Pergamon

Tetrahedron, Vol. 52, No. 24, pp. 8297-8306, 1996

0040-4020/96 $15.00 + 0.00

PII: S0040-4020(96)00383-3

An Efficient Synthesis of C_{20}-C_{25} Building Blocks for Calyculin A

Yasumasa Hamada,[a] Fumiaki Yokokawa,[b] Mototsugu Kabeya,[c]
Keiichiro Hatano,[b] Yukihisa Kurono,[b] and Takayuki Shioiri*[b]

[a]*Faculty of Pharmaceutical Sciences, Chiba University, 1-33, Yayoi-cho, Inage-ku, Chiba 263, Japan*

[b]*Faculty of Pharmaceutical Sciences, Nagoya City University, Tanabe-dori, Mizuho-ku, Nagoya 467, Japan*

[c]*Tokyo Research Laboratories, Kowa Co. Ltd., Noguchi-cho, Higashimurayama, 189, Japan*

Abstract: The C_{20}-C_{25} building blocks **2** and **3a** for calyculin A, a protein phosphatase inhibitor, have been efficiently prepared from L-malic acid utilizing the Grignard reaction of the Weinreb amides **8** and **14**, followed by stereoselective reduction of the ketones **9** and **15**, respectively, as the key steps.

Calyculin A (**1**), isolated from the marine sponge *Discodermia calyx*,[1] is an attractive target for total synthesis[2] because of its structural curiosity as well as intriguing biological activities such as inhibition of protein phosphatases and strong cytotoxicity.[1,3] Our continuous interests on the synthesis of marine natural products led us to synthesize calyculin A.[4] We now wish to report an efficient synthesis of C_{20}-C_{25} building blocks **2** and **3a** for calyculin A (**1**) (Fig. 1).

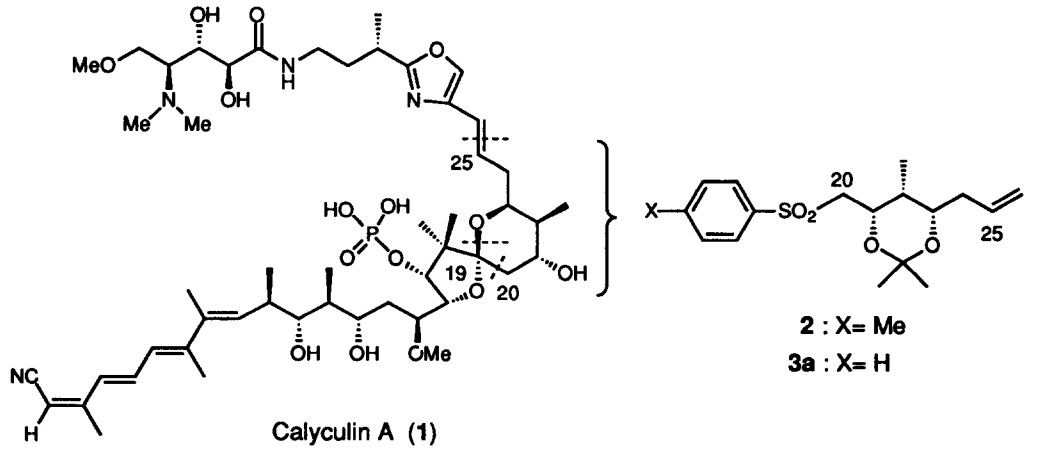
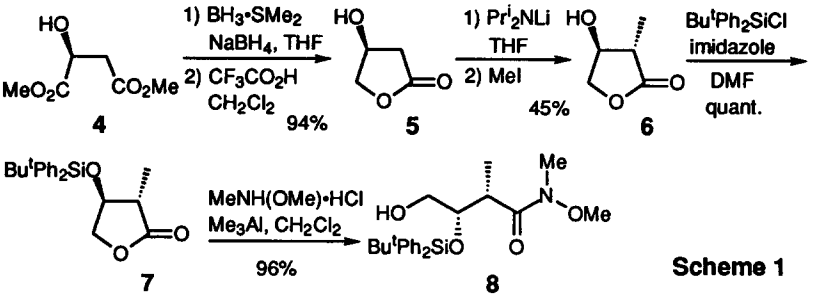


Fig. 1 Calyculin A and Its C_{20}-C_{25} Building Units

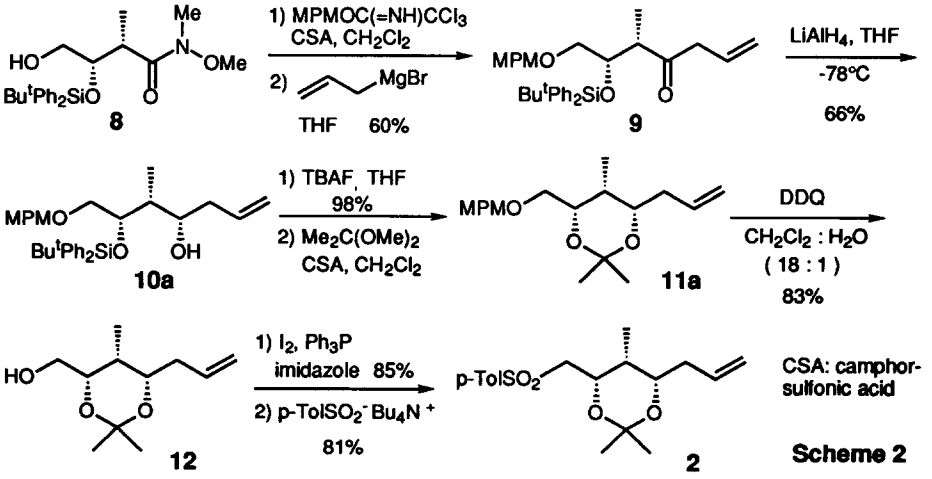
Dedicated to Professor Dr. Richard Neidlein on the occasion of his 65th birthday.

The hydroxy-γ-lactone **5**, prepared from dimethyl L-malate (**4**) according to the literature,[5] was first converted to the methylated lactone **6** via the dianion[6] from **5**, shown in Scheme 1. After protection of the alcoholic function with tert-butyldiphenylsilyl chloride, treatment of the silylated lactone **7** with the aluminum salt of methoxymethylamine afforded the Weinreb amide **8** in excellent yield.



