Chem. Pharm. Bull. **45**(9) 1428—1434 (1997) Vol. 45, No. 9

Synthetic Study of Piericidins. I. Synthesis of the Side Chain of Piericidin B_1

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Received March 21, 1997; accepted May 7, 1997

The side chain of piericidin B_1 having four (*E*)-olefinic linkages was prepared. The coupling reaction of the non-conjugated aldehyde (22) derived from 4,4-dimethoxy-2-butanone and the sulfone (13) afforded a diastereomeric mixture of the hydroxy sulfone (27). Benzoylation of 27 followed by reductive olefin formation with sodium amalgam gave the desired all-*trans*-tetraene (29) possessing an (*E*)-C(5)–C(6) double bond, which was transformed to the alcohol (1) corresponding to the side chain of piericidin B_1.

Key words piericidin B_1 side chain; Julia coupling; reductive olefin-formation; β,γ-unsaturated aldehyde; (*E*,*Z*)-olefin-isomerization

Piericidin A_1 and B_1, inhibitors of the electron-transport system in the respiratory chain, have been isolated as metabolites of *Streptomyces mobaraensis* and *S. pactam*.[1] The respiratory chain includes the section so-called complex I, responsible for the oxidation of NADH to NAD^+, and this complex is inhibited by various natural products, *e.g.*, rotenone and barbiturates, in addition to piericidins, all of which bind at the same site in mitochondria in a competitive manner.[2] Piericidins contain a 2,3,5,6-tetrasubstituted 4-pyridinol ring, whose substitution pattern is similar to that of ubiquinone (coenzyme Q), which plays a role as a hydrogen acceptor in the oxidation of NADH to NAD^+ in mitochondria. Although piericidins were expected to be useful for studies of the respiratory mechanism , this has not been feasible because of their chemical instability and high toxicity to mammals. From this point of view, a synthesis of piericidin analogues, possessing a simple aromatic ring and the same side chain as piericidin B_1, is of interest. In this paper, we wish to report a preparation of the side chain of piericidin B_1, which has a long side chain at the 2-position of the pyridinol ring (Chart 1).

The side chain of piericidin B_1 contains two chiral centers at the C_9- and C_{10}-positions and four (*E*)-olefinic linkages, of which two double bonds (C_2- and C_{11}-positions) are isolated and the other two (C_5- and C_7-positions) are conjugated (Chart 1). Our synthethic plan was based on the Julia procedure, involving coupling of the sulfone **13** (segment A) synthesized from tiglic aldehyde in 8 steps and the non-conjugated aldehyde **22** (segment B) prepared from 4,4-dimethoxy-2-butanone, as shown in Chart 1.

Preparation of Segment A Reaction of tiglic aldehyde and methyl α-bromopropionate in the presence of zinc metal afforded a mixture of the *anti*-α-methyl-β-hydroxy ester **2** and *syn*-α-methyl-β-hydroxy ester **3** (*anti*-**2**:*syn*-**3**=1:1) in 91% yield. Both compounds were separable by silica gel column chromatography. The less polar compound is *syn*-**3** and the more polar compound is *anti*-**2**, which was identical with optically active *anti*-**2** prepared by the aldol condensation of tiglic aldehyde and (4*S*)-(−)-isopropyl-2-oxazolidinone, formed from L-valinol.[3] Furthermore, the relative configuration between the 2- and 3-positions of α-methyl-β-hydroxy esters **2** or **3** was supported as follows: Swern oxidation of a mixture of **2** and **3** gave the β-keto ester **4**, which was reduced with zinc borohydride to give *syn*-**3** with high diastereoselectivity (>99%), because zinc borohydride reduction of α-methyl-β-keto ester was reported to give predominantly *syn*-α-methyl-β-hydroxy ester[4] (Chart 2). On the other hand, reduction of **4** with tetra-*n*-butylammonium borohydride[5] mainly gave *anti*-**2** (*anti*-**2**:*syn*-**3**=7:1). *Anti*-configuration is necessary for preparation of the side chain **1**. Methylation of *anti*-**2** afforded the β-methoxy ester **5** (79% yield), which was reduced with diisobutyl aluminum hydride (DIBAL) to give the alcohol **6** in 95%

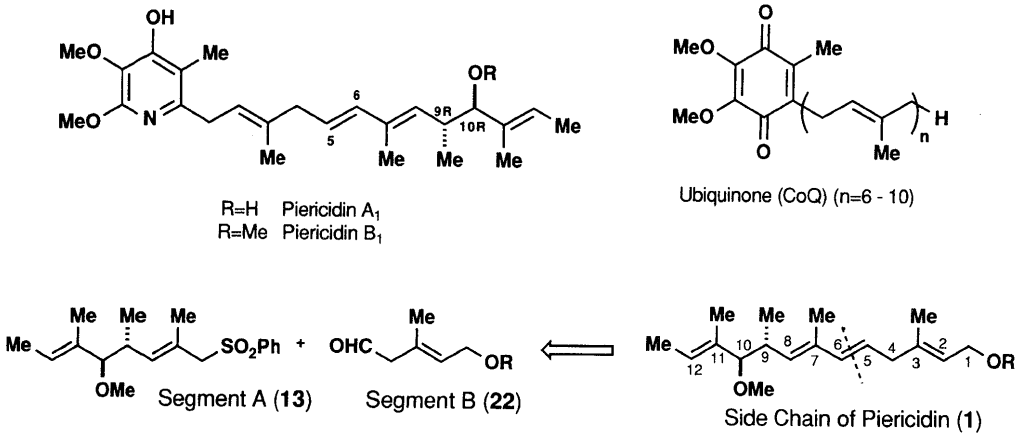

Chart 1

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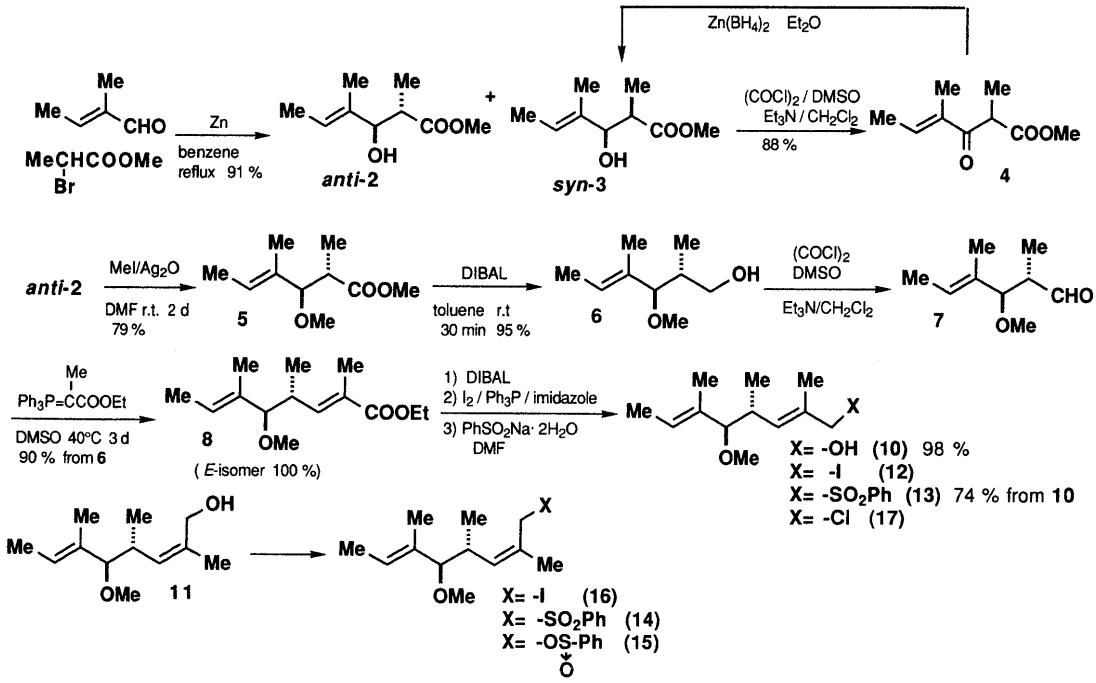


