Pergamon

Tetrahedron, Vol. 53, No. 28, pp. 9777-9788, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)00625-X

An Alternative Efficient Synthesis of the C_{20}-C_{25} Building Unit for Calyculin A

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Abstract : We have explored the efficient synthetic route to the C_{20}-C_{25} building unit **3** for calyculin A (**1**) starting from the chiral γ-lactone **5** using the Wittig reaction, followed by hydroboration as the key steps.

Calyculin A (**1**), isolated from the marine sponge *Discodermia calyx*,[1] is an attractive target for total synthesis[2] since it has a unique structure as well as strong biological activities such as inhibition of protein phosphatases and cytotoxicity.[1,3] In our previous paper,[4] the C_{20}-C_{25} building units **2a** and **2b** have already been prepared from L-malic acid using the Grignard reaction of the Weinreb amides, followed by stereoselective reduction as the key steps, as shown in Figure 1. Moreover, we have explored a simple and safe route to the γ-lactone derivative **5** from the potassium glycerate **4** as the key intermediate for the spiloketal fragment of **1** without the use of hazardous diazomethane on a large scale, the details of which have been described in the preceding paper.[5] In this paper, we now wish to report the alternative efficient synthetic route to the C_{20}-C_{25} building unit **3** for calyculin A (**1**).

We started the synthesis of **3** from the silylated chiral γ-lactone **5**.[5] Reduction of the chiral γ-lactone **5** with sodium borohydride in THF-H_2O (4:1), followed by the selective acetylation of the primary alcohol **6** with acetyl chloride in the presence of 2,4,6-collidine[6] at -78℃ afforded the monoacetate **7**. Protection of the secondary alcoholic functions of **7** with 2,2-dimethoxypropane in the presence of a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS) quantitatively afforded the acetal derivative **8**. Treatment of the acetate **8** with K_2CO_3 produced the primary alcohol **9**, as shown in Scheme 1.

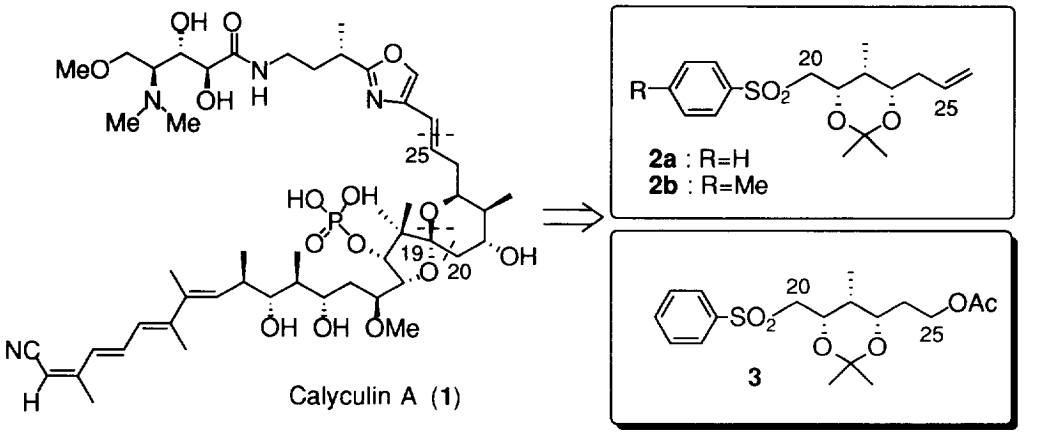
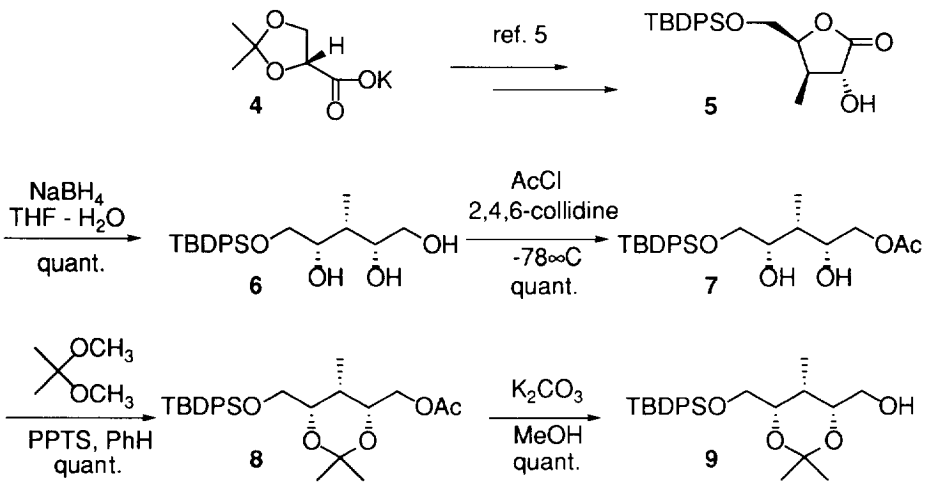
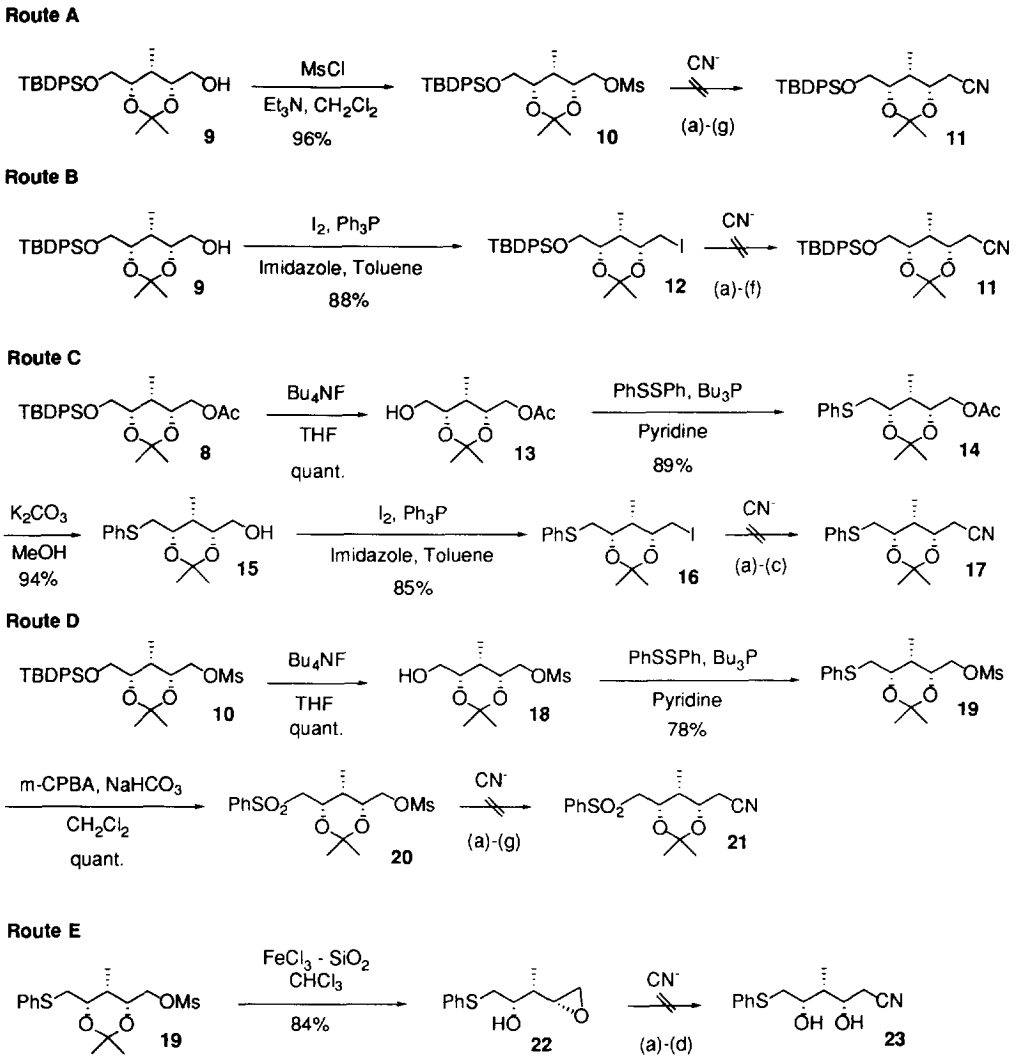


