Pergamon

Tetrahedron: *Asymmetry* 12 (2001) 943–947

TETRAHEDRON: *ASYMMETRY*

# Efficient stereoselective synthesis of a 1-hydroxymethyl-2-methylglycidol derivative

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Received 15 March 2001; accepted 23 March 2001

**Abstract**—A highly stereoselective synthesis of (2*R*,3*S*)-3,4-epoxy-3-methyl-1-(triphenylmethyl)oxybutan-2-ol **3**, which is a substructure found in some naturally-occurring bioactive compounds, was achieved starting from commercially available 3-methyl-2-buten-1-ol **4** in three steps, using two applications of the Sharpless asymmetric epoxidation as the key stereochemistry establishing reactions. 

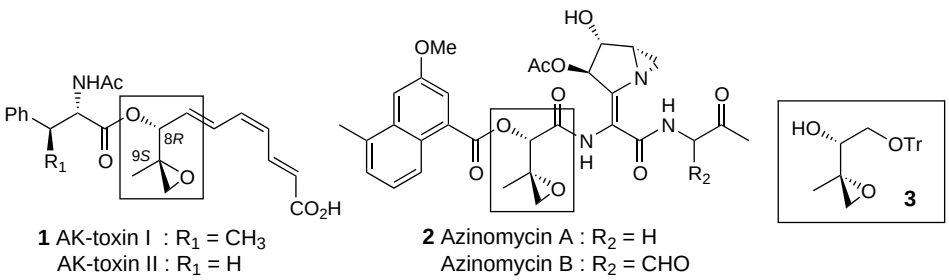
## 1. Introduction

1-Substituted 2-methylglycidol substructures are found in some naturally-occurring bioactive compounds and the stereochemistry of this moiety often affects the activity of the compound. For example, the substructure is present in AK-toxins **1**,[1] which are host-specific toxins produced by *Alternaria alternata* Japanese pear pathotype. Their (8*R*,9*S*)-configuration has been shown to be essential for their phytotoxicity to the toxin-sensitive cultivars of Japanese pear (Fig. 1).[2] The same substructure is also found in Azinomycins **2**,[3] antitumor antibiotics which have been isolated from the culture broth of *Streptomyces griseofuscus*. In this case, the glycidol moiety plays a key role in the formation of the interstrand cross-links in the DNA duplex.[4] Structure–activity relationship studies of **2** have shown that, of the possible configurations of this moiety, the naturally-occurring configuration is the most favorable for activity.[5]

As a result considerable effort has been expended in developing a stereoselective synthesis of this key moiety, not only regarding total synthesis, but also for the structure–activity studies of these biologically active compounds.[6] However, none of the hitherto described methods are completely satisfactory for convenient and large-scale preparations. We describe herein the facile and stereoselective preparation of (2*R*,3*S*)-3,4-epoxy-3-methyl-1-(triphenylmethyl)oxybutan-2-ol **3**, which represents a promising intermediate for the purposes outlined above.

## 2. Results and discussion

The construction of asymmetry in the method we present relies on the Sharpless asymmetric epoxidation (SAE), which uses a catalytic amount of Ti(O*i*Pr)$_4$/tartrate complex (Scheme 1).[7] Commercially available 3-




**1** AK-toxin I : $R_1 = CH_3$
AK-toxin II : $R_1 = H$

**2** Azinomycin A : $R_2 = H$
Azinomycin B : $R_2 = CHO$

**Figure 1.**

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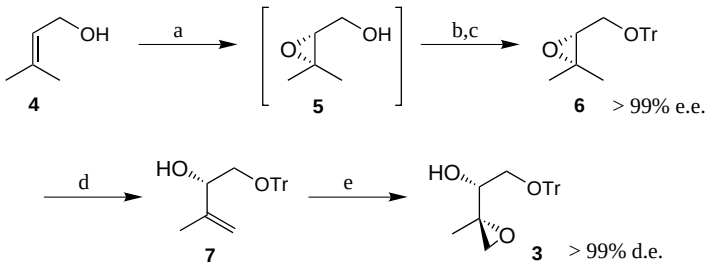
PII: S0957-4166(01)00149-5