Chart 2

yield. Swern oxidation of **6** provided the aldehyde **7** without epimerization at the α-position. The reaction of crude **7** and triethyl 2-phosphonopropionate in the presence of *n*-butyllithium in tetrahydrofuran (THF) afforded the (*E*)-ester **8** together with the (*Z*)-ester **9** (**8**:**9**=1:2), which is similar to the result reported by Cox and Whiting.[6] An inseparable mixture of the (*E*,*Z*)-ester (**8**, **9**) was reduced with DIBAL to give the separable (*E*,*Z*)-alcohol (**10**, **11**). Determination of the geometry was done by ^{1}H-NMR (proton nuclear magnetic resonance) spectroscopy: 5.0% nuclear Overhauser effect (NOE) was observed at 1-H (δ 4.00 ppm) in the (*E*)-alcohol **10** on irradiation of 3-H (δ 5.31 ppm). In the case of the (*Z*)-alcohol **11**, irradiation of 3-H (δ 5.05 ppm) gave 3.2% NOE at the methyl group (δ 1.83) at the 2-position. On the other hand, when the crude aldehyde **7** was treated with carbethoxyethylidene triphenylphosphorane in dimethylsulfoxide (DMSO) at 40 °C for 3 d, the α,β-unsaturated ester **8** ((2*E*)-isomer 100%) was obtained in 90% yield from **6** (Chart 2). The (2*E*)-alcohol **10** was treated with iodine–triphenylphosphine–imidazole in acetonitrile–ether in the dark at 0 °C for 30 min to give the (2*E*)-iodide **12** quantitatively. The reaction of crude (2*E*)-**12** with sodium benzenesulfinate in dimethylformamide (DMF) in the dark at 0 °C for 3 h afforded a single product, the (2*E*)-sulfone **13** corresponding to segment A, in 74% yield from **10**. In room light, a different result was obtained. When the (2*E*)-alcohol **10** was treated in the above manner in the light, the (2*E*)-sulfone **13** (67% yield from **10**) was obtained together with the (2*Z*)-sulfone **14** (14% yield from **10**). The geometry of **13** and **14** at the 2-position was determined by means of an NOE experiment (see Experimental). The structure of the (2*Z*)-sulfone **14** was confirmed by direct comparison with a standard sample prepared by the reaction of the (2*Z*)-alcohol **11** and sodium benzenesulfinate *via* the iodide **16** (Chart 2). Benzenesulfinate ion is an ambident anion, so the sulfinate ester might be formed. However the alternative structure, (2*Z*)-sulfinate **15**, was ruled out by an X-ray analysis (see Experimental). The reason why the (2*Z*)-sulfone **14** was obtained from the (2*E*)-alcohol **10** *via* the iodide is attributable to the ease of *E*,*Z*-olefin isomerization at the 2-position of (2*E*)-**12** to afford (2*Z*)-**16** in the light. Indeed, when a chloroform solution of pure (2*E*)-**12**, obtained by means of quick silica gel chromatography in the dark, was allowed to stand for 2 h under light at ambient temperature, it changed to a mixture of (2*Z*)-**16** and (2*E*)-**12** (**16**:**12**=2:1). Although the iodide **12** could not be easily handled, it is a better substrate than other allyl halides such as the chloride **17**. Chlorination of the (2*E*)-alcohol **10** with *N*-chlorosuccinimide–triphenylphosphine in acetonitrile at 0 °C for 30 min gave the chloride **17**, which reacted with sodium benzenesulfinate in DMF at ambient temperature overnight in the dark to give the (2*E*)-sulfone **13** in only 56% yield from **10**.

Preparation of Segment B The non-conjugated aldehyde **22** corresponding to the C(1)–C(5) unit of the side chain of piericidin B_1 was prepared starting from 4,4-dimethoxy-2-butanone in 4 steps (Chart 3). Reaction of 4,4-dimethoxy-2-butanone and trimethylphosphonoacetate in the presence of *n*-butyllithium in THF afforded a mixture of the (*E*)-ester **18** and (*Z*)-ester **19** (**18**:**19**=7:3) in 97% yield. They were separated and the geometry of (*E*)-**18** and (*Z*)-**19** was confirmed by NOE experiments as shown in Chart 3. Reduction of (*E*)-**18** with DIBAL provided an allylalcohol **20** (92% yield), which was reacted with pivaloyl chloride in the presence of diisopropylethylamine to afford the pivaloyl ester **21** in 98% yield. To obtain the non-conjugated aldehyde **22** by acid hydrolysis of the dimethyl acetal moiety, various kinds of hydrolysis conditions were checked. When a solution of **21** in isopropanol including hydrochloric acid was allowed to stand overnight at ambient temperature, the undesired conjugated aldehyde **23** was obtained quantitatively. A

