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# A Formal Synthesis of Aplysiatoxin: Enantioselective Synthesis of Kishi's Aldehyde

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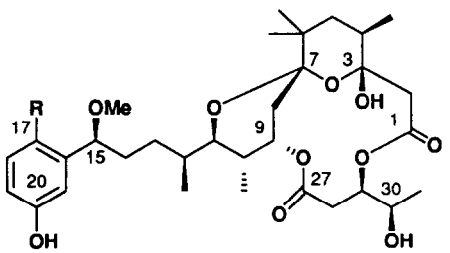
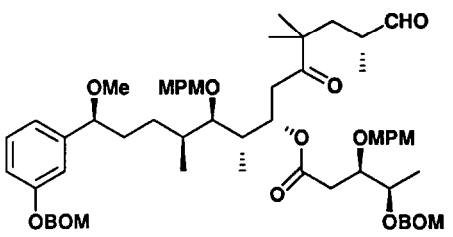
***Abstract*** This paper describes the enantioselective synthesis of key fragments (**12**, **18**, **24**, and **35**) for the synthesis of aplysiatoxin (**1a**), a potent cancer promoter, and their convergent assembly to Kishi's aldehyde (**2**) Since **2** has already been transformed into **1a** in a short step, its synthesis constitutes a formal total synthesis of **1a**

Aplysiatoxin (**1a**) and debromoaplysiatoxin (**1b**) isolated from the digestive grand of sea hare, *Stylocheilus longicauda*, have received much attention as attractive targets for total synthesis due to their sterically complex and unique molecular architecture including spiro acetal, hemiacetal, and diolide functionalities together with peculiar biological activities such as strong cancer promotion [1] Several synthetic approaches[2] to this class of compounds, including the total synthesis of dehydroxyaplysiatoxin by Yamamura et al [2b,c] and Ireland et al ,[2a] have appeared in literatures, but only one total synthesis of **1a** and **1b** has been reported to date by Kishi et al [3] Recently we developed an efficient methodology for the construction of polypropionate segment which was characteristic to macrolide chemistry and contained also in **1** as a $C_9$-$C_{12}$ fragment [4] By taking the advantage of this procedure and titanium mediated asymmetric epoxidation,[5] we could achieve the enantioselective construction of Kishi's aldehyde (**2**) which has all the stereogenic centers required for the synthesis of aplysiatoxin (**1a**) Since **2** has been transformed into **1**, this constitutes a formal total synthesis of **1a** Results obtained are described here in detail [6]




**1a** R = Br Aplysiatoxin
**1b** R = H Debromoaplysiatoxin

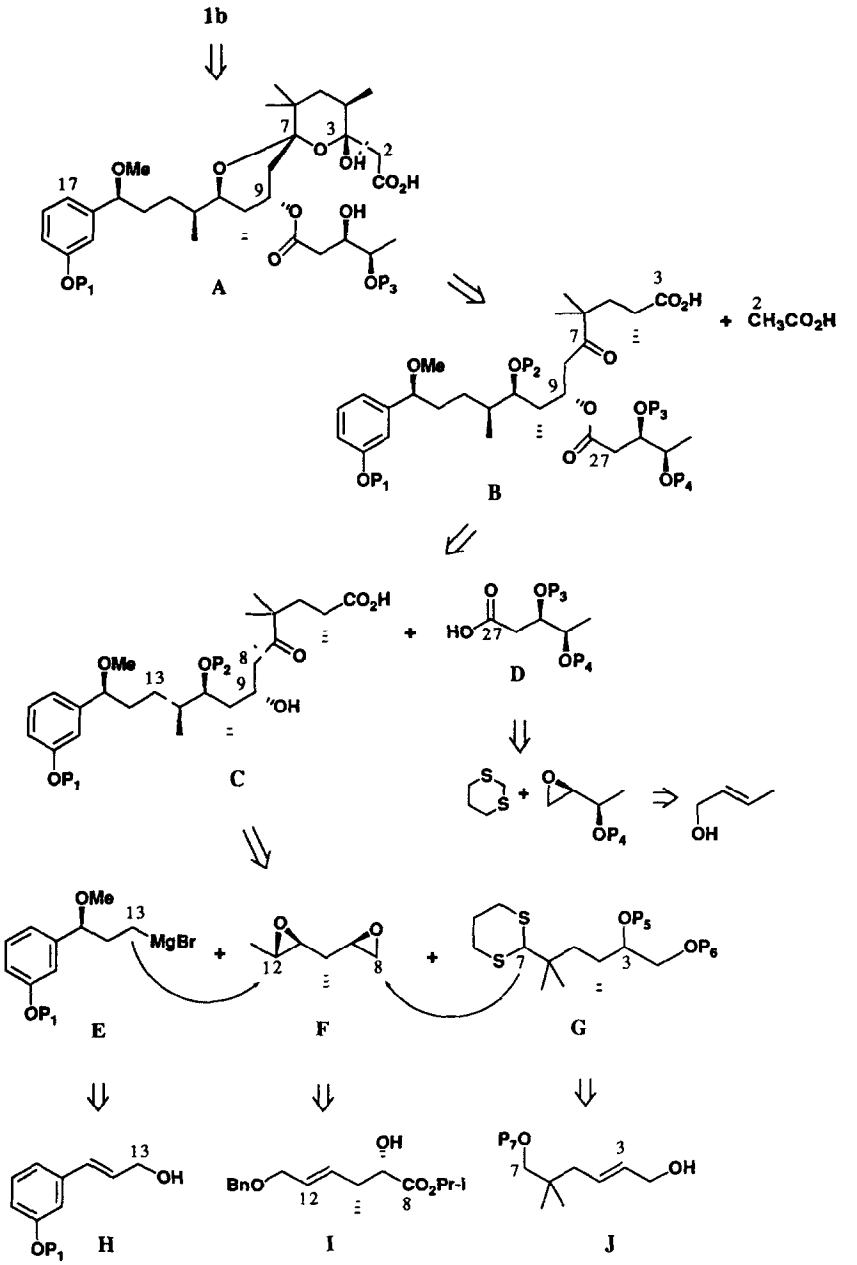



**2** Kishi's aldehyde

## Retrosynthetic Analysis

Aplysiatoxin (**1a**) and debromoaplysiatoxin (**1b**) have the common structure except for the aromatic moiety, $C_{17}$-carbon in which is not brominated in **1b** but in **1a**, and **1b** can be converted into **1a** by treatment

with bromine [1d] Therefore, the synthesis of **1b** is a primary goal of our research Compound **1b** has ten stereogenic centers but two of them, $C_3$ and $C_7$ acetal carbons, are expected to be introduced with the desired chirality upon the lactonization of the corresponding seco-acid **A** Based on these analyses, our synthetic strategy was elaborated as described in a retrosynthetic manner in **Scheme 1**

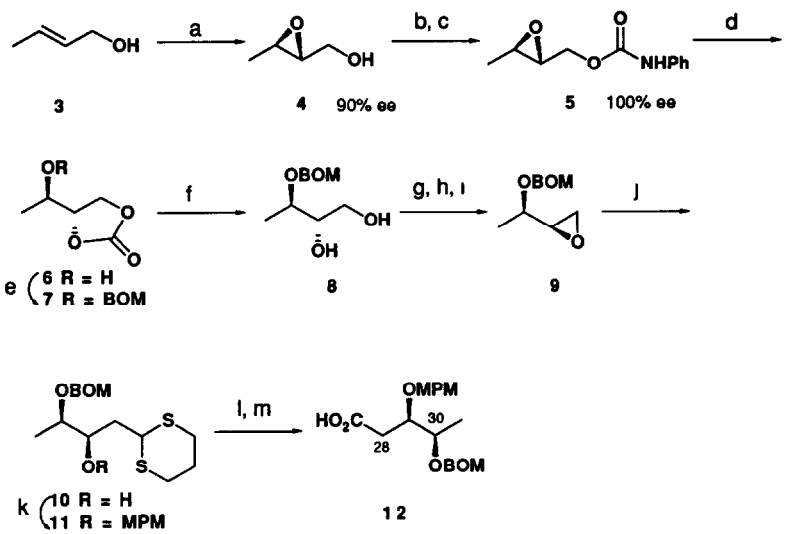



**Scheme 1**

Dissociation of $C_1$ ester linkage in **1** gave seco-acid **A** as an immediate precursor of **1** Further cleavage of the bond $C_2$-$C_3$ provided acid **B** and acetic acid, which might be recombined by Claisen condensation reaction Since the hemiacetal moiety in **1** had been reported to be very unstable,[1c] introduction of $C_1$-$C_2$ unit was set at the later stage of the synthesis Dissociation of another $C_{27}$ ester linkage envisioned two hydroxy acid-fragments **C** and **D** as plausible intermediates Further disconnection of fragment **C** between bonds $C_7$-$C_8$ and $C_{12}$-$C_{13}$ generated three fragments **E**, **F**, and **G**, which were considered to be recombined by nucleophilic opening of two different epoxides in **F** with Grignard reagent (fragment **E**) and with lithiodithiane derivative generated by base treatment of **G**, respectively In the actual synthesis, the terminal epoxide in **F** was masked as a protected diol until the coupling with **G** The carboxylic acid in **G** was also masked as a protected diol until an appropriate stage in order to avoid the epimerization at $C_4$ Stereogenic carbons in fragments **D**, **E**, and **G** seemed to be introduced by using titanium-mediated asymmetric epoxidation[5] (hereafter referred to as A E ) and the contiguous stereogenic carbons in fragment **F** was considered to be derived stereospecifically from ε-benzyloxylated α-hydroxy acid (**I**) which could be readily prepared by the use of titanium-mediated [2,3]Wittig rearrangement [4d] Although the configuration of α-carbon in **I** was opposite to that of $C_9$ in **1**, α-hydroxy ester was expected to be converted into a terminal epoxide with the inversion of its α-configuration According to this synthetic plan, we started the synthesis of fragments **D**, **E**, **F**, and **G**

## Synthesis of Fragments

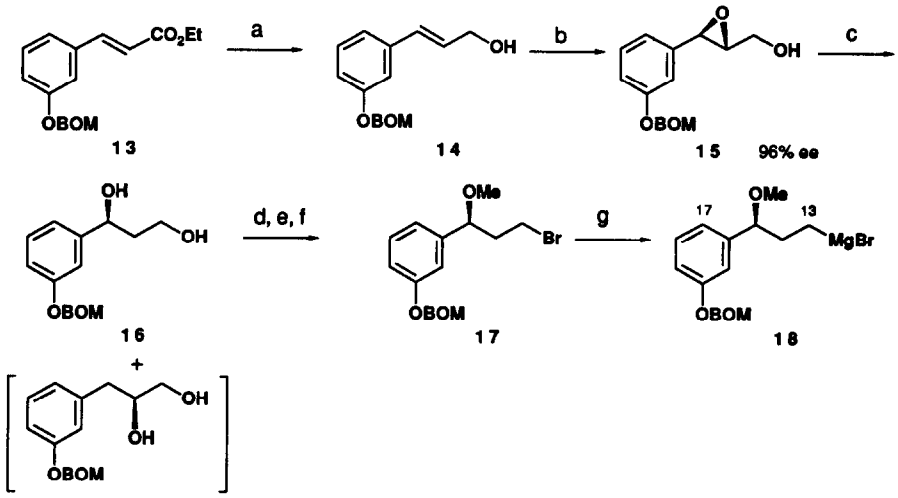
Synthesis of fragment **D** started with epoxy alcohol **4** which was readily prepared from crotyl alcohol (**3**) according to the literature procedure[5b] (**Scheme 2**) Treatment of **4** with phenyl isocyanate gave crystalline




a) $Ti(O^iPr)_4$, (-)-DET, TBHP, MS 4Å b) $Et_3N$, PhNCO c) recrystalization from AcOEt (74% for 3 steps) d) dil $HClO_4$ (15%) e) $^iPr_2NEt$, BOMCl (70%) f) $K_2CO_3$, MeOH (93%) g) $(CH_3)_3CCOCl$, $Et_3N$ then MsCl h) DIBAL i) KOH, MeOH (59% for 3 steps) j) 1,3-dithiane, BuLi (99%) k) NaH, MPMCl (82%) l) MeI, $CaCO_3$ (65%) m) $NaClO_2$, 2-methyl-2-butene (82%)

**Scheme 2**

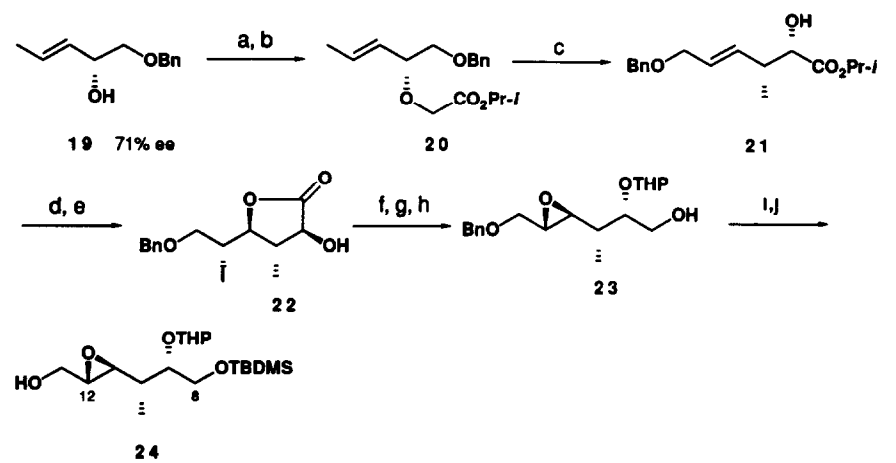
carbamate **5** Since the optical purity of the starting **4** was 90% ee, the carbamate was recrystallized to obtain the optically pure compound Compound **5** thus obtained was treated with perchloric acid and the resulting




a) DIBAL (92%) b) $Ti(O^iPr)_4$, (-)-DIPT, TBHP, MS 4Å (90%) c) Red-al, then $NaIO_4$ (91%)
d) TsCl, $Et_3N$, DMAP e) MeI, NaH f) NaBr (63% for 3 steps) g) Mg

**Scheme 3**

alcohol **6** was protected as a benzyloxymethyl (BOM) ether **7** Compound **7** was subjected to alcoholysis to give diol **8** and then converted into epoxide **9** by the sequence i) protection of the resulting primary hydroxy group as a pivalate, ii) mesylation of the remaining secondary hydroxy group, iii) reductive cleavage of pivaloyl group, and iv) alkaline treatment of the hydroxy mesylate One carbon elongation to **10** was achieved by the treatment of **9** with 2-lithio-1,3-dithiane Dithiane **10** was transformed into the desired carboxylic acid **12** corresponding to fragment **D** in three steps i) protection of hydroxy group as a *p*-methoxybenzyl (MPM) ether