Figure 1 The structures of calyculin A (**1**) and its C_{20}-C_{25} building units **2** and **3**.



Scheme 1

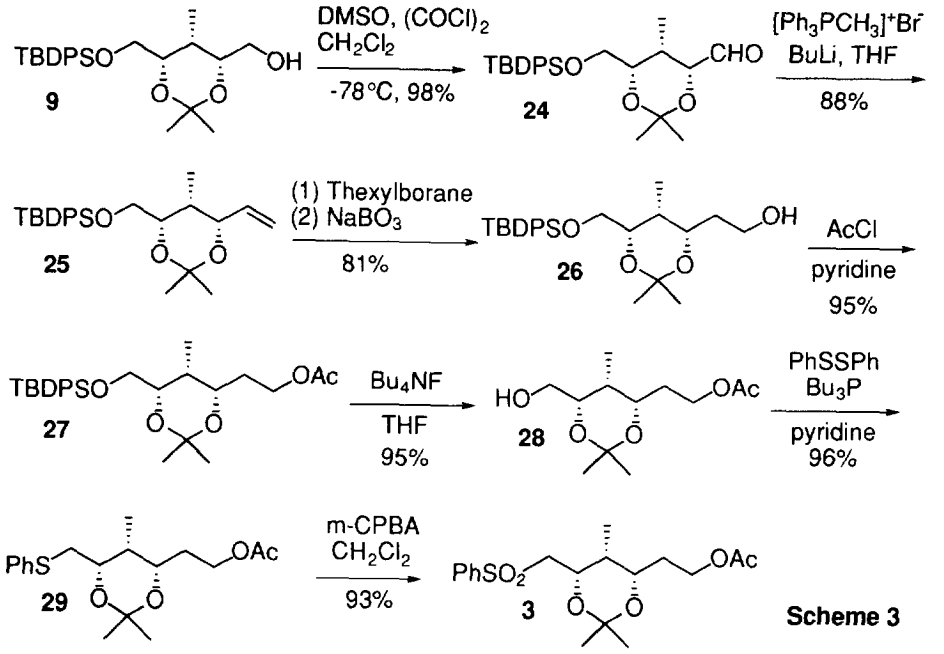
Next we tried to convert the primary alcoholic function of **9** to the cyano group by the S_N2 reaction. Unfortunately the many known procedures using the corresponding mesylates (**10**, **19**, and **20**), iodides (**12** and **16**), and epoxide (**22**) were too difficult to add a C_1-unit. The reactions attempted gave many products including the desilylated products or no reaction occurred, as summarized in Scheme 2. From these experimental results, we thought that the steric hindrance caused by the acetal ring and the *tert*-butyldiphenylsilyl (TBDPS) function would prevent the substitution reaction with the cyanide ion.



Scheme 2 The reaction conditions in order to introduce the cyano group as a C_1-unit : (a) KCN, DMF, r.t., 48 h, (b) KCN, DMSO, r.t., 24 h, (c) KCN, DMF, 100℃, 13.5 h, (d) KCN, DMSO, 100℃, 2 h, (e) KCN, 18-crown-6, toluene, 110℃, 14 h, (f) Bu4NCN, toluene, 90℃, 12 h, (g) Bu4NCN, DMF, 90℃, 1.5 h.

After all, the addition of the C_1-unit was accomplished by the Wittig reaction via the Swern oxidation of the primary alcohol **9**, as outlined in Scheme 3. Thus, the Swern oxidation of the primary alcohol **9** provided the unstable aldehyde **24**. After purification on a silica gel column, the aldehyde **24** was converted to the exo-olefin **25** in excellent yield by the Wittig reaction using methylenetriphenylphosphorane prepared from methyltriphenylphosphonium bromide and n-butyllithium. Hydroboration of the olefin **25** by using $BH_3 \cdot Me_2S$, 9-BBN, and catechol borane reagents unexpectedly gave the desired alcohol **26** in poor yield, as summarized in Table 1. Surprisingly, however, treatment with thexylborane (20 eq.) followed by sodium

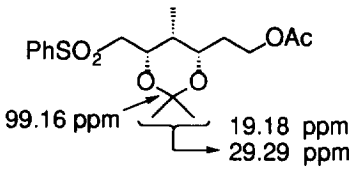
perborate[7] afforded the primary alcohol **26** in 81% yield. After protection of the primary alcohol function of **26** with acetyl chloride, treatment of the acetate **27** with tetrabutylammonium fluoride (TBAF) afforded the alcohol derivative **28**. Conversion to the thioether **29** was achieved by the action of diphenyl disulfide and tributylphosphine,[8] as shown in Scheme 3. Finally, oxidation of the sulfide **29** with m-chloroperoxybenzoic acid (m-CPBA) afforded the required sulfone **3** in excellent yield. The relative configuration of the sulfone **3** was determined by the chemical shifts of the ^{13}C-NMR spectra according to the literatures,[4,9] as shown in Figure 2.



