[Chem. Pharm. Bull. 31(6)1972—1979(1983)]

Synthetic Studies on a Picrotoxane Sesquiterpene, Coriamyrtin. III.[1] Completion of the Stereocontrolled Total Synthesis of (±)-Coriamyrtin

KIYOSHI TANAKA, FUMIAKI UCHIYAMA, KIYOSHI SAKAMOTO, and YASUO INUBUSHI*

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

(Received November 26, 1982)

The stereocontrolled total synthesis of (±)-coriamyrtin (**1**) has now been completed, starting from protoanemonin and 2-methyl-1,3-cyclopentanedione, through fifteen steps. The Wittig reaction of the ditetrahydrofuranyl ether (**3**) with triphenylphosphonium methylide gave the *exo*-methylenic compound (**4**), which was derived to the lactone (**6**) by consecutive hydrolysis, alkaline hydrolysis, and lactonization. The lactone (**6**) was transformed into the bromoether (**8**), which was subjected to allylic hydroxylation to give the allyl alcohol (**10**). Epoxidation of the allyl alcohol (**10**) provided selectively the epoxy-alcohol (**11**), which was derived to the mesylate (**16**). Elimination of the *O*-mesyl group gave the olefin (**17**). Epoxidation of **17** with *m*-chloroperbenzoic acid gave (±)-bromocoriamyrtin (**18**) and finally, reductive debromination of **18** furnished (±)-coriamyrtin (**1**).

Keywords——coriamyrtin synthesis; Wittig reaction; allylic hydroxylation; lactonization; bromination; elimination; debromination

In the preceding paper,[2] we reported an effective stereocontrolled synthesis of the picrotoxane skeleton, except for a C_1 unit at the C_9 position, starting from protoanemonin and 2-methyl-1,3-cyclopentanedione through five steps, and we examined several approaches for functionalization of the five-membered ring. In this paper, we wish to present a full account of the completion of the stereocontrolled total synthesis of (±)-coriamyrtin (**1**).

An effective stereocontrolled synthesis of the hydroxy ester (**2**) was reported in the preceding paper.[2] After protection of two hydroxy groups of **2** with tetrahydrofuranyl groups, the ditetrahydrofuranyl ether (**3**)[2] was subjected to the Wittig reaction with triphenylphosphonium methylide under Conia's conditions[3] (*tert*-AmOK–*tert*-AmOH in toluene, reflux), which are effective for the Wittig reaction of a highly enolizable ketone function. Under these reaction conditions, the *exo*-methylenic compound (**4**) was obtained in 72% yield and hydrolysis of **4** with oxalic acid under mild conditions gave the hydroxy ester (**5**). Alkaline hydrolysis of **5** furnished the hydroxy acid in good yield, and this was lactonized by means of the mixed anhydride method using 2,4,6-trichlorobenzoyl chloride and triethylamine[4] to give the lactone (**6**) in 57% yield. In this lactonization procedure, the *endo*-olefinic lactone (**7**) was occasionally produced in an appreciable amount depending upon subtle differences in the work-up procedures. The lactone (**6**) and the *endo*-olefinic lactone (**7**) were transformed into the bromoethers, (**8**) and (**9**),[3,5] respectively. Allylic hydroxylation of **8** with *tert*-butyl hydroperoxide in the presence of a catalytic amount of selenium dioxide by Sharpless' method[6] gave selectively the allyl alcohol (**10**) in 95% yield based on the consumed material. On the other hand, photooxidation of the bromoether (**9**) with singlet oxygen using rose bengal as a sensitizer, followed by reduction of the product with sodium sulfite, afforded solely the same allyl alcohol (**10**) as above in 87% yield based on the consumed material. Therefore, the *endo*-olefinic lactone (**7**) could also be utilized along the synthetic route. The α configuration of the allylic hydroxy group was inferred from the following considerations. Thus, inspection of the molecular models of **8** and **9** showed that the β site of the molecule (that is, the concave face) is highly shielded by the lactone ring and the attack of the electrophile should take place from the less hindered α site. Furthermore, this deduction on the configuration of the allylic hydroxy group was supported by the following consideration: the downfield shift of the angular methyl signal of the allyl alcohol (**10**) at δ 1.24 in the proton nuclear magnetic resonance (^{1}H-NMR) spectrum compared with that of the bromoether (**8**) at δ 0.96 and the bromoether (**9**) at δ 1.09, may be attributable to the α oriented hydroxy group. The next stage of the synthesis is the introduction of the oxirane ring possessing the α configuration at the position of the double bond of the allyl alcohol (**10**) by Sharpless' method and hence the α configuration of the allylic hydroxy group is an essential requirement for this purpose. Conclusive evidence on the configurational assignment of this hydroxy group will be given in the next stage.