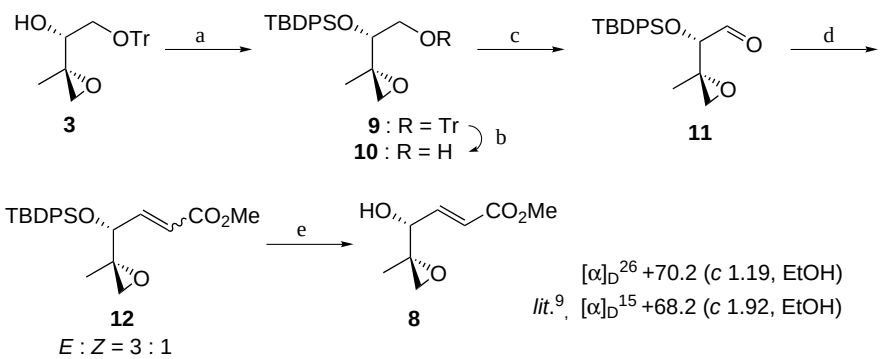

**Scheme 1.** *Reagents and conditions*: (a) $Ti(OiPr)_4$, D-(−)-DET, *t*-BuOOH, 3 Å MS, −25°C, 2 h; (b) $(CH_3)_2S$, rt, 1 h; (c) TrCl, DMAP, $NEt_3$, rt, overnight; (d) LDA, THF, −50°C to rt, 5 h; (e) $Ti(OiPr)_4$, D-(−)-DIPT, *t*-BuOOH, 3 Å MS, −20°C, overnight.

methyl-2-buten-1-ol **4** was used as the starting material. SAE of **4** using D-(−)-diethyl tartrate gave epoxyalcohol **5**, which was derivatized in situ with trityl chloride to give the corresponding trityl ether **6** in 70% yield.[8] Epoxide cleavage of **6** by LDA gave the secondary alcohol **7** in 91% yield. The e.e. of **7**, as determined by NMR analysis after derivatization of **7** to the corresponding Mosher ester with (*S*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA), was >99% when **6** was purified by recrystallization after chromatography on silica gel. Without recrystallization, the e.e. attained was no more than 83%. The conversion of **7** to the desired epoxyalcohol **3** was effected by the second SAE using D-tartrate, although the reaction was somewhat slow and required a prolonged time to reach completion. The yield was 79% with a d.e. of >99%, based on NMR analysis, after a single recrystallization of the crude product. This excellent diastereoselectivity may be due to the bulk of the trityl group, which is likely to cause a high degree of steric hindrance in one of the diastereofaces and would, therefore, favor epoxidation on the other face.

Compound **3** was derivatized to the known ester **8** in order to establish the absolute configuration,[9] as follows (Scheme 2). The secondary hydroxyl group of **3** was protected as *tert*-butyldiphenylsilyl (TBDPS) ether using TBDPS chloride and imidazole with a catalytic amount of 4-(dimethylamino)pyridine. The trityl group of the resultant TBDPS ether **9** was removed in aqueous acetic acid to give the corresponding primary alcohol **10** in 75% yield. Oxidation of **10** using Dess–Martin periodinane provided the aldehyde **11** in excellent yield without any racemization at the α-carbon.[10] The Horner–Wadsworth–Emmons reaction of **11** with trimethyl phosphonoacetate was effected by the protocol developed by Masamune to yield the ester **12** with 3:1 geometrical selectivity in favor of the (*E*)-isomer.[11] NMR analysis of **12** showed that the configuration at the α-carbon remained unchanged. Since it was impossible to separate these geometrical isomers, this isomeric mixture was used directly in the next reaction. Desilylation of **12** with tetrabutylammonium fluoride gave the targeted ester **8** in an isomerically pure form by flash column chromatography. The specific rotation of **8** thus obtained was +70.2, which was in fairly good agreement with the reported value for (4*R*,5*S*)-**8** of +68.2.[9] Since no racemization at the asymmetric centers of **3** was observed in this derivatization, its absolute configuration could be unambiguously assigned as (2*R*,3*S*).