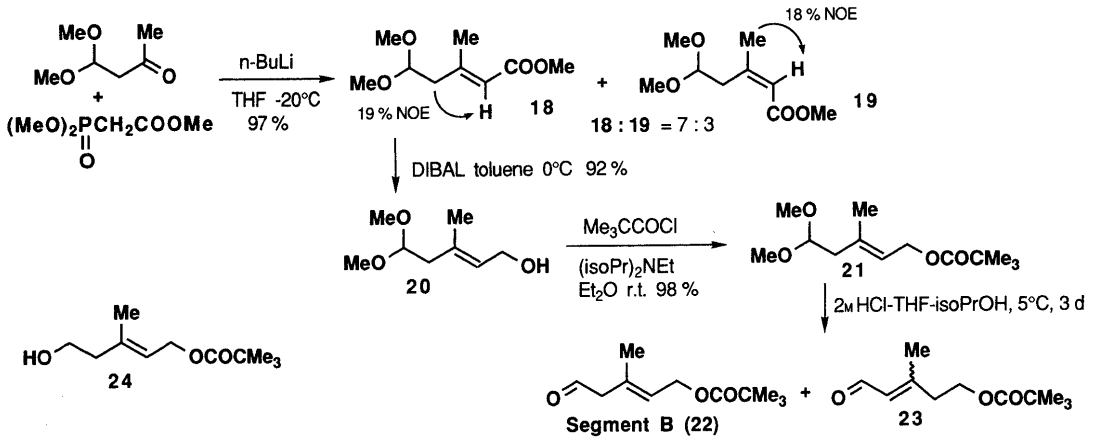


Chart 3

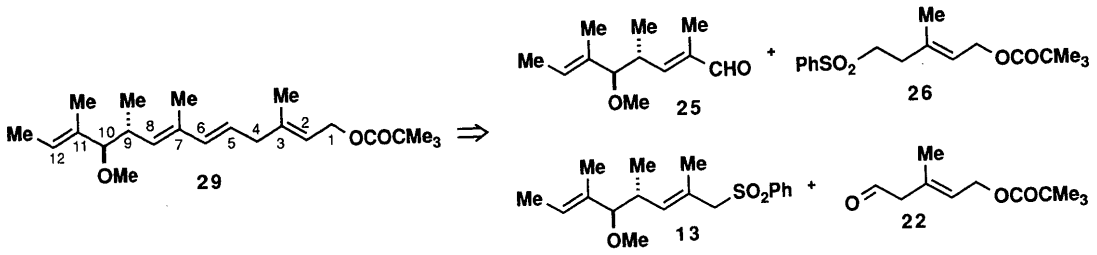


Chart 4

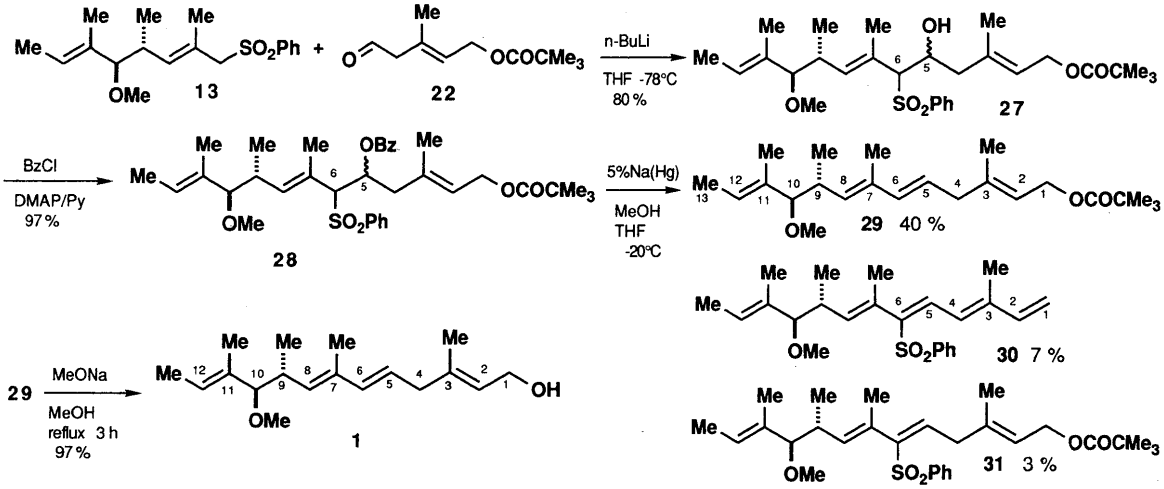
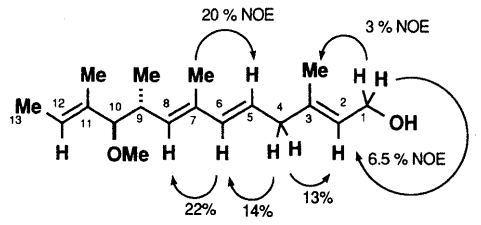


Chart 5

brief treatment at ambient temperature afforded a mixture of **22** and **23** (5 : 1), along with the starting material **21**. Thus, olefin-isomerization (change of β,γ-unsaturated ester to α,β-unsaturated ester) proceeded in parallel with hydrolysis of the acetal function at ambient temperature. Finally we could obtain the non-conjugated aldehyde **22** along with a small amount of **23** by controlling the reaction temperature at 5 °C for 3 d. Therefore, the crude aldehyde containing a small amount of **23** was employed without further purification. An attempt to prepare non-conjugated **22** by oxidation (pyridium chlorochlomate or Swern oxidation) of the alcohol **24**, which was synthesized starting from 4-hydroxy-2-butanone through the same route as used for **21**, was unsuccessful.

Preparation of Side Chain of Piericidin B_1 (1) Formation of the desired olefin with (*E*)-geometry between the C_5- and C_6- positions could be achieved by the Julia method.[7] In our strategy, two routes are possible as shown in Chart 4. One is a coupling between the aldehyde **25** corresponding to the C(6)–C(13) unit, and the sulfone **26** corresponding to the C(1)–C(5) unit. The other is a reverse coupling between the sulfone **13** and aldehyde **22**. Swern oxidation of **10** gave the aldehyde **25**, which was treated with the sulfone **26** prepared from **24** in the presence of *n*-butyllithium in THF to provide the recovered aldehyde **25**. On the other hand, the corresponding reaction of **13** and crude **22** under the same conditions proceeded smoothly to afford a diastereomeric mixture of the hydroxy-sulfone **27** in 80% yield. Then benzoylation of **27** with benzoyl chloride in the presence of 4-(dimethylamino)pyridine (DMAP) gave a diasteromeric mixture of **28** in good yield (Chart 5). But one-pot synthesis



5-position δ 5.49 ppm, 1H, dt, $J_{5,6}$=16.0 Hz, $J_{5,4}$=7.0 Hz
6-position δ 6.10 ppm, 1H, d, J = 16.0 Hz

1 in $CDCl_3$ (400MHz)

Chart 6

of **28** from **13** and crude **22** by the above-mentioned procedure resulted in a low overall yield (13%). However, reductive *trans*-olefin formation at the 5-position of **28** using sodium amalgam at 0 °C in methanol–THF gave a small amount of the desired (*E*)-tetraene **29** in 6% yield, together with the pentaene **30** (36% yield). Formation of **30** means that an elimination reaction predominated over reductive olefin-formation because of the basic condition. When the same olefin formation from **28** was carried out at −20 °C, the desired **29** (40% yield) and **30** (7% yield) were obtained along with **31** (3% yield). Finally, the side chain of piericidin B_1 (**1**) was obtained in good yield by methanolysis of **29**. The structure of **1** was confirmed by ^{1}H-NMR and mass spectroscopy. The chemical shifts of **1** in ^{1}H-NMR (CCl_4) were similar to those of the natural piericidine B_1 side chain except for the 1-position, and an NOE experiment suggested all (*E*)-tetraene form, as shown in Chart 6.

In conclusion, the stereocontrolled synthesis of the side chain **1** corresponding to that of piericidin B_1 was achieved. In the forthcoming paper the preparation of a piericidin analogue will be described.

Experimental

The melting points were determined on Yanaco MP-S3 micro melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO FT/IR-300 spectrometer. ^{1}H-NMR spectra were recorded on a JEOL EX-400 (400 MHz) spectrometer with tetramethylsilane as an internal standard. The following abbreviations are used: singlet (s), doublet (d), triplet (t), quartet (q), double doublet (dd), double triplet (dt), multiplet (m), and broad (br). High-resolution mass spectra (HR-MS) were obtained with a JEOL JMS-AM II 50 spectrometer. Mass spectra (MS) were recorded on a JEOL JMS-AM II 50 (EI) or JEOL JMS-DX303 (FAB) mass spectrometer. For column chromatography, Silica gel 60 (Merck 1.07734) was employed.