Scheme 3

Table 1 The hydroboration from the olefin **25** to the primary alcohol **26**

Run	Reagents (equiv.)		Reaction conditions Temp.( )	Time (h)	Yield (%)
1	$BH_3 \cdot Me_2S$	(10)	0 rt	2.5 13.5	31
2	$BH_3 \cdot Me_2S$	(10)	5~6	13.5	14.4
3	9-BBN	(10)	0 r.t.	0.5 14	45
4	9-BBN	(2)	0 r.t.	0.5 24	trace
5	9-BBN	(20)	0 r.t.	0.5 13	48
6	Catechol borane	(20)	0 r.t.	1.5 13	29
7	Thexyl borane	(20)	0 r.t.	2 14	81



	For the syn form[9]	For the anti form[9]
	19.4±0.21 ppm	24.6±0.76 ppm (2)
	30.0±0.15 ppm	100.6±0.25 ppm
	98.1±0.83 ppm	

Figure 2 The ^{13}C-NMR spectrum of **3** in comparison with the reported data[9]

In summary, we have attained an efficient and high yield synthetic route to the sulfone derivative **3** using the potassium glycerate **4** as the starting material. The synthesis is practical and will be useful to construct the whole molecule of calyculins. Synthetic studies along this line are being actively pursued in our laboratories.

Experimental

(2*R*,3*R*,4*S*)-5-*tert*-Butyldiphenylsiloxy-3-methyl-1,2,4-pentanetriol (6). To a solution of 2.8 g (7.28 mmol) of **5** in 50 ml of 75 % aqueous THF was added portionwise 1.37 g (36.4 mmol) of $NaBH_4$ at 0℃. After being stirred for 30 min, the mixture was stirred at room temperature for 2 h and then quenched by the addition of 50 ml of 1N HCl. The mixture was extracted three times with 100 ml portions of EtOAc. The organic layer was washed with 50 ml of brine, dried ($MgSO_4$), filtered, and then concentrated. Purification of the residue by column chromatography (60 g of silica gel BW-820 MH, $CHCl_3$: MeOH = 20 : 1) afforded 2.85 g (quantitative) of the triol **6** as a colorless oil; $[\alpha]_D^{23}$ +1.7° (c 0.7, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3400, 1471, 1428, 1113, 938, 823, 740; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 0.85 (3H, d, J=7.0Hz), 1.06 (9H, s), 1.69-1.78 (1H, m), 2.57 (1H, bs, disappeared with D_2O), 2.89 (1H, bs, disappeared with D_2O), 3.00 (1H, bs, disappeared with D_2O), 3.45-3.71 (2H, m), 3.60(1H, dd, J=4.6, 10.2 Hz), 3.68 (1H, dd, J=8.0, 10.2 Hz), 3.73-3.82 (1H, m), 3.95-4.00 (1H, m), 7.36-7.47 (6H, m), 7.63-7.67 (4H, m); EIMS m/z (relative intensity) 331 (M^+-Bu^t, 3.7), 326 (1.3), 313 (7.7), 253 (12.2), 235 (100), 199 (50), 181 (98); HRMS Calcd for $C_{18}H_{23}O_4Si$ (M^+-^{t}Bu) 331.1365; Found : 331.1356.

(2*R*,3*R*,4*S*)-1-Acetyloxy-5-*tert*-butyldiphenylsiloxy-3-methyl-2,4-pentanediol (7). To a stirred solution of 1.34 g (3.45 mmol) of the triol **6** in 17 ml of CH_2Cl_2 was added 1.59 ml (12.96 mmol) of 2,4,6-collidine at -78℃. After 15 min, 0.74 ml (10.35 mmol) of acetyl chloride was cautiously added and the reaction mixture was stirred at -78℃ for 1 h and allowed to warm to -40℃ ~ -30℃. After 2 h, the reaction was quenched by the addition of 10 ml of water and the resulting mixture was extracted with three 100 ml portions of EtOAc. The combined organic extracts were washed with 100 ml portions of 1N HCl, saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), filtered and concentrated to give 1.48 g (quantitative) of **7** as a colorless oil, which was used for the next step without further purification; $[\alpha]_D^{24}$ -2.5° (c 0.75, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3459, 1740, 1428, 1240, 1113, 1044, 824; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 0.88 (3H, d, J=7.0Hz), 1.06 (9H, s), 1.68-1.80 (1H, m), 2.07 (3H, s), 2.72-2.78 (1H, bs, disappeared with D_2O), 3.00-3.04 (1H, bs, disappeared with D_2O), 3.60 (1H, dd, J=5.1, 10.2 Hz), 3.67 (1H, dd, J=7.5, 10.2 Hz), 3.96-4.10 (4H, m), 7.36-7.44 (6H, m), 7.63-7.66 (4H, m); EIMS m/z (relative intensity) : 455 (M^+-CH_3, 8.4), 413 (2), 355 (100), 295 (70), 241 (80); HRMS Calcd for $C_{26}H_{35}O_5Si$ (M^+-CH_3) :

455.2254, Found : 455.2225.

(4*R*, 5*R*, 6*S*)-4-Acetyloxymethyl-6-*tert*-butyldiphenylsiloxymethyl-2,2,5-trimethyl-1,3-dioxane (8). To a solution of 650 mg (15.1 mmol) of the diol **7** in 6 ml of benzene-CH_2Cl_2 (1 : 1) was added 1.1 g (10.57 mmol) of 2,2-dimethoxypropane and 190 mg (0.75 mmol) of pyridinium *p*-toluenesulfonate and the resulting solution was stirred at room temperature for 13.5 h. The mixture was diluted with 300 ml of EtOAc and washed with 100 ml portions of saturated aqueous $NaHCO_3$ and brine. The organic layer was dried (Na_2SO_4), filtered and concentrated. Purification of the residue by columm chromatography (70 g silica gel BW-820 MH, hexane : Et_2O = 5 : 1) afforded 592 mg (82 % in 2 steps from **6**) of **8** as a colorless oil; $[\alpha]_D^{24}$ -24.0° (c 0.9, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 1745, 1428, 1373, 1239, 1113, 1040, 823; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.80 (3H, d, J=6.8 Hz), 1.05 (9H, s), 1.37 (3H, s), 1.40 (3H, s), 1.65-1.77 (1H, m), 2.08 (3H, s), 3.57 (1H, dd, J=7.3, 10.2 Hz), 3.68 (1H, dd, J=6.1, 10.2 Hz), 3.97-4.14 (4H, m), 7.33-7.45 (6H, m), 7.63-7.69 (4H, m); EIMS m/z (relative intensity) : 455 (M^+-CH_3, 8.4), 413 (2), 355 (100), 295 (70), 241 (80); HRMS Calcd for $C_{26}H_{35}O_5Si$ (M^+-CH_3) : 455.2254, Found : 455.2225.