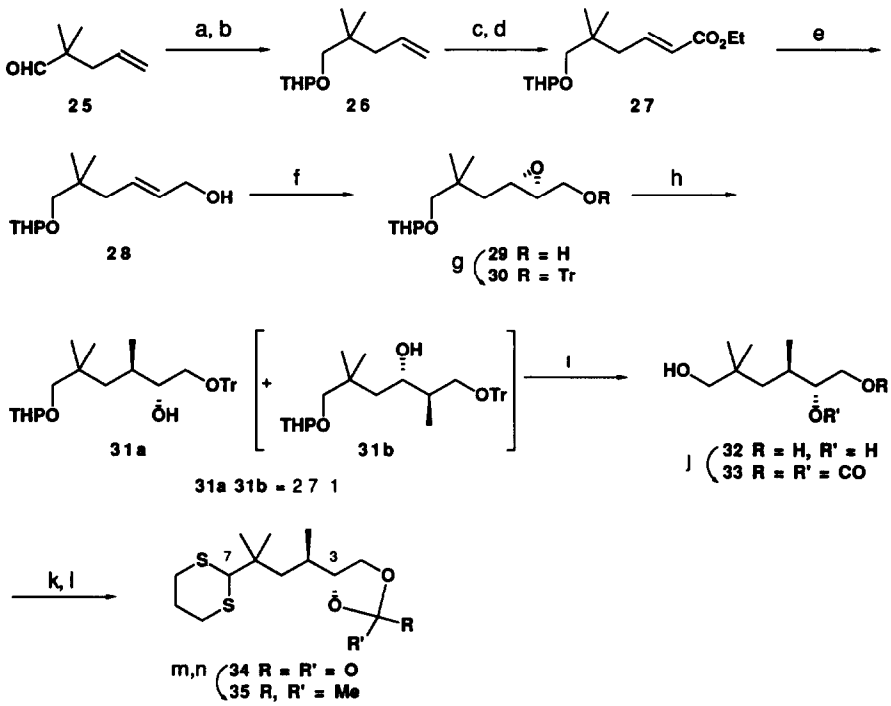

a) bromoacetic acid, NaH b) $^i$PrI, $Na_2CO_3$ (75% for 2 steps) c) LDA, $Cp_2TiCl_2$ (72%)
d) KOH e) $I_2$ (62% for 2 steps) f) DHP, PPTS g) $K_2CO_3$, MeOH
h) LAH (74% for 3 steps) i) TBDMSCl, ImH j) $H_2$, Pd/C (84% for 2 steps)

**Scheme 4**

11,[7] ii) hydrolysis of dithioacetal, and iii) oxidation of the resulting aldehyde into carboxylic acid with sodium chlorite.[8]

For the synthesis of fragment **E**, **13** was employed as a starting material which was readily prepared from *m*-hydroxycinnamic acid by a conventional manner (**Scheme 3**) Ester **13** was converted into allylic alcohol **14** in good yield by diisobutylaluminum hydride (DIBAL) reduction A E. of **14** proceeded smoothly with enantioselectivity of 96% ee to give epoxy alcohol **15**, although structurally similar *p*-methoxycinnamyl alcohol was a poor substrate for this titanium-mediated A E [9] Reduction of **15** with sodium bis(methoxyethoxy)-aluminum hydride (Red-al)[10] gave a mixture of 1,3- (**16**) and 1,2-diol in a ratio of 17 1 [11] The mixture was treated with $NaIO_4$ and subjected to silica gel chromatography to give the desired **16** in a pure form Transformation of **16** to bromide **17** was effected by the sequence i) tosylation of primary hydroxy group, ii) methylation of secondary hydroxy group, and iii) substitution of the tosylate with bromide anion. Bromide **17** was converted in a usual manner into Grignard reagent **18** to be used for the coupling with fragment **F**

Synthesis of fragment **F** started with (2*R*,3*E*)-1-benzyloxy-3-buten-2-ol (**19**) of 71% ee,[12] which was obtained by kinetic resolution of *dl*-**19**[4c] (**Scheme 4**) Compound **19** was converted into ester **20** according to the reported procedure [13] Titanium-mediated [2,3]Wittig rearrangement of **20** afforded ε-benzyloxylated hydroxy ester **21** with quantitative chirality transfer together with high *syn*,*E*-selectivity [14] After alkaline

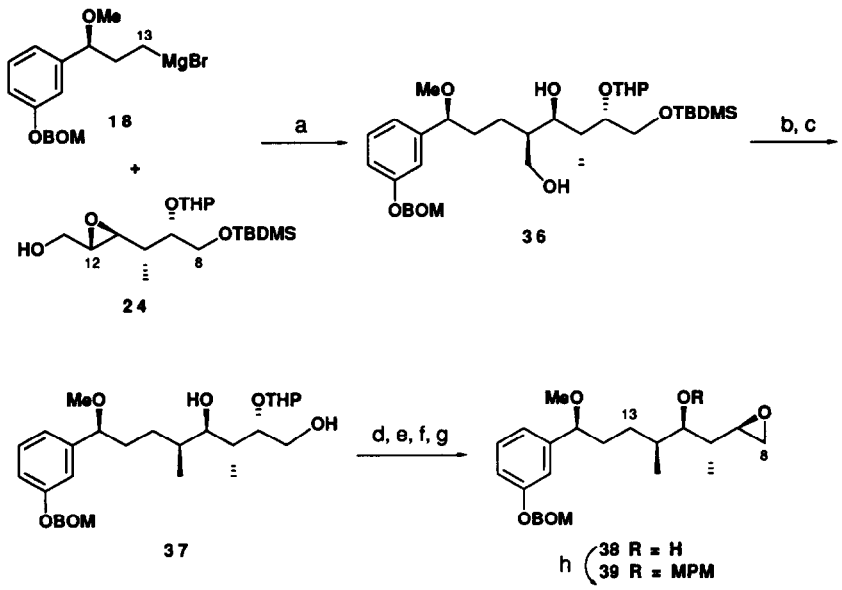



a) $NaBH_4$ b) DHP, TsOH (56% for 2 steps) c) $OsO_4$, $NaIO_4$ d) $(^iPrO)_2P(O)CH_2CO_2Et$, NaH (82% for 2 steps) e) DIBAL (95%) f) $Ti(O^iPr)_4$, (+)-DIPT, TBHP (86%) g) TrCl, $Et_3N$, DMAP (85%) h) MeMgBr, CuI i) CSA, MeOH (56% for 2 steps) j) $COIm_2$, DMAP then dil HCl (89%) k) Swern oxdn l) 1,3-propanedithiol, $BF_3{\cdot}OEt_2$ (72% for 2 steps) m) $K_2CO_3$, MeOH n) 2,2-dimethoxypropane, PPTS (90% for 2 steps)

**Scheme 5**

hydrolysis, **21** was subjected to iodolactonization [15] The resulting lactone **22** was converted into 2,3-*syn*-3,4-*anti*-epoxy alcohol **23** in three steps, i) protection of hydroxy group as a tetrahydropyranyl (THP) ether,[16] ii) methanolysis of lactone along with epoxide formation, and iii) lithium aluminum hydride (LAH) reduction of the resulting methyl ester Hydroxy protection as a *t*-butyldimethylsilyl (TBDMS) ether followed by hydrogenolysis afforded epoxy alcohol **24** which was a synthetic equivalent of fragment **F**.

Fragment **G** was derived from easily available aldehyde **25** (**Scheme 5**) [17] Aldehyde **25** was first converted into THP ether **26** in a conventional manner Conversion of **26** into **27** was achieved by oxidative cleavage of olefin and subsequent Wittig-Horner olefination [18] DIBAL reduction of **27** afforded allylic alcohol **28** which was transformed into epoxy alcohol **29** of 95% ee After hydroxy protection as a trityl ether **30**, compound **29** was exposed to methylmagnesium bromide in the presence of catalytic amount of CuI giving a mixture of **31a** and its regioisomer **31b** in a ratio of 2 7 1 [19] Acid treatment of the mixture followed by chromatographic separation afforded the desired triol **32** which was converted into carbonate **33** by treatment with carbonyldiimidazole Transformation of **33** to dithioacetal **35** corresponding to fragment **G** was carried out by the sequence, i) oxidation of primary alcohol to aldehyde,[20] ii) dithioacetalization of the resulting aldehyde giving dithioacetal **34**, iii) alcoholysis of carbonate, and iv) reprotection of the resulting diol as an acetonide




a) CuI (88%) b) MsCl, $Et_3N$ c) LAH (59% for 2 steps) d) $Ac_2O$, DMAP e) PPTS, MeOH
f) MsCl, $Et_3N$, DMAP g) KOH, MeOH (24% for 4 steps) h) MPMCl, NaH (87%)

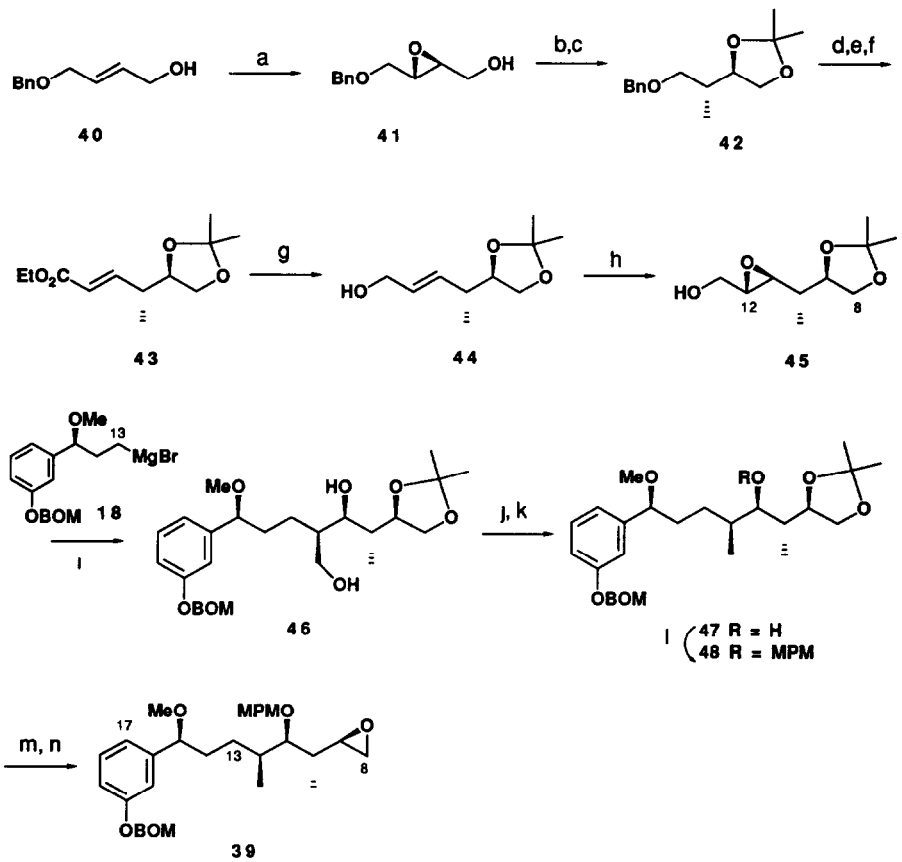
**Scheme 6**

## Assembly of Fragments

With fragments **D**, **E**, **F**, and **G** in hand, the stage was set for the construction of **1** The construction was started with the coupling of fragments **E** and **F** as described in **Scheme 6** Treatment of epoxy alcohol **24** with Grignard reagent **18** in the presence of catalytic amount of CuI provided 1,3-diol **36** and a small amount of the undesired stereoisomer due to insufficient optical purity (71% ee) of **24** In **Scheme 6**, all the structures of the undesired minor stereoisomers have been omitted for clarification Since the separation of **36** and its diastereomer was difficult at this stage, the mixture was used for the next step without separation The

resulting hydroxymethyl group in **36** was converted into methyl group by mesylation and subsequent LAH reduction, establishing the structure of the $C_8$-$C_{21}$ fragment In this LAH reduction, however, the cleavage of the TBDMS ether occurred simultaneously to give 1,4-diol **37** Therefore, **37** was reprotected as a diacetate and converted into **38** by the sequence; i) acid hydrolysis of THP ether,[16] ii) mesylation of the resulting hydroxy group, and iii) alkaline hydrolysis of acetates accompanying epoxide ring formation The undesired minor diastereomer produced at the coupling of **18** and **24** (*vide supra*), could be removed at this stage by repeated silica gel column chromatography Although protection of hydroxy group of **38** as a MPM ether[7] gave compound **39** and set the stage for the coupling with **35** corresponding to fragment **G**, difficulty in separation of diastereomeric by-product and tedious operation of protecting groups caused by the unexpected cleavage of TBDMS ether, prompted us to explore another approach to **39**

In order to avoid these difficulties, we examined the approach to **39**, using A E of *E*-allylic alcohols as a tool of introducing chirality at $C_9$-$C_{12}$, because A E of *E*-allylic alcohols has been well established to proceed

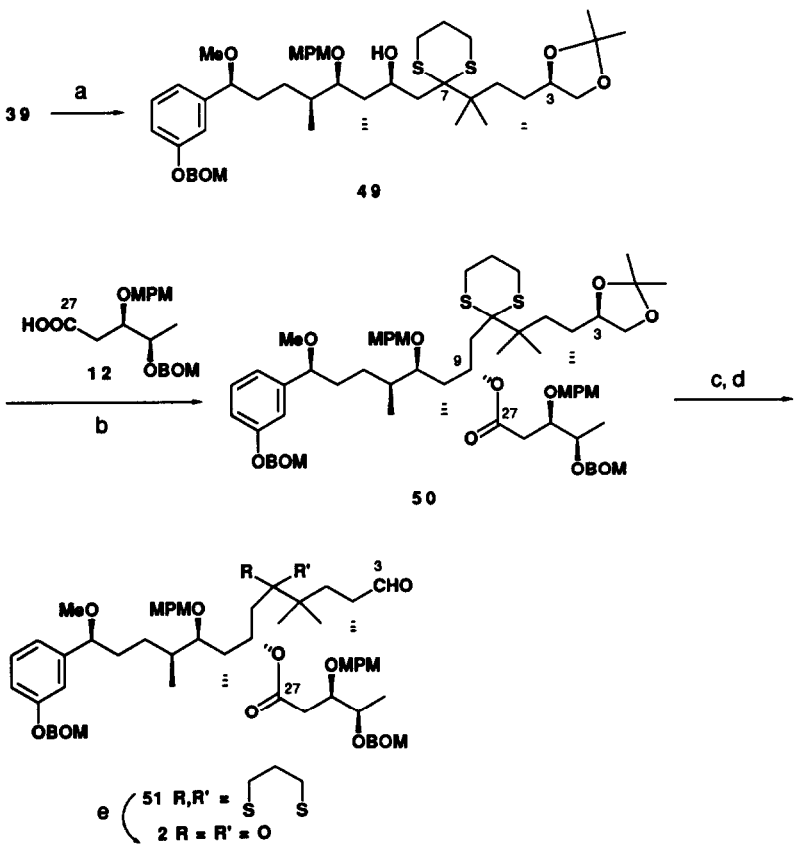



a) $Ti(O^iPr)_4$, (+)-DIPT, TBHP (79%) b) $Me_3Al$ c) 2,2-dimethoxypropane, CSA (58% for 2 steps) d) $H_2$, Pd/C e) Swern oxdn f) $(^iPrO)_2P(O)CH_2CO_2Et$, $^t$BuOK (44% for 3 steps) g) DIBAL (96%) h) $Ti(O^iPr)_4$, (+)-DIPT, TBHP (82%) i) CuI (73%) j) TsCl, $Et_3N$ k) LAH (90% for 2 steps) l) MPMCl, NaH (74%) m) PPTS, MeOH (48%) n) TsCl, $^t$BuOK (78%)

**Scheme 7**

with high enantioselectivity (**Scheme 7**) Thus, the synthesis started with epoxy alcohol **41** (95% ee) which was readily prepared by A E. of allylic alcohol **40**.[21] Epoxy alcohol **41** was treated with trimethylaluminum, according to Oshima's method [22] Although this procedure provided a mixture of 1,2- and 1,3-diols in a ratio of 5 1, the undesired 1,3-diol was readily separated with silica gel column chromatography after its conversion into the corresponding acetonides Further conversion of acetonide **42** into two carbon elongated *E*-allylic alcohol **44** was carried out in four steps, i) hydrogenolysis of benzyl ether, ii) Swern oxidation of the resulting alcohol to aldehyde, iii) Wittig-Horner olefination,[18] wherein an inseparable mixture of **43** and its epimer[23] was produced in a ratio of 13 1, and iv) DIBAL reduction, after which **44** and its epimer were separated by column chromatography. A E of **44** proceeded with diastereoselectivity of 86% de, and the resulting mixture of **45** and its diastereomer was used for the next reaction without separation

