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Synthetic Studies on a Picrotoxane Sesquiterpene, Coriamyrtin. II.[1] An Effective Stereocontrolled Synthesis of the Picrotoxane Skeleton Except for a C_1 Unit at the C_9 Position and Functionalization of the Five-membered Ring

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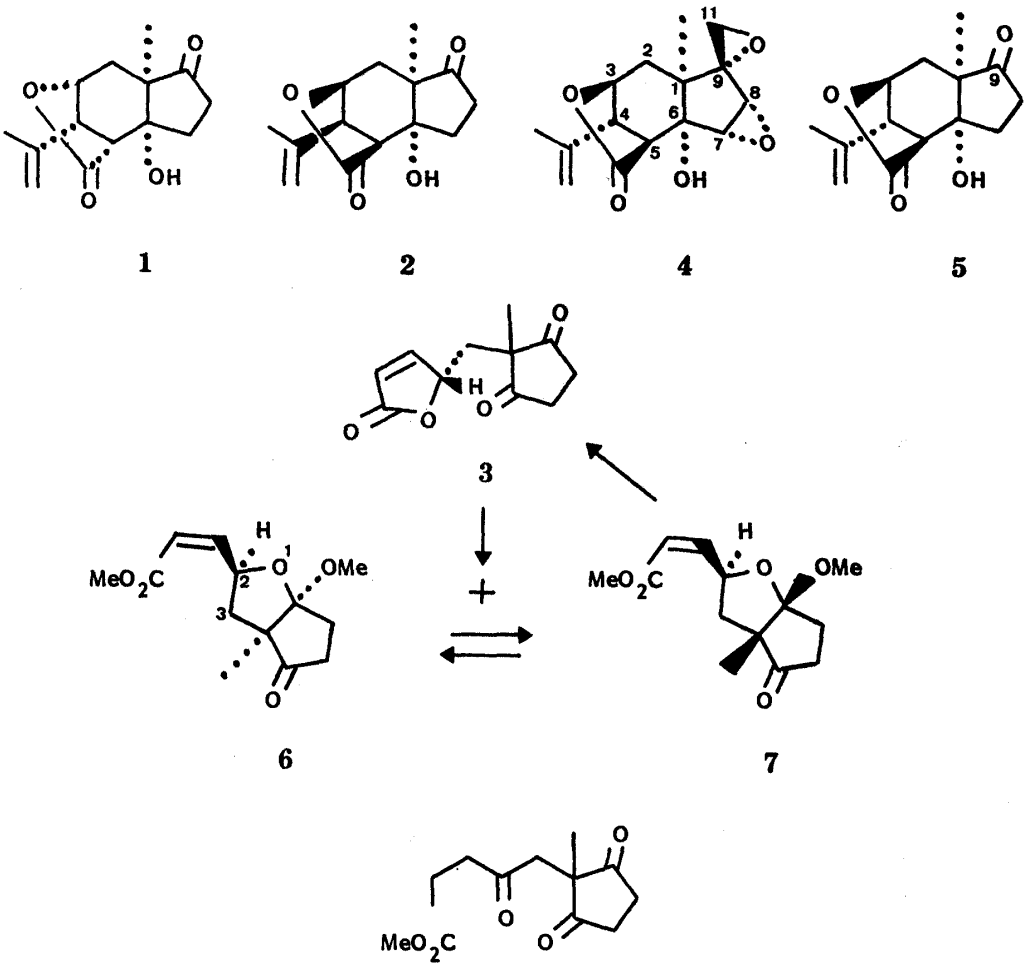
The picrotoxane skeleton (**5**) except for a C_1 unit at the C_9 position was effectively synthesized starting from protoanemonin and 2-methyl-1,3-cyclopentanedione through five steps. The key reaction of this synthesis was the Grignard reaction of the ester (**6**) with isopropenylmagnesium bromide. A synthetic approach for completing the total synthesis of coriamyrtin (**4**) by functionalization of the five-membered ring of the lactone (**5**) was also examined.

Keywords——coriamyrtin synthesis; protoanemonin; 2-methyl-1,3-cyclopentanedione; Grignard reaction; retroaldol cleavage; internal aldol cyclization; lactonization; bromination; Wittig reaction; epoxidation

In the preceding paper,[2] we reported an effective synthesis of two lactones, (**1**) and (**2**), by means of the Grignard reaction of 5-(2-methyl-1,3-dioxo-2-cyclopentyl)methyl-2,5*H*-furanone (**3**) with isopropenylmagnesium bromide. These lactones, however, did not possess the correct stereostructures for the synthesis of coriamyrtin (**4**), and so conversion of **1** into the desired lactone (**5**) was accomplished. This synthetic route, however, was not wholly satisfactory because of the large number of steps and the poor overall yield. In this paper, we wish to present a full account of an effective stereocontrolled synthesis of the picrotoxane skeleton (**5**) except for a C_1 unit at the C_9 position and functionalization of its five-membered ring. The results obtained so far indicated that the configurations of the C_4 isopropenyl group and the C_5 carboalkoxyl group in **1** and **2** were convertible into the desired configurations, but the configuration of the C_3 hydroxy group could not be effectively converted into the desired configuration after the skeletal ring system was constructed. From these results, it was anticipated that this type of Grignard reaction should be applied to compounds (such as **6**; refer to **6**→**9**) in which the configuration of the C_3 functional group is fixed in the *trans* position with respect to the angular methyl group.

1,6-Addition of 2-methyl-1,3-cyclopentanedione to protoanemonin gave 5-(2-methyl-1,3-dioxo-2-cyclopentyl)methyl-2,5*H*-furanone (**3**) as reported in the preceding paper.[2] Methanolysis of **3** in the presence of a catalytic amount of hydrochloric acid afforded a separable mixture of the esters, (**6**) and (**7**), in equal proportions and in 88% total yield together with a 10% yield of the triketone (**8**). At this stage of the investigation, the stereostructures of **6** and **7** could not be specified, but the stereostructural assignments for these compounds are discussed below. After separation of **6**, the ester (**7**) was equilibrated with **6** in the presence of methanol and hydrochloric acid under the same conditions as above to furnish **6** in 35% yield, together with a 49% yield of the recovered ester (**7**). Furthermore, acidic hydrolysis of the ester (**7**) with methanol–hydrochloric acid–water regenerated the original compound (**3**) in 75% yield. Accordingly, the undesired ester (**7**) could be utilized along the synthetic route. In the ester (**6**), the configuration of the C_2–O_1 bond of the perhydrocyclopenta[*b*]furan ring. which is transformed afterwards into the C_3 lactone alkoxy function of the desired lactone (**5**), is fixed in the *trans* position with respect to the angular methyl group, and the configuration of the acrylic ester moiety is β. If the 1,4-addition of the Grignard reagent to the α,β-unsaturated



1 2 4 5

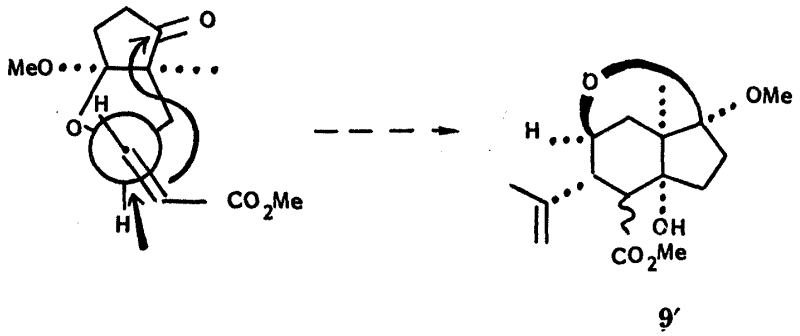
3

6 7

8

Chart 1

ester moiety of the ester (**6**), and the subsequent internal aldol cyclization take place as shown in Fig. 1, the acetal (**9**) will be obtained. The Grignard reaction of the ester (**6**) with isopropenylmagnesium bromide in the presence of a catalytic amount of cuprous iodide and the subsequent internal aldol cyclization afforded two kinds of acetals, (**9**) and (**10**), in a four-to-three ratio in 84% yield. In contrast to the ester (**6**), the same Grignard reaction of the ester (**7**) gave only the 1,4-adduct (**11**) and no cyclized product was detected. This result indicated the stereostructures of the esters, (**6**) and (**7**).



