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SYNTHESIS OF (2S,3R,1'R)-STEGOBINONE, THE PHEROMONE OF THE DRUGSTORE BEETLE, WITH STEREOCONTROL AT C-2 AND C-1'†

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Abstract--(2S,3R,1'R)-Stegobinone [2,3-dihydro-2,3,5-trimethyl-6-(1'-methyl-2'-oxobutyl)-4H-pyran-4-one], the pheromone of Stegobium paniceum L., was synthesized with stereocontrol at C-2 and C-1' starting from ethyl (R)-3-hydroxybutanoate and methyl (R)-3-hydroxy-2-methylpropanoate. The dihydro-γ-pyrone ring of the pheromone was constructed by an intramolecular acylation followed by acid-catalyzed cyclization.

Stegobinone [2,3-dihydro-2,3,5-trimethyl-6-(1'-methyl-2'-oxobutyl)-4H-pyran-4-one] **1** is the sex pheromone produced by the female drugstore beetle, Stegobium paniceum L..[1,2] Because of its unusual tetrasubstituted dihydro-γ-pyrone structure with three chiral centers, its synthesis was investigated by several groups of workers including ourselves.[3~7] At the time when we initiated our work, the stereochemistry of the pheromone was obscure except that the vicinal Me groups at C-2 and C-3 were thought to be in cis-relationship.[2] The synthetic works both by Hoffmann and Ladner[5] and by us[6] established the (2S,3R)-stereochemistry of **1**. The absolute configuration of the remaining chiral center at C-1' was shown by Hoffmann et al.[7] to be R by the X-ray analysis of the crystalline C-1' epimer of **1** [(2S,3R,1'S)-**1**]. The Hoffmann synthesis of **1** was not stereocontrolled at C-1'.[7] This lack of stereoselectivity at C-1', however, was beneficial to the German workers, because it enabled them to secure both **1** and its crystalline epimer at C-1' after HPLC separation. To achieve an efficient synthesis of the natural pheromone itself, it is essential to devise a route by which the stereochemistry at C-1' can be controlled. This is not an easy task, because C-1' is adjacent to both a CO group (C-2') and a latent CO group (C-6). Another driving force to attempt a stereocontrolled synthesis of (2S,3R,1'R)-**1** was the fact that our synthetic (2S,3R,1'RS)-**1** showed bioactivity lower than that of the natural pheromone probably due to the inhibitory effect by (2S,3R,1'S)-**1**. In order to secure the most potent pheromone sample for bioassay, the natural stereoisomer (2S,3R,1'R)-**1** must be synthesized in a stereocontrolled manner. Herein we describe our work along this line.

Our synthetic plan is shown in Fig.1. To avoid racemization at C-1', the CO group at C-2' must be generated in the final step (**2**→**1**) under a mild condition. The dihydro-γ-pyrone ring of **2** is to be constructed by an intramolecular acylation followed by acid-catalyzed cyclization of the product (**3**→**2**). The ester **3** can be disconnected to two building blocks: a hydroxy ketone **4** and a carboxylic acid **5**. These two compounds were the key-intermediates in our synthesis, and can be derived from ethyl (R)-3-hydroxybutanoate **6**[8] and methyl (R)-3-hydroxy-2-methylpropanoate **7**[9], respectively. Both of these two esters **6** and **7** are of microbial origin and readily available in high optical purity.[8,9]

†Pheromone Synthesis--87. Part 86, K. Mori and T. Ebata, Tetrahedron in press. The experimental part of this work was taken from the doctoral dissertation of T. E. (March, 1986). The numbering system used in this paper is that depicted in **1**. An alternative numbering system[5~7] was not employed because of its inconsistency with the systematic name of **1**.

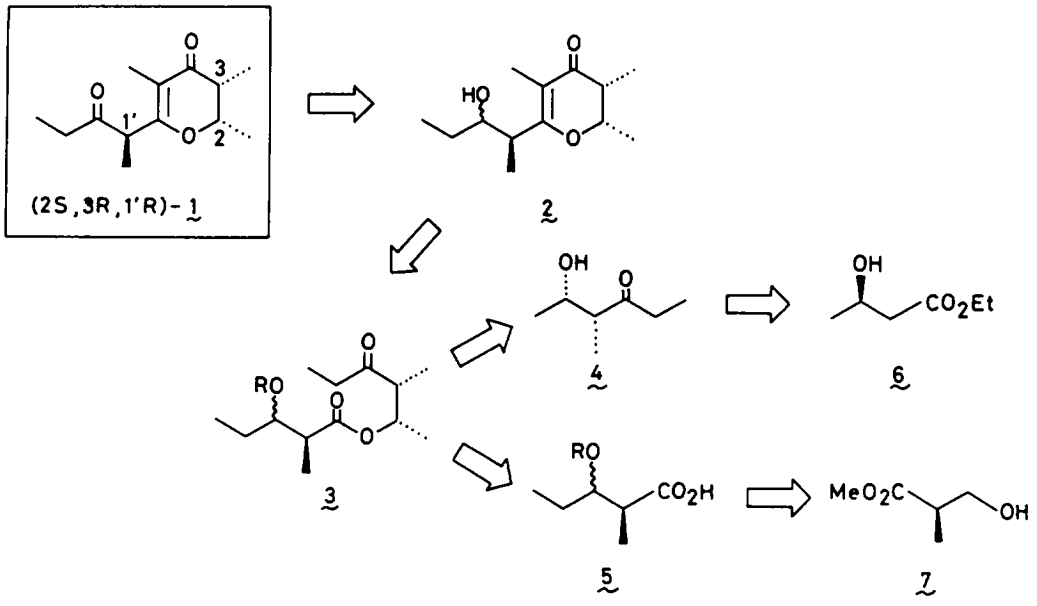

Fig.1. The target molecule and its synthetic plan.