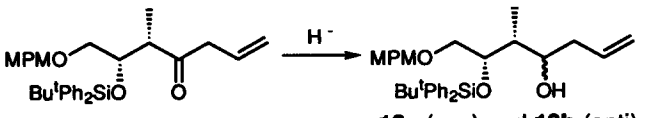
Scheme 1

Attachment of a three carbon unit to the amide **8** was accomplished as outlined in Scheme 2. Protection of the primary alcoholic function of **8** with the 4-methoxyphenylmethyl (MPM) group,[7] followed by the Grignard reaction with allyl magnesium bromide afforded the allyl ketone **9**. Stereoselective reduction of the ketone **9** toward the desired syn-1,3-diol derivative **10a** was found to be problematic, as summarized in Table 1. Reduction with sodium borohydride afforded the anti-1,3-diol derivative **10b** as the major product while addition of ceric trichloride[8] yielded the syn isomer **10a** as the major product. Diisobutylaluminum hydride, lithium borohydride, and sodium cyanoborohydride-ceric trichloride showed the analogous behavior to sodium borohydride. However, lithium aluminum hydride and lithium tri-(tert-butoxy)aluminum hydride mainly gave the desired syn isomer **10a**. Addition of lithium iodide to lithium aluminum hydride[9] did not raise the ratio of the syn-isomer. Reduction with lithium aluminum hydride followed by separation of the mixture on a silica gel column afforded the desired syn-isomer **10a** as a colorless oil in 66% yield. Treatment of **10a** with tetrabutylammonium fluoride (TBAF) followed by acetalization afforded the acetal derivative **11a**. Analogously, the anti-isomer **10b** was transformed to the acetal **11b**. The relative configuration of the acetals **11**, hence **10**, was determined as shown in Fig. 2 by the chemical shifts of their ^{13}C-NMR spectra according to the literatures.[10]



Scheme 2

Table 1. Stereoselective Reduction of the Allyl Ketone **9**



9 → **10a** (syn) and **10b** (anti)
α-OH β-OH

Run	Reagents (equiv)	Reaction Conditions Temp. (°C)	Time (h)	Yield (%)	Ratio[a] **10a** : **10b**
1	$NaBH_4$ (2)	0	1	91	1 : 1.8
2	$NaBH_4$ (2) $CeCl_3 \cdot H_2O$ (2)	0	1	84	2.6 : 1
3	$NaBH_3CN$ (2)	0 - r.t.		trace	-
4	$NaBH_3CN$ (2) $CeCl_3 \cdot H_2O$ (2)	0	1	78	1 : 1.4
5	$LiAlH_4$ (0.5)	-78	1	78	3.2 : 1
6	$LiAlH_4$ (1) LiI (1.2)	-78	1	74	2.2 : 1
7	Bu^i_2AlH (1.5 + 1.5)	-78 0	1 0.5	75	1 : 3.6
8	$LiBH_4$ (1)	-8	1	79	1 : 1.2
9	K-selectride[b] (1.5)	-78 - 0		decomp.	-
10	$LiAl(OBu^t)_3H$ (2)	-78	1.5	56	3.6 : 1
11	$LiAl(OBu^t)_3H$ (3) LiI (3)	-8	1	95	1.7 : 1

a) Determined by ^1H NMR. b) Potassium tri-sec-butylborohydride.

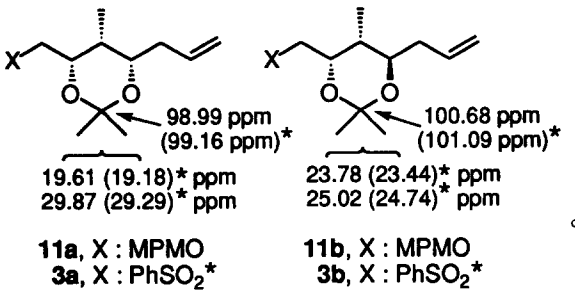


Fig. 2 ^{13}C NMR Spectra of **11** and **3**

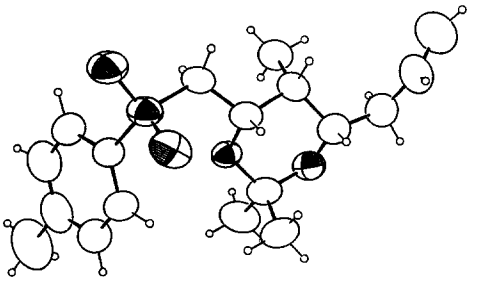
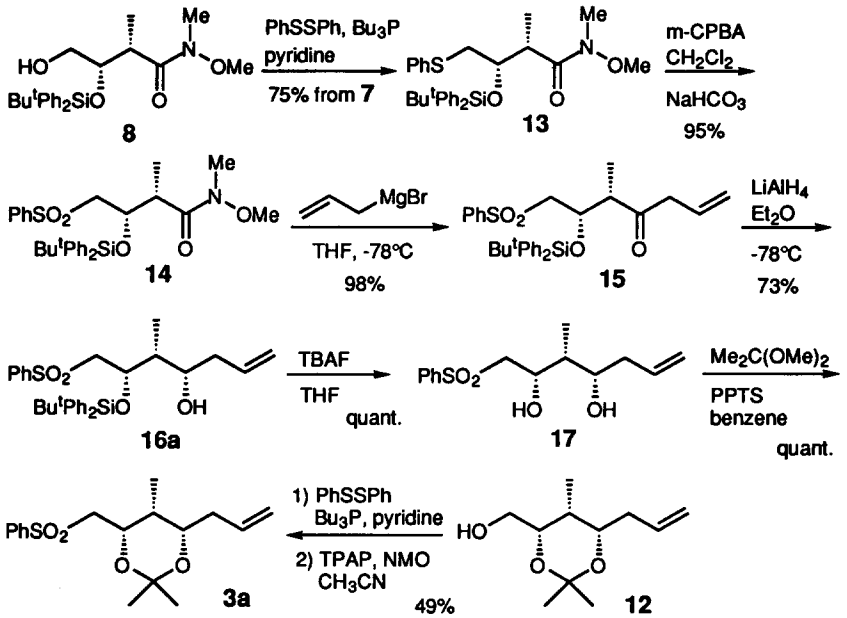


Fig. 3 ORTEP Representation of the Sulfone **2**

Oxidative deprotection of the MPM ether **11a** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[11] furnished the alcohol **12**, which was treated with iodine and triphenylphosphine followed by tetrabutylammonium *p*-toluenesulfinate[12] to give the required C20-C25 building block **2** for calyculins. The structure and stereoconfiguration of the sulfone **2** was fully confirmed by its X-ray crystallography whose ORTEP view was shown in Fig. 3.