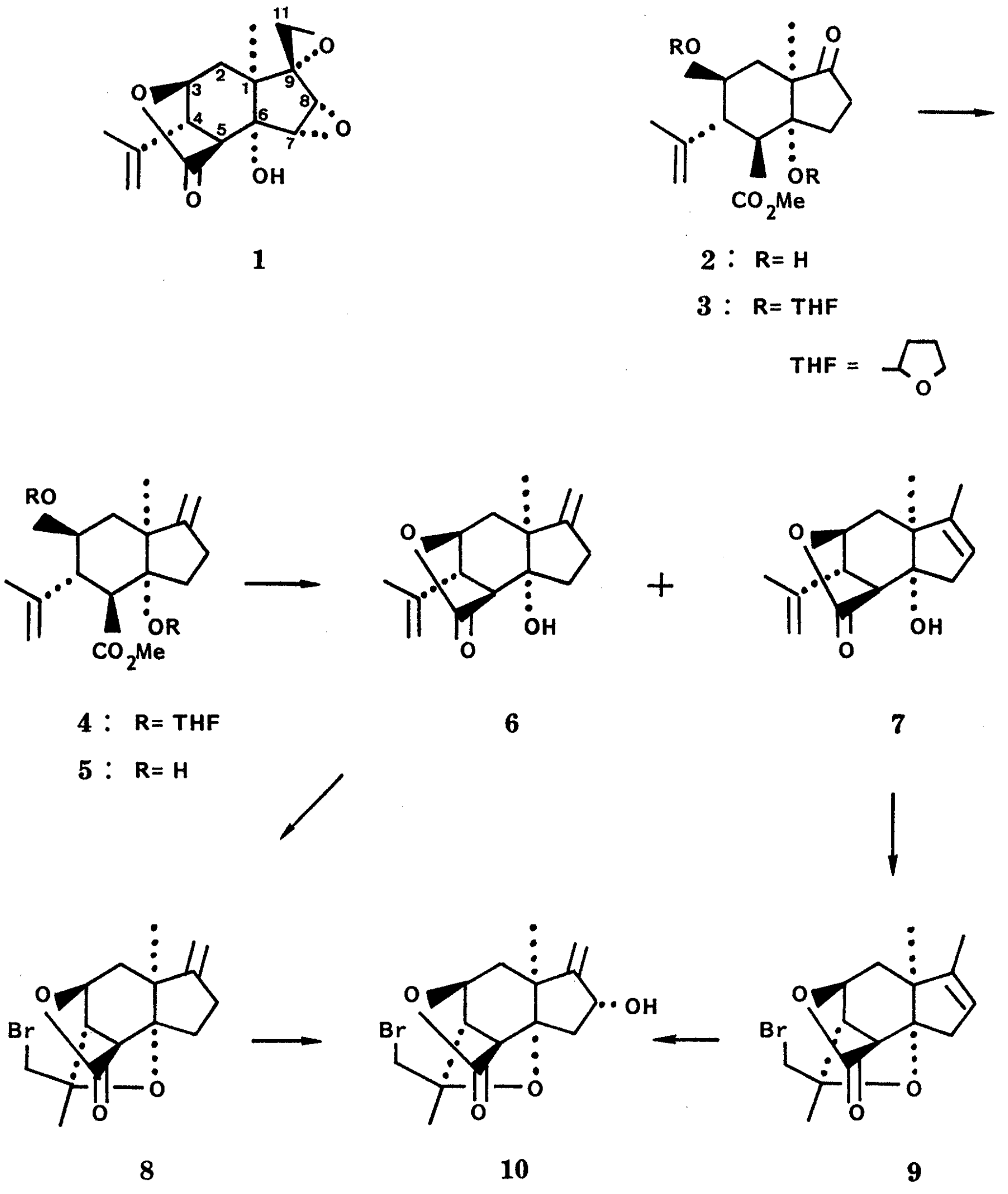
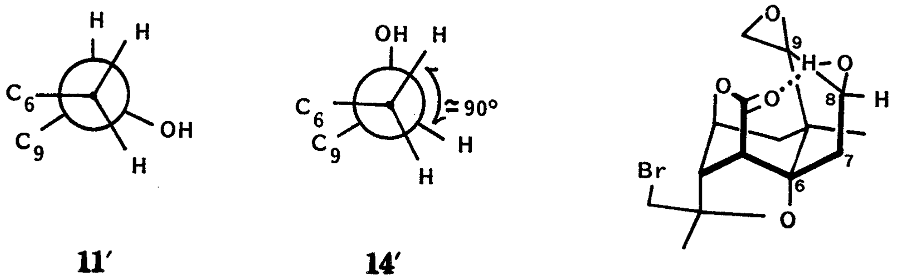


Chart 1

Epoxidation of the allyl alcohol (**10**) with *tert*-butyl hydroperoxide in the presence of VO(acac)$_2$$^{7)}$ gave stereospecifically the epoxy-alcohol (**11**) in 64% yield. The configuration of the hydroxy group of the allyl alcohol (**10**) and hence that of the oxirane ring of the epoxy-alcohol (**11**) were conclusively established as follows. Oxidation of **10** with Collins' reagent gave the enone (**12**) and epoxidation of **12** with *tert*-butyl hydroperoxide in the presence of Triton B⁸⁾ afforded selectively the epoxy-ketone (**13**). Alternatively, oxidation of the epoxy-alcohol (**11**) with Collins' reagent furnished the same epoxy-ketone (**13**) as above. Reduction of **13** with sodium borohydride afforded selectively the epoxy-alcohol (**14**), which is a diastereomer of the epoxy-alcohol (**11**). In the infrared (IR) absorption spectrum, the lowering of the lactone carbonyl frequency (1760 cm^{-1}) of **14** compared with that of **11** (1774 cm^{-1}) is attributable to the hydrogen bonding between the C_8 hydroxy group and the lactone carbonyl group, indicating the β configuration of the C_8 hydroxy group of **14**. Consequently, the configuration of the C_8 hydroxy group of the epoxy-alcohol (**11**) is α. Furthermore, inspection of the molecular models of **11** and **14** suggested a doublet signal of the C_8–H of **14** and a triplet signal of **11** in the ^{1}H-NMR spectra, as shown in Fig. 1. The observed triplet signal of the C_8–H of **11** at δ 4.19 with a J value of 8 Hz and the observed doublet signal of that of **14** at δ 4.21 with a J value of 8.5 Hz indicated the α configuration of the C_8 hydroxy group of **11** and the β configuration of that of **14**, respectively. The lowfield shift of the signal of the angular methyl group of **11** at δ 1.22 in the ^{1}H-NMR spectrum compared with that of **14** at δ 1.12 supported the configurational assignments of the hydroxy groups mentioned above. Since the α configuration of the C_8 hydroxy group of the allyl alcohol (**10**) was established, the α configuration of the oxirane ring of the epoxy-alcohol (**11**) was deduced from the reaction mechanism of Sharpless' epoxidation reaction.⁷⁾



