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Biogenetically Patterned Transformation of Eudesmanolide to Eremophilanolide. III.*,1) Acid Treatment of 4α,5α-Epoxy-eudesman-8β,12-olide

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As a continuative study to clarify the structure requirement for the ready conversion of 5α,6α-epoxy-eudesman-8β,12-olide (1) to eremophilane-type compounds *via* the biogenetic-type 1,2-shift of 10-Me, acid treatment under a variety of acid conditions of 4α,5α-epoxy-eudesman-8β,12-olide (2) has been examined.

It has been found that acid treatment of 2 with HCOOH-acetone, BF_3-etherate-benzene, CF_3COOH–$CHCl_3$, or *p*·TsOH·H_2O–EtOH furnish no eremophilane-type compound, but yield four products such as AT-1 (**10**), AT-2 (**11**), AT-3 (**12**), and AT-4 (**13**) with different compositions depending upon the reaction conditions. The reaction pathways are also discussed.

In the previous papers,1,3) we reported that treatment with formic acid (HCOOH)-acetone of 5α,6α-epoxy-eudesman-8β,12-olide (**1**) furnished five eremophilanolides in good yields along with minor quantities of eudesmanolides, and discussed some factors associated with the successful biogenetic-type 1,2-shift of 10-Me in **1**. In order to clarify the structure requirement for the ready conversion of **1** (perspective figure **i**) to eremophilane-type compounds, acid treatment under a variety of conditions of 4α,5α-epoxy-eudesman-8β,12-olide (**2**), which carries a γ-lactone moiety and an isomeric epoxide function but suffers less spacial interaction of three methyls (4-Me, 5-Me, and 11-Me) as compared with **1** (**i**) as shown by a perspective figure **ii**. The present paper deals with a full account on the product analysis.4)

Treatment of dihydroisoalantolactone (**3**)5) with *p*-toluenesulfonic acid (*p*·TsOH)-AcOH furnished an isomer (**4**), which possesses no vinyl proton but a newly formed vinyl methyl (δ 1.64, s) as shown by its proton magnetic resonance (PMR) spectrum and the structure **4** (including the configuration at C-11) was assured by catalytic hydrogenation to afford tetrahydroalantolactone (**5**).5) *m*-Chloroperbenzoic acid oxidation of **4** gave two epoxides (**2** and **6**, yield ratio=5 : 1) both of which carry no vinyl methyl but a methyl attached to an epoxide ring (δ 1.29 in **2**, δ 1.32 in **6**). The major epoxide is assigned as 4α,5α (**2**) and the minor as 4β,5β (**6**) as based on the stereochemical viewpoint, which was further confirmed by the following conversion. Thus, oxymercuration-demercuration6) of **3** gave two hydroxylated derivatives (**7**, **8**). The configuration of hydroxyl in each product was assured by examination of the

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* Dedicated to the memory of Prof. Eiji Ochiai.

1) Part II: I. Kitagawa, H. Shibuya, H. Takeno, T. Nishino, and I. Yosioka, *Chem. Pharm. Bull.* (Tokyo), in press.

2) Location: *133-1, Yamada-kami, Suita, Osaka, 565, Japan.*

3) I. Kitagawa, Y. Yamazoe, H. Shibuya, R. Takeda, H. Takeno, and I. Yosioka, *Chem. Pharm. Bull.* (Tokyo), 22, 2662 (1974).

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5) *a*) K. Tsuda, K. Tanabe, I. Iwai, and K. Funakoshi, *J. Am. Chem. Soc.*, **79**, 5721 (1957); *b*) J.A. Marshall and N. Cohen, *J. Org. Chem.*, **29**, 3727 (1964).

6) H.C. Brown and P.J. Geoghegan, *J. Org. Chem.*, 37, 1937 (1972).

7) *a*) P.V. Demarco, E. Farkas, D. Doddrell, B.L. Mylari, and E. Wenkert, *J. Am. Chem. Soc.*, **90**, 5480 (1968); *b*) I. Kitagawa, M. Yoshikawa, and I. Yosioka, *Tetrahedron Letters*, **1974**, 469.

