ml) at 0°. After the reaction mixture was maintained for 30 min at 0°, it was poured into ice-water and extracted with AcOEt. The combined extracts were washed successively with 2 N HCl, 1 N $NaHCO_3$, and saturated NaCl solution, and then dried over $MgSO_4$. Evaporation of the solvent left 54 mg of a pale yellow oil which crystallized on standing at room temperature. These crystals were applied to a preparative TLC plate. The plate was developed twice with 10: 1 mixture of benzene–AcOEt. Extraction from the plate gave 16 mg (32%) of **14** (*Rf* 0.6), 13 mg (26%) of **15** (*Rf* 0.7), 5 mg (10%) of **16** (*Rf* 0.8), and 2.5 mg (5%) of a mixture of **16** and an unidentified compound {(MS *m/e*: 250 (M^+); *Rf* 0.7—0.8)}. Compound **14** was recrystallized to colorless prisms (petr. ether) or colorless needles (hexane), mp 151—153°. *Anal.* Calcd. for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.64; H, 8.73. Recrystallization of **15** from petr. ether afforded colorless needles, mp 110—111°. *Anal.* Calcd. for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.74; H, 8.89. Compound **16** was also recrystallized from petr. ether as

colorless needles, mp 99—101°. *Anal.* Calcd. for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.76; H, 8.86. Table I.

Dehydration of 12 with (Carboxysulfamoyl)triethylammonium Hydroxide Inner Salt Methyl Ester——**12** (26.8 mg, 0.1 mmol) was added to a solution of (carboxysulfamoyl)triethylammonium hydroxide inner salt methyl ester (71 mg, 0.3 mmol) in benzene (5 ml) at room temperature under nitrogen. After 2.5 hr of stirring, the temperature was raised to 50° and then maintained at that temperature for 5 hr. When cooled, H_2O was added and the mixture was extracted with AcOEt. The combined extracts were washed with H_2O and dried over $MgSO_4$. The solvent was evaporated to afford a pale yellow oil. This oil was separated by preparative TLC (developed with benzene–AcOEt=10: 1, two times) to afford 4 mg (16%) of **14**, 14 mg (56%) of **15**, and 2 mg (8%) of **16**. These compounds were identical with the samples obtained by the reaction of **12** with $SOCl_2$ in TLC, GLC, and IR and PMR spectra.

Oxidation of 15 with CrO_3-Pyridine Complex——CrO_3 (60 mg, 0.6 mmol) was added to a stirred solution of dry pyridine (94.8 mg, 1.2 mmol) in CH_2Cl_2 (3 ml) under nitrogen. After 15 min, **15** (25 mg, 0.1 mmol) was added and then stirring was continued for 5 hr. Usual procedure afforded 25 mg of a solid mass, which was separated by preparative TLC with benzene–AcOEt (1: 1) as a developing solvent, and 14 mg (52.7%) of the epoxide (**13**) was obtained as the main product.

Oxidation of 15 with *m*-Chloroperbenzoic Acid——To a stirred mixture of **15** (25 mg, 0.1 mmol) and 1 N $NaHCO_3$ solution (0.2 ml) in CH_2Cl_2 (2 ml), MCPBA (20.6 mg, 0.12 mmol) was added at room temperature (Method B). After 10 min, usual treatment afforded 26 mg of a colorless solid which was separated by preparative TLC with benzene–AcOEt (1: 1) as a developing solvent, and the epoxide (**13**), 22 mg (82.8%) was obtained.

Oxidation of 20 with *t*-Butyl Hydroperoxide–Vanadyl Acetylacetonate {*t*-BuOOH–VO(acac)$_2$}——To a solution of **20** (25 mg, 0.1 mmol) and $VO(acac)_2$ (0.5 mg, 0.002 mmol) in 2 ml of refluxing benzene, 70% *t*-BuOOH (15.5 mg, 0.12 mmol) was added. After 30 min, additional 15.5 mg of 70% *t*-BuOOH was added and refluxing was further continued for 1 hr. After the reaction mixture was cooled, H_2O was added and the mixture was extracted with AcOEt. The combined solvents were washed with 1 N $NaHCO_3$ and saturated NaCl solution, and dried over $MgSO_4$. Evaporation of the solvent left 27 mg of a solid mass which was separated by preparative TLC with benzene–AcOEt (1: 1) as a developing solvent, and 17 mg (63.5%) of **22** was obtained, mp 159—161°. This compound was identical with the sample obtained by epoxidation of **20** with MCPBA.

Acetylation of Epoxyalcohol (21)——A stirred solution of **21** (26.6 mg, 0.1 mmol) and Ac_2O (20.4 mg, 0.2 mmol) in pyridine (5 ml) was heated for 20 hr at 50°. The same procedure as for **3** afforded 30.8 mg (100%) of **24**. Recrystallization from ether–petr. ether gave colorless needles, mp 187—188°. *Anal.* Calcd. for $C_{17}H_{24}O_5$: C, 66.21; H, 7.85. Found: C, 65.87; H, 7.83. Table II.