9′

Fig. 1

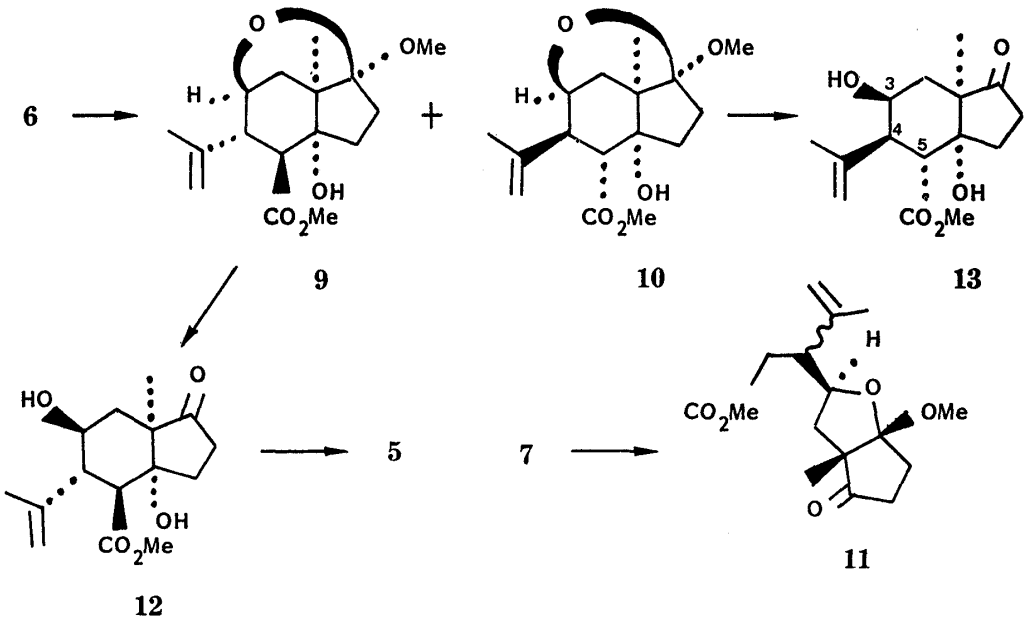


Chart 2

The stereostructures of the acetals, (**9**) and (**10**), were deduced from the subsequent experimental results. Acidic hydrolysis of the acetal (**9**) gave the hydroxy ester (**12**) possessing the correct stereostructure in an almost quantitative yield, and the product was identical with an authentic sample.[2] On the other hand, acidic hydrolysis of the acetal (**10**) afforded another hydroxy ester (**13**). The proton nuclear magnetic resonance (^{1}H-NMR) spectrum of **13** revealed coupling of the double doublet signal due to the C_4–H at δ 2.99 with J values of 2.5 and 12 Hz, and coupling of the doublet signal of the C_5–H at δ 3.60 with a J value of 12 Hz. This observation indicated the *cis* relationship of the C_3 hydroxy group with the C_4 isopropenyl group as shown in the formula (**13**). The hydroxy ester (**13**) was then converted into the desired hydroxy ester (**12**) as follows. Thus, Jones' oxidation of **13** gave the ketone (**14**), which was reduced with sodium borohydride at −30——50°C to furnish two kinds of hydroxy esters, (**13**) and (**15**), in 28 and 25% yields, respectively, and the undesired hydroxy ester (**13**) was recycled. The C_3 hydroxy group of the hydroxy ester (**15**) was protected with a *tert*-butyldimethylsilyl group[3] to give the silyl ether (**16**). Treatment of **16** with potassium *tert*-butoxide in dimethylformamide (DMF)–tetrahydrofuran (THF) gave the compound (**17**) possessing the correct stereostructure through retroaldol cleavage and subsequent internal aldol recyclization to the C_9 carbonyl group as shown in the formula (**16**) in good yield, together with the original silyl ether (**16**), which was recycled. Deprotection of the C_3 hydroxy group[3] of **17** with tetra-*n*-butylammonium fluoride afforded the desired hydroxy ester (**12**). Therefore, the undesired Grignard reaction product, the acetal (**10**), could also be utilized along the synthetic route. Since the hydroxy ester (**12**) had been converted into the lactone (**5**) as reported in the preceding paper,[2] the picrotoxane carbon skeleton (**5**), except for a C_1 unit at the C_9 position, was effectively constructed through five steps starting from protoanemonin and 2-methyl-1,3-cyclopentanedione.

The next stage of the synthesis is the introduction of a C_1 unit at the C_9 position of the lactone (**5**). The hydroxy ester (**12**) was transformed into the bromoether (**18**)[2] *via* the lactone (**5**) in the same manner as reported in the preceding paper.[2] The Wittig reaction of the bromoether (**18**) with triphenylphosphonium methylide did not take place, possibly due to steric crowding and/or the highly enolizable nature of the C_9 ketone function. Thus several other approaches for this purpose were examined. The reaction of the bromoether (**18**)

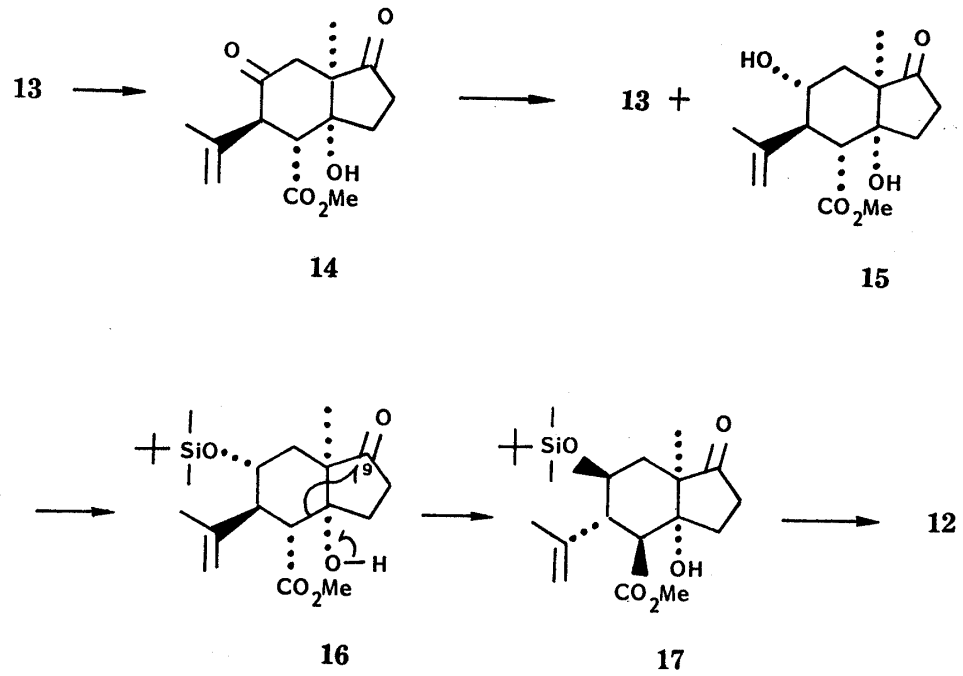
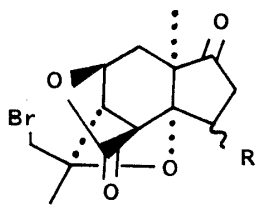


Chart 3

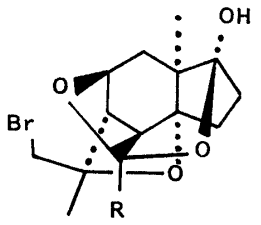
with methylmagnesium iodide gave the hemiacetal (**19**), which resulted from the attack of the reagent at the lactone carbonyl function, and subsequent acetal formation. Successive treatments of the bromoether (**18**) with phenylselenyl chloride and hydrogen peroxide gave the phenylselenoxide,[4] which was subjected to Cope-type elimination to give the enone (**20**). Treatment of **20** with methyllithium gave the undesired 1,4-adduct (**21**). Reduction of the bromoether (**18**) with diisobutylaluminum hydride (DIBAL-H) furnished the hemiacetal (**22**), which was heated with methyl orthoformate[5] in the presence of pyridinium *p*-toluenesulfonate (PPTS)[6] to give the methyl ether (**23**). The methyl ether (**23**) was then converted into the enone (**24**) in a manner similar to that used for the transformation of the bromoether (**18**) into the enone (**20**). In the enone (**24**), the lactone carbonyl function is masked and the C_9 ketone group is not enolizable. The Wittig reaction of the enone (**24**) with triphenylphosphonium methylide, however, did not proceed and the reaction of **24** with methyllithium or methylmagnesium iodide gave only the undesired 1,4-adduct (**25**). These 1,4-adducts (**21**) and (**25**) were single diastereomers, but the stereochemistries of these compounds are not specified.

Since all attempts to introduce a C_1 unit at the C_9 position of the compounds, **18**, **20**, and **24**, were unsuccessful, other approaches for this purpose were examined using the hydroxy ester-type compounds, in which the steric crowding around the C_9 position is appreciably released. Treatment of the hydroxy ester (**12**) with *tert*-butyldimethylsilyl chloride gave the silyl ether (**17**), which was treated with dihydrofuran in the presence of PPTS[6] to give the silyl-tetrahydrofuranyl ether (**26**). When dihydropyran was used for the protection of the C_6 hydroxy group, no protected compound was obtained. The silyl-tetrahydrofuranyl ether (**26**) was converted into the enone (**27**) in a manner similar to that used for the conversion of **23** into **24**. Reaction of the enone (**27**) with dimethylsulfonium methylide[7] gave the oxirane (**28**) in 78% yield; the stereochemistry of the oxirane ring is not established. Hydrolysis of the C_5 methoxycarbonyl group is essential for the lactonization[2] of the oxirane (**28**). Deprotection of the silyl group of the oxirane (**28**) with tetra-*n*-butylammonium fluoride afforded the hydroxy ester (**29**). All attempts to hydrolyze **28** and **29** using a variety of reagents[8] under various reaction conditions failed, presumably because of the steric hindrance caused by the C_6 tetrahydrofuranyl ether group. Thus, deprotection of the tetrahydrofuranyl group of the C_6



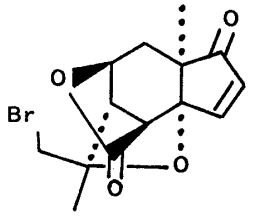
18 : R= H

21 : R= Me



19 : R= Me

22 : R= H



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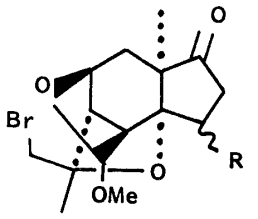

23 : R= H

25 : R= Me

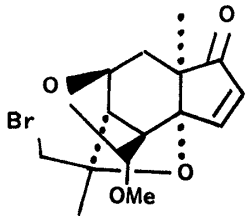

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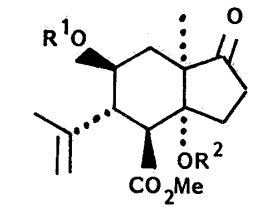
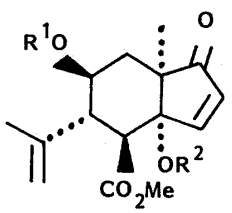
Chart 4

hydroxy function was tried, but acid treatment of the oxirane (**28**) gave the aldehyde (**30**) and that of **29** gave the ether (**31**). The structures of **30** and **31** were deduced from the ^{1}H-NMR and the infrared absorption (IR) spectral analysis of these compounds (see "Experimental"). Next, protection of two hydroxy groups at C_3 and C_6 of the hydroxy ester (**12**) by using excess dihydrofuran in the presence of PPTS gave the ditetrahydrofuranyl ether (**32**) quantitatively, and this was transformed into the enone (**33**) in the same manner as used for the conversion of **23** into **24**. The Wittig reaction of **33** with triphenylphosphonium methylide using dimethylsulfinyl carbanion[9] as a base afforded the diene (**34**) in 85% yield. Since hydrolysis of the C_5 methoxycarbonyl group of **34** was unsuccessful, as was the case for the oxirane (**28**), deprotection of the two hydroxy groups of **34** was examined. When treated with methanol–water–oxalic acid, the diene (**34**) gave the allyl alcohol (**35**) and the allyl methyl ether (**36**), which resulted from the S_N' type reaction of the diene (**34**). Hydrolysis of the diene (**34**) was successfully carried out under mild conditions using PPTS in tetrahydrofuran containing water[6] to furnish the desired hydroxy ester (**37**) in 85% yield. However, alkaline hydrolysis of the C_5 ester group of **37** readily caused retroaldol cleavage even under mild conditions using ammonia or sodium bicarbonate to give **38**. Demethylation of the C_5 methoxycarbonyl group of **37** using several nucleophiles[8] was also unsuccesful. The ready retroaldol cleavage of **37** may be attributable to the presence of the double bond at the C_7 position.