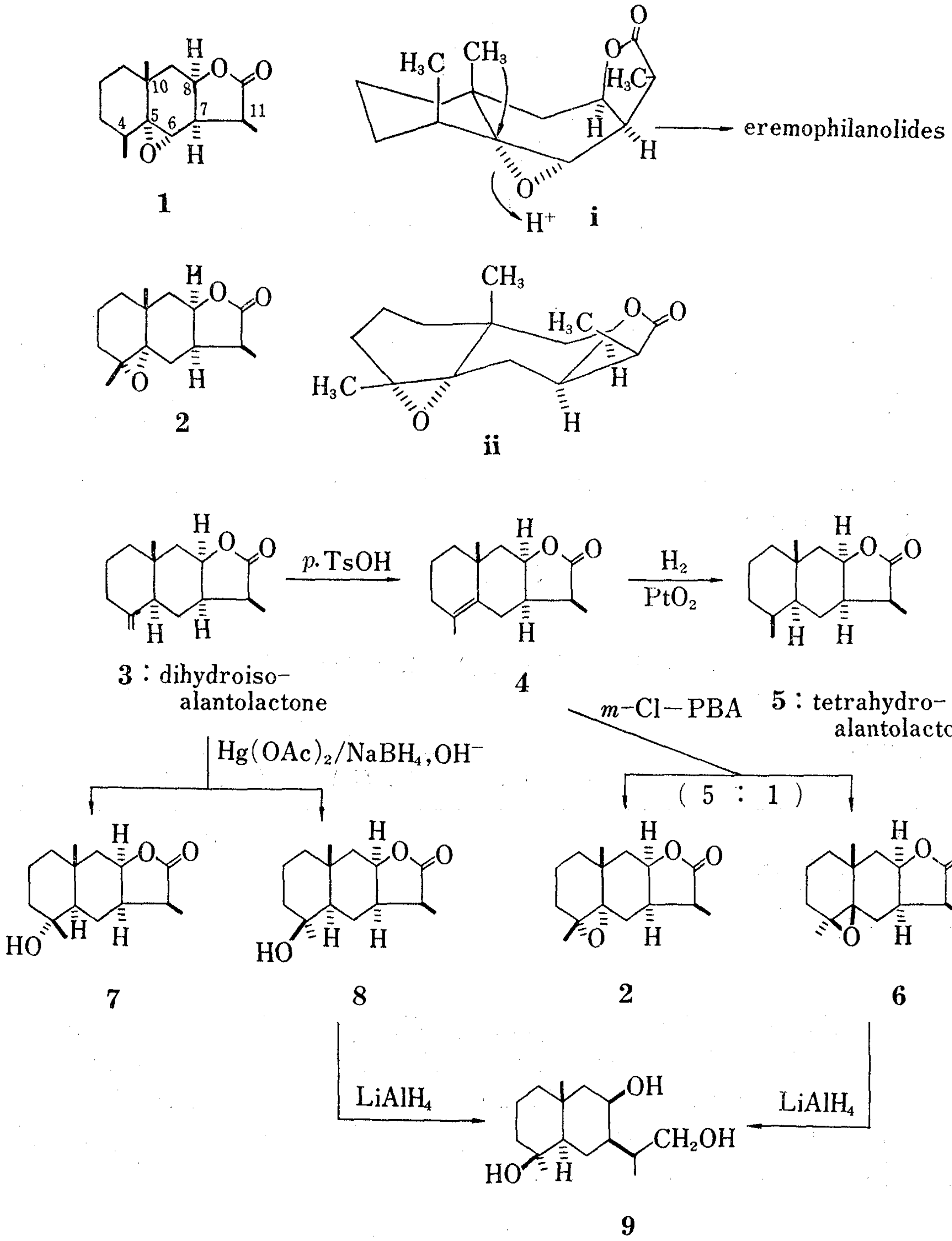


Chart 1

pyridine-induced solvent shift[7] of the 10-Me signal (δ 0.95 in **7**; δ 1.19 in **8**): δ (in $CDCl_3$)$-\delta$ (in d_5-pyridine)$=-0.02$ in **7**; -0.22 in **8**). Lithium aluminum hydride ($LiAlH_4$) reduction of **8** gave a triol (**9**) which was found identical with a $LiAlH_4$ reduction product of the above-described minor epoxide (**6**).

4α,5α-Epoxy-eudesman-8β,12-olide (**2**) was treated under a variety of acid conditions monitoring by thin-layer and gas-liquid chromatography (TLC and GLC) and four products designated as AT-1 (=product G (**10**)[1]), AT-2 (**11**), AT-3 (**12**), and AT-4 (**13**) were obtained under four acid conditions such as HCOOH-acetone, boron trifluoride (BF_3)-etherate-benzene, trifluoroacetic acid (CF_3COOH)-$CHCl_3$, and *p*-TsOH·H_2O-EtOH as summarized in Table I.

AT-1, a dienic compound, was obtained under three acid conditions other than BF_3-etherate and was identified with previously described product G (**10**)[1] by direct comparison.

AT-2 (**11**), formed predominantly on treatment of **2** with BF_3-etherate in benzene, carries a γ-lactone and a ketone function (IR). The PMR spectrum (d_6-benzene) of AT-2 shows the signals ascribable to two tertiary methyls (δ 0.72, 0.76, each s), one secondary methyl (δ

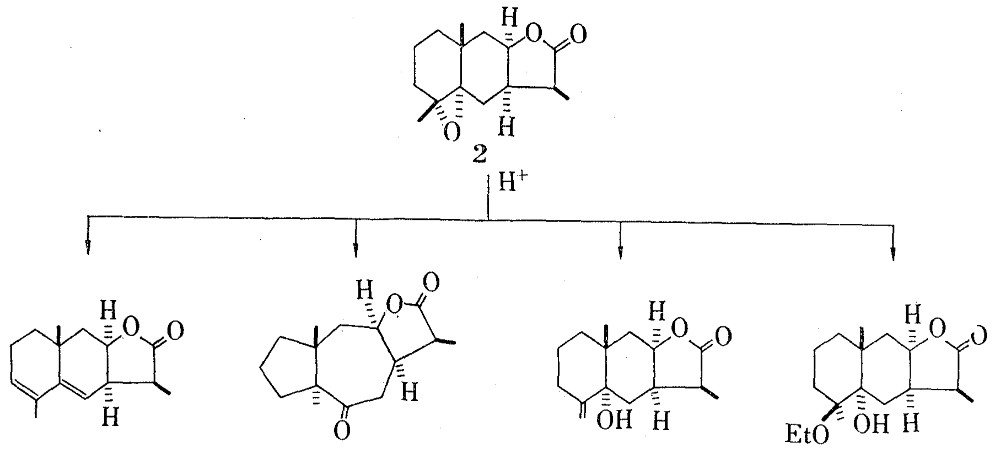


Chart 2

Table I. Isolated Yields (%) of Reaction Products

Conditions	Products			
	AT-1 (**10**)	AT-2 (**11**)	AT-3 (**12**)	AT-4 (**13**)
HCOOH–acetone	36	48	0	0
BF_3-etherate–benzene	0	76	0	0
CF_3COOH–$CHCl_3$	19	64	0	0
p-TsOH·H_2O–EtOH	12	0	6	33

0.85, d, $J=7$ Hz), and one methine proton (δ 3.96, q-like, $J=6$ Hz) geminal to a lactonic carbonyloxy group. Based on the mechanistic viewpoint (Chart 3), the plane structures **iii**, **iv**, and **v**, which appear to satisfy these spectral data, have become plausible, and among the three the structure **iii** is favored on the basis of mass fragmentation of AT-2 which gives a base peak of m/e 95 ($C_7H_{11}^+$) derived as shown in Chart 3.