Alternatively, another analogous building block **3** was efficiently constructed from the same Weinreb amide **8** through a shorter step, as outlined in Scheme 3. Conversion of **8** to the thioether **13** was achieved by

the action of diphenyl disulfide and tributylphosphine[13] in 75% yield from **7**. Oxidation of **13** with m-chloroperoxybenzoic acid (m-CPBA) afforded the sulfone **14**, which underwent the Grignard reaction with allylmagnesium bromide to give the unstable ketone **15** in almost quantitative yield. Reduction of the ketone **15** with lithium aluminum hydride as in the reduction of **9** yielded a mixture of diastereoisomeric syn-and anti-alcohols **16a** and **16b** in a ratio of 3.4:1 in 95% yield. After separation on a silica gel column, the syn-isomer **16a** was treated with TBAF to give the diol **17**, which was converted to the desired syn-acetal **3a** in excellent yield. Analogously, the anti-isomer **16b** was transformed to the anti-acetal **3b**. The configurational assignment of the syn- and anti-isomers was unambiguously made by the chemical shifts of their ^{13}C-NMR spectra (Fig. 2).[10] Furthermore, the alcohol **12** was converted to the syn-acetal **3a** by thiophenylation followed by oxidation, which established the absolute configuration of **3a**.



Scheme 3

In summary, efficient and high-yielding syntheses of the two syn-acetals **2** and **3a** were achieved starting from readily available L-malic acid. The both syntheses are practical and will be useful for the construction of the whole molecule of calyculins.[4b] The synthetic studies along this line is actively pursuing in our laboratories.

Experimental

(3S)-3-Hydroxy-4-butanolide (5). The title compound was prepared according to the published procedure as follows.[5] To a solution of 38.8 g (0.24 mol) of **4** in 500 ml of THF was added 24.4 ml (0.244 mol) of borane-dimethylsulfide complex and the mixture was stirred at room temperature for 30 min. Then, 0.4 g (12 mmol) of sodium borohydride was added to the mixture and the resulting mixture was stirred for an additional 30 min, followed by the addition of 154 ml of methanol. The mixture was concentrated. The residue was treated with 6 ml of trifluoroacetic acid in 300 ml of CH_2Cl_2 at room temperature for 1 day. After concentration, the residue was treated again with 10 ml of trifluoroacetic acid in 300 ml of CH_2Cl_2 at room

temperature for 2 days. The mixture was concentrated and purified by column chromatography (150 g of silica gel BW-820 MH, hexane:EtOAc = 2:3) to afford 23.1 g (94%) of the lactone **5** as a colorless oil: bp 100-107 °C / 0.2 mmHg (Kugelrohr), $[\alpha]_D^{25}$ -80.2° (c 3.0, EtOH) (lit[5]: $[\alpha]_D^{9}$ -85.9° (c 2.2, EtOH)); IR ν_{max}^{neat} cm^{-1}: 3406, 1769, 1176; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.82-2.40 (1H, bs, disappeared with D_2O), 2.52 (1H, ddd, J=0.9, 2.2, 17.8 Hz), 2.76 (1H, dd, J=6.1, 17.8 Hz), 4.31 (1H, ddd, J=0.9, 1.7, 10.2 Hz), 4.44 (1H, dd, J=4.4, 10.2 Hz), 4.67-4.72 (1H, m); HRMS Calcd for $C_4H_6O_3$ (M^+): 102.0317. Found: 102.0314.

(2S,3S)-3-Hydroxy-2-methyl-4-butanolide (6). The title compound was prepared according to the published procedure as follows.[6] To a dry flask containing 217 mmol lithium diisopropylamide (prepared from 31.4 ml (223 mmol) of diisopropylamine and 136 ml (217 mmol) of n-butyllithium (1.60 M in hexane)) in 200 ml of THF at -78 °C was added a solution of 5.41 g (53.0 mmol) of the lactone **5** in 100 ml of THF by cannula. After 1 h at -78 °C, the resulting solution was transferred by cannula to a stirred, cooled (-78 °C) solution of 83 ml (1.33 mmol) of methyl iodide in 400 ml of THF. After 6 h, the reaction was quenched with 12.4 ml (217 mmol) of glacial acetic acid. The reaction mixture was allowed to warm to room temperature and stirred overnight. The resulting insoluble material was removed by filtration and the filtrate was concentrated. Column chromatography (200 g of silica gel BW-820 MH, hexane:EtOAc = 1:1) afforded 2.77 g (45%) of **6** as a pale yellow oil: $[\alpha]_D^{25}$ -64.2° (c 1.0, $CHCl_3$); IR ν_{max}^{neat} cm^{-1}: 3417, 1767, 1642, 1459, 1386, 1181, 1016; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.31 (3H, d, J=7.6 Hz), 2.51-2.61 (1H, m), 2.00-3.41 (1H, bs, disappeared with D_2O), 4.08 (1H, dd, J=4.8, 9.5 Hz, 4.22-4.28 (1H, m), 4.45 (1H, dd, J=5.6, 9.5 Hz); HRMS Calcd for $C_5H_8O_3$ (M^+): 116.0473. Found: 116.0471.

(2S,3S)-3-*tert*-Butyldiphenylsiloxy-2-methyl-4-butanolide (7). To a solution of 907 mg (7.81 mmol) of the hydroxylactone **6** in 6 ml of DMF was added 1.28 g (18.74 mmol) of imidazole and 2.45 ml (9.38 mmol) of tert-butylchlorodiphenylsilane at room temperature. After 27 h, the mixture was diluted with 200 ml of EtOAc-benzene (2:1), and washed with 200 ml each portions of 1M $KHSO_4$, water, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated to give 3.06 g of **7** as a pale yellow oil. Column chromatography (120 g of silica gel BW 820 MH, eluted with hexane:ether (10:1) and then hexane:ether (2:1)) afforded 2.78 g (quantitative) of **7** as a colorless oil: $[\alpha]_D^{24}$ -12.8° (c 2.0, $CHCl_3$); IR ν_{max}^{neat} cm^{-1}: 3521, 1782, 1589, 1472, 1391, 1172, 1024; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.02 (3H, d, J=7.5 Hz) 1.07 (9H, S), 2.56 (1H, dq, J=5.3, 7.5 Hz), 3.97-4.16 (m, 3H), 7.37-7.50 (6H, m), 7.60-7.73 (4H, m); HRMS Calcd for $C_{17}H_{17}O_3Si$ (M^+-^{t}Bu): 297.0947. Found: 297.0938.