The above plan was realized as shown in Fig.2 to give (2S,3R,1'R)-**1**. The first stage of our work was the conversion of **6** to **4**. The starting material **6** was proved to be of 100 % e.e.[8] by the HPLC analysis of its α-methoxy-α-trifluoromethylphenylacetate (MTPA ester).[10] Alkylation of a dianion derived from **6** according to Fráter[11] afforded **8a** (OH and Me in anti-orientation) as the major product contaminated with a small amount of the syn-isomer of **8a** (**8a** : the syn-isomer = 93 : 6.6)[12] together with negligible amounts of **6** and the dimethylated product. This mixture was treated with dihydropyran in the presence of PPTS to give **8b** in 99 % yield. Reduction of **8b** with LAH yielded **9a** (96.3 %), whose benzylation gave **9b** in 92.9 % yield. Treatment of **9b** with TsOH in MeOH afforded **9c** in 96.5 % yield. The alcohol **9c** was submitted to a Walden inversion under the Mitsunobu condition[13] using 3,5-dinitrobenzoic acid instead of benzoic acid in the original procedure.[8b] The resulting **10a** was crystalline, and could be purified by recrystallization. Saponification of **10a** with KOH aq gave **10b**, whose GLC analysis showed its chemical purity to be 100 %. The optical purity of **10b** was also confirmed to be 100 % by the HPLC analysis of the corresponding MTPA ester **10e**. Silylation of **10b** with t-butyldimethylsilyl chloride gave **10c**, which was hydrogenolyzed over Pd-C to give **10d**. Oxidation of **10d** under the Swern condition[14] was followed by immediate treatment with EtLi to give a diastereomeric mixture **11** (1:3) in 78.2 % yield. This mixture was again oxidized by the Swern method to give **12** in 82.1 % yield. Deprotection of **12** furnished one of the key-intermediates **4** in 82.8 % yield. GLC analysis of **4** showed its chemical purity to be > 97 %.

Preparation of another key-intermediates **5** was carried out in the following manner. First, the optical purity of **7a** was determined by the HPLC analysis of its MTPA ester **7c** to be 97 % e.e.[15] Treatment of **7a** with ethyl vinyl ether and PPTS gave **7b** in 98.1 % yield. This was reduced with LAH to **13** quantitatively. Oxidation of **13** under the Swern condition was followed by immediate treatment of the crude aldehyde with EtLi to afford a diastereomeric mixture **14a** (2:3) in 81.6 % yield. The mixture was used without separation of the diastereoisomers. Silylation of **14a** with t-butyldimethylsilyl chloride gave **14b** in 96.8 % yield, which in turn was treated with PPTS in EtOH to give **14c** in 84.5 %

yield. Oxidation of **14c** with $RuCl_3$-$NaIO_4$ furnished **5** in 89.8 % yield under the Sharpless condition[16] using a phosphate buffer (pH 7) instead of water to avoid deprotection of the silyl-protected oxygen function.

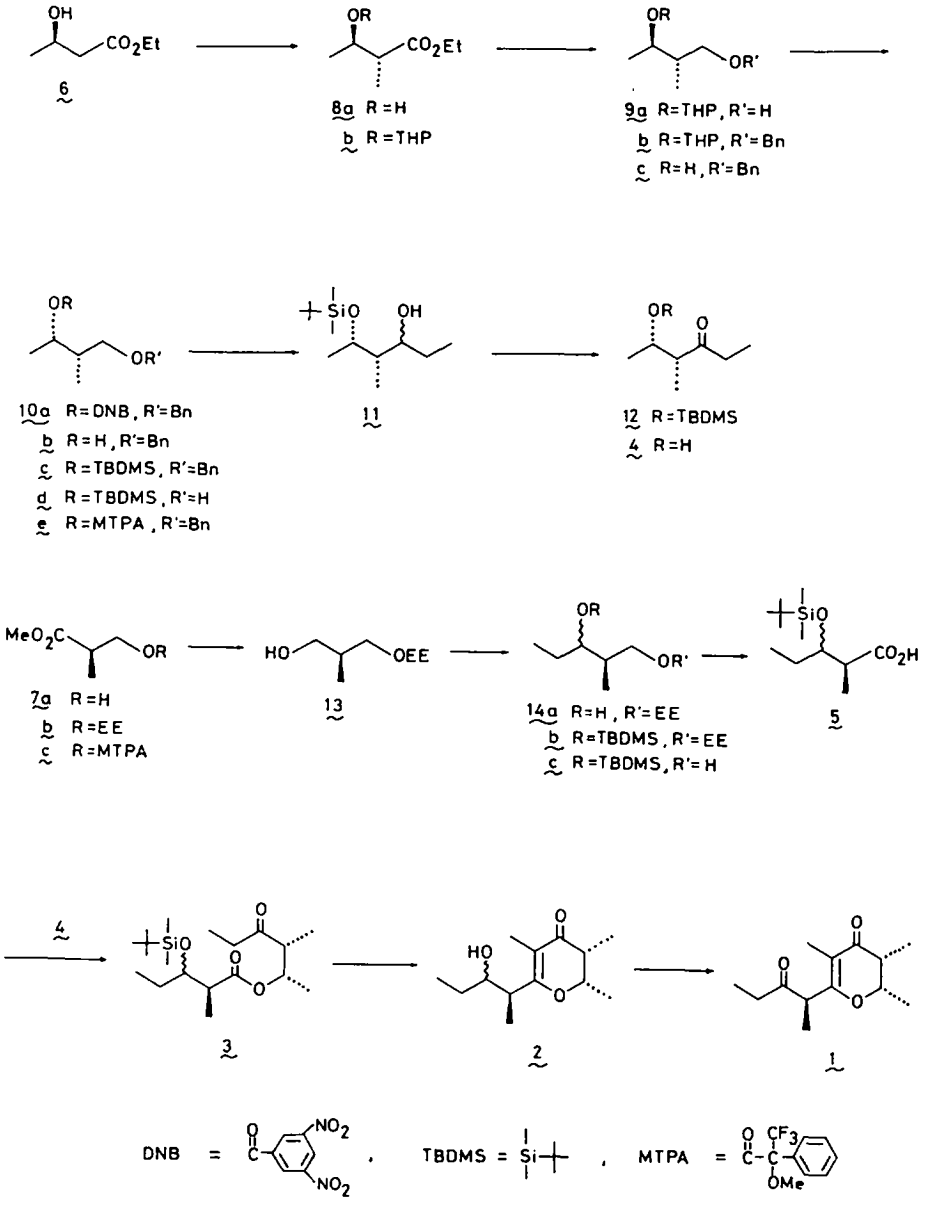

Fig.2. Synthesis of (2S,3R,1'R)-stegobinone.