Reaction of Tiglic Aldehyde and Methyl α-Bromopropionate Fresh zinc dust was used after activation by washing 5% HCl, water, ethanol, and ether, followed by drying. Zinc dust (7.85 g, 0.12 mol) was added to a benzene solution (200 ml) of tiglic aldehyde (8.41 g, 0.10 mol) and methyl α-bromopropionate (18.37 g, 0.11 mol), and the whole was warmed gradually to about 80 °C. After the violent reaction ceased, the reaction mixture was refluxed for 1.0 h. The solution was cooled, 2 M HCl (50 ml) was added to it and the precipitate was filtered off. The filtrate was washed with 2 M HCl, 7% aqueous $NaHCO_3$ and H_2O successively. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The above mentioned procedure was conducted twice. The obtained mixture of *anti*-**2** and *syn*-**3** (34.38 g) was subjected to column chromatography (hexane/AcOEt, 7 : 1) to afford *syn*-**3** (15.50 g, 45.0%) and *anti*-**2** (15.85 g, 46.0%), each as a colorless oil. *Anti*-**2**: *Anal.* Calcd for $C_9H_{16}O_3 \cdot 1/4H_2O$: C, 61.17; H, 9.41. Found: C, 61.02; H, 9.65. EI-MS *m/z*: 172 (M^+). IR (neat): 3440, 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.01 (3H, d, *J*=7.0 Hz, C_2-Me), 1.61 (3H, s, C_4-Me), 1.63 (3H, d, *J*=7.0 Hz, 6-H), 2.49 (1H, br s, OH), 2.65 (1H, dq, *J*=7.0, 9.0 Hz, 2-H), 3.73 (3H, s, –COOMe), 4.09 (1H, d, *J*=9.0 Hz, 3-H), 5.52 (1H, q, *J*=7.0 Hz, 5-H). *Syn*-**3**: *Anal.* Calcd for $C_9H_{16}O_3 \cdot 1/2H_2O$: C, 59.65; H, 9.46. Found: C, 59.88; H, 9.69. EI-MS *m/z*: 172 (M^+). IR (neat): 3440, 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.14 (3H, d, *J*=7.0 Hz, C_2-Me), 1.59 (3H, s, C_4-Me), 1.62 (3H, d, *J*=7.0 Hz, 6-H), 2.70 (1H, dq, *J*=5.0, 7.0 Hz, 2-H), 3.68 (3H, s, –COOMe), 4.26 (1H, d, *J*=5.0 Hz, 3-H), 5.55 (1H, q, *J*=7.0 Hz, 5-H).

Preparation of the β-Ketoester 4 Under an Ar atmosphere, a solution of oxalyl chloride (15.18 g, 0.12 mol) in CH_2Cl_2 (120 ml) was cooled to −78 °C, and DMSO (18.72 g, 0.24 mol) in CH_2Cl_2 (30 ml) was added dropwise *via* a syringe. After 30 min, a solution of a mixture of *anti*-**2** and *syn*-**3** (10.32 g, 0.06 mol) in CH_2Cl_2 (30 ml) was introduced at a slow rate. After an additional 30 min, triethylamine (48.36 g, 0.50 mol) was added, and the mixture was warmed to −20 °C. Then, CH_2Cl_2 (400 ml) and H_2O (300 ml) were added under stirring. The organic layer was washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue (13.01 g) was subjected to column chromatography (hexane/AcOEt, 15 : 1) to afford **4** as a colorless oil (8.99 g, 88.0%). HR-MS *Anal.* Calcd for $C_9H_{14}O_3$ (M^+, *m/z*): 170.0943. Found: 170.0948. IR (neat): 1730, 1660 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.36 (3H, d, *J*=7.0 Hz, C_2-Me), 1.81 (3H, s, C_4-Me), 1.89 (3H, d, *J*=7.0 Hz, 6-H), 3.69 (3H, s, –COOMe), 4.17 (1H, q, *J*=7.0 Hz, 2-H), 6.80 (1H, q, *J*=7.0 Hz, 5-H).

Reduction of the β-Ketoester 4 with $Zn(BH_4)_2$ Under an Ar atmosphere at −20 °C, 0.13 M $Zn(BH_4)_2/Et_2O$ solution (25 ml, 0.003 mol) was added to a solution of **4** (0.34 g, 0.002 mol) in absolute ether (3 ml) with stirring. After 1.5 h, Et_2O (20 ml) and 2 M HCl (5 ml) were added to the reaction mixture with stirring. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give *syn*-**3** (0.27 g, 79.3%). Only signals of *syn*-**3** was observed in the ^{1}H-NMR ($CDCl_3$) spectrum of the crude sample.

Reduction of the β-Ketoester 4 with *n*-Bu_4NBH_4 A solution of *n*-Bu_4NBH_4 (9.10 g, 0.035 mol) in MeOH (50 ml) was added to a solution of **4** (4.00 g, 0.024 mol) in MeOH (20 ml) at −20 °C with stirring. After 30 min, acetone (5 ml) was added to quench excess reducing reagent. After an additional 30 min, Et_2O (200 ml) and 5% HCl (50 ml) were added with stirring. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a crude oil (3.56 g), which was subjected to column chromatography (hexane/AcOEt, 15 : 1—7 : 1) to afford *syn*-**2** (0.32 g, 7.8%), *anti*-**3** (2.41 g, 59.5%) and 2,4-dimethyl-3-hydroxyhexenol-4 (2,3-anti configuration) (0.43 g, 12.7%). The third compound was identical with the *anti*-diol, prepared by reduction of *anti*-**2** with DIBAL. 2,4-Dimethyl-3-hydroxyhexenol-4: Colorless oil. FAB-MS *m/z*: 145 (MH^+). ^{1}H-NMR ($CDCl_3$) δ: 0.68 (3H, d, *J*=7.0 Hz, C_2-Me), 1.61 (3H, s, C_4-Me), 1.62 (3H, br d, *J*=7.0 Hz, 6-H), 1.86—1.95 (1H, m, 2-H), 3.85 (1H, d, *J*=9.0 Hz, 3-H), 5.46 (1H, br q, *J*=6.0 Hz, 5-H).

Methylation of *anti*-2 A solution of *anti*-**2** (15.31 g, 0.089 mol) in DMF (90 ml) was added to a vigorously stirred suspension of Ag_2O (30.90 g, 0.13 mol) under ice cooling, then methyl iodide (37.90 g, 0.27 mol) was added to the mixture at a slow rate. The whole was stirred for 2 d at ambient temperature. After filtration to remove excess Ag_2O and silver iodide, the filtrate was concentrated. The residue (27.70 g) was subjected to column chromatography (hexane/AcOEt, 20 : 1) to afford **5** as a colorless oil (13.10 g, 79.0%). EI-MS *m/z*: 186 (M^+). HR-MS *Anal.* Calcd for $[C_{10}H_{18}O_3 - CH_3]$ (M − 15, *m/z*): 171.1021. Found: 171.1020. IR (neat): 1740 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H, d, *J*=7.0 Hz, C_2-Me), 1.51 (3H, s, C_4-Me), 1.67 (3H, br d, *J*=7.0 Hz, 6-H), 2.62 (1H, dq, *J*=9.0, 7.0 Hz, 2-H), 3.12 (3H, s, OMe), 3.57 (1H, d, *J*=9.0 Hz, 3-H), 3.71 (3H, s, –COOMe), 5.52 (1H, br q, *J*=7.0 Hz, 5-H).

Reduction of the Methoxy Ester 5 with DIBAL Under an Ar atmosphere at 0 °C, 1.5 M DIBAL–toluene solution (55.2 ml, 0.083 mol) was added to a solution of the methoxy ester **5** (7.00 g, 0.037 mol) in toluene (55 ml) *via* a syringe at a slow rate. The whole was warmed to ambient temperature, and then cooled again after 30 min. Ether (100 ml) and 1 M NaOH (75 ml) were added to the reaction mixture with stirring. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude **6** was subjected to column chromatography (hexane/AcOEt, 5 : 1) to give colorless pure **6** (5.66 g, 95.1%). *Anal.* Calcd for $C_9H_{18}O_2 \cdot 1/10H_2O$: C, 67.54; H, 11.46. Found: C, 67.38; H, 12.11. FAB-MS *m/z*: 158 (M^+). IR (neat): 3424 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.67 (3H, d, *J*=7.0 Hz, C_2-Me), 1.53 (3H, s, C_4-Me), 1.66 (3H, br d, *J*=8.0 Hz, 6-H), 1.93 (1H, m, 2-H), 3.17 (3H, s, OMe), 3.30 (1H, d, *J*=10.0 Hz, 3-H), 3.53 (1H, br s, OH), 3.60 (2H, m, 1-H), 5.43 (1H, br q, *J*=8.0 Hz, 5-H).

