[Chem. Pharm. Bull. 31(6)1943—1957(1983)]

Synthetic Studies on a Picrotoxane Sesquiterpene, Coriamyrtin. I.[1] The Grignard Reaction of 5-(2-Methyl-1,3-dioxo-2-cyclopentyl)methyl-2,5*H*-furanone with Isopropenylmagnesium Bromide and Stereochemistries of the Products

Kiyoshi Tanaka, Fumiaki Uchiyama, Atae Asada, Yasuhide Furusawa, and Yasuo Inubushi*

Faculty of Pharmaceutical Sciences, Kyoto University, Sakyo-ku, Kyoto 606, Japan

(Received November 26, 1982)

1,6-Addition of 2-methyl-1,3-cyclopentanedione (**8**) to protoanemonin (**7**) gave 5-(2-methyl-1,3-dioxo-2-cyclopentyl)methyl-2,5*H*-furanone (**6**). The Grignard reaction of **6** with isopropenylmagnesium bromide-cuprous iodide provided two kinds of lactones, (**10**) and (**11**), in excellent yield through 1,4-addition of the Grignard reagent to **6** and the subsequent internal aldol cyclization. These lactones, however, possessed the undesired stereostructures for the present synthesis and conversion of the lactone (**10**) into the desired lactone (**4**) was performed by retroaldol cleavage and subsequent internal aldol recyclization as shown in Chart 6.

Keywords——coriamyrtin synthesis; protoanemonin; 2-methyl-1,3-cyclopentanedione; 5-(2-methyl-1,3-dioxo-2-cyclopentyl)methyl-2,5*H*-furanone; Grignard reaction; retroaldol cleavage; aldol cyclization; picrotoxane skeleton

Various naturally occuring picrotoxane sesquiterpenes such as picrotoxinin (**1**), coriamyrtin (**2**), tutin (**3**) *etc.* are known. Coriamyrtin was first isolated from the European *Coriaria* species, *Coriaria myrtifolia* in 1864 by Riban[2a] and was later found to be the major toxic constituent of Japanese-grown *Coriaria japonica* by Kariyone *et al.*[2b] Its characteristic structure of two vicinal oxirane rings on the picrotoxane skeleton was confirmed on the basis of degradative and spectroscopic evidence by Okuda and Yoshida.[3] All picrotoxane sesquiterpenes possess powerful physiological activity on the central nervous system (CNS). Because of its antagonism of the inhibitory action of γ-aminobutyric acid (GABA) at synapses, picrotoxinin (**1**) is a useful research tool in the study of the pharmacology of the CNS, and coriamyrtin (**2**) has similar activity.[4] Despite the unique structures at a higher oxidation level and the interesting physiological activities, there was no report on the total synthesis of any member of the picrotoxane sesquiterpenes[5] until the elegant synthesis of picrotoxinin (**1**)[6] in 1979 and that of picrotin[7] in 1980 were reported by Corey *et al.* In this series of papers, we wish to present a full account of a stereocontrolled total synthesis of (±)-coriamyrtin[1] through a synthetic strategy entirely different from that used in picrotoxinin synthesis.[6] In this paper, synthesis and stereostructural assignment of two lactones, (**10**) and (**11**), and conversion of the lactone (**10**) into the lactone (**4**) possessing the correct stereostructure for the present synthesis are described.

The basic synthetic plan was developed from the retrosynthetic analysis of coriamyrtin (**2**), which involved the disconnections illustrated in Chart 1. On the basis of this analysis, our synthesis was undertaken starting from readily available protoanemonin (**7**)[8] and 2-methyl-1,3-cyclopentanedione (**8**).

1,6-Addition of **8** to **7** in the presence of sodium hydroxide or potassium fluoride in the dark gave 5-(2-methyl-1,3-dioxo-2-cyclopentyl)methyl-2,5*H*-furanone (**6**) in 14% yield. The poor yield was due to the dimerizing nature[9] of protoanemonin (**7**)[8] but this was not a serious obstacle to the present synthesis since **7** can be readily prepared from commercially available levulinic acid[8b] on a rather large scale as required. When potassium fluoride was used in

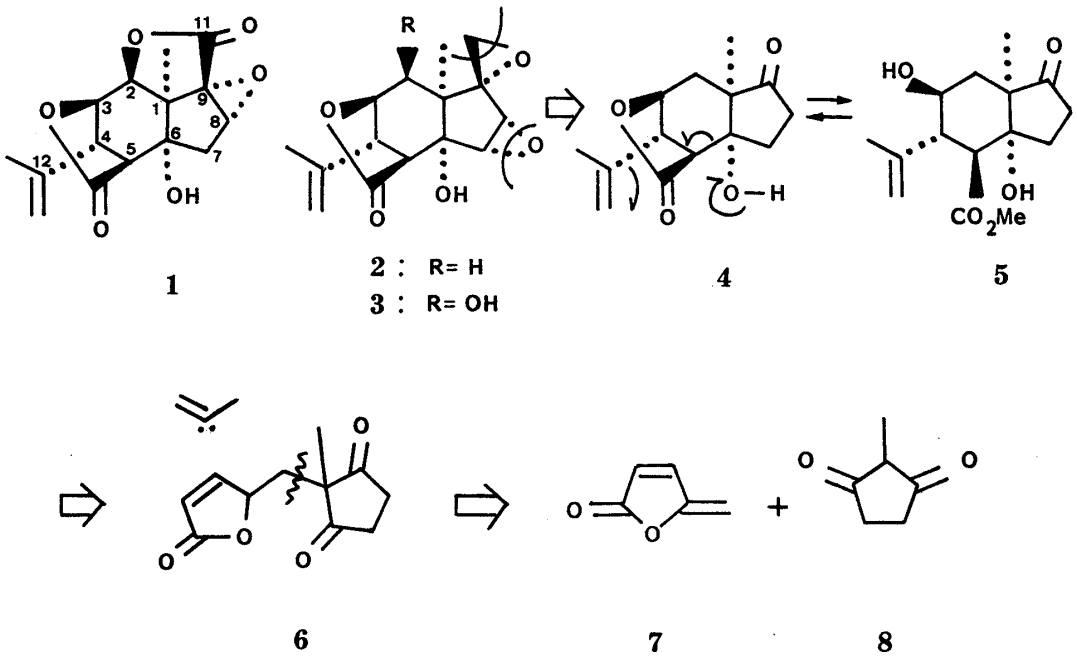


Chart 1

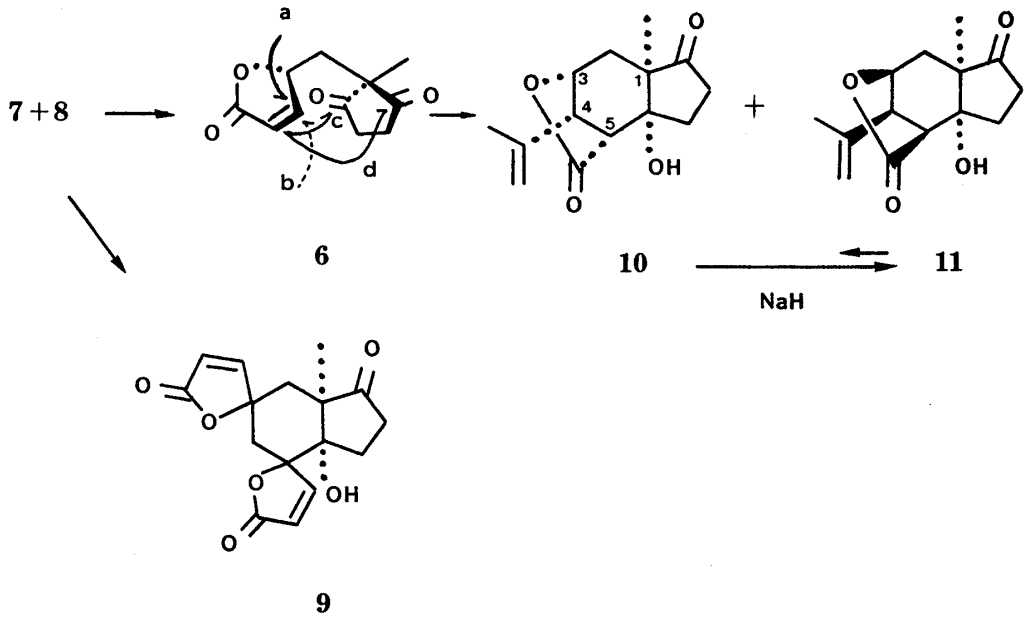
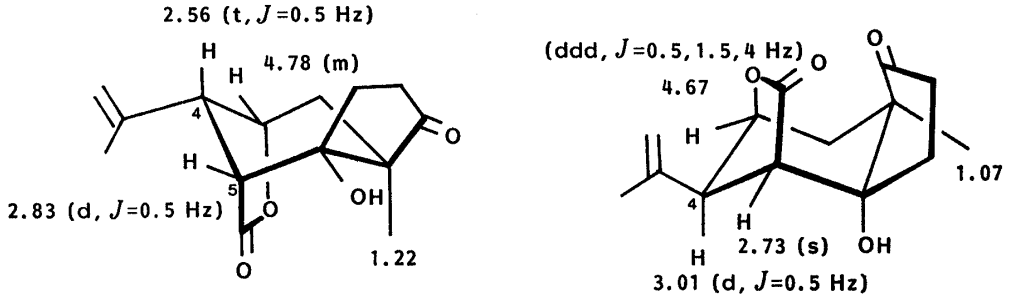


Chart 2

dimethyl sulfoxide as a solvent in this reaction, the spiro lactone (**9**) was formed to some extent through double Michael additions and subsequent internal aldol cyclization; the stereochemistry of this spiro compound was not established.