The final stage of the synthesis was the coupling of the two building blocks to complete the synthesis of **1**. At first, the alcohol **4** was esterified with **5** under the Yamaguchi condition [17] using commercially available 2,6-dichlorobenzoyl chloride instead of 2,4,6-trichlorobenzoyl chloride in the original procedure[17] to give **3** in 95.5 % yield. Treatment of **3** with 2 eq of $(Me_3Si)_2NLi$ followed by acidification ($ClCH_2CO_2H$ aq) and deprotection (HF) afforded crude **2**. At this stage racemization at C-3 and C-1' was possible, but that at C-1' was negligible as proved later (vide infra). Racemization at

C-3 took place to some extent. The crude **2** was oxidized under the Swern condition to give (2S,3R,1'R)-stegobinone **1** in 14.0 % yield from **3** after purification by prep TLC. The unwanted by-product, (2S,3S,1'R)-stegobinone, could be removed by TLC separation. The IR and mass spectral properties of our (2S,3R,1'R)-**1** coincided with those reported for the natural pheromone.[2] The overall yield of (2S,3R,1'R)-**1** was 3.61 % in 18 steps from **6**, or 7.86 % in 12 steps from **7**.

Table 1. CD Spectral data of stegobinone (n-hexane)

	Natural[7]	Synthetic		
		(2S,3R,1'R)*	(2S,3R,1'RS)[6]	
λ 360 nm	Δε -0.42	-0.46	359 nm	-0.63
345	-0.87	-0.86	343.5	-1.39
332		-0.69	332	-1.39
290	-13.0	-12.9	283.5	+0.11
262	+9.1	+8.8		

*c=0.03, room temp=20°

The CD spectral data of our (2S,3R,1'R)-**1**, (2S,3R,1'RS)-**1** and the natural pheromone[2] were listed in Table 1. As can be seen from the Table, the CD data of (2S,3R,1'R)-**1** were in good accord with those of the natural pheromone.[2] On the other hand, the CD data of (2S,3R,1'RS)-**1** were slightly different from those of the natural product. The above CD comparison confirmed the correctness of our stereorational approach to synthesize (2S,3R,1'R)-**1**. The present derivation of the natural pheromone **1** from (R)-**7** constitutes the chemical proof of the R-configuration at C-1' of **1**. The stereochemical homogeneity at C-1' of our synthetic **1** was confirmed to be > 96.5 % by its NMR measurement at 500 MHz and also by its HPLC analysis. This means that almost no racemization at C-1' took place in the course of the cyclization and Swern oxidation. Like in the case of Hoffmann *et al*,[7] we were unable to obtain a crystalline sample of (2S,3R,1'R)-**1**. The natural pheromone was reported to be crystalline (m.p. 52.5~53.5°).[2] It should be added that (2S,3R,1'S)-**1** was also crystalline (m.p. 46~48°).[7] Direct comparison of our synthetic (2S,3R,1'R)-**1** with the natural pheromone could not be realized due to the unavailability of the natural pheromone as kindly informed us by Prof. Y. Kuwahara. Our synthetic **1** was so unstable that its storage at room temp caused complete racemization at C-1' within two weeks. Even in a refrigerator at -40°, 15 % epimerization was detected by the HPLC analysis after two weeks. This instability of **1** made us to abandon any further attempt to purify it.

In conclusion, (2S,3R,1'R)-stegobinone **1** was synthesized with satisfactory stereocontrol at C-2 and C-1'. Unfortunately the degree of stereocontrol at C-3 could not be defined rigorously owing to the difficulty in securing (2S,3S,1'R)-**1** in pure state. Our samples of the synthetic pheromone were kindly bioassayed by Dr. H. Kodama of Japan Tobacco Inc. His results indicated the following order of the pheromone activity against *Stegobium paniceum* L. : the extract of female drugstore beetle > (2S,3R,1'R)-**1** > (2S,3R,1'RS)-**1**. As expected, our (2S,3R,1'R)-**1** was more potent than (2S,3R,1'RS)-**1**. The fact that (2S,3R,1'R)-**1** was less potent than the extract of the female insect suggested the presence of some other pheromone component(s) or synergist(s) in the female beetle. We are currently clarifying this point in cooperation with the workers at Japan Tobacco Inc. The result will be published in due course.

EXPERIMENTAL

All b.ps and m.ps were uncorrected. IR spectra were measured as films for oils or as Nujol mulls for solids on a Jasco IRA-102 spectrometer. ^{1}H-NMR spectra were recorded at 60 MHz with TMS as an internal standard on a Hitachi R-24A spectrometer unless otherwise stated. ^{1}H-NMR at 500 MHz were recorded on a Bruker AM-500 spectrometer. Optical rotations were measured on a Jasco DIP-140 polarimeter. CD spectra were recorded on a Jasco J-20 automatic spectropolarimeter. GLC analyses were performed on a Yanaco G-180 gas chromatograph. GLC-MS were measured on a JMS-DX 300 apparatus.

Ethyl (2R,3R)-3-hydroxy-2-methylbutanoate **8a**. A soln of LDA was prepared by the dropwise addition of n-BuLi (1.70 N in n-hexane, 196 ml, 333 mmol) to a stirred and cooled soln of i-Pr_2NH (33.7 g, 333 mmol) in dry THF (80 ml) at 0° under Ar. The mixture was stirred for 1 h at 0°. To the stirred and cooled (-60°) soln of LDA was added dropwise a soln of **6** (100 % e.e., 20 g, 152 mmol) in dry THF (20 ml) at -60° to -40°. The mixture was stirred for 30 min at -10°. To the stirred and cooled (-30°) mixture was added dropwise a soln of MeI (25.8 g, 182 mmol) in HMPA (46 ml) at -30° to -25°. The stirring was continued for 45 min after the addition with a gradual raise of the reaction temp to room temp. The mixture was poured into sat NH_4Cl aq. The organic layer was separated and the aq layer was extracted with ether. The combined organic soln was washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by chromatography over SiO_2 (Merck Kieselgel 60, 300 g). Elution with n-hexane-ether (2:1) gave **8a**, which was distilled to give 18.9 g (85.5 %) of **8a**, b.p. 90~92°/12 Torr; n_D^{23} 1.4196; $[\alpha]_D^{23}$ -30.3° (c=1.00, $CHCl_3$); νmax 3490 (br), 3020 (m), 2970 (m), 1735 (s), 1465 (m), 1380 (m), 1265 (m), 1190 (s), 1115 (m), 1075 (m), 1050 (m), 1030 (m) cm^{-1}; δ (CCl_4) 1.14 (3H, d, J=7 Hz), 1.27 (3H, t, J=7 Hz), 2.34 (1H, dq, J=7, 7 Hz), 2.7 (1H, br.s), 3.74 (1H, dq, J=7, 7 Hz), 4.09 (2H, q, J=7 Hz). GLC (Column, OV-101, 50 m x 0.25 mm at 90°; Carrier gas, N_2, 1.0 kg/cm^2): Rt 9.4 min (0.1 % **6**), 13.3 min (93.1 % **8a**), 14.4 min (6.6 % syn-isomer of **8a**), 19.7 min (0.2 % dimethylated product); (Found: C, 57.35; H, 9.40. Calc for $C_7H_{14}O_3$: C, 57.51; H, 9.65 %).