Swern Oxidation of the Alcohol 6 Under an Ar atmosphere, a solution of oxalyl chloride (6.63 g, 0.052 mol) in CH_2Cl_2 (60 ml) was cooled to −78 °C and DMSO (8.12 g, 0.10 mol) in CH_2Cl_2 (10 ml) was added dropwise *via* a syringe at a slow rate, with stirring. After 10 min, a solution of **6** (4.13 g, 0.026 mol) in CH_2Cl_2 (7 ml) was introduced. After an additional 20 min, Et_3N (21.0 g, 0.21 mol) was added, and the mixture was warmed to −20 °C. Then, CH_2Cl_2 (200 ml) and H_2O (60 ml) were added with stirring. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Hexane/ether (2 : 1) (15 ml) was added to the residue, then the precipitate was filtered off and the filtrate was concentrated to give crude **7** (4.25 g), which was used without further purification.

Preparation of the (2*E*)-Ester 8 by Wittig Reaction Under an Ar atmosphere, a solution of the crude aldehyde **7** (4.25 g, 0.026 mol) and carbethoxyethylidenetriphenylphosphorane (18.85 g, 0.052 mol) in DMSO (40 ml) was warmed at 40 °C for 3 d. The mixture was filtered, then ether (50 ml) and H_2O (15 ml) were added to the filtrate with stirring. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue (6.53 g) was subjected to column chromatography (hexane/AcOEt, 40 : 1) to give (2*E*)-**8** (5.63 g, 90.1% from **6**) as a colorless oil. *Anal.* Calcd for $C_{14}H_{24}O_3 \cdot 1/2H_2O$: C, 67.44; H, 10.11. Found: C, 67.79; H, 10.12. FAB-MS *m/z*: 241 (MH^+). IR (neat): 1710 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.81 (3H, d, J=7.0 Hz, C_4-Me), 1.30 (3H, t, J=7.0 Hz, $COOCH_2C\underline{H}_3$), 1.53 (3H, s, C_6-Me), 1.66 (3H, d, J=7.0 Hz, 8-H), 1.86 (3H, d, J=1.5 Hz, C_2-Me), 2.61—2.72 (1H, m, 4-H), 3.12 (3H, s, OMe), 3.25 (1H, d, J=9.0 Hz, 5-H), 4.19 (2H, q, J=7.0 Hz, $-COOC\underline{H}_2CH_3$), 5.46 (1H, br q, J=7.0 Hz, 7-H), 6.69 (1H, dq, J=10.0, 1.5 Hz, 3-H).

Reduction of the (2*E*)-Ester 8 with DIBAL Under an Ar atmosphere at 0 °C, 1.5 M DIBAL–toluene solution (42.4 ml, 0.054 mol) was added to a solution of **8** (6.38 g, 0.027 mol) in toluene (40 ml) *via* a syringe at a slow rate with stirring. After 30 min, ether (40 ml) and 1 M HCl (40 ml) were added to the reaction mixture with stirring. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was subjected to column chromatography (hexane/AcOEt, 8 : 1) to give (2*E*)-**10** (5.13 g, 98.4%) as a colorless oil. *Anal.* Calcd for $C_{12}H_{22}O_2 \cdot 1/4H_2O$: C, 71.07; H, 11.18. Found: C, 71.26; H, 11.96. EI-MS *m/z*: 198 (M^+). IR (neat): 3369 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.77 (3H, d, J=8.0 Hz, C_4-Me), 1.53 (3H, s, C_6-Me), 1.65 (3H, d, J=7.0 Hz, 8-H), 1.68 (3H, s, C_2-Me), 1.88—1.96 (1H, br s, OH), 2.51—2.62 (1H, m, 4-H), 3.12 (3H, s, OMe), 3.17 (1H, d, J=8.0 Hz, 5-H), 4.00 (2H, s, 1-H), 5.31 (1H, d, J=9.0 Hz, 3-H), 5.42 (1H, q, J=7.0 Hz, 7-H). An NOE experiment was conducted; the result are described in the text.

Reaction of the Aldehyde 7 and Triethyl 2-Phosphonopropionate Under an Ar atmosphere at −20 °C, 1.6 M *n*-BuLi–hexane solution (21.0 ml, 0.034 mol) was added to a solution of triethyl 2-phosphonopropionate (7.43 g, 0.031 mol) in anhydrous THF (50 ml) *via* a syringe at a slow rate with stirring. After 1.0 h, a solution of the crude aldehyde **7**, prepared from the alcohol **6** (3.75 g, 0.024 mol) by Swern oxidation, in anhydrous THF (20 ml) was introduced at −20 °C. The whole was warmed to ambient temperature and allowed to stand overnight. Then 10% aqueous NH_4Cl (5 ml) was added with stirring and the reaction mixture was concentrated under reduced pressure. Ether (50 ml) and H_2O (20 ml) were added to the mixture. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was subjected to column chromatography (hexane/AcOEt, 20 : 1) to give a mixture of (2*E*)-**8** and (2*Z*)-**9** esters (3.92 g, 68% from **6**). The mixture showed a single spot on thin layer chromatography (TLC) and the ratio of (2*E*)-**8**: (2*Z*)-**9** was 1 : 2, as estimated from ^{1}H-NMR analysis. Signals were assigned as follows ($CDCl_3$) δ: (2*E*)-**8**, 0.81 (3H, C_4-Me), 1.85 (3H, C_2-Me), 2.66 (1H, 4-H), 3.25 (1H, 5-H), 5.46 (1H, 7-H), 6.70 (1H, 3-H). (2*Z*)-**9**, 0.84 (3H, C_4-Me), 1.91 (3H, C_2-Me), 3.15 (1H, 5-H), 3.40 (1H, 4-H), 5.43 (1H, 7-H), 5.88 (1H, 3-H).

Reduction of a Mixture of (2*E*)-8 and (2*Z*)-9 with DIBAL A mixture of (2*E*)-**8** and (2*Z*)-**9** was reduced with DIBAL in the same manner as described for (2*E*)-**8** to give the (2*Z*)-alcohol **11** (1.79 g, 55.5%) in the first eluate, and the (2*E*)-alcohol **10** (0.94g, 29.2%) in the second eluate. (2*Z*)-Alcohol **11**: Colorless oil *Anal.* Calcd for $C_{12}H_{22}O_2 \cdot 1/4H_2O$: C, 71.07; H, 11.18. Found: C, 71.47; H, 11.27. EI-MS *m/z*: 198 (M^+). IR (neat): 3360 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.75 (3H, d, J=7.0 Hz, C_4-Me), 1.52 (3H, br s, C_6-Me), 1.65 (3H, d, J=7.0 Hz, C_7-Me), 1.83 (3H, s, C_2-Me), 2.63 (1H, m, 4-H), 3.00 (1H, d, J=10.0 Hz, 5-H), 3.10 (3H, s, OMe), 3.41 (1H, d, J=10.0 Hz, OH), 3.64 (1H, dd, J=11.0, 10.0 Hz, 1-H), 4.30 (1H, d, J=11.0 Hz, 1-H), 5.05 (1H, br d, J=10.0 Hz, 3-H), 5.43 (1H, br q, J=7.0 Hz, 7-H). An NOE experiment was conducted; the result are described in the text.