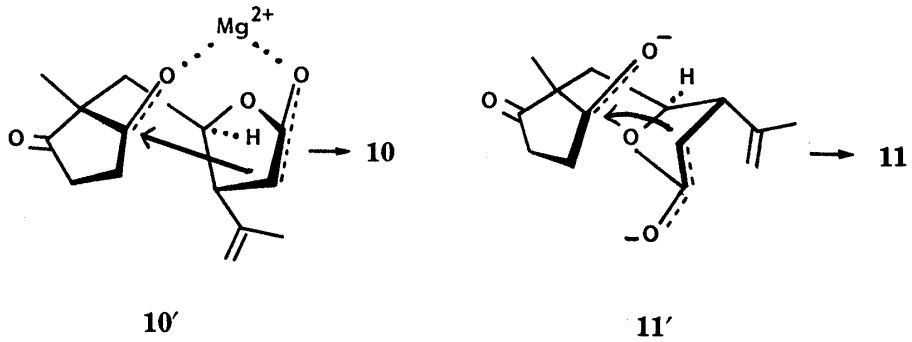
The Grignard reaction of **6** with isopropenylmagnesium bromide in the presence of a catalytic amount of cuprous iodide provided two kinds of lactones, (**10**), mp 148—149°C (a→c) and (**11**), mp 153°C (a→d), which resulted from 1,4-addition of the Grignard reagent to **6** and subsequent internal aldol cyclization, in an eight-to-one ratio and in 95% yield, and the desired lactone (**4**) (b→d) was not detected. When **10** was equilibrated with sodium hydride in dimethylformamide, it was mostly converted into **11**. The undesired equatorial orientation

of the isopropenyl group [this group is axial in the desired lactone (**4**)] and the *cis* relationship of the lactone ring with the isopropenyl group in these lactones were indicated by the proton nuclear magnetic resonance (^{1}H-NMR) spectrum, which revealed coupling of three vicinal protons at C_3, C_4, and C_5 with J values of 0—0.5 Hz (Fig. 1). However, the relative configuration of the lactone ring and the isopropenyl group with respect to the angular substituents in **10** and **11** remained obscure. Although more reliable indications regarding the stereostructures of **10** and **11** will be described later in this paper, the structures **10** and **11**, respectively, were suggested by the ^{1}H-NMR spectra of these lactones. Thus, the downfield shift (0.15 ppm) of the angular methyl signal in the ^{1}H-NMR spectrum of **10** compared with that of **11** may be due to the anisotropic effect of the lactone ring, suggesting the *cis* relationship of the lactone ring with the angular substituents in **10**. The predominant production of **10** in the Grignard reaction and conversion of **10** into **11** under the equilibrium conditions could be explained by assuming chelate formation by the participation of Mg^{2+} (**10′**) in the Grignard reaction and repulsion between carbonyl oxygens (**11′**) under the equilibrium conditions, as shown in Fig. 2.



10 **11**

Fig. 1



10′ **11′**

Fig. 2

With the object of establishing the stereostructures of **10** and **11**, and conversion of **10** or **11** into the desired compounds, **4** and **5**, a sequence of reactions was investigated first for the lactone (**11**), and then for the lactone (**10**).

In order to avoid the retroaldol cleavage, the angular hydroxy group of **11** was protected as its methylthiomethyl ether.[9] Alkaline hydrolysis of the lactone ring of the ether (**12**) resulted in recovery of the original ether under mild conditions and **12** decomposed under forcing conditions. Then, reduction of **12** with sodium borohydride gave solely the hydroxy ether (**13**), in which the β configuration of the resulting hydroxy group was presumed by supposing the hydride attack to have occurred from the convex face. Alkaline hydrolysis of **13**, followed by esterification with diazomethane, gave the dihydroxy ether (**14**), which

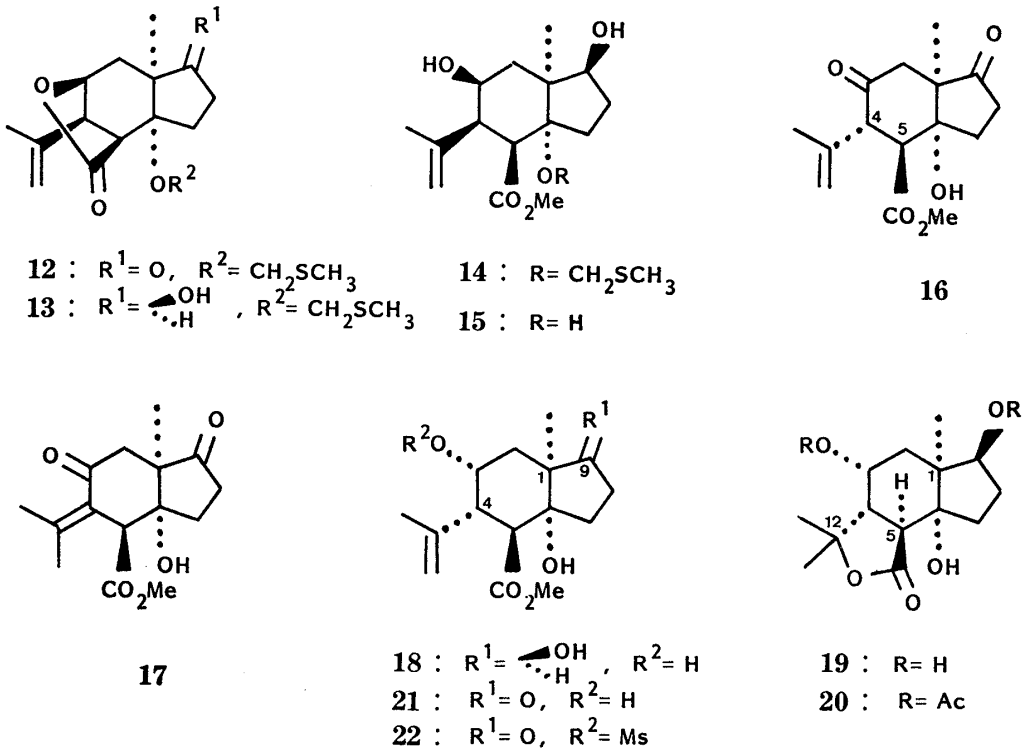
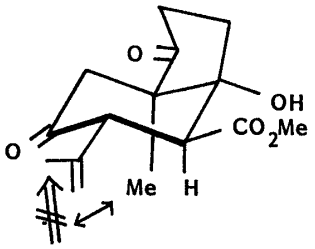


Chart 3

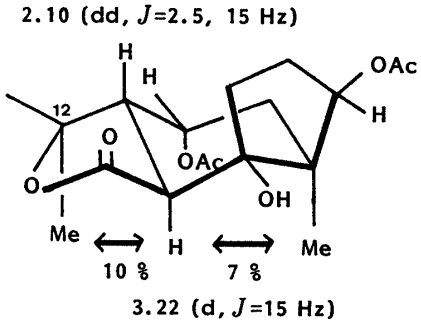
upon deprotection[10] of the angular hydroxy group with mercuric chloride afforded the trihydroxy ester (**15**). The *cis* relationship among the substituents at C_3, C_4, and C_5 with respect to each other in **15** was indicated by the ^{1}H-NMR spectrum, which revealed coupling of a triplet-like signal of the C_4–H with a J value of 4 Hz. Oxidation of **15** with Collins' reagent or Jones' reagent gave the diketone (**16**) and the α,β-unsaturated ketone (**17**) arising from the migration of the double bond. The ^{1}H-NMR spectrum of **16** revealed coupling of the C_4–H signal with a J value of 13 Hz, indicating the *trans* equatorial relationship of the isopropenyl group with the methoxycarbonyl group. This observation indicated that the configuration of the isopropenyl group of **15** epimerized during the oxidation procedure. Reduction of **16** with sodium borohydride afforded soley the trihydroxy ester (**18**), and the β configuration of the C_9 hydroxy group of **18** was presumed by analogy with the reduction of **12**. The ^{1}H-NMR spectrum of **18** revealed coupling of the double doublet signal of the C_4–H at δ 2.64 with J values of 2.5 and 13 Hz. This observation indicated the undesired *cis* relationship of the C_3 hydroxy group with the C_4 isopropenyl group in **18**. All attempts to obtain the desired hydroxy ester (**5**), in which the configuration of the C_3 hydroxy group is β, by reduction of the C_3 ketone function of **16** using a variety of reducing reagents were unsuccessful. The obstruction of hydride attack from the convex face can be attributed to the 1,3-diaxial interaction between the approaching reagent and the angular methyl group, as shown in Fig. 3. Acid treatment of the trihydroxy ester (**18**) gave the lactone (**19**), which on acetylation afforded the diacetyl lactone (**20**). In the ^{1}H-NMR spectrum of **20**, nuclear Overhauser effect (NOE) enhancements were observed between the C_5–H and angular methyl protons (7%) and between the C_5–H and one of the C_{12} geminal dimethyl protons (10%). This observation showed the *trans* relationship of the methoxycarbonyl group with the angular methyl group and consequently, the stereostructure of the lactone (**11**), in which the lactone ring and the angular substituents are situated in the *trans* positions with respect to each other, was established. The selective reduction of the C_3 ketone function of the diketone (**16**) was accomplished by so-

dium borohydride reduction at low temperature to give the hydroxy ester (**21**). The hydroxy ester (**21**) was derived to the *O*-mesyl ester (**22**) and all attempts to obtain the hydroxy ester (**5**) type compound possessing the correct stereostructure by S_N2 type replacement of the *O*-mesyl group failed.



16′

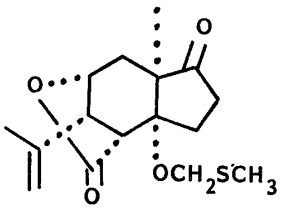
Fig. 3



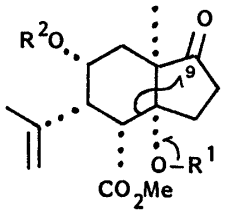
20

Fig. 4

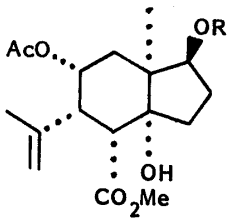
In order to establish the stereostructure of another Grignard reaction product, the lactone (**10**), the following experiments were carried out. The angular hydroxy group of **10** was protected as its methylthiomethyl ether[10] and alkaline hydrolysis of the ether (**23**), followed by esterification with diazomethane afforded the hydroxy ether (**24**). Acetylation of **24** gave the acetyl ether (**25**) and the epimerization reaction of the methoxycarbonyl group of **25** under a variety of reaction conditions did not take place. Deprotection of the angular hydroxy group of **25** by treatment with methyl iodide in the presence of water[11] afforded the acetyl ester (**26**).