It is assumed that this type of cleavage reaction of the hydroxy ester (**37**) will be prevented when hydrolysis is applied to a compound possessing an sp^3 carbon atom at the C_7 position. Thus, epoxidation of **37** by Sharpless' method[10] was tried but the only isolable product of this reaction was the hydroxy ether (**39**), which resulted from epoxidation of the double bond, followed by cleavage of the resulting oxirane ring by the internal attack of the C_3 hydroxy group. Acetylation of **39** gave the corresponding monoacetate (**40**). The structures of **39** and **40** were deduced from the ^{1}H-NMR spectral analyses of the monoacetate (**40**) (see "Experi-

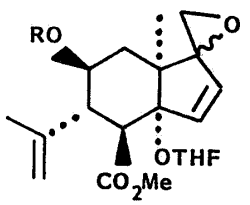


17 : R^1= Si, R^2= H
26 : R^1= Si, R^2= THF
32 : R^1= R^2= THF

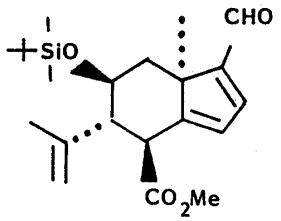


27 : R^1= Si, R^2= THF
33 : R^1= R^2= THF

THF = 



28 : R= Si
29 : R= H



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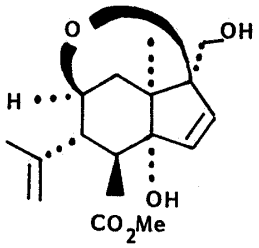

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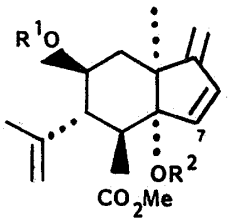
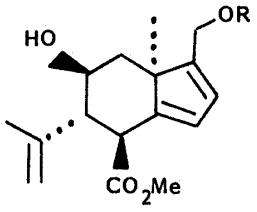
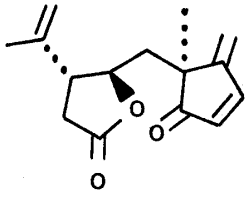


34 : R^1= R^2= THF
37 : R^1= R^2= H
41 : R^1= Ac, R^2= H



35 : R= H
36 : R= Me



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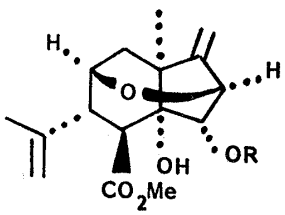
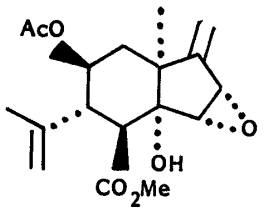


39 : R= H
40 : R= Ac

Chart 5

mental"). Then epoxidation by Sharpless' method was applied to the monoacetate (**41**) derived from the hydroxy ester (**37**) to give selectively the epoxide (**42**). The α configuration of the oxirane ring of **42** was presumed on the basis of the reaction mechanism of Sharpless' allylic alcohol epoxidation and from the formation of the hydroxy ether (**39**) (*vide ante*). Alkaline hydrolysis of the epoxide (**42**), followed by lactonization of the product gave no isolable product.

Our next synthetic strategy was to cleave the oxirane ring with a suitable nucleophile, which has the advantage of permitting the reconstruction[11] of the oxirane ring in the subsequent synthetic stage, and then to lactonize the cleaved product, and finally to reconstruct the oxirane ring by means of the S_N type reaction. Reaction of the epoxide (**42**) with lithium thiophenoxide[12] afforded **43** and **44**, in 90 and 7% yields, respectively. The structure of **43** was suggested by the ^{1}H-NMR spectrum, which revealed coupling of the double triplet signal due to the C_8-H at δ 4.04 with J values of 2 and 8 Hz, indicating that the thiophenoxide anion had attacked the C_8 position. The structure of **43** was also supported by the formation of the



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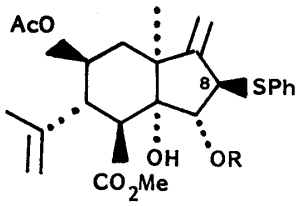
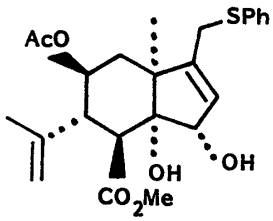


43 : R= H

49 : R= THF



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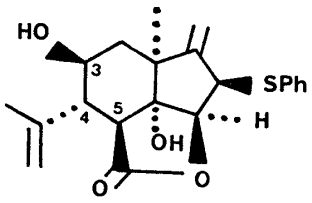

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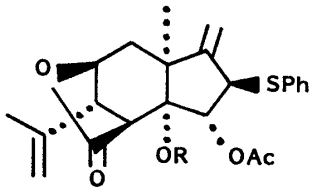
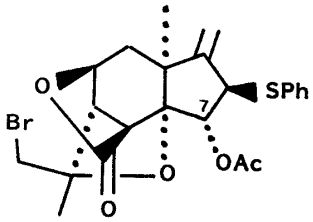


46 : R= H

47 : R= Ac



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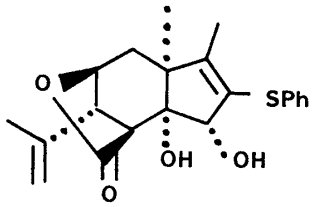

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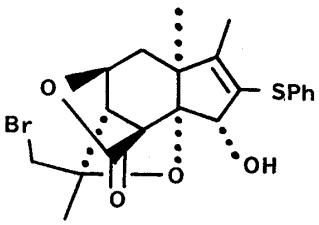

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Chart 6

γ-lactone (**45**) (*vide infra*). After hydrolysis of **43**, the product was lactonized by using methyl chloroformate and triethylamine[13] to give the γ-lactone (**45**), the IR spectrum of which showed a band at 1790 cm^{-1}. That this γ-lactone is different from the γ-lactone formed between the C_3 hydroxy group and the C_5 carboxylic acid group having the lactone carbonyl group axial, was suggested by the ^1H-NMR spectrum. Thus, the ^1H-NMR spectrum of the γ-lactone (**45**) revealed a doublet signal due to the C_5 axial proton (J=12 Hz); that is, the configuration of the lactone carbonyl group of **45** is equatorial. The formation of the γ-lactone (**45**) can be explained by supposing that the C_7 hydroxy group is first acylated and then the carboxylate anion attacks the C_7 carbon in the S_N2 type fashion.

On the other hand, the lactonization of the carboxylic acid derived from **43** using acetic anhydride and sodium acetate[14] afforded two kinds of the lactones, (**46**) and (**47**), in 26% and 10% yields, respectively. Treatment of **46** with *N*-bromo succinimide (NBS) gave the bromoether (**48**). In order to reconstruct the oxirane ring, hydrolysis of the C_7 acetoxy group

was tried but selective hydrolysis of the C_7 *O*-acyl group could not be achieved. The C_7 hydroxy group was then protected as its tetrahydrofuranyl ether, and the lactonization of the hydroxy carboxylic acid derived from the tetrahydrofuranyl ether (**49**) using 2,4,6-trichlorobenzoyl chloride[15] gave only the lactone (**50**), which resulted from lactonization and migration of the double bond. When treated with NBS, the lactone (**50**) afforded the bromoether (**51**); the structures of **50** and **51** were deduced from the ^{1}H-NMR spectral analyses of these compounds (see "Experimental").

The information accumulated during the present studies opened the way to the total synthesis of (±)-coriamyrtin, and the completion of this synthesis will be reported in the subsequent paper.

Experimental

Melting points and boiling points are uncorrected. The IR (ν_{max}) spectra were determined on a Shimadzu IR-400 spectrometer in chloroform. The ^{1}H-NMR spectra were obtained in chloroform-*d* at 60 MHz on a JEOL PMX-60, or at 100 HMz on a Varian HA-100 or JEOL FX 100 instrument. Chemical shifts are reported as δ units [parts per million downfield from a tetramethylsilane internal standard (δ 0.00)] 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 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. Preparative HPLC was performed with a Waters Prep. LC/system 500A instrument using a prep. PAK 500 silica column.