Preparation of the (2*E*)-Sulfone 13 through the Iodide 12 in the Dark Powdered Ph_3P (0.52 g, 0.002 mol) and imidazole (0.20 g, 0.003 mol) were added to a solution of the (2*E*)-alcohol **10** (0.21 g, 0.001 mol) in $MeCN/Et_2O$ (1 : 1) (4 ml) with vigorous stirring at 0 °C. After 5 min, iodine (0.72 g, 0.003 mol) was introduced and the whole was stirred for 30 min. Ether (20 ml) and brine (10 ml) were added to the reaction mixture with stirring. The organic layer was washed with 10% aqueous Na_2SO_3, dried over $MgSO_4$, filtered and concentrated under reduced pressure at low temperature. The crude (2*E*)-iodide **12**, which showed single spot on TLC (hexane/AcOEt, 5 : 1), was dissolved in DMF (2 ml), and sodium benzenesulfinate hydrate (0.24 g, 0.0012 mol) was added with stirring. After 3 h at 0 °C, ether (20 ml) and H_2O (10 ml) were added. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue, which showed single spot on TLC (hexane/AcOEt, 2 : 1), was subjected to column chromatography (hexane/AcOEt, 10 : 1) to give only the (2*E*)-sulfone **13** (0.24 g, 73.8% from **10**). mp 83 °C (from benzene). *Anal.* Calcd for $C_{18}H_{26}O_3S$: C, 67.04; H, 8.13. Found: C, 66.81; H, 8.21. EI-MS *m/z*: 322 (M^+). IR ($CHCl_3$): 1300, 1150 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.54 (3H, d, J=7.0 Hz, C_4-Me), 1.46 (3H, s, C_6-Me), 1.61 (3H, d, J=7.0 Hz, 8-H), 1.75 (3H, s, C_2-Me), 2.40—2.50 (1H, m, 4-H), 2.70 (1H, d, J=9.0 Hz, 5-H), 3.04 (3H, s, OMe), 3.76 (2H, s, 1-H), 4.97 (1H, d, J=9.0 Hz, 3-H), 5.33 (1H, q, J=7.0 Hz, 7-H), 7.50—7.55, 7.59—7.65, 7.83—7.88 (5H, phenyl). In an NOE experiment, irradiation at the 1-position (δ 3.76 ppm) caused a 12% enhancement at the 3-position (δ 4.97 ppm) and a 2% enhancement at the C_2-Me group (δ 1.75 ppm). A large-scale experiment was also run, starting from **10** (3.32 g, 0.017 mol).

Preparation of the (2*Z*)-Sulfone 14 through the (2*Z*)-Iodide 16 in the Dark Powdered Ph_3P (0.52 g, 0.002 mol) and imidazole (0.20 g, 0.003 mol) were added to a solution of the (2*Z*)-alcohol **11** (0.19 g, 0.001 mol) in $MeCN/Et_2O$ (1 : 1) (4 ml) with vigorous stirring at 0 °C. After 5 min, iodine (0.72 g, 0.003 mol) was introduced and the whole was stirred for 30 min. Ether (20 ml) and brine (10 ml) were added to the reaction mixture with stirring. The organic layer was washed with 10% aqueous Na_2SO_3, dried over $MgSO_4$, filtered and concentrated under reduced pressure at low temperature. The crude (2*Z*)-iodide **16**, which showed a single spot on TLC (hexane/AcOEt, 5 : 1), was dissolved in DMF (2 ml), and sodium benzenesulfinate hydrate (0.24 g, 0.0012 mol) was added with stirring. After 30 min at 0 °C, ether (20 ml) and H_2O (10 ml) were added. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue, which showed a single spot on TLC (hexane/AcOEt, 2 : 1), was subjected to column chromatography (hexane/AcOEt, 10 : 1) to give only the (2*Z*)-sulfone **14** (0.24 g, 77.7% from **11**). mp 96 °C (from MeOH). *Anal.* Calcd for $C_{18}H_{26}O_3S$: C, 67.04; H, 8.13. Found: C, 66.96; H, 8.17. EI-MS *m/z*: 322 (M^+). IR ($CHCl_3$): 1135 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.41 (3H, d, J=7.0 Hz, C_4-Me), 1.39 (3H, s, C_6-Me), 1.60 (3H, d, J=7.0 Hz, 8-H), 1.85 (3H, s, C_2-Me), 1.98—2.08 (1H, m, 4-H), 2.91 (1H, d, J=10.0 Hz, 5-H), 3.01 (3H, s, OMe), 3.59 (1H, d, J=14.0 Hz, 1-H), 4.32 (1H, d, J=14.0 Hz, 1-H), 5.24 (1H, d, J=11.0 Hz, 3-H), 5.32 (1H, q, J=7.0 Hz, 7-H), 7.50—7.57, 7.59—7.64, 7.88—7.93 (5H, phenyl). In an NOE experiment, irradiation at the 3-position (δ 5.24 ppm) caused 2% enhancement at the C_2-Me group (δ 1.85 ppm) and 9% enhancement at the 5-position (δ 2.91 ppm).

Preparation of the (2*E*)-Sulfone 13 through the Iodide 12 under Light This experiment was carried out under room light. Powdered Ph_3P (8.80 g, 0.034 mol) and imidazole (2.97 g, 0.044 mol) were added to a solution of the (2*E*)-alcohol **10** (3.32 g, 0.017 mol) in $MeCN/Et_2O$ (1 : 1) (50 ml) with stirring at 0 °C. After 5 min, iodine (10.64 g, 0.043 mol) was added and the whole was vigorously stirred for 30 min at 0 °C. After addition of hexane (80 ml) and Celite (3.0 g), insoluble material was filtered off. The filtrate was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue (4.22 g), which showed two spots on TLC (hexane/AcOEt, 5 : 1) and was pale brown in color, was dissolved in DMF (12 ml) and sodium benzenesulfinate hydrate (3.20 g, 0.016 mol) was added. The whole was stirred for 30 min at ambient temperature, then ether (100 ml) and H_2O (30 ml) were added. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue (5.10 g), which showed

two spots on TLC (hexane/AcOEt, 2:1), was subjected to column chromatography to give the (2*Z*)-sulfone **14** (0.60 g, 14.0%) and the (2*E*)-sulfone **13** (2.87 g, 67.0%).

X-Ray Crystal Structure Determination of the (2*Z*)-Sulfone 14 Crystal Data: $C_{18}H_{26}O_3S$, $M=322.47$, monoclinic, space group $P2_1/a$ (#14), $a=8.627$ (2) Å, $b=14.824$ (2) Å, $c=14.661$ (2) Å, $\beta=101.32$ (1)°, $V=1838.5$ (4) Å^3, $z=4$, Dcalcd = 1.107 g/cm^3. The diffraction intensities were collected from a crystal with dimensions of $0.20\times0.20\times0.30$ mm on a Rigaku AFC-7R diffractometer with graphite-monochromated Cu$K\alpha$ radiation and an 18 kW rotating anode generator. Of the total of 3088 reflections observed within a 2θ range of 120.1°, 2876 were unique (Rint = 0.018). The final cycle of full-matrix least-squares refinement was based on 1725 observed reflections ($I>3.00\sigma$ (I)) and 304 variable parameters. The final R value was 0.044 (Rw = 0.038).