(4*R*, 5*R*, 6*S*)-6-*tert*-Butyldiphenylsiloxy-4-hydroxymethyl-2,2,5-trimethyl-1,3-dioxane (9). A suspension of 577 mg (1.22 mmol) of **8** and 675 mg (4.88 mmol) of K_2CO_3 in 20 ml of MeOH was stirred at room temperature for 2 h. The reaction was quenched by the addition of 5 ml of 1M $KHSO_4$. The mixture was extracted with three 100 ml portions of Et_2O and the organic extracts were washed with 100 ml of brine, dried ($MgSO_4$), filtered, and concentrated. Purification of the residue by column chromatography (60 g of silica gel BW-820 MH, hexane : Et_2O = 5 : 1 and then hexane : Et_2O = 2 : 1) afforded 524 mg (quantitative) of the alcohol **9** as a colorless oil; $[\alpha]_D^{25}$ -15.3° (c 0.9, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3448, 1472, 1428, 1265, 11200, 1113, 823, ^1H NMR ($CDCl_3$, 270 MHz) δ 0.77 (3H, d, J=6.8 Hz), 1.05 (9H, s), 1.37 (3H, s), 1.41 (3H, s), 1.64-1.71 (1H, m), 3.48-3.72 (5H, m, J=7.3, 10.2 Hz, 1H disappeared with D_2O) 4.00-4.06 (2H, m), 7.34-7.45 (6H, m), 7.63-7.69 (4H, m); EIMS; m/z (relative intensity) 313 (M^+-Bu^t and C_3H_6O, 38), 241 (39), 199 (100); HRMS Calcd for $C_{18}H_{21}O_3Si$ (M^+-Bu^t and C_3H_6O) : 313.1260, Found : 313.1259.

(4*R*, 5*S*, 6*S*)-6-*tert*-Butyldiphenylsiloxymethyl-4-methanesulfonyloxymethyl-2,2,5-tri-methyl-1,3-dioxane (10). To a solution of 33 mg (0.076 mmol) of the alcohol **9** in 2 ml of CH_2Cl_2 was added 32 ml (0.23 mmol) of Et_3N at 0℃. After 15 min, 12 ml (0.15 mmol) of methanesulfonyl chloride was added and the reaction mixture was stirred at room temperature for 15 h. The reaction was quenched with water, and the resulting mixture was extracted with three 10 ml portions of ether. The combined organic extracts were washed with 20 ml portions of saturated aqueous $NaHCO_3$, H_2O, and brine. The organic layer was dried (Na_2SO_4), filtered and concentrated. Purification by column chromatography (5 g of silica gel BW-820MH, hexane : Et_2O = 5 : 1) afforded 37 mg (96 %) of the mesylate **10** as a colorless oil; $[\alpha]_D^{28}$ -14.5° (c 0.7, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 2935, 1589, 1472, 1428, 1359, 1264, 1173, 1112, 822; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.80 (3H, d, J=6.8 Hz), 1.05 (9H, s), 1.35 (3H, s), 1.39 (3H, s), 3.03 (3H, s), 3.57 (1H, dd, J=7.5, 10.2 Hz), 3.67 (1H, dd, J=6.1, 10.2 Hz), 4.01-4.08 (1H, m), 4.15-4.27 (3H, m), 7.32-7.48 (6H, m), 7.60-7.71 (4H. m); EIMS m/z (relative intensity) : 449 (M^+-Bu^t, 2.5), 431 (2), 391 (10), 295 (30), 277 (76), 241 (90), 199 (100); HRMS Calcd for $C_{22}H_{29}O_6SiS$(M^+-Bu^t) : 449.1454; Found : 449.1466.

(4R,5S,6S)-6-*tert*-Butyldiphenylsiloxymethyl-4-iodomethyl-2,2,5-trimethyl-1,3-dioxane (12). To a mixture of 100 mg (0.23 mmol) of the alcohol **9**, 184 mg (0.7 mmol) of triphenylphosphine, 63 mg (0.92 mmol) of imidazole in 5 ml of toluene was added 175 mg (0.7 mmol) of iodine under an argon atmosphere. The mixture was heated to 10℃ for 1 h. The reaction was quenched by the addition of 10 ml of saturated aqueous Na_2CO_3 and the resultant mixture was extracted with 50 ml of ether. The organic layer was washed with 10 ml of brine, dried (Na_2SO_4), filtered and concentrated. Column chromatography of the residue (20 g of silica gel BW-820MH, hexane : EtOAc = 10 : 1) afforded 109 mg (88 %) of the iodide **12** as a colorless oil; $[\alpha]_D^{27}$ -8.3° (c 2.4, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 2932, 1589, 1428, 1261, 1104, 1017, 936, 823; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.72 (3H, d, J=6.8 Hz), 1.05 (9H, s), 1.37 (3H, s), 1.38 (3H, s), 1.89-2.01 (1H, m), 3.05 (1H, dd, J=7.0, 10.0 Hz), 3.06 (1H, dd, J=7.0, 10.0 Hz), 3.59 (1H, dd, J=7.0, 10.2 Hz), 3.70 (1H, dd, J=6.1, 10.2 Hz), 3.92-4.10 (2H, m), 7.30-7.48 (6H, m), 7.60-7.74 (4H, m); EIMS m/z (relative intensity) : 538 (M^+, 1.2), 199 (100); HRMS Calcd for $C_{25}H_{35}O_3SiI(M^+)$: 538.1401; Found : 538.1368.

