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Biogenetically Patterned Transformation of Eudesmanolide to Eremophilanolide. II.[1] Structures of Minor Products obtained by Acid Treatment of 5α,6α-Epoxy-eudesman-8β,12-olide

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As a continuation of the previous work, the structures of four minor products, which were obtained by HCOOH–acetone (1: 2) treatment of 5α,6α-epoxy-eudesman-8β,12-olide (**1**) along with previously elucidated four products: A (**2**), B (**3**), C (**4**), and D (**5**), have been elucidated as E (**6**), F (**7**), G (**8**), and H (**9**).

It has become clear that **1** was converted to five eremophilanolides (A, B, D, F, and H) *via* a biogenetic-type 1,2-shift of the angular methyl at C-10, and the structure requirement for the ready conversion has been discussed. In addition, preparative liquid chromatography was undertaken to clarify the accurate product composition of the above acid treatment.

As a continuative study on the biogenetically patterned transformation of natural terpenoids,[3] we reported in the previous paper that treatment with HCOOH–acetone (1: 2) mixture of 5α,6α-epoxy-eudesman-8β,12-olide (**1**) furnished eight products: product A (10%), B (34%), C (2.2%), D (2.0%), E (0.5%), F (3.4%), G (2.4%), and H (0.3%), and elucidated the structures of product A (**2**), B (**3**), C (**4**), and D (**5**).[1] Product A (**2**), B (**3**), and D (**5**) were the desired eremophilanolides and this was the first success of the chemical transformation of eudesmanolide to eremophilanolides *via* a biogenetic-type 1,2-shift of the angular methyl at C-10. In addition, it was found that treatment of **1** with HCOOH-acetone mixture of different composition (2: 1) resulted in the formation of a richer amount of eremophilanolides: product A (52%) and B (16%), and it was suggested that the conversion would provide with a biogenetically patterned synthetic route of eremophilane-type sesquiterpenoid *via* a precursory eudesmane-type compound.

In this paper, we wish to present the evidence which is in accord with the formulations of the rest of the above reaction products, *i.e.*: E (**6**), F (**7**), G (**8**), and H (**9**), among which product F and H are the additional examples of eremophilanolides.[4]

Product E (**6**) carries a hydroxyl, a γ-lactone, and an ester function as shown by its infrared (IR) spectrum. The proton magnetic resonance (PMR) spectrum of product E exhibits the signals due to two methine protons (6-H, 8-H) which are respectively geminal to a formyloxy and a lactonic carbonyloxy functions and the signals ascribable to two secondary methyls (4-Me, 11-Me) and one tertiary methyl (10-Me), but lacks the signal due to a vinyl proton (Table I). These spectral properties have led us to presume that product E holds an eudesmanolide skeleton in which only the epoxide ring of **1** is cleaved. In order to assign the structure **6** to product E, a *cis*-α-glycol (**11**), prepared from dihydroalantolactone (**10**)[1]

1) Part I: I. Kitagawa, Y. Yamazoe, H. Shibuya, R. Takeda, H. Takeno, and I. Yosioka, *Chem. Pharm. Bull.* (Tokyo), **22**, 2662 (1974).
2) Location: *133–1, Yamada-kami, Suita, Osaka, 565, Japan.*
3) *a*) I. Kitagawa, K. Kitazawa, and I. Yosioka, *Tetrahedron*, **28**, 907 (1972); *b*) I. Kitagawa, K. Kitazawa, K. Aoyama, M. Asanuma, and I. Yosioka, *ibid.*, **28**, 923 (1972).
4) Presented at the 95th Annual Meeting of Pharmaceutical Society of Japan, Nishinomiya, April, 1975. Abstract Papers: II-234.

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by OsO_4 oxidation (attacking from the less hindered α-side),[5] was converted to a monoformate (**6**). The formate thus obtained was found identical with product E in all respects. The *cis* configuration of 5α-OH and 6α-OCHO in product E appears to be derived through an apparent *cis* opening of the α-epoxide ring in **1**. The result could be explained by presuming that the epoxide ring is first cleaved at $C_{(5)}$-O bond and the resulting carbonium ion at C-5 is attacked by a hydroxyl anion from the α-side (in a non-concerted manner) followed by formylation at 6-OH since the β-side is spacially crowded, or by presuming that the epoxide ring cleavage at $C_{(6)}$-O bond is followed by a formate anion attack at C-6 from the α-side due to the similar reason.