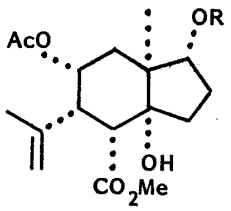
23



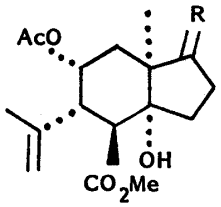
24 : R^1= CH_2SCH_3, R^2= H
25 : R^1= CH_2SCH_3, R^2= Ac
26 : R^1= H, R^2= Ac



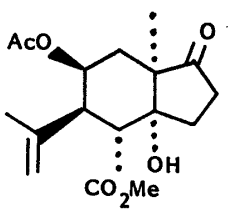
27 : R= H
29 : R= Ac



28 : R= H
30 : R= Ac



31 : R= OAc, H
32 : R= O

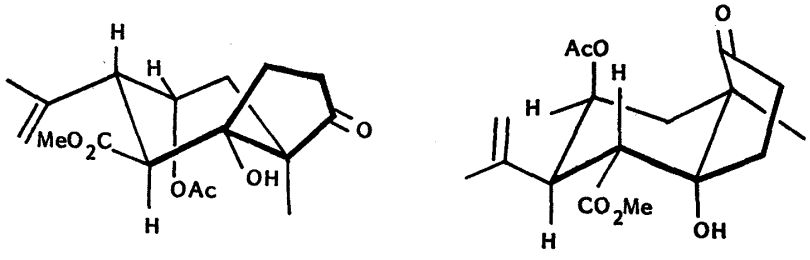


33

Chart 4

The ^{1}H-NMR spectrum of **26** revealed coupling of a triplet signal of the C_4–H at δ 3.32 with a J value of 6 Hz, indicating the *cis* relationship of the three substituents at C_3, C_4, and C_5 with respect to each other. Then, epimerization of the methoxycarbonyl group of **26** through retroaldol cleavage and aldol recyclization with the participation of the angular hydroxy group was attempted. In order to avoid the aldol recyclization to the C_9 carbonyl group, the acetyl ester (**26**) was reduced with sodium borohydride. In contrast to the ether (**12**), reduction of **26** occurred in two directions to give predominantly the dihydroxy ester (**27**) together with a moderate amount of the epidihydroxy ester (**28**). Acetylation of **27** and **28** afforded the diacetate (**29**) and the epidiacetate (**30**), respectively. The β configuration of the C_9 acetoxy group of **29** was deduced by comparison of the chemical shift of the signal due to the proton geminal to the C_9 acetoxy group at δ 5.03 with that of **30** at δ 4.72. Thus, the downfield shift of the signal of **29** can be attributed to the anisotropic effect of the α oriented angular hydroxy group. Treatment of the diacetate (**29**) with potassium *tert*-butoxide in tetrahydrofuran gave the diacetyl ester (**31**) in 75% yield. The ^{1}H-NMR spectrum of **31** revealed coupling of the C_5–H signal at δ 3.08 with a J value of 13 Hz and coupling of the double doublet signal of the C_4–H at δ 2.57 with J values of 3 and 13 Hz. The diacetyl ester (**31**) was identical with the diacetate derived from the trihydroxy ester (**18**). This result indicated that the α oriented methoxycarbonyl group of the diacetate (**29**) epimerized by this treatment through the retroaldol cleavage and the subsequent recyclization at the original angular hydroxy position to give the diacetyl ester (**31**), in which the configuration of the methoxycarbonyl group is β. Consequently, the lactone ring and the isopropenyl group of the lactone (**10**) are in the *cis* position with respect to the angular substituents and the stereostructure of the lactone (**10**) is as shown by the formula (**10**). Then, this epimerization reaction was applied to the acetyl ester (**26**) possessing the carbonyl group at C_9. In this case, the aldol recyclization occurred in two directions to give the acetyl ester (**32**) and the epiacetyl ester (**33**) in 31 and 15% yields, respectively. The acetyl ester (**32**), obtained from **26** by retroaldol cleavage, subsequent aldol recyclization at the original angular hydroxy position and epimerization of the methoxycarbonyl group, was identical with the acetate derived from the hydroxy ester (**21**). On the other hand, the ^{1}H-NMR spectrum of the epiacetyl ester (**33**), obtained from the acetyl ester (**26**) by retroaldol cleavage, subsequent aldol recyclization to the C_9 carbonyl group and epimerization of the methoxycarbonyl group, revealed coupling of the double doublet signal of the C_4–H with J values of 2.5 and 13 Hz. This observation indicated a structure for the epiacetyl ester (**33**) in which the C_3 acetoxy group and the C_4 isopropenyl group are in the *cis* relationship to each other, and the isopropenyl group and the methoxycarbonyl group are in the *trans* relationship. It is noteworthy that the methoxycarbonyl group is equatorial in both **32** and **33**, as shown in Fig. 5.

After protection of the C_9 carbonyl group of the lactone (**10**) with ethylene glycol, alkaline hydrolysis of the acetal (**34**), followed by esterification with diazomethane provided the acetal



32 **33**

Fig. 5

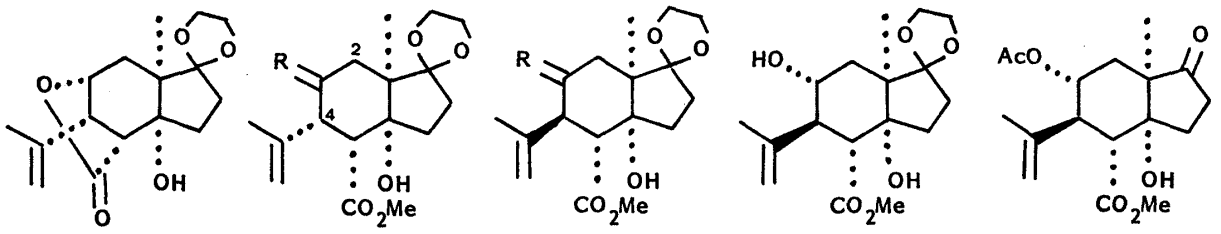
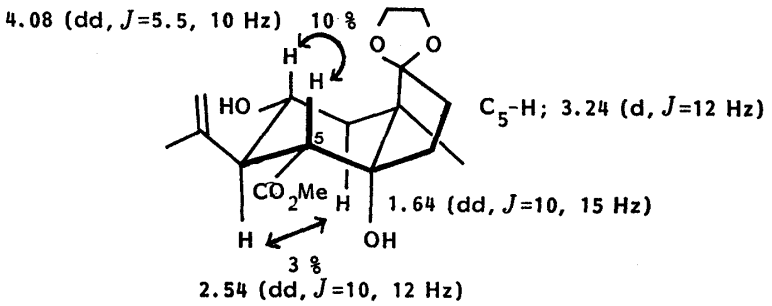


Chart 5

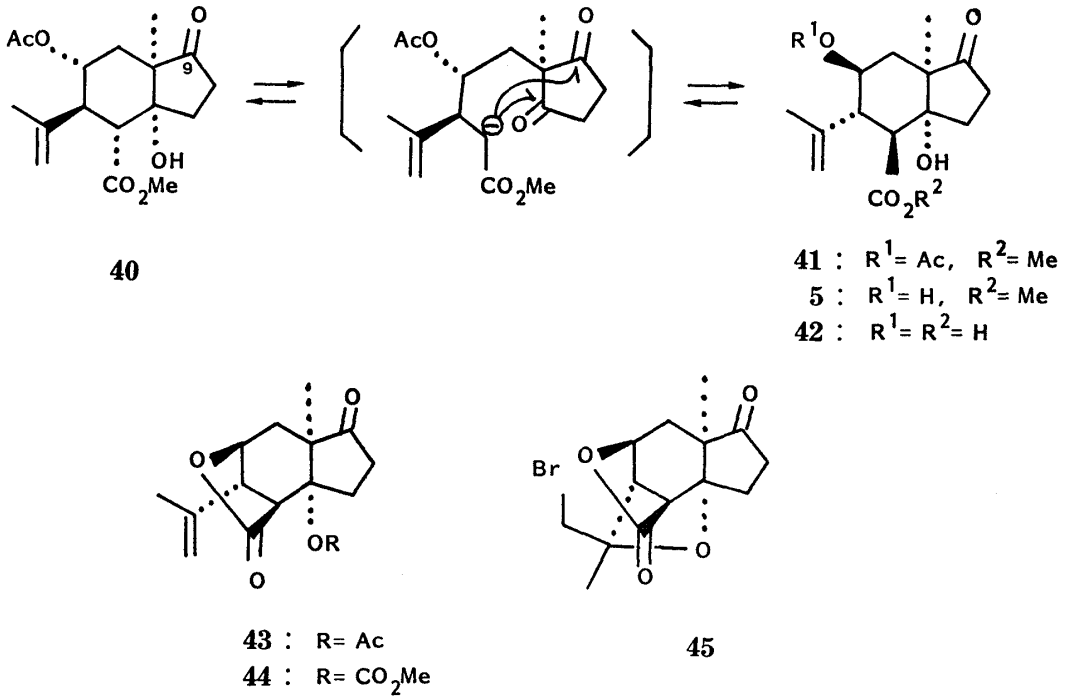
ester (**35**) in excellent yield, in contrast to hydrolysis of the lactone (**10**) itself, in which the retroaldol fragmentation occurred. Oxidation of **35** with pyridinium chlorochromate (PCC)[12] gave the acetal ketone (**36**) and the ^{1}H-NMR spectrum of **36** revealed coupling of the double doublet signal of the C_4–H at δ 3.42 with J values of 1 and 7.5 Hz. A small coupling of the C_4–H signal (J=1 Hz) indicated existence of the W path long-range coupling of the C_4–H with one of the methylene protons at C_2. This observation showed that the interacting protons take on a pseudo 1,3-diequatorial relationship and consequently, the isopropenyl group of the acetal ketone (**36**) is pseudo axial. Treatment of **36** with basic alumina resulted in the epimerization of the isopropenyl group to give the epiacetal ketone (**37**) in 72% yield. The ^{1}H-NMR spectrum of **37** revealed coupling of the doublet signal of the C_4–H with a J value of 13.5 Hz, and NOE enhancement (4%) was observed between the C_4–H and one of the methylene protons at C_2. This observation indicated the axial orientation of the C_4–H and the *trans* equatorial relationship of the isopropenyl group with the methoxycarbonyl group in the epiacetal ketone (**37**).