11′ **14′** **14**

Fig. 1

In order to construct the second oxirane ring on the five-membered ring, the dehydration reaction of the epoxy-alcohol (**11**) was examined. Contrary to our expectation, heating of **11** with potassium bisulfate⁹⁾ afforded the enone (**12**). Dehydration of the epoxy-alcohol (**11**) using phosphorus oxychloride, methyl chlorosulfinate,¹⁰⁾ and dimethyl sulfoxide,¹¹⁾ and dehydration of **11** using Burgess' reagent,¹²⁾ which is effective for the dehydration of epoxy-alcohols, were examined but all were unsuccessful. When treated with thionyl chloride, the epoxy-alcohol (**11**) gave solely the chloride (**15**), in which the configuration of the C_8–Cl bond is not established. Next, a two-step dehydration procedure for the epoxy-alcohol (**11**) was tried. Treatment of **11** with mesyl chloride in the presence of 4-dimethylaminopyridine (DMAP) afforded the mesylate (**16**) in quantitative yield. When this was treated with potassium *tert*-butoxide in dimethyl sulfoxide (DMSO), the elimination reaction of **16** did not take place and S_N2-type replacement occurred to give the epoxy-alcohol (**14**). This result provided further evidence for the configuration of the C_8 hydroxy group of **11**, **14** and **16**. On the other hand, the mesylate (**16**) was heated with DBU in toluene under reflux to give the desired olefin (**17**) in good yield. This compound was highly labile under acidic or even neutral conditions. The elimination product, without purification, was immediately refluxed with excess *m*-chloroperbenzoic acid in a buffered methylene chloride solution containing sodium acetate¹³⁾ or sodium phosphate for 10 d to give selectively (±)-bromocoriamyrtin (**18**) in rather low yield. Forcing conditions for the epoxidation according to Kishi¹⁴⁾ did not improve