The Esters, (6) and (7), and the Triketone (8)——A mixture of 13.0 g of **3**, 500 ml of dry methanol, and 5 ml of dry methanol saturated with HCl gas was stirred for one week at room temperature. After concentration of the mixture, the residue was poured into ice-water and extracted with chloroform. The chloroform extract was washed with dil. NH_4OH, water, dried and evaporated to give 18.5 g of the residue. Column chromatography of the residue on silica gel with chloroform afforded 4.5 g of the ester (**6**) from the fast-eluted fractions and 11.2 g of a mixture of **6**, **7**, and **8** from the slowly eluted fractions. The mixture was subjected to prep. high performance liquid chromatography (HPLC) with hexane–methylene chloride–acetonitrile (5 : 4 : 1) and the first eluted peak contained 2.1 g of **6**. The total yield of **6** was 45%. **6**: mp 66°C (flakes from ether–hexane). IR: 1730, 1715, and 1643 cm^{-1}. ^{1}H-NMR (100 MHz): 1.07 (3H, s), 3.36 (3H, s), 3.70 (3H, s), 5.47 (1H, m), 5.77 (1H, dd, J=1.5 and 11.5), 6.17 (1H, dd, J=7 and 11.5). *Anal.* Calcd for $C_{13}H_{18}O_5$: C, 61.40; H, 7.14. Found: C, 61.68; H, 7.22. The ester (**7**) was obtained from the second eluted fraction as a colorless oil (6.3 g, 43% yield). **7**: bp 130—132°C/1 Torr. IR: 1735, 1714, and 1640 cm^{-1}. ^{1}H-NMR (100 MHz): 1.05 (3H, s), 1.65 (1H, dd, J=8 and 13), 2.88 (1H, dd, J=8 and 13), 3.40 (3H, s), 3.68 (3H, s), 5.43 (1H, dq, J=1.5 and 8), 5.73 (1H, dd, J=1.5 and 11.5), 6.28 (1H, dd, J=8 and 11.5). *Anal.* Calcd for $C_{13}H_{18}O_5$: C, 61.40; H, 7.14. Found: C, 61.31; H, 7.30. The last fraction contained the triketone (**8**), which was crystallized from ether–hexane to furnish 1.5 g of **8** as colorless plates in 10% yield. **8**: mp 63—64°C. IR: 1722 cm^{-1}. ^{1}H-NMR (60 MHz): 1.07 (3H, s), 2.50 (2H, t, J=6), 2.68 (2H, t, J=6), 2.89 (4H, s), 3.19 (2H, s), 3.67 (3H, s). *Anal.* Calcd for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71. Found: C, 59.72; H, 6.59.

Equilibrium Reaction of the Ester (7)——A mixture of 302 mg of **7**, 1 ml of methanol saturated with HCl gas and 30 ml of methanol was allowed to stand at room temperature for 6 d. The usual work-up gave the residue, which was shown by GLC to be a mixture of **7** and **6** in approximately 10 : 7 ratio. The mixture was separated by prep. TLC to afford 107 mg of **6** together with 150 mg of recovered **7**.

Acidic Hydrolysis of the Ester (7)——A mixture of 6.78 g of **7**, 30 ml of 10% HCl and 20 ml of methanol was stirred overnight at room temperature. The same work-up of the mixture as above yielded crystals, which were recrystallized from ether–acetone to afford 4.15 g of **3** in 75% yield. A sample of the crystals was identical with an authentic sample previously reported.[2]

The Acetals, (9) and (10)——Cuprous iodide (500 mg) was added portionwise to a solution of isopropenylmagnesium bromide (0.33 M) in THF (150 ml) and the mixture was stirred vigorously at 0°C. After continued stirring for 40 min, the mixture was cooled to −40°C and a solution of 2.65 g of the ester (**6**) in 50 ml of THF was added dropwise. The mixture was stirred for 30 min at the same temperature and then quenched with an aq. NH_4Cl solution and extracted with chloroform. The chloroform extract was washed with dil. HCl, brine, dried, and evaporated to give an oil, which was chromatographed on a silica gel column. The first fraction eluted with chloroform gave the acetal (**9**) (920 mg) and the second fraction eluted with the same solvent gave a mixture of the acetals, (**9**) and (**10**), (1.60 g), while the third fraction eluted contained 310 mg

of **10**. The above mixture was subjected to prep. HPLC to afford additional crops of **9** (500 mg) and **10** (980 mg) [hexane–methylene chloride (1 : 1)]. The total yields of **9** and **10** were 46% and 42%, respectively. **9**: mp 140°C (prisms from ether–chloroform). IR: 3490, 1737, 1650, and 900 cm^{-1}. ^1H-NMR (60 MHz): 1.08 (3H, s), 1.80 (3H, br s), 2.64 (2H, t, $J=12$, C_4, C_5–H), 3.32 (3H, s), 3.71 (3H, s), 4.01 (1H, q, $J=2$ and 4.5), 4.80 (2H, br s), MS *m/z*: 296 (M^+), 278, 264 (base), and 246. *Anal.* Calcd for $C_{16}H_{24}O_5$: C, 64.84; H, 8.16. Found: C, 64.59; H, 8.12. **10**: mp 101—102°C (prisms from ether–acetone). IR: 3450, 1720, 1645 and 905 cm^{-1}. ^1H-NMR (60 MHz): 1.04 (3H, s), 1.78 (3H, br s), 1.67 (1H, d, $J=12$, C_2–H), 2.00 (1H, dd, $J=6.5$ and 12, C_2–H), 2.55 (1H, d, $J=11$, C_4–H), 3.00 (1H, d, $J=11$, C_5–H), 3.27 (3H, s), 3.66 (3H, s), 4.20 (1H, d, $J=6.5$, C_3–H), 4.75 (2H, br s). *Anal.* Calcd for $C_{16}H_{24}O_5$: C, 64.84; H, 8.16. Found: C, 65.03; H, 8.26.

The 1,4-Adduct (11)——A mixture of 8 mg of cuprous iodide and 10 ml of 0.1 M solution of isopropenylmagnesium bromide in THF was stirred vigorously at 0°C for 1 h. After the solution had been cooled to −50°C, a solution of 127 mg of the ester (**7**) in 2.0 ml of THF was added, and the reaction mixture was stirred for 2 h at the same temperature. A similar work-up to that used for the preparation of **9** and **10** gave an oily substance, which was purified by prep. TLC to yield 130 mg of the 1,4-adduct (**11**) as a mixture of diastereomers. **11**: colorless oil. IR: 1732, 1640, and 905 cm^{-1}. ^1H-NMR (60 MHz): 1.13 (3H, s), 1.83 (3H, br s), 3.37 (3H, s), 3.40 (3H, s), 4.02 (1H, m, $W_{h/2}=9$), 4.81 (2H, br s). MS *m/z*: 296 (M^+) and 264 (base).

The Hydroxy Ester (12)——A mixture of 2.00 g of the acetal (**9**), 5% HCl (20 ml) and methanol (20 ml) was allowed to stand at room temperature overnight. The mixture was made alkaline with dil. NH_4OH, salted out and extracted with chloroform. The chloroform extract was washed with brine, dried, and evaporated to afford a crystalline mass. Recrystallization from acetone–ether–chloroform yielded 1.85 g of the hydroxy ester (**12**) (98% yield), which was shown to be identical with an authentic sample previously reported.[2)]

The Hydroxy Ester (13)——A mixture of 300 mg of the acetal (**10**), 3 ml of methanol and 3 ml of 5% HCl was treated in the same manner as above to furnish a crystalline residue (305 mg). Recrystallization from acetone–ether gave 270 mg of the hydroxy ester (**13**) (95% yield). **13**: mp 147—148°C (prisms). IR: 3450, 1733, 1708, 1645, and 907 cm^{-1}. ^1H-NMR (60 MHz): 1.02 (3H, s), 1.66 (1H, dd, $J=4$ and 13, C_2–H), 1.74 (3H, br s), 2.99 (1H, dd, $J=2.5$ and 12, C_4–H), 3.06 (1H, d, $J=12$, C_5–H), 3.67 (3H, s), 3.82 (1H, m, $W_{h/2}=11$, C_3–H), 4.67, 4.87 (each 1H, br s). *Anal.* Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 63.54; H, 7.93.

The Ketone (14) and the Hydroxy Ester (15)——Jones' reagent was added dropwise to a stirred solution of 2.50 g of the hydroxy ester (**13**) in 100 ml of acetone at 0°C until the color of the reagent no longer faded. The mixture was stirred for 1 h at 0°C, then the excess reagent was decomposed with methanol and the mixture was concentrated under reduced pressure. Ice-water was added to the residue and the mixture was made alkaline with dil. NH_4OH and extracted with chloroform. The extract was washed with water, dried, and evaporated to give an oily residue, which was purified by column chromatography on alumina. Elution with benzene and concentration of the eluate yielded 1.70 g of the ketone (**14**) as crystals in 69% yield. **14**: mp 114—115°C (prisms from ether). IR: 3460, 1742, 1715, 1650, and 910cm^{-1}. ^1H-NMR (60 MHz): 1.18 (3H, s), 1.68 (3H, s), 2.82 (1H, d, $J=13$, C_5–H), 3.51 (1H, d, $J=13$, C_4–H), 3.73 (3H, s), 4.28 (1H, s, O<u>H</u>), 4.77 (1H, s), 4.95 (1H, s). *Anal.* Calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 64.08; H, 7.30. A solution of 58 mg of sodium borohydride in 15 ml of ethanol and 15 ml of isopropanol was added dropwise to a stirred solution of 847 mg of the ketone (**14**) in 15 ml of methanol at −78°C for 15 min. The mixture was stirred for 2 h at the same temperature and the usual work-up furnished 900 mg of a crude mixture of the hydroxy esters, (**13**) and (**15**). The mixture was separated by column chromatography on silica gel with chloroform to afford 217 mg of the hydroxy ester (**13**) from the fast-eluted fractions, and 238 mg of the hydroxy ester (**15**, 28% yield) was obtained from the slowly eluted fractions as crystals. **15**: mp 129°C (prisms from acetone). IR: 3460, 1740, 1710, 1648 and 908 cm^{-1}. ^1H-NMR (60 MHz): 1.09 (3H, s), 1.70 (3H, br s), 2.63 (1H, d, $J=13$, C_5–H), 3.68 (3H, s), 3.80—4.38 (1H, m, C_3–H), 4.82 (2H, br s). *Anal.* Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 63.83; H, 7.85.

The Silyl Ether (16)——A mixture of 238 mg of the hydroxy ester (**15**), 190 mg of *tert*-butyldimethylsilyl chloride, 95 mg of imidazole and 5 ml of DMF was stirred at 40°C for 15 h. After concentration of the mixture, the residual oil was poured into ice-water and extracted with chloroform. The extract was washed successively with dil. HCl, water, aq. $NaHCO_3$, water, and dried. Evaporation of the solvent left an oil, which was purified by column chromatography on Al_2O_3 with benzene to furnish 294 mg of the silyl ether (**16**) as colorless flakes in 88% yield. **16**: mp 105°C (from ether–hexane). IR: 3420, 1735, 1708 and 835 cm^{-1}. ^1H-NMR (60 MHz): 0.10 (6H, s), 0.88 (9H, s), 1.10 (3H, s), 1.68 (3H, br s), 2.29 (1H, dd, $J=12$ and 13.5, C_4–H), 3.43 (1H, d, $J=13.5$, C_5–H), 3.67 (3H, s), 4.00 (1H, m, $W_{h/2}=22$, C_3–H), 4.33 (1H, s, O<u>H</u>), 4.75 (2H, br s). *Anal.* Calcd for $C_{21}H_{36}O_5Si$: C, 63.59; H, 9.15. Found: C, 63.45; H, 9.36.