The IR spectrum of product F (**7**) shows the presence of a hydroxyl, a γ-lactone, and a double bond, while the PMR spectrum exhibits the signals due to a vinyl proton (1-H) and two methine protons (6-H, 8-H) geminal to a lactonic carbonyloxy function and a hydroxyl, and the signals of two secondary methyls (4-Me, 11-Me) and one tertiary methyl (5-Me) (Table I). Although the coupling pattern of the signal due to 8-H is alike to that in product D (**5**) (δ 4.67, d.t, J=7 and 10 Hz),[1] the δ value is shifted higher. In addition, the signal due to 6-H is observed with a larger coupling constant and at a slightly lower position as compared with that of product D (**5**) (δ 3.90, d, J=4 Hz).[1] Since these spectral features are ascribed

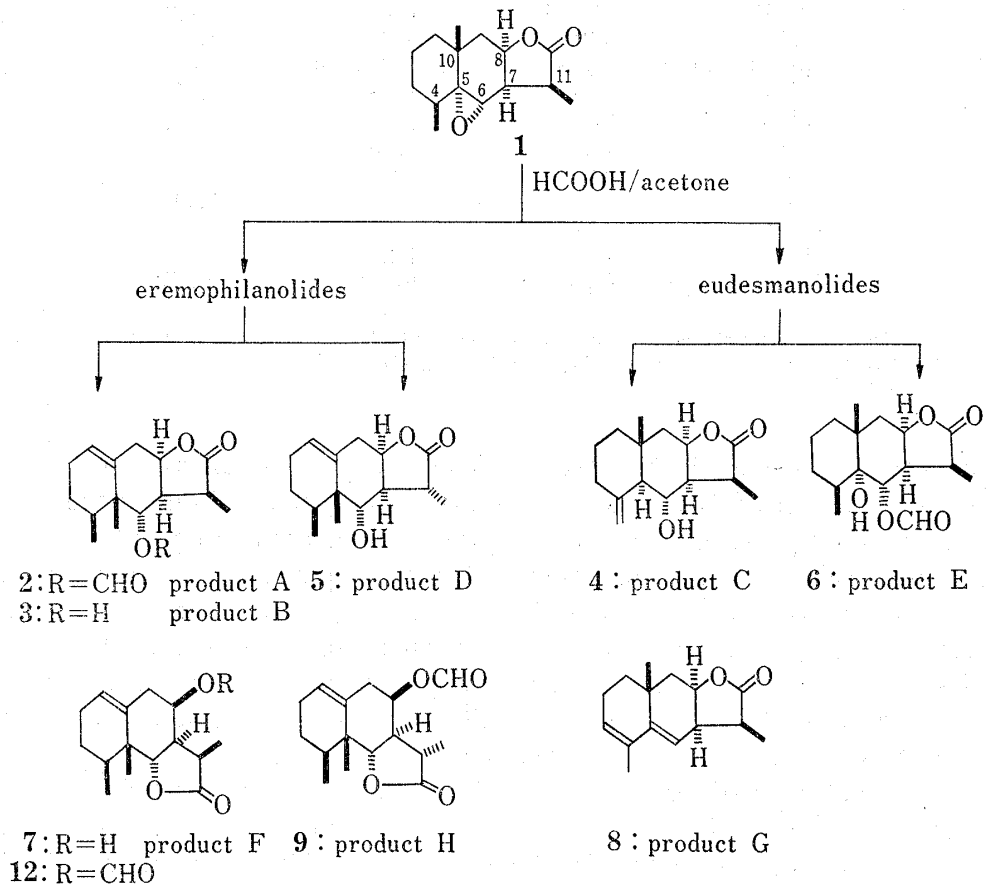

Chart 1

5) Although the OsO_4 oxidation of **10** was previously reported to give a 5β,6β-glycol as the major while **11** as the minor,[6] the latter has been obtained as the major in our hands. The *cis*-α-glycol structure is rationalized by the stereochemical consideration of the OsO_4 oxidation and also is supported by PMR examinations in which no significant pyridine-induced solvent shift[7] of the signals due to 4-Me and 10-Me was observed in the PMR spectrum of **11** in d_5-pyridine (see Experimental).

