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SYNTHESIS OF (2S,3R,1'S,2'S)-STEGOBIOL, A NEW COMPONENT OF THE DRUGSTORE BEETLE PHEROMONE†

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Abstract--(2S,3R,1'S,2'S)-Stegobiol **1**, a new pheromone component of Stegobium paniceum L., was synthesized with stereocontrol at C-2, C-1' and C-2', starting from ethyl (R)-3-hydroxybutanoate and methyl (S)-3-hydroxypentanoate. The stereochemistry of the naturally occurring **1** was confirmed to be 2S,3R,1'S,2'S by the present synthesis.

Stegobiol [2,3-dihydro-2,3,5-trimethyl-6-(2'-hydroxy-1'-methylbutyl)-4H-pyran-4-one] **1** was recently isolated by Kodama *et al.* as a new component of the sex pheromone produced by females of the drugstore beetle, Stegobium paniceum L..[1] The drugstore beetle is known as a devastating pest of stored food and crops. Stegobinone [(2S,3R,1'R)-2,3-dihydro-2,3,5-trimethyl-6-(1'-methyl-2'-oxobutyl)-4H-pyran-4-one] **2** was previously isolated by Kuwahara *et al.* as its pheromone.[2] The fact that a synthetic sample of (2S,3R,1'R)-**2** was less

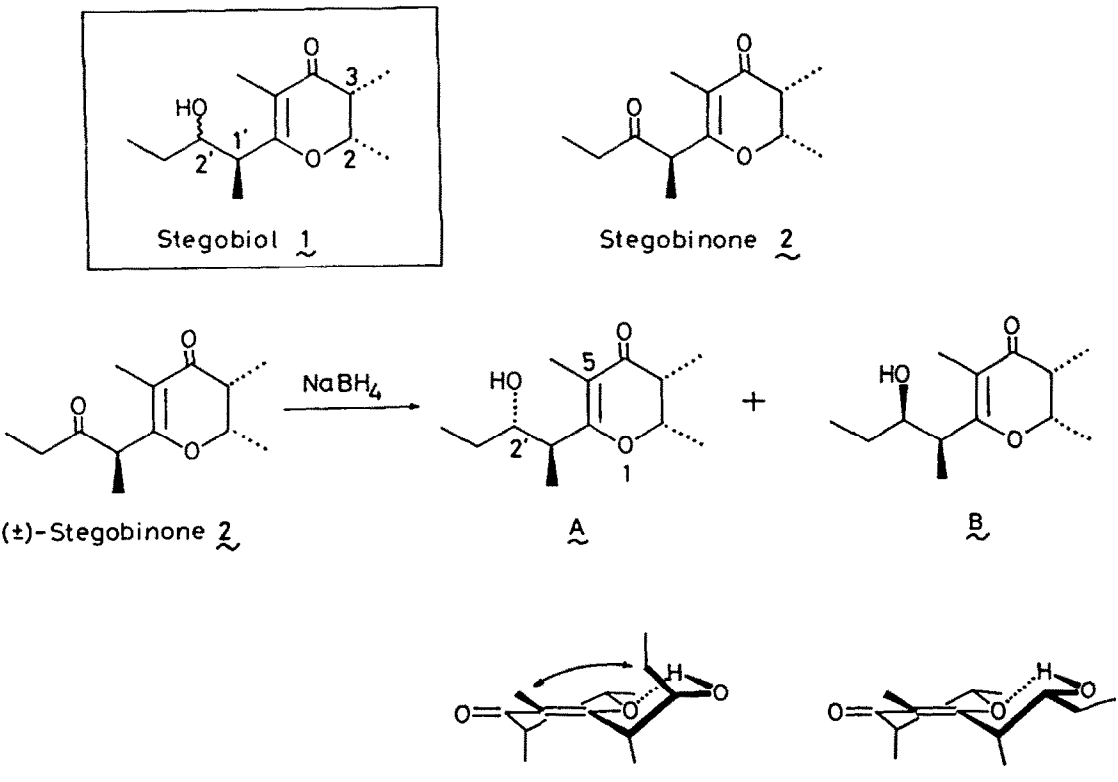

Fig.1. The target molecule and a preliminary experiment.

†Pheromone Synthesis--91. Part 90, M. Fujiwhara and K. Mori, Agric. Biol. Chem. in press.

attractive to the male drugstore beetles than the extract of the female insect suggested the presence of some other pheromone components.[3] Kodama's reinvestigation resulted in the isolation of 9.7 mg of a new attractant together with 10 mg of non-crystalline **2** from 150,000 adult beetles of mixed sex.[1] The new attractant showed the same level of biological activity as that of **2** even at 10^{-3} μg, and was named stegobiol. The structure (2S*,3R*,1'S*)-**1** was proposed for stegobiol basing on the spectral evidence coupled with the observation that reduction of (±)-**2** with $Zn(BH_4)_2$ generated (±)-**1** and its diastereoisomer.[1] No information was available, however, concerning the stereochemistry at C-2'. In order to clarify the complete absolute stereochemistry of natural stegobiol, we became interested in synthesizing optically active **1** stereoselectively.

Prior to our attempt to achieve a chiral synthesis of **1**, we had to settle the problem of the stereochemistry of C-2' relative to that of C-1'. To obtain information for that purpose, we reduced (±)-stegobinone [(2S*,3R*,1'R*)-**2**] with $NaBH_4$ to give a separable mixture of alcohols **A** and **B** as shown in Fig.1. The separated alcohols were analyzed by 500 MHz ^1H NMR, MS and TLC. The more polar one was identical with natural stegobiol **1**.