Coupling of **18** and the above mixture of epoxy alcohols proceeded regioselectively to give the corresponding diastereomeric mixture of 1,3-diols which were separated chromatographycally to give **46** as a single isomer The following transformation of hydroxymethyl group in **46** to the corresponding methyl group was carried out in the same manner as described for the preparation of **37** Conversion of the resulting **47** into the desired **39** was effected straightforwardly by the sequence i) protection of hydroxy group as a MPM ether




a) **35**, BuLi (59%) b) TCBC, $Et_3N$, then DMAP (85%) c) PPTS, MeOH
d) $Pb(AcO)_4$, KOAc (77% for 2 steps) e) NCS, $AgNO_3$ (89%)

**Scheme 8**

**48**,[7] ii) acid hydrolysis of acetonide, and iii) treatment of the resulting diol with *p*-toluenesulfonyl chloride in the presence of excess potassium *t*-butoxide

Having established an efficient route to **39**, we next examined the coupling of **39** and **35** as shown in **Scheme 8** Thus epoxide **39** was exposed to the lithiodithiane generated by treatment of **35** with butyllithium, giving **49** in 59% yield Condensation of the resulting alcohol **49** and carboxylic acid **12** was accomplished by using Yamaguchi method[24] to give ester **50** which contained all the asymmetric centers in **1** except for two acetal carbons. After acid hydrolysis of the acetonide, treatment of **50** with lead tetraacetate[25] gave aldehyde **51** which was an intermediate in Kishi's synthesis of **1** [3] For the further structure confirmation, **51** was converted into another Kishi's intermediate **2** that gave identical $^1$H NMR spectrum in every respect with the corresponding authentic sample

Since **2** has been reported to be convertible to **1** in 6 steps,[3] our accomplishment constitutes a formal total synthesis of optically active aplysiatoxin in a highly convergent and enantioselective manner

## Experimental

NMR spectra were recorded at 400 MHz on a JEOL GX-400 or at 90 MHz on a JEOL FX-90Q instrument All signals were expressed as ppm down field from tetramethylsilane used as an internal standard ($\delta$-value in $CDCl_3$) IR spectra were obtained with a JASCO IR-700 instrument Optical rotation was measured with a JASCO DIP-360 automatic digital polarimeter Column chromatography was conducted on Silica Gel 60, 70-230 mesh ASTM, available from E Merck Preparative thin layer chromatography was performed on 0 5 mm x 20 cm x 20 cm E Merck silica gel plate (60 F-254) Solvents were dried and distilled shortly before use Reactions were carried out under an atmosphere of nitrogen if necessary

**(2*R*,3*R*)-1-[(*N*-Phenylcarbamoyl)oxy]-2,3-epoxybutane (5)** To a suspension of MS 4Å (20 g) in dichloromethane (700 ml) was added (-)-diisopropyl tartrate (4 3 g, 18 4 mmol) Titanium tetraisopropoxide (4 19 ml, 14 1 mmol) and *t*-butyl hydroperoxide (48 ml, 3 53 mol dm$^{-3}$ in toluene) were then added to the mixture at -20 °C After being stirred for 30 min, (*E*)-2-butenol (12 0 ml, 141 mmol) was added at the same temperature After another 1 h, the mixture was left in refrigerator (-20 °C) for 36 h To the solution was added dimethylsulfide (5 8 ml, 79 mmol) and the reaction temperature was gradually raised to room temperature To this solution were added triethylamine (23 4 ml, 168 mmol) and phenyl isocyanate (20 1 ml, 185 mmol), and the mixture was further stirred for 24 h The mixture was treated with aqueous acetone (205 ml, acetone-$H_2O$ = 40 1) and stirred for 12 h The resulting precipitate was filtrated off and the filtrate was diluted with ethyl acetate The organic layer was washed with water, dried over $MgSO_4$, filtrated through a short silica gel column (hexane-ethyl acetate = 1 1), and concentrated to give **5** (21 4 g, 74 %), $[\alpha]_D^{26}$ +46 8° (c 1 29, MeOH) IR (KBr) 3280, 1730, 1597, 1547, 1499, 1439, 1307, 1222, 1052, 899, 860, 746cm$^{-1}$ $^1$H NMR (400 MHz) 7 39~7 33 (m, 2H), 7 32~7 29 (m, 2H), 7 07 (t, *J* = 7 33 Hz, 1H), 6 90~6 75 (br s, 1H), 4 50 (dd, *J* = 2 93, 12 21 Hz, 1H), 3 99, (dd, *J* = 6 34, 12 21 Hz, 1H), 3 01~2 96, (m, 2H), 1 35, (d, *J* = 5 40 Hz, 3H) Calcd for $C_{11}H_{13}NO_3$ C, 63 76, H, 6 32, N, 6 76% Found C, 63 83, H, 6 19, N, 6 86% Three recrystallizations of the product from hexane-ethyl acetate, gave optically pure carbamate **5** as a crystalline [2 4 g, $[\alpha]_D^{26}$ +48 1° (c 0 964, MeOH)]

**(2*S*,3*R*)-1,2-Carbonyldioxybutan-3-ol (6)** Aqueous $HClO_4$ (166 ml, 5 %) was added to a solution of carbamate **5** (23 54 g, 113 mmol) in acetonitrile (150 ml) and the mixture was stirred at room temperature After 24 h, saturated aqueous $NaHCO_3$ (100 ml) was added and bulk of acetonitrile was removed under reduced pressure The residue was diluted with ether, washed with water, dried over $MgSO_4$, and concentrated Silica gel column chromatography of the residue (hexane-ethyl acetate = 6 4) gave carbonate **6** (2 27 g, 15 %) as an oil, $[\alpha]_D^{26}$ -5 4° (c 5 03, $CHCl_3$) IR (neat) 3450, 2976, 1789, 1393, 1185, 1075, 772cm$^{-1}$ $^1$H NMR (90 MHz) 4 65~4 30 (m, 3H), 4 05 (dq, *J* = 6 56, 3 50 Hz, 1H), 2 38~2 04 (br s, 1H), 1 14 (d, *J* = 6 56 Hz, 3H) Calcd for $C_5H_8O_4$ C, 45 46, H, 6 10% Found C, 45 43, H, 6 12%

**(2*S*,3*R*)-3-Benzyloxymethoxy-1,2-carbonyldioxybutane** (7) To a solution of carbonate **6** (2 11 g, 16 0 mmol) and diisopropylethylamine (6 0 ml, 34 mmol) in dichloromethane (20 ml) was added benzyl chloromethyl ether (3 1 ml, 20 mmol) at room temperature After being stirred for 48 h, methanol (3 ml) was added to the solution and the mixture was stirred for additional 12 h The solution was concentrated under reduced pressure The resulting slurry was diluted with ether, washed with water, dried over $MgSO_4$, and concentrated. Silica gel column chromatography of the residue (hexane-ethyl acetate = 8 2~7 3) gave BOM ether **7** (2 82 g, 70 %) as an oil, $[\alpha]_D^{26}$ +7 4° (c 1 20, $CHCl_3$) IR (neat) 2928, 1796, 1451, 1375, 1171, 1022, 742, 697cm$^{-1}$ $^1$H NMR (400 MHz)· 7 38~7 29 (m, 5H), 4 83 (ABq, *J* = 6 84 Hz, 2H), 4 63 ABq, *J* = 11 72 Hz, 2H), 4.59~4 56 (m, 1H), 4 47 (s, 1H), 4 45 (d, *J* = 1 96 Hz, 1H), 4 09 (dq, *J* = 6 35, 3 90 Hz, 1H), 1 22 (d, *J* = 6 35 Hz, 3H) Calcd for $C_{13}H_{16}O_5$ C, 61 90, H, 6 39% Found C, 61 87, H, 6 42%

**(2*S*,3*R*)-3-Benzyloxymethoxy-butane-1,2-diol** (8) $K_2CO_3$ (1 0 g, 7 2 mmol) was added to a solution of BOM ether **7** (1 41 g, 5 59 mmol) in methanol (30 ml) at room temperature After being stirred for 10 h, bulk of methanol was removed under reduced pressure The residue was diluted with ether, washed with water, dried over $MgSO_4$, and concentrated Silica gel chromatography of the residue (hexane-ethyl acetate = 6 4~3 7) gave diol **8** (1 18 g, 93 %) as an oil, $[\alpha]_D^{26}$ -30 8° (c 3 10, $CHCl_3$) IR (neat) 3404, 2884, 1641, 1378, 1167, 1037, 740, 697cm$^{-1}$ $^1$H NMR (90 MHz) 7 54~7 26 (m, 5H), 4 80 (s, 2H), 4 61 (s, 2H), 4 05~3 49 (m, 4H), 2 99~2 74 (br s, 1H), 2 54~2 23 (br s, 1H), 1 20 (d, *J* = 5 78 Hz, 3H), Anal Calcd for $C_{12}H_{18}O_4$ C, 63 70, H, 7 91% Found C, 63 43, H, 8 02%

**(2*R*,3*R*)-3-Benzyloxymethoxy-1,2-epoxybutane** (9) To a solution of diol **8** (1 14 g, 5 03 mmol), 4-dimethylaminopyridine (100 mg, 0 82 mmol), and triethylamine (1 6 ml, 12 mmol) in dichloromethane (20 ml) were added pivaloyl chloride (630 µl, 5 12 mmol) at room temperature After being stirred for 10 h, methanesulfonyl chloride (430 µl, 5 6 mmol) was added and the mixture was stirred for another 1 h The solution was concentrated under reduced pressure, diluted with ether, and washed with water The organic layer was separated, dried over $MgSO_4$, filtrated through a pad of silica gel, and concentrated to give the corresponding mesylate (1 29 g, 66 %), $^1$H NMR (90 MHz) 7 36~7 16 (br s, 5H), 4 88~4 68 (m, 1H), 4 73 (s, 2H), 4 56 (s, 2H), 4 42~3 92 (m, 3H), 2 98 (s, 3H), 1 21 (d, *J* = 6 56 Hz, 3H), 1 15 (s, 9H)

The mesylate (360 mg, 0 927 mmol) was dissolved in dichloromethane (10 ml) and cooled to -78 °C To the solution was added diisobutylaluminum hydride (1 9 ml, 1 0 mol dm$^{-3}$ in hexane) After being stirred for 1 h, the mixture was quenched with methanol (0 5 ml) at the temperature After additional 5 min, the solution was gradually warmed to room temperature At this point, the solution became a white gel To the gel, saturated aqueous potassium sodium tartrate (10 ml) was added and the whole mixture was left with stirring until it became a clear solution The resulting solution was extracted with ether, dried with $MgSO_4$, filtrated through a pad of silica gel, and concentrated to give β-mesyloxy alcohol (271 mg, 96 %), $^1$H NMR (400 MHz) 7 38~7 30 (m, 5H), 4 81 (s, 2H), 4 69 (ddd, *J* = 5 85, 3 90, 3 90 Hz, 1H), 4 64 (ABq, *J* = 11.72 Hz, 2H), 4 07 (dq, *J* = 3 90, 6 53 Hz, 1H), 3 88~3 84 (m, 2H), 3 10 (s, 3H), 2 58~2 45 (br s, 1H), 1 27 (d, *J* = 6 35 Hz, 3H)

The β-mesyloxy alcohol (707 mg, 2 32 mmol) was added to the mixture of methanol (10 ml) and aqueous KOH (4 6 ml, 1 0 mol dm$^{-3}$), and stirred at room temperature After 1 h, bulk of methanol was removed under diminished pressure The resulting solution was extracted with ether, dried over $MgSO_4$, concentrated, and chromatographed on silica gel (hexane-ethyl acetate = 8 2) to give epoxide **9** (450 mg, 93 %) as an oil, $[\alpha]_D^{26}$ +24 0° (c 5 38, $CHCl_3$) IR (neat) 3026, 2882, 1449, 1376, 1039, 738, 697cm$^{-1}$ $^1$H NMR (90 MHz) 7 41~7 26 (m, 5H), 4 88 (ABq, *J* = 6 90 Hz, 2H), 4 65 (s, 2H), 3 58 (dq, *J* = 6 56, 6 56 Hz, 1H), 3 02 (ddd, *J* = 2 62, 5 30, 6 56 Hz, 1H), 2 78 (br t, *J* = 5 03 Hz, 1H), 2 56 (dd, *J* = 2 62, 5 03 Hz, 1H), 1 27 (d, *J* = 6 56 Hz, 3H) Calcd for $C_{12}H_{16}O_3$ C, 69 21, H, 7 74% Found C, 69 04, H, 7 67%

**(3*R*,4*R*)-4-Benzyloxymethoxy-3-hydroxy-1,1-propylenedithiopentane (10)** Butyllithium (3 5 ml, 1 6 mol $dm^{-3}$ in hexane) was added to a solution of 1,3-dithiane (678 mg, 5 64 mmol) in THF (20 ml) at 0 °C After being stirred for 1 h, a solution of epoxide **9** (783 mg, 3 76 mmol) in THF (10 ml) was added to the mixture at the temperature After being stirred for another 10 h, the mixture was quenched with aqueous $H_3PO_4$ (10 ml, 5 %) at 0 °C and allowed to warm to room temperature The solution was extracted with ether, dried over $MgSO_4$, and concentrated. Silica gel column chromatography of the residue (hexane-ethyl acetate = 8 2~6 4) gave thioacetal **10** (1 23 g, 99 %) as an oil, $[\alpha]_D^{26}$ +3 6° (c 0 731, $CHCl_3$) IR (neat) 3460, 2892, 1378, 1275, 1101, 1038, 739, 699$cm^{-1}$ $^1H$ NMR (400 MHz) 7 38~7 26 (m, 5H), 4 84 (ABq, $J$ = 7 33 Hz, 2H), 4 64 (ABq, $J$ = 11 72 Hz, 2H),4 33 (dd, $J$ = 4 88, 9 76 Hz, 1H), 3 83~3 77 (m, 1H), 3 64 (dq, $J$ = 6 35, 6 35 Hz, 1H), 2.97~2 82 (m, 4H), 2 63 (d, $J$ = 4 88 Hz, 1H), 2 16~2 09 (m, 1H), 1 97~1 83 (m, 3H), 1 22 (d, $J$ = 6 35 Hz, 3H) Calcd for $C_{16}H_{24}O_3S_2$ C, 58 50, H, 7 38% Found C, 58 54, H, 7 35%