(2S,3S)-N-Methoxy-N,2-dimethyl-3-*tert*-butyldiphenylsiloxy-4-hydroxybutanamide (8). To a suspension of 4.43 g (45.3 mmol) of N,O-dimethylhydroxylamine hydrochloride in 45 ml of CH_2Cl_2 at -10 °C was added dropwise 21.9 ml of 2.0 M trimethylaluminum in hexane (43.9 mmol) accompanied with evolution of gas. The resulting colorless solution was stirred at room temperature for 30 min and recooled to 0 °C. The lactone **7** (5.19 g, 14.6 mmol) in 10 ml of CH_2Cl_2 (plus 20 ml of CH_2Cl_2 rinse) was added and the mixture was stirred at room temperature for 12 h. $KHSO_4$ (1 M, 50 ml) was cautiously added to the resulting mixture and the mixture was extracted with three 100 ml portions of CH_2Cl_2. The combined organic extracts were washed with 50 ml of brine, dried (Na_2SO_4), filtered, and concentrated to give 5.86 g (96%) of **8** as a white wax, which was used for the next step without further purification. $[\alpha]_D^{23}$ +12.3° (c 0.99, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3474, 1782, 1634, 1472, 1428; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.08 (9H, s), 1.15 (3H, d, J = 6.9 Hz), 2.55 (1H, brt, J = 6.4 Hz, disappeared with D_2O), 3.16 (3H, s), 3.32 (1H, br), 3.48 (2H, m), 3.67 (3H, s), 3.98 (1H, m), 7.41 (6H, m), 7.71 (4H, m). Anal. Calcd for $C_{23}H_{33}NO_4Si$: C, 66.47; H, 8.00; N, 3.37. Found: C, 66.18; H, 7.85; N, 3.22.

(5S,6S)-6-*tert*-Butyldiphenylsiloxy-5-methyl-7-*p*-methoxybenzyloxy-1-hepten-4-one (9). To a solution of 7.362 g (17.7 mmol) of **8** in 60 ml of CH_2Cl_2 was added 6 ml (28.9 mmol) of *p*-

methoxybenzyl trichloroacetimidate and 420 mg (1.81 mmol) of camphorsulfonic acid at room temperature. The resulting solution was stirred overnight. The mixture was diluted with 700 ml of ether and washed with 200 ml each portions of saturated aqueous $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated. The resulting white crystals were removed by filtration with hexane and the filtrate was concentrated. Column chromatography (200 g of silica gel BW-820MH, hexane:EtOAc = 7:1) afforded 8.144 g (contained trichloroacetamide) of the MPM ether as a yellow oil.

For the subsequent Grignard reaction, the crude product was taken up in 60 ml of THF. Allylmagnesium bromide (32 ml of 1 M solution, 32 mmol) in ether was added with ice-salt cooling. The resulting solution was stirred for 30 min and then quenched by the addition of 200 ml of 1 M $KHSO_4$. The mixture was extracted with 700 ml of ether. The organic layer was washed with 200 ml of brine, dried ($MgSO_4$), filtered, and concentrated. Column chromatography (200 g of silica gel BW-820 MH, haxane:ether = 15:1) afforded 5.539 g (crude 60%, contained unknown products) of **9** as a colorless oil, which was directly used for the next step.

(4S,5R,6S)-6-*tert*-Butyldiphenylsiloxy-4-hydroxy-5-methyl-7-*p*-methoxybenzyloxy-1-heptene (10a). To a solution of 1.631 g (3.15 mmol) of **9** in 15 ml of ether was added 1.6 ml of 1.0 M $LiAlH_4$ in ether (1.6 mmol) at -78 °C. The resulting solution was stirred for 20 min and then quenched by the addition of 50 ml of 1 M $KHSO_4$. The mixture was extracted with 200 ml of ether. The organic layer was washed with 50 ml of brine, dried ($MgSO_4$), filtered, and concentrated. The residue (mixture of **10a** and anti isomer of **10a**) was purified by column chromatography (100 g of silica gel BW-200, hexane:ether = 10:1) to give 966 mg (66%) of **10a** as a colorless oil: $[\alpha]_D^{23}$ -22.0° (c 1, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3447, 1613, 1514, 1250, 1111; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.85 (3H, d, J = 7.3 Hz), 1.04 (9H, s), 1.82 (1H, m), 2.13 (1H, m), 2.27 (1H, m), 3.24 (1H, dd, J = 10.2, 4.95 Hz), 3.34 (1H, dd, J = 10.2, 3.6 Hz), 3.47 (1H, br, disappeared with D_2O), 3.70 (3H, s), 3.84 (1H, m), 4.11 (1H, br, +D_2O, m), 4.18 (2H, m), 5.08 (2H, m), 5.86 (1H, m), 6.80 (2H, d, J = 8.6 Hz), 7.03 (2H, d, J = 8.6 Hz), 7.35 (6H, m), 7.65 (4H, m). Anal. Calcd for $C_{32}H_{42}O_4Si$: C, 74.09; H, 8.16. Found: C, 74.12; H, 8.19.

The analytical sample of the undesired anti isomer **10b** was obtained through purification on a column. The undesired anti isomer **10b**: $[\alpha]_D^{23}$ -25.8° (c 1, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3494, 1615, 1514, 1248, 1111; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.82 (3H, d, J = 7.25 Hz), 1.03 (9H, s), 1.78 (1H, m), 2.13 (1H, m), 2.35 (1H, m), 3.06 (1H, d, J = 3.6 Hz, disappeared with D_2O), 3.42 (2H, m), 3.66 (1H, m), 3.79 (3H, s), 4.09 (2H, s), 4.15 (1H, m), 5.09 (2H, m), 5.88 (1H, m), 6.76 (2H, d, J = 8.9 Hz), 6.93 (2H, d, J = 8.6 Hz), 7.35 (6H, m), 7.65 (4H, m). Anal. Calcd for $C_{32}H_{42}O_4Si$: C, 74.09; H, 8.16. Found: C, 74.02; H, 8.16.

(4S,5R,6S)-5-Methyl-7-*p*-methoxybenzyloxy-1-hepten-4,6-diol. To a solution of 966 mg (1.86 mmol) of **10a** in 5 ml of THF was added a solution of 1.77 g (3.71 mmol) of TBAF in 4 ml of THF at room temperature. The reaction mixture was stirred for 1 h and then concentrated. Column chromatography (70 g of silica gel BW-820 MH, hexane:EtOAc = 2:1) afforded 509 mg (98%) of the diol as a colorless oil. This material was directly used for the next step. IR ν_{max}^{neat} cm^{-1} 3400, 1613, 1514, 1248, 1094; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.91 (3H, d, J = 7.3 Hz), 1.68 (1H, m), 2.25 (2H, m), 2.83 (2H, s, disappeared with D_2O), 3.46 (2H, m), 3.81 (3H, s), 3.89 (1H, m), 4.01 (1H, m),4.48 (2H, d, J = 3 Hz), 5.11 (2H, m), 5.79 (1H, m), 6.88 (2H, d, J = 8.6 Hz), 7.26 (2H, d, J = 8.6 Hz).