(4*R*,5*S*,6*S*)-4-Acetyloxymethyl-6-hydroxymethyl-2,2,5-trimethyl-1,3-dioxane (13). To a solution of 37 mg (0.07 mmol) of **8** in 3 ml of THF was added 95 mg (0.36 mmol) of TBAF at 0℃. The reaction mixture was stirred for 13 h at room temperature and then concentrated. Column chromatography (5g of silica gel BW-820MH, hexane : EtOAc = 2 : 1) of the residue afforded 19 mg (quantitative) of the alcohol **13** as a colorless oil; $[\alpha]_D^{27}$ -16.6° (c 0.75, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3466, 2991, 1743, 1456, 1379, 1244, 1035; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.87 (3H, d, J=6.8 Hz), 1.43 (3H, s), 1.47 (3H, s), 1.52-1.65 (1H, m), 1.72-1.89 (1H, bs, disappeared with D_2O), 2.07 (3H, s), 3.49 (1H, dd, J=3.9, 11.2 Hz), 3.68 (1H, dd, J=8.3, 11.2 Hz), 3.98-4.21 (4H, m); EIMS m/z (relative intensity) : 217 (M^+-CH_3, 25), 199 (11), 157 (32), 97 (100); HRMS Calcd for $C_{10}H_{17}O_5(M^+-CH_3)$: 217.1076; Found : 217.1055.

(4*R*,5*R*,6*S*)-4-Acetyloxymethyl-6-phenylthiomethyl-2,2,5-trimethyl-1,3-dioxane (14). To a solution of 115 mg (0.49 mmol) of the alcohol **13** and 1.1 g (4.95 mmol) of diphenyldisulfide in 1 ml of pyridine was added dropwise 1.23 ml (4.95 mmol) of tributylphosphine at room temperature under an argon atmosphere, and the resulting solution was stirred at room temperature for 20 h and then concentrated. Column chromatography (20g of silica gel BW-820MH, hexane and then hexane : Et_2O = 5 : 1) of the residue afforded 143 mg (89 %) of the sulfide **14** as a colorless oil; $[\alpha]_D^{28}$ -42.2° (c 1.0, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 2991, 1742, 1481, 1439, 1380, 1239, 1199, 1036, 740; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.87 (3H, d, J=6.8 Hz), 1.40 (3H, s), 1.41 (3H, s), 1.67-1.78 (1H, m), 2.06 (3H, s), 2.88 (1H, dd, J=7.0, 13.1 Hz), 3.08 (1H, dd, J=6.8, 13.1 Hz), 4.00-4.18 (4H, m), 7.14-7.41 (5H, m); EIMS m/z (relative intensity) : 324 (M^+, 22), 309 (17), 249 (4), 143 (100); HRMS Calcd for $C_{17}H_{24}O_4S(M^+)$: 324.1395; Found : 324.1382.

(4*R*,5*R*,6*S*)-4-Hydroxymethyl-6-phenylthiomethyl-2,2,5-trimethyl-1,3-dioxane (15). A suspension of 80 mg (0.24 mmol) of the sulfide **14** and 102 mg (0.74 mmol) of K_2CO_3 in 3.5 ml of methanol was stirred at room temperature for 3 h. The reaction was quenched by the addition of 2 ml of 1M $KHSO_4$. The mixture was extracted with three 20 ml portions of $CHCl_3$ and organic extracts were washed with 50 ml of brine, dried (Na_2SO_4), filtered, and concentrated. Purification of the residue by column chromatography (5g of silica gel BW-820MH, hexane : EtOAc = 4 : 1) afforded 65 mg (94 %) of the alcohol **15** as a colorless oil.; $[\alpha]_D^{27}$ -27.6° (c 1.3, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3440, 2990, 1583, 1481, 1439, 1381,

1267, 1199, 1026; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 0.85 (3H, d, J=6.8 Hz), 1.41 (6H, s), 1.60-1.80 (1H, m), 1.92 (1H, bs, disappeared with D_2O), 2.88 (1H, dd, J=7.3, 13.1 Hz), 3.08 (1H, dd, J=6.8, 13.1 Hz), 3.40-3.58 (1H, m), 3.61-3.75 (1H, m), 3.93-4.11 (2H, m), 7.11-7.42 (5H, m); EIMS m/z (relative intensity) : 282 (M^+, 46), 267 (29), 207 (5), 199 (25), 159 (32), 123 (26), 101 (100); HRMS Calcd for $C_{15}H_{22}O_3S(M^+)$: 282.1290; Found : 282.1278.

(4*R*,5*S*,6*S*)-4-Iodomethyl-6-phenylthiomethyl-2,2,5-trimethyl-1,3-dioxane (16). To a mixture of 53 mg (0.18 mmol) of the alcohol **15**, 146 mg (0.56 mmol) of triphenylphosphine, 51 mg (0.74 mmol) of imidazole in 2.5 ml of toluene was added 142 mg (0.56 mmol) of iodine under an argon atmosphere. The mixture was heated to 80℃ for 25 min. The reaction was quenched by addition of 10 ml of saturated aqueous Na_2SO_3, and the resulting mixture was extracted with 50 ml of EtOAc. The organic layer was washed with 30 ml of brine, dried ($MgSO_4$), filtered, and concentrated. Purification of the residue by column chromatography (10 g of silica gel BW-820MH, hexane : ether = 100 : 1) afforded 62 mg (85 %) of the iodide **16** as a colorless oil; $[\alpha]_D^{27}$ -20.2° (c 1.2, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 2990, 1583, 1480, 1439, 1381, 1266, 1199, 1010, 738; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 0.80 (3H, d, J=6.8 Hz), 1.38 (3H, s), 1.41 (3H, s), 1.89-2.01 (1H, m), 2.90 (1H, dd, J=6.8, 13.1 Hz), 3.04 (1H, dd, J=7.0, 10.0 Hz), 3.07-3.20 (2H, m), 3.95-4.01 (2H, m), 7.15-7.41 (5H, m); EIMS m/z (relative intensity) : 392 (M^+, 40), 377 (12), 317 (8), 269 (56), 211 (100); HRMS Calcd for $C_{15}H_{21}O_2SI(M^+)$: 392.0308; Found : 392.0279.

(4*R*,5*S*,6*S*)-6-Hydroxymethyl-4-methanesulfonyloxymethyl-2,2,5-trimethyl-1,3-dioxane (18). To a solution of 266 mg (0.52 mmol) of **10** in 5 ml of THF was added 411 mg (1.57 mmol) of TBAF at 0℃. The reaction mixture was stirred for 15 h and concentrated. Purification of the residue by column chromatography (20 g of silica gel BW-820MH, hexane : EtOAc = 1 : 1 and then EtOAc) afforded 140 mg (quantitative) of the alcohol **18** as a colorless oil; $[\alpha]_D^{26}$ -3.3° (c 1.4, EtOH); IR ν_{max}^{neat} cm^{-1} 3438, 1460, 1355, 1275, 1169, 1113, 1013, 962, 859; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 0.87 (3H, d, J=6.8 Hz), 1.42 (3H, s), 1.46 (3H, s), 1.58-1.71 (1H, m), 1.82-1.92 (1H, m, disappeared with D_2O), 3.04 (3H, s), 3.44-3.57 (1H, m), 3.62-3.75 (1H, m), 4.01-4.28 (4H, m); EIMS m/z (relative intensity) : 253 (M^+-CH_3, 52), 193 (10), 92 (100); HRMS Calcd for $C_{10}H_{20}O_6S(M^+-CH_3)$: 253.0746; Found : 253.0747.