39

Fig. 6

Sodium borohydride reduction of the epiacetal ketone (**37**) gave the 3-epidihydroxy acetal (**38**) and the dihydroxy acetal (**39**), in a three-to-two ratio in 80% total yield. NOE enhancements were observed between the C_4–H and one of the methylene protons (3%) and between the C_3–H and the C_5–H (10%) in the ^{1}H-NMR spectrum of the dihydroxy acetal (**39**), as shown in Fig. 6. On the other hand, the ^{1}H-NMR spectrum of the 3-epidihydroxy acetal (**38**) revealed coupling between the C_4–H and the C_3–H with a J value of 3 Hz, indicating the *cis* relationship of the isopropenyl group with the C_3 hydroxy group. The reduction behavior of the epiacetal ketone (**37**) is quite different from that of the diketone (**16**), for which a single reduction product was obtained by the same treatment (ref. to Fig. 3). Reduction of the epiacetal ketone (**37**)



40

41 : R^1= Ac, R^2= Me
5 : R^1= H, R^2= Me
42 : R^1= R^2= H

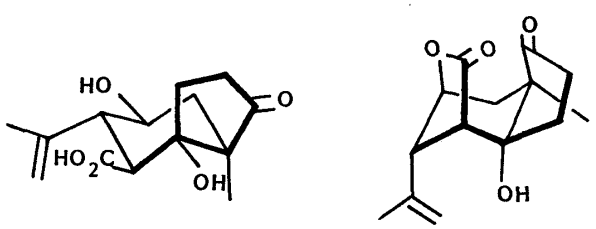
43 : R= Ac
44 : R= CO_2Me

45

Chart 6

in two directions may be attributable to the difference of the steric situation around the C_3 carbonyl group owing to the change of the conformation, that is, the equatorial orientation of the angular methyl group in **37** (ref. to Fig. 6). The undesired 3-epidihydroxy acetal (**38**) was recycled to the epiacetal ketone (**37**) by oxidation. Acetylation of the dihydroxy acetal (**39**), followed by deacetalization gave the acetyl ester (**40**). All three substituents at C_3, C_4, and C_5 in **40** are in the *trans* position with respect to each other, but the relative configuration of these substituents to the angular substituents is incorrect. The acetyl ester (**41**) possessing the correct stereostructure should be obtained by retroaldol cleavage and subsequent aldol recyclization at the C_9 carbonyl position in **40** as shown in Chart 6. In fact, treatment of the acetyl ester (**40**) with potassium *tert*-butoxide in tetrahydrofuran at room temperature gave the desired acetyl ester (**41**) in 36% yield together with the recovered acetyl ester (**40**). Base-catalyzed deacetylation of **41** with sodium methoxide gave the desired hydroxy ester (**5**). The ^{1}H-NMR spectrum of **5** revealed coupling of the double doublet signal of the C_4–H at δ 2.49 with J values of 10 and 13 Hz. This observation indicated that three protons at C_3, C_4, and C_5 are axial, that is, all three substituents are in the equatorial orientation.

For the lactonization of the hydroxy ester (**5**), it is essential that all four substituents at C_3, C_4, C_5, and C_6 should be changed to the axial orientation by the ring flip shown in Fig. 7. This means that some activation method[13] for lactonization will be required.



42 **4**

Fig. 7

Alkaline hydrolysis of **5** afforded the hydroxy acid (**42**), which was subjected to the lactonization reaction. Lactonization by the mixed anhydride method using a variety of reagents was examined as shown in Table I. When acetic anhydride and sodium acetate were used,[14] the desired lactone (**4**) was obtained but the *O*-acetyl lactone (**43**) was formed at the same time

TABLE I. Lactonization of **42**

Reagents	Conditions	Product: % yield from **5**		
		4	**43**	**44**
DCC/pyr.	100°C, 2h	13	—	—
$ClCO_2Me/Et_3N$	room temp., overnight	0	—	67
$Ac_2O/NaOAc$	Benzene, room temp., overnight	18	67	—
$Ac_2O/NaOAc$	Benzene, reflux, 2h	58	23	—
$Ac_2O/NaOAc$	Toluene, reflux, 1.5h	73	6	—
$ArCOCl/Et_3N$	Toluene, reflux, 8h	43	—	—

Ar : 2,4,6-Trichlorophenyl.

in an appreciable amount. The method using methyl chloroformate and triethylamine[15] gave only *O*-carbomethoxy lactone (**44**). The formation of **43** and **44** may be due to neighboring group participation. Then, Yamaguchi's method using 2,4,6-trichlorobenzoyl chloride and triethylamine[16] was applied to **42** and the desired lactone (**4**) was selectively obtained. Treatment of the lactone (**4**) with *N*-bromosuccinimide (NBS)[6] gave the bromoether (**45**) in good yield, and formation of the bromoether (**45**) indicated chemically the correctness of the stereochemical assignments of **5**, **41**, and **42**.

Starting from protoanemonin (**7**) and 2-methyl-1,3-cyclopentanedione (**8**), two kinds of lactones, (**10**) and (**11**) possessing the picrotoxane skeleton except for a C_1 unit at C_9 and its configuration, were synthesized in excellent yields. These lactones, however, did not possess the correct stereostructures for the present synthesis. Thus, conversion of the lactone (**10**) into the desired lactone (**4**) was performed through retroaldol cleavage and subsequent internal recyclization as shown in Chart 6.

Experimental

Melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. The infrared spectra (IR ν_{max}) were determined on a Shimadzu IR-400 spectrophotometer in chloroform. The ^{1}H-NMR spectra were obtained in chloroform-*d* at 60 MHz on a Varian A-60 or JEOL PMX-60, or at 100 MHz on a Varian HA-100, or at 200 MHz on a JEOL FX 200 instrument with chemical shifts being reported as δ units [parts per million downfield from a tetramethylsilane internal standard (δ 0.0)] and couplings are expressed in hertz. Mass spectra (MS) were taken on a JEOL JMS 01SG-2 instrument by direct insertion at 70 eV. All reactions were carried out under an atmosphere of argon, and solutions were dried over anhydrous $MgSO_4$. Column chromatography was carried out with Silica gel 60 (E.M. Merck, 70—230 mesh), Mallinckrodt silicic acid (100 mesh) or aluminum oxide 90 (nach Brockmann). Analytical gas–liquid chromatography (GLC) was carried out with a Hitachi 063 instrument using 1.5% SE30 on Chromosorb W (AW-DMCS) in a 2 m glass column. Preparative high performance liquid chromatography (HPLC) was performed with a Waters Prep LC/system 500A instrument using a prep PAK 500 silica column. Preparative thin–layer chromatography (prep. TLC) was run on 20×20 cm plates coated with a 0.5—1.5 mm layer of Merck silica gel PF 254 or GF 254.

5-(2-Methyl-1,3-dioxo-2-cyclopentyl)methyl-2,5*H*-furanone (**6**)——a) A solution of 50 g of protoanemonin (**7**) (75% purity by GLC analysis) in dry ethanol was added to a stirred suspension of 110 g of 2-methyl-1,3-cyclopentanedione (**8**) and 5 g of sodium hydroxide in 500 ml of dry ethanol, and the mixture was stirred for one week in the dark at 0—5°C. The reaction mixture was concentrated under reduced pressure, poured into ice water and made acidic with dilute hydrochloric acid. Precipitated 2-methyl-1,3-cyclopentanedione (68 g) was filtered off. The filtrate was extracted with chloroform and the extract was washed with brine, dried, and concentrated to give 40 g of an oily residue which was chromatographed in chloroform on a silica gel column. The fast-eluted fraction contained 9.5 g of anemonin,[9] and a mixture of anemonin and 5-(2-methyl-1,3-dioxo-2-cyclopentyl)methyl-2,5*H*-furanone (**6**) was obtained from the more slowly eluted fraction. This mixture was separated by preparative HPLC to give 5.5 g of anemonin and 13.8 g of **6** as a white solid, mp 93—94°C from ether, in 13% yield. IR: 1787, 1762, 1728 cm^{-1}. ^{1}H-NMR (60 MHz): δ 1.19 (3H, s), 2.91 (4H, s), 5.08 (1H, m), 6.05 (1H, dd, J=6, 2), 7.47 (1H, dd, J=6, 1.5). MS *m/z*: 208 (M^+), 125, 84. *Anal.* Calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.53; H, 6.02.

b) A mixture of 3.80 g of protoanemonin, 3.30 g of 2-methyl-1,3-cyclopentanedione, and 1.80 g of

potassium fluoride in 55 ml of dry ethanol was stirred for one week in the dark at 0—5°C. The mixture was worked up in the same manner as above to yield 550 mg of anemonin and 850 mg of **6** in 14% yield.

The Spiro Lactone (9)——A solution of protoanemonin (**7**) (450 mg) in 11 ml of tetrahydrofuran (THF) was added to a solution of 350 mg of 2-methyl-1,3-cyclopentanedione (**8**) and 300 mg of potassium fluoride in 20 ml of dimethylsulfoxide (DMSO) and the mixture was stirred for 20 h at 0—5 °C in the dark. The precipitated solid mass was filtered off and the filtrate was concentrated under reduced pressure to give a residue, which was extracted with ethyl acetate. The organic extract was washed with aq. $NaHCO_3$ and brine, then dried. Evaporation of the solvent left a crystalline residue which was purified by silica gel column chromatography to furnish 100 mg (7% yield) of the spiro lactone (**9**) as colorless flakes. mp >300°C. IR: 3440, 1760, 1745, 1605, 815 cm^{-1}. ^1H-NMR (60 MHz): 1.27 (3H, s), 6.06 (1H, d, $J=6$), 6.22 (1H, d, $J=6$), 7.58 (1H, d, $J=6$), 7.88 (1H, d, $J=6$). *Anal.* Calcd for $C_{16}H_{16}O_6 \cdot 1/2H_2O$: C, 61.33; H, 5.47. Found: C, 61.22; H, 5.24. MS *m/z*: 304 (M^+), 286.

The Lactones, (10) and (11)——Cuprous iodide (143 mg, 5 molar %) was added portionwise to a stirred 1.5 M solution of isopropenylmagnesium bromide (10 ml) in THF, and the mixture was stirred vigorously for 40 min at 0°C, then cooled to −30°C. A solution of 670 mg of **6** in 10 ml of THF was added dropwise to the above mixture over 15 min and stirring was continued for 30 min at the same temperature. The reaction mixture was quenched by addition of aq. NH_4Cl and extracted with chloroform. The extract was washed with water, dried and concentrated to give 800 mg of residue. GLC analysis revealed that the residue consisted of the lactones (**10**) and (**11**) in an 8 : 1 ratio. Crystallization of the residue from ether afforded 470 mg of the lactone (**10**) as colorless prisms. Column chromatography of the mother liquor, after removal of the crystals, on SiO_2 gave another crop of **10** (207 mg) from the fast-eluted fractions ($CHCl_3$) and 85 mg of the lactone (**11**) in 11% yield from the more slowly eluted fractions. The total yield of **10** was 84%. **10**: mp 148—149°C. IR: 3600—3250, 1770, 1740, 1655, 905 cm^{-1}. ^1H-NMR (100 MHz): 1.22 (3H, s), 1.82 (3H, br s), 2.56 (1H, t, $J=0.5$, C_4–H), 2.83 (1H, d, $J=0.5$, C_5–H), 3.20 (1H, s, exchangeable with D_2O), 4.78 (1H, m, $W_{h/2}=7.5$, C_3–H), 4.87 (1H, br s), 4.99 (1H, br s). MS *m/z*: 250 (M^+, base), 232 (M^+-H_2O), 222. *Anal.* Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.14; H, 7.27. **11**: mp 153°C (prisms from ether). IR: 3420, 1769, 1743, 1650, 908 cm^{-1}. ^1H-NMR (100 MHz): 1.07 (3H, s), 1.77 (3H, br s), 2.73 (1H, s, C_5–H), 2.95 (1H, s, exchangeable with D_2O), 3.01 (1H, d, $J=0.5$, C_4–H), 4.67 (1H, ddd, $J=4$, 1.5, 0.5, C_3–H), 4.78 (1H, br s), 4.91 (1H, br s). MS *m/z*: 250 (M^+, base), 232, 222. *Anal.* Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.13; H, 7.22.