(4S,5R,6S)-4-Allyl-6-*p*-methoxybenzyloxymethyl-2,2,5-trimethyl-1,3-dioxane (11a). To a solution of 1.116 g (3.98 mmol) of the above diol in 15 ml of CH_2Cl_2 was added 4.9 ml (39.8 mmol) of 2,2-dimethoxypropane and 46 mg (0.198 mmol) of camphorsulfonic acid, and the resulting solution was stirred at room temperature for 1.5 h. The mixture was diluted with 150 ml of ether and washed with 50 ml each portions of saturated aqueous $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated to afford 1.245 g (3.89 mmol) of the acetonide as a colorless oil. This material was used for the

next step without further purification. The analytical sample was purified through column chromatography (silica gel BW-820 MH, hexane:ether = 10:1).

The desired syn acetonide **11a**: $[\alpha]_D^{23}$ -22.4° (c 1, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 1613, 1514, 1248, 1102; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.82 (3H, d, J = 6.9 Hz), 1.40 (3H, s), 1.44 (3H, s), 1.53 (1H, m), 2.13 (1H, m), 2.27 (1H, m), 3.37 (1H, dd, J = 9.6, 6.3 Hz), 3.45 (1H, dd, J = 9.6, 6.3 Hz), 3.80 (3H, s), 3.93 (1H, td, J = 6.9, 2.3 Hz), 4.13 (1H, td, J = 6.3, 2.6 Hz), 4.47 (2H, ABq, J = 11.7 Hz), 5.09 (2H, m), 5.75 (1H, m), 6.87 (2H, d, J = 8.6 Hz), 7.25 (2H, d, J = 8.6 Hz, ArH); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 4.71, 19.61, 29.87, 32.24, 37.02, 55.22, 70.59, 72.27, 72.62, 73.05, 98.99, 113.75, 116.91, 129.40, 130.23, 134.30, 159.21. Anal. Calcd for $C_{19}H_{28}O_4$: C, 71.22; H, 8.81. Found: C, 70.95; H, 8.81.

The same procedure as described above was applied to the anti isomer **10b** to give the undesired anti acetonide **11b** as a colorless oil: $[\alpha]_D^{25}$ -29.1° (c 1, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 1615, 1514, 1248; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.82 (3H, d, J = 6.9 Hz), 1.35 (3H, s), 1.38 (3H, s), 1.76 (1H, m), 2.27 (2H, m), 3.35 (1H, m), 3.43 (2H, m), 3.80 (3H, s), 4.11 (1H, m), 4.48 (2H, ABq, J = 11.55 Hz), 5.06 (2H, m), 5.85 (1H, m), 6.87 (2H, d, J = 8.6 Hz), 7.25 (2H, d, J = 8.6 Hz); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 11.57, 23.78, 25.02, 37.67, 38.65, 55.24, 67.98, 69.36, 72.96, 74.31, 100.68, 113.73, 116.53, 129.31, 130.35, 135.11, 159.16. Anal. Calcd for $C_{19}H_{28}O_4$: C, 71.22; H, 8.81. Found: C, 71.30; H, 8.72.

(4S,5R,6S)-4-Allyl-6-hydroxymethyl-2,2,5-trimethyl-1,3-dioxane (12). To a solution of 1.245 g (3.89 mmol) of the acetonide **11a** in 18 ml of CH_2Cl_2 was added 1 ml of water. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (1.3 g, 5.73 mmol) was added to the rapidly stirred biphasic mixture in one portion, showing a green color which slowly faded to orange-brown. After 20 min, the reaction was quenched by the addition of 50 ml of saturated aqueous $NaHCO_3$ and the resultant mixture was extracted with three 50 ml portions of CH_2Cl_2. The combined CH_2Cl_2 extracts were washed with 50 ml of water, dried (Na_2SO_4), filtered, and concentrated. Purification by column chromatography (80 g of silica gel BW-820 MH, hexane:EtOAc = 5:1) afforded 659 mg (83%) of **12** as a colorless oil: $[\alpha]_D^{23}$ -10.8° (c 0.99, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3400, 1644, 1381, 1200; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.85 (3H, d, J = 6.6 Hz), 1.42 (3H, s), 1.46 (3H, s), 1.50 (1H, m), 1.83 (1H, br, disappeared with D_2O), 2.15 (1H, m), 2.31 (1H, m), 3.49 (1H, br, +D_2O, dd, J = 11.2, 3.6 Hz), 3.70 (1H, m, +D_2O, dd, J = 11.2, 8.2 Hz), 3.95 (1H, td, J = 7.3, 2.3 Hz), 4.03 (1H, m), 5.15 (2H, m), 5.80 (1H, m). Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 65.88; H, 9.99.

(4S,5R,6S)-4-Allyl-6-*p*-toluenesulfonylmethyl-2,2,5-trimethyl-1,3-dioxane (2). To a mixture of 123 mg (0.615 mmol) of **12**, 323 mg (1.23 mmol) of triphenylphosphine, 105 mg (1.23 mmol) of imidazole in 3 ml of toluene was added 312 mg (1.23 mmol) of iodine. The mixture was heated to 80 °C for 20 min. The reaction was quenched by the addition of 10 ml of saturated aqueous $Na_2S_2O_3$ and the resultant mixture was extracted with 30 ml of ether. The organic layer was washed with 10 ml of brine, dried ($MgSO_4$), filtered, and concentrated. The resulting white crystals were removed by filtration with hexane and the filtrate was concentrated. Column chromatography (17 g of silica gel BW-820 MH, hexane:ether = 300:1) afforded 162 mg (85%) of the iodide as a colorless oil. This material was directly used for the next step.

A mixture of 162 mg (0.523 mmol) of the above iodide and 565 mg (0.785 mmol) of tetrabutylammonium *p*-toluenesulfinate in 2.5 ml of DMF was heated at 80 °C for 18 h. The mixture was diluted with 60 ml of ether and washed with 10 ml each portions of water and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated. Column chromatography (17 g of silica gel BW-820 MH, hexane:EtOAc = 10:1) afforded 143 mg (81%) of **2** as white crystals: mp 92-93 °C (ether-pentane); $[\alpha]_D^{25}$ -20.5° (c 1, $CHCl_3$); IR ν_{max}^{KBr} cm^{-1} 1646, 1601, 1460, 1391, 1283, 1200; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.82 (3H, d, J = 6.9 Hz), 1.10 (3H, s), 1.32 (3H, s), 1.46 (1H, m), 2.10 (1H, m), 2.24 (1H, m), 2.45 (3H, s), 3.08 (1H, dd, J = 14.5, 3 Hz), 3.35 (1H, dd, J = 14.5, 8.6 Hz), 3.94 (1H, td, J = 7.3, 2.3 Hz),

4.51 (1H, m), 5.10 (2H, m), 5.71 (1H, m), 7.32 (2H, d, J = 8.6 Hz), 7.77 (2H, d, J = 8.25 Hz). Anal. Calcd for $C_{18}H_{26}O_4S$: C, 63.88; H, 7.74. Found: C, 64.06; H, 7.64.