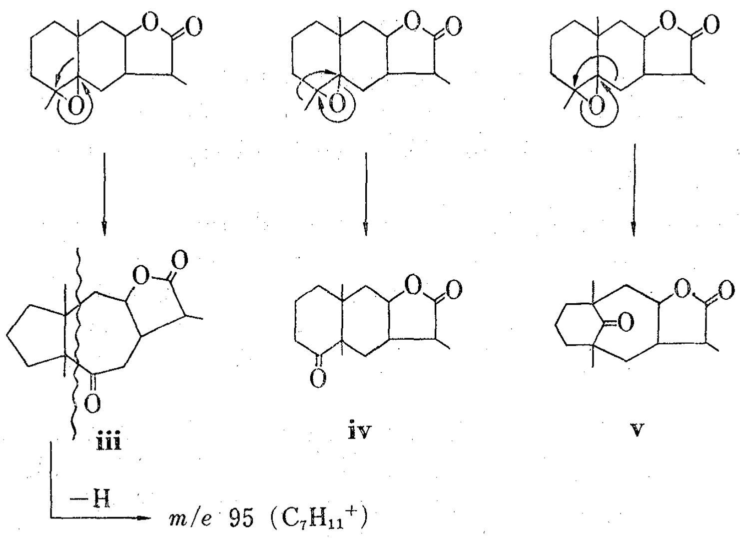
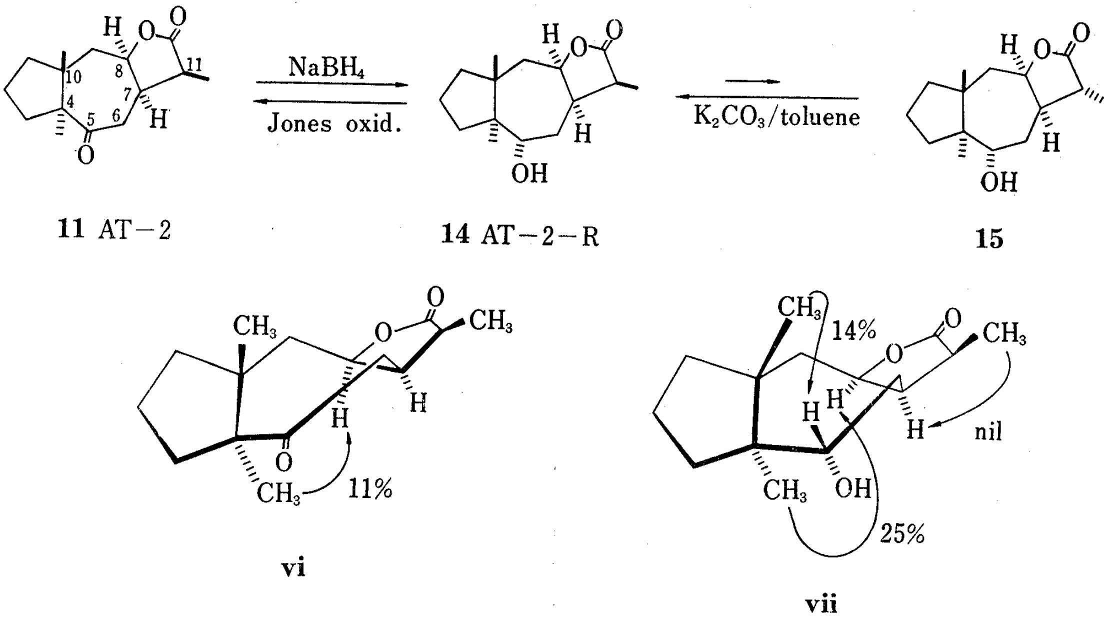


Chart 3

NaBH$_4$ reduction of AT-2 (**11**) gave AT-2-R (**14**) as a sole product which possesses a newly formed hydroxyl and retains the γ-lactone as shown by its IR spectrum and gives the same base peak at *m/e* 95 in its mass spectrum. Jones oxidation of AT-2-R resumed AT-2. The PMR spectrum of AT-2-R shows the signals due to two tertiary methyls (4-Me, 10-Me), one secondary methyl (11-Me), and two methine protons (5-H, 8-H) which are respectively geminal to a hydroxyl and a lactonic carbonyloxy function, along with two methine protons which are respectively assigned to 11-H and 7-H on the basis of the double resonance (PMDR) experiments (Table II).

The coupling pattern of the signal due to 5-H of AT-2-R excludes the structure **v**, and the following PMR findings of AT-2-R rule out the structure **iv** from the possible structure of AT-2: i) The signal due to 7-H is observed at the lower position than expected, which is assumed to be due to anisotropic effect of 5α-OH and the assumption is supported by the pyridine-induced shift[7] of the signal ($\Delta = -0.22$, Table II): ii) The 5α-OH configuration is substantiated by the nuclear Overhauser effect (NOE) enhancement (14%) observed between 10-Me and 5-H (Chart 4).



11 AT−2 **14** AT−2−R **15**

vi **vii**

Chart 4

Table II. PMR Data of AT-2-R (**14**) (90 MHz, δ, Hz)

Assignment	Solvent CDCl$_3$	d_5-pyridine	d_6-benzene
10-Me	0.89(6H, s)	0.86	0.73
4-Me			0.65
11-Me	1.19(3H, d, J=7)[a]	1.17	1.00
11-H	2.76(1H, m)[a]	2.80	2.40
7-H	3.20(1H, m)[a]	3.42	2.90
5-H	3.73(1H, t-like, J=*ca.* 4)	3.84	3.38
8-H	4.85(1H, d.d.d, J=10, 8, 6)[a]	[b]	4.56

[a] The assignments were confirmed by PMDR experiments: $J_{7,11}$=10 Hz.
[b] Overlapped by the signal due to contaminated H$_2$O.

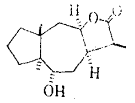
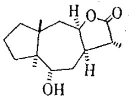
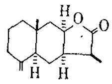
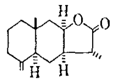
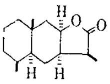
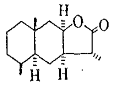
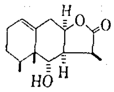
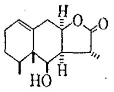
Based on the above evidence, especially the coupling pattern of 8-H and the spacial correlation of 5α-OH and 7α-H, the Dreiding model examination has led us to depict the stereostructure of AT-2-R (**14**) as **vii** and that of AT-2 (**11**) as **vi**, and the NOE enhancement observed in the following pairs has verified correctness of the formulations: 25% NOE between 4α-Me and 8α-H and 14% between 10β-Me and 5β-H in AT-2-R (**vii**); 11% NOE between 4α-Me and 8α-H in AT-2 (**vi**) (Chart 4).

Consequently, the structures of AT-2 and AT-2-R have been disclosed to be **11** and **14** respectively, except the configuration at C-11.

Since AT-2 and AT-2-R are readily convertible from each other, both compounds hold the same configuration at C-11. In the circular dichroism (CD) spectrum of AT-2-R (**14**), a positive maximum ($[\theta]_{224}$ +290) due to n→π^* transition of lactone carbonyl was observed, while an 11-epimer of AT-2-R (**15**), which was prepared by K_2CO_3-toluene treatment3) of AT-2-R (**14**), gave a negative CD curve ($[\theta]_{227}$ −3070). These findings, as based on the Snatzke's modified rule,8) have led us to assign 11β-Me to AT-2-R and 11α-Me to the epimer. In order to ensure the assignment, the CD spectra of the other lactonic compounds having the known C-11 configuration were examined. As summarized in Table III, the CD data of examined compounds agree with the application of the above rule. On the other hand, if based on the Beecham's chirality rule,9) all of these lactonic compounds are anticipated to give the negative CD spectra which are not in accord with the present findings as in case of stenine.10) It follows therefore in the present case that the configuration of adjacent methyl is dominating the CD spectrum due to n→π^* transition of lactone carbonyl. The facts, that 11α-Me derivatives gave the larger absolute values of molecular ellipticity, also agree with the consideration referring to the Snatzke's projection.