Reaction of 4,4-Dimethoxy-2-butanone and Trimethoxyphosphonoacetate Under an Ar atmosphere at 0 °C, 1.6 M *n*-BuLi–hexane solution (65 ml, 0.104 mol) was added to a solution of trimethylphosphonoacetate (14.57 g, 0.08 mol) in anhydrous THF (50 ml) *via* a syringe, with stirring. After 30 min, a solution of 4,4-dimethoxy-2-butanone (10.56 g, 0.104 mol) in anhydrous THF (50 ml) was introduced at −20 °C. The whole was warmed to ambient temperature and allowed to stand overnight. Under ice-cooling, 10% aqueous NH_4Cl (20 ml) was added and the whole was concentrated to 1/4 volume under reduced pressure. Ether (100 ml) and H_2O (20 ml) were added to the mixture. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue (9.09 g) was subjected to column chromatography (hexane/AcOEt, 40:1) to give the (*Z*)-acetal **19** (4.38 g, 29.1%) and the (*E*)-acetal **18** (10.22 g, 67.9%). (*Z*)-Acetal **19**: Colorless oil, *Anal.* Calcd for $C_9H_{16}O_4$: C, 57.43; H, 8.57. Found C, 57.16; H, 8.56. EI-MS *m/z*: 188 (M^+). IR (neat): 1740 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.96 (3H, s, C_3-Me), 2.96 (2H, d, $J=6.0$ Hz, 4-H), 3.37 (6H, s, OMe), 3.69 (3H, s, –COOMe), 4.56 (1H, t, $J=6.0$ Hz, 5-H), 5.76 (1H, br s, 2-H). (*E*)-Acetal **18**: Colorless oil, *Anal.* Calcd for $C_9H_{16}O_4$: C, 57.43; H, 8.57. Found: C, 57.23; H, 8.81. EI-MS *m/z*: 188 (M^+). IR (neat): 1740 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.21 (3H, s, C_3-Me), 2.45 (2H, d, $J=6.0$ Hz, 4-H), 3.35 (6H, s, OMe), 3.68 (3H, s, –COOMe), 4.55 (1H, t, $J=6.0$ Hz, 5-H), 5.75 (1H, br s, 2-H). An NOE experiment was conducted; the result are described in the text.

Reduction of the (*E*)-Acetal 18 with DIBAL Under an Ar atmosphere at 0 °C, 1.5 M DIBAL–toluene solution (39.0 ml, 0.058 mol) was added to a solution of (*E*)-acetal **18** (5.00 g, 0.026 mol) in toluene (25 ml) with stirring. The whole was warmed to ambient temperature and stirred for 30 min. After ice-cooling, ether (60 ml) and 1 M NaOH (20 ml) were added to the reaction mixture with stirring. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was subjected to column chromatography (hexane/AcOEt, 4:1) to give the alcohol **20** (4.26 g, 92.0%) as a colorless oil. *Anal.* Calcd for $C_8H_{16}O_3$: C, 59.97; H, 10.07. Found: C, 59.57; H, 10.30. FAB-MS *m/z*: 160 (M^+). IR (neat): 3360 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.72 (3H, s, C_3-Me), 2.34 (2H, d, $J=6.0$ Hz, 4-H), 3.33 (6H, s, OMe), 4.16 (2H, d, $J=7.0$ Hz, 1-H), 4.51 (1H, d, $J=7.0$ Hz, 5-H), 5.49 (1H, t, $J=7.0$ Hz, 2-H).

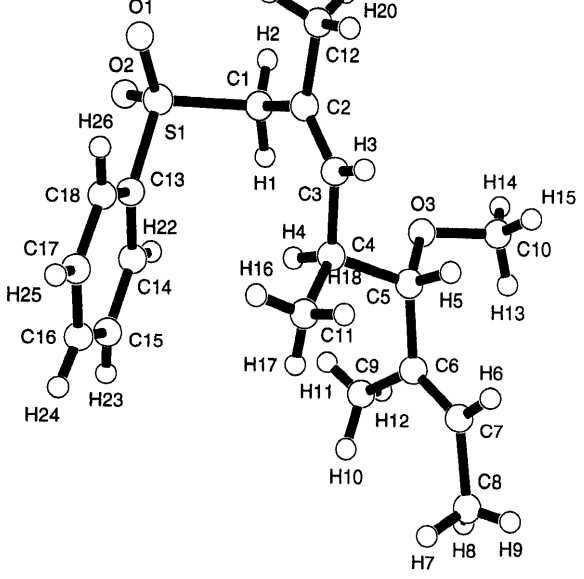


Fig. 1. X-Ray Crystal Structure of the (2*Z*)-Sulfone **14**

Reaction of the Alcohol 20 and Pivaloyl Chloride Pivaloyl chloride (3.76 g, 0.031 mol) in ether (5 ml) was added to a mixture of **20** (2.51 g, 0.016 mol) and diisopropylethylamine (6.05 g, 0.047 mol) in ether (20 ml) with stirring at 0 °C. The whole was allowed to stand for 2 d at ambient temperature. Ether (50 ml) and brine (20 ml) were added to the reaction mixture and the organic layer was washed with 7% aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated under reduced pressure. The residue (5.0 g) was subjected to column chromatography (hexane/AcOEt, 30:1) to give the pivaloyl ester **21** (3.53 g, 98.3%) as a colorless oil. *Anal.* Calcd for $C_{13}H_{24}O_4\cdot1/2H_2O$: C, 61.63; H, 9.95. Found C, 61.72; H, 9.63. FAB-MS *m/z*: 244 (M^+). IR (neat): 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.20 (9H, s, $COCMe_3$), 1.74 (3H, s, C_3-Me), 2.35 (2H, d, $J=6.0$ Hz, 4-H), 3.32 (6H, s, OMe), 4.49 (1H, t, $J=6.0$ Hz, 5-H), 4.59 (2H, d, $J=7.0$ Hz, 1-H), 5.42 (1H, t, $J=7.0$ Hz, 2-H).

Acid Hydrolysis of the Acetal 21 Under ice-cooling, cold 2 M HCl (5 ml) was added slowly to a solution of acetal **21** (3.66 g, 0.015 mol) in isopropanol/THF (3:1) (20 ml) with stirring. The whole was kept in a refrigerator at 5 °C for 3 d. Cold 7% aqueous $NaHCO_3$ (30 ml) was introduced into the reaction mixture with stirring. The whole was extracted with ether (20 ml × 3). The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a colorless oil (3.31 g). As judged from ^{1}H-NMR ($CDCl_3$) data, the main component was the non-conjugated aldehyde **22** (δ 9.67 ppm, t, $J=2.5$ Hz, CHO), along with two minor components **23** ((*E*) and (*Z*) isomers, δ 9.95, 10.00 ppm, each d, $J=8.0$ Hz, CHO). This crude residue was employed without further purification.