6) P. Vita-Finzi, Y. Kashman, E. Glotter, and D. Lavie, *Tetrahedron*, **24**, 5847 (1968).

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.

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to the change of chemical environment (including conformation) of the ring B, the structure of product F has been assumed to be **7** possessing an angular eremophilanolide skeleton. The assumption has been verified by a fact that aqueous K_2CO_3 treatment of either product D (**5**) (linear eremophilanolide) or product F ends up with the formation of a same equilibrium mixture of **5** and **7**. The latter is contained in a richer amount, presumably due to the less ring strain resulted from the change to a *trans* γ-lactone structure as deduced from the Dreiding model examination. The isolation yields of product D (**5**) and F (**7**) are also in parallel with the presumption. The significant intramolecular nuclear Overhauser effect (NOE) between 6-H and 5-Me in **7** was observed (24%), which is figured out by a perspective formula **i**.

Table I. PMR Data of **6**, **7**, **8**, **9**, and **12** (Chemical Shifts in δ Values, Coupling Constants and Half-height Band Width in Hz)[a]

	Eremophilanolides			Eudesmanolides	
	7	**9**	**12**	**6**	**8**[b]
1-H	5.41 (m)	5.50 (d-like)	5.50 (t-like)[c]	—[d]	—[d]
6-H	4.30 (d, 12)	3.94 (d, 11)	4.24 (d, 11)	5.42 (d, 10)	5.32 (d, 4)
8-H	4.10 (d.t, 6 and 8)	5.19 (br. s, $W_{h/2}=5$)	5.20 (d.t, 6 and 8)	4.67 (m)	4.77 (q-like)[c]
4-Me	1.08 (d, 6)	0.98 (d, 7)	1.08 (d, 6)	1.06 (d, 7)	1.77 (d, 2)
5-Me	1.18 (s)	1.22 (s)	1.20 (s)	—	—
10-Me	—	—	—	1.14 (s)	1.06 (s)
11-Me	1.21 (d, 6.5)	1.27 (d, 7)	1.21 (d, 7)	1.23 (d, 7)	1.25 (d, 7)

a) abbreviations: br.s=broad singlet; d=doublet; d.t=doublet of triplet; m=multiplet; q=quartet; s=singlet
b) A vinyl proton signal due to 3-H is observed at δ 5.57 (m, $W_{h/2}=11$).
c) $J=ca.$ 3 Hz
d) unclear

Product G (**8**) possesses a γ-lactone (IR), a diene chromophore (ultraviolet (UV) spectrum), and one each of vinyl methyl (4-Me), secondary methyl (11-Me), and tertiary methyl (10-Me), and one methine proton (8-H) geminal to a lactonic carbonyloxy function and two vinyl protons (3-H, 6-H) (PMR, Table I). In connection with the presumed formation mechanism,[1] the structure **8** has been assigned to product G, and the assignment is supported by agreement of the physicochemical properties of product G with those reported for **8**.[6]

The IR spectrum of product H (**9**) shows the presence of a γ-lactone, an ester function, and a double bond, while the PMR spectrum exhibits the signals ascribable to one vinyl proton (1-H), two methine protons (6-H, 8-H) geminal to a lactonic carbonyloxy and formyloxy functions, two secondary methyls (4-Me, 11-Me), and one tertiary methyl (5-Me) (Table I). Based on comparison of the line positions of the signals due to 6-H and 8-H with those of product F (**7**) and product F formate (**12**) which was prepared by formylation of **7**, in addition to the quite similar mass fragmentation pattern of product H with those of **7** and **12** (almost identical with the latter), the structure of product H is expressed as **9** which corresponds to an 11-epimer of **12**.

As a conclusion hitherto elucidated by the product analysis of HCOOH–acetone (1:2) treatment of 5α,6α-epoxy-eudesman-8β,12-olide (**1**), five eremophilanolides: product A (**2**), B (**3**), D (**5**), F (**7**), and H (**9**) (combined yield: 49.7%) and three eudesmanolides: product C (**4**), E (**6**), and G (**8**) (combined yield: 5.1%) have been isolated by combination of silica gel column and thin-layer chromatography (TLC). In order to clarify the more accurate product composition of the acid treatment, preparative liquid chromatography of the total reaction