Acetylation of Epoxyalcohol (22)——To a stirred solution of **22** (26.6 mg, 0.1 mmol) and pyridine (0.3 ml) in $CHCl_3$ (2 ml), Ac_2O (20.4 mg, 0.2 mmol) was added at 0° and then the solution was stirred for 3 days at room temperature. The same procedure as for **3** afforded colorless crystals in a quantitative yield. Recrystallization from ether–petr. ether gave colorless needles, mp 159—162°. *Anal.* Calcd. for $C_{17}H_{24}O_5$: C, 66.21; H, 7.85. Found: C, 65.95; H, 7.13. IR (cm^{-1}): 1765, 1735. PMR ($CDCl_3$, δ): 1.05 (3H, d, J=6.5 Hz, H-14), 1.30 (3H, d, J=6.0 Hz, H-13), 1.47 (3H, s, H-15), 2.05 (3H, s, CH_3CO), 3.52 (1H, m, H-3), 4.32 (1H, dd, J=8.5, 2.5 Hz, H-6), 5.36—5.70 (3H, m, H-1, H-2, H-5).

Acetylation of Epoxyalcohol (23)——To a stirred solution of **23** (28.2 mg, 0.1 mmol) and pyridine (0.3 ml) in $CHCl_3$ (2 ml), Ac_2O (20.4 mg, 0.2 mmol) was added at 0° and then the solution was stirred for 2 days at room temperature. Usual treatment afforded a colorless solid, which was separated by preparative TLC with benzene–AcOEt (1: 1) as a developing solvent to give 31 mg (95.5%) of **26**. Recrystallization from ether–pentane afforded colorless prisms, mp 166—167°. *Anal.* Calcd. for $C_{17}H_{24}O_6$: C, 62.95; H, 7.46. Found: C, 62.89; H, 7.44. IR (cm^{-1}): 1780, 1740. PMR ($CDCl_3$, δ): 1.21 (3H, broad s, H-14), 1.38 (3H, d, J=6.0 Hz, H-13), 1.47 (3H, s, H-15), 2.04 (3H, s, CH_3CO), 2.68 (1H, d, J=6.5 Hz, H-6), 3.25 (1H, dd, J= 6.5, 2.5 Hz, H-2), 4.37 (1H, dd, J=9.0, 2.5 Hz, H-6), 5.73 (1H, d, J=2.5 Hz, H-5).

Oxidation of 21 with MnO_2——To a solution of **21** (13.3 mg, 0.05 mmol) in $CHCl_3$ (2 ml), MnO_2 (87 mg, 1 mmol) was added. After the mixture was stirred for 24 hr at room temperature, additional MnO_2 (43.5 mg, 0.5 mmol) was added and stirring was continued for 24 hr. Filtration and evaporation of the solvent afforded a pale yellow oil, which was separated by preparative TLC with benzene–AcOEt (5: 2) as a developing solvent, and 5 mg (37.8%) of **27** was obtained. This material was identical with the sample obtained by epoxidation of **34** with MCPBA.

Cyclization Reaction of 21——(i) A solution of **21** (26.6 mg, 0.1 mmol) and 2 N HCl (0.1 ml) in MeOH (1 ml) was stirred for 24 hr at room temperature. After evaporation of the solvent, the residue was neutralized with 1 N $NaHCO_3$ and followed by extraction with AcOEt to give 26.5 mg (99.8%) of **29** as colorless crystals, mp 159—160°.

(ii) A solution of **21** (13.3 mg, 0.05 mmol) and *m*-chlorobenzoic acid (23.5 mg, 0.15 mmol) in MeOH (2 ml) was stirred for 4 days at room temperature. The same work up as above gave **29** in a quantitative yield.

Cyclization Reaction of 23——A solution of **23** (14.1 mg, 0.05 mmol) and 2 N HCl (0.1 ml) in MeOH (1 ml) was stirred for 24 hr at room temperature. The same procedure as described for **21** afforded 14.1 mg (100%) of **30** as colorless crystals, mp 228—229°.

Acetylation of 29——To a stirred solution of **29** (26.6 mg, 0.1 mmol) and pyridine (0.5 ml) in $CHCl_3$ (2 ml), Ac_2O (20.4 mg, 0.2 mmol) was added at 0° and then the solution was stirred for 5 hr at room temperature. Usual treatment afforded a solid mass which was separated by preparative TLC with benzene–AcOEt (1: 1) as a developing solvent to give 27.6 mg (89.5%) of **31**. Recrystallization from ether–pentane afforded colorless needles, mp 153—155°. *Anal.* Calcd. for $C_{17}H_{24}O_5$: C, 66.21; H, 7.85. Found: C, 66.41; H, 7.78. Table II.

Oxidation of 29 with CrO_3-Pyridine Complex——CrO_3 (60 mg, 0.6 mmol) was added in one portion to a stirred solution of dry pyridine (94.8 mg, 1.2 mmol) in CH_2Cl_2 (3 ml) under nitrogen. The mixture was stirred for 15 min at room temperature and then **29** (26.6 mg, 0.1 mmol) was added in one portion. Stirring was continued for further 1 hr. The CH_2Cl_2 solution was decanted and the tarry deposit was washed with CH_2Cl_2. Evaporation of the solvent left a brown solid, which was separated by chromatography over a short column (SiO_2 5 g, elution with hexane–AcOEt=5: 2) to give 23 mg (87.2%) of **32** as colorless crystals. Recrystallization from AcOEt–hexane afforded colorless prisms, mp 109—110°. *Anal.* Calcd. for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.16; H, 7.67. Table II.

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