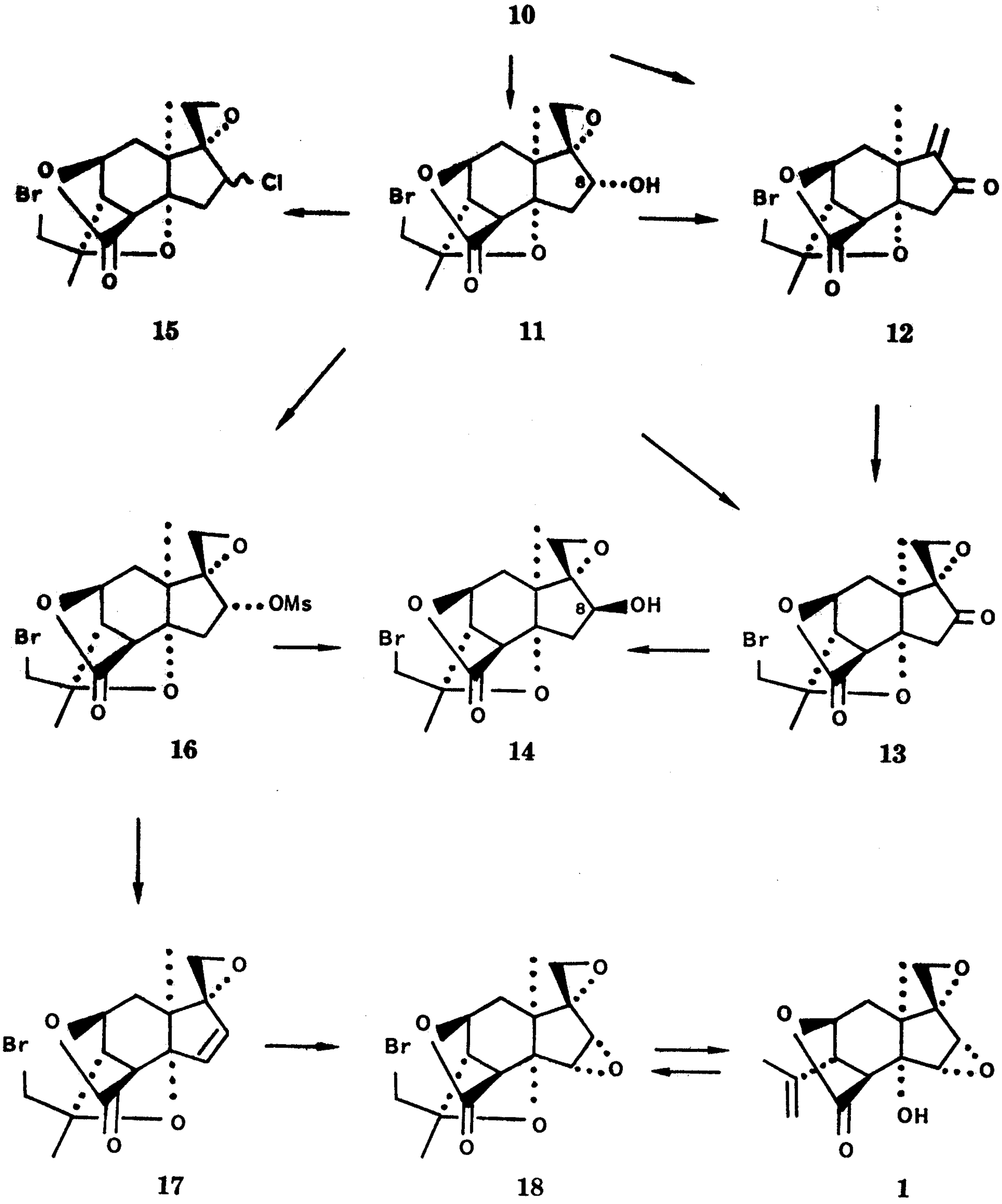


Chart 2

the yield of bromocoriamyrtin. Synthetic bromocoriamyrtin and that derived from natural coriamyrtin[15] exhibited identical IR ($CHCl_3$), ^1H-NMR ($CDCl_3$) and mass spectra (MS), and showed identical thin–layer chromatography (TLC), gas liquid chromatography (GLC), and high–performance liquid chromatography (HPLC) behavior. Finally, reductive debromination of **18** with zinc-copper couple[16] and ammonium chloride gave (±)-coriamyrtin, prisms, mp 224—225°C, in 64% yield. Synthetic (±)-coriamyrtin and natural coriamyrtin exhibited identical IR ($CHCl_3$) and ^1H-NMR ($CDCl_3$) spectra and showed identical TLC, GLC, and HPLC behavior.

The stereocontrolled total synthesis of (±)-coriamyrtin (**1**) has now been completed, starting from protoanemonin and 2-methyl-1,3-cyclopentanedione, through fifteen steps. In this synthesis isomeric products arising in some synthetic steps could also be utilized along the synthetic route. The information on the chemistry of the picrotoxane-type compounds accumulated during the course of the present study should open the way to the synthesis of other members of picrotoxane sesquiterpenes, especially those possessing two vicinal oxirane rings.

Experimental

All melting points are uncorrected. The infrared (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 200 MHz on a JEOL FX-200 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. Unless otherwise specified, 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. Merck, 70—230 mesh), Mallinckrodt silicic acid (100 mesh) or aluminum oxide 90 (nach Brockmann). Analytical GLC was carried out with a Hitachi 063 instrument using 1.5% SE-30 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. High-performance liquid chromatography (HPLC) was done on a Waters Associates ALC/GPC 244 instrument equipped with two kinds of μ-Porasil pre-packed columns (3.9 mm × 30 cm and 7.8 mm × 30 cm) for analytical and preparative pourposes, respectively.

The *exo*-Methylenic Compound (4)——A solution of potassium *tert*-amylate[3] (1.36 M solution in toluene; 0.33 ml) was added dropwise to a suspension of 160 mg of methyl triphenylphosphonium bromide in 5 ml of toluene and the mixture was refluxed with stirring for 30 min. A solution of 63 mg of the ditetrahydrofuranyl ether (3) in 2 ml of toluene was added to the above solution and the reaction mixture was refluxed for 4 h with stirring. After cooling, the mixture was quenched with an aq. NH_4Cl solution and extracted with chloroform. The chloroform extract was washed with water, dried, and evaporated to leave an oily residue, which was subjected to prep. TLC. The less polar band contained 45 mg of the *exo*-methylenic compound (**4**), and the more polar band contained 14 mg of the original ditetrahydrofuranyl ether (3). The yield of **4** was 72%. **4**: colorless oil. IR: 1725, 1642, 1025, 990, 914, 900 cm^{-1}. ^{1}H-NMR (60 MHz) δ: 1.13 (3H, s), 1.83 (3H, br s), 2.82 (1H, d, J=13, C_5-H), 3.53 (3H, s), 3.33—3.91 (5H, m), 4.73 (2H, br s), 5.02 (4H, br s). MS *m/z*: 420 (M$^+$), 350, 332, 262.

The Hydroxy Ester (5)——A mixture of 948 mg of **4**, 406 mg of oxalic acid, 2 ml of water, and 20 ml of methanol was stirred for 3 h at room temperature. After cooling, the mixture was mixed with NH_4Cl, salted out and extracted with chloroform. The chloroform extract was washed with water, dried and evaporated to give 850 mg of the residue. Purification of the residue by column chromatography on silica gel with chloroform furnished 610 mg of the hydroxy ester (**5**) as a colorless oil in 97% yield. **5**: IR: 3420, 1728, 1660, 908, 890 cm^{-1}. ^{1}H-NMR (60 MHz) δ: 1.20 (3H, s), 1.78 (3H, br s), 1.91 (1H, s, O$\underline{H}$), 2.44 (1H, dd, J=10, 13, C_4-H), 2.88 (1H, d, J=13, C_5-H), 3.62 (3H, s), 3.68 (1H, m, $W_{h/2}$=28, C_3-H), 4.87 (4H, br s). MS *m/z*: 280 (M$^+$), 262 (base), 244, 185. Calcd for $C_{16}H_{24}O_4$: 280.1674 (M$^+$). Found: 280.1674.

The Lactone (6) and the *endo*-Olefinic Lactone (7)——a) A mixture of 63 mg of **5**, 4 ml of 1 N NaOH and 2 ml of methanol was refluxed with stirring for 5 h. After cooling, the mixture was made acidic with 5% HCl, salted out and extracted with ethyl acetate. The extract was dried and evaporated under reduced pressure to leave the residue of the crude carboxylic acid, which without purification was used for the lactonization reaction. A mixture of the above residue, 286 mg of triethylamine and 20 ml of dry toluene was refluxed with stirring for 30 min. After addition of 532 mg of 2,4,6-trichlorobenzoyl chloride in 2 ml of toluene, the reaction mixture was refluxed with stirring for 3 h. The mixture was poured into ice-water and extracted with ethyl acetate. The organic extract was washed successively with dilute HCl, aq. $NaHCO_3$ and brine, then dried. Removal of the solvent under reduced pressure left an oily residue, which was purified by prep. TLC to give 32 mg of the lactone (**6**) as crystals in 57% yield. Recrystallization from ether gave a pure sample of **6**: mp 139°C. IR: 3560, 1777, 1648, 920, 892 cm^{-1}. ^{1}H-NMR (60 MHz) δ: 1.00 (3H, s), 1.94 (3H, br s), 2.78—3.15 (2H, m, $C_{4,5}$-H), 4.83 (4H, br s), 5.02 (1H, m, $W_{h/2}$=6, C_3-H). *Anal.* Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.70; H, 8.18.