(2S,3S)-3-tert-butyldiphenylsiloxy-N,2-dimethyl-N-methoxy-4-phenylthiobutanamide (13). A mixture of 5.86 g (13.5 mmol) of **8**, 7.33 g (33.5 mmol) of diphenyldisulfide, and 6.79 g (33.5 mmol) of tributylphosphine in 5.5 ml of pyridine was stirred for 15 h at room temperature under an argon atmosphere. The mixture was concentrated in vacuo. Column chromatography (150 g of silica gel BW-820 hexane:EtOAc = 20:1 then hexane:EtOAc = 3:1) afforded 5.54 g (75% in 2 steps from **7**) of the thioether **13** as a colorless wax: $[\alpha]_D^{24}$ -39.1° (c 1, $CHCl_3$); IR ν_{max}^{neat} cm^{-1}. 2962, 2933, 1660, 1471, 1376, 1110, 821; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.05 (9H, s), 1.18 (3H, d, J=6.8 Hz), 2.91 (1H, dd, J=7.6, 13.4 Hz), 3.00 (1H, dd, J=4.15, 13.4 Hz), 3.13 (3H, s), 3.30-3.40 (1H, m), 4.40-4.42 (1H, m), 6.80-6.90 (2H, m), 7.00-7.20 (3H, m), 7.31-7.50 (6H, m), 7.61-7.80 (4H, m); EIMS $^m/_z$ (relative intensity): 450 (M^+-$^+$Bu, 100), 251 (31), 199 (2), 142 (75); HRMS Calcd for $C_{25}H_{28}NO_3SSi$: 450.1559. Found: 450.1558.

(2S,3S)-3-tert-butyldiphenylsiloxy-N,2-dimethyl-N-methoxy-4-phenylsulfonylbutanamide (14). To a suspension of 2.38 g (4.68 mmol) of **13** and 865 mg (10.29 mmol) of $NaHCO_3$ in 40 ml of CH_2Cl_2 at 0°C was added portionwise 3.55 g (10.29 mmol) of m-chloroperoxybenzoic acid at this temperature. The reaction mixture was stirred for 1.5 h at 0°C. The mixture was diluted with 300 ml of EtOAc and washed with 100 ml each portions of saturated aqueous $NaHCO_3$, H_2O, and brine. The organic layer was dried ($MgSO_4$), filtered and concentrated. Purification of the residue by column chlormatography (300 g of silica gel BW 820 MH, hexane:EtOAc = 4:1) afforded 2.4 g (95 %) of the sulfone **14** as a colorless oil: $[\alpha]_D^{24}$ -23.7° (c 0.95, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3071, 2935, 2894, 1667, 1472, 1112, 845; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.02 (9H, s), 1.18 (3H, d, J=7.1 Hz), 3.10 (3H, s), 3.10-3.20 (m, 1H), 3.30-3.50 (2H, m), 3.59 (3H, s), 4.76-4.82 (1H, m), 7.27-7.80 (15H, m); EIMS $^m/_z$ (relative intensity): 482 (M^+-^{t}Bu, 61), 423 (2), 323 (6), 199 (55), 142 (100); HRMS Calcd for $C_{25}H_{28}NO_5SSi$ (M^+-^{t}Bu): 482.1457. Found: 482.1436.

(5S,6S)-6-tert-Butyldiphenylsiloxy-5-methyl-7-phenylsulfonyl-1-hepten-4-one (15). To a solution of 1.34 g (2.48 mmol) of **14** in 50 ml of THF was added 3.2 ml of 1.0 M allylmagnesium bromide in ether (3.22 mmol) at -78°C under an argon atmosphere. The resulting solution was stirred for 1 h at -78°C and then cautiously quenched by the addition of 10 ml of 10% citric acid. The mixture was extracted with three 50 ml portions of EtOAc-CH_2Cl_2 (2:1). The combined organic extracts were washed with 50 ml saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), filtered and concentrated to give 1.26 g (98%) of **15** as a colorless oil, which was used for the next step without further purification: $[\alpha]_D^{26}$ +18.4° (c 1, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3412, 3131, 1716, 1472, 1463, 1428, 1112; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.97 (9H, s), 1.17 (3H, d, J=6.8 Hz), 2.96-3.17 (2H, m), 3.21 (1H, dd, J=3.2, 14.2 Hz), 3.34 (1H, dd, J=8.55, 14.2 Hz), 4.58-4.64 (1H, m), 4.99 (1H, dd, J=1.7, 17.3 Hz), 5.14 (1H, dd J=1.7, 10.2 Hz), 5.74-5.82 (1H, m), 7.26-7.61 (15 H, m); EIMS $^m/_z$ (relative intensity): 463 (M^+-^{t}Bu, 31), 385 (15), 321 (15), 199 (100), 77 (20); HRMS Calcd for $C_{26}H_{27}O_4SSi$ (M^+-^{t}Bu): 463.1399. Found: 463.1401.

(4S,5R,6S)-6-tert-Butyldiphenylsiloxy-4-hydroxy-5-methyl-7-phenysulfonyl-1-hepetene (16a). To a solution of 78 mg (0.149 mmol) of **15** in 4 ml of ether was added 75 μl of 1.0 M $LiAlH_4$ in ether (0.075 mmol) at -78°C under an argon atmosphere. The resulting solution was stirred for 30 min and then quenched by the addition of 1.0 ml of 1M $KHSO_4$. The mixture was extracted with 100 ml of EtOAc. The organic layer was washed with 30 ml of brine, dried (Na_2SO_4), filtered, and then concentrated. The residue (a mixture of the syn product **16a** and anti isomer **16b**) was purified by column chromatography (8 g of silica gel BW-200, hexane:ether = 4:1) to give 57 mg (73%) of the syn alcohol **16a** as a colorless oil.