Ethyl (2R,3R)-2-methyl-3-tetrahydropyranyloxybutanoate **8b**. To a stirred soln of **8a** (5.0 g, 34.2 mmol) and dihydropyran (5.18 g, 61.6 mmol) in dry CH_2Cl_2 (50 ml) was added PPTS (1 g, 4.2 mmol). The stirring was continued for 5 h at room temp. The mixture was diluted with ether (50 ml). This was washed with sat $NaHCO_3$ soln, water and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (Merck Kieselgel 60, 100g). Elution with n-hexane-ether (20:1~5:1) gave **8b**, which was distilled to give 7.80 g (99.0 %) of **8b**, b.p. 98~100°/4 Torr; n_D^{20} 1.4385; $[\alpha]_D^{20}$ -30.9° (c=1.06, $CHCl_3$); νmax 2980 (s), 2910 (m), 1745 (s), 1455 (m), 1380 (m), 1180 (s), 1120 (s), 1075 (s), 1035 (s), 1025 (s), 985 (s), 870 (m) cm^{-1}; δ (CCl_4) 1.05 (1.5H, d, J=7 Hz), 1.06 (1.5H, d, J=7 Hz), 1.10 (1.5H, d, J=7 Hz), 1.16 (1.5H, d, J=7 Hz), 1.24 (3H, t, J=7 Hz), 1.4~2.1 (7H, br.s), 2.20~2.83 (1H, m), 3.16~4.40 (5H, m, containing 4.05, 2H, q, J=7 Hz), 4.45~4.76 (1H, m). (Found: C, 62.29; H, 9.69. Calc for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63 %).

(2S,3R)-2-Methyl-3-tetrahydropyranyloxy-1-butanol **9a**. A soln of **8b** (19.7 g, 85.7 mmol) in dry ether (200 ml) was added dropwise to a stirred suspension of LAH (4.23 g, 111 mmol) in dry ether (400 ml) under ice-cooling. The mixture was stirred overnight at room temp. It was then ice-cooled and the excess LAH was destroyed by the successive addition of water (4 ml), 2N NaOH aq (8 ml) and water (4 ml). After stirring for 1.5 h at room temp, the mixture was filtered and the filter cake was washed with THF. The combined filtrate and washings were concentrated in vacuo. The residue was distilled to give 15.5 g (96.3 %) of **9a**, b.p. 99~102°/4 Torr; n_D^{20} 1.4521; $[\alpha]_D^{20}$ -41.6° (c=1.21, $CHCl_3$); νmax 3460 (br), 2980 (s), 2910 (s), 1460 (m), 1450 (m), 1350 (m), 1130 (s), 1120 (s), 1075 (s), 1025 (s), 985 (s), 870 (m) cm^{-1}; δ (CCl_4) 0.87 (1.5H, d, J=7 Hz), 0.91 (1.5H, d, J=7 Hz), 1.10 (1.5H, d, J=7 Hz), 1.16 (1.5H, d, J=7 Hz), 1.3~2.1 (7H, br.s), 2.9~4.1 (5H, m), 4.4~4.75 (1H, m). (Found: C, 63.67; H, 10.61. Calc for $C_{10}H_{20}O_3$: C, 63.79; H, 10.71 %).

(2S,3R)-2-Methylbutane-1,3-diol 1-benzyl,3-THP-ether **9b**. To a stirred suspension of 50 % NaH (1.88 g, 39.1 mmol) in dry THF (54 ml) was added dropwise a soln of **9a** (4.60 g, 24.5 mmol) in dry THF (68 ml). The mixture was stirred and heated under reflux for 1 h. Subsequently a soln of $PhCH_2Cl$ (4.33 g, 34.3 mmol) in dry THF (18 ml) was added dropwise and the mixture was stirred and heated under reflux overnight. After cooling, the mixture was poured into ice-water and concentrated in vacuo to remove THF. The residue was extracted with ether. The ether soln was washed with water and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (Merck Kieselgel 60, 150 g). Elution with n-hexane-ether (10:1) gave **9b**, which was distilled to give 6.32 g (92.9 %) of **9b**, b.p. 139~142°/0.71 Torr; n_D^{23} 1.4929; $[\alpha]_D^{23}$ -17.8° (c=0.98, $CHCl_3$); νmax 3100 (w), 3060 (w), 2960 (s), 2880 (s), 1500 (w), 1455 (m), 1115 (s), 1090 (s), 1075 (s), 1020 (s), 985 (s) cm^{-1}; δ (CCl_4) 0.87 (1.5H, d, J=7 Hz), 0.92 (1.5H, d, J=7 Hz), 0.99 (1.5H, d, J=7 Hz), 1.11 (1.5H, d, J=7 Hz), 1.2~2.1 (7H, m), 3.1~4.0 (5H, m), 4.35 (2H, s), 4.3~4.7 (1H, m), 7.16 (5H, s). (Found: C, 73.64; H, 9.51. Calc for $C_{17}H_{26}O_3$: C, 73.34; H, 9.41 %).

(2S,3R)-2-Methylbutane-1,3-diol 1-benzyl ether **9c**. TsOH (50 mg, 0.3 mmol) was added to a soln of **9b** (3.30 g, 11.9 mmol) in MeOH (25 ml). The soln was stirred for 50 min at room temp and neutralized by the addition of sat $NaHCO_3$ aq (2.5 ml). It was then concentrated in vacuo to remove MeOH. The residue was diluted with water (15 ml) and extracted with ether. The ether soln was washed with water and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was distilled to give 2.22 g (96.5 %) of **9c**, b.p. 119~121°/5 Torr; n_D^{21} 1.4990; $[\alpha]_D^{20}$ +9.25° (c=1.07, C_6H_6); νmax 3460 (br), 3100 (w), 3060 (w), 3000 (m), 2900 (m), 1500 (w), 1455 (m), 1365 (m), 1090 (s), 1075 (sh), 735 (m), 695 (m) cm^{-1}; δ (CCl_4) 0.82 (3H, d, J=7 Hz), 1.06 (3H, d, J=7 Hz), 1.30~1.95 (1H, m), 2.86 (1H, br.s), 3.40 (2H, d, J=6 Hz), 3.58 (1H, dq, J=6, 6 Hz), 4.42 (2H, s), 7.24 (5H, s). (Found: C, 73.98; H, 9.48. Calc for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34 %).