b) Hydrolysis of 100 mg of **5**, followed by lactonization in the same manner as above afforded a mixture of the lactone (**6**) and the *endo*-olefinic lactone (**7**). Separation of the mixture by repeated prep. TLC furnished 32 mg of **6** from the eluate of the upper zone and 21 mg of the *endo*-olefinic lactone (**7**) from that of the lower zone. In this lactonization reaction, the *endo*-olefinic lactone (**7**) was obtained occasionally in the range of 0—24% yield depending upon subtle differences in the work-up operation. However, the total yield of **6** and **7** was invariably *ca.* 60%. **7**: mp 171°C (prisms from ether). IR: 3530, 1772, 1645, 906 cm^{-1}. ^{1}H-NMR (60 MHz) δ: 0.97 (3H, s), 1.60 (3H, br s), 1.92 (3H, br s), 2.20 (1H, s, O$\underline{H}$), 2.70—3.04 (2H, m, $C_{4,5}$-H), 4.80 (2H, br s), 5.02 (1H, m, $W_{h/2}$=6, C_3-H), 5.10 (1H, m, $W_{h/2}$=10, C_8-H). MS *m/z*: 248 (M$^+$), 230. Calcd for $C_{15}H_{20}O_3$: 248.1412 (M$^+$). Found: 248.1414.

The Bromoether (8)——A mixture of 95 mg of NBS, 133 mg of **6** and 5 ml of tetrahydrofuran (THF) was stirred for 40 min in the dark at room temperature. The mixture was quenched by addition of an aq. Na_2SO_3 solution and stirred at room temperature for 10 min. The mixture was extracted with chloroform and the extract was washed with brine, dried and evaporated to furnish 172 mg of the bromoether (**8**) as crystals in 98% yield. **8**: mp 136—137°C (prisms from ether). IR: 1775, 1670, 1038, 892 cm^{-1}. ^1H-NMR (200 MHz) δ: 0.96 (3H, s), 1.51 (3H, s), 2.88 (1H, d, $J=5.5$, C_5–H), 3.19 (1H, t, $J=5.5$, C_4–H), 3.48, 3.76 (each 1H, d, $J=10$), 4.83 (1H, m, $W_{h/2}=7$, C_3–H), 3.94 (1H, br s), 5.04 (1H, br s). *Anal.* Calcd for $C_{15}H_{19}BrO_3$: C, 55.03; H, 5.85. Found: C, 55.01; H, 6.00.

The Bromoether (9)——A mixture of 67 mg of the *endo*-olefinic lactone (**7**) and 3.5 ml of THF was treated with NBS and the same work-up as above gave 80 mg of residue. Purification of the residue by prep. TLC afforded 53 mg of the bromoether (**9**) as crystals in 85% yield. **9**: mp 148—151°C (prisms from ether). IR: 1773, 1037 cm^{-1}. ^1H-NMR (200 MHz) δ: 1.09 (3H, s), 1.55 (3H, s), 1.65 (3H, br s), 2.34, 2.70 (each 1H, br d, $J=16$, C_7–H_2), 2.87 (1H, d, $J=5.5$, C_5–H), 3.13 (1H, t, $J=5.5$, C_4–H), 3.50, 3.78 (each 1H, d, $J=10$), 5.00 (1H, m, $W_{h/2}=11$, C_3–H), 5.37 (1H, br s, C_8–H). MS *m/z*: 328, 326 (M^+). Calcd for $C_{15}H_{19}BrO_3$: 326.0517 (M^+). Found: 326.0520.

The Allyl Alcohol (10) from the Bromoether (8)——A solution of 20 mg of **8** in 2 ml of methylene chloride was added to a suspension of 7 mg of freshly sublimed selenium dioxide in *tert*-butyl hydroperoxide (0.24 M solution in methylene chloride; 1 ml) and the reaction mixture was stirred vigorously for 30 h at room temperature. The mixture was quenched by addition of an aq. Na_2SO_3 solution, stirred for 10 min, and then extracted with chloroform. The chloroform extract was washed successively with dilute HCl, dilute NaOH and brine, then dried. Evaporation of the solvent gave 25 mg of residue, which was subjected to prep. TLC. The original bromoether (**8**; 10 mg) was recovered from the upper zone and 10 mg of the allyl alcohol (**10**) was obtained as colorless crystals in 48% yield from the lower zone. The yield of **10** was 95% based on the consumed material. **10**: mp 210—211°C (plates from acetone–ether). IR: 3450, 1775, 1673, 1037, 910 cm^{-1}. ^1H-NMR (200 MHz) δ: 1.24 (3H, s), 1.52 (3H, s), 1.81 (1H, dd, $J=3$, 16, C_2–H), 2.49 (1H, dd, $J=1.5$, 16, C_2–H), 2.85 (1H, d, $J=5.5$, C_5–H), 3.19 (1H, t, $J=5.5$, C_4–H), 3.48, 3.75 (each 1H, d, $J=12$), 4.82 (1H, t, $J=8$, C_8–H), 5.05 (1H, m, $W_{h/2}=12.5$, C_3–H), 5.26, 5.32 (each 1H, br s). MS *m/z*: 344, 342 (M^+), 329, 327 (base). *Anal.* Calcd for $C_{15}H_{19}BrO_4$: C, 52.49; H, 5.58. Found: C, 52.74; H, 5.56.