## 3. Conclusion

We report here the development of an efficient and highly stereoselective synthesis of (2*R*,3*S*)-3,4-epoxy-3-methyl-1-(triphenylmethyl)oxybutan-2-ol **3**, which has considerable potential for use as a versatile chiral intermediate. The procedure is of great practical value, since it requires only three steps to obtain **3** from the commercially available material **4**, and was applicable up to a 300 mmol scale without significant loss of yield or e.e. Compound **3** is now utilized in our ongoing research on the total synthesis of AK-toxins, as well as their structure–activity relationship.




**Scheme 2.** *Reagents and conditions*: (a) TBDPSCl, DMAP, imidazole, DMF, rt, overnight; (b) 90% aq. AcOH, 50°C, 3 h; (c) Dess–Martin periodinane, $CH_2Cl_2$, 1 h; (d) LiCl, DBU, trimethyl phosphonoacetate, $CH_3CN$, 2 h; (e) $(n\text{-}Bu)_4NF$, THF, rt, 4 h.

## 4. Experimental

Melting points were collected on a Yanagimoto MP apparatus. $^1$H and $^{13}$C NMR spectra were measured on a Bruker AC-300 spectrometer (300 MHz for $^1$H; 75 MHz for $^{13}$C) and $CDCl_3$ was used as the solvent and tetramethylsilane as the internal standard. IR spectra were recorded on a Shimadzu IR-420 or Shimadzu FTIR-8100AI spectrometer. Optical rotations were measured on a JASCO DIP-1000 polarimeter. Elemental analyses were performed at the Microanalytical Center of Kyoto University.

Reactions requiring anhydrous conditions were carried out under an inert atmosphere (argon or nitrogen) in oven-dried glassware. Solvents were dehydrated in accordance with standard protocols. Reagents were used as purchased except for an anhydrous dichloromethane solution of *t*-butyl hydroperoxide and a Dess–Martin periodinane, both of which were prepared by the procedures in the literature.[7,10] Molecular sieves (MS) were activated by heating under high vacuum prior to use. Column chromatography and flash column chromatography were performed on silica gel (Wakogel C-200 and Merck Kieselgel 60, respectively).

### 4.1. (2*R*)-2,3-Epoxy-3-methyl-1-(triphenylmethyl)-oxybutane 6

To a stirred suspension of powdered 3 Å MS (13 g) in dichloromethane (300 mL) was added titanium tetra-*iso*-propoxide (4.55 g, 16 mmol) followed by diethyl D-tartrate (4.12 g, 20 mmol) at −25°C as solutions in dichloromethane (5 mL for each reagent). The resulting mixture was stirred for 1 h, then 3-methyl-2-buten-1-ol **4** (20.0 mL, 200 mmol) was added dropwise. Anhydrous *t*-butyl hydroperoxide in dichloromethane solution (4.3 M, 50 mL, 215 mmol) was added dropwise, keeping the temperature below −20°C, and the mixture stirred for 2 h at this temperature. Dimethyl sulfide (2.0 mL, 27 mmol) was added, the cooling bath was removed and the reaction mixture was allowed to warm to room temperature over 1 h. Triethylamine (55 mL, 400 mmol) and 4-(dimethylamino)pyridine (1.34 g, 11 mmol) were sequentially added to the mixture. Trityl chloride (61.33 g, 220 mmol) was then added portionwise, keeping the temperature below 30°C and the mixture was stirred overnight at room temperature. The resulting orange suspension was poured onto a mixture of diethyl ether (1.0 L) and brine (300 mL), which was then stirred vigorously for 30 min. The two-phase mixture was filtered through a pad of Celite® to remove insoluble material; the organic phase of the filtrate was separated and washed with water (3×300 mL) and brine (300 mL). The organic phase was dried over magnesium sulfate, followed by filtration and concentration to give a brown oil. Column chromatography (5% ethyl acetate in hexane) and subsequent recrystallization (diethyl ether–hexane) gave **6** as colorless needles (48.22 g, 70%). Mp 84°C; $^1$H NMR $\delta$ (ppm) 1.12 (s, 3H), 1.32 (s, 3H), 3.02 (dd, $J$=4.9, 5.8 Hz, 1H), 3.13 (dd, $J$=5.8, 10.3 Hz, 1H), 3.31 (dd, $J$=4.9, 10.3 Hz, 1H), 7.21–7.33 (m, 9H), 7.44–7.48 (m, 6H); $^{13}$C NMR $\delta$ (ppm) 18.9, 24.7, 57.9, 62.4, 63.0, 77.2, 127.0, 127.8, 128.7, 143.7; IR (Nujol) $\nu_{max}$ 1490, 1075, 760, 725, 705 cm$^{-1}$; $[\alpha]_D^{25}$ = −15.2 (*c* 1.09, $CHCl_3$); Anal. Found: C, 83.56; H, 6.91. Calcd for $C_{24}H_{24}O_2$: C, 83.69; H, 7.02%.