Conversion of the Lactone (10) into the Lactone (11) under Equilibrium Conditions——A solution of 530 mg of the lactone (**10**) in 1.5 ml of DMF and 1.0 ml of THF was added to a suspension of 120 mg of sodium hydride (50% in oil) in DMF (1.5 ml) and the mixture was stirred for 2.5 h at −40——50°C, then quenched by addition of diluted cold HCl, and extracted with chloroform. The extract was washed with water and dried. After evaporation of the solvent under reduced pressure, crystallization of the residue from acetone–ether furnished 300 mg of **11**, which was collected by filtration, and the mother liquor was subjected to silica gel column chromatography ($CHCl_3$). From the less polar fractions, the starting material (31 mg, 6% yield) was recovered and another crop of the lactone (**11**) (165 mg) was obtained from the more polar fractions. The total yield of **11** was 88%. A sample of **11** was shown to be identical with an authentic sample by comparisons of TLC and GLC behavior and NMR and IR spectra.

The Hydroxy Ether (13)——A mixture of 3.00 g of the lactone (**11**), 10 ml of DMSO and 10 ml of acetic anhydride was allowed to stand for 40 h at 40—50°C. Concentration of the mixture under reduced pressure gave an oily residue, which was mixed with ice-water and extracted with ether. The ether extract was washed with brine, dried and evaporated to give a crystalline solid. Recrystallization from hexane–$CHCl_3$ afforded 3.50 g of the ether (**12**), mp 148°C (prisms). IR: 1768, 1745, 1653, 1162, 1056, 908 cm^{-1}. ^1H-NMR (60 MHz): 1.10 (3H, s), 1.80 (3H, br s), 2.23 (3H, s), 2.97 (1H, br s), 3.02 (1H, br s), 4.64 (2H, s), 4.71 (1H, m), 4.83, 4.93 (each 1H, br s), MS *m/z*: 310 (M^+), 280, 233. *Anal.* Calcd for $C_{16}H_{22}O_4S$: C, 61.91; H, 7.14. Found: C, 61.80; H, 7.10. Sodium borohydride (2.0 g) was added portionwise to a stirred solution of 4.80 g of **12** in 10% aqueous methanol and the mixture was stirred for 48 h at room temperature. The usual work-up gave a crystalline mass, and recrystallization from ether gave 4.65 g of the hydroxy ether (**13**) as colorless needles, mp 82°C. IR: 3550, 1764, 1652, 1157, 1033, 904 cm^{-1}. ^1H-NMR (60 MHz): 1.13 (3H, s), 1.81 (3H, br s), 2.20 (3H, s), 2.92 (2H, br s), 2.01 (1H, br s, exchangeable with D_2O), 4.24 (1H, m), 4.53 (2H, s), 4.72 (1H, dt, $J=0.5$, 3), 4.87, 4.96 (each 1H, br s). *Anal.* Calcd for $C_{16}H_{24}O_4S$: C, 61.52; H, 7.75. Found: C, 61.37; H, 7.70.

The Dihydroxy Ether (14) and the Trihydroxy Ester (15)——A mixture of 4.65 g of the hydroxy ether (**13**), 100 ml of 1.5 N NaOH and 50 ml of methanol was refluxed for 1.2 h and then poured into ice-water, made acidic with dilute HCl, salted out and extracted with chloroform. The extract was washed with brine, dried and evaporated to leave the crude acid, which was dissolved in 50 ml of methanol. Excess diazomethane in ether was added to the above solution and the mixture was allowed to stand at 0°C for 1 h. After decomposition of excess diazomethane, the solvent was removed to leave an oily residue, which was subjected to SiO_2 column chromatography ($CHCl_3$). The fast-eluted fractions gave recovered starting material (980 mg, 21% yield) and the dihydroxy ether (**14**) was obtained from the more slowly eluted fractions. The yield of **14** was 3.53 g (69% yield); colorless oil. IR: 3400, 1720, 1177, 1025, 895 cm^{-1}. ^1H-NMR (60 MHz):

1.11 (3H, s), 1.87 (3H, br s), 2.15 (3H, s), 2.84 (1H, t, $J=4$, C_4–H), 3.32 (1H, d, $J=4$, C_5–H), 3.75 (3H, s), 3.82 (1H, m), 4.25 (1H, m), 4.56 (2H, s), 4.65, 4.91 (each 1H, br s). MS *m/z*: 344 (M^+), 326, 249. a) Mercuric chloride (470 mg) was added to a solution of 180 mg of **14** in 4 ml of acetone and 1.5 ml of water, and the mixture was stirred for 1.5 h then diluted with ethyl acetate and filtered. The filtrate was cooled, made alkaline with aq. $NaHCO_3$ and extracted with ethyl acetate. The extract was washed with brine, dried and concentrated to give the residue (250 mg). Purification of the residue by prep. TLC yielded 117 mg of the trihydroxy ester (**15**) as colorless crystals (68% yield), mp 174°C. IR: 3560, 1720, 915 cm^{-1}. ^1H-NMR (60 MHz): 1.11 (3H, s), 1.75 (3H, br s), 2.93 (1H, d, $J=5$, C_5–H), 3.18 (1H, t, $J=5$, C_4–H), 3.69 (3H, s), 4.00—4.37 (2H, m), 5.10 (2H, br s). *Anal.* Calcd for $C_{15}H_{24}O_5$: C, 63.36; H, 8.51. Found: C, 63.14; H, 8.49.

b) A mixture of 70 mg of **14**, 20 mg of K_2CO_3, 150 mg of methyl iodide, 5 ml of acetone and 3 drops of water was refluxed for 7 h. The mixture was poured into ice-water, salted out and extracted with $CHCl_3$–AcOEt (1 : 4). The extract was washed with brine, and removal of the solvent left 67 mg of residue, which was purified by prep. TLC to furnish 38 mg of the trihydroxy ester (**15**) (66% yield).

The Diketone (16) and the α,β-Unsaturated Ketone (17)——a) A mixture of 1.40 g of the trihydroxy ester (**15**), 14.0 g of Collins' reagent and 85 ml of dry methylene chloride was stirred for 1 h at 0°C and then for 15 h at room temperature. Excess reagent was decomposed by addition of methanol and the mixture was poured into ice-water and extracted with methylene chloride. The extract was washed successively with dil. NH_4OH, dil. HCl, brine and dried. After removal of the solvent, the residue (1.58 g) was subjected to column chromatography on silica gel. The diketone (**16**) was obtained as colorless prisms (1.00 g, 71% yield) from the first eluate and the α,β-unsaturated ketone (**17**) was obtained as needles (230 mg, 16% yield) from the second eluate. **16**: mp 165°C (prisms from ether–acetone). IR: 3560, 1740, 1720, 908 cm^{-1}. ^1H-NMR (100 MHz): 1.10 (3H, s), 1.77 (3H, br s), 2.08 (1H, d, $J=15$, C_2–H), 2.42 (1H, d, $J=15$, C_2–H), 3.28 (1H, d, $J=13$, C_5–H), 3.50 (1H, d, $J=13$, C_4–H), 3.77 (3H, s), 4.78, 5.03 (each 1H, br s). *Anal.* Calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 64.00; H, 7.31. **17**: mp 151°C (needles from chloroform–acetone). IR: 3450, 1740, 1680, 1600 cm^{-1}. ^1H-NMR (60 MHz): 1.16 (3H, s), 1.88 (3H, s), 2.18 (3H, br s), 3.75 (3H, s), 4.08 (1H, br s, C_5–H). *Anal.* Calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 64.27; H, 7.27.

b) Jones' reagent (3 drops) was added dropwise to a stirred cold solution of 14 mg of **15** in 5 ml of acetone and the mixture was stirred for 10 min at 0°C. After the usual work-up the residue was separated by prep. TLC to give 4 mg of the diketone (**16**) from the eluate of the upper zone and 9 mg of the α,β-unsaturated ketone (**17**) from that of the lower zone.

The Trihydroxy Ester (18) and the Hydroxy Ester (21)——a) A mixture of 85 mg of the diketone (**16**), 30 mg of sodium borohydride and 6 ml of 10% aqueous methanol was stirred for 3 h at room temperature. After the usual work-up, the trihydroxy ester (**18**) was obtained as a colorless oil (80 mg; 92% yield). **18**: IR: 3550, 1728, 1645, 908 cm^{-1}. ^1H-NMR (60 MHz): 1.29 (3H, s), 1.82 (3H, br s), 2.58 (1H, dd, $J=3$, 12.5, C_4–H), 3.04 (1H, d, $J=12.5$, C_5–H), 3.68 (3H, s), 4.00 (1H, m), 4.22 (1H, t, $J=8$, C_9–H), 4.88, 5.05 (each 1H, br s). MS *m/z*: 284 (M^+), 268, 250, 237.

b) Sodium borohydride (5 mg) in 1.0 ml of methanol was added dropwise to a solution of 20 mg of the diketone (**16**) in 10% aqueous methanol (1.0 ml) and 1.5 ml of isopropanol at −78°C. After continued stirring for 1 h at the same temperature, the usual work-up gave the hydroxy ester (**21**) (17 mg, 85% yield). **21**: mp 182°C (prisms from acetone–ether). IR: 3520, 1730, 1645, 908 cm^{-1}. ^1H-NMR (60 MHz): 1.29 (3H, s), 1.82 (3H, br s), 2.64 (1H, dd, $J=2.5$, 13, C_4–H), 3.17 (1H, d, $J=13$, C_5–H), 3.74 (3H, s), 3.95 (1H, m), 4.90, 5.08 (each 1H, br s). *Anal.* Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 63.56; H, 7.98.

The Lactone (19) and the Diacetyl Lactone (20)——A mixture of 15 mg of **18**, 0.5 ml of *c*-HCl and 3.0 ml of methanol was heated on a water bath for 3.5 h. The reaction mixture was poured onto ice, and extracted with ethyl acetate, and the extract was washed with brine, dried and concentrated to afford a crystalline residue (17 mg). Recrystallization from methanol gave 12 mg of the lactone (**19**): mp >300°C. IR: 3450, 1745 cm^{-1}. ^1H-NMR (pyr-d_5, 100 MHz): 1.51 (3H, s), 1.63 (3H, s), 1.88 (3H, s), 3.79 (1H, d, $J=15$, C_5–H), 4.55—4.85 (2H, m). A mixture of 12 mg of **19**, 0.5 ml of acetic anhydride, and 1.0 ml of pyridine was kept standing overnight and the usual work-up furnished the diacetyl lactone (**20**), mp 211—218°C as flakes from acetone. IR: 3520, 1755, 1738, and 1205—1245 cm^{-1}. ^1H-NMR (100 MHz): 1.20 (3H, s), 1.36 (3H, s), 1.53 (3H, s), 2.03 (3H, s), 2.08 (3H, s), 2.10 (1H, dd, $J=2.5$, 15, C_4–H), 2.92 (1H, s, OH, chelated), 3.22 (1H, d, $J=15$, C_5–H), 5.17 (1H, t, $J=8$, C_9–H), 5.36 (1H, q, $J=3$, C_3–H). MS *m/z*: Calcd for $C_{18}H_{26}O_7$: 354.1678 (M^+). Found: 354.1672. *Anal.* Calcd for $C_{18}H_{26}O_7 \cdot 1/4H_2O$: C, 60.14; H, 7.44. Found: C, 60.35; H, 7.37.