The Allyl Alcohol (10) from the Bromoether (9)——A solution of 155 mg of **9** and 180 mg of rose bengal in 80 ml of methanol was irradiated with a 500W halogen lamp under a stream of oxygen at room temperature for 40 h. Removal of the solvent under reduced pressure left the residue, which was dissolved in 5 ml of methanol. An aqueous saturated Na_2SO_3 solution (10 ml) was added to the above solution and the mixture was stirred for 2 h, then extracted with chloroform. The extract was washed with brine, dried and evapoorated to give 180 mg of the residue. Separation of the residue by prep. TLC afforded 90 mg of the original bromoether (**9**) from the eluate of the upper zone and 59 mg of the allyl alcohol (**10**) as crystals in 36% yield from that of the lower zone. The yield of **10** was 81% based on the consumed material and a sample of **10** was shown to be identical with an authentic sample obtained from the preceding experiment.

The Epoxy-alcohol (11)——A mixture of 12 mg of **10**, 3 mg of vanadyloxy acetylacetonate, 0.5 ml of *tert* butyl hydroperoxide (2.08 M solution in benzene) and 2.5 ml of benzene was stirred for 4 h at room temperature. The usual work-up gave the residue, which was separated by prep. TLC. The epoxy-alcohol (**11**, 8 mg) was obtained as crystals in 64% yield from the upper zone together with 3 mg of the recovered original allyl alcohol (**10**). **11**: mp 174—175°C (prisms from ether–acetone). IR: 3520, 1774, 1037 cm^{-1}. ^1H-NMR (200 MHz) δ: 1.22 (3H, s), 1.51 (3H, s), 1.52 (1H, dd, $J=3$, 16, C_2–H), 1.89 (1H, dd, $J=2$, 16, C_2–H), 2.33 (1H, dd, $J=8$, 18, C_7–H), 2.39 (1H, dd, $J=8$, 18, C_7–H), 2.82 (1H, d, $J=5$, C_{11}–H), 2.96 (1H, d, $J=5.5$, C_5–H), 3.26 (1H, t, $J=5.5$, C_4–H), 3.27 (1H, d, $J=5$, C_{11}–H), 3.49, 3.72 (each 1H, d, $J=11$), 4.19 (1H, t, $J=8$, C_8–H), 5.04 (1H, m, $W_{h/2}=13$, C_3–H). *Anal.* Calcd for $C_{15}H_{19}BrO_5$: C, 50.14; H, 5.33. Found: C, 50.25; H, 5.26.

The Enone (12) from the Allyl Alcohol (10)——A mixture of 22 mg of **10**, 165 mg of Collins' reagent and 5 ml of methylene chloride was stirred for 4 h at room temperature. After cooling, the reaction mixture was made alkaline with dilute NH_4OH, and then extracted with chloroform. The extract was washed with dilute HCl and brine, then dried. Evaporation of the solvent gave the residue, which was purified by prep. TLC to furnish 20 mg of the enone (**12**) as a colorless oil in 91% yield. **12**: IR: 1776, 1730, 1645 cm^{-1}. ^1H-NMR (200 MHz) δ: 1.22 (3H, s), 1.56 (3H, s), 2.55, 2.92 (each 1H, d, $J=19$, C_7–H), 2.97 (1H, d, $J=5.5$, C_5–H), 3.26 (1H, t, $J=5.5$, C_4–H), 3.53, 3.80 (each 1H, d, $J=11$), 5.14 (1H, m, $W_{h/2}=11$, C_3–H), 5.40 (1H, s, C_{11}–H), 6.12 (1H, s, C_{11}–H). MS *m/z*: 342, 340 (M^+), 327, 325, 261. Calcd for $C_{15}H_{17}BrO_4$: 340.0310 (M^+). Found: 340.0315. Calcd for $C_{15}H_{17}Br^*O_4$: 342.0291. Found: 342.0299.

The Enone (12) from the Epoxy-alcohol (11)——A mixture of 19 mg of **11** and 100 mg of a powder of freshly fused potassium bisulfate was heated on an oil bath at 160°C for 2 min. Ice was added to the reaction mixture and the whole was extracted with chloroform. The extract was washed with water, dried and concentrated. The residue was separated by prep. TLC to afford 8 mg of the enone (**12**) in 44% yield and 6 mg of the recovered original epoxy-alcohol (**11**). A sample of this enone was identical with that derived from **10** described above.

The Epoxy-ketone (13) from the Enone (12)——A mixture of 8 mg of the enone (**12**), 0.02 ml of *tert*-butyl hydroperoxide (2.08 M solution in benzene), 24 mg of Triton B (free from methanol) and 2 ml of benzene was stirred for 1 h at room temperature. After addition of an aq. saturated Na_2SO_3 solution, the reaction mixture was stirred for 10 min. The mixture was neutralized with 2 N HCl and extracted with chloroform. The extract was washed with water, dried and evaporated to give the residue. Purification of the residue by prep. TLC furnished 6 mg of the epoxy-ketone (**13**) in 72% yield as crystals. **13**: mp 198—199°C (prisms from ether). IR: 1776, 1760 cm^{-1}. ^1H-NMR (200 MHz) δ: 1.28 (3H, s), 1.65 (3H, s), 3.08 (1H, d, $J=6$, C_{11}–H), 3.12 (1H, d, $J=5.5$, C_5–H), 3.23 (1H, d, $J=6$, C_{11}–H), 3.38 (1H, t, $J=5.5$, C_4–H), 3.59, 3.80 (each 1H, d, $J=11$), 5.16 (1H, m, $W_{h/2}=12$, C_3–H). MS *m/z*: 358, 356 (M^+), 341, 328, 249. Calcd for $C_{15}H_{17}BrO_5$: 356.0257 (M^+). Found: 356.0254. Calcd for $C_{15}H_{17}Br^*O_5$: 358.0238. Found: 358.0217.