Compound (17) from the Silyl Ether (16)——A solution of the silyl ether (**16**, 396 mg) in 5 ml of THF was added dropwise to a mixture of 123 mg (1.1 eq) of potassium *tert*-butoxide and 5.0 ml of DMF and the mixture was stirred for 30 min at 0°C, then the temperature was raised to room temperature. After continued stirring for 15 h, the mixture was quenched by the dropwise addition of cold dil. HCl and extracted with chloroform. The chloroform extract was washed with aq. $NaHCO_3$, brine, dried, and evaporated under reduced pressure to give 475 mg of residue, which was subjected to prep. TLC. The original silyl ether (**16**) (30 mg, 8% yield)

was recovered from the eluate of the upper zone and 362 mg of the compound (**17**) was obtained from that of the lower zone in 91% yield. **17**: mp 124°C (flakes from ether). IR: 3500, 1735, 1650, and 840 cm^{-1}. ^1H-NMR (60 MHz): 0.02 (6H, s), 0.74 (9H, s), 1.16 (3H, s), 1.81 (3H, br s), 2.49 (1H, dd, $J=10$ and 12, C_4–H), 2.86 (1H, d, $J=12$, C_5–H), 3.67 (3H, s), 3.70—4.20 (1H, m, C_3–H), 4.77, 4.84 (each 1H, br s). *Anal.* Calcd for $C_{21}H_{36}O_5Si$: C, 63.59; H, 9.15. Found: C, 63.30; H, 9.29.

The Hydroxy Ester (12) from Compound (17)——Tetrabutylammonium fluoride (0.5 M solution in THF, 2 ml) was added to a solution of 100 mg of the compound (**17**) in 2 ml of THF and the mixture was stirred for 2 h at room temperature. The reaction mixture was poured into ice-water and extracted with chloroform, and the extract was washed with water and dried. Removal of the solvent gave 75 mg of a crystalline residue, which was recrystallized from acetone-chloroform to furnish 68 mg of the hydroxy ester (**12**) in 95% yield. A sample of **12** was shown to be identical with an authentic sample previously reported.[2)]

The Hemiacetal (19)——Methylmagnesium iodide (2 M solution, 0.2 ml) was added to a solution of 40 mg of the bromoether (**18**)[2)] in 2 ml of ether and 1.0 ml of THF at 0°C and the solution was stirred for 3 h at the same temperature. The mixture was quenched with cold aq. NH_4OH, and the usual work-up gave 47 mg of residue, which was separated by prep. TLC to afford 22 mg of the hemiacetal (**19**) together with 16 mg of the starting material (**18**). **19**: colorless oil. IR: 3360 cm^{-1} (no carbonyl absorption). ^1H-NMR (60 MHz): 1.00 (3H, s), 1.45 (3H, s), 1.48 (3H, s), 3.38 (1H, d, $J=11$), 3.63 (1H, d, $J=11$), 4.41 (1H, m, $W_{h/2}=10$, C_3–H), 3.20 (1H, br s, OH). MS *m/z*: 346, 344 (M^+), 329, and 327.

The Enone (20)——A mixture of 180 mg of the bromoether (**18**), 158 mg of phenylselenyl chloride, one drop of conc. HCl and 5 ml of ethyl acetate was stirred for one week at room temperature. The mixture was diluted with chloroform and the organic layer was washed with aq. $NaHCO_3$, water, and dried. Evaporation of the solvent left the crude selenide, which without further purification was dissolved in 3 ml of THF and 3 drops of pyridine. Hydrogenperoxide (30%, 0.3 ml) was added to the above solution. After continued stirring for 3 h at room temperature, the mixture was extracted with chloroform and the extract was washed with dil. HCl, water, dried, and evaporated to leave an oily residue. Purification of the residue by prep. TLC furnished 130 mg of the enone (**20**): mp 148—151°C (prisms from ether). IR: 1783, 1728 cm^{-1}. ^1H-NMR (100 MHz): 1.28 (3H, s), 1.62 (3H, s), 3.21 (1H, d, $J=5$, C_5–H), 3.33 (1H, t, $J=5$, C_4–H), 3.57, 3.78 (each 1H, d, $J=11$), 5.12 (1H, m, $W_{h/2}=11$, C_3–H), 6.32 (1H, d, $J=6$, C_8–H), 7.36 (1H, d, $J=6$, C_7–H). MS *m/z*: 328, 326 (M^+), 298, 300, 247, 233. Calcd for $C_{14}H_{15}BrO_4$: 326.0153 (M^+). Found: 326.0158. Calcd for $C_{14}H_{15}Br^*O_4$: 328.0132 (M^+). Found: 328.0130.

The 1,4-Adduct (21)——Methyllithium (0.5 M solution in ether, 0.05 ml) was added to a solution of 33 mg of the enone (**20**) in 3 ml of ether at −30°C and the mixture was stirred for 1 h, during which time the temperature was brought to 0°C. After quenching of the mixture with aq. NH_4Cl, the same work-up as that used for the preparation of **19** gave 30 mg of residue, which was subjected to prep. TLC. The 1,4-adduct (**21**) (8 mg, 21% yield) was obtained from the upper zone as a single diastereomer, but the stereochemistry of the C_7 position was not specified. The enone (**20**) (7 mg) was recovered from the lower zone. **21**: colorless oil. IR: 1780, 1745 cm^{-1}. ^1H-NMR (60 MHz): 1.15 (3H, s), 1.26 (3H, d, $J=5$), 1.63 (3H, s), 3.48, 3.70 (each 1H, d, $J=11$), 5.19 (1H, m, $W_{h/2}=11$, C_3–H). MS *m/z*: 344, 342 (M^+).

The Hemiacetal (22), the Methyl Ether (23) and the Enone (24)——Diisobutylaluminum hydride (1 M solution in hexane, 1.14 ml) was added dropwise to a solution of 165 mg of the bromoether (**18**) in toluene (2.5 ml) and THF (0.5 ml) at −78°C, and the reaction mixture was stirred for 1.5 h at the same temperature. Sodium hydroxide (0.5 N, 5 ml) was then added and the mixture was stirred for 1 h at room temperature. The mixture was extracted with chloroform and the extract was washed with water, dried and evaporated under reduced pressure to afford 163 mg of residue. Separation of the residue by prep. TLC afforded 50 mg of the starting material (**18**) from the eluate of the upper zone and 116 mg of the hemiacetal (**22**) from that of the lower zone. **22**: colorless oil. IR: 3370, 1010 cm^{-1}. ^1H-NMR (60 MHz): 1.02 (3H, s), 1.48 (3H, s), 3.33 (1H, d, $J=5.5$), 3.45, 3.65 (each 1H, d, $J=11$), 4.43 (1H, m, $W_{h/2}=9$, C_3–H), 5.52 (1H, d, $J=5.5$). A mixture of 100 mg of the hemiacetal (**22**), 68 mg of PPTS, 1.7 ml of methyl orthoformate, and 10 ml of dry methylene chloride was refluxed for 2 h. The mixture was mixed with ice and extracted with chloroform and the extract was washed with aq. $NaHCO_3$ and water, then dried. Removal of the solvent under reduced pressure left 105 mg of residue, which was purified by prep. TLC to yield 77 mg of the methyl ether (**23**) as a colorless oil. **23**: IR: 1740, 1015 cm^{-1}. ^1H-NMR (60 MHz): 1.07 (3H, s), 1.49 (3H, s), 3.31 (3H, s), 3.47, 3.66 (each 1H, d, $J=11$), 4.65 (1H, s), 4.63 (1H, m, $W_{h/2}=10$). MS: *m/z*: 346, 344 (M^+), 315, 313, 286 and 284. A solution of diisopropylamine (12 mg) in 0.5 ml of THF was treated with 0.1 ml of *n*-butyllithium (1.5 M solution in hexane) at −50°C and the mixture was stirred for 1 h, during which time the temperature rose to 0°C. Then the mixture was cooled to −78°C, and a solution of 32 mg of the methyl ether (**23**) in 1.5 ml of THF was added. The whole was further stirred for 1 h at the same temperature. Phenylselenyl chloride (23 mg) in 0.5 ml of THF was added to the mixture at −78°C. After continued stirring for 30 min at −78°C, the mixture was quenched with aq. NH_4Cl and extracted with ether. The extract was washed with aq. $NaHCO_3$, water, dried, and evaporated to give the crude selenide, which without purification was dissolved in 4 ml of methylene chloride and one drop of pyridine. Hydrogen peroxide (30%, 0.1 ml) was added and the reaction mixture was stirred for 1 h at 0°C, then for 1.5 h at room temperature. The usual work-up and concentration of the reaction mixture gave 41 mg of residue, which was purified by prep. TLC to furnish

20 mg of the enone (**24**) as an oil in 63% yield. **24**: colorless oil. IR: 1712, 1012 cm^{-1}. ^1H-NMR (60 MHz): 1.18 (3H, s), 1.62 (3H, s), 3.28 (3H, s), 3.54, 3.69 (each 1H, d, $J=11$), 4.27 (1H, s), 4.65 (1H, m, $W_{h/2}=10$, C_3–H), 6.28 (1H, d, $J=6.5$, C_8–H), 7.45 (1H, d, $J=6.5$, C_7–H). MS *m/z*: 344, 342 (M^+), 313 and 311. Calcd for $C_{15}H_{19}BrO_4$: 342.0467 (M^+). Found: 342.0478.