Therefore, the stereostructure of AT-2 and AT-2-R are now formulated as **11** and **14**, respectively.

Table III. CD Maxima of Lactonic Compounds

	λ_{max}^{MeOH}	$[\theta]$		λ_{max}^{MeOH}	$[\theta]$
 14	224	+290	 15	227	−3070
 3	225	+460	 16a)	216	−7130
 5	224	+620	 17a)	228	−1740
 18 (product B3))	218	+1530	 193)	218	−3760

a) Prepared from the corresponding 11β-Me derivatives by treatment with K_2CO_3 in toluene (see the Experimental section).

AT-3 (**12**) was formed on *p*·TsOH–EtOH treatment of **2** as a minor product. The IR spectrum of AT-3 shows the hydroxyl, γ-lactone, and terminal methylene absorption bands, while the PMR spectrum exhibits the signals due to one tertiary methyl (δ 0.93, s, 10-Me), one methine proton (δ 4.52, m, 8-H) geminal to a lactonic carbonyloxy function, and a terminal methylene (δ 4.71, 4.86, br. s each). These spectral data along with the mechanistic conside-

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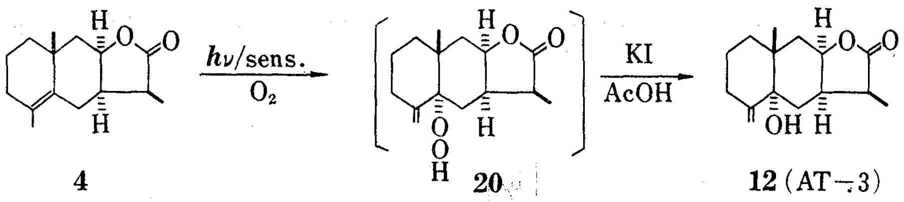
8) G. Snatzke, H. Ripperger, C. Horstmann, and K. Schreiber, *Tetrahedron*, **22**, 3103 (1966).
9) A.F. Beecham, *Tetrahedron Letters*, **1968**, 2355, 3591.
10) H. Harada, H. Irie, N. Masaki, K. Osaki, and S. Uyeo, *Chem. Comm.*, **1967**, 460.

ration has led us to propose **12** for AT-3, which corresponds to dihydrotelekin previously reported by Benešová, *et al.*11) Since the direct comparison was impossible, the structure **12** of AT-3 was assured by preparing it by photosensitized oxygenstion of **4** (giving **20**, not isolated)12) followed by KI–AcOH treatment. The 5α-OH configuration in **12** is based on the stereochemical reason for the photooxygenation of **4**.



4 **20** **12** (AT-3)

Chart 5

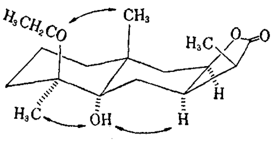
AT-4 (**13**), a major product of p·TsOH–EtOH treatment, was not formed under the other acid conditions. In addition to a hydroxyl and a γ-lactone (IR), AT-4 possesses an ethoxyl group (3H, t, at δ 1.11; 2H, q, at δ 3.32) as shown by its PMR spectrum ($CDCl_3$) which also shows the signals due to two tertiary methyls (δ 1.08, s, 10-Me; δ 1.26, s, 4-Me), one secondary methyl (δ 1.20, d, $J=7$ Hz, 11-Me), and three methine protons (δ 2.82, m, 11-H; δ 4.48, m, 8-H; δ 2.71, m, 7-H), the assignment being ensured by the PMDR experiments (d_5-pyridine) (Table IV). The presence of an ethoxyl is also supported by a fragment ion peak at m/e 250 ($M^+-C_2H_5OH$) in the mass spectrum of AT-4. Based on the pyridine-induced solvent shifts7) observed for the signals due to 10-Me, 4-Me, and 7-H (Table V) and on the mechanistic viewpoint, the structure of AT-4 is formulated as **13** (perspective figure **viii**).

Table IV. PMDR Experiments of AT-4 (**13**) (90 MHz, d_5-pyridine, δ)

decoupled proton	Irradiated at δ					
	1.06	1.13	2.77	2.89	3.28	4.49
4-$OCH_2\underline{H_3}$(1.06, t)	—				s	
11-Me(1.13, d)		—	s			
11-H(2.77, m)		deformed	—			
7-H(2.89, m)				—		deformed
4-$O\underline{CH_2}CH_3$(3.28, q)	s				—	
8-H(4.49, m)				deformed		—

Table V. Pyridine-induced Solvent Shifts in AT-4 (**13**)

	δ_{CDCl_3}	$\delta_{d_5\text{-pyridine}}$	$\delta_{CDCl_3}-\delta_{d_5\text{-pyridine}}$
10-Me	1.08	1.24	−0.16
4-Me	1.26	1.42	−0.16
7-H	2.71	2.89	−0.18



viii AT-4 (13)

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11) V. Benešová, V. Herout, and F. Šorm, *Coll. Czech. Chem. Comm.*, **26**, 1350 (1961).

12) *a*) A. Nickon and J.F. Bagli, *J. Am. Chem. Soc.*, **83**, 1498 (1961); *b*) J.A. Marshall, N. Cohen, and A.R. Hochstetler, *J. Am. Chem. Soc.*, **88**, 3408 (1966).

As for the reaction pathways on the formation of above-described four products: AT-1 (=product G (**10**)), AT-2 (**11**), AT-3 (**12**), and AT-4 (**13**), a scheme is summarized in Chart 6, in which the reactions giving **10**, **11**, and **12** are initiated by the $C_{(4)}$–O bond cleavage to proceed *via* **ixa**. AT-2 (**11**) was obtained in high yields under three acid conditions (Table I), which could be ascribable to the favorable location of $C_{(5)}$–$C_{(10)}$ bond in a probable intermediate carbonium ion as shown by **ixb** (path b). In case of *p*-TsOH–EtOH treatment, the nucleophilic attack of EtOH (solvent) at C-4 of **2** appears to have taken place thus furnishing AT-4 (**13**) as the major product.