(2S,3S)-3-(3',5'-Dinitrobenzoyloxy)-2-methylbutan-1-ol benzyl ether **10a**. To a stirred and ice-cooled soln of **9c** (2.0 g, 10.3 mmol), Ph_3P (5.40 g, 20.6 mmol) and 3,5-dinitrobenzoic acid (4.37 g, 20.6 mmol) in dry THF (16 ml) was added dropwise a soln of $EtO_2CN{=}NCO_2Et$ (3.59 g, 20.6 mmol) in dry THF (16 ml). After the addition, the ice-bath was removed, and the mixture was stirred for 20 h at room temp. Then it was concentrated in vacuo to remove THF and the residue was filtered through SiO_2 (Merck Kieselgel 60, 140 g) using $CHCl_3$ as the solvent to remove Ph_3PO. The filtrate was concentrated in vacuo and the residue was chromatographed over SiO_2 (Merck Kieselgel 60, 170 g). Elution with n-hexane-ether (20:1~5:1) gave crude **10a**. This was repeatedly recrystallized from n-hexane-ether (5:1) to give 3.40 g (85 %) of pure **10a**, m.p. 62~63°; $[\alpha]_D^{21}$ +46.5° (c=0.94, $CHCl_3$); νmax 3130 (w), 3080 (w), 1730 (s), 1625 (m), 1550 (s), 1340 (s), 1270 (s), 1165 (m), 1110 (m), 1090 (m), 1065 (m), 730 (m) cm^{-1}; δ (CCl_4) 1.09 (3H, d, J=7 Hz), 1.38 (3H, d, J=7 Hz), 1.7~2.4 (1H, m), 3.37 (2H, d, J=6 Hz), 4.30 (2H, s), 5.34 (1H, dq, J=4, 7 Hz), 7.01 (5H, s), 8.7~9.05 (3H, m). (Found: C, 58.60; H, 5.20; N, 7.17. Calc for $C_{19}H_{20}O_7N_2$: C, 58.76; H, 5.19; N, 7.21 %).

(2S,3S)-2-Methylbutane-1,3-diol 1-benzyl ether **10b.** To a stirred and ice-cooled soln of **10a** (11.4 g, 29.4 mmol) in THF-EtOH (1:1, 138 ml) was added dropwise N KOH aq (38 ml, 38 mmol). The red-violet-coloured reaction mixture was stirred for 2 h at 0°. It was then concentrated in vacuo to remove THF and EtOH. The residue was extracted with ether. The ether soln was washed with water and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was distilled to give 5.61 g (98.4 %) of pure **10b**, b.p. 125~126°/4 Torr; n_D^{20} 1.5027; $[\alpha]_D^{20}$ +10.6° (c=1.3, $CHCl_3$); νmax 3420 (br), 3075 (w), 3040 (w), 2980 (m), 2940 (m), 2900 (m), 2875 (m), 1495 (w), 1365 (m), 1100 (s), 1070 (s), 735 (m), 695 (m) cm^{-1}; δ (CCl_4) 0.86 (3H, d, J=7 Hz), 1.06 (3H, d, J=7 Hz), 1.3~2.1 (1H, m), 2.51 (1H, br.s), 3.38 (1H, d, J=6 Hz), 3.39 (1H, d, J=7 Hz), 3.55~4.10 (1H, m), 4.41 (2H, s), 7.22 (5H, s). (Found: C, 74.05; H, 9.18. Calc for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34 %).

Determination of the optical purity of **10b.** Acylation of **10b** with MTPA-Cl prepared from either (R)-MTPA or (S)-MTPA gave two diastereomers of **10c** in the usual manner.[10] HPLC analysis of **10c** (Column, NUCLEOSIL®50-5, 25 cm x 4.6 mm ; Solvent, n-hexane-THF-MeOH (10000:100:1), 1.1 ml/min; Detected at 254 nm) Rt 11.7 min [(R)-MTPA ester], 12.0 min [(S)-MTPA ester]. The optical purity of **10b** was estimated to be 100 %.

(2S,3S)-3-t-Butyldimethylsilyloxy-2-methylbutan-1-ol benzyl ether **10c.** Imidazole (4.56 g, 67 mmol) and TBDMSCl (6.05 g, 40.2 mmol) was added to a stirred soln of **10b** (5.20 g, 26.8 mmol) in dry DMF (40 ml). The mixture was stirred overnight at room temp. It was then poured into ice-water and extracted with ether. The ether soln was washed with water and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was distilled to give 8.03 g (97.2 %) of **10c**, b.p. 140~143°/5 Torr; n_D^{21} 1.4702; $[\alpha]_D^{21}$ +6.5° (c=1.01, $CHCl_3$); νmax 3070 (w), 3040 (w), 2960 (s), 2940 (s), 2900 (s), 2860 (s), 1495 (w), 1250 (s), 1095 (s), 1070 (s), 1045 (s), 830 (s), 770 (s) cm^{-1}; δ (CCl_4) 0.00 (6H, s), 0.85 (3H, d, J=7 Hz), 0.88 (9H, s), 1.08 (3H, d, J=7 Hz), 1.45~1.95 (1H, m), 3.14 (1H, dd, J=6, 9 Hz), 3.38 (1H, dd, J=7, 9 Hz), 3.95 (1H, dq, J=4, 7 Hz), 4.38 (2H, s), 7.21 (5H, s). (Found: C, 70.00; H, 10.66. Calc for $C_{18}H_{32}O_2Si$: C, 70.07; H, 10.45 %).

(2S,3S)-3-t-Butyldimethylsilyloxy-2-methylbutan-1-ol **10d.** 10 % Pd-C (1.1 g) was added to a soln of **10c** (7.51 g, 24.4 mmol) in EtOAc and the suspension was shaken under H_2 until the H_2 uptake ceased. The mixture was filtered through Celite and the filtrate was concentrated in vacuo. The residue was distilled to give 4.55 g (85.5 %) of **10d**, b.p. 89~90°/5 Torr; n_D^{22} 1.4336; $[\alpha]_D^{22}$ +13.6° (c=0.98, $CHCl_3$); νmax 3360 (br), 2960 (s), 2930 (s), 2890 (s), 2860 (s), 1460 (m), 1250 (s), 1105 (s), 1090 (s), 1040 (s), 830 (s), 770 (s) cm^{-1}; δ (CCl_4) 0.05 (6H, s), 0.76 (3H, d, J=7 Hz), 0.88 (9H, s), 1.11 (3H, d, J=7 Hz), 1.5~2.0 (1H, m), 2.6 (1H, br.s), 3.27~3.60 (2H, m), 3.94 (1H, dq, J=4, 7 Hz). (Found: C, 60.46; H, 12.20. Calc for $C_{11}H_{26}O_2$: C, 60.49; H, 12.00 %).