**(3*R*,4*R*)-4-Benzyloxymethoxy-3-(*p*-methoxybenzyloxy)-1,1-propylenedithiopentane (11)** To a suspension of thioacetal **10** (1 23 g, 3 74 mmol) and NaH (180 mg, 60 % in mineral oil, 4 5 mmol) in THF-DMF (40 ml, 3 1) was added *p*-methoxybenzyl chloride (560 µl, 4 1 mmol) at room temperature After being stirred for 24 h, the mixture was quenched with aqueous $H_3PO_4$ (20 ml, 5%), extracted with ether, dried over $MgSO_4$, and concentrated Silica gel chromatography of the residue (hexane-ethyl acetate = 9 1~7 3) gave MPM ether **11** (1 38 g, 82 %) as an oil, $[\alpha]_D^{21}$ +18 3 ° (c 0 731, $CHCl_3$) IR (neat) 2890, 1608, 1510, 1453, 1246, 1038, 821, 739, 699$cm^{-1}$ $^1H$ NMR (90 MHz) 7 48~7 26 (m, 5H), 7 28 (d, $J$ = 13 61 Hz, 2H), 6 82 (d, $J$ = 13 61 Hz, 2H), 4 75 (s, 2H), 4 56 (s, 2H), 4 21~3 75 (m, 3H), 3 70 (s, 3H), 3 04~2 68 (m, 4H), 2 24~1 80 (m, 4H), 1 18 (d, $J$ = 9 72 Hz, 3H) Calcd for $C_{24}H_{32}O_4S_2$ C, 64 25, H, 7 19% Found C, 64 16, H, 7 11%

**(3*R*,4*R*)-4-Benzyloxymethoxy-3-(*p*-methoxybenzyloxy)pentanoic acid (12)** Methyl iodide (350 µl, 5 6 mmol) was added to a suspension of MPM ether **11** (491 mg, 1 10 mmol) and calcium carbonate (1 1 g, 11 mmol) in aqueous acetonitrile (10 ml, acetonitrile-$H_2O$ = 4 1) After being stirred for 10 h at room temperature, the mixture was extracted with ether, dried over $MgSO_4$, and concentrated Silica gel chromatography of the residue (hexane-ethyl acetate = 8 2) gave the corresponding aldehyde (256 mg, 65 %), $^1H$ NMR (400 MHz) 9 74, (t, $J$ = 1 46 Hz, 1H), 7 38~7 21 (m, 5H), 7 22 (d, $J$ = 8 30 Hz, 2H), 6 85 (d, $J$ = 8 30 Hz, 2H), 4 78 (ABq, $J$ = 7 32 Hz, 2H), 4 59 (s, 2H), 4 52 (ABq, $J$ = 11 23 Hz, 2H), 4 04~3 97 (m, 2H), 3 79 (s, 3H), 2 68~2 62 (m, 2H), 1 19 (d, $J$ = 5 86 Hz, 3H)

To a mixture of the aldehyde (128 mg, 0 357 mmol), *t*-butanol (2 ml), saturated aqueous $NaH_2PO_4$ (2 ml), and 2-methylbutene (210 µl, 2 0 mmol) were added $NaClO_2$ (33 mg, 0 36 mmol) at 0 °C After 5 min, aqueous $H_3PO_4$ (5 ml, 5 %) was added and the solution was extracted with ether, dried over $MgSO_4$, and concentrated Silica gel chromatography of the residue ($CHCl_3$-MeOH = 25 1) gave carboxylic acid **12** (109 mg, 82 %) as an oil, IR (neat) 2932, 1709, 1609, 1511, 1247, 1037, 822, 740, 699$cm^{-1}$ $^1H$ NMR (90 MHz) 7 46~7 18, (m, 5H), 7 18 (d, $J$ = 8 86 Hz, 2H), 6 78 (d, $J$ = 8 86 Hz, 2H), 4 73 (s, 2H), 4 53 (s, 2H), 4 47 (s, 2H), 4 02~3 70 (m, 2H), 3 70 (s, 3H), 2 65~2 45 (m, 2H), 1 10 (d, $J$ = 5 82 Hz, 3H)

***m*-Benzyloxymethoxycinnamyl alcohol (14)** Diisobutylaluminum hydride (70 ml, 1 0 mol $dm^{-3}$ in hexane) was added to a solution of ester **13** (10 3 g, 33 0 mmol) in dichloromethane (160 ml) at -78 °C and the mixture was stirred for 1 h at the temperature Methanol (10 ml) was added to this solution and the whole mixture was stirred for another 5 min The solution was gradually warmed to room temperature At this point, the solution became a white gel To the gel was added saturated aqueous potassium sodium tartrate (200 ml) and the whole mixture was left until it became a clear solution The solution was extracted with ether, dried over $MgSO_4$, and concentrated to give allylic alcohol **14** (8 17 g, 92 %) as an oil, IR (neat) 3374, 3026, 2896, 1577, 1087, 1018, 773, 741, 694cm-1 $^1H$ NMR (400 MHz) 7 37~7 23, (m, 6H), 7 11 (t, $J$ = 1 95 Hz, 1H), 7 05 (br d, $J$ = 7 82 Hz, 1H), 6 98 (dd, $J$ = 1 95, 8 32 Hz, 1H), 6 59 (br d, $J$ = 16 12 Hz, 1H), 6 36 (ddd, $J$ = 5 37, 5 86, 16 12 Hz, 1H), 5 30 (s, 2H), 4 73 (s, 2H), 4 32 (d, $J$ = 5 86 Hz, 1H), 4 31 (d, $J$ =

5 37 Hz, 1H), 1 50~1 44 (br s, 1H) HREIMS m/z calcd for $C_{17}H_{18}O_3$ 270 12549, found 270 12573 (M+).

**(2*R*,3*R*)-3-(*m*-Benzyloxymethoxyphenyl)-2,3-epoxypropan-1-ol (15)** To a suspension of (-)-diisopropyl tartrate (1 4 ml, 6 6 mmol) and powdered MS 4Å (1.7 g) in dichloromethane (120 ml) were added titanium tetraisopropoxide (1 7 ml, 5 7 mmol) and *t*-butyl hydroperoxide (31 ml, 3 7 mol $dm^{-3}$ in toluene) at -20 °C After being stirred for 30 min, a solution of allylic alcohol **14** (15 65 g, 58.1 mmol) in dichloromethane (20 ml) was added at the temperature After another 1 h, the mixture was left in refrigerator (-20 °C) for 10 h The mixture was quenched with pre-cooled (-20 °C) aqueous acetone (60 ml, acetone-$H_2O$ = 5 1), and the reaction temperature was gradually raised to room temperature After being stirred for 3 h, the resulting precipitate was filtered off and the filtrate was concentrated Silica gel column chromatography of the residue (hexane-ethyl acetate = 6 4) gave epoxy alcohol **15** (14 82 g, 90 %) as an oil, $[\alpha]_D^{19}$ +26 8° (c 0 821, $CHCl_3$) IR (neat): 3440, 2900, 1586, 1489, 1233, 1158, 1088, 789, 742, 698$cm^{-1}$ $^1H$ NMR (400 MHz) 7 37~7 24 (m, 6H), 7 05~6 97 (m, 2H), 6 95 (d, *J* = 7 33 Hz, 1H) 5.29 (ABq, *J* = 7 33 Hz, 2H), 4 72 (s, 2H), 4 04 (ddd, *J* = 2 44, 4 88, 12 70 Hz, 1H), 3 91 (d, *J* = 1 95 Hz, 1H), 3 79 (ddd, *J* = 3 90, 7 80, 12 70 Hz, 1H), 3 20 (ddd, *J* = 1 95, 2 44, 3 90 Hz, 1H), 1 78 (dd, *J* = 4 88, 7 82 Hz, 1H) Calcd for $C_{17}H_{18}O_4$ C, 71 31, H, 6 34% Found C, 71 24, H, 6 30%

**(*S*)-3-(*m*-Benzyloxymethoxyphenyl)propane-1,3-diol (16)** Red-al (10 ml, 3 6 mol $dm^{-3}$ in toluene) was added to a stirring solution of epoxy alcohol **15** (6 57 g, 22 9 mmol) in THF (50 ml) at 0 °C and stirred for 10 min Then the mixture was left in refrigerator (0 °C) for 10 h The mixture was quenched with aqueous NaOH (10 ml, 15 %), allowed to warm to room temperature, and poured into water The mixture was extracted with ether, dried with $MgSO_4$, and concentrated The residue was dissolved in aqueous THF (50 ml, THF-$H_2O$ = 1 1) and to this solution was added $NaIO_4$ (1 0 g, 4 7 mmol) at room temperature After vigorous stirring for 3 h, the mixture was extracted with ether, dried over $MgSO_4$, and concentrated Silica gel column chromatography of the residue (hexane-ethyl acetate = 1 1~3 7) gave 1,3-diol **16** (6 0 g, 91 %) as an oil, $[\alpha]_D^{19}$ -29 1° (c 1 33, $CHCl_3$) IR (neat) 3402, 2938, 1585, 1239, 1158, 1018, 788, 742, 699$cm^{-1}$ $^1H$ NMR (400 MHz) 7 36~7 25 (m, 6H), 7 10 (br s, 1H), 7 03~7 00 (m, 2H) 5 30 (s, 2H), 4 96~4 93 (m, 1H), 4 73 (s, 2H), 3 86 (br t, *J* = 5 62 Hz, 2H), 2 90~2 70 (br s, 1H), 2 35~2 20 (br s, 1H), 2 06~1 90 (m, 2H) Calcd for $C_{17}H_{20}O_4$ C, 70 81, H, 6 99% Found C, 70 86, H, 6 77%

**(*S*)-3-(*m*-Benzyloxymethoxyphenyl)-1-bromo-3-methoxypropane (17)** *p*-Toluenesulfonyl chloride (5 1 g, 27 mmol) was added to a solution of diol **16** (7 33 g, 25 4 mmol), 4-dimethylaminopyridine (100 mg, 0 82 mmol), and triethylamine (4 3 ml, 31 mmol) in dichloromethane (250 ml) at room temperature After 4 h, bulk of dichloromethane was removed under diminished pressure, and the residue was diluted with ether, washed with water, dried over $MgSO_4$, filtrated through a pad of silica gel, and concentrated to give tosylate (10.45 g, 93 %) as an oil

To a solution of the above tosylate (6 34 g, 14 3 mmol) and methyl iodide (2 5 ml, 40 mmol) in DMF-THF (120 ml, 3 1) was added sodium hydride (900 mg, 60 % in mineral oil, 23 mmol) at room temperature After being stirred for 5 h, the mixture was quenched with aqueous $H_3PO_4$ (10 ml, 5 %) The mixture was poured into water and extracted with ether The organic layer was dried over $MgSO_4$, concentrated, and diluted with DMF (50 ml). To the solution was added NaBr (11 3 g, 110 mmol) and the mixture was stirred at room temperature for 2 d, then poured into water (300 ml), and extracted with hexane-ethyl acetate (8 2) The organic layer was dried over $MgSO_4$, concentrated, and chromatographed on silica gel (hexane-ethyl acetate = 9.1~8.2) to give bromide **17** (3 63 g, 68 %) as an oil, $[\alpha]_D^{20}$ -46 1° (c 3 63, $CHCl_3$) IR (neat) 2896, 1586, 1482, 1449, 1241, 1156, 1091, 1021, 788, 737, 697$cm^{-1}$ $^1H$ NMR (400 MHz) 7 34~7 26 (m, 6H), 7 04~7 02 (m, 2H), 6 96 (d, *J* = 7 31 Hz, 1H), 5 31 (s, 2H), 4 75 (s, 2H), 4 31 (dd, *J* = 4 39, 7 81 Hz, 1H), 3.55 (ddd, *J* = 5 86, 8 30, 9 76 Hz, 1H), 3 37 (ddd, *J* = 5 86, 5 86, 9 76 Hz, 1H), 3 25 (s, 3H),

2 32~2 25 (m, 1H), 2 13~2 05 (m, 1H) Calcd for $C_{18}H_{21}O_3Br$ C, 59 19, H, 5 79% Found C, 59 15, H, 5 79%

**Isopropyl [(1*R*,2*E*)-1-benzyloxymethyl-2-butenyloxy]acetate (20)** To a stirred mixture of allylic alcohol **19** (1 05 g, 5 46 mmol) and sodium hydride (670 mg, 60 % in mineral oil, 17 mmol) in THF (9 ml) was added dropwise a solution of bromoacetic acid (823 mg, 5 92 mmol) in THF (9 ml) The mixture was refluxed for 12 h, cooled to room temperature, poured into water, and extracted with ether The aqueous layer was adjusted to pH 1 and extracted with dichloromethane The organic layers were combined, dried, and concentrated. The residue was added to the mixture of $Na_2CO_3$ (360 mg, 3 40 mmol), water (6 drops), and hexamethylphosphoric triamide (6 ml), and stirred for 5 min After isopropyl iodide (0 810 ml, 8 11 mmol) was added, the mixture was further stirred for 12 h The mixture was then poured to water, extracted with hexane, dried, and concentrated. Column chromatography of the residue on silica gel (hexane-ethyl acetate = 5 1) gave ester **20** (1 20 g, 75 %) as an oil, $^1$H NMR (90 MHz) 7 03 (s, 5H), 6 00~4.86 (m, 2H), 4 58 (s, 2H), 4 05 (s, 2H), 4 02 (m, 1H), 3 64~3 34 (m, 2H), 1 71 (d, $J$ = 5 4 Hz, 3H), 1 54~1 69 (m, 1H), 1 23 (d, $J$ = 6 3 Hz, 6H) Calcd for $C_{17}H_{24}O_4$ C, 69 84, H, 8 27% Found C, 69 64, H, 8 32%

**Isopropyl (2*S*,3*R*,4*E*)-6-benzyloxy-2-hydroxy-3-methyl-4-hexenoate (21)** A solution of ester **20** (2 14 g, 7 32 mmol) in THF (5 ml) was added dropwise to a solution of LDA [(9 45 ml, 0 815 mol dm$^{-3}$ in THF-hexane (1 1)] at -100 °C After 1h, a solution of $Cp_2TiCl_2$ (2 37 g, 9 52 mmol) in THF (100 ml) was added to the mixture at the same temperature After another 15 min, the reaction temperature was gradually raised to -20 °C and the mixture was kept standing in refrigerator (-20 °C) for 19 h The mixture was quenched with a saturated aqueous solution of KF (3 6 ml) and allowed to warm to room temperature The mixture was then filtered through a pad of Celite and concentrated in vacuo Column chromatography of the residue on silica gel (hexane-ethyl acetate = 5 1) gave hexenoate **21** (1 54 g, 72 %) as an oil, $^1$H NMR (400 MHz) 7 38~7 26 (m, 5H), 5 77 (dd, $J$ = 15 6, 6 8 Hz, 1H), 5 70 (dt, $J$ = 15 6, 5 4 Hz, 1H), 5 11 (m, 1H), 4 12 (br s, 1H), 4 01 (d, $J$ = 5 4 Hz, 2H), 2 80 (m, 1H), 2 67 (m, 1H), 1 29 (d, $J$ = 5 4 Hz, 3H), 1 28 (d, $J$ = 5 9 Hz, 3H), 1 01 (d, $J$ = 6 8 Hz, 3H) Calcd for $C_{17}H_{24}O_4$ C, 69 84, H, 8 27% Found C, 69 67, H, 8 25%

**(2*S*,3*S*,4*S*,5*R*)-6-Benzyloxy-2-hydroxy-5-iodo-3-methylhexan-4-olide (22)** Aqueous potassium hydroxide (4 4 ml, 1 0 mol dm$^{-3}$) was added at room temperature to a solution of hexenoate **21** (430 mg, 1 47 mmol) in methanol (14 ml) After 1 day, a bulk of methanol was removed under diminished pressure The residual solution was diluted with water, adjusted to pH 4 by using aqueous $H_3PO_4$ (5 %), and extracted with dichloromethane The organic layer was concentrated under vacuum and diluted with acetonitrile (20 ml) To this solution was added $I_2$ (1 12 g, 4 41 mmol) and the mixture was stirred at 0 °C for 18 h The mixture was decolorized with aqueous $Na_2S_2O_3$, extracted with ether, dried over $Na_2SO_4$, and concentrated Column chromatography of the residue on silica gel (hexane-ethyl acetate = 7 3) gave iodolactone **22** (345 mg, 62 %) as an oil, $^1$H NMR (90 MHz) 7 32 (s, 5H), 4 54 (s, 2H), 4 51~4 35 (m, 1H), 4 32~3 95 (m, 2H), 3 94~3 70 (m, 2H), 3 35~3 06 (m, 1H), 2 71~2 23 (m, 1H), 1 33 (d, $J$ = 6 8 Hz, 3H) Calcd for $C_{14}H_{17}O_4I$ C, 44 70, H, 4 55% Found C, 44 67, H, 4 54%