### 4.2. (2*S*)-1-(Triphenylmethyl)oxy-3-methylbut-3-en-2-ol 7

A solution of *n*-butyllithium in hexanes (1.5 M, 130 mL, 195 mmol) was added dropwise to a stirred solution of di-*iso*-propylamine (28.0 mL, 202 mmol) in tetrahydrofuran (300 mL), keeping the temperature below −60°C. After stirring for 1 h, a solution of **6** (37.89 g, 110 mmol) in tetrahydrofuran (50 mL) was added dropwise. Stirring was continued for 1 h at −60°C, then for 5 h at room temperature. To the resulting red solution was added water (200 mL) and the mixture was stirred vigorously for a few minutes. After evaporating the tetrahydrofuran, the residue was extracted with diethyl ether (3×200 mL). The combined organic extract was washed with brine (200 mL), dried over magnesium sulfate, filtered and concentrated to give a yellow oil. Flash column chromatography (10% EtOAc in hexane) provided **7** as a colorless oil (34.59 g, 91%). $^1$H NMR $\delta$ (ppm) 1.60 (s, 3H), 2.43 (d, $J$=3.5 Hz, 1H), 3.16 (dd, $J$=7.5, 9.5 Hz, 1H), 3.27 (dd, $J$=9.5, 3.7 Hz, 1H), 4.16 (ddd, $J$=7.5, 3.7, 3.5 Hz, 1H), 4.88 (s, 1H), 5.00 (s, 1H), 7.21–7.33 (m, 9H), 7.43–7.46 (m, 6H); $^{13}$C NMR $\delta$ (ppm) 18.7, 66.6, 74.4, 86.9, 111.9, 127.1, 127.9, 128.7, 143.8, 144.1; IR (film) $\nu_{max}$ 3390, 3050, 1490, 1070, 900, 765, 745, 700 cm$^{-1}$; $[\alpha]_D^{26}$ = +2.1 (*c* 1.00, $CHCl_3$); Anal. Found: C, 83.55; H, 7.10. Calcd for $C_{24}H_{24}O_2$: C, 83.69; H, 7.02%.