The *O*-Mesyl Ester (22)——A mixture of 160 mg of the hydroxy ester (**21**), 20 mg of 4-dimethylaminopyridine, 0.3 ml of methanesulfonyl chloride and 5.0 ml of pyridine was stirred for 20 h at 0°C. The reaction mixture was concentrated under reduced pressure, and extracted with chloroform. The extract was washed successively with dil.HCl, aq.$NaHCO_3$ and drine, then dried. Evaporation of the solvent gave a crystalline solid, which was recrystallized from acetone to yield 150 mg of the *O*-mesyl ester (**22**) (74% yield): mp 186—187°C (prisms). IR: 3550, 1730, 1360, 1160, 908 cm^{-1}. ^1H-NMR (60 MHz): 1.29 (3H, s), 1.87 (3H, br s), 2.68 (1H, dd, $J=3$, 13, C_4–H), 2.95 (3H, s), 3.19 (1H, d, $J=13$, C_5–H), 4.93 (1H, br s), 5.00 (1H, m, C_3–H), 5.07 (1H, br s). *Anal.* Calcd for $C_{16}H_{24}O_7S$: C, 53.33; H, 6.71. Found: C, 53.50; H, 6.89.

The Acetyl Ester (26) from the Lactone (10)——A mixture of 180 mg of the lactone (**10**), 2.5 ml of DMSO and 2.5 ml of acetic anhydride was allowed to stand at room temperature for 52 h, and the mixture was

worked up in a similar manner to that used for the preparation of **12** to yield 230 mg of residue. Crystallization of the residue from hexane–chloroform gave 200 mg of the ether (**23**) as prisms (91% yield), mp 93—94°C. IR: 1788, 1740, 1655, 1155, 1080, 908 cm^{-1}. ^1H-NMR (60 MHz): 1.25 (3H, s), 1.80 (3H, br s), 2.24 (3H, s), 3.09 (1H, s, C_5–H), 4.70 (1H, d, $J=11$), 4.75 (1H, m, C_3–H), 4.95 (1H, d, $J=11$), 4.89, 5.00 (each 1H, br s). *Anal.* Calcd for $C_{16}H_{22}O_4S$: C, 61.91; H, 7.14. Found: C, 61.80; H, 7.10. A mixture of 180 mg of **23**, 2 ml of 2 N NaOH and 1.5 ml of methanol was heated on a water bath for 2 h and the mixture was poured onto ice, made acidic with dil.HCl, salted out and extracted with chloroform. The chloroform extract was washed with brine, dried and evaporated to give 230 mg of residue, which without purification was dissolved in 2 ml of methanol. An excess of diazomethane solution in ether was added to the above methanol solution and the mixture was allowed to stand for 2 h at 0°C. After decomposition of excess diazomethane, the solvent was removed to leave the crude product, which was subjected to prep. TLC. The starting material (30 mg, 10% yield) was recovered from the eluate of the upper zone and 145 mg of the hydroxy ether (**24**) (73% yield) was obtained from that of the lower zone. **24**: mp 100°C (prisms from ether). IR: 3370, 1735, 1717, 1645 cm^{-1}. ^1H-NMR (60 MHz): 1.34 (3H, s), 1.88 (3H, br s), 2.13 (3H, s), 3.65 (1H, d, $J=5$, C_5–H), 3.79 (3H, s), 4.22 (1H, m), 4.72 (2H, s), 4.97, 5.06 (each 1H, br s), 5.64 (1H, d, $J=10$, O<u>H</u>). *Anal.* Calcd for $C_{17}H_{26}O_5$: C, 59.63; H, 7.65. Found: C, 59.34; H, 7.76. A mixture of 100 mg of **24**, 1.5 ml of pyridine and 0.5 ml of acetic anhydride was heated on a water bath for 10 h. The mixture was worked up in the usual manner to yield 120 mg of residue, which was separated by prep. TLC to give 80 mg of the acetyl ether (**25**) (72% yield) as a colorless oil together with 18 mg of recovered starting material (**24**). **25**: IR: 1736, 1200—1250, 905 cm^{-1}. ^1H-NMR (100 MHz): 1.38 (3H, s), 1.85 (3H, br s), 2.04 (3H, s), 2.13 (3H, s), 2.81 (1H, m, $W_h/_2=10$, C_4–H), 3.18 (1H, d, $J=6$, C_5–H), 3.65 (3H, s), 4.72 (2H, s), 4.85, 4.90 (each 1H, br s), 5.05 (1H, m, $W_h/_2=12$, C_3–H). MS *m/z*: 384 (M^+), 322. A mixture of 150 mg of the acetyl ether (**25**), 3.0 ml of methyl iodide, 0.9 ml of water, 215 mg of potassium carbonate and 20 ml of acetone was refluxed with stirring for 15 h. After removal of the solvent under reduced pressure, the residue was poured onto ice and extracted with chloroform. The chloroform extract was washed with water, dried and concentrated to furnish 148 mg of the crude product, which was purified by short column chromatography on silica gel. A pure sample of the acetyl ester (**26**) (120 mg, 95% yield) was obtained. **26**: mp 111°C (flakes from ether–acetone). IR: 3480, 1735, 1720, 1640, 1200—1250, 910 cm^{-1}. ^1H-NMR (60 MHz): 1.15 (3H, s), 1.92 (3H, br s), 2.00 (3H, s), 2.67 (1H, d, $J=6$, C_5–H), 3.32 (1H, t, $J=6$, C_4–H), 3.70 (3H, s), 4.72 (1H, dd, $J=6$, 8, C_3–H), 4.87 (2H, br s), 5.05 (1H, s, O<u>H</u>). *Anal.* Calcd for $C_{17}H_{24}O_6$: C, 59.99; H, 7.11. Found: C, 59.70; H, 7.14.

The Diacetate (29) and the Epidiacetate (30)——Sodium borohydride (100 mg) was added portionwise to a stirred solution of 330 mg of the acetyl ester (**26**) in 20 ml of 10% aqueous methanol and the mixture was stirred for 30 min at room temperature. After removal of the solvent, the residue was extracted with chloroform and the chloroform extract was washed with brine, dried and evaporated to afford 400 mg of the residue, which was separated by prep. TLC. The epidihydroxy ester (**28**) (98 mg, 29% yield) was obtained from the upper zone as an oil. **28**: IR: 3460, 1720, 1638, 910 cm^{-1}. ^1H-NMR (60 MHz): 1.12 (3H, s), 1.96 (3H, br s), 2.02 (3H, s), 2.89 (1H, d, $J=6$, C_5–H), 3.17 (1H, t, $J=6$, C_4–H), 3.69 (3H, s), 4.00 (1H, m, C_9–H), 4.75, 4.87 (each 1H, br s), 4.88 (1H, s, O<u>H</u>), 5.23 (1H, dt, $J=6$, 9, C_3–H). The dihydroxy ester (**27**) (200 mg, 61% yield) was obtained from the lower zone as an oil. **27**: IR: 3460, 1715, 1200—1250, 902 cm^{-1}. ^1H-NMR (60 MHz): 1.15 (3H, s), 1.95 (3H, br s), 1.98 (3H, s), 2.60 (1H, br s, O<u>H</u>), 3.00 (1H, t, $J=5$, C_4–H), 3.18 (1H, d, $J=5$, C_5–H), 3.68 (3H, s), 4.05 (1H, dd, $J=5.5$, 7.5, C_9–H), 4.65, 4.84 (each 1H, br s), 4.67 (1H, s, O<u>H</u>), 5.54 (1H, dt, $J=5$, 7, C_3–H). Acetylation of **28** in the usual manner gave the epidiacetate (**30**) quantitatively. **30**: mp 153—154°C (prisms from acetone). IR: 3470, 1725, 1635, 1200—1260, 908 cm^{-1}. ^1H-NMR (100 MHz): 1.19 (3H, s), 1.82 (3H, br s), 2.00 (3H, s), 2.07 (3H, s), 2.74 (1H, m, C_4–H), 3.60 (1H, d, $J=6$, C_5–H), 3.68 (3H, s), 4.65 (1H, br s), 4.72 (1H, t, $J=8$, C_9–H), 4.93 (1H, br s), 5.22 (1H, dt, $J=5$, 8, C_3–H). *Anal.* Calcd for $C_{19}H_{28}O_7$: C, 61.94; H, 7.66. Found: C, 61.65; H, 7.86. Acetylation of **27** (200 mg) in the usual manner yielded 220 mg of the diacetate (**29**) as a colorless oil. **29**: IR: 3490, 1725, 1200—1260, 903 cm^{-1}. ^1H-NMR (60 MHz): 1.18 (3H, s), 1.82 (3H, br s), 1.99 (3H, s), 2.11 (3H, s), 3.72 (3H, s), 4.68 (1H, br s), 4.85 (1H, br s), 5.03 (1H, dd, $J=4$, 7, C_9–H), 5.49 (1H, m, $W_h/_2=18$, C_3–H). MS *m/z*: Calcd for $C_{19}H_{28}O_7$: 368.1834 (M^+). Found: 368.1841.

The Diacetyl Ester (31) from the Diacetate (29)——A solution of the diacetate (**29**; 20 mg) in 1.0 ml of the THF was added to a mixture of 8 mg of potassium *tert*-butoxide and 1.0 ml of THF, and the mixture was stirred for 42 h at room temperature. The mixture was quenched with aq. NH_4Cl and extracted with chloroform. The extract was washed with water, dried and evaporated to give an oily residue, which was subjected to prep. TLC. The starting material (**29**) (2 mg, 10% yield) was recovered from the eluate of the upper zone and the diacetyl ester (**31**) was obtained from that of the lower zone as crystals (15 mg, 75% yield). **31**: mp 240°C (prisms from ether). IR: 1730, 1210—1250, 903 cm^{-1}. ^1H-NMR (100 MHz): 1.22 (3H, s), 1.78 (3H, br s), 1.99 (3H, s), 2.03 (3H, s), 2.57 (1H, dd, $J=3$, 13, C_4–H), 3.08 (1H, d, $J=13$, C_5–H), 3.68 (3H, s), 4.75, 4.86 (each 1H, br s), 5.00—5.40 (2H, m). *Anal.* Calcd for $C_{19}H_{28}O_7$: C, 61.94; H, 7.66. Found: C, 61.73; H, 7.54.