(4*R*,5*R*,6*S*)-4-Methanesulfonyloxymethyl-6-phenylthiomethyl-2,2,5-trimethyl-1,3-dioxane (19). To a solution of 139 mg (0.52 mmol) of the alcohol **18**, and 568 mg (2.6 mmol) of diphenyldisulfide in 1 ml of pyridine was added dropwise 0.65 ml (2.6 mmol) of tributylphosphine at room temperature under an argon atmosphere, and the resulting solution was stirred at room temperature for 40 h and concentrated. Purification of the residue by column chromatography (15 g of silica gel BW-820MH, hexane and then hexane : ether = 3 : 1) afforded 146 mg (78 %) of the sulfide **19** as a colorless oil; $[\alpha]_D^{24}$ -7.1°(c 1.0, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 2991, 1582, 1356, 1274, 1178, 1013, 961, 815; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 0.87 (3H, d, J=6.8 Hz), 1.40 (6H, s), 1.70-1.82 (1H, m), 2.87 (1H, dd, J=7.3, 13.4 Hz), 3.03 (3H, s), 3.08 (1H, dd, J=6.8, 13.4 Hz), 4.00-4.31 (4H, m), 7.16-7.42 (5H, m); EIMS m/z (relative intensity) : 360 (M^+, 38), 345 (11), 285 (12), 237 (100), 189 (7); HRMS Calcd for $C_{16}H_{24}O_5S_2(M^+)$: 360.1065; Found : 360.1062.

(4*R*,5*R*,6*S*)-4-Methanesulfonyloxymethyl-6-phenylsulfonylmethyl-2,2-5-trimethyl-1,3-dioxane (20). To a solution of 119 mg (0.33 mmol) of the sulfide **19** and 110 mg (1.32 mmol) of

$NaHCO_3$ in 3 ml of CH_2Cl_2 at 0℃ was added portionwise 255 mg (0.99 mmol) of m-chloroperoxybenzoic acid at this temperature. The reaction mixture was stirred at room temperature for 13 h. The mixture was diluted with 100 ml of EtOAc, and washed with 30 ml each portions of saturated aqueous $NaHCO_3$, H_2O, and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated. Purification of the residue by column chromatography (10 g of silica gel BW-820 MH, hexane : EtOAc = 3 : 1 and then hexane : EtOAc = 1 : 1) afforded 130 mg (quantitative) of the sulfone **20** as a colorless oil; $[\alpha]_D^{25}$ -1.7° (c 1.0, EtOH); IR ν_{max}^{neat} cm^{-1} 2991, 1448, 1355, 1305, 1202, 1175, 1145, 962; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.85 (3H, d, J=6.8 Hz), 1.08 (3H, s), 1.33 (3H, s), 1.59-1.71 (1H, m), 3.02 (3H, s), 3.10 (1H, dd, J=3.1, 14.6 Hz), 3.38 (1H, dd, J=8.5, 14.6 Hz), 4.08 (1H, dd, J=4.1, 10.2 Hz), 4.18 (1H, dd, J=7.0, 10.2 Hz) 4.19-4.29 (1H, m), 4.56 (1H, dt, J=2.6, 5.3Hz), 7.50-7.69 (3H, m), 7.81-7.91 (2H, m); EIMS m/z (relative intensity) : 377 (M^+-CH_3, 67), 317 (11), 239 (25), 221 (35), 185 (20), 77 (100); HRMS Calcd for $C_{15}H_{21}O_7S_2$(M^+-CH_3) : 377.0728; Found : 377.0730.

(2*R*,3*S*,4*S*)-1,2-Epoxy-4-hydroxy-3-methyl-5-phenylthiopentane (22). To a solution of 107 mg (0.29 mmol) of the mesylate **19** in 3 ml of $CHCl_3$ was added 30 mg of the powder of $FeCl_3$-SiO_2,[10] and the mixture was stirred at room temperature for 48 h. The reaction mixture was diluted with 30 ml of $CHCl_3$ and washed with 20 ml of brine, dried (Na_2SO_4), filtered, and concentrated. Purification of the residue by column chromatography (8g of silica gel BW-820MH, hexane and then hexane : EtOAc = 5 :1) afforded 56 mg (84 %) of the epoxide **22** as a colorless oil; $[\alpha]_D^{28}$ -43.8° (c 1.2, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3585, 2965, 1583, 1481, 1439, 1082, 981, 738; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.90 (3H, d, J=7.3 Hz), 1.83 (1H, bs, disappeared with D_2O), 2.11-2.30 (1H, m), 2.96 (1H, dd, J=7.3, 12.9 Hz), 3.17 (1H, dd, J=6.8, 12.9 Hz), 3.59-3.72 (1H, m), 4.06-4.19 (2H, m), 4.22-4.35 (1H, m) 7.11-7.42 (5H, m); EIMS m/z (relative intensity) : 224 (M^+, 98), 199 (43), 124 (45), 101 (100); HRMS Calcd for $C_{12}H_{16}O_2S$(M^+) : 224.0871; Found : 224.0824.