The 1,4-Adduct (**25**)——Methyllithium (0.3 M solution in ether, 0.2 ml) was added to a solution of 18 mg of the enone (**24**) in 0.5 ml of THF and 0.2 ml of ether, and the mixture was stirred for 2 h at 0°C. The mixture was quenched with aq. NH_4Cl, and the same work-up as that used for the preparation of **21** afforded 30 mg of residue, which was subjected to prep. TLC. Elution of the upper zone gave 10 mg of the 1,4-adduct (**25**) in 53% yield, and that of the lower zone gave 5 mg of the enone (**24**). **25**: mp 117—120°C (prisms from ether). IR: 1747, 1028 cm^{-1}. ^1H-NMR (200 NHz): 1.13 (3H, s), 1.28 (3H, d, $J=5$), 1.55 (3H, s), 2.84 (1H, t, $J=5$, C_4–H), 3.30 (3H, s), 3.47, 3.64 (each 1H, d, $J=10$), 4.57 (1H, s), 4.62 (1H, m, $W_{h/2}=12$, C_3–H). MS *m/z*: 360, 358 (M^+), 329, 327, 298, and 219 (base). Calcd for $C_{16}H_{23}BrO_4$: 358.0780. Found: 358.0788.

The Silyl-tetrahydrofuranyl Ether (**26**) **and the Enone** (**27**)——A mixture of 56 mg of the hydroxy ester (**12**), 90 mg of *tert*-butyldimethylsilyl chloride, 45 mg of imidazole and 2 ml of DMF was stirred for 5 h at 40°C. The mixture was worked up in the same manner as that used for the preparation of **16** to give the residue. Crystallization from ether–hexane yielded 40 mg of the silyl ether (**17**). The mother liquor was concentrated and purified by prep. TLC to give another crop of **17** (37 mg) as crystals. The total yield **17** was 98%. A mixture of 105 mg of **17**, 3 mg of PPTS, 42 mg of dihydrofuran and 5 ml of methylene chloride was refluxed with stirring for 5 h. Then, the mixture was made alkaline with dil. NH_4OH and extracted with methylene chloride. The organic extract was washed with water, dried, and evaporated to give an oily residue, which was subjected to column chromatography on Al_2O_3 with benzene–methylene chloride. The first fraction contained 92 mg of the silyl-tetrahydrofuranyl ether (**26**, 75% yield), and 10 mg of the starting material (**17**) was recovered from the second fraction. The silyl-tetrahydrofuranyl ether (**26**) was shown to be a mixture of diastereomers due to the protective tetrahydrofuranyl ether moiety in a three-to-two ratio judging from the intensity of the signal at δ 3.62 relative to that at δ 3.69 in the ^1H-NMR spectrum. **26**: colorless oil. IR: 1730, 1650, and 835 cm^{-1}. ^1H-NMR (60 MHz): 0.01 (6H, s), 0.84 (9H, s), 1.14 (3H, s), 1.78 (3H, br s), 2.90 (1H, d, $J=12$, C_5–H), 3.62 (3H, s), 3.50—4.00 (3H, m), 4.82 (2H, br s), 5.11 (1H, m, $W_{h/2}=12$). MS *m/z*: 396 (M^+-THF). The silyl-tetrahydrofuranyl ether (**26**, 246 mg) was converted into the enone (**27**) in the same manner as that used for the conversion of **23** into **24**. The residue (240 mg) was purified by prep. TLC to furnish 197 mg of the enone (**27**) as a colorless oil. **27**: IR: 1720, 1645, 900, and 835 cm^{-1}. ^1H-NMR (60 MHz): 0.01 (6H, s), 0.84 (9H, s), 1.20 (3H, s), 1.72 (3H, br s), 2.30 (1H, dd, $J=8.5$ and 13, C_4–H), 3.03 (1H, d, $J=13$, C_5–H), 3.58—4.00 (3H, m), 3.72 (3H, s), 4.82 (2H, br s), 5.20 (1H, m, $W_{h/2}=6$), 6.49 (1H, d, $J=6.5$, C_8–H), 8.00 (1H, d, $J=6.5$, C_7–H). MS *m/z*: 394 (M^+-THF).

The Oxirane (**28**)——A solution of dimethylsulfinyl carbanion (1 M solution in DMSO, 2.5 ml) was added to a suspension of 520 mg of trimethylsulfonium iodide in 1 ml of THF and the mixture was stirred for 20 min at 0°C. Then, a solution of 200 mg of the enone (**27**) in 2 ml of THF was added to the above mixture and the reaction mixture was stirred for 20 min at 0°C and then for 2.5 h at room temperature. After being quenched with aq. NH_4Cl, the mixture was extracted with ether and the extract was washed with water and dried. Removal of the solvent left the residue, which was purified by prep. TLC to yield 160 mg of the oxirane (**28**) as a colorless oil. The oxirane (**28**) was shown to be a mixture of diastereomers in a three-to-two ratio judging from the relative intensities of six pairs of signals at δ 0.89 to 0.86; δ 2.88 to 2.87; δ 3.64 to 3.62; δ 5.02 to 5.12; δ 5.90 to 6.02; δ 6.76 to 6.65, in the ^1H-NMR spectrum. **28**: colorless oil. IR: 1722, 1650, and 835 cm^{-1}. ^1H-NMR (100 MHz): 0.01 (6H, s), 0.81 (9H, s), 0.89 (3H, s), 0.96 (3H, s), 1.72 (3H, br s), 2.28 (1H, dd, $J=10$ and 13, C_4–H), 2.82 (1H, d, $J=5$, C_{11}–H), 2.88 (1H, d, $J=13$, C_5–H), 2.87 (1H, d, $J=13$, C_5–H), 3.03 (1H, d, $J=5$, C_{11}–H), 3.50—3.88 (3H, m), 3.64 (3H, s), 3.62 (3H, s), 4.78 (1H, s), 4.83 (1H, br s), 5.02 (1H, m), 5.12 (1H, m), 5.90 (1H, d, $J=6.5$, C_8–H), 6.02 (1H, d, $J=6.5$, C_8–H), 6.76 (1H, d, $J=6.5$, C_7–H), 6.65 (1H, d, $J=6.5$, C_7–H). MS *m/z*: 408 (M^+-THF), 377.

The Hydroxy Ester (**29**)——A mixture of 160 mg of the oxirane (**28**), tetrabutylammonium fluoride (0.5 M solution in THF, 4 ml) and 1 ml of THF was stirred for 10 min at 0°C, and then for 3 h at room temperature. The same work-up as that used for the conversion of **17** into **12** gave the residue, which was purified by prep. TLC to furnish 118 mg of the hydroxy ester (**29**) as an oil in 97% yield. **29**: IR: 3450, 1725, 1645, and 900 cm^{-1}. ^1H-NMR (60 MHz): 1.10 (3H, s), 1.73 (3H, br s), 2.80 (1H, d, $J=13$, C_5–H), 3.57 (1H, d, $J=5$, C_{11}–H), 3.68 (3H, s), 3.80 (1H, d, $J=5$, C_{11}–H), 3.60—4.10 (3H, m), 4.78 (2H, br s), 5.20 (2H, m), 6.01 (1H, d, $J=6$, C_7–H or C_8–H), 6.30 (1H, d, $J=6$, C_7–H or C_8–H). MS *m/z*: 364 (M^+), 294 (base) and 276.

The Aldehyde (**30**)——A mixture of 38 mg of the oxirane (**28**), 2 ml of 2.5% HCl and 5 ml of THF was allowed to stand at room temperature for 5 h. The reaction mixture was salted out and extracted with chloroform and the chloroform extract was washed with brine and dried. Evaporation of the solvent left 35 mg of residue, which was purified by prep. TLC to afford 16 mg of the aldehyde (**30**) as an oil in 51% yield. **30**: IR: 1732, 1690, 1658, 1600, 903, and 840 cm^{-1}. ^1H-NMR (60 MHz): 0.01 (6H, s), 0.79 (9H, s), 1.20 (3H, s), 1.79 (3H, br s), 2.48 (1H, dd, $J=10$ and 12, C_4–H), 3.60 (1H, dd, $J=2$ and 12, C_5–H), 3.70 (3H, s), 3.71—4.40 (1H, m, C_3–H), 4.80 (2H, br s), 6.07 (1H, t, $J=2$, C_7–H), 7.17 (1H, d, $J=2$, C_8–OH), 9.61 (1H, s, CHO). MS *m/z*: 390 (M^+), 362.

The Ether (**31**)——A mixture of 30 mg of the hydroxy ester (**29**), 1.0 ml of 2.5% HCl and 8 ml of THF

was allowed to stand for 40 h at room temperature, then the reaction mixture was worked up in the same manner as that used for the transformation of **28** into **30**. The residue (41 mg) was purified by prep. TLC to yield 11 mg of the ether (**31**) as an oil in 46% yield. **31**: IR: 3420, and 1722 cm^{-1}. ^1H-NMR (60 MHz): 1.20 (3H, s), 1.78 (3H, br s), 2.60 (1H, d, $J=13$, C_4–H), 2.80 (1H, d, $J=13$, C_5–H), 3.00 (1H, s, OH), 3.57 (2H, s, C_{11}–H), 3.71 (3H, s), 4.02 (1H, dd, $J=5$ and 15, C_3–H), 4.77 (2H, br s), 5.69 (1H, d, $J=6$, C_7–H or C_8–H), 5.95 (1H, d, $J=6$, C_7–H or C_8–H). MS *m/z*: 294 (M^+), 277 and 263.

The Ditetrahydrofuranyl Ether (32) and the Enone (33)——A mixture of 1.00 g of the hydroxy ester (**12**), 30 mg of PPTS, 996 mg of dihydrofuran and 80 ml of dry methylene chloride was refluxed with stirring for 3 h. The reaction mixture was worked up in the same manner as that used for the preparation of **26** to afford an oily residue. Purification of the residue by column chromatography on alumina with benzene–methylene chloride furnished 1.37 g of the ditetrahydrofuranyl ether (**32**) as a colorless oil in 92% yield. **32**: IR: 1730, 1650, 1030, 990, 915, and 905 cm^{-1}. ^1H-NMR (60 MHz): 1.12 (3H, s), 1.76 (3H, br s), 2.88 (1H, d, $J=12$, C_5–H), 3.64 (3H, s), 3.55—4.29 (5H, m), 4.88 (2H, br s), 5.13 (2H, br s). MS *m/z*: 422 (M^+), 352, 246. Calcd for $C_{23}H_{34}O_7$: 422.2305 (M^+). Found: 422.2320. The ditetrahydrofuranyl ether (**32**, 33 mg) was converted into the enone (**33**) in the same manner as that used for the transformation of **26** into **27**. Purification by prep. TLC gave 27 mg of the enone (**33**) as a colorless oil in 82% yield. **33**: IR: 1720, 1650, 1020, 905 cm^{-1}. ^1H-NMR (60 MHz): 1.07 (3H, s), 1.70 (3H, br s), 3.05 (1H, d, $J=13$, C_5–H), 3.68 (3H, s), 3.50—4.00 (5H, m), 4.77 (2H, br s), 5.06 (2H, m), 6.40 (1H, d, $J=7$, C_8–H), 7.97 (1H, d, $J=7$, C_7–H). MS *m/z*: 420 (M^+). Calcd for $C_{23}H_{32}O_7$: 420.2145 (M^+). Found: 420.2114.