**(2*S*,3*S*,4*S*,5*S*)-6-Benzyloxy-4,5-epoxy-3-methyl-2-(2-tetrahydropyranyloxy)hexan-1-ol (23)** A mixture of the iodolactone **22** (345 mg, 0 917 mmol) and powdered anhydrous $Na_2CO_3$ (194 mg, 1 83 mmol) in methanol (18 ml) was stirred at room temperature for 2 days in the dark The mixture was then concentrated under reduced pressure and partitioned between water and ether The ether layer was washed with water and brine successively, dried over $Na_2SO_4$, and concentrated Column chromatography of the residue on silica gel (hexane-ethyl acetate = 7 3) gave the corresponding epoxy methyl ester (231 mg, 90 %) as an oil, $^1$H NMR (90 MHz) 7 35 (S, 5H), 4 56 (s, 2H), 4 48~4 32 (m, 1H), 3 88 (s, 3H), 3 72~3 30 (m, 2H), 3 14~2 66 (m, 3H), 2 00~1 54 (m, 1H), 0 90 (d, $J$ = 6 8 Hz, 3H) Calcd for $C_{15}H_{20}O_5$ C, 64 27, H, 7 19% Found C, 64 00, H, 7 12%

A solution of the epoxy methyl ester (599 mg, 2 14 mmol) and dihydropyran (234 μl, 2.56 mmol) in dry dichloromethane (22 ml) containing pyridinium *p*-toluenesulfonate (55 0 mg, 0 219 mmol) was stirred for 6 h at room temperature, and the solvent was evaporated Column chromatography of the residue on silic gel (hexane-ethyl acetate = 5 1) gave the corresponding THP ether (755 mg, 97 %) which contained two isomers epimeric at stereogenic carbon at THP moiety, as an oil, $^1$H NMR (90 MHz) 7 32 (s, 5H) ,4.55 (s, 2H), 4 84~4 48 (m, 1H), 4 15 (d, $J$ = 4 5 Hz, 1H), 3 72 (s, 3H), 4 04~3 28 (m, 4H), 3 20~2 92 (m, 1H), 2 82 (dd, $J$ = 8 1, 1 8 Hz, 1H), 2 09~1 34 (m, 7H), 1 00 (d, $J$ = 6 8 Hz, 3H) (NMR data are described for the major isomer in the diastereomeric mixture) Calcd for $C_{20}H_{28}O_6$ C, 65 92, H, 7 74% Found. C, 65 76, H, 7 74% (Hereafter, compounds **23**, **24**, **36**, and **37** were dealt with as diastereomeric mixtures )

Lithium aluminum hydride (2 8 ml, 1 0 mol dm$^{-3}$ in THF) was added at -78 °C to a solution of the THP ether (1 02 g, 2 80 mmol) in THF (28 ml). After being stirred for 1 h, the reaction mixture was quenched with a saturated aqueous solution of KF (2 8 ml), extracted with ether, dried over $Na_2SO_4$, and concentrated. Column chromatography of the residue on silica gel (hexane-ethyl acetate = 7 3) gave *anti*-epoxy alcohol **23** (0 803 g, 85 %) $^1$H NMR (400 MHz) 7 20 (s, 5H), 4 77~4 39 (m, 3H), 4 01~3 14 (m, 8H) 2.84~2 71 (m, 2H), 1 70 ~1 04 (m, 7H), 1 03 (d, $J$=7 08 Hz, 3H) (NMR data are described for the major isomer in the diastereomeric mixture) Calcd for $C_{19}H_{28}O_5$ C, 67 83, H, 8 39% Found C, 67 74, H, 8 36%

**(2*S*,3*S*,4*S*,5*S*)-6-(*t*-Butyldimethylsiloxy)-2,3-epoxy-4-methyl-5-(2-tetrahydropyranyloxy)hexan-1-ol (24)** Triethylamine (0 277 ml, 1 99 mmol), 4-dimethylaminopyridine (20 2 mg, 0 165 mmol), and *t*-butyldimethylsilyl (TBDMS) chloride (0 275 g, 1 82 mmol) were successively added at room temperature to a solution of *anti*-epoxy alcohol **23** (0 557 g, 1 66 mmol) in dry dichloromethane (17 ml). After being stirred for 12 h, the mixture was concentrated in vacuo Column chromatography of the residue on silica gel (hexane-ethyl acetate = 6 1) gave the corresponding TBDMS ether (0 709 g, 95 %) as an oil

A mixture of the TBDMS ether (1 58 g, 3 51 mmol) and 10 % Pd/C (2 89 g) in ethanol (35 ml) was placed under hydrogen and stirred for 8 h The mixture was then filtered through Celite and concentrated Column chromatography of the residue on silica gel (hexane-ethyl acetate = 7 3) gave epoxy alcohol **24** (1 11 g, 88 %) as an oil, $^1$H NMR (400 MHz) 4 66 (m, 1H), 3 92~3 20 (m, 7H), 3 03 (m, 1H), 2 93 (dd, $J$ = 1 95, 9 28 Hz, 1H), 1 83 (br t, $J$ = 9 00 Hz, 1H), 1 60~1 15 (m, 7H), 1 05 (d, $J$ = 6 84 Hz, 3H), 0 89 (s, 9H), 0 06 (s, 3H), 0 05 (s, 3H) (NMR data are described for the major isomer in the diastereomeric mixture)

**Ethyl (2*E*)-5,5-dimethyl-6-(2-tetrahydropyranyloxy)-2-hexenoate (27)** To a well stirred solution of 2,2-dimethyl-1-(2-tetrahydropyranyloxy)-4-pentene (10 0 g, 50 4 mmol)[17] and $OsO_4$ (1 28 ml, 5 0 % in *t*-butanol, 0 20 mmol) in aqueous THF (450 ml, THF $H_2O$ = 2 1), $NaIO_4$ (22 6 g, 106 mmol) was added over the period of 2 h at 50 °C After the addition was completed, the solution was stirred for additional 1h at the same temperature and a saturated aqueous solution of $Na_2SO_3$ (150 ml) was added After being stirred for 12 h, the mixture was extracted with ether, dried over $MgSO_4$, and concentrated Column chromatography of the residue on silica gel (hexane-ethyl acetate = 7 1) gave aldehyde (8 4 g, 83 %) as an oil, IR (neat) 2948, 2734, 1716, 1470, 1379, 1199, 1122, 1033, 974, 904, 869, 815cm$^{-1}$ $^1$H NMR (400 MHz) 9 82 (t, $J$ = 2 93 Hz, 1H), 4 54 (t, $J$ = 2 93 Hz, 1H), 3 78~3 72 (m, 1H), 3 54 (d, $J$ = 9 28 Hz, 1H), 3 50~3 54 (m, 1H), 3 07 (d, $J$ = 9 28 Hz, 1H), 2 29 (dd, $J$ = 1 46, 2 93 Hz, 2H), 1 79~1 47 (m, 6H), 1 08 (s, 3H), 1 04 (s, 3H) Calcd for $C_{11}H_{20}O_3$ C, 65 97, H, 10 07% Found C, 66 06, H, 10 11%

Sodium hydride (2 1 g, 60 % in mineral oil, 53 mmol) was added to a stirred solution of ethyl diisopropyl phosphonoacetate (14 4 ml, 64 5 mmol) in THF (180 ml) at 0 °C and the mixture was warmed to room temperature After being stirred for 30 min, the reaction temperature was lowered to -78 °C To this solution was added a solution of the obtained aldehyde (8 40 g, 41 9 mmol) in THF (20 ml) After being stirred for 1 h, the mixture was quenched with saturated aqueous $NH_4Cl$ (100 ml) and extracted with ether The organic layer was dried over $MgSO_4$ and concentrated Silica gel column chromatography of the residue (hexane-ethyl acetate = 9 1) gave unsaturated ester **27** (11 2 g, 99 %) as an oil Geometry of the double bond in **27** was determined to be *E* based on the coupling constant of the vinyl proton, IR (neat) 2938, 1721, 1649,

1468, 1364, 1311, 1263, 1186, 1135, 1034, 973, 903, 867, 813cm$^{-1}$ $^1$H NMR (400 MHz). 7 01 (dt, $J$ = 15 63, 7 81 Hz, 1H), 5.82 (dt, $J$ = 15 63, 1 46 Hz, 1H), 4 56 (t, $J$ = 3 42 Hz, 1H), 4 19 (q, $J$ = 7 32 Hz, 2H), 3.86~3.80 (m, 1H), 3 53~3 49 (m, 1H), 3 48 (d, $J$ = 9 28 Hz, 1H), 3.01 (d, $J$ = 9.28 Hz, 1H), 2.22 (ddd, $J$ = 1.46, 7 81, 13 67 Hz, 1H), 2 17 (ddd, $J$ = 1 46, 7 81, 13 67 Hz, 1H), 1 87~1.50 (m, 6H), 1.29 (t, $J$ = 7 32 Hz, 3H), 0 96 (s, 3H), 0 94 (s, 3H) Calcd for $C_{15}H_{26}O_4$ C, 66 64, H, 9 69% Found C, 66 65, H, 9 49%.

**(2*E*)-5,5-Dimethyl-6-(2-tetrahydropyranyloxy)-2-hexen-1-ol (28)** Diisobutylaluminum hydride (93 ml, 1 0 mol dm$^{-3}$ in hexane) was added to a solution of ester **27** (11 2 g, 41 4 mmol) in dichloromethane (100 ml) at -78 °C and stirred for 30 min at the temperature Methanol (11 ml) was added to this solution and the whole mixture was stirred for another 5 min The solution was gradually warmed to room temperature At this point, the solution became a white gel To the gel was added saturated aqueous potassium sodium tartrate (100 ml) and the whole mixture was left until it became a clear solution The solution was extracted with ether, dried over $MgSO_4$, concentrated, and chromatographed on silica gel (hexane-ethyl acetate = 3 1) to give allylic alcohol **28** (8 96 g, 95 %) as an oil, IR (neat) 3396, 2946, 1469, 1378, 1119, 1061, 1032, 971, 903, 867, 812cm$^{-1}$ $^1$H NMR (400 MHz) 5 77~5 61 (m, 2H), 4 55 (t, $J$ = 3 60 Hz, 1H), 4 11 (br t, $J$ = 4 20 Hz, 2H), 3 84 (ddd, $J$ = 3 40, 8 20, 11 60 Hz, 1H), 3 53~3 47 (m, 1H), 3 47 (d, $J$ = 8 40 Hz, 1H), 2 97 (d, $J$ = 8 40 Hz, 1H), 2 09 (dd, $J$ = 2 20, 6 60 Hz, 2H), 1 89~1 45 (m, 6H), 0 91 (s, 3H), 0 90 (s, 3H) Calcd for $C_{13}H_{24}O_3$ C, 68 38, H, 10 59% Found C, 68 14, H, 10 55%

**(2*S*, 3*S*)-2,3-Epoxy-5,5-dimethyl-6-(2-tetrahydropyranyloxy)-1-trityloxyhexane (30)** To a suspension of MS 4Å (1 19 g) in dichloromethane (120 ml), (+)-diisopropyl tartrate (1 0 ml, 4 7 mmol) was added Titanium tetraisopropoxide (1 18 ml, 4 0 mmol) and *t*-butyl hydroperoxide (28 6 ml, 2 77 mol dm$^{-3}$ in toluene) were added to the mixture at -20 °C After being stirred for 30 min, allylic alcohol **28** (8 96 g, 39 2 mmol) was added at the same temperature The mixture was stirred for 1 h and, then, left in refrigerator (-20 °C) for another 10 h The mixture was quenched with pre-cooled (-20 °C) aqueous acetone (55 ml, acetone-$H_2O$ = 10 1) and gradually warmed to room temperature After being stirred for 3 h, the resulting suspension was filtrated and the filtrate was concentrated Silica gel column chromatography of the residue (hexane-ethyl acetate = 6 4) gave epoxy alcohol **29** (8 22 g, 86 %) as an oil, $[\alpha]_D^{23}$ +21 0° (c 1 95, $CHCl_3$) IR (neat) 3412, 2946, 1467, 1380, 1120, 1030, 902, 866, 812cm$^{-1}$ $^1$H NMR (400 MHz) 4 55 (t, $J$ = 3 50 Hz, 1H), 4 05~3 48 (m, 4H), 3 52 (d, $J$ = 9 41 Hz, 1H), 3 09 (d, $J$ = 9 41 Hz, 1H), 3 08~3 02 (m, 1H), 2 89~2 86 (m, 1H), 1 94~1 50 (m, 8H), 1 02 (s, 3H), 1 01 (s, 3H) (NMR data are described for the major isomer in the mixture which contains two isomers epimeric at stereogenic carbon in THP moiety) Calcd. for $C_{13}H_{24}O_4$ C, 63 91, H, 9 90% Found C, 63 92, H, 9 92%

Triphenylmethyl chloride (9 7 g, 35 mmol) was added to a solution of 4-dimethylaminopyridine (400 mg, 3 3 mmol), triethylamine (5 3 ml, 38 mmol), and **29** (7 72 g, 31 6 mmol) in dichloromethane (100 ml) at room temperature After being stirred for 10 h, the mixture was concentrated under reduced pressure, diluted with ether, and washed with water The organic layer was dried over $MgSO_4$, concentrated, and chromatographed on silica gel (hexane-ethyl acetate = 10 1) to give trityl ether **30** (13 13 g, 85 %) as a viscous oil, $[\alpha]_D^{20}$ +9 5° (c 0 750, $CHCl_3$) IR (neat) 2944, 1444, 1120, 1065, 1032, 901, 763, 703, 633cm$^{-1}$ $^1$H NMR (400 MHz) 7 46~7 44 (m, 6H), 7 31~7 21 (m, 9H), 4 54 (br t, $J$ = 3 42 Hz, 1H), 3 79 (ddd, $J$ = 3 42, 8 09, 10 42 Hz, 1H), 3 53 (d, $J$ = 9 28 Hz, 1H), 3 52~3 44 (m, 1H), 3 22 (dd, $J$ = 3 42, 10 25 Hz, 1H), 3 16 (dd, $J$ = 5 37, 10 74 Hz, 1H), 3 04 (d, $J$ = 9 28 Hz, 1H), 2 91~2 88 (m, 1H), 1 72~1 43 (m, 7H), 1 00 (s, 3H), 0 99 (s, 3H) (NMR data are described for the major isomer in the mixture) Calcd for $C_{32}H_{38}O_4$ C, 78 98, H, 7 87% Found C, 78 74, H, 7 92%

**(2*R*,3*R*)-1,2-Carbonyldioxy-6-hydroxy-3,5,5-trimethylhexane (33)** Methylmagnesium bromide (1 7 ml, 3 0 mol dm$^{-3}$ in ether) was added to a suspension of CuI (145 mg, 0 761 mmol) in THF (20 ml) at -20 °C and the mixture was stirred for 30 min After a solution of trityl ether **30** (1 24 g, 2 55 mmol) in