### 4.3. (2*R*,3*S*)-3,4-Epoxy-3-methyl-1-(triphenylmethyl)-oxybutan-2-ol 3

To a stirred suspension of powdered 3 Å MS (11 g) in dichloromethane (250 mL) was added titanium tetra-*iso*-propoxide (2.84 g, 10 mmol) followed by di-*iso*-propyl D-tartrate (2.93 g, 13 mmol) at −20°C as solutions of dichloromethane (5 mL for each). After 1.5 h, a solution of **7** (34.45 g, 100 mmol) in dichloromethane (50 mL) and anhydrous *t*-butyl hydroperoxide solution in dichloromethane (4.2 M, 27 mL, 108 mmol) were added. After 4 h, stirring was stopped and the reaction vessel was stored at −20°C (refrigerator) overnight. Water (100 mL) was poured into the mixture with vigorous stirring at room temperature. Aqueous sodium hydroxide (30%, 50 mL) was added to hydrolyze the tartrate and vigorous stirring was continued for another 30 min. The resultant emulsion was filtered through a pad of Celite® to give a clear two-phase solution. The organic phase was diluted with diethyl ether (700 mL), washed with water (300 mL) and saturated brine (300 mL), dried over magnesium sulfate and filtered. The filtrate was concentrated to give a colorless oil, which was purified by recrystallization (diethyl ether–hexane) to afford **3** as colorless needles (25.19 g, 70%). Mp 80°C; $^1$H NMR $\delta$ (ppm) 1.21 (s, 3H), 2.36 (d, $J$=2.0 Hz, 1H), 2.61 (d, $J$=4.8 Hz, 1H), 2.96 (d, $J$=4.8 Hz, 1H), 3.18 (dd, $J$=5.5, 10.0 Hz, 1H), 3.37 (dd, $J$=3.7, 10.0 Hz, 1H), 3.75 (ddd, $J$=2.0, 3.7, 5.5 Hz, 1H), 7.21–7.33 (m, 9H), 7.44–7.47 (m, 6H); $^{13}$C NMR $\delta$

(ppm) 18.2, 51.0, 57.3, 64.5, 71.7, 86.8, 127.1, 127.9, 128.6, 143.8; IR (Nujol) $\nu_{max}$ 3450, 1094, 1025, 795, 770, 750, 705 $cm^{-1}$; $[\alpha]_D^{26}=+1.4$ (*c* 1.29, $CHCl_3$); Anal. Found: C, 80.15; H, 6.67. Calcd for $C_{24}H_{24}O_3$: C, 79.97; H, 6.71%.

### 4.4. (2*R*,3*S*)-2-(*tert*-Butyldiphenylsilyl)oxy-3,4-epoxy-3-methyl-1-(triphenylmethyl)oxybutane 9

*tert*-Butylchlorodiphenylsilane (26.0 mL, 100 mmol) was added dropwise to a stirred solution of **3** (30.00 g, 83 mmol), imidazole (17.02 g, 250 mmol), and 4-(dimethylamino)pyridine (2.44 g, 20 mmol) in *N*,*N*-dimethylformamide (80 mL) at room temperature. The resultant solution was stirred overnight, and then poured onto water (600 mL) with vigorous stirring. The mixture was extracted with diethyl ether (3×250 mL). The combined organic layer was washed with water (200 mL) and brine (200 mL), dried over magnesium sulfate and filtered. The filtrate was concentrated to give an oily residue, which was then purified by flash column chromatography and subsequent recrystallization (hexane) to give **9** as colorless columns (40.83 g, 82%). Mp 101°C; $^1$H NMR $\delta$ (ppm) 1.06 (s, 9H), 1.17 (s, 3H), 2.20 (s, 2H), 3.19 (dd, $J=9.7$, 4.5 Hz, 1H), 3.25 (dd, $J=9.7$, 5.5 Hz, 1H), 3.51 (dd, $J=5.5$, 4.5 Hz, 1H), 7.20–7.44 (m, 21H), 7.64–7.67 (m, 4H); $^{13}$C NMR $\delta$ (ppm) 16.6, 19.4, 27.0, 53.5, 56.9, 65.8, 75.8, 86.8, 126.9, 127.5, 127.7, 128.8, 129.6, 129.8, 133.6, 133.8, 135.9, 136.1, 143.9; IR (KBr) $\nu_{max}$ 2855, 1490, 1450, 1100, 705; $[\alpha]_D^{25}=-28.9$ (*c* 1.59, $CHCl_3$); Anal. Found: C, 80.19; H, 7.30. Calcd for $C_{40}H_{42}O_3Si$: C, 80.23; H, 7.07%.