The desired syn alcohol **16a**: $[\alpha]_D^{25}$ +7.8° (c 1.85, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3530, 1428, 1391, 1306, 1147, 1111, 822; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.88 (3H, d, J=6.8 Hz), 1.05 (9H, s), 1.87-2.09 (3H, m, 1H disappeared with D_2O), 3.20 (1H, dd, J=4.4, 14.4 Hz), 3.40 (1H, dd, J=7.6, 14.4 Hz), 3.81-3.89 (1H, m), 4.34-4.40 (1H, m), 5.03-5.11 (2H, m), 5.61-5.76 (1H, m), 7.33-7.67 (15 H, m); EIMS $^m/_z$ (relative intensity): 465 (M^+-^{t}Bu, 40), 447 (5), 387 (12), 323 (6), 199 (100); HRMS Calcd for $C_{26}H_{29}O_4SSi$ (M^+-^{t}Bu): 465.1556. Found: 465.1560.

The undesired anti alcohol **16b** (17 mg, 22%), colorless crystals: mp 118.5-120°C (ether-hexane); $[\alpha]_D^{25}$ -15.0° (c 0.65, $CHCl_3$); IR ν_{max}^{KBr} cm^{-1} 3536, 2957, 2934, 1307, 1143, 1037; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.93 (3H, d, J=6.8 Hz), 0.99 (s, 9H), 1.56 (1H, d, J=5.4 Hz, disappeared with D_2O), 1.91-2.13 (2H, m), 2.35-2.40 (1H, m), 3.15 (1H, dd, J=2.9, 14.1 Hz), 3.35 (1H, dd, J=9.8, 14.1 Hz), 3.42-3.52 (1H, m), 4.60-4.65 (1H, m), 5.08-5.19 (2H, m), 5.70-5.86 (1H, m), 7.28-7.57 (m, 15H); EIMS m/z (relative intensity): 465 (M^+-tBu, 2.8), 447 (5), 387 (40), 323 (3), 199 (100); Anal. Calcd for $C_{30}H_{38}O_4SSi$: C, 68.93; H, 7.46. Found: C, 69.01, H, 7.41.

(4S,5R,6S)-5-Methyl-7-phenylsulfonyl-1-hepten-4,6-diol (17). To a solution of 54 mg (0.1 mmol) of **16a** in 2.5 ml of THF was added 81 mg (0.3 mmol) of TBAF at 0°C. The reaction mixture was stirred for 2 h at room temperature and then concentrated. Column chromatography (10 g of silica gel BW-820 MH, hexane:ether = 2:1 and then hexane:ether = 1:2) afforded 29 mg (quantitative) of the diol **17** as a colorless oil: $[\alpha]_D^{25}$ +11.2° (c 1.1, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3491, 3072, 2934, 1447, 1305, 1085, 972; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.90 (3H, d, J=7.1 Hz), 1.55-1.78 (1H, m), 2.12-2.36 (2H, m), 2.58 (1H, d, J=1.95 Hz, disappeared with D_2O), 3.18 (1H, dd, J=2.2, 14.6 Hz), 3.37 (1H, dd, J=9.3, 14.6 Hz), 3.73 (1H, bs, disappeared with D_2O), 3.91-4.01 (1H, m), 4.34-4.40 (1H, m), 5.02-5.21 (2H, m), 5.65-5.82 (1H, m), 7.52-7.72 (3H, m), 7.85-8.00 (2H, m); EIMS m/z (relative intensity): 225 (M^+-Allyl-H_2O, 19), 141 (7), 84 (100), 51 (38); HRMS Calcd for $C_{11}H_{13}O_3S$ (M^+-Allyl-H_2O): 225.0585. Found: 225.0581,

(4R,5R,6S)-5-Methyl-7-phenylsulfonyl-1-hepten-4,6-diol. The undesired anti diol of **17** was obtained from **16b** as a colorless oil: $[\alpha]_D^{26}$ +6.4° (c 1.25, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3485, 2977, 1447, 1305, 1147, 1085; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.92 (3H, d, J=7.1 Hz), 1.60-1.71 (1H, m), 2.14-2.25 (1H, m), 2.23-2.43 (1H, m), 2.62 (1H, d, J=4.4 Hz, disappeared with D_2O), 3.13 (1H, dd, J=1.95, 14.2 Hz), 3.39 (1H, dd, J=9.5, 14.2 Hz), 3.57-3.64 (2H, m, 1H disappeared with D_2O), 4.52-4.57 (1H, m), 5.05-5.14 (2H, m), 5.71-5.87 (1H, m), 7.52-7.71 (3H, m), 7.93-7.97 (2H, m); EIMS m/z (relative intensity): 225 (M^+-Allyl-H_2O, 45), 141 (50), 77 (100), 51 (20); HRMS Calcd for $C_{11}H_{13}O_3S$ (M^+-Allyl-H_2O): 225.0585. Found: 225.0585.

(4S,5R,6S)-4-Allyl-6-phenylsulfonylmethyl-2,2,5-trimethyl-1.3-dioxane (3a). (i) From 17. To a solution of 24 mg (0.08 mmol) of the diol **17** in 2 ml of benzene was added 0.4 ml (0.34 mmol) of 2,2-dimethoxypropane and 21.0 mg (0.08 mmol) of pyridinium *p*-toluenesulfonate, and the resulting solution was stirred at room temperature for 24 h. After additional 10 ml (0.08 mmol) of 2,2-dimethoxypropane was added, the mixture was stirred at room temperature for 12 h and then concentrated. Column chromatography (5.0 g of silica gel BW-820 MH, hexane:ether = 3:1 and then hexane:ether = 1:1) afforded 27 mg (quantitative) of the syn acetonide **3a** as white crystals: mp 94.5-95.5°C (pentane); $[\alpha]_D^{26}$ -15.6° (c 1.5, $CHCl_3$); IR ν_{max}^{KBr} cm^{-1} 1646, 1449, 1381, 1291, 1200; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.82 (3H, d, J=6.9 Hz), 1.05 (3H, s), 1.30 (3H, s), 1.49 (1H, m), 2.11 (1H, m), 2.23 (1H, m), 3.09 (1H, dd, J=2.6, 14.5 Hz), 3.39 (1H, dd, J=8.5, 14.5 Hz), 4.51 (1H, dt, J=2.6, 8.6 Hz), 5.07 (2H, m), 5.71 (1H, m), 7.60 (3H, m), 7.88 (2H, m); EIMS m/z (relative intensity): 309 (M^+-CH_3, 30), 283 (5), 225 (5), 200 (26), 199 (100); Anal. Calcd. for $C_{17}H_{24}O_4S$: C, 62.94; H, 7.46. Found: C, 62.85; H, 7.46.