(4*R*,5*R*,6*S*)-6-*tert*-Butyldiphenylsiloxymethyl-4-formyl-2,2,5-trimethyl-1,3-dioxane (24). To a stirred solution of 0.22 ml (2.56 mmol) of oxalyl chloride in 4 ml of CH_2Cl_2 at -78℃ was added dropwise a solution of 0.25 ml (3.57 mmol) of DMSO in 3 ml of CH_2Cl_2 under an argon atmosphere. After the reaction mixture was stirred for 20 min at this temperature, a solution of 440 mg (1.02 mmol) of the alcohol **9** in 6 ml of CH_2Cl_2 was added slowly, and the mixture was stirred for 45 min. Then 0.85 ml (6.12 mmol) of Et_3N was added at -78℃. The reaction mixture was allowed to warm to 0℃ and stirred for 30 min. After being quenched with water, the resulting mixture was extracted with three 100 ml portions of EtOAc. The combined organic extracts were washed with 100 ml portions of saturated aqueous $NaHCO_3$, H_2O, and brine. The organic layer was dried (Na_2SO_4), filtered and concentrated. Purification of the residue by column chromatography (50 g of silica gel BW-820 MH hexane : EtOAc = 4 : 1) afforded 427 mg (98 %) of the aldehyde **24** as a colorless oil; $[\alpha]_D^{25}$ +1.4° (c 0.9, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3792, 1739, 1589, 1428, 1382, 1113; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.83 (3H, d, J=6.8 Hz), 1.05 (9H, s), 1.41 (3H, s), 1.45 (3H, s), 2.13-2.20 (1H, m), 3.56 (1H, dd, J=7.5, 10.2 Hz), 3.67 (1H, dd, J=5.8, 10.2 Hz), 4.03-4.09 (1H, m), 4.34 (1H, d, J=2.6 Hz), 7.35-7.46 (6H, m), 7.63-7.67 (4H, m), 9.57 (1H, s); EIMS m/z (relative intensity) 411 (M^+-CH_3, 2.9), 369 (20), 351 (7.1), 311 (52), 241 (100); HRMS Calcd for $C_{24}H_{31}O_4Si$ (M^+-CH_3) : 411.1991, Found : 411.1989.

(4*S*,5*R*,6*S*)-*tert*-Butyldiphenylsiloxymethyl-2,2,5-trimethyl-4-vinyl-6-1,3-dioxane

(**25**). Methyltriphenylphosphonium bromide (355 mg, 0.99 mmol) was added to a dry round-bottom flask equipped with stirring bar and rubber septum. The flask was evacuated with a vacuum pump (0.1 mmHg) for 2.5 h, keeping the temperature at 120℃, and then purged with argon. THF (2 ml) was injected and the slurry was cooled to -15℃, where 0.36 ml (0.59 mmol) of n-butyllithium (1.66 M in hexane) was added dropwise by syringe. After the reaction mixture was stirred for 20 min at -15℃, a solution of 82 mg (0.19 mmol) of the aldehyde **24** in 1 ml of THF was added. The resulting mixture was stirred for 1 h at -5℃, and then the reaction mixture was gradually warmed to room temperature and the stirring was continued for 13h at this temperature. The reaction mixture was quenched by the addition of 2 ml of water. The mixture was extracted with three 50 ml portions of EtOAc. The combined organic extracts were washed with 50 ml portions of brine, dried (Na_2SO_4), filtered, and concentrated. Purification of the residue by column chromatography (20 g of silica gel BW-820 MH, hexane and then hexane : EtOAc = 10 : 1) afforded 71 mg (81 %) of the olefin **25** as a colorless oil; $[\alpha]_D^{25}$ -13.8° (c 0.75, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 1472, 1428, 1253, 1200, 1134; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.79 (3H, d, J=6.8 Hz), 1.05 (9H, s), 1.38 (3H, s), 1.42 (3H, s), 1.60-1.71 (1H, m), 3.58 (1H, dd, J=7.3, 10.2 Hz), 3.67 (1H, dd, J=6.1, 10.2 Hz), 4.06-4.11 (1H, m), 4.44-4.47 (1H, m), 5.16 (1H, dt, J=1.7, 10.7 Hz), 5.26 (1H, dt, J=1.7, 17.3 Hz), 5.79 (1H, ddd, J=1.7, 5.1, 10.5 Hz), 7.34-7.45 (6H, m), 7.64-7.69 (4H, m); EIMS m/z (relative intensity) 409 (M^+-CH_3, 1.2), 349 (2.5), 309 (22), 241 (100); HRMS Calcd for $C_{26}H_{36}O_3Si$ (M^+-CH_3) : 409.2199, Found : 409.2200.

(4*S*, 5*R*, 6*S*)-6-*tert*-Butyldiphenylsiloxymethyl-4-hydroxyethyl-2,2,5-trimethyl-1,3-dioxane (26). To a dry flask containing 1 mmol of thexylborane (prepared from 1 ml (1 mmol) of 2,3-dimethyl-2-butene (1M solution in THF) and 1 ml (1 mmol) of borane-tetrahydrofuran complex (1M solution in THF)) in 2 ml of THF at -18℃ was added a solution of 21 mg (0.05 mmol) of the olefin **25** in 1.5 ml of THF under an argon atmosphere, and the reaction mixture was stirred for 3.5 h at -5℃ and then at room temperature for 13 h. After addition of 2 ml of water and 16 mg (0.1 mmol) of $NaBO_3$, the reaction mixture was stirred at room temperature for 13 h, and then diluted with 20 ml of EtOAc and washed with 10 ml of brine. The organic layer was dried (Na_2SO_4), filtered and concentrated. Purification of the residue by column chromatography (7 g of silica gel BW-820 MH, hexane : EtOAc = 10 : 1) afforded 18 mg (81 %) of the alcohol **26** as a colorless oil; $[\alpha]_D^{27}$ -14.6° (c 0.45, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3455, 1590, 1472, 1428, 1357, 1113, 823; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.82 (3H, d, J=6.8 Hz), 1.05 (9H, s), 1.35 (3H, s), 1.43 (3H, s), 1.53-1.68 (1H, m), 1.83-1.97 (1H, m), 2.20-2.40 (1H, bs, disappeared with D_2O), 3.58 (1H, dd, J=7.3, 10.2 Hz), 3.67 (1H, dd, J=6.1, 10.2 Hz), 3.75-3.79 (2H, m), 4.03-4.09 (1H, m), 4.13 (1H, dt, J=2.6, 10.0 Hz), 7.33-7.45 (6H, m), 7.64-7.68 (4H, m); EIMS m/z (relative intensity) 427 (M^+-CH_3, 5.1), 327 (23.5), 309 (14.7), 249 (64), 241 (100); HRMS Calcd for $C_{25}H_{35}O_4Si$ (M^+-CH_3) : 427.2304, Found : 427.2304.