The Acetyl Ester (32) and the Epiacetyl Ester (33) from the Acetyl Ester (26)——A solution of 225 mg of the acetyl ester (**26**) in 4 ml of THF was added to a stirred mixture of 100 mg of potassium *tert*-butoxide and

4 ml of THF. After continued stirring for 20 h at room temperature, the mixture was quenched by addition of cold dil. HCl and extracted with chloroform. The extract was washed with brine, dried, and evaporated to leave 235 mg of the residue, which was shown by GLC to be a mixture of **26**, **33** and **32** in approximately 1: 1: 2 ratio. Preparative TLC separation of the residue gave 40 mg of recovered starting material (**26**) (18% yield) from the least polar zone, 33 mg of the epiacetyl ester (**33**) (15% yield) from the middle zone, and 69 mg of the acetyl ester (**32**) (31% yield) from the most polar zone. **32**: mp 225°C (flakes from ether). IR: 3480, 1735, 1652, 1210—1250, 905 cm^{-1}. ^{1}H-NMR (60 MHz): 1.24 (3H, s), 1.80 (3H, br s), 2.03 (3H, s), 2.61 (1H, dd, J=3, 13, C_4–H), 3.22 (1H, d, J=13, C_5–H), 3.77 (3H, s), 4.80 (1H, s), 4.93 (1H, br s), 5.29 (1H, q, J=3, C_3–H). *Anal.* Calcd for $C_{17}H_{24}O_6$: C, 62.95; H, 7.46. Found: C, 62.61; H, 7.63. **33**: mp 133°C (prisms from ether–acetone). IR: 3450, 1733, 1712, 1650, 1205—1240, 903 cm^{-1}. ^{1}H-NMR (60 MHz): 1.04 (3H, s), 1.73 (3H, s), 1.93 (3H, s), 2.68 (1H, dd, J=2.5, 13, C_4–H), 3.07 (1H, d, J=13, C_5–H), 3.74 (3H, s), 4.00 (1H, s, OH), 4.75 (1H, br s), 4.84 (1H, br s), 4.99 (1H, m, $W_{h/2}$=10, C_3–H). *Anal.* Calcd for $C_{17}H_{24}O_6$: C, 62.95; H, 7.46. Found: C, 63.06; H, 7.41.

The Acetal Ketone (36) from the Lactone (10) *via* the Acetal (34) and the Acetal Ester (35)——A mixture of 100 mg of the lactone (**10**), 5 mg of *p*-TsOH, 1 ml of ethylene glycol and 20 ml of benzene was refluxed with azeotropic removal of water for 15 h (Dean–Stark trap). After cooling, the mixture was washed with aq. $NaHCO_3$, water and dried and evaporated to leave 123 mg of the residue as crystals. Recrystallization from ether–acetone afforded 113 mg of the acetal (**34**) (97% yield). **34**: mp 96—98°C (plates). IR: 3540, 1770, 1652, 910 cm^{-1}. ^{1}H-NMR (60 MHz): 1.10 (3H, s), 1.80 (3H, br s), 2.45 (1H, br s), 2.68 (1H, br s), 3.97 (4H, s), 4.78 (1H, m, $W_{h/2}$=8, C_3–H), 4.78, 4.96 (each 1H, br s). *Anal.* Calcd for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53. Found: C, 65.34; H, 7.63. A mixture of 96 mg of the acetal (**34**), 14 mg of NaOH, 6 ml of water and 6 ml of methanol was refluxed for 30 min. The usual work-up and esterification of the product with diazomethane gave 100 mg of residue, which was separated by prep. TLC to afford 88 mg of the acetal ester (**35**) (83% yield) from the lower zone, together with 10 mg of the recovered acetal (**34**). **35**: colorless oil. IR: 3360, 1710, 1642, 910 cm^{-1}. ^{1}H-NMR (60 MHz): 1.20 (3H, s), 1.88 (3H, br s), 3.71 (3H, s), 3.33 (1H, d, J=5, C_5–H), 3.93 (4H, s), 3.95—4.50 (1H, m), 4.88 (1H, br s), 5.04 (1H, br s). MS *m/z*: Calcd for $C_{17}H_{26}O_6$: 326.1727 (M^+). Found: 326.1724. A mixture of 400 mg of **35**, 1.0 g of PCC,[12] 500 mg of sodium acetate and 90 ml of methylene chloride was stirred overnight at room temperature and then poured into ice-water, made alkaline with dil. NH_4OH and extracted with chloroform. The chloroform extract was washed with water, dried and concentrated to give a crystalline residue. Purification by short column chromatography on SiO_2 gave 390 mg of the acetal ketone (**36**) (98% yield). **36**: mp 137—138°C (needles from ether). IR: 3450, 1705, 910 cm^{-1}. ^{1}H-NMR (90 MHz): 1.16 (3H, s), 1.80 (3H, br s), 2.10 (1H, dd, J=1, 16, C_2–H), 2.51 (1H, d, J=16, C_2–H), 3.43 (1H, dd, J=1, 7.5, C_4–H), 3.61 (1H, d, J=7.5, C_5–H), 3.75—4.05 (4H, m), 4.52 (1H, s, OH), 4.90 (1H, br s), 5.12 (1H, s). MS *m/z*: 324 (M^+), 306 (base). *Anal.* Calcd for $C_{17}H_{24}O_6$: C, 62.95; H, 7.46. Found: C, 62.67; H, 7.54.

The Epiacetal Ketone (37) from the Acetal Ketone (36)——A mixture of 180 mg of the acetal ketone (**36**), 2.0 g of basic alumina (activity II—III, nach Brockmann) and 10 ml of chloroform was stirred for 1 h at room temperature. Alumina was filtered off and the residual alumina was washed with chloroform. The filtrate and washings were combined and the whole was concentrated under reduced pressure to leave a crystalline residue. Recrystallization of the residue from ether-acetone afforded 130 mg of the epiacetal ketone (**37**) (72% yield), mp 142—143°C, as prisms. IR: 3450, 1705, 1645, 903 cm^{-1}. ^{1}H-NMR (100 MHz): 1.13 (3H, s), 1.75 (3H, br s), 2.22 (1H, d, J=16, C_2–H), 2.27 (1H, d, J=16, C_2–H), 3.40 (1H, d, J=13.5, C_4–H), 3.71 (3H, s), 3.78 (1H, d, J=13.5, C_5–H), 3.75—4.00 (4H, m), 4.52 (1H, s, OH), 4.73 (1H, s), 4.92 (1H, br s). MS *m/z*: 324 (M^+), 290, 280, 250. *Anal.* Calcd for $C_{17}H_{24}O_6$: C, 62.95; H, 7.46. Found: C, 62.78; H, 7.49.

The Dihydroxy Acetal (39)——A mixture of 100 mg of the epiacetal ketone (**37**), 100 mg of sodium borohydride and 10% aq. methanol was stirred for 2 h at room temperature. The usual work-up gave a mixture of the alcohols, which was separated by prep. TLC to afford 45 mg of 3-epidihydroxy acetal (**38**) from the upper zone in 45% yield and 35 mg of the dihydroxy acetal (**39**) as crystals from the lower zone in 35% yield. **38**: mp 85—86°C (prisms from ether). IR: 3420, 1710, 1652, 905 cm^{-1}. ^{1}H-NMR (60 MHz): 1.11 (3H, s), 1.79 (3H, br s), 2.70 (1H, dd, J=13, 3, C_4–H), 3.18 (1H, d, J=13, C_5–H), 3.65 (3H, s), 3.75—4.20 (5H, m), 4.73, 4.82 (each 1H, br s). *Anal.* Calcd for $C_{17}H_{26}O_6$: C, 62.56; H, 8.03. Found: C, 62.66; H, 7.75. **39**: mp 141—142°C (prisms from ether–acetone). IR: 3450, 1708, 1645, 905 cm^{-1}. ^{1}H-NMR (100 MHz): 1.08 (3H, s), 1.64 (1H, dd, J=10, 15, C_2–H), 1.75 (3H, br s), 1.89 (1H, dd, J=5.5, 15, C_2–H), 2.54 (1H, dd, J=10, 12, C_4–H), 3.24 (1H, d, J=12, C_5–H), 3.67 (3H, s), 3.87—3.97 (4H, m), 4.08 (1H, dd, J=5.5, 10, C_3–H), 4.88 (2H, br s). *Anal.* Calcd for $C_{17}H_{26}O_6$: C, 62.56; H, 8.03. Found: C, 62.39; H, 8.20.

The Acetyl Ester (40)——Acetylation of the dihydroxy acetal (**39**) in the usual manner (Ac_2O/pyr.) gave the crude acetate (33 mg), which without purification was dissolved in 0.5 ml of methanol and 1 ml of 3% aq.HCl. The mixture was allowed to stand at room temperature overnight and then poured onto ice, salted out and extracted with chloroform. The chloroform extract was washed with water, dried, and concentrated to give 31 mg of a crystalline residue. Purification of the residue by column chromatography on Al_2O_3, and recrystallization of the crystalline residue from acetone–ether furnished 27 mg of the acetyl ester (**40**) (82% yield). **40**: mp 133°C. IR: 3450, 1741, 1710, 1650, 1200—1250, 905 cm^{-1}. ^{1}H-NMR (60 MHz): 1.08 (3H, s), 1.62 (3H, br s), 1.97 (3H, s), 2.85 (1H, d, J=12, C_5–H), 3.69 (3H, s), 4.48 (1H, s,OH),

4.79 (2H, br s). *Anal.* Calcd for $C_{17}H_{24}O_6$: C, 62.95; H, 7.46. Found: C, 62.74; H, 7.45.

The Acetyl Ester (41) from the Acetyl Ester (40) by Base Treatment——Potassium *tert*-butoxide (40 mg) was added to a solution of 103 mg of the acetyl ester (**40**) in 3 ml of THF, and the mixture was stirred for 40 h at room temperature. The mixture was quenched with aq. NH_4Cl, made acidic with cold dil. HCl and extracted with chloroform. The extract was washed with water, dried and evaporated to afford 98 mg of the residue, which was shown to be a mixture of **40** and **41** in approximately a 1: 1 ratio judging from GLC analysis. Separation of the residue by prep. TLC afforded 31 mg of the original acetyl ester (**40**) from the eluate of the upper zone and 37 mg (36% yield) of the acetyl ester (**41**) from that of the lower zone. **41**: mp 199°C (needles from chloroform–acetone). IR: 3580, 1738, 910 cm^{-1}. ^1H-NMR (60 MHz): 1.21 (3H, s), 1.72 (3H, br s), 1.98 (3H, s), 2.63 (1H, dd, $J=10$, 12, C_4–H), 2.92 (1H, d, $J=12$, C_5–H), 3.70 (3H, s), 4.75—5.22 (1H, m, C_3–H), 4.85 (2H, br s). *Anal.* Calcd for $C_{17}H_{24}O_6$: C, 62.95; H, 7.46. Found: C, 62.96; H, 7.63.