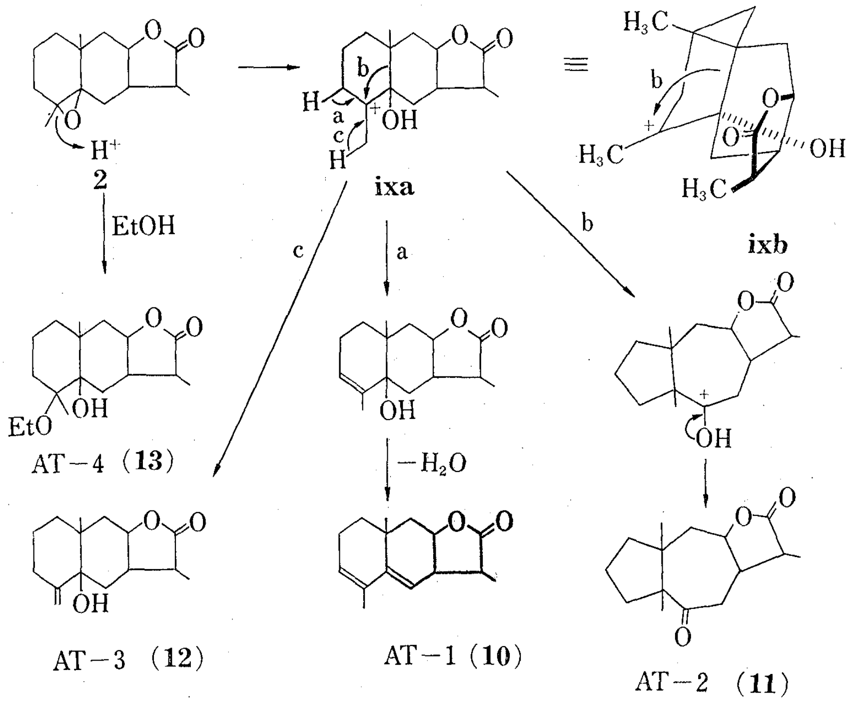

Chart 6. Reaction Pathways

As has become apparent from the above-described results, acid treatment of 4α,5α-epoxyeudesman-8β,12-olide (**2**) does not give any eremophilane-type compound, and the combined evidence accumulated so far[1,3] has led us to conceive that, for the formation of eremophilane-type transformation product from the eudesmanolides such as **1** and **2**, the spacial interaction of methyls and/or the location of epoxide function in the starting eudesmanolide is the necessary feature. The further investigation in this line is currently under way in this laboratory.

Experimental[13]

Treatment of Dihydroisoalantolactone (3) **With *p*-TsOH-AcOH**——A solution of 3 (1.02 g) in AcOH (10 ml) was added with *p*-TsOH·H_2O (0.15 g) and refluxed under N_2 atmosphere for 1.5 hr. The reaction mixture was treated with ice-water (200 ml) and extracted with EtOAc (200 ml × 2). The EtOAc extract

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[13] The instruments used in the experimental section were same as for Part II.[1] The PMR chemical shifts are given in δ value, coupling constant (J) and half-height band width ($W_{h/2}$) are in Hz, and coupling patterns are given with abbreviations: br.s = broad singlet, d = doublet, d.d.d = doublet of double doublet, m = multiplet, q = quartet, s = singlet, t = triplet. NOE experiments were undertaken with a Hitachi R-22 NMR spectrometer operating at 90 MHz in the frequency-swept and external CF_3COOH-locked mode, for the degassed solution in d_6-benzene. NOE values were obtained as percentage increases in the integrated signal intensities (accuracies within ± 2%). For GLC, Hitachi Gas Chromatograph Model 063 was used under the following conditions: 3% SE-30 on chromosorb W (2 m × 3 mm); carrier gas (N_2) flow rate: 30 ml/min; temp. 180° or 210°. For TLC, silica gel D-5 (Camag) or PF_{254} (Merck) was used and detection by 1% $Ce(SO_4)_2$ in 10% H_2SO_4 with heating or by fluorescence. For column chromatography, silica gel (Merck, 0.05—0.2 mm) was used.

was washed with aq. 5% $NaHCO_3$ and water, and dried over $MgSO_4$. Evaporation of the filtrate gave a colorless oil (1.00 g) which was chromatographed on a silica gel column (packed with *n*-hexane) eluting with *n*-hexane–ether (100: 1) to afford **4** (0.65 g, amorphous), $[\alpha]_D^{15}$ +52.2° (c=0.50, $CHCl_3$). *Anal.* Calcd. for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.87; H, 9.43. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1769 (γ-lactone). PMR ($CDCl_3$): 1.10 (3H, s, 10-Me), 1.20 (3H, d, J=7, 11-Me), 1.64 (3H, s, 4-Me), 4.43 (1H, m, $W_{h/2}$=8, 8-H). Mass Spectrum m/e (%): 234 (M^+, 24), 145 (100).

Catalytic Hydrogenation of 4 giving Tetrahydroalantolactone (**5**)——A stirred solution of **4** (10 mg) in 95% EtOH (5 ml) was hydrogenated over PtO_2 (10 mg) at room temperature under atmospheric pressure for 3 hr, filtered to remove the catalyst, and evaporated under reduced pressure to give a crude product (9 mg), which was purified by preparative TLC (*n*-hexane–ether=1: 1) to give tetrahydroalantolactone (**5**) (5 mg) (identified with the authentic sample[5]) by GLC and TLC (*n*-hexane–ether=1: 1; *n*-hexane–$CHCl_3$=1: 2; $CHCl_3$–ether=10: 1).

Epoxidation of 4 giving α-Epoxide (**2**) **and β-Epoxide** (**6**)——To a stirred solution of **4** (790 mg) in CH_2Cl_2 (60 ml) was added dropwise a solution of *m*-chloroperbenzoic acid (880 mg) in CH_2Cl_2 (40 ml) and the total solution was kept stirring at 20° for 40 min and treated with aq. 5% Na_2SO_3 (10 ml). The CH_2Cl_2 layer was taken and washed successively with aq. 5% $NaHCO_3$ and water and dried over $MgSO_4$. Evaporation of the solvent gave white powder (700 mg) which was purified by preparative TLC (*n*-hexane–ether=2: 3) to give **2** (510 mg) and **6** (100 mg). Recrystallization from *n*-hexane-acetone gave colorless needles of **2**, mp 119—120°, $[\alpha]_D^{21}$ +54.7° (c=1.17, $CHCl_3$). *Anal.* Calcd. for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.67; H, 9.10. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1770 (γ-lactone), 891 (epoxide). PMR ($CDCl_3$): 1.15 (3H, d, J=7, 11-Me), 1.16 (3H, s, 10-Me), 1.29 (3H, s, 4-Me), 2.66 (1H, m, 7-H), 2.81 (1H, m, 11-H), 4.51 (1H, m, $W_{h/2}$=9, 8-H). Mass Spectrum m/e (%): 250 (M^+, 13), 107 (100). Recrystallization from *n*-hexane-acetone gave **6** (colorless needles), mp 118—119°, $[\alpha]_D^{21}$ +5.5° (c=0.52, $CHCl_3$). *Anal.* Calcd. for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.71; H, 8.84. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1772 (γ-lactone), 883, 868 (epoxide). PMR ($CDCl_3$): 1.11 (3H, s, 10-Me), 1.17 (3H, d, J=7, 11-Me), 1.32 (3H, s, 4-Me), 2.45 (1H, m, 7-H), 2.82 (1H, m, 11-H), 4.54 (1H, q, J=4, 8-H). Mass Spectrum m/e (%): 250 (M^+, 4), 119 (100).