The Diene (34)——A solution of 3.2 ml of dimethylsulfinyl carbanion (1 M solution in DMSO) was added to a suspension of 1.138 g of methyl triphenylphosphonium bromide in 2 ml of THF. After continued stirring for 20 min, a solution of 268 mg of the enone (**33**) in 2 ml of THF was added dropwise to the above solution and the reaction mixture was stirred for 3.5 h at room temperature. The reaction mixture was quenched by addition of an aq. NH_4Cl solution and extracted with ether. The extract was washed with brine, dried and evaporated to leave an oil. Purification of the oily residue by column chromatography on alumina with benzene afforded 228 mg of a pure sample of the diene (**34**) as a colorless oil in 85% yield. **34**: IR: 1728, 1647, 993 cm^{-1}. ^1H-NMR (60 MHz): 1.25 (3H, s), 1.75 (3H, s), 3.00 (1H, d, $J=12$, C_5–H), 3.70 (3H, s), 3.50—4.50 (5H, m), 4.78 (2H, br s), 4.90 (1H, s), 5.06 (1H, s), 5.10 (2H, m), 6.53 (1H, d, $J=7$, C_7–H or C_8–H), 6.60 (1H, d, $J=7$, C_7–H or C_8–H). MS *m/z*: 418 (M^+), 362. Calcd for $C_{24}H_{34}O_6$: 418.2356 (M^+). Found: 418.2357.

The Allyl Alcohol (35), the Allyl Methyl Ether (36), and the Hydroxy Ester (37) from the Diene (34)——a) A solution of 71 mg of the diene (**34**), 25 mg of PPTS in 1 ml of water and 10 ml of THF was stirred for one day at room temperature. The reaction mixture was made alkaline with aq. NH_4OH and extracted with chloroform. The chloroform extract was washed with brine, dried and evaporated to give the residue. Purification of the residue by prep. TLC afforded 40 mg of the hydroxy ester (**37**) as a colorless oil in 85% yield. **37**: IR: 3550, 1725, 1642, 908, 887 cm^{-1}. ^1H-NMR (60 MHz): 1.27 (3H, s), 1.77 (3H, br s), 2.25 (1H, dd, $J=10$ and 13, C_4–H), 2.91 (1H, d, $J=13$, C_5–H), 3.42—4.00 (1H, m, C_3–H), 3.70 (3H, s), 4.92 (2H, s), 5.00 (1H, br s), 5.09 (1H, s, C_{11}–H), 6.36 (1H, d, $J=6$, C_7–H or C_8–H), 6.66 (1H, d, $J=6$, C_7–H or C_8–H). MS *m/z*: 278 (M^+), 260, 234. Calcd for $C_{16}H_{22}O_4$: 278.1519 (M^+). Found: 278.1524.

b) A mixture of 50 mg of the diene (**34**), 13 mg of oxalic acid, 1.0 ml of water and 4 ml of methanol was refluxed for 5 h. The same work-up as above gave 41 mg of residue, which was subjected to prep. TLC. From the eluate of the upper zone, the allyl methyl ether (**36**) was obtained in 57% yield (20 mg) and from that of the lower zone, 8 mg of the allyl alcohol (**35**) was obtained in 24% yield as a colorless oil. **36**: IR: 3500, 1730, 1650, 910 cm^{-1}. ^1H-NMR (60 MHz): 1.16 (3H, s), 1.85 (3H, br s), 2.25 (1H, t, $J=12$, C_4–H), 3.34 (3H, s), 3.45 (1H, dd, $J=2$ and 12, C_5–H), 3.76 (3H, s), 3.70—4.12 (1H, m, C_3–H), 4.19 (2H, s), 4.96 (1H, br s), 5.06 (1H, br s), 5.92 (1H, t, $J=2$, C_7–H), 6.24 (1H, d, $J=2$, C_8–H). MS *m/z*: 292 (M^+), 260 (base), 242. **35**: IR: 3380, 1722, 1640, 900 cm^{-1}. ^1H-NMR (60 MHz): 1.19 (3H, s), 1.87 (3H, br s), 2.42 (1H, dd, $J=10$ and 12, C_4–H), 3.55 (1H, dd, $J=2$ and 12, C_5–H), 3.79 (3H, s), 4.09 (1H, m, C_3–H), 4.46 (2H, br s), 5.00 (1H, br s), 5.09 (1H, br s), 5.96 (1H, t, $J=2$), 6.27 (1H, d, $J=2$, C_8–H). MS *m/z*: 278 (M^+), 260.

Compound (38)——A solution of 40 mg of the hydroxy ester (**37**) in 3 ml of methanol and 1.5 ml of 28% NH_4OH was refluxed for 2 h. The reaction mixture was made acidic with cold dilute HCl and extracted with chloroform. The chloroform extract was washed with brine, dried and evaporated to give 30 mg of residue. Purification of the residue by prep. TLC afforded 18 mg of **38** as a colorless oil in 52% yield. **38**: IR: 1776, 1708, 1640, 905 cm^{-1}. ^1H-NMR (60 MHz): 1.19 (3H, s), 1.70 (3H, br s), 4.57 (1H, ddd, $J=3$, 8, and 10), 4.78 (1H, br s), 4.93 (1H, br s), 5.17 (1H, s), 5.40 (1H, s), 6.23 (1H, d, $J=6$), 7.67 (1H, d, $J=6$). MS *m/z*: 246 (M^+), 218.

The Hydroxy Ether (39) and Its Monoacetate (40)——A mixture of 19 mg of the hydroxy ester (**37**), 4 mg of vanadyloxy acetylacetonate, 0.2 ml of 70% *tert*-butyl hydroperoxide and 2 ml of benzene was stirred for 2 h at room temperature, then cooled. Aqueous Na_2SO_3 solution was added and the mixture was further stirred for 10 min and then extracted with chloroform. The extract was washed with water, dried and evaporated to yield 18 mg of residue. Purification of the residue by prep. TLC furnished 12 mg of the hydroxy ether (**39**) as a colorless oil in 60% yield. The hydroxy ether (**39**) was transformed into its monoacetate (**40**) in the usual manner (Ac_2O/pyr.; 80% yield) and characterized. **40**: colorless oil. IR: 3500, 1730, 1200—

1240, 905 cm^{-1}. ^{1}H-NMR (60 MHz): 1.18 (3H, s), 1.83 (3H, br s), 2.05 (3H, s), 2.50 (1H, d, J=12, C_4–H or C_5–H), 3.03 (1H, d, J=12, C_4–H or C_5–H) [since the dihedral angel between C_3–H and C_4–H is nearly 0°, no coupling was observed between them], 3.77 (3H, s), 3.90 (1H, d, J=3, C_3–H), 4.30 (1H, d, J=2, C_8–H), 4.87 (3H, br s), 5.00 (1H, s), 5.38 (1H, d, J=2, C_7–H). MS m/z: 336 (M^+), 276.

The Epoxide (42)——Acetylation of the hydroxy ester (**37**, 20 mg) in the usual manner gave the acetate (**41**) quantitatively as a colorless oil. **41**: IR: 3550, 1725, 1200—1250, 908, 890 cm^{-1}. ^{1}H-NMR (60 MHz): 1.36 (3H, s), 1.73 (3H, br s), 1.96 (3H, s), 2.50 (1H, dd, J=10 and 13, C_4–H), 3.00 (1H, d, J=13, C_5–H), 3.70 (3H, s), 4.79 (1H, s), 4.89 (2H, s), 5.08 (1H, s, C_{11}–H), 6.33 (1H, d, J=6, C_7–H or C_8–H), 6.63 (1H, d, J=6, C_7–H or C_8–H). MS m/z: 320 (M^+), 303, 260, 242. A mixture of 22 mg of the acetate (**41**), 5 mg of vanadyloxy acetylacetonate, 0.2 ml of 70% *tert*-butyl hydroperoxide and 2 ml of dry benzene was stirred for 1.5 h at room temperature. The same work-up as that used for the epoxidation of **37** gave 20 mg of the residue, which was subjected to prep. TLC to furnish 18 mg of the epoxide (**42**) as crystals in 77% yield. **42**: mp 151—153°C from ether. IR: 3490, 1725, 910, 860 cm^{-1}. ^{1}H-NMR (60 MHz): 1.17 (3H, s), 1.73 (3H, br s), 2.00 (3H, s), 2.60 (1H, dd, J=11 and 13, C_4–H), 3.07 (1H, d, J=13, C_5–H), 3.70 (3H, s), 4.00 (1H, d, J=3, C_7–H), 4.63 (1H, d, J=3, C_8–H), 4.90 (2H, br s), 5.13 (1H, s, C_{11}–H), 5.43 (1H, s, C_{11}–H). MS m/z: 336 (M^+), 293, 276. Calcd for $C_{18}H_{24}O_6$: 336.1573 (M^+). Found: 336.1574.