THF (5 ml) was added, the mixture was allowed to warm to 0 °C and left in refrigerator (0 °C) for 10 h The mixture was quenched with saturated aqueous $NH_4Cl$ (20 ml), extracted with ether, dried over $MgSO_4$, and concentrated. The residue was added to a solution of (*dl*)-camphorsulfonic acid (100 mg, 0 43 mmol) in methanol (20 ml) at room temperature and stirred for 10 h To this solution was added triethylamine (1.0 ml, 7 2 mmol) and the resulting mixture was concentrated under reduced pressure Silica gel column chromatography of the residue ($CHCl_3$-methanol = 10 1) gave the desired 1,2,6-triol **32** (252 mg, 56 %) and the undesired 1,3,6-triol (97 mg, 22 %) as an oil **32**, $[\alpha]_D^{20}$ +2 5° (c 0 867, $CHCl_3$) IR (neat) 3348, 2952, 1468, 1044, 909, 879cm$^{-1}$ $^1$H NMR (400 MHz) 3 75 (dd, *J* = 2 93, 10 74 Hz, 1H), 3 49 (d, *J* = 11 23 Hz, 1H), 3.46 (dd, *J* = 7 32, 10 74 Hz, 1H), 3 37 (br dt, *J* = 2 93, 7 32 Hz, 1H), 3 15 (d, *J* = 11 23 Hz, 1H), 3 14~3 02 (br s, 3H), 1 84 (dd, *J* = 1 95, 14 16 Hz, 1H), 1 57 (bq, *J* = 6 35 Hz, 1H), 0 93 (s, 3H), 0 91 (d, *J* = 6 84 Hz, 3H) 0 97~0 92 (m, 1H) 0 82 (s, 3H)

To a solution of triol **32** (237 mg, 1 34 mmol) in THF (10 ml) was added carbonyldiimidazole (652 mg, 4 02 mmol) at room temperature After being stirred for 3 h, aqueous HCl (10 ml, 3 mol dm$^{-3}$) was added to the mixture The whole mixture was stirred for 3 h, extracted with ether, dried over $MgSO_4$, concentrated, and chromatographed on silica gel (hexane-ethyl acetate = 6 4~3 7) to give carbonate **33** (241 mg, 89 %) as an oil, $[\alpha]_D^{20}$ +11 2° (c 0 654, $CHCl_3$) IR (neat) 3502, 2954, 1793, 1474, 1392, 1178, 1065, 774cm$^{-1}$. $^1$H NMR (400 MHz) 4 54 (br q, *J* = 6.83 Hz, 1H), 4 47 (t, *J* = 8 30 Hz, 1H), 4 19 (dd, *J* = 7 32, 8 30 Hz, 1H), 3 33 (ABq, *J* = 11 23 Hz, 2H), 1 96 (dddq, 6 83, 6 83, 6 83, 2 44 Hz, 1H), 1 64~1 52 (br s, 1H), 1 50 (dd, *J* = 2 93, 14 16 Hz, 1H), 1 14 (dd, *J* = 6 83, 14 16 Hz, 1H), 1 01 (d, *J* = 6 83 Hz, 3H), 0 93 (s, 3H), 0 90 (s, 3H) Calcd. for $C_{10}H_{18}O_4$ C, 59 39, H, 8 97% Found C, 59 49, H, 8 95%

**(2*R*,3*R*)-1,2-Carbonyldioxy-3,5,5-trimethyl-6,6-propylenedithiohexane (34)** Dimethyl sulfoxide (115 µl, 1 62 mmol) was added to a solution of oxalyl chloride (97 µl, 1 1 mmol) in dichloromethane (10 ml) at -78 °C After 10 min, a solution of carbonate **33** (200 mg, 0 989 mmol) in dichloromethane (1 ml) was added to the solution and stirred for 30 min To the solution was added triethylamine (0 70 ml, 5 0 mmol) and the mixture was stirred for another 30 min Then the reaction temperature was gradually raised to room temperature. The mixture was concentrated under diminished pressure, diluted with ether, filtrated through a pad of silica gel, and concentrated, and diluted with dichloromethane (10 ml) To this solution were successively added propanedithiol (120 µl, 1 2 mmol) and $BF_3$•$OEt_2$ (10 µl, 0 081 mmol) at 0 °C and the mixture was stirred for 1 h After saturated aqueous $NaHCO_3$ (20 ml) was added, the mixture was extracted with ether, dried over $MgSO_4$, and concentrated Silica gel chromatography of the residue (hexane-ethyl acetate = 7 3~6.4) gave thioacetal **34** (207 mg, 72 %) as an oil, $[\alpha]_D^{20}$ +9 4° (c 0 796, $CHCl_3$) IR (neat) 2960, 1799, 1465, 1387, 1172, 1074, 773cm$^{-1}$ $^1$H NMR (400 MHz) 4 63 (ddd, *J* = 6 35, 7 32, 8 31 Hz, 1H), 4 47 (t, *J* = 8.30 Hz, 1H), 4 22 (dd, *J* = 6 84, 8 31 Hz, 1H), 4 01 (s, 1H), 2 91~2 87 (m, 4H), 2 12~2 02 (m, 2H), 1 84~1 78 (m, 1H), 1 63 (dd, *J* = 2 93, 14 16 Hz, 1H), 1 36 (dd, *J* = 6 84, 14 16 Hz, 1H), 1 14 (s, 3H), 1 12 (s, 3H), 1 03 (d, *J* = 6 84 Hz, 3H) Calcd for $C_{13}H_{22}O_3S_2$ C, 53 76, H, 7 63% Found C, 53 69, H, 7 60%

**(2*R*,3*R*)-1,2-Isopropylidenedioxy-3,5,5-trimethyl-6,6-propylenedithiohexane (35)** To a suspension of $K_2CO_3$ (200 mg, 1 4 mmol) in methanol was added thioacetal **34** (193 mg, 0 664 mmol) at 40 °C After 5 h, bulk of methanol was removed under reduced pressure The residue was diluted with ether, washed with water, dried over $MgSO_4$, filtrated through a pad of silica gel, concentrated, and diluted with dichloromethane (7 ml) To this solution were added PPTS (20 mg, 0 080 mmol) and 2,2-dimethoxypropane (100 µl, 0 81 mmol) at room temperature After being stirred for 3 h, the mixture was concentrated Silica gel chromatography of the residue (hexane-ethyl acetate = 8 2) gave acetonide **35** (179 mg, 90 %) as an oil, $[\alpha]_D^{20}$ -5 1° (c 0 450, $CHCl_3$) IR (neat) 2966, 1459, 1366, 1257, 1211, 1157, 1056, 861, 777cm$^{-1}$ $^1$H NMR (400 MHz). 4 04 (s, 1H), 4 00~3 96 (m, 2H), 3 64 (dt, *J* = 5 37, 10 74 Hz, 1H), 2 92~2 83 (m, 4H), 2 11~2 05 (m, 1H), 1 87~1 75 (m, 2H), 1 67 (dd, *J* = 2 92, 14 16 Hz, 1H), 1 55 (s, 3H), 1 41 (s, 3H), 1 32

(dd, $J$ = 6.84, 14 16 Hz, 1H), 1 12 (s, 3H), 1 10 (s, 3H), 0 95 (d, $J$ = 6 83 Hz, 3H) Calcd. for $C_{15}H_{28}O_2S_2$ C, 59 16, H, 9 27% Found C, 59 03, H, 9 24%

**(2*S*,3*R*,4*R*,5*R*,8*S*)-8-(*m*-Benzyloxymethoxyphenyl)-1-(*t*-butyldimethylsiloxy)-5-hydroxymethyl-8-methoxy-3-methyl-2-(2-tetrahydropyranyloxy)octan-4-ol (36)** A solution of bromide **17** (200 mg, 0 548 mmol) in THF (2 ml) was added dropwise to a suspension of magnesium (14 6 mg, 0.601 mmol) in THF (1 ml). The mixture was kept standing under ultrasonification for 1 h The solution was added to a slurry of CuI (10 4 mg, 0 0546 mmol) in THF (1 ml) at -30 °C After epoxy alcohol **24** (30 0 mg, 0 0832 mmol) was added to this cuprate solution, the mixture was quenched with a saturated aqueous solution of $NH_4Cl$, extracted with ether, dried, and concentrated Column chromatography of the residue on silica gel (hexane-ethyl acetate = 5 1) gave diol **36** (47 3 mg, 88 %) as an oil, $^1$H NMR (400 MHz) 7.33 (s, 5H), 7 31~6 93 (m, 4H), 5 30 (s, 2H), 4 76 (m, 1H), 4 74 (s, 2H), 4 07~3.32 (m, 9H), 3 20 (s, 3H), 2 23~1.51 (m, 14H), 0 88 (s, 9H), 0 89 (d, $J$ = 6 83 Hz, 3H), 0 60 (s, 3H), 0 54 (s, 3H) (NMR data are described for the major isomer in the diastereomeric mixture)

**(2*S*,3*R*,4*R*,5*S*,8*S*)-8-(*m*-Benzyloxymethoxyphenyl)-8-methoxy-3,5-dimethyl-2-(2-tetrahydropyranyloxy)octane-1,4-diol (37)** 4-Dimethylaminopyridine (40 0 mg, 0 327 mmol) and methanesulfonyl chloride (15 0 µl, 0 194 mmol) were added at room temperature to a solution of the diol **36** (105 mg, 0 163 mmol) in THF (2 ml) After being stirred for 12 h, the mixture was concentrated Column chromatography of the residue on silica gel (hexane-ethyl acetate = 4 1) gave the corresponding methanesulfonate (109 mg, 93 %) as an oil, $^1$H NMR (400 MHz) 7 33 (s, 5H), 7 31~6 92 (m, 4H), 5 30 (s, 2H), 4 74 (s, 2H),4 72 (m, 1H), 4 44~3 50 (m, 9H), 3 20 (s, 3H), 2 95 (s, 3H), 2 13~1 50 (m, 13H), 0 94 (d, $J$ = 7 32 Hz, 3H), 0 88 (s, 9H), 0 06 (s, 6H) (NMR data are described for the major isomer in the diastereomeric mixture)

Lithium aluminum hydride (500 µl, 1 0 mol dm$^{-3}$ in THF) was added at room temperature to a solution of the methanesulfonate (164 mg, 0 227 mmol) in THF (6 ml) After being stirred for 14 h, the reaction mixture was quenched with a saturated aqueous solution of KF (0 5 ml), extracted with ether, dried, and concentrated Column chromatography of the residue on silica gel (hexane-ethyl acetate = 7 3) gave diol **37** (72 8 mg, 62 %) as an oil, $^1$H NMR (400 MHz) 7 33 (s, 5H), 7 31~6 93 (m, 4H), 5 30 (s, 2H), 4 74 (s, 2H),4 55 (m, 1H), 4 05~3 50 (m, 7H), 3 21 (s, 3H), 2 25 (m, 1H), 1 82~1 58 (m, 13H), 0 82 (d, $J$ = 6 35 Hz, 3H), 0 81 (d, $J$ = 6 84 Hz, 3H) (NMR data are described for one of the isomer in the mixture)

**(2*R*,3*R*,4*R*,5*S*,8*S*)-8-(*m*-Benzyloxymethylphenyl)-1,2-epoxy-8-methoxy-3,5-dimethyloctan-4-ol (38)** 4-Dimethylaminopyridine (75 0 mg, 0 614 mmol) and acetic anhydride (43 0 µl, 0 455 mmol) were added at room temperature to a solution of diol **37** (78 6 mg, 0 152 mmol) in dichloromethane (2 ml) After being stirred for 12 h, the mixture was concentrated in *vacuo* Column chromatography of the residue on silica gel (hexane-ethyl acetate = 5 1) gave the corresponding diacetate (82 8 mg, 91 %) as an oil, $^1$H NMR (400 MHz) 7 33 (s, 5H), 7 31~6 91 (m, 4H), 5 31 (s, 2H), 4 93 (m, 1H),4 74 (s, 2H), 4 50~3 43 (m, 7H), 3 20 (s, 3H), 2 05 (s, 3H), 2 03 (s, 3H), 2 02~1 26 (m, 12H), 0 85 (d, $J$ = 6 84 Hz, 3H), 0 85 (d, $J$ = 6 84 Hz, 3H) (NMR data are described for the major isomer in the diastereomeric mixture)

A solution of the diacetate (82 8 mg, 0 138 mmol) and PPTS (6 9 mg, 0 028 mmol) in methanol (2 8 ml) was stirred at room temperature for 36 h and concentrated Column chromatography of the residue (hexane-ethyl acetate = 7 3) gave the corresponding hydroxy diacetate (60 9 mg, 86 %) as an oil, $^1$H NMR (400 MHz) 7 33 (s, 5H), 7 32~6 82 (m, 4H), 5 31 (s, 2H), 4 74 (s, 2H), 4 12~4 00 (m, 4H), 3 69 (m, 1H), 3 20 (s, 3H), 2 90 (m, 1H), 2 09 (s, 3H), 2 05 (s, 3H) 1 76~1 63 (m, 2H), 1 35 (m, 2H), 1 17 (m, 2H), 0 85 (d, $J$=17 58 Hz, 3H), 0 85 (d, $J$=14 65 Hz, 3H)

4-Dimethylaminopyridine (29 0 mg, 0 237 mmol) and methanesulfonyl chloride (14 0 µl, 0 181 mmol) were added at room temperature to a solution of the hydroxy diacetate (60 9 mg, 0 118 mmol) in

dichloromethane After being stirred for 12 h, the solvent was evaporated under reduced pressure Column chromatography of the residue on silica gel (hexane-ethyl acetate = 4 1) gave the corresponding methanesulfonate (68 4 mg, 97 %) as an oil, $^1$H NMR (400 MHz) 7 33 (s, 5H), 7 32~6.91 (m, 4H), 5.31 (s, 2H), 4 92 (m, 1H), 4 83 (dd, $J$ = 9 77, 2 45 Hz, 1H), 4 74 (s, 2H), 4 31 (m, 1H), 4 19 (m, 1H),4 02 (m, 1H), 3 20 (s, 3H), 3 07 (s, 3H), 2 12 (s, 3H), 2 08 (s, 3H) 1 78~1 69 (m, 4H), 1 31~1 29 (m, 2H), 0.92 (d, $J$ = 6 84 Hz, 3H), 0.85 (d, $J$ = 6 83 Hz, 3H)

Aqueous potassium hydroxide (0.25 ml, 1 0 mol dm$^{-3}$) was added at room temperature to a solution of the methanesulfonate (29 8 mg, 0 050 mmol) in methanol (1 ml) After being stirred for 24 h, a bulk of methanol was removed The residual solution was diluted with water and extracted with ether. The organic layer was dried and concentrated Repeated column chromatography of the residue (hexane-ethyl acetate = 8 2~7 3) gave epoxy alcohol **38** (6 4 mg, 31 %) as an oil **38**, $^1$H NMR (400 MHz) 7 33 (s, 5H), 7 31~6.94 (m, 4H), 5 30 (s, 2H), 4 74 (s, 2H), 4 05 (m, 1H), 3 50 (m, 1H), 3 21 (s, 3H), 2 88 (m, 1H), 2 75 (dd, $J$ = 4 40, 4 40 Hz, 1H), 2 47 (dd, $J$ = 4 88, 2 93 Hz, 1H), 2 32 (m, 1H), 1 88~1 49 (m, 6H), 0 88 (d, $J$ = 6 84 Hz, 3H), 0.83 (d, $J$ = 6.34 Hz, 3H)