The Hydroxy Ester (5)——A mixture of the acetyl ester (**41**) (90 mg), sodium methoxide (30 mg) and 5 ml of methanol was refluxed with stirring for 4 h. The mixture was poured into an ice-cooled aq. NH_4Cl solution, made acidic with dil. HCl and extracted with chloroform. The extract was washed with water, dried and evaporated to give 82 mg of crystalline residue, which was recrystallized from chloroform–acetone to yield 73 mg of the hydroxy ester (**5**) (93% yield). **5**: mp 173°C (needles). IR: 3550—3400, 1735, 1645, 910 cm^{-1}. ^1H-NMR (200 MHz): 1.15 (3H, s), 1.37 (1H, dd, $J=11$, 14, C_2–H), 1.72 (1H, dd, $J=4.5$, 14, C_2–H), 1.78 (3H, br s), 2.49 (1H, dd, $J=10$, 13, C_4–H), 2.86 (1H, d, $J=13$, C_5–H), 3.70 (3H, s), 3.68 (1H, oct, $J=4.5$, 10, 11, C_3–H), 4.96, 5.50 (each 1H, br s). MS *m/z*: 282 (M^+), 264 (base). *Anal.* Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 64.06; H, 7.89.

The Lactone (4)——a) A mixture of 26 mg of the hydroxy ester (**5**), 3 ml of 0.5 N NaOH and 1.5 ml of methanol was refluxed on a water bath for 2 h and then poured onto ice, made acidic with 5% HCl and extracted with ethyl acetate. After drying of the extract, removal of the solvent gave the crude hydroxy acid (**42**), which was dissolved in 10 ml of toluene and 14 mg of triethylamine, and the mixture was refluxed for 30 min. A solution of 14 mg of 2,4,6-trichlorobenzoyl chloride in 2 ml of toluene was added to the above mixture and the reaction mixture was refluxed with stirring for 8 h. After cooling, the mixture was extracted with chloroform and the chloroform extract was washed successively with dil. HCl, water, 5% NaOH and water, and dried. Evaporation of the solvent left an oil which was subjected to prep. TLC to yield 10 mg (43% yield) of the lactone (**4**). **4**: mp 154°C (flakes from acetone–ether). IR: 3530, 1780, 1742, 1648, 918 cm^{-1}. ^1H-NMR (100 MHz): 1.00 (3H, s), 1.97 (3H, br s), 2.90—3.13 (2H, m, $C_{4,5}$–H), 4.85 (1H, m, $W_{h/2}=10$, C_3–H), 4.96, 5.17 (each 1H, br s). *Anal.* Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.37; H, 7.30.

b) The hydroxy ester (**5**; 1.10 g) was hydrolyzed with NaOH in the same manner as in procedure a) to give the crude hydroxy acid (**42**), which without purification was dissolved in 130 ml of toluene. Acetic anhydride (1.0 g) and 200 mg of sodium acetate were added to the above solution and the mixture was refluxed with stirring for 1.5 h. After evaporation of the solvent under reduced pressure, the mixture was extracted with chloroform and the chloroform extract was washed with water, dried and evaporated to leave an oily residue. Column chromatography of the residue on silica gel in chloroform afforded 70 mg of the *O*-acetyl lactone (**43**) (6% yield) as colorless crystals from the first fraction and 705 mg of the lactone (**4**) (73% yield) from the second fraction. **43**: mp 163°C (prisms from ether). IR: 1782, 1745, 1733, 1652, 1205—1240, 900 cm^{-1}. ^1H-NMR (100 MHz): 1.07 (3H, s), 1.78 (3H, br s), 2.03 (3H, s), 3.82 (1H, d, $J=4.5$, C_5–H), 4.82 (1H, br s), 4.95 (1H, m, $W_{h/2}=11$, C_3–H), 5.04 (1H, br s). *Anal.* Calcd for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.90; H, 6.79.

c) A mixture of the crude hydroxy acid (**42**) [obtained from hydrolysis of 28 mg of the hydroxy ester (**5**)], 10 mg of methyl chloroformate, 12 mg of triethylamine and 10 ml of benzene was stirred at room temperature overnight. The cooled reaction mixture was poured into an ice-cooled aq. NH_4Cl solution and extracted with chloroform. The extract was washed with dil. HCl and water and dried. Removal of the solvent left 30 mg of an oil, which was purified by prep. TLC to furnish 21 mg of the *O*-carbomethoxy lactone (**44**) (67% yield). **44**: colorless oil. IR: 1782, 1748, 1655, 910 cm^{-1}. ^1H-NMR (100 MHz): 1.09 (3H, s), 1.73 (3H, s), 3.00 (1H, m, $W_{h/2}=12$, C_4–H), 3.77 (3H, s), 3.87 (1H, d, $J=4.5$, C_5–H), 4.76 (1H, br s), 4.87 (1H, dt, $J=2$, 4.5, C_3–H), 5.02 (1H, br s). MS *m/z*: 308 (M^+), 232.

The Bromoether (45)——A mixture of 205 mg of the lactone (**4**), 130 mg of NBS and 10 ml of THF was stirred in the dark for 15 min at room temperature, then cooled. Excess NBS was decomposed by addition of 10 ml of a saturated aqueous Na_2SO_3 solution and the reaction mixture was extracted with chloroform. The chloroform extract was washed with water, dried and evaporated to leave the residue. Crystallization of the residue from ether gave 185 mg of the bromoether (**45**). The mother liquor after removal of the crystalline bromoether (**45**) was concentrated and the residue was purified by prep. TLC to afford another crop of the bromoether (**45**) (59 mg) as crystals. The total yield of **45** was 90%. **45**: mp 165—166°C (prisms). IR: 1780, 1745, 1032 cm^{-1}. ^1H-NMR (100 MHz): 1.09 (3H, s), 1.56 (3H, s), 1.66 (1H, dd, $J=3$, 17, C_2–H), 2.78 (1H, dd, $J=2$, 17, C_2–H), 3.02 (1H, d, $J=5$, C_5–H), 3.25 (1H, t, $J=5$, C_4–H), 3.50 (1H, d, $J=11$), 3.70 (1H, d, $J=11$), 5.04 (1H, m, $W_{h/2}=11$, C_3–H). MS *m/z*: 330, 328 (M^+), 303, 300, and 249. MS *m/z*: Calcd for $C_{14}H_{17}BrO_4$: 328.0310 (M^+). Found: 328.0330. Calcd for $C_{14}H_{17}Br^*O_4$: 330.0291 (M^+). Found: 330.0304.

Acknowledgement This work was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture, Japan. We are also grateful to Prof. T. Shingu, Faculty of Pharmaceutical Sciences, Kobe Gakuin University, for the ^{1}H-NMR spectral measurements and valuable discussions on the spectra.

References and Notes

1) A preliminary communication of this work appeared in *J. Am. Chem. Soc.*, **104**, 4965 (1982). All synthetic compounds reported in this series of papers are racemic, but are shown as one of the enantiomers leading to natural coriamyrtin.
2) *a*) M.J. Riban, *Bull. Soc. Chim., France*, **1**, 87 (1864); **7**, 79 (1867); *b*) T. Kariyone and T. Sato, *Yakugaku Zasshi*, **50**, 106, 659 (1930).
3) T. Okuda and T. Yoshida, *Tetrahedron Lett.*, **1964**, 439; *idem, ibid.*, **1965**, 4191; *idem, Chem. Pharm. Bull.*, **15**, 1955 (1967).
4) For a review of the chemistry, biosynthesis, and physiology of picrotoxane sesquiterpenes and related substances, see: L.A. Porter, *Chem. Rev.*, **67**, 441 (1967).
5) For synthesis of dendrobine, an alkaloid in the same structural class, see: *a*) K. Yamada, M. Suzuki, A. Hayakawa, H. Nakamura, H. Nagase, and Y. Hirata, *J. Am. Chem. Soc.*, **94**, 8278 (1972); *b*) Y. Inubushi, T. Kikuchi, T. Ibuka, K. Tanaka, I. Saji, and K. Tokane, *J. Chem. Soc., Chem. Commun.*, **1972**, 1252; *idem, Chem. Pharm. Bull.*, **22**, 349 (1974); *c*) A. Kende, J. Bentley, R. Mader, and D. Ridge, *J. Am. Chem. Soc.*, **96**, 4332 (1974); *d*) R.F. Borch, A.J. Evans, and J.J. Wade, *J. Am. Chem. Soc.*, **97**, 6282 (1975); *e*) W.R. Roush, *J. Am. Chem. Soc.*, **100**, 3599 (1978).
6) E.J. Corey and H.L. Pearce, *J. Am. Chem. Soc.*, **101**, 5841 (1979).
7) E.J. Corey and H.L. Pearce, *Tetrahedron Lett.*, **1980**, 1823.
8) *a*) Y. Asahina and A. Fujita, *Yakugaku Zasshi*, **396**, 81 (1915); H. Baer, M. Holden, and B.C. Seegal, *J. Biol. Chem.*, **162**, 65 (1949); *b*) C. Grundmann, and E. Kober, *J. Am. Chem. Soc.*, **77**, 2332 (1955).
9) R.M. Moriarty, C.R. Romain, I.L. Karle, and J. Karle, *J. Am. Chem. Soc.*, **87**, 3251 (1965).
10) K. Yamada, R. Kato, H. Nagase, and Y. Hirata, *Tetrahedron Lett.*, **1976**, 65.
11) P.M. Pojer and S.A. Angyal, *Tetrahedron Lett.*, **1976**, 3067.
12) E.J. Corey and J.W. Suggs, *Tetrahedron Lett.*, **1975**, 2647.
13) *cf.* E.J. Corey and K.C. Nicoleau, *J. Am. Chem. Soc.*, **96**, 5614 (1974).
14) R.B. Woodward, F.E. Bader, H. Bickel, A.J. Frey, and R.W. Kierstead, *Tetrahedron*, **2**, 1 (1958).
15) P.A. Bartlett and F.R. Green III, *J. Am. Chem. Soc.*, **100**, 4858 (1978).
16) J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, and M. Yamaguchi, *Bull. Chem. Soc. Jpn.*, **52**, 1989 (1979).