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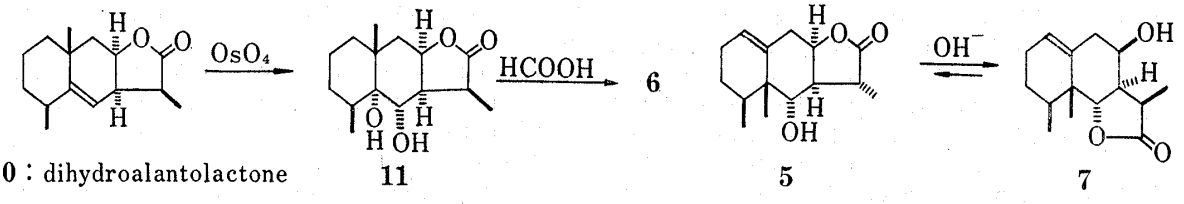
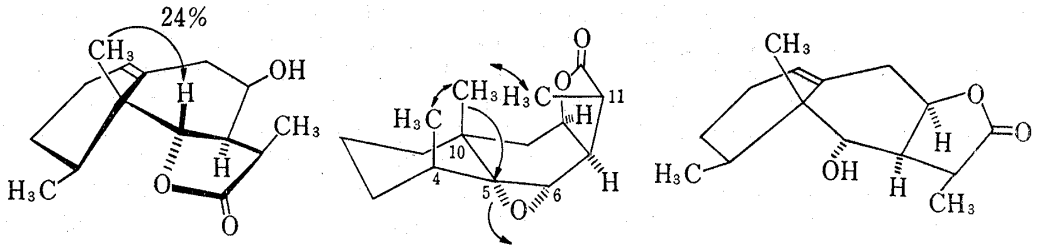


10 : dihydroalantolactone 11 5 7



i (7) ii (1) iii (product B (3))

Chart 2

product was undertaken. As described in the Experimental, the major reaction products: product A (12.1%), B (40.0%), C (5.0%), and G (4.0%), were isolated in better yields and in shorter time than by ordinary silica gel chromatography.

In regard to the structure requirement for the facile 1,2-shift of 10-Me in 5α,6α-epoxy-eudesman-8β,12-olide (**1**), the following three factors have been taken up: i) the presence of *cis*-γ-lactone in **1** which would fix somehow the B-ring conformation during the epoxide ring opening; ii) the location of 5α,6α-epoxide in **1** which, probably with a combination of the presence of *cis*-γ-lactone, would force the B-ring to take a boat-like conformation, so that 10-Me being favorably located for shifting to C-5 on the epoxide ring opening initiated by the $C_{(5)}$-O bond cleavage; iii) the spacial interactions which are brought about by three methyls in **1** (4-Me, 5-Me, and 11-Me) as shown in **ii** and are released in the eremophilane-type product: *cf.* a perspective figure **iii** of product B (**3**).

In order to investigate these structural factors in detail, the further work is under way in this laboratory.

Experimental[8]

Product E (**6**)——Recrystallization from *n*-hexane–acetone of product E obtained before[1] gave colorless needles (**6**) of mp 197°, $[\alpha]_D^{22}$ −50° (c=0.01, $CHCl_3$). High Resolution Mass Spectrum *m/e*: 296.162 (M^+). Calcd. for $C_{16}H_{24}O_5$: 296.162. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600 (OH), 1770 (γ-lactone), 1728 (formate). PMR ($CDCl_3$): 1.57 (1H, br. s, OH, D_2O exchangeable), 8.07 (1H, s, OCHO), and other signals as given in Table I. Mass Spectrum *m/e* (%): 296 (M^+, 3), 126 (100).

Product F (**7**)——Recrystallization from *n*-hexane of product F[1] gave colorless needles (**7**) of mp 114—115°, $[\alpha]_D^{22}$ −130° (c=1.00, $CHCl_3$). *Anal.* Calcd. for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.86; H, 8.84. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3550 (OH), 1762 (γ-lactone), 1608 (C=C). PMR ($CDCl_3$): 2.79 (1H, d.q, J=6.5 & 11, 11-H), and other signals as given in Table I. Mass Spectrum *m/e* (%): 250 (M^+, 3), 41 (100).

Product G (**8**)——Recrystallization from ether product G[1] gave colorless needles (**8**) of mp 81—82°, $[\alpha]_D^{29}$ −11° (c=0.76, $CHCl_3$). High Resolution Mass Spectrum *m/e*: 232.146 (M^+). Calcd. for $C_{15}H_{20}O_2$: 232.146.