(4S,5S)-5-t-Butyldimethylsilyloxy-4-methylhexan-3-ol **11.** To a cooled (-70°) and stirred soln of oxalyl chloride (2.18 g, 17.2 mmol) in CH_2Cl_2 (30 ml) was added dropwise a soln of DMSO (1.79 g, 22.9 mmol) in CH_2Cl_2 (6 ml) under Ar. The mixture was stirred for 2 min at -70°. Et_3N (5.79 g, 57.3 mmol) was added dropwise and the stirring was continued for 15 min at -70°. The mixture was allowed to warm to 0°, stirred for 20 min at this temp, and then partitioned between a mixture of C_6H_6-ether (4:1, 40 ml) and water (40 ml). The organic layer was washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was dissolved in ether (40 ml) and filtered to remove the insoluble material. The filtrate was concentrated in vacuo to give a crude aldehyde. This product was immediately used for the next step without further purification. The soln of the aldehyde in dry ether (10 ml) was added dropwise to a soln of EtLi, which was prepared in the usual manner from EtBr (3.81 g, 35 mmol) and Li (490 mg, 70 mg atom) in dry ether (20 ml), with stirring and ice-cooling. The stirring was continued for 15 min. The mixture was then poured into ice and sat NH_4Cl aq and extracted with ether. The ether soln was washed with water and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was distilled to give 2.23 g (78.2 %) of **11** (3:1 mixture), b.p. 86~87°/3 Torr; n_D^{23} 1.4370; $[\alpha]_D^{23}$ +19.9° (c=0.95, $CHCl_3$); νmax 3510 (m), 3450 (sh), 2960 (s), 2930 (s), 2890 (s), 2855 (s), 1460 (m), 1250 (s), 1055 (s), 950 (s), 830 (s), 770 (s) cm^{-1}; δ (CCl_4) 0.07 (6H, s), 0.6~1.8 (21H, m, containing 0.87, 9H, s), 3.1~3.55 (2H, m), 3.7~4.2 (1H, m). GLC (Column, 3 % SE-30, 2 m x 2 mm at 100~200°,10°/min Carrier gas, N_2, 1.2 kg/cm^2): Rt 4.5 min (24.4 %), 4.8 min (75.6 %). (Found: C, 63.24; H, 12.48. Calc for $C_{13}H_{30}O_2$: C, 63.35; H, 12.27 %).

(4R,5S)-5-t-Butyldimethylsilyloxy-4-methylhexan-3-one **12.** To a cooled (-70°) and stirred soln of oxalyl chloride (1.53 g, 12.1 mmol) in CH_2Cl_2 (20 ml) was added dropwise a soln of DMSO (1.26 g, 16.1 mmol) in CH_2Cl_2 (4 ml) under Ar. The mixture was stirred for 2 min at -70°, and then a soln of **11** (1.98 g, 8.05 mmol) in CH_2Cl_2 (6 ml) was added dropwise with stirring. After 50 min at -70°, Et_3N (4.06 g, 40.2 mmol) was added dropwise and the stirring was continued for 15 min at this temp. The mixture was allowed to warm to 0°, stirred for 20 min at this temp and then partitioned between a mixture of C_6H_6-ether (4:1, 30 ml) and water (30 ml). The organic layer was washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (Merck Kieselgel 60, 30 g). Elution with n-hexane-ether (40:1) gave **12.** This was distilled to give 1.61 g (82.1 %) of pure **12**, b.p. 90~92°/5 Torr; n_D^{23} 1.4286; $[\alpha]_D^{23}$ -29.4° (c=1.03, $CHCl_3$); νmax 2970 (s), 2950 (s), 2900 (s), 2870 (s), 1715 (s), 1460 (m), 1255 (s), 1100 (s), 1050 (s), 835 (s), 770 (s) cm^{-1}; δ (CCl_4) 0.03 (6H, s), 0.7~1.2 (18H, m, containing 0.85, 3H, s), 2.37 (2H, q, J=7 Hz), 3.87 (1H, dq, J=7, 7 Hz). (Found: C, 63.42; H, 11.43. Calc for $C_{13}H_{28}O_2$: C, 63.88; H, 11.54 %).

(4R,5S)-5-Hydroxy-4-methylhexan-3-one **4.** A soln of n-Bu_4NF soln in THF (1 M, 6.39 ml, 6.39 mmol) was added dropwise to a soln of **12** (1.30g , 5.33 mmol) in dry THF (5 ml) with ice-cooling and stirring. After stirring overnight at room temp, the mixture was concentrated in vacuo to remove THF. The residue was diluted with water (15 ml) and extracted with ether. The ether soln was washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed over SiO_2 (Merck Kieselgel 60, 20 g). Elution with n-hexane-ether (10:1-3:1) gave **4.** This was distilled to give 574 mg (66.8 %) of pure **4**, b.p. 72~73°/5 Torr; n_D^{21} 1.4320; $[\alpha]_D^{21}$ -30.2° (c=1.43, ether); νmax 3460 (br), 2980 (m), 2950 (m), 2900 (m), 1700 (s), 1460 (sh), 1455 (m), 1375 (m), 1150 (m), 1090 (m), 1015 (m), 965 (m),910 (m) cm^{-1}; δ (CCl_4) 0.95 (3H, d, J=7 Hz), 1.06 (3H, d, J=7 Hz), 1.08 (3H, t, J=7 Hz), 2.2~2.8 (3H, m, containing 2.47, 2H, q, J=7 Hz), 3.05 (1H, br.s), 3.65~4.18 (1H, m); GLC (Column, PEG 20M, 50 m x 0.25 mm at 120°; Carrier gas, N_2, 0.9 kg/cm^2): Rt 6.7 min (2.8 %, (4S,5R)-isomer), 7.0 min (97.2 %). (Found: C, 64.54; H, 10.78. Calc for $C_7H_{14}O_2$: C, 64.58; H, 10.84 %).