(ii) From 12. To a solution 31 mg (0.155 mmol) of the alcohol **12** and 94 mg (0.43 mmol) of diphenyldisulfide in 0.7 ml of pyridine was added dropwise 0.11 ml (0.44 mmol) of tributylphosphine at room temperature under argon. After being stirred at room temperature for 25 h, the reaction mixture was diluted with 30 ml of ether , washed with 10 ml of 10% aqueous citric acid, and 10 ml of saturated brine, and dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified by column chromatography (8g of silica gel BW-820 MH; hexane - ether = 100 : 1) to give 44 mg (97%) of the sulfide as a colorless oil: ^{1}H-NMR δ 0.87 (3H, d, J = 6.9 Hz), 1.39 (3H, s), 1.40 (3H, s), 1.61 (1H, m), 2.15 (1H, m), 2.28 (1H, m), 2.90 (1H, dd, J = 12.9, 6.9 Hz), 3.08 (1H, dd, J = 12.9, 6.9 Hz), 3.88 (1H, td, J = 6.9, 2.3 Hz), 4.03 (1H, td, J = 6.9, 2.3 Hz), 5.07 (2H, m), 5.75 (1H, m), 7.30 (5H, m); ^{13}C-NMR δ 4.42, 19.59, 29.81, 33.34, 36.12, 37.13, 77.20, 72.83, 99.37, 117.02, 126.07, 128.90, 129.29, 134.23, 136.23.

To a stirred solution 21 mg (0.072 mmol) of the sulfide in 0.4 ml of CH_3CN was added 20 mg of powdered molecular sieves 4A, followed by 25 mg (0.213 mmol) of N-methylmorpholine N-oxide at room temperature under argon. After 5 min, 1.3 mg (0.0037 mmol) of tetrapropylammonium perruthenate was added and the reaction mixture was warmed to 40 °C. After 2 h, the reaction mixture was filtered through a pad of celite and the filtrate was concentrated in vacuo and the residue was purified by chromatography (silica gel BW-820 MH, hexane : ether = 5 : 1) to give the sulfone **3a** (12 mg, 51 %) as white crystals.

(4R,5R,6S)-4-Allyl-6-phenylsulfonylmethyl-2,2,5-trimethyl-1,3-dioxane (3b). The undesired anti acetonide **3b** was obtained from the undesired anti diol of **17** as a colorless oil: $[\alpha]_D^{26}$ -34.4° (c 0.95, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 2988, 1642, 1447, 1382, 1305, 1199, 1027; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 0.83 (3H, d, J=6.8 Hz), 1.14 (3H, s), 1.24 (3H, s), 1.71-1.81 (1H, m), 2.23-2.28 (2H, m), 3.12 (1H, dd, J=3.2, 14.65 Hz), 3.23-3.28 (1H, m), 3.35 (1H, dd, J=9.3, 14.65 Hz), 4.44-4.50 (1H, m), 5.03-5.11 (2H, m), 5.72-5.88 (1H, m), 7.51-7.66 (3H, m), 7.89-7.93 (2H, m); EIMS m/z (relative intensity): 309 (M^+-CH_3, 95), 283 (100), 225 (28), 200 (32); HRMS Calcd for $C_{16}H_{21}O_4S$ (M^+-CH_3): 309.1160. Found: 309.1152.

Acknowledgement: This work was financially supported in part by Grant-in-Aids from Ministry of Education, Science, Sports and Culture, Japan.

References and Notes

1. (a) Kato, Y.; Fusetani, N.; Matsunaga, S.; Hashimoto, K.; Fujita, S.; Furuya, T. *J. Am. Chem. Soc.* **1986**, *108*, 2780. (b) Kato, Y.; Fusetani, N.; Matsunaga, S.; Hashimoto, K.; Koseki, K. *J. Org. Chem.* **1988**, *53*, 3930. (c) Matsunaga, S.; Fujiki, H.; Sakata, D.; Fusetani, N. *Tetrahedron* **1991**, *47*, 2999.
2. (a) Evans, D.A.; Gage, J.R.; Leighton, J.L. *J. Am. Chem. Soc.* **1992**, *114*, **9434**, and references therein. (b) Tanimoto, N.; Gerritz, S.W.; Sawabe, A.; Noda, T.; Filla, S.A.; Masamune, S. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 673, and references therein.
3. (a) Ishihara, H.; Martin, B.L.; Brautigan, D.L.; Karaki, H.; Ozaki, H.; Kato, Y.; Fusetani, N.; Watabe, S.; Hashimoto, K.; Uemura, D.; Hartshorne, D.J. *Biochem. Biophys. Res. Commun.* **1989**, *159*, 871. (b) Suganuma, M.; Fujiki, H.; Furuya-Suguri, H.; Yoshizawa, S.; Yasumoto, S.; Kato, Y.; Fusetani, N.; Sugimura, T. *Cancer Res.* **1990**, *50*, 3521. (c) Suganuma, M.; Fujiki, H.; Okabe, S.; Nishiwaki, S.; Brautigan, D.; Ingebritsen, T.S.; Rosner, M.R. *Toxicon* **1992**, *30*, 873.
4. For our recent studies, see (a) Takebuchi, K.; Hamada, Y.; Shioiri, T. *Tetrahedron Lett.* **1994**, *35*, 5239. (b) Yokokawa, F.; Hamada, Y.; Shioiri, T. *J. Chem. Soc. Chem. Commun.* in press.
5. Saito, S.; Hasegawa, T.; Inaba, M.; Nishida, R. *Chem. Lett.* **1984**, 1389.
6. Cf. Chamberlin, A.R.; Dezube, M. *Tetrahedron Lett.* **1982**, *23*, 3055.
7. Nakajima, N.; Horita, K.; Abe, R.; Yonemitsu, O. *Tetrahedron Lett.* **1988**, *29*, 4139.
8. Luche, J.-L.; Gemal, A.L. *J. Am. Chem. Soc.* **1979**, *101*, 5848.
9. Mori, Y.; Suzuki, M. *Tetrahedron Lett.* **1989**, *30*, 4383.
10. (a) Rychnovsky, S.D.; Skalitzky, D.J. *Tetrahedron Lett.* **1990**, *31*, 945. (b) Evans, D.A.; Rieger, D.L.; Gage, J.R. *Terahedron Lett.* **1990**, *31*, 7099. (c) Rychnovsky, S.D.; Rogers, B.; Yang, G. *J. Org Chem.* **1993**, *58*, 3511.
11. Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 885.
12. Vennstra, G.E.; Zwanenburg, B. *Synthesis* **1975**, 519.
13. Nakagawa, I.; Hata, T. *Tetrahedron Lett.* **1975**, 1409.

(*Received in UK* 8 *March* 1996; *revised* 16 *April* 1996; *accepted* 18 *April* 1996)