8) The following instruments were used for obtaining the physical data: mp (Yanagimoto Micro-meltingpoint Apparatus; recorded uncorrected); specific rotation (Rex Photoelectric Polarimeter NEP-2, measured with l=1 dm); IR spectra (Hitachi IR Spectrometer EPI-G3 or EPI-S2); UV spectra (Hitachi EPS-3T UV Spectrometer); Mass spectra (Hitachi RMU-6D Mass Spectrometer); High resolution mass spectra (JEOL JMS-OlSG Mass Spectrometer); PMR spectra (Hitachi R-22 NMR Spectrometer, Me_4Si as an internal standard). The chemical shifts are given in δ value and coupling constants (J) and half-height band width ($W_h/_2$) are in Hz. For gas liquid chromatography (GLC), Hitachi Gas Chromatograph Model 063 was used under the following conditions: 3% SE-30 on chromosorb W (1 m×3 mm); carrier gas (N_2) flow rate 20—50 ml/min; temp. 170° or 210°. For TLC, silica gel (Camag D-5) was used and detection by 1% $Ce(SO_4)_2$ in 10% H_2SO_4 with heating. For liquid chromatography, Waters Assoc. Liquid Chromatograph Model ALC-100 was used.

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IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1767 (γ-lactone). UV λ_{max}^{EtOH} nm (ε): 232 (7800), 239 (8200), 247 (5600). PMR ($CDCl_3$): as given in Table I. Mass Spectrum *m/e* (%) 232 (M^+, 30), 41 (100).

Product H (9)——Recrystallization from *n*-hexane of product H[1] gave colorless needles (**9**) of mp 112—113°, $[\alpha]_D^{22}$ −32° (c=0.30, $CHCl_3$). High Resolution Mass Spectrum *m/e*: 278.151. Calcd. for $C_{16}H_{22}O_4$: 278.152. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1779 (γ-lactone), 1725 (formate), 1643 (C=C). PMR ($CDCl_3$): 8.09 (1H, s, OCHO), and other signals as given in Table I. Mass Spectrum *m/e* (%): 278 (M^+, 1), 41 (100).

OsO_4 Oxidation of 10 giving 11——To a stirred solution of **10** (92 mg) in pyridine (1.5 ml) was added OsO_4 (100 mg) and the total mixture was kept stirring at room temperature overnight. The reaction mixture was treated with $NaHSO_3$ (180 mg), water (3 ml), and pyridine (2 ml), and stirred further for 30 min and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with aq. 10% HCl, aq. 5% $NaHCO_3$, and water successively, and dried over $MgSO_4$. Evaporation of the solvent gave a yellow powder (82 mg) which was crystallized from benzene to afford **11** (77 mg) of mp 213—214° as colorless needles, $[\alpha]_D^{23}$ −62° (c=1.90, pyridine). *Anal.* Calcd. for $C_{15}H_{24}O_4$: C, 67.13; H, 9.02. Found: C, 67.02; H, 9.11. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3530 (OH), 1760 (γ-lactone). PMR ($CDCl_3$): 1.04 (3H, d, J=7, 4-Me), 1.08 (3H, s, 10-Me), 1.36 (3H, d, J=7, 11-Me), 3.87 (1H, m, varied to d of J=8 on D_2O addition, 6-H), 4.54 (1H, m, 8-H); (d_5-pyridine): 1.09 (3H, d, J=7, 4-Me), 1.19 (3H, s, 10-Me), 1.62 (3H, d, J=7, 11-Me), 4.18 (1H, d, J=8, 6-H), 4.66 (1H, m, 8-H). Mass Spectrum *m/e* (%): 268 (M^+, 1), 126 (100).

Formylation of 11——A solution of **11** (50 mg) in aq. 88% HCOOH (3 ml) was refluxed for 2 hr, and after cooling, poured into water (10 ml), and extracted with EtOAc. The EtOAc extract was washed with aq. 5% $NaHCO_3$ and water, dried over $MgSO_4$, and evaporated under reduced pressure to give a crude product (37 mg). Purification of the product by preparative TLC ($CHCl_3$–ether=1: 1) furnished **6** (7 mg) and **11** (21 mg, recovered). The formate thus obtained was identified with product E (**6**) by mixed mp, IR ($CHCl_3$), TLC ($CHCl_3$–ether=5: 2; *n*-hexane–ether=1: 2; benzene–EtOAc=5: 2), and GLC (3% SE-30).