Methyl (R)-3-(1'-ethoxyethoxy)-2-methylpropanoate **7b.** PPTS (800 mg, 3.36 mmol) was added to an ice-cooled soln of **7a** (10 g, 84.7 mmol) in ethyl vinyl ether (20 ml) and dry CH_2Cl_2 (100 ml). The mixture was stirred for 4 h at room temp and diluted with ether (100 ml). This was washed with sat $NaHCO_3$ soln, water and brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was distilled to give 15.8 g (98.1 %) of **7b**, b.p. 66~69.5°/4 Torr; n_D^{21} 1.4108; $[\alpha]_D^{21}$ -12.6° (c=1.02, $CHCl_3$); νmax 3030 (m), 2990 (m), 2925 (m), 1745 (s), 1445 (m), 1200 (s), 1180 (s), 1135 (s), 1090 (s), 1065 (s), 1005 (m)

cm^{-1}; δ (CCl_4) 1.12 (3H, t, J=7 Hz), 1.12 (3H, d, J=7 Hz), 1.20 (3H, d, J=5 Hz), 2.25~2.90 (1H, m), 2.95~3.90 (7H, m, containing 3.59, 3H, s), 4.55 (1H, q, J=5 Hz). (Found: C, 56.70; H, 9.40. Calc for $C_9H_{18}O_4$: C, 56.82; H, 9.54 %).

(S)-3-(1'-Ethoxyethoxy)-2-methylpropan-1-ol **13**. A soln of **7b** (14.0 g, 73.7 mmol) in dry ether (100 ml) was added dropwise to a stirred suspension of LAH (4.20 g, 111 mmol) in dry ether (150 ml) under ice-cooling. The mixture was stirred overnight at room temp. It was then ice-cooled and the excess LAH was destroyed by the successive addition of water (4.2 ml), 2N NaOH (8.4 ml) and water (4.2 ml). After stirring for 2 h at room temp, the mixture was filtered and the filter-cake was washed with THF. The combined filtrate and washings were concentrated in vacuo. The residue was distilled to give 11.8 g (quantitative) of **13**, b.p. 90~92°/7 Torr; n_D^{21} 1.4196; $[\alpha]_D^{21}$ -10.0° (c=1.04, $CHCl_3$); νmax 3480 (br), 3020 (s), 2950 (s), 2920 (s), 1455 (m), 1135 (s), 1090 (s), 1045 (s), 1000 (m), 940 (m) cm^{-1}; δ (CCl_4) 0.91 (3H, t, J=7 Hz), 1.20 (3H, d, J=7 Hz), 1.23 (3H, d, J=5 Hz), 1.45~2.25 (1H, m), 2.7~3.7 (7H, m), 4.54 (1H, q, J=5 Hz). (Found: C, 58.83; H, 11.26. Calc for $C_8H_{18}O_3$: C, 59.23; H, 11.18 %).

(2R)-1-(1'-Ethoxyethoxy)-2-methylpentan-3-ol **14a**. In the same manner as described for the preparation of **11**, 6.50 g (40.1 mmol) of **13** gave 6.22 g (81.6 %) of **14a** (3:2 mixture), b.p. 85.5~87.0°/4 Torr; n_D^{21} 1.4264; $[\alpha]_D^{21}$ -9.5° (c=1.0, $CHCl_3$); νmax 3490 (br), 3020 (m), 2975 (m), 2920 (m), 1460 (m), 1135 (s), 1100 (sh), 1085 (s), 1055 (s), 975 (m) cm^{-1}; δ (CCl_4) 0.91 (6H, t, J=7 Hz), 1.21 (3H, d, J=7 Hz), 1.23 (3H, d, J=5 Hz), 1.0~2.6 (3H, m), 2.29 (0.6H, br.s), 2.70 (0.4H, br.s), 3.05~3.92 (5H, m), 4.56 (1H, q, J=5 Hz). (Found: C, 62.71; H, 11.66. Calc for $C_{10}H_{22}O_3$: C, 63.12; H, 11.65 %).

(2R)-3-t-Butyldimethylsilyloxy-2-methylpentan-1-ol EE ether **14b**. Imidazole (2.24 g, 32.9 mmol) and TBDMSCl (2.77 g, 18.4 mmol) was added to a stirred soln of **14a** (2.50 g, 13.2 mmol) in dry DMF (20 ml). The mixture was stirred overnight at room temp. It was then poured into ice-water and extracted with ether. The ether soln was washed with water and brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was distilled to give 3.86 g (96.8 %) of **14b**, b.p. 96~97.5°/5 Torr; n_D^{20} 1.4285; $[\alpha]_D^{18}$ +8.0° (c=0.96, $CHCl_3$); νmax 3020 (s), 3000 (s), 2940 (s), 2910 (s), 1470 (m), 1260 (m), 1140 (s), 1100 (s), 1060 (s), 860 (m), 835 (s), 775 (m) cm^{-1}; δ (CCl_4) 0.03 (6H, s), 0.6~1.05 (15H, m, containing, 0.88, 9H, s), 1.18 (3H, d, J=7 Hz), 1.20 (3H, d, J=5 Hz), 1.3~2.1 (2H, m), 2.9~3.75 (5H, m), 4.04 (1H, q, J=5 Hz). (Found: C, 63.18; H, 12.22. Calc for $C_{16}H_{36}O_3Si$: C, 63.10; H, 11.91 %).

(2R)-3-t-Butyldimethylsilyloxy-2-methylpentan-1-ol **14c**. PPTS (400 mg, 1.68 mmol) was added to a soln of **14b** (3.80 g, 12.5 mmol) in dry EtOH (90 ml) at room temp. The mixture was stirred overnight at room temp. It was then diluted with sat $NaHCO_3$ aq (20 ml) and ether (100 ml). The mixture was filtered to remove the insoluble material. The organic layer of the filtrate was separated, washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was distilled to give 2.45 g (84.5 %) of **14c**, b.p. 86~88°/6 Torr; n_D^{20} 1.4405; $[\alpha]_D^{20}$ +10.5° (c=0.94, $CHCl_3$); νmax 3350 (br), 2960 (s), 2940 (s), 2890 (s), 2960 (s), 1460 (m), 1250 (s), 1100 (m), 1050 (s), 1015 (s), 1005 (sh), 855 (s), 835 (s), 770 (s) cm^{-1}; δ (CCl_4) 0.05 (6H, s), 0.6~1.1 (15H, m, containing 0.87, 9H, s), 1.2~2.0 (3H, m), 2.36 (1H, br.s), 3.25~3.75 (3H, m). (Found: C, 61.64; H, 12.44. Calc for $C_{12}H_{28}O_2Si$: C, 62.01; H, 12.14 %).