The Epoxy-ketone (13) from the Epoxy-alcohol (11)——A mixture of 5 mg of **11**, 40 mg of Collins' reagent and 2 ml of methylene chloride was stirred for 8 h at room temperature. The same work-up as that used for oxidation of **10** described above gave the crude epoxy-ketone (**13**). Purification by prep. TLC afforded 3 mg of **13** in 60% yield; this product was identical with a sample derived from the enone (**12**) described above.

The Epoxy-alcohol (14) from the Epoxy-ketone (13)——Sodium borohydride (3 mg) was added to a stirred solution of 5 mg of **13** in 2 ml of ethanol at −50°C and the reaction mixture was stirred for 6.5 h at the same temperature. The usual work-up of the mixture gave the residue, which was purified by prep. TLC to yield 4 mg of the epoxy-alcohol (**14**) as crystals in 80% yield. **14**: mp 196°C (prisms from ether–acetone). IR: 3470, 1760 cm^{-1}. ^1H-NMR (200 MHz) δ: 1.12 (3H, s), 1.55 (3H, s), 3.00, 3.17 (each 1H, d, $J=5$, C_{11}–H), 3.10 (1H, d, $J=5.5$, C_5–H), 3.32 (1H, t, $J=5.5$, C_4–H), 3.48, 3.70 (each 1H, d, $J=10$), 4.21 (1H, d, $J=8.5$, C_8–H), 5.11 (1H, m, $W_{h/2}=11$, C_3–H). MS *m/z*: 360, 358 (M^+), 343, 312, 310 (base). Calcd for $C_{15}H_{19}BrO_5$: 358.0414 (M^+). Found: 358.0389.

The Chloride (15)——A mixture of 8 mg of **11**, 2 drops of thionyl chloride and 1.0 ml of pyridine was stirred for 4.5 h at 0°C. After addition of an aq. NH_4Cl solution, the mixture was made acidic with dilute HCl and extracted with chloroform. The extract was washed with water, dried and evaporated to yield 10 mg of the residue, which was purified by prep. TLC. The pure chloride (**15**, 6 mg) was obtained as a colorless oil in 71% yield. **15**: IR: 1778 cm^{-1}. ^1H-NMR (200 MHz) δ: 1.25 (3H, s), 1.52 (3H, s), 2.76, 2.88 (each 1H, d, $J=5$, C_{11}–H), 2.95 (1H, d, $J=5.5$, C_5–H), 3.25 (1H, t, $J=5.5$, C_4–H), 3.47, 3.70 (each 1H, d, $J=10$), 4.90 (1H, m, C_8–H), 5.02 (1H, m, $W_{h/2}=11$, C_3–H). MS *m/z*: 341, 256 (base).

The Mesylate (16)——A mixture of 40 mg of **11**, 5 mg of 4-dimethylaminopyridine, 0.1 ml of methanesulfonyl chloride, 1.5 ml of benzene, and 1 ml of pyridine was stirred for 2.5 h at 0°C. After addition of an aq. NH_4Cl solution, the mixture was extracted with chloroform and the extract was washed with dilute HCl, aq. $NaHCO_3$ and brine, then dried. Removal of the solvent left the crude mesylate as crystals, which were recrystallized from acetone–ether to furnish 49 mg of the mesylate (**16**) quantitatively. **16**: mp 194—196°C. IR: 1772, 1357, 1173, 955 cm^{-1}. ^1H-NMR (200 MHz) δ: 1.25 (3H, s), 1.52 (3H, s), 1.54 (1H, dd, $J=3$, 17, C_2–H), 1.83 (1H, dd, $J=2$, 17, C_2–H), 2.52, 2.57 (each 1H, dd, $J=7.5$, 21, C_7–H_2), 2.96 (1H, d, $J=5.5$, C_5–H), 2.92, 3.21 (each 1H, d, $J=5$, C_{11}–H), 3.09 (3H, s), 3.26 (1H, t, $J=5.5$, C_4–H), 3.48, 3.70 (each 1H, d, $J=11$), 5.05 (1H, m, $W_{h/2}=10$, C_3–H), 5.12 (1H, t, $J=7.5$, C_8–H). *Anal.* Calcd for $C_{16}H_{21}BrO_7S$: C, 43.94; H, 4.84. Found: C, 44.20; H, 4.80.

The Epoxy-alcohol (14) from the Mesylate (16)——A mixture of 5 mg of the mesylate (**16**), 1 mg of potassium *tert*-butoxide, 1.0 ml of DMSO and 0.5 ml of THF was stirred for 2.5 h at room temperature. After addition of an aq. NH_4Cl solution, the mixture was made acidic with dilute HCl and extracted with ether. The extract was washed with brine, dried and evaporated to give 4 mg of the residue, which was subjected to prep. TLC. A pure sample of the epoxy-alcohol (**14**; 3 mg) was obtained in 73% yield as crystals and this sample was shown to be identical with an authentic one obtained by sodium borohydride reduction of **13**.