Reaction of the (2*E*)-Sulfone 13 and Non-conjugated Aldehyde 22 Under an Ar atmosphere at −20 °C, 1.6 M *n*-BuLi–hexane solution (6.6 ml, 0.011 mol) was added to a solution of the (2*E*)-sulfone **13** (1.70 g, 0.005 mol) in anhydrous THF (10 ml) *via* a syringe, with stirring. After 1 h, the whole was cooled to −78 °C, then a solution of the crude aldehyde **22** (1.26 g, 0.006 mol) in anhydrous THF (5 ml) was introduced. The whole was warmed to −20 °C and allowed to stand overnight. Ether (50 ml) and 10% aqueous NH_4Cl (10 ml) were added with stirring. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was subjected to column chromatography (hexane/AcOEt, 15:1) to give **27** as a diastereomeric mixture (1.50 g, 80.0% from **13** (0.92 g)) and recovered **13** (0.58 g, 34.0%). Not all the signals of **27** could be assigned. The presence of the hydroxyl group was confirmed by the IR spectrum (3400 cm^{-1}). ^{1}H-NMR ($CDCl_3$) δ: 0.38, 0.74 (each 3H, d, $J=7.0$ Hz, C_9-Me), 1.18, 1.19 (each 9H, s, $COCMe_3$), 1.48, 1.60 (each 3H, d, $J=7.0$ Hz, 13-H), 1.73, 1.79 (each 3H, s, C_3-Me), 2.00—2.59 (3H, m, 4-H, 9-H), 3.02, 3.03 (each 3H, s, OMe), 2.95, 3.07 (each 1H, d, $J=9.0$ Hz, 10-H), 3.46, 3.62 (each 1H, d, $J=5.0$, 9.0 Hz, 6-H).

Benzoylation of Hydroxy Sulfone 27 The reaction solution of **27** (1.60 g, 0.003 mol), BzCl (1.73 g, 0.012 mol) and DMAP (1.88 g, 0.015 mol) in pyridine (10 ml) was allowed to stand overnight at ambient temperature. Ether (50 ml) and 7% aqueous $NaHCO_3$ (15 ml) were added, and the whole was extracted with ether (50 ml × 3). The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue (2.89 g) was subjected to column chromatography (hexane/AcOEt, 10:1) to give diastereomeric **28** (1.86 g, 97.0%), which was employed without identification.

Reaction of Diastereomeric 28 with 5% Na(Hg) At −20 °C, 5% Na (Hg) (8.10 g, 0.015 mol) was added in portions to a solution of the benzoyl sulfone **28** (1.84 g, 0.003 mol) in THF/MeOH (1:3) (240 ml) with vigorous stirring. After 2 h, the same amount of 5% Na (Hg) was added again, and the reaction mixture was stirred for 2 h at −20 °C. Brine (100 ml) was then added and the whole was concentrated to about 1/2 volume at low temperature, and extracted with ether (50 ml × 3). The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue (1.0 g) was subjected to column chromatography (hexane/AcOEt, 30:1—10:1) to give **29** (0.38 g, 40.2%), **30** (0.073 g, 7.0%) and **31** (0.041 g, 3.2%) along with recovered **28** (0.28 g, 15.1%). Compounds **30** and **31** could not be stored. Compound **29**: Colorless oil, *Anal.* Calcd for $C_{23}H_{38}O_3\cdot1/4H_2O$: C, 75.26; H, 10.57. Found C, 75.49; H, 11.01. FAB-MS *m/z*: 362 (M^+). IR (neat): 1760 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.77 (3H, d, $J=7.0$ Hz, C_9-Me), 1.20 (9H, s, $COCMe_3$), 1.51 (3H, s, C_{11}-Me), 1.65 (3H, d, $J=7.0$ Hz,

13-H), 1.69 (3H, s, C_3-Me), 1.76 (3H, s, C_7-Me), 2.60—2.70 (1H, m, 9-H), 2.79 (2H, d, J=8.0 Hz, 4-H), 3.15 (3H, s, OMe), 3.17 (1H, d, J=9.0 Hz, 10-H), 4.58 (2H, d, J=7.0 Hz, 1-H), 5.32 (1H, d, J=9.0 Hz, 8-H), 5.35 (1H, br t, J=7.0 Hz, 2-H), 5.42 (1H, br q, J=7.0 Hz, 12-H), 5.49 (1H, dt, J=16.0, 8.0 Hz, 5-H), 6.10 (1H, d, J=16.0 Hz, 6-H). Compound **30**: Colorless oil, EI-MS m/z: 400 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 0.52 (3H, d, J=7.0 Hz, C_9-Me), 1.50 (3H, s, C_{11}-Me), 1.62 (3H, d, J=7.0 Hz, 13-H), 1.80 (3H, s, C_7-Me), 2.05 (3H, d, J=2.0 Hz, C_3-Me), 2.48—2.58 (1H, m, 9-H), 2.92 (1H, d, J=10.0 Hz, 10-H), 3.06 (3H, s, OMe), 4.73 (1H, br d, J=9.0 Hz, 8-H), 5.21 (1H, d, J=10.0 Hz, 1-H), 5.33 (1H, q, J=7.0 Hz, 12-H), 5.43 (1H, d, J=17.0 Hz, 1-H), 6.22 (1H, d, J=12.0 Hz, 4-H), 6.43 (1H, dd, J=17.0, 11.0 Hz, 2-H), 7.62 (1H, d, J=12.0 Hz, 5-H) 7.43—7.58, 7.81—7.87 (5H, phenyl). Compound **31**: Colorless oil, EI-MS m/z: 502 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 0.52 (3H, d, J=7.0 Hz, C_9-Me), 1.19 (9H, s, $COCMe_3$), 1.47 (3H, s, C_{11}-Me), 1.62 (3H, d, J=7.0 Hz, 13-H), 1.71 (3H, s, C_3-Me), 1.75 (3H, s, C_7-Me), 2.45—2.55 (1H, m, 9-H), 2.89 (1H, d, J=10.0 Hz, 10-H), 2.90 (2H, d, J=8.0 Hz, 4-H), 3.01 (3H, s, OMe), 4.56 (2H, d, J=7.0 Hz, 1-H), 4.68 (1H, br d, J=10.0 Hz, 8-H), 5.32 (1H, br q, J=7.0 Hz, 12-H), 5.33 (1H, br t, J=8.0 Hz, 2-H), 6.87 (1H, t, J=8.0 Hz, 5-H), 7.44—7.50, 7.53—7.59, 7.80—7.84 (5H, phenyl).

Methanolysis of the Pivaloylester 29 A solution of **29** (0.35 g, 0.001 mol) in MeOH (3.5 ml) was treated with 1 M MeONa/MeOH solution (1.5 ml). The reaction mixture was refluxed for 3 h, then cooled. Ether (50 ml) and brine (10 ml) were added. The combined organic layers (three extractions) were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was subjected to column chromatography (hexane/AcOEt, 9:1) to give the alcohol **1** (0.26 g, 97.0%) as a colorless oil. HR-MS Calcd for $C_{18}H_{30}O_2$ (MH^+, m/z): 279.2324. Found: 279.1562. IR (neat): 3300 cm^{-1}. ^{1}H-NMR δ: 0.78 (3H, d, J=7.0 Hz, C_9-Me), 1.15 (1H, s, OH), 1.53 (3H, s, C_{11}-Me), 1.65 (3H, br d, J=7.0 Hz, 13-H), 1.68 (3H, s, C_3-Me), 1.75 (3H, d, J=1.0 Hz, C_7-Me), 2.61—2.69 (1H, m, 9-H), 2.78 (2H, d, J=7.0 Hz, 4-H), 3.12 (3H, s, OMe), 3.17 (1H, d, J=9.0 Hz, 10-H), 4.16 (2H, d, J=7.0 Hz, 1-H), 5.32 (1H, br d, J=9.0 Hz, 8-H), 5.42 (1H, br q, J=7.0 Hz, 12-H), 5.45 (1H, br t, J=7.0 Hz, 2-H), 5.49 (1H, dt, J=16.0, 7.0 Hz, 5-H), 6.10 (1H, d, J=16.0 Hz, 6-H). An NOE experiment was conducted; the results are described in the text.

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