### 4.5. (2*R*,3*S*)-2-(*tert*-Butyldiphenylsilyl)oxy-3,4-epoxy-3-methylbutan-1-ol 10

Compound **9** (18.00 g, 30 mmol) was dissolved in acetic acid (200 mL) at 50°C with stirring. Water (22 mL) was added to the solution, and the resultant cloudy mixture became clear after stirring at the same temperature for 3 h. Concentration of the solution gave an oily residue containing the powdery solid of triphenylmethylalcohol (TrOH). After this mixture was diluted with 10% diethyl ether in hexane, the TrOH was filtered off. Flash column chromatography (16% ethyl acetate in hexane) of the concentrated filtrate afforded **10** as a colorless oil (7.85 g, 73%). $^1$H NMR $\delta$ (ppm) 1.09 (s, 9H), 1.36 (s, 3H), 1.83 (t, $J=6.4$ Hz, 1H), 2.15 (d, $J=4.8$ Hz, 1H), 2.31 (d, $J=4.8$ Hz, 1H), 3.36 (t, $J=4.9$ Hz, 1H), 3.71 (m, 2H), 7.36–7.45 (m, 6H), 7.65–7.70 (m, 4H); $^{13}$C NMR $\delta$ (ppm) 16.5, 19.4, 27.0, 53.8, 57.2, 64.4, 76.2, 127.7, 127.9, 130.1, 133.1, 133.4, 135.7, 136.0; IR (film) $\nu_{max}$ 3420, 2920, 2850, 1430, 1115, 1080, 700 $cm^{-1}$; $[\alpha]_D^{25}=-5.6$ (*c* 1.02, $CHCl_3$); Anal. Found: C, 70.68; H, 7.99. Calcd for $C_{21}H_{28}O_3Si$: C, 70.74; H, 7.92%.

### 4.6. (2*S*,3*S*)-2-(*tert*-Butyldiphenylsilyl)oxy-3,4-epoxy-3-methylbutanal 11

Dess–Martin periodinane (10.57 g, 25 mmol) was added portionwise to a stirred solution of **10** (7.85 g, 22 mmol) in dichloromethane (110 mL) over 30 min at room temperature. After stirring for 30 min, the resultant cloudy solution was diluted with diethyl ether (200 mL) and washed with 10% w/v aqueous sodium thiosulfate solution saturated with sodium bicarbonate (150 mL). The organic phase was further washed with saturated brine, dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was purified by flash column chromatography to afford **11** as a colorless oil (7.11 g, 91%). $^1$H NMR $\delta$ (ppm) 1.12 (s, 9H), 1.34 (s, 3H), 2.29 (d, $J=4.8$ Hz, 1H), 2.44 (d, $J=4.8$ Hz, 1H), 3.74 (d, $J=1.0$ Hz, 1H), 7.36–7.46 (m, 6H), 7.61–7.68 (m, 4H), 9.58 (d, $J=1.0$ Hz, 1H); $^{13}$C NMR $\delta$ (ppm) 17.3, 19.4, 26.9, 51.6, 56.2, 80.4, 127.8, 127.9, 130.2, 130.2, 132.5, 132.7, 135.8, 200.5; IR (film) $\nu_{max}$ 2920, 2850, 1740, 1430, 1115, 705; $[\alpha]_D^{25}=+3.3$ (*c* 1.03, $CHCl_3$); Anal. Found: C, 70.89; H, 7.52. Calcd for $C_{21}H_{26}O_3Si$: C, 71.15; H, 7.39%.