Compounds (43) and (44)——A solution of *n*-butyllithium (1.56 M solution in hexane; 0.5 ml) was added to a solution of 0.08 ml of thiophenol in 2 ml of benzene and the mixture was stirred for 1 h at room temperature to give a 0.3 M solution of lithium thiophenoxide. A solution of 42 mg of the epoxide (**42**) in 2 ml of benzene was added dropwise to 1.0 ml of the above solution of lithium thiophenoxide and the whole was stirred for 3 h at room temperature. After being quenched with an aq. NH_4Cl solution, the mixture was extracted with chloroform and the extract was washed with 5% NaOH and brine, then dried. Removal of the solvent under reduced pressure left 85 mg of an oily mixture, which was separated by prep. TLC. From the eluate of the upper zone, 50 mg of **43** was obtained in 90% yield, while 4 mg of **44** was isolated from that of the lower zone in 7% yield. **43**: mp 138—139°C (prisms from ether–acetone). IR: 3450, 1720, 1200—1240, 905 cm^{-1}. ^{1}H-NMR (100 MHz): 1.30 (3H, s), 1.70 (3H, br s), 1.95 (3H, s), 2.60 (1H, dd, J= 11 and 13, C_4–H), 3.00 (1H, d, J=13, C_5–H), 3.75 (3H, s), 4.04 (1H, dt, J=2 and 8, C_8–H), 4.70—5.10 (4H, m), 5.07 (1H, d, J=2, C_{11}–H), 5.25 (1H, d, J=2, C_{11}–H), 7.20—7.70 (5H, m). MS m/z: 446 (M^+), 429, 386. Calcd for $C_{24}H_{30}O_6S$: 446.1762 (M^+). Found: 446.1778. *Anal.* Calcd for $C_{24}H_{30}O_6S \cdot 2/3H_2O$: C, 62.86; H, 6.81. Found: C, 62.72; H, 6.55. **44**: colorless oil. IR: 3480, 1720, 1200—1240, 908 cm^{-1}. ^{1}H-NMR (60 MHz): 1.23 (3H, s), 1.67 (3H, br s), 1.93 (3H, s), 2.33 (1H, dd, J=10 and 12, C_4–H), 2.89 (1H, d, J=12, C_5–H), 3.57 (2H, s), 3.63 (3H, s), 4.76 (2H, br s), 4.80—5.24 (1H, m, C_3–H), 5.23 (1H, br s), 5.46 (1H, br s), 7.07—7.68 (5H, m). MS m/z: 446 (M^+), 429, 323 (base).

The γ-Lactone (45)——A mixture of 18 mg of **43**, 20 mg of sodium hydroxide, 0.3 ml of water and 1.0 ml of methanol was refluxed with stirring for 6 h and the resulting crude carboxylic acid (19 mg) was isolated in a manner similar to that described previously. A mixture of the crude acid (19 mg), 16 mg of triethylamine, 14 mg of methyl chloroformate and 3 ml of benzene was stirred for 30 min at room temperature. Then, the mixture was extracted with chloroform and the chloroform extract was washed successively with dilute HCl, water, aq. $NaHCO_3$ and water, then dried. Concentration of the extract yielded 16 mg of residue, which was purified by prep. TLC to give 6 mg of the γ-lactone (**45**) as a colorless oil. **45**: IR: 3350, 1790, 1670, 910 cm^{-1}. ^{1}H-NMR (60 MHz): 1.27 (3H, s), 1.83 (3H, br s), 2.27 (1H, d, J=12, C_4–H), 2.66 (1H, d, J=12, C_5–H) [since the dihedral angle between the C_3–H and the C_4–H is nearly 0°, no coupling was observed between these protons], 3.72 (1H, m, C_3–H), 4.40 (1H, dd, J=2 and 9, C_8–H), 4.58 (1H, s), 4.99 (1H, br s), 5.20 (1H, d, J=9, C_7–H), 5.44 (1H, d, J=2, C_{11}–H), 5.79 (1H, d, J=2, C_{11}–H), 7.25—7.75 (5H, m). MS m/z: 372 (M^+, base).

The Lactones (46) and (47)——A mixture of 30 mg of **43**, 180 mg of potassium carbonate, 1.0 ml of water and 1.0 ml of methanol was heated at 90°C with stirring for 2 h. The reaction mixture was worked up in the same manner as described previously for the lactonization reaction to give 30 mg of crude acidic residue. A mixture of 30 mg of the above residue, 100 mg of acetic anhydride and 5 ml of toluene was refluxed for 2 h, and then the mixture was concentrated under reduced pressure to leave the residue, which was extracted with chloroform. The chloroform extract was washed successively with cold dilute HCl, aq. $NaHCO_3$ and brine, then dried. Removal of the solvent left 32 mg of residue, which was subjected to prep. TLC separation. From the eluate of the upper zone, 8 mg of the lactone (**47**) was isolated as a colorless oil in 26% yield, while 3 mg of the lactone (**46**) was obtained from the eluate of the lower zone as a colorless oil in 10% yield. **46**: IR: 3500, 1777, 1740, 1650, 1200—1240, 900 cm^{-1}. ^{1}H-NMR (100 MHz): 1.20 (3H, s), 1.72 (3H, br s), 1.80 (3H, s), 2.98 (2H, m, $C_{4,5}$–H), 4.24 (1H, d, J=6, C_8–H), 4.68 (1H, br s), 4.88 (1H, br s), 4.99 (1H, m, $W_{h/2}$=10, C_3–H), 5.44 (1H, br s), 5.60 (1H, br s), 5.80 (1H, d, J=6, C_7–H), 7.42—7.80 (5H, m). MS m/z: 414 (M^+), 397, 354. **47**: IR: 1770, 1735, 1650, 1200—1240, 900 cm^{-1}. ^{1}H-NMR (100 MHz): 1.21 (3H, s), 1.73 (3H, br s), 1.85 (3H, s), 1.99 (3H, s), 2.90 (1H, m, C_4–H), 3.69 (1H, d, J=5, C_5–H), 3.97 (1H, dd, J=3 and 6, C_8–H), 4.81 (2H, br s), 4.99 (1H, m, $W_{h/2}$=11, C_3–H), 5.33 (1H, d, J=3, C_{11}–H), 5.61 (1H, d, J=3, C_{11}–H), 6.04 (1H, d, J=6, C_7–H), 7.00—7.75 (5H, m). MS m/z: 456 (M^+), 412, 370, 347.

The Bromoether (48) from the Lactone (46)——A mixture of 6 mg of the lactone (**46**), 2.5 mg of NBS and 1 ml of THF was stirred for 2 h in the dark at 0°C. The reaction mixture was poured into ice-water

and extracted with chloroform. The chloroform extract was washed successively with an aq. Na_2SO_3 solution, dilute HCl and water, then dried. Removal of the solvent furnished 10 mg of residue, which was purified by prep. TLC. A pure sample of **48** (5 mg) was isolated as a colorless oil in 70% yield. **48**: IR: 1780, 1735, 1200—1240 cm^{-1}. ^{1}H-NMR (100 MHz): 1.25 (3H, s), 1.64 (3H, s), 2.08 (3H, s), 3.10 (1H, t, J=5.5, C_4–H), 3.56 (1H, d, J=5.5, C_5–H), 3.60 (1H, d, J=10), 3.75 (1H, d, J=10), 4.24 (1H, d, J=6, C_8–H), 5.04 (1H, m, $W_{h/2}$=11, C_3–H), 5.40, 5.55 (each 1H, br s), 5.80 (1H, d, J=6, C_7–H), 7.30—7.80 (5H, m). MS m/z: 464, 386, 384 (base).

The Tetrahydrofuranyl Ether (49), the Lactone (50), and the Bromoether (51)——A mixture of 48 mg of **43**, 1 mg of PPTS, 0.1 ml of dihydrofuran and 5 ml of dry methylene chloride was stirred for 3 h at room temperature. The reaction mixture was worked up in the same manner as that used for the preparation of **26** to give the residue. Purification of the residue by prep. TLC afforded 50 mg of the tetrahydrofuranyl ether (**49**) (a mixture of diastereomers) as a colorless oil in 90% yield. **49**: IR: 3500, 1730, 1200—1240, 900 cm^{-1}. ^{1}H-NMR (60 MHz): 1.25 (3H, s), 1.75 (3H, br s), 2.02 (3H, s), 2.88 (1H, d, J=12, C_5–H), 2.33 (1H, dd, J=10 and 12, C_4–H), 3.65 (3H, s), 4.00 (2H, m), 4.70—5.60 (6H, m). MS m/z: 431 (M^+−THF−Me). A mixture of 50 mg of **49**, 4.0 ml of 0.5 N NaOH and 2.0 ml of methanol was refluxed with stirring for 8 h. The same work-up as described previously gave 40 mg of the crude carboxylic acid. A mixture of 40 mg of the residue, 0.14 ml of triethylamine, 244 mg of 2,4,6-trichlorobenzoyl chloride and 20 ml of toluene was refluxed with stirring for 4.5 h. After cooling, the mixture was poured into ice-water and extracted with chloroform. The extract was washed with dilute HCl and water, then dried and evaporated under reduced pressure to afford 289 mg of residue. Preparative TLC of the residue yielded 12 mg of the lactone (**50**) as a colorless oil in 33% yield. **50**: IR: 3500, 1773, 900 cm^{-1}. ^{1}H-NMR (100 MHz): 1.12 (3H, s), 1.80 (3H, br s), 1.95 (3H, br s), 2.84 (1H, d, J=5.5, C_5–H), 2.97 (1H, m, C_4–H), 4.27 (1H, s, C_7–H), 4.65 (1H, br s), 4.86 (1H, m, $W_{h/2}$=12, C_3–H), 5.00 (1H, br s), 7.26—7.70 (5H, m). MS m/z: 372 (M^+), 355. The lactone **50** (12 mg) was transformed into the bromoether **51** (9 mg, 62% yield) with NBS in the same manner as that used for the transformation of **46** into **48**. **51**: colorless oil. IR: 3550, 1774 cm^{-1}. ^{1}H-NMR (100 MHz): 1.37 (3H, s), 1.52, 1.55 (each 3H, br s), 2.85 (1H, d, J=5.5, C_5–H), 3.20 (1H, t, J=5.5, C_4–H), 3.52, 3.77 (each 1H, d, J=11), 4.23 (1H, s, C_7–H), 5.03 (1H, m, $W_{h/2}$=12, C_3–H), 7.22—7.75 (5H, m). MS m/z: 452, 450 (M^+), 437, 435. Calcd for $C_{21}H_{23}BrO_4S$: 450.0499 (M^+). Found: 450.0499. Calcd for $C_{21}H_{23}Br^*O_4S$: 452.0478. Found: 452.0473.

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References and Notes

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