***(2R,3R,4R,5S,8S)*-8-[*m*-(Benzyloxymethoxy)phenyl]-1,2-epoxy-8-methoxy-4-(*p*-methoxybenzyloxy)-3,5-dimethyloctane (39)** To a suspended solution of alcohol **38** (15 0 mg, 0.0362 mmol) and NaH (2.9 mg, 60 % in mineral oil, 0 073 mmol) in THF-DMF (3 ml, 3 1) was added *p*-methoxybenzyl chloride (8 7 μl, 0 064 mmol) at room temperature After being stirred for 24 h, the mixture was quenched with a 5% aqueous $H_3PO_4$ solution (5 0 ml) The solution was extracted with ether, dried over MgSO4, and concentrated Silica gel chromatographic purification of the residue (hexane-ethyl acetate = 8 2) gave MPM ether **39** (16 9 mg, 87 %) as an oil, $[\alpha]_D^{23}$ -42° (c 0 31, $CHCl_3$) IR (neat) 2926, 1607, 1510, 1451, 1245, 1089, 1023, 787, 699cm$^{-1}$ $^1$H NMR (400 MHz) 7 35~7 21 (m, 6H), 7 23 (d, $J$ = 8 30 Hz, 2H), 7 02~7 00 (m, 2H), 6 94 (d, $J$ = 7 32 Hz, 1H), 6 85 (d, $J$ = 8 30 Hz, 2H), 5 30 (s, 2H), 4 73 (s, 2H), 4 45 (ABq, $J$ = 10 74 Hz, 2H), 4 03 (dd, $J$ = 5 86, 7 32 Hz, 1H), 3 79 (s, 3H), 3 21 (s, 3H), 3 17 (t, $J$ = 5 37 Hz, 1H), 3 02 (ddd, $J$ = 2 39, 4 40, 6 83 Hz, 1H), 2 67 (dd, $J$ = 4 40, 4 89 Hz, 1H), 2 44 (dd, $J$ = 2 93, 4 89 Hz, 1H), 1 87~1 59 (m, 4H), 1 46~1 40 (m, 2H), 0 93 (d, $J$ = 6 34 Hz, 3H), 0 88 (d, $J$ = 6 84 Hz, 3H) Calcd for $C_{33}H_{42}O_6$ C, 74 13, H, 7 92% Found C, 73 94, H, 7 90%

**(2*R*,3*R*)-4-Benzyloxy-1,2-isopropylidenedioxy-3-methylbutane (42).** To a solution of epoxide **41** (5 10 g, 26 3 mmol) in dichloromethane (30 ml) was added trimethylaluminum (55 ml, 1 0 mol dm$^{-3}$ in hexane) at -20 °C After being stirred for 30 min, the mixture was left in refrigerator (0 °C) for 12 h and quenched with aqueous HCl (20 ml, 3 mol dm$^{-3}$) The mixture was extracted with ether, dried over $MgSO_4$, filtrated through a pad of silica gel, and concentrated to give a mixture of 1,2- and 1,3- diol (4 53 g, 82 %)

To a solution of the mixture of isomeric diols (4 53 g, 21 5 mmol) in dichloromethane (40 ml) were added 2,2-dimethoxypropane (2 9 ml, 24 mmol) and (*dl*)-camphorsulfonic acid (100 mg, 0 43 mmol) at room temperature After being stirred for 3 h, the solution was concentrated and chromatographed on silica gel (hexane-ethyl acetate = 10 1 ~ 9 1) to give 1,2-acetonide **42** (3 80 g, 71 %) and its 1,3-isomer (1 04 g, 19 %) **42**, $[\alpha]_D^{19}$ +1 4° (c 1 25, $CHCl_3$) IR (neat) 2978, 1451, 1367, 1212, 1157, 1065, 859, 736, 698cm$^{-1}$ $^1$H NMR (90 MHz) 7 48~7 14 (br s, 5H), 4 49 (s, 2H), 4 17~3 84 (m, 2H), 3 81~3 19 (m, 3H), 2 18~1 78 (m, 1H), 1 37 (s, 3H), 1 33 (s, 3H), 0 94 (d, $J$ = 7 31 Hz, 3H) Calcd for $C_{15}H_{22}O_3$ C, 71 97, H, 8 86% Found C, 71 97, H, 8 85%

**Ethyl (2*E*,4*R*,5*R*)-5,6-isopropylidenedioxy-4-methyl-2-hexenoate (43)** To a solution of acetonide **42** (1 10 g, 4 39 mmol) in ethanol (40 ml) was added Pd-charcoal (100 mg, 5 % Pd on charcoal) at room temperature and the resulting suspension was vigorously stirred under hydrogen atmosphere (1 atm) After 10 h, the mixture was filtered through a pad of Celite and the filtrate was concentrated to give alcohol (670 mg, 4 18 mmol) which was immediately used for the following reaction without further purification

Dimethylsulfoxide (650 μl, 9 2 mmol) was added to a solution of oxalyl chloride (410 μl, 4,7 mmol) in dichloromethane (30 ml) at -78 °C. After 10 min, a solution of the above alcohol (670 mg, 4 18 mmol) in dichloromethane (5 ml) was added to the mixture and stirred for 15 min After triethylamine (3 0 ml, 22 mmol) was added, the resulting mixture was stirred for another 30 min and allowed to warm to room temperature The mixture was concentrated under diminished pressure, diluted with ether, filtrated through a pad of silica gel, and concentrated to give the corresponding aldehyde which was immediately used for the next reaction

To a solution of ethyl diisopropyl phosphonoacetate (2 60 g, 10 mmol) in THF (40 ml) was added potassium *t*-butoxide (1.10 g, 9 8 mmol) at room temperature After being stirred for 1 h, the mixture was cooled to -78 °C To this mixture was added a solution of the above aldehyde in THF (5 ml) and the whole mixture was stirred for another 1 h The mixture was quenched with saturated aqueous $NH_4Cl$ (20 ml) and warmed to room temperature The solution was extracted with ether, dried over $MgSO_4$, and concentrated. Silica gel column chromatography of the residue (hexane-ethyl acetate = 9 1~8 2) gave the desired *E*-unsaturated ester **43** (440 mg, 44 % from **42**) as an oil which contained a small amount (3 %) of by-product which is epimeric to **43** at C4 **43**; $[\alpha]_D^{20}$ +21 3° (c 1 13, $CHCl_3$) IR (neat) 2980, 1717, 1651, 1456, 1368, 1182, 1062, 857cm$^{-1}$ $^1$H NMR (400 MHz) 6 97 (dd, *J* = 7 56, 15 62 Hz, 1H), 5 86 (dd, *J* = 1 46, 15 62 Hz, 1H), 4 19 (q, *J* = 7 08 Hz, 2H), 4 05~3 98 (m, 2H), 3 66~3 62 (m, 1H), 2 49 (ddq, *J* = 6 83, 6 83, 6 83 Hz, 1H), 1 41 (s, 3H), 1 35 (s, 3H), 1 29 (t, *J* = 7 08 Hz, 3H), 1 05 (d, *J* = 6 83 Hz, 3H) (NMR data are described for the major isomer in the mixture) Calcd for $C_{12}H_{20}O_4$ C, 63 14, H, 8 83% Found C, 63 08, H, 8 77%

**(2*E*,4*R*,5*R*)-5,6-Isopropylidenedioxy-4-methyl-2-hexen-1-ol (44)** Diisobutylaluminum hydride (2 4 ml, 1 0 mol dm$^{-3}$ in hexane) was added to a solution of ester **43** (222 mg, 0 972 mmol) in dichloromethane (10 ml) at -78 °C and stirred for 1 h at the temperature Methanol (0 5 ml) was added to this solution and the whole mixture was stirred for another 5 min The solution was gradually warmed to room temperature At this point, the solution became a white gel To the gel was added saturated aqueous potassium sodium tartrate (10 ml) and the whole mixture was left until it became a clear solution The solution was extracted with ether, dried over $MgSO_4$, concentrated, and chromatographed on silica gel (hexane-ethyl acetate = 6 4) to give allylic alcohol **44** (174 mg, 96 %) as an oil, $[\alpha]_D^{22}$ +9 1° (c 0 867, $CHCl_3$) IR (neat) 3410, 2978, 1370, 1212, 1064, 976, 858cm$^{-1}$ $^1$H NMR (400 MHz) 5 75~5 69 (m, 2H), 4 15~4 10 (m, 2H), 4 02~3 93 (m, 2H), 3 67 (dd, *J* = 6 83, 7 10 Hz, 1H), 2 35 (ddq, *J* = 6 84, 6 84, 6 84 Hz, 1H), 1 73 (bt, *J* = 5 37 Hz, 1H), 1 41 (s, 3H), 1 35 (s, 3H), 1 00 (d, *J* = 6 84 Hz, 3H) Calcd for $C_{10}H_{18}O_3$ C, 64 49, H, 9 74% Found C, 64 27, H, 9 70%

**(2*S*,3*S*,4*R*,5*R*)-2,3-Epoxy-5,6-isopropylidenedioxy-4-methylhexan-1-ol (45)** To a solution of (+)-diisopropyl tartrate (241 mg, 1 03 mmol) in dichloromethane (7 ml) were added titanium tetraisopropoxide (278 μl, 0 934 mmol) and *t*-butyl hydroperoxide (670 μl, 2 7 mol dm$^{-3}$ in toluene) at -20 °C After 30 min, a solution of allylic alcohol **44** (174 mg, 0 934 mmol) in dichloromethane (3 ml) was added After being stirred for 1 h, the mixture was left in refrigerator (-20 °C) for 10 h The mixture was quenched with pre-cooled (-20 °C) aqueous acetone (22 ml, acetone-$H_2O$ = 10 1) and gradually warmed to room temperature with stirring After 3 h, Celite (5 g) was added and the resulting suspension was further stirred for 3 h The mixture was filtrated through a pad of Celite and concentrated under reduced pressure The residue was chromatographed on silica gel (hexane-ethyl acetate = 6 4~1 1) to give epoxy alcohol **45** (154 mg, 82 %) which was contaminated with a small amount (5 8 %) of inseparable diastereomer based on NMR analysis, $[\alpha]_D^{24}$ -23 6° (c 1 08, $CHCl_3$) IR (neat) 3462, 2978, 1453, 1371, 1215, 1158, 1060, 858cm$^{-1}$ $^1$H NMR (400 MHz) 4 09~4 00 (m, 2H), 3 95~3 90 (m, 1H), 3 80~3 74 (m, 2H), 3 69~3 61 (m, 1H), 3 05~3 01 (m, 2H) 2 01 (br t, *J* = 6 59 Hz, 1H), 1 75 (ddq, *J* = 6 84, 6 84, 6 84 Hz, 1H), 1 43 (s, 3H), 1 37 (s, 3H), 0 95 (d, *J* = 6 84 Hz, 3H) (NMR data are described for the major isomer in the mixture) Calcd for $C_{10}H_{18}O_4$ C, 59 39, H, 8 97% Found C, 59 14, H, 8 94%

**(2*R*,3*R*,4*R*,5*R*,8*S*)-8-[*m*-(Benzyloxymethoxy)phenyl]-5-hydroxymethyl-1,2-isopropylidene-dioxy-8-methoxy-3-methyloctan-4-ol (46)** To a gently refluxing suspension of Mg (243 mg, 10 0 mmol, turning) in THF (10 ml) were added dibromoethane (50 µl, 0 58 mmol) and bromide **17** (2 55 g, 6 98 mmol) dropwise After being stirred for 1 h, the mixture was cooled to room temperature and added to a suspension of CuI (251 mg, 1 32 mmol) in THF (10 ml) at -20 °C

To a solution of epoxide **45** (890 mg, 4 40 mmol) in THF (10 ml) was added a solution of methylmagnesium bromide (4 58 ml, 1 0 mol $dm^{-3}$ in THF) at 0 °C After being stirred for 5 min, the solution was gradually warmed to room temperature and added to the above suspension of copper reagent at -20 °C The whole mixture was left in refrigerator (-20 °C) for 10 h To the mixture was added saturated aqueous $NH_4Cl$ (20 ml) and the solution was vigorously stirred until the aqueous layer became a clear blue solution at room temperature The organic layer was extracted with ether, dried over $MgSO_4$, and concentrated Silica gel chromatography of the residue (hexane-ethyl acetate = 6 4 ~1 1) gave diol **46** (1 57 g, 73 %) as an oil, $[\alpha]_D^{21}$ -28° (c 0 35, $CHCl_3$) IR (neat) 3444, 2932, 1585, 1451, 1378, 1241, 1092, 861, 790, 750, 700$cm^{-1}$ $^1H$ NMR (400 MHz)· 7 35~7 26 (m, 6H), 7 03~7 00 (m, 2H), 6 96 (d, *J* = 7 81 Hz, 1H), 5 31 (s, 2H), 4 74 (s, 2H), 4 14 (dd, *J* = 5 86, 8 30 Hz, 1H), 4 09 (br t, *J* = 5 86 Hz, 1H), 3 97~3 93 (m, 2H), 3 65 (t, *J* = 8 03 Hz, 1H), 3 67~3 61 (m, 2H), 3 22 (s, 3H), 1 94~1 83 (m, 3H), 1 76~1 60 (m, 2H), 1 58~1 53 (m, 3H), 1 41 (s, 3H), 1 36 (s, 3H), 0 69 (d, *J* = 6 84 Hz, 3H) Calcd for $C_{28}H_{40}O_7$ C, 68 83, H, 8 25% Found C, 68 55, H, 8 21%

**(2*R*,3*R*,4*R*,5*S*,8*S*)-8-[*m*-(Benzyloxymethoxy)phenyl]-1,2-isopropylidenedioxy-8-methoxy-3,5-dimethyloctan-4-ol (47)** *p*-Toluenesulfonyl chloride (430 mg, 2 3 mmol) was added to a solution of 4-dimethylaminopyridine (50 mg, 0 41 mmol), triethylamine (400 µl, 2 9 mmol), and diol **46** (980 mg, 2 01 mmol) in dichloromethane (20 ml) at room temperature After being stirred for 1 h, the mixture was concentrated under reduced pressure, diluted with ether, and washed with water The organic layer was dried over $MgSO_4$, filtrated through silica gel, concentrated, and diluted with THF (10 ml) To this solution was added LAH (2.9 ml, 1 0 mol $dm^{-3}$ in THF) at room temperature After being stirred for 5 min, the mixture was quenched with aqueous NaOH (1 0 ml, 15 %) and filtrated The filtrate was poured into water, extracted with ether, dried over $MgSO_4$, and concentrated Silica gel chromatography of the residue (hexane-ethyl acetate = 8 2~7 3) gave alcohol **47** (858 mg, 90 %) as an oil, $[\alpha]_D^{21}$ -23 4° (c 1 37, $CHCl_3$) IR (neat) 3516, 2930, 1585, 1451, 1377, 1242, 1156, 1089, 1021, 860, 739, 699$cm^{-1}$ $^1H$ NMR (400 MHz) 7 34~7 24 (m, 6H), 7 01 (d, *J* = 0 97 Hz, 1H), 6 99 (dd, *J* = 0 97, 2 44 Hz, 1H), 6 95 (d, *J* = 7 33 Hz, 1H), 5 30 (s, 2H), 4 74 (s, 2H), 4 10 (dd, *J* = 5 86, 8 30 Hz, 1H), 4 04 (dd, *J* = 5 38, 7 81 Hz, 1H), 3 95 (ddd, *J* = 5 86, 7 81, 8 30 Hz, 1H), 3 76 (br s, 1H), 3 62 (t, *J* = 8 05 Hz, 1H), 3 46 (br d, *J* = 8 79 Hz, 1H), 3 22 (s, 3H), 1 84~1 72 (m, 1H), 1 71~1 65 (m, 2H), 1 56~1 40 (m, 2H), 1 37~1 35 (m, 1H), 1 41 (s, 3H), 1 36 (s, 3H), 0 85 (d, *J* = 6 35 Hz, 3H), 0 68 (d, *J* = 6 35 Hz, 3H) Calcd for $C_{28}H_{40}O_6$ C, 71 16, H, 8 53% Found C, 70 84, H, 8 53%