Oxymercuration-Demercuration of 3 giving 7 and 8——To a solution of **3** (200 mg) in tetrahydrofuran (5 ml) was added a solution of $Hg(OAc)_2$ (272 mg) in dist. water (1 ml) and the total solution was kept stirring at room temperature for 2 hr and treated with aq. 3M NaOH (0.5 ml). The reaction mixture was then added with 0.5M $NaBH_4$–3M NaOH solution until Hg separated out, neutralized with AcOH, and filtered to remove Hg. The filtrate was extracted with $CHCl_3$ and the $CHCl_3$ extract was washed with water and treated as usual. White powder (191 mg) thus obtained was purified by preparative TLC ($CHCl_3$–ether=5: 1) to give **3** (78 mg, recovered), **7** (48 mg), and **8** (10 mg). Recrystallization from *n*-hexane gave **7** as colorless needles of mp 148—150°, $[\alpha]_D^{10}$ −35.3° (c=1.20, $CHCl_3$). *Anal.* Calcd. for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.43; H, 9.69. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600, 3520 (OH), 1768 (γ-lactone). PMR ($CDCl_3$): 0.95 (3H, s, 10-Me), 1.11 (3H, s, 4-Me), 1.20 (3H, d, J=7, 11-Me), 4.43 (1H, m, $W_{h/2}$=8, 8-H); (d_5-pyridine): 0.97 (3H, s, 10-Me), 1.13 (3H, d, J=7, 11-Me), 1.18 (3H, s, 4-Me), 4.32 (1H, m, 8-H). Mass Spectrum m/e (%): 252 (M^+, 3), 165 (100). **8**, amorphous, $[\alpha]_D^{21}$ −51.8° (c=0.30, $CHCl_3$). *Anal.* Calcd. for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.31; H, 9.56. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3670, 3590 (OH), 1764 (γ-lactone). PMR ($CDCl_3$): 1.12 (3H, s, 4-Me), 1.19 (3H, s, 10-Me), 1.21 (3H, d, J=7, 11-Me), 4.43 (1H, m, $W_{h/2}$=11, 8-H); (d_5-pyridine): 1.10 (3H, d, J=7, 11-Me), 1.30 (3H, s, 4-Me), 1.41 (3H, s, 10-Me), 4.41 (1H, m, 8-H). Mass Spectrum m/e (%): 252 (M^+, 2), 165 (100).

$LiAlH_4$ Reduction of 8 giving Triol (**9**)——A solution of **8** (30 mg) in tetrahydrofuran (5 ml) was treated with $LiAlH_4$ (20 mg) and the total mixture was refluxed under N_2 atmosphere for 2 hr and treated with aq. ether to decompose excess $LiAlH_4$. The ether layer was taken, washed successively with aq. 5% $NaHCO_3$ and water, and worked up as usual to give a colorless oil (27 mg). Purification by preparative TLC ($CHCl_3$–ether=1: 4) gave **9** as white powder, $[\alpha]_D^{20}$ −38.5° (c=1.10, $CHCl_3$). High Resolution Mass Spectrum m/e: 256.203 (M^+). Calcd. for $C_{15}H_{28}O_3$: 256.204. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3650, 3600, 3380 (br) (OH). PMR ($CDCl_3$): 0.98 (3H, d, J=7, 11-Me), 1.09 (3H, s, 4-Me), 1.15 (3H, s, 10-Me), 3.32 (3H, center, OH × 3, D_2O exchangeable), 3.55 (2H, m, 11-$C\underline{H}_2OH$), 3.98 (1H, m, 8-H). Mass Spectrum m/e (%): 256 (M^+, 3), 43 (100).

$LiAlH_4$ Reduction of 6 giving Triol (**9**)——To a solution of **6** (20 mg) in tetrahydrofuran (4 ml) was added $LiAlH_4$ (14 mg) and the total mixture was refluxed under N_2 atmosphere for 1 hr, treated with aq. ether and aq. 5% H_2SO_4, and extracted with ether. The ether extract was washed successively with aq. 5% $NaHCO_3$ and water, and worked up in a usual manner to give a colorless oil (16 mg), which was purified by preparative TLC ($CHCl_3$–ether=1: 4). White powder (13 mg) thus obtained was identified with **9** described above by TLC ($CHCl_3$–ether=1: 4; $CHCl_3$–MeOH=5: 1; benzene–acetone=1: 1) and IR ($CHCl_3$).

Treatment of 4α,5α-Epoxide (**2**) **with HCOOH-Acetone**——A solution of **2** (50 mg) in acetone (2 ml, freshly distilled) was added with 99% HCOOH (4 ml) and refluxed under N_2 atmosphere for 3 hr. After cooling, the reaction mixture was diluted with water (100 ml), neutralized with aq. 20% NaOH, concentrated under reduced pressure to remove acetone, and extracted with $CHCl_3$ (100 ml × 3). Working up of the $CHCl_3$ extract in a usual manner gave a colorless oil (45 mg) which was purified by preparative TLC (*n*-hexane–ether=65: 100) to afford AT-1 (**10**) (18 mg) and AT-2 (**11**) (24 mg). AT-1 (**10**), mp 81—82° (colorless needles from ether), $[\alpha]_D^{29}$ −10.5° (c=0.76, $CHCl_3$). High Resolution Mass Spectrum m/e: 232.146 (M^+). Calcd.