(±)-Bromocoriamyrtin (18) *via* the Olefin (17)——A mixture of 40 mg of the mesylate (**16**), 8 drops of DBU and 4 ml of toluene was refluxed on an oil bath for 35 h, then cooled. An aqueous solution of NH_4Cl was added to the above solution and the mixture was extracted with chloroform. The extract was washed with dilute HCl and brine, then dried and evaporated to give 32 mg of the crude olefin (**17**) quantitatively as an oil. Since this olefin turned out to be highly labile even on standing, the oily residue of **17** was used for the next epoxidation reaction immediately without purification. **17**: oil. IR: 1773 cm^{-1}. ^1H-NMR (200 MHz) δ: 1.24, 1.58 (each 3H, s), 1.61 (1H, dd, $J=3$, 18, C_2–H), 1.97 (1H, dd, $J=2$, 18, C_2–H), 2.82, 3.12 (each 1H, d, $J=4$, C_{11}–H_2), 2.92 (1H, d, $J=5.5$, C_5–H), 3.24 (1H, t, $J=5.5$, C_4–H), 3.52, 3.78 (each 1H, d, $J=11$), 5.07 (1H, m, $W_{h/2}=12$, C_3–H), 5.74, 6.10 (each 1H, d, $J=6$, $C_{7\text{ or }8}$–H). A mixture of 82 mg of the above residue of **17**, 150 mg of freshly fused sodium acetate, 200 mg of *m*-chloroperbenzoic acid and 10 ml of methylene chloride was stirred under reflux for 10 d, then cooled. Excess reagent was decomposed with an aq. Na_2SO_3 solution, and the reaction mixture was stirred for 30 min. The mixture was extracted with chloroform and the extract was washed with aq. $NaHCO_3$ and brine, then dried. Removal of the solvent left the crude residue, which was subjected to prep. TLC. The crude original olefin (**17**; 30 mg; 65% purity by GLC analysis) was recovered from the the eluate of the upper zone and crude (±)-bromocoriamyrtin was obtained from that of the lower zone. The prep. HPLC of this crude product with methylene chloride–hexane (4 : 6) as an eluent gave 1.5 mg of pure (±)-bromocoriamyrtin (**18**) as a colorless oil. The yield of **18** was 3% based on the consumed material. In this reaction, no other isomer was detected on TLC or by

GLC analysis. A sample of (±)-bromocoriamyrtin was identical with that derived from natural coriamyrtin15) in terms of IR ($CHCl_3$), ^1H-NMR ($CDCl_3$) and MS. Both samples showed identical TLC, GLC, and HPLC behavior. The molecular ion of the synthetic sample was in good agreement with the theoretical value in the high resolution MS. (±)-Bromocoriamyrtin; colorless oil. IR: 1778, 1041 cm^{-1}. ^1H-NMR (200 MHz) δ: 1.25 (3H, s), 1.44 (1H, dd, $J=3$, 17, C_2–H), 1.58 (3H, s), 1.84 (1H, dd, $J=2$, 17, C_2–H), 2.86, 3.08 (each 1H, d, $J=4$, C_{11}–H), 3.14 (1H, d, $J=5$, C_5–H), 3.28 (1H, t, $J=5$, C_4–H), 3.29 (1H, d, $J=3$, $C_{7\ \mathrm{or}\ 8}$–H), 3.49 (1H, d, $J=11$), 3.68 (1H, d, $J=3$, $C_{7\ \mathrm{or}\ 8}$–H), 3.74 (1H, d, $J=11$), 5.08 (1H, m, $W_{h/2}=11$, C_3–H). MS *m/z*: 358, 356 (M^+), 277 (M^+-Br; base), 233. Calcd for $C_{15}H_{17}BrO_5$: 356.0257 (M^+). Found: 356.0241. Calcd for $C_{15}H_{17}Br^*O_5$: 358.0238. Found: 358.0228.

(±)-Coriamyrtin (**1**)——A mixture of 4.0 mg of (±)-bromocoriamyrtin (**18**), 5 mg of Zn–Cu couple,16) 5 mg of NH_4Cl, 1 drop of water and 1 ml of ethanol was refluxed with stirring for 1.5 h. After cooling, the mixture was extracted with chloroform and the extract was washed with brine, dried and evaporated to afford 3 mg of the residue. Purification of the residue by prep. TLC yielded 2.0 mg of (±)-coriamyrtin (**1**) as crystals in 64% yield. Recrystallization from acetone–ether furnished a pure sample of (±)-coriamyrtin (**1**) as prisms, which melted at 224—225°C. This synthetic (±)-coriamyrtin and natural coriamyrtin exhibited identical IR ($CHCl_3$), ^1H-NMR ($CDCl_3$) spectra and showed identical TLC, GLC and HPLC (methylene chloride–hexane, 1: 1) behavior. (±)-Coriamyrtin: mp 224—225°C. IR: 3580, 1773, 910 cm^{-1}. ^1H-NMR (200 MHz) 1.16 (3H, s), 1.66 (1H, dd, $J=4$, 16, C_2–H), 1.80 (1H, dd, $J=1.5$, 16, C_2–H), 1.95 (3H, s), 2.90 (1H, d, $J=4$, C_{11}–H), 3.08 (1H, m, $W_{h/2}=10$, C_4–H), 3.10 (1H, d, $J=4$, C_{11}–H), 3.15 (1H, d, $J=4.5$, C_5–H), 3.29, 3.76 (each 1H, d, $J=3$, $C_{7\ \mathrm{or}\ 8}$–H), 4.68 (1H, br s), 4.88 (1H, m, $W_{h/2}=10$, C_3–H), 4.99 (1H, br s).

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 grateful to Prof. T. Shingu, Faculty of Pharmaceutical Sciences, Kobe Gakuin University, for the ^1H-NMR spectral measurements and valuable discussions on the spectra. We are also indebted to Prof. T. Okuda, Faculty of Pharmaceutical Sciences, Okayama University, for his generous gift of an authentic sample of natural coriamyrtin.

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