**(2*R*,3*R*,4*R*,5*S*,8*S*)-8-[*m*-(Benzyloxymethoxy)phenyl]-1,2-isopropylidenedioxy-8-methoxy-4-(*p*-methoxybenzyloxy)-3,5-dimethyloctane (48)** To a suspended solution of alcohol **47** (760 mg, 1 61 mmol) and NaH (100 mg, 60 % in mineral oil, 2 5 mmol) in THF-DMF (16 ml, 3 1) was added *p*-methoxybenzyl chloride (240 µl, 1 8 mmol) at room temperature After being stirred for 48 h, the mixture was quenched with aqueous $H_3PO_4$ (5 0 ml, 5 %) The solution was extracted with ether, dried over MgSO4, and concentrated Silica gel chromatographic purification of the residue (hexane-ethyl acetate = 8 2) gave MPM ether **48** (708 mg, 74 %) as an oil, $[\alpha]_D^{23}$ -40 3° (c 1 17, $CHCl_3$) IR (neat) 2930, 1608, 1510, 1451, 1367, 1246, 1157, 1089, 862, 788, 699$cm^{-1}$ $^1H$ NMR (400 MHz) 7 33~7 24 (m, 6H), 7 19 (d, *J* = 8 30 Hz, 2H), 7 02~6 92 (m, 2H), 6 93 (d, *J* = 7 81 Hz, 1H), 6 85 (d, *J* = 8 30 Hz, 2H), 5 29 (s, 2H), 4 73 (s, 2H), 4 37 (ABq, *J* = 10 74 Hz, 2H), 4 24 (ddd, *J* = 7 81, 6 35, 5 86 Hz, 1H), 4 02 (dd, *J* = 5 37, 7 82 Hz, 1H), 3 84 (dd, *J* = 6 35, 8 30 Hz, 1H), 3 82 (s, 1H), 3 64 (dd, *J* = 7 81, 8 30 Hz, 1H), 3 21 (s, 3H), 3 11 (t, *J* = 5 37 Hz, 1H), 2 19~2 15 (m, 1H), 1 86~1 82 (m, 1H), 1 73~1 71 (m, 1H), 1 63~1 55 (m, 1H), 1 44~1 31

(m, 2H), 1 38 (s, 3H), 1 30 (s, 3H), 0 93 (d, $J$ = 6 35 Hz, 3H), 0 89 (d, $J$ = 7 33 Hz, 3H) Calcd for $C_{36}H_{48}O_7$ C, 72 94, H, 8 16% Found C, 72 75, H, 8 10%

**(*2R,3R,4R,5S,8S*)-8-[*m*-(Benzyloxymethoxy)phenyl]-1,2-epoxy-8-methoxy-4-(*p*-methoxybenzyloxy)-3,5-dimethyloctane (39)** PPTS (20 mg, 0 08 mmol) was added to a solution of MPM ether **48** (697 mg, 1 18 mmol) in MeOH (10 ml) at room temperature After being stirred for 10 h, the solution was concentrated under reduced pressure, diluted with ether, filtrated through a pad of silica gel, and concentrated Silica gel chromatography of the residue (hexane-ethyl acetate = 6 4) gave diol (313 mg, 48 %) and the recovered MPM ether **48** (190 mg, 27 %)

The obtained diol (313 mg, 0 566 mmol) and potassium *t*-butoxide (200 mg, 1 78 mmol) were dissolved in THF (5 0 ml) To this solution was added a solution of *p*-toluenesulfonyl chloride (800 µl, 1 mol $dm^{-3}$ in THF) at room temperature After being stirred for 30 min, aqueous $H_3PO_4$ (1 0 ml, 5 %) was added to the solution and the mixture was poured into water, extracted with ether, dried over $MgSO_4$, and concentrated Silica gel chromatography of the residue (hexane-ethyl acetate = 8 2) gave the pure epoxide **39** (231 mg, 78 %) as an oil Compound **39** thus obtained gave the same spectral and analytical data as compound **39** prepared from **38** (*vide supra*)

**(*2R,3R,8S,9S,10R,11S,14S*)-14-[*m*-(Benzyloxymethoxy)phenyl]-1,2-isopropylidenedi-oxy-14-methoxy-10-(*p*-methoxybenzyloxy)-6,6-propylenedithio-3,5,5,9,11-pentamethyltetra-decan-8-ol (49)** Butyllithium (430 µl, 1 6 mol $dm^{-3}$ in hexane) was added to a solution of tetramethylethylenediamine (340 µl, 2 3 mmol) and **35** (137 mg, 0 450 mmol) in THF (4 0 ml) at -20 °C After being stirred for 1 h, the mixture was left in refrigerator (-20 °C) for 10 h To the solution was added a solution of epoxide **39** (184 mg, 0 344 mmol) in THF (1 0 ml) at -20 °C and the mixture was again left in refrigerator (-20 °C) After 10 h, the mixture was quenched with aqueous $H_3PO_4$ (1.0 ml), poured into water, extracted with ether, dried over $MgSO_4$, and concentrated. Silica gel chromatography of the residue (hexane-ethyl acetate = 9 1~8 2~7 3) gave alcohol **49** (171 mg, 59 %) and the recovered epoxide **39** (69 mg, 38 %) **49**, $[\alpha]_D^{21}$ -5 8° (c 1 10, $CHCl_3$) IR (neat) 3424, 2926, 1607, 1510, 1451, 1377, 1245, 1157, 1085, 753, 700$cm^{-1}$ $^1H$ NMR (400 MHz) 7 35~7 20 (m, 6H), 7 22 (d, $J$ = 8 31 Hz, 2H), 7 01~6 98 (m, 2H), 6 94 (d, $J$ = 7 82 Hz, 1H), 6 83 (d, $J$ = 8 79 Hz, 2H), 5 28 (s, 2H), 4 72 (s, 2H), 4 61 (d, $J$ = 10 74 Hz, 1H), 4 45 (dd, $J$ = 4 40, 9 27 Hz, 1H), 4 37 (d, $J$ = 10 74 Hz, 1H), 4 16 (br s, 1H), 4 04 (br t, $J$ = 6 59 Hz, 1H), 3 95 (dd, $J$ = 6 35, 7 81 Hz, 1H), 3 89 (dd, $J$ = 6 35, 13 19 Hz, 1H), 3 78 (s, 3H), 3 58 (dd, $J$ = 7 33, 7 81 Hz, 1H), 3 26 (dd, $J$ = 3 42, 7 81 Hz, 1H), 3 21 (s, 3H), 2 94 (dt, $J$ = 14 65, 6 83 Hz, 1H), 2 83 (dd, $J$ = 5 86, 6 83 Hz, 2H), 2 70 (dt, $J$ = 14 65, 5 86 Hz, 1H), 2 15 (d, $J$ = 15 63 Hz, 1H), 2 10~1 96 (m, 2H), 1 90~1 81 (m, 3H), 1 77~1 60 (m, 3H), 1 45 (dd, $J$ = 7 08, 15 38 Hz, 2H), 1 38 (s, 3H), 1 33 (s, 3H), 1 11 (br s, 6H), 0 94~0 90 (m, 9H) Calcd for $C_{48}H_{70}O_8S_2$ C, 68 70, H, 8 41% Found C, 68 71, H, 8 18%

**(*2R,3R,8S,9S,10R,11S,14S*)-14-[*m*-(Benzyloxymethoxy)phenyl]-1,2-isopropylidene-dioxy-14-methoxy-10-(*p*-methoxybenzyloxy)-6,6-propylenedithio-3,5,5,9,11-pentamethyl-tetradecan-8-yl (*3R,4R*)-4-benzyloxymethoxy-3-(*p*-methoxybenzyloxy)pentanoate (50)** To a solution of **12** (84 mg, 0 22 mmol) and triethylamine (40 µl, 0 29 mmol) in toluene (1 0 ml) was added 2,4,6-trichlorobenzoyl chloride (41 µl, 0 26 mmol) at room temperature After being stirred for 3 h, a supernatant solution of the resulting suspension was added to a solution of alcohol **49** (60 mg, 0 071 mmol) and 4-dimethylaminopyridine (33 mg, 0 27 mmol) in toluene (1 0 ml) at 50 °C After being stirred for 1h, the mixture was cooled to room temperature and poured into water The organic layer was extracted with ether, dried over $MgSO_4$, filtrated through a pad of silica gel, and concentrated Preparative thin layer chromatography of the residue on silica gel (toluene-ethyl acetate = 10 1) gave ester **50** (72 mg, 85 %) and the recovered alcohol **49** (5 mg, 8 %) **50**, $[\alpha]_D^{20}$ -2 5° (c 0 63, $CHCl_3$) IR (neat) 2930, 1725, 1608, 1510, 1452, 1378, 1246, 1171, 1037, 822, 742, 699$cm^{-1}$ $^1H$ NMR (400 MHz) 7 34~7 23 (m, 15H), 7 02~6 99

(m, 2H), 6 95 (d, $J$ = 7 32 Hz, 1H), 6 83 (dd, $J$ = 1 46, 8 79 Hz, 4H), 5 68 (br d, $J$ = 7 81 Hz, 1H), 5 23 (s, 2H), 4 80 (ABq, $J$ = 6 83 Hz, 2H), 4 72 (s, 2H), 4 62~4 58 (m, 4H), 4 54 (d, $J$ = 10 26 Hz, 1H), 4 46 (d, $J$ = 10 26 Hz, 1H), 4 09~4 05 (m, 2H), 3 96~3 86 (m, 3H), 3 77 (s, 3H), 3 76 (s, 3H), 3 58 (t, $J$ = 6 83 Hz, 1H), 3 18 (s, 3H), 3 13 (dd, $J$ = 5 37, 6 83 Hz, 1H), 2 80~2 68 (m, 1H), 2 59~2 44 (m, 5H), 2 19 (t, $J$ = 8 30 Hz, 1H), 2.16 (t, $J$ = 7 81 Hz, 1H), 1 85~1 42 (m, 11H), 1 38 (s, 3H), 1 32 (s, 3H), 1 19 (d, $J$ = 6 35 Hz, 3H), 1.07 (s, 3H), 1 04 (s, 3H), 0 95 (d, $J$ = 6 35 Hz, 3H), 0 92 (d, $J$ = 7 32 Hz, 3H), 0 88 (d, $J$ = 6 83 Hz, 3H) Calcd for $C_{69}H_{94}O_{13}S_2$ C, 69 32, H, 7 92% Found C, 69 13, H, 7 82%

**(*2R,7S,8S,9R,10S,13S*)-13-[*m*-(Benzyloxymethoxy)phenyl]-13-methoxy-9-(*p*-methoxy-benzyloxy)-1,5-dioxo-2,4,4,8,10-pentamethyltridecan-7-yl (*3R,4R*)-4-benzyloxymethoxy-3-(*p*-methoxybenzyloxy)pen-tanoate (Kishi's aldehyde) (2).** PPTS (5 mg, 0 02 mmol) was added to a solution of ester **50** (60 mg, 0.050 mmol) in methanol (1 0 ml) at room temperature After being stirred for 40 h, the mixture was concentrated and filtrated through a pad of silica gel to give diol (52 mg, 90 %)

The resulting diol (52 mg, 0 045 mmol) and potassium acetate (44 mg, 0 45 mmol) was dissolved in acetonitrile and cooled to -20 °C To this solution was added lead tetraacetate (20 mg, 0 045 mmol) After being stirred for 30 min, the mixture was concentrated under reduced pressure, diluted with ether, filtrated through a pad of silica gel, and concentrated Preparative thin layer chromatography (hexane-ethyl acetate = 7 3) of the residue on silica gel gave aldehyde **51** (43 mg, 85 %) as an oil, $^1$H NMR (400 MHz) 9 42 (br s, 1H), 7 37~7 23 (m, 15H), 7 02~6 94 (m, 3H), 6 83 (d, $J$ = 8 31 Hz, 4H), 5 65 (br d, $J$ = 7 81 Hz, 1H), 5 28 (s, 2H), 4 80 (ABq, $J$ = 7 32 Hz, 2H), 4 72 (s, 2H), 4 60~4 46 (m, 6H), 4 10~4 05 (m, 2H), 3 95 (m, 1H), 3 77 (s, 3H), 3 76 (s, 3H), 3 17 (s, 3H), 3 13 (t, $J$ = 6 35 Hz, 1H), 2 83~2 76 (m, 1H), 2 60~2 49 (m, 4H), 2 37~2 33 (m, 1H), 2 21~2 13 (m, 3H), 1 90~1 70 (m, 2H), 1 75~1 50 (m, ), 1 20 (d, $J$ = 6 35 Hz, 3H), 1 03~0 79 (m, 15H).

To a solution of aldehyde **51** (5 0 mg, 0 0044 mmol) in acetone (0 45 ml), were successively added aqueous $AgNO_3$ (0 05 ml, 1 mol dm$^{-3}$) and *N*-chlorosuccinimide (1 0 mg, 0 0075 mmol) at room temperature The mixture was stirred for 30 min, poured into saturated aqueous $Na_2SO_3$, and extracted with ether The organic layer was dried over $MgSO_4$, concentrated, and purified by using preparative thin layer chromatography (hexane-ethyl acetate = 7 3) to give Kishi's intermediate **2** (4 1 mg, 89 %) as an oil, $[\alpha]_D^{20}$ -7 4° (c 0 18, $CHCl_3$) IR (neat) 2930, 1728, 1608, 1510, 1454, 1379, 1246, 1172, 1089, 1037, 822, 737, 699cm$^{-1}$ $^1$H NMR (400 MHz) 9 42 (d, $J$ = 1 95 Hz, 1H), 7 36~7 18 (m, 15H), 7 02~6 99 (m, 2H), 6 94 (d, $J$ = 7 33 Hz, 1H), 6 84~6 80 (m, 4H), 5 66~5 63 (m, 1H), 5 30 (s, 2H), 4 78 (ABq, $J$ = 7 33 Hz, 2H), 4.71 (s, 2H), 4 60 (ABq, $J$ = 11 72 Hz, 2H), 4 54 (ABq, $J$ = 11 23 Hz, 2H), 4,39 (ABq, $J$ = 10 26 Hz, 2H), 4 08~3 99 (m, 2H), 3 91 (dd, $J$ = 4 88, 6 35 Hz, 1H), 3 78 (s, 3H), 3 76 (s, 3H), 3 19 (s, 3H), 3 10 (dd, $J$ = 4 88, 6 35 Hz, 1H), 2 79~2 77 (m, 1H), 2 58 (dd, $J$ = 3 91, 16 11 Hz, 1H), 2 47 (dd, $J$ = 8 79, 16 11 Hz, 1H), 2 21~2 12 (m, 2H), 1 98 (dd, $J$ = 7 32, 14 16 Hz, 1H), 1 87~1 83 (m, 1H), 1 75~1 50 (m, 5H), 1 33 (dd, $J$ = 4 40, 14 65 Hz, 1H), 1 16 (d, $J$ = 6 35 Hz, 3H), 0 99~0 88 (m, 15H) HRFABMS *m/z* calcd for $C_{62}H_{79}O_{13}$ 1031 552, found 1031 5529 [(M-H)$^-$]

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