for $C_{15}H_{20}O_2$: 232.146. Physical data including IR, UV, PMR, and mass spectra are identical with those of product G (**10**).[1] AT-2 (**11**), mp 157—158° (colorless needles from *n*-hexane), $[\alpha]_D^{21}$ +48.5° (c=1.00, $CHCl_3$). *Anal.* Calcd. for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.78; H, 9.12. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1769 (γ-lactone), 1696 (C=O). CD (c=0.334, MeOH): $[\theta]_{294}^{21}$ +3260 (pos. max.), $[\theta]_{245}^{21}$ +100 (pos. min.), $[\theta]_{223}^{21}$ +740 (pos. max.). ORD (c=0.352, dioxane): $[\Phi]_{700}^{27}$ +30°, $[\Phi]_{589}^{27}$ +43°, $[\Phi]_{321}^{27}$ +2170° (peak), $[\Phi]_{296}^{27}$ 0°, $[\Phi]_{271}^{27}$ −2240° (trough), $[\Phi]_{245}^{27}$ −920°. PMR (d_6-benzene): 0.72 (3H, s, 4-Me), 0.76 (3H, s, 10-Me), 0.85 (3H, d, J=7, 11-Me), 3.96 (1H, q-like, J=*ca.* 6, 8-H). Mass Spectrum m/e (%): 250 (M^+, 5), 95 (100).

Treatment of 4α,5α-Epoxide (2) with BF_3-etherate-Benzene——A stirred solution of **2** (100 mg) in dry benzene (20 ml) was treated with BF_3-etherate (0.25 ml) under N_2 atmosphere at 25° for 10 min and added with aq. 5% $NaHCO_3$ (1 ml). The benzene layer was taken, washed with water, and worked up as usual. White powder (87 mg) thus obtained was purified by preparative TLC ($CHCl_3$) to give a white crystalline product (76 mg) which was identified with AT-2 (**11**) by mixed mp, IR ($CHCl_3$), GLC, and TLC ($CHCl_3$; *n*-hexane–ether=1: 2; $CHCl_3$–ether=5: 2).

Treatment of 4α,5α-Epoxide (2) with CF_3COOH-$CHCl_3$——A solution of **2** (52 mg) in $CHCl_3$ (1 ml) was added with CF_3COOH (0.5 ml) and left standing under N_2 atmosphere at 28° for 2 hr. After neutralizing with aq. 5% $NaHCO_3$, the reaction mixture was extracted with $CHCl_3$ and the $CHCl_3$ extract was washed with water and worked up as usual to give a yellow oil (50 mg). Purification of the product by preparative TLC (*n*-hexane–ether=1: 2) furnished AT-1 (**10**) (10 mg) and AT-2 (**11**) (33 mg), which were respectively identified by IR ($CHCl_3$), GLC, and TLC ($CHCl_3$; *n*-hexane–ether=1: 2; $CHCl_3$–ether=5: 2).

Treatment of 4α,5α-Epoxide (2) with *p*-TsOH·H_2O-EtOH——A solution of **2** (152 mg) in 95% EtOH (10 ml) was treated with *p*-TsOH·H_2O (140 mg) and the total solution was refluxed under N_2 atmosphere for 2 hr. After cooling, the reaction mixture was diluted with water (200 ml) and extracted with $CHCl_3$. The $CHCl_3$ extract was then washed with aq. 5% $NaHCO_3$ until the washings showed neutral and with water. Working up of the $CHCl_3$ layer in a usual manner gave a glassy product (150 mg), which was purified by preparative TLC (*n*-hexane–ether=1: 2) to afford AT-1 (**10**) (18 mg), AT-3 (**12**) (9 mg), and AT-4 (**13**) (50 mg). AT-1 (**10**) was identified by IR ($CHCl_3$), GLC, and TLC (*n*-hexane–ether=1: 2; $CHCl_3$–ether=5: 1; $CHCl_3$). AT-3 (**12**), mp 191—192° (colorless needles from benzene–petr. ether), $[\alpha]_D^{21}$ +80.9° (c=0.55, $CHCl_3$). *Anal.* Calcd. for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.90; H, 8.60. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3590 (OH), 1770 (γ-lactone), 1644, 888 (terminal methylene). PMR ($CDCl_3$): 0.93 (3H, s, 10-Me), 1.20 (3H, d, J=7, 11-Me), 4.52 (1H, m, 8-H), 4.71, 4.86 (1H each, br.s, $C_{(4)}=CH_2$). Mass Spectrum m/e (%): 250 (M^+, 9), 232 (7), 121 (100). AT-4 (**13**), mp 169—170° (colorless needles from *n*-hexane), $[\alpha]_D^{20}$ +25.9° (c=1.16, $CHCl_3$). *Anal.* Calcd. for $C_{17}H_{28}O_4$: C, 68.89; H, 9.52. Found: C, 68.84; H, 9.31. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3685 (OH), 1765 (γ-lactone), 1111, 1076 (C–O–C). PMR ($CDCl_3$): 1.08 (3H, s, 10-Me), 1.11 (3H, t, J=7, $OCH_2C\underline{H}_3$), 1.20 (3H, d, J=7, 11-Me), 1.26 (3H, s, 4-Me), 2.82 (1H, m, 11-H), 2.71 (1H, m, 7-H), 3.32 (2H, q, J=7, $OC\underline{H}_2CH_3$), 4.48 (1H, m, 8-H); (d_5-pyridine): 1.06 (3H, t, J=8, $OCH_2C\underline{H}_3$), 1.13 (3H, d, J=7, 11-Me), 1.24 (3H, s, 10-Me), 1.42 (3H, s, 4-Me), 2.77 (1H, m, 11-H), 2.89 (1H, m, 7-H), 3.28 (2H, q, J=8, $OC\underline{H}_2CH_3$), 4.49 (1H, m, 8-H). Mass Spectrum m/e (%): 296 (M^+, 4), 250 ($M^+-C_2H_5OH$, 11), 99 (100).

$NaBH_4$ Reduction of AT-2 (11) giving AT-2-R (14)——A stirred solution of **11** (35 mg) in tetrahydrofuran (3 ml) was treated with $NaBH_4$ (20 mg) under ice-cooling for 30 min. The reaction mixture was then diluted with water (100 ml), treated with aq. 5% H_2SO_4 (1 ml), and extracted with CH_2Cl_2. Working up of the CH_2Cl_2 extract in a usual way gave white powder (32 mg) which, on purification by preparative TLC ($CHCl_3$–ether=5: 2), gave AT-2-R (**14**) (25 mg). AT-2-R (**14**), mp 106—107° (colorless needles from *n*-hexane–benzene), $[\alpha]_D^{20}$ +18.5°. *Anal.* Calcd. for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.28; H, 9.54. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3610 (OH), 1759 (γ-lactone). CD (c=0.653, MeOH): $[\theta]_{224}^{21}$ +290 (pos. max.), $[\theta]_{250}^{21}$ 0. PMR: as given in Table II. Mass Spectrum m/e (%): 252 (M^+, 2), 95 (100).