### 4.7. Methyl (4*R*,5*S*)-4-(*tert*-butyldiphenylsilyl)oxy-5,6-epoxy-5-methylhex-2-enoate 12

Trimethyl phosphonoacetate (1.62 mL, 10 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (1.42 mL, 9.5 mmol) were added successively at room temperature to a stirred suspension of lithium chloride (0.40 g, 9.5 mmol) in acetonitrile (30 mL). After stirring for 30 min, a solution of **11** (2.60 g, 7.3 mmol) in acetonitrile (4 mL) was added dropwise to the resultant clear solution and the mixture was stirred for a further 2 h. The reaction mixture was poured onto saturated aqueous ammonium chloride solution (30 mL) and the bulk of the acetonitrile was removed by evaporation. The residue was extracted with diethyl ether (3×30 mL). The combined extract was washed with saturated aqueous sodium bicarbonate solution (50 mL) and brine (50 mL), dried over magnesium sulfate and filtered. The filtrate was concentrated and the residue was purified by flash column chromatography to give **12** (2.57 g, 85%) as a colorless oil. The isomeric ratio of the product was determined to be 2(*E*):2(*Z*)=3:1 by $^1$H NMR analysis. $^1$H NMR $\delta$ (ppm) (2*E*)-isomer: 1.10 (s, 9H), 1.30 (s, 3H), 1.86 (d, $J=4.7$, 1H), 2.21 (d, $J=4.7$ Hz, 1H), 3.75 (s, 3H), 3.86 (dd, $J=4.4$, 1.7 Hz, 1H), 6.16 (dd, $J=15.7$, 1.7 Hz, 1H), 6.99 (dd, $J=15.7$, 4.4 Hz, 1H), 7.3–7.5 (m, 6H), 7.6–7.7 (m, 4H); (2*Z*)-isomer: 1.07 (s, 9H), 1.34 (s, 3H), 2.44 (d, $J=5.1$ Hz, 1H), 2.58 (d, $J=5.1$ Hz, 1H), 3.48 (s, 3H), 5.39 (d, $J=9.0$ Hz, 1H), 5.61 (d, $J=11.7$, 1H), 6.07 (dd, $J=11.7$, 9.0 Hz, 1H), 7.3–7.5 (m, 6H), 7.6–7.7 (m, 4H); IR (film) $\nu_{max}$ 2920, 2850, 1725, 1430, 1270, 1115, 1080, 820, 700; $[\alpha]_D^{24}=-7.3$ (*c* 1.09, $CHCl_3$); Anal. Found: C, 70.18; H, 7.47. Calcd for $C_{24}H_{30}O_4Si$: C, 70.21; H, 7.36%.

### 4.8. Methyl (2*E*,4*R*,5*S*)-5,6-epoxy-4-hydroxy-5-methylhex-2-enoate 8

To a stirred solution of **11** (2.47 g, 6.0 mmol) in tetrahydrofuran was added dropwise a solution of tetrabutylammonium fluoride in tetrahydrofuran (1 M, 9.0 mL, 9 mmol). After stirring for 4 h at room temperature, the reaction mixture was poured onto saturated aqueous ammonium chloride solution (30

mL). The bulk of the tetrahydrofuran was removed by evaporation. The aqueous residue was extracted with three portions of ethyl acetate (30 mL). The combined extract was washed with water (50 mL) and brine (50 mL), dried over magnesium sulfate, filtered and concentrated. Purification of the residual oil by flash column chromatography afforded isomerically pure **8** (0.71 g, 69%). $^1$H NMR $\delta$ (ppm) 1.41 (s, 3H), 2.63 (d, $J$=4.6 Hz, 1H), 2.88 (d, $J$=4.6 Hz, 1H), 3.76 (s, 3H), 4.32 (dd, $J$=5.0, 1.6 Hz, 1H), 6.18 (dd, $J$=15.6, 1.6 Hz, 1H), 6.93 (dd, $J$=15.6, 5.0 Hz, 1H); $^{13}$C NMR $\delta$ (ppm) 18.0, 49.9, 51.7, 58.4, 71.4, 122.3, 144.7, 166.6; IR (KBr) $\nu_{max}$ 3400, 1713, 1125, 990, 928, 866, 818 cm$^{-1}$; $[\alpha]_D^{26}$=+70.2 ($c$ 1.19, EtOH), lit.[9] +68.2 (EtOH at 15°C), (4*S*,5*S*)-isomer: +61.9 ($c$ 1.34, EtOH at 15°C); Anal. Found: C, 56.06; H, 6.92. Calcd for $C_8H_{12}O_4$: C, 55.81; H, 7.02%.

## Acknowledgements

This research was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture of Japan (No. 10460048). The authors thank Dr. Masahiko Seki of Tanabe Seiyaku Co. for critical reading of the manuscript and helpful suggestions.

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