(2R)-3-t-Butyldimethylsilyloxy-2-methylpentanoic acid **5**. $NaIO_4$ (2.77 g, 12.9 mmol) was added to a biphasic soln of **14c** (1.0 g, 4.31 mmol) in CCl_4 (9 ml), MeCN (9 ml) and phosphate buffer (pH 7, 0.4 M, 13.5 ml). After stirring for 5 min, $RuCl_3 \cdot 3H_2O$ (21.2 mg, 9.4 μmol) was added to the mixture. It was stirred vigorously for 6 h at room temp. Then CH_2Cl_2 (30 ml) was added, and the organic layer was separated. The aq layer was extracted with CH_2Cl_2. The combined organic soln was dried ($MgSO_4$) and concentrated in vacuo. The residue was diluted with ether (50 ml), filtered through Celite and concentrated. The residue was chromatographed over SiO_2 (Merck Kieselgel 60, 15 g). Elution with n-hexane-ether (20:1~10:1) gave 952 mg (89.8 %) of **5**, νmax ~3000 (br), 2960 (s), 2940 (s), 2900 (s), 2860 (s), 1710 (s), 1250 (s), 1110 (s), 1050 (s), 1015 (s), 1010 (sh), 835 (s), 775 (s) cm^{-1}. This was used in the next step without further purification.

(1'S,2'R)-1',2'-Dimethyl-3'-oxopentyl (2R)-3-t-butyldimethylsilyloxy-2-methylpentanoate **3**. 2,6-Dichlorobenzoyl chloride (838 mg, 4.00 mmol) was added to a mixture of **5** (984 mg, 4.00 mmol) and Et_3N (435 mg, 4.31 mmol) in dry THF (20 ml) under Ar. The mixture was stirred overnight at room temp. After the removal of $Et_3N \cdot HCl$ by filtration, the filtrate was concentrated under N_2, and the residue was dissolved in dry C_6H_6 (15 ml). To this soln were added a soln of **4** (400 mg, 3.08 mmol) in dry C_6H_6 (3 ml) and DMAP (526 mg, 4.31 mmol) in dry C_6H_6 (3 ml) at 0° under Ar. The resulting mixture was stirred for 3 h at 0°. It was then diluted with ether (20 ml), washed with N HCl, water, sat $NaHCO_3$ aq and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by chromatography over SiO_2 (Merck Kieselgel 60, 20 g). Elution with n-hexane-ether (40:1) gave 1.05 g (95.5 %) of **3**, νmax 2960 (s), 2940 (s), 2880 (m), 2860 (m), 1730 (s), 1720 (s), 1250 (s), 1175 (s), 1105 (s), 1090 (s), 1045 (s), 1010 (s), 830 (s), 770 (s) cm^{-1}; δ (CCl_4) 0.05 (3H, s), 0.07 (3H, s), 0.7~1.8 (26H, m, containing 0.87, 9H, s), 2.2~3.0 (4H, m), 3.6~4.0 (1H, m), 4.8~5.3 (1H, m). This was employed in the next step without further purification.

(2S,3R,1'R)-Stegobinone **1**. To a soln of **3** (100 mg, 0.28 mmol) in dry THF (5 ml) and TMEDA (1 ml) was added dropwise and slowly a soln of $(Me_3Si)_2NLi$ in dry THF (0.34 M, 0.83 ml, 0.28 mmol) with stirring at -70° under Ar. The reaction temp was gradually raised to 0° over 2 h. Then the reaction mixture was cooled (-70°) again, and to it was added dropwise a soln of $(Me_3Si)_2NLi$ in dry THF (0.34 M, 0.83 ml, 0.28 mmol). The reaction temp was gradually raised again to 0° over 2 h. The mixture was poured into 10 % $ClCH_2CO_2H$ aq (25 ml) and THF (25 ml). After stirring overnight at room temp, this was concentrated in vacuo to remove THF. The residue was extracted with ether. The ether soln was washed with water, sat $NaHCO_3$ aq and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was dissolved in MeCN (2 ml). To this soln was added 3 drops of 46 % HF aq. After stirring for 5 h at room temp, this was diluted with ether (10 ml). The mixture was washed with water, dried ($MgSO_4$) and concentrated in vacuo. The residue was roughly purified by preparative TLC (Merck Kieselgel 60 F_{254}, n-hexane-ether=1:1, Rf=0.1~0.4) to give a crude product containing **2**. This was used in the next oxidation without further purification. To a cooled (-70°) and stirred soln of oxalyl chloride (49 mg, 0.39 mmol) in CH_2Cl_2 (0.5 ml) was added dropwise a soln of DMSO (60.7 mg, 0.78 mmol) in dry CH_2Cl_2 (0.1 ml) under Ar. The mixture was stirred for 2 min at -70° and then a soln of the above crude product in dry CH_2Cl_2 (0.1 ml) was added dropwise with stirring. After 50 min at -70°, Et_3N (98 mg, 0.97 mmol) was added dropwise and the stirring was continued for 15 min at this temp. The mixture was allowed to warm to 0°, stirred for 20 min at this temp, and partitioned between a mixture of C_6H_6-ether (4:1, 2 ml) and water (2 ml). The organic layer was washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by preparative TLC (Merck Kieselgel 60 F_{254}, n-hexane-ether=1:1, Rf=0.40) to give 8.8 mg (14.0 %) of **1**, $[\alpha]_D^{23}$ -282±10° (c=0.11, $CHCl_3$); νmax 2995 (s), 2950 (s), 2885 (m), 1725 (s), 1665 (s), 1610 (s), 1455 (m), 1385 (s),

1345 (s), 1210 (m), 1145 (s), 1120 (s), 1095 (m), 1050 (s), 955 (m), 915 (m), 705 (m) cm^{-1}; δ (500 MHz, $CDCl_3$) 1.04 (3H, d, J=7 Hz), 1.06 (3H, t, J=7 Hz), 1.29 (3H, d, J=7 Hz), 1.31 (3H, d, J=7 Hz), 1.79 [3H, s, CH_3 at C-5 96.8 %, 1.80 CH_3 at C-5 of (1'S)-isomer 3.2 %], 2.3~2.5 (3H, m), 3.62 (1H, q, J=7 Hz), 4.55 (1H, dq, J=3.5, 7 Hz). MS m/z 224 (M^+, 17 %), 168 (100 %, base peak), 139 (14 %), 124 (18 %), 113 (52 %), 112 (16 %), 109 (17 %), 83 (24 %), 57 (90 %), 55 (13 %); HPLC (Column, NUCLEOSIL® 50-5, 25 cm x 4.6 mm ; Solvent, n-hexane-THF-MeOH (6000:100:1), 1.1 ml/min; Detected at 254 nm) Rt 2.13 h [3.5 %, (1'S)-isomer], 2.25 h (96.5 %). (Found: m/z 224.1391. Calc for $C_{13}H_{20}O$: 224.1412).

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