K_2CO_3 Treatment of Product D (5)——A solution of **5** (10 mg)[1] in aq. MeOH (5 ml) was added with K_2CO_3 powder (20 mg), heated under reflux for 10 min, and after cooling, filtered to remove K_2CO_3. The filtrate was acidified with p·TsOH·H_2O and extracted with CH_2Cl_2. Working up of the CH_2Cl_2 extract in a usual manner gave a glassy product (6 mg), which was shown to be a mixture of **5** and product F (**7**) by TLC ($CHCl_3$–ether=5: 2) and GLC (3% SE-30).

K_2CO_3 Treatment of Product F (7)——A solution of **7** (7 mg) in aq. MeOH (5 ml) was added with K_2CO_3 powder (20 mg), heated under reflux for 10 min, and treated as above. A glassy product (5 mg) thus obtained was identified with the above-described product by TLC and GLC as above.

Formylation of 7 giving 12——A solution of **7** (15 mg) in acetone (2 ml)-99% HCOOH (2 ml) was heated under reflux for 1 hr. After cooling, the reaction mixture was diluted with water, neutralized with aq. 10% KOH, and extracted with EtOAc. The EtOAc extract was washed with aq. 5% $NaHCO_3$ and water successively, and dried over $MgSO_4$. A product obtained by usual work up was crystallized from *n*-hexane to give colorless needles (11 mg) of **12** of mp 115—116°, $[\alpha]_D^{21}$ −46° (c=0.70, $CHCl_3$). High Resolution Mass Spectrum *m/e*: 278.152 (M^+). Calcd. for $C_{16}H_{22}O_4$: 278.152. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1772 (γ-lactone), 1722 (formate). PMR ($CDCl_3$): 8.05 (1H, s, OCHO), and other signals as given in Table I.

Liquid Chromatography of HCOOH-Acetone Treatment Product of 1——1) Using Analytical Column: A total reaction product, which was obtained by HCOOH–acetone (1: 2) treatment of **1** as described before,[1] was subjected to a high speed liquid chromatograph with an RI detector at room temperature; column: CORASIL I (37—50 μ), 1/8″×6′; solvent: *n*-hexane–$CHCl_3$ (1: 1, v/v); flow rate: 1.0 ml/min; pressure: 66.5 kg/cm^2 (950 psi). The following peaks were identified by co-chromatography with authentic samples (elution time after injection): product G (**8**), 3′54″; product A (**2**), 5′24″; product C (**4**), 11′12″; product B (**3**), 20′54″. The other minor peaks were not identified.

2) Using Preparative Column: The above reaction product (110 mg, dissolved in 2 ml of $CHCl_3$) was subjected to the liquid chromatograph with an RI detector at room temperature; column: PORASIL T (25—37 μ), 3/8″×6′; solvent: *n*-hexane–$CHCl_3$ (2: 1) to fr. 1—154, *n*-hexane–$CHCl_3$ (1.5: 1) to fr. 155—300, *n*-hexane–$CHCl_2$ (1: 1) to fr. 301—406, $CHCl_3$ to fr. 407—509, EtOAc to fr. 510; flow rate: 0.8 ml/min; volume of each fraction: 1.6 ml/fr. (fr. 1—201), 4.8 ml/fr. (fr. 202—208), 2.8 ml/fr. (fr. 209—220), 4.8 ml/fr. (fr. 221—509), 100 ml/fr. (fr. 510); pressure: 21 kg/cm^2 (300 psi). The following products were isolated and identified with authentic samples by TLC ($CHCl_3$–EtOAc=9: 1): product G (**8**) (4.4 mg, 4.0%) from fr. 60—80, product A (**2**) (13.3 mg, 12.1%) from fr. 98—200, product C (**4**) (5.5 mg, 5.0%) from fr. 235—300, product B (**3**) (44.0 mg, 4.0%) from fr. 347—386. Product H (**9**), D (**5**), and E, F (**6**, **7**) were detected respectively in the eluates of fr. 51—59, fr. 301—323, and fr. 387—406, but not isolated. The total eluates were 105.5 mg (95.9% recovery).

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