Jones Oxidation of AT-2-R (14) resuming AT-2 (11)——An ice-cooled stirred solution of **14** (10 mg) in acetone (2 ml) was treated with Jones reagent (4 drops) for 30 min and diluted with ice-water. The mixture was extracted with ether and working up of the ether extract in a usual manner gave white powder (7 mg) which was identified with AT-2 (**11**) by GLC and TLC ($CHCl_3$–ether=5: 2; *n*-hexane–ether=2: 1; *n*-hexane–$CHCl_3$=1: 1).

Epimerization of AT-2-R (14) with K_2CO_3-Toluene giving 15——A stirred solution of **14** (42 mg) in dry toluene (3 ml) was treated with K_2CO_3 (200 mg) under reflux for 11 hr. After cooling, the reaction mixture was filtered to remove K_2CO_3 and filtrate was evaporated under reduced pressure to give white powder (41 mg) which was purified by preparative TLC ($CHCl_3$–ether=5: 1) to afford **14** (20 mg, recovered) and **15** (7 mg). **15**, mp 137—138° (colorless needles from *n*-hexane–benzene), $[\alpha]_D^{13}$ +44.2° (c=0.55, $CHCl_3$). *Anal.* Calcd. for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.49; H, 9.55. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3610 (OH), 1762 (γ-lactone). CD (c=0.248, MeOH): $[\theta]_{227}^{23}$ −3070 (neg. max.), $[\theta]_{250}^{23}$ 0. PMR ($CDCl_3$): 0.88 (6H, s, 4-Me and 10-Me), 1.22 (3H, d, J=7, 11-Me), 3.68 (1H, d, J=8, 5-H), 4.91 (1H, m, 8-H). Mass Spectrum m/e (%): 252 (M^+, 18), 95 (100).

Epimerization of Dihydroisoalantolactone (3) with K_2CO_3-Toluene giving 16——A stirred solution of **3** (120 mg) in dry toluene (6 ml) was treated with K_2CO_3 (1.0 g) under reflux for 11 hr. Working up of the reaction mixture as above gave white powder (116 mg) which was purified by preparative TLC (*n*-hexane–ether=2: 1, developing twice) to afford **3** (70 mg, recovered) and 11-epimer (**16**) (13 mg). **16**, mp 110—112°

(colorless needles from *n*-hexane), $[\alpha]_D^{15}$ +59.3° (c=0.39, $CHCl_3$). *Anal.* Calcd. for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 77.02; H, 9.39. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1767 (γ-lactone), 1646, 890 (terminal methylene). CD (c=0.542, MeOH): $[\theta]_{216}^{20}$ −7130 (neg. max.), $[\theta]_{256}^{20}$ 0. PMR ($CDCl_3$): 0.83 (3H, s, 10-Me), 1.30 (3H, d, J=8, 11-Me), 2.39 (1H, m, 11-H), 4.45, 4.75 (1H each, br.s, $C_{(4)}$=CH_2), 4.67 (1H, m, 8-H). Mass Spectrum *m/e* (%): 234 (M^+, 22), 41 (100).

Epimerization of Tetrahydroalantolactone (5) **with K_2CO_3-Toluene giving 17**——A stirred solution of **5** (100 mg) in dry toluene (6 ml) was treated with K_2CO_3 (1.0 g) under reflux for 10 hr. Working up as above gave white powder (99 mg), which was purified by preparative TLC (*n*-hexane–ether=1: 1) to furnish **5** (54 mg, recovered) and 11-epimer (**17**) (26 mg). **17**, mp 62—64° (colorless needles from *n*-hexane), $[\alpha]_D^{15}$ +31.1° (c=0.64, $CHCl_3$). *Anal.* Calcd. for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24. Found: C, 76.16; H, 10.12. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1763 (γ-lactone). CD (c=0.456, MeOH): $[\theta]_{228}^{19}$ −1740 (neg. max.), $[\theta]_{252}^{19}$ 0. PMR ($CDCl_3$): 0.87 (3H, d, J=7, 4-Me), 1.00 (3H, s, 10-Me), 1.26 (3H, d, J=8, 11-Me), 2.38 (1H, q, J=8, 11-H), 4.63 (1H, m, 8-H). Mass Spectrum *m/e* (%): 236 (M^+, 5), 81 (100).

CD Data of Dihydroisoalantolactone (3), **Tetrahydroalantolactone** (5), **Product B** (**18**), **and 6-Epimer of Product D** (**19**)——**3**, (c=1.003, MeOH): $[\theta]_{225}^{22}$ +460 (pos. max.), $[\theta]_{248}^{22}$ 0. **5**, (c=0.326, MeOH): $[\theta]_{224}^{21}$ +620 (pos. max.), $[\theta]_{250}^{21}$ 0. **18**, (c=0.510, MeOH): $[\theta]_{218}^{21}$ +1530 (pos. max.), $[\theta]_{248}^{21}$ 0. **19**, (c=0.449, MeOH): $[\theta]_{213}^{21}$ −3760 (neg. max.), $[\theta]_{250}^{21}$ 0.

Photooxygenation followed by KI-AcOH Treatment of 4 giving AT-3 (**12**)——A solution of **4** (135 mg) in dry pyridine (5 ml) was placed in a Pyrex tube (OD=1 cm) and added with a solution of hematoporphyrin dihydrochloride (20 mg) in dry pyridine (5 ml) and the total solution, while bubbling with slow stream of oxygen, was irradiated externally (distance=15 cm) with fluorescence lamps (standard desk lamp, 15 W × 3) at 20° for 6 hr. After diluting with ether, the reaction mixture was treated with active charcoal (1 g) with warming for a while, filtered, and evaporated to give a white product (126 mg, hydroperoxide (**20**)). The product, without further purification, was dissolved in ether (4 ml)–MeOH (6 ml) mixture and added with a solution of KI (200 mg) in dist. water (3 ml)–AcOH (8 ml). The total mixture was kept stirring at 18° for 3 hr, neutralized with aq. 5% $NaHCO_3$, and extracted with ether. The ether extract was washed successively with aq. satur. $Na_2S_2O_3$ solution and aq. satur. NaCl solution, and dried over $MgSO_4$. Evaporation of the solvent gave a white crystalline product (100 mg) which was identified with AT-3 (**12**) by mixed mp, IR ($CHCl_3$), GLC, and TLC.

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