(4*R*, 5*R*, 6*S*)-4-Acetyloxyethyl-6-*tert*-butyldiphenylsiloxymethyl-2,2,5-trimethyl-1,3-dioxane (27). To a solution of 8 mg (0.018 mmol) of the alcohol **26** in 1 ml of CH_2Cl_2 was added 22 ml (0.27 mmol) of pyridine at 0℃. After 15 min, 13 ml (0.18 mmol) of acetyl chloride was cautiously added, and the reaction mixture was stirred at 0℃ for 1 h and allowed to warm to room temperature. The reaction mixture was stirred at this temperature for 13 h and then quenched by the addition of 2 ml of water. The mixture was extracted with 20 ml of EtOAc. The organic layer was washed with 10 ml each portions of 1N HCl, saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and concentrated. The residue was

purified by column chromatography (3 g of silica gel BW-200, hexane : EtOAc = 10 : 1) to afforded 8.3 mg (95 %) of **27** as a colorless oil; $[\alpha]_D^{26}$ -20.0° (c 0.9, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 1742, 1472, 1428, 1380, 1113, 823; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.80 (3H, d, J=6.8 Hz), 1.05 (9H, s), 1.33 (3H, s), 1.37 (3H, s), 1.63-1.72 (2H, m), 1.80-1.85 (1H, m), 2.06 (3H, s), 3.57 (1H, dd, J=7.3, 10.2 Hz), 3.68 (1H, dd, J=6.1, 10.2 Hz), 3.96-4.17 (4H, m), 7.34-7.45 (6H, m), 7.64-7.68 (4H, m),; EIMS m/z (relative intensity) 469 (M^+-CH_3, 8.4), 409 (4), 369 (75), 309 (37.5), 241 (100); HRMS Calcd for $C_{27}H_{37}O_5Si$ (M^+-CH_3) : 469.2410, Found : 4269.2413.

(4*R*,5*R*,6*S*)-4-Acetyloxyethyl-6-hydroxymethyl-2,2,5-trimethyl-1,3-dioxane (28). To a solution of 13 mg (0.026 mmol) of **27** in 2 ml of THF was added 35 mg (0.13 mmol) of TBAF at 0℃. The reaction mixture was stirred for 13 h at room temperature and then concentrated. Column chromatography (5 g of silica gel BW-820 MH, hexane : EtOAc = 10 : 1) of the residue afforded 6.1 mg (95 %) of the alcohol **28** as a colorless oil; $[\alpha]_D^{27}$ -21.2° (c 0.5, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3459, 1739, 1462, 1382, 1243, 1034, 1011; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.85 (3H, d, J=7.0 Hz), 1.40 (3H, s), 1.43 (3H, s), 1.52-1.70 (2H, m), 1.80-1.91 (1H, m), 2.05 (3H, s), 3.33-3.57 (1H, bs, disappeared with D_2O), 3.49 (1H, dd, J=3.9, 10.9 Hz), 3.69 (1H, dd, J=8.0, 10.9 Hz); EIMS m/z (relative intensity) 231 (M^+-CH_3, 100), 189 (5.2), 111 (78). 68 (26); HRMS Calcd for $C_{11}H_{19}O_5$ (M^+-CH_3) : 231.1232, Found : 231.1234.

(4*R*,5*R*,6*S*)-4-Acetyloxyethyl-6-phenylthiomethyl-2,2,5-trimethyl-1,3-dioxane (29). To a solution of 10 mg (0.04 mmol) of the alcohol **28** and 88 mg (0.4 mmol) of diphenyldisulfide in 0.2 ml of pyridine was added dropwise 0.1 ml (0.4 mmol) of tributylphosphine at room temperature under an argon atmosphere and the resulting solution was stirred at room temperature for 15 h. Additional 44 mg (0.2 mmol) of diphenyldisulfide and 50 ml (0.2 mmol) of tributylphosphine were added. The mixture was stirred at room temperature for 24 h and then concentrated. Column chromatography (10 g of silica gel BW-820 MH, hexane and then hexane : EtOAc = 10 : 1) of the residue afforded 13.0 mg (96 %) of the sulfide **29** as a colorless oil; $[\alpha]_D^{27}$ -35.3° (c 0.6, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 1740, 1583, 1381, 1242, 1198, 1010, 739; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.87 (3H, d, J=6.8 Hz), 1.37 (3H, s), 1.38 (3H, s), 1.55-1.71 (2H, m), 1.78-1.91 (1H, m), 2.04 (3H, s), 2.88 (1H, dd, J=7.3, 13.1 Hz), 3.09 (1H, dd, J=6.5, 13.1 Hz), 3.92-4.17 (4H, m), 7.15-7.37 (5H, m); EIMS m/z (relative intensity) 338 (M^+, 46), 323 (19), 215 (44), 157 (100); HRMS Calcd for $C_{18}H_{26}O_4S$ (M^+) : 338.1552, Found : 338.1553.

(4*R*,5*R*,6*S*)-4-Acetyloxyethyl-6-phenylsulfonylmethyl-2,2,5-trimethyl-1,3-dioxane (3). To a suspension of 12 mg (0.035 mmol) of **29** and 8 mg (0.088 mmol) of $NaHCO_3$ in 1.5 ml of CH_2Cl_2 at 0℃ was added portionwise 22.8 mg (0.08 mmol) of m-chloroperoxybenzoic acid at this temperature. The reaction mixture was stirred for 1 h at 0℃. The mixture was diluted with 30 ml of EtOAc and washed with 10 ml each portions of saturated aqueous $NaHCO_3$, H_2O, and brine. The organic layer was dried (Na_2SO_4), filtered and concentrated. Purification of the residue by column chromatography (3g of silica gel BW-820 MH, hexane : EtOAc = 5 : 1 and then hexane : EtOAc = 2 : 1) afforded 12.1 mg (93 %) of the sulfone **3** as a colorless oil; $[\alpha]_D^{27}$ -22.6° (c 0.6, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 2991, 1741, 1447, 1380, 1305, 1263, 11246, 1144, 936; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.83 (3H, d, J=6.8 Hz), 1.04 (3H, s), 1.28 (3H, s), 1.41-1.49 (1H, m), 1.55-1.72 (1H, m), 1.72-1.84 (1H, m), 2.05 (3H, s), 3.09 (1H, dd, J=2.9, 14.6 Hz), 3.38 (1H, dd, J=8.5, 14.6 Hz), 3.98-4.15 (3H, m), 4.54 (1H, dt, J=2.9, 8.5 Hz), 7.50-7.67 (5H, m), 7.87-7.92 (2H, m); EIMS m/z (relative intensity) 355 (M^+-CH_3, 25), 295 (13.7), 265 (89), 235 (29), 93

(100), HRMS Calcd for $C_{17}H_{23}O_6S$ (M^+-CH_3) : 355.1215, Found : 355.1203.

Acknowledgment : This work was financially supported in part by Grants-in Aid from Ministry of Education, Science, Sports and Culture, Japan.

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(*Received in UK* 21 *March* 1997; *revised* 28 *May* 1997; *accepted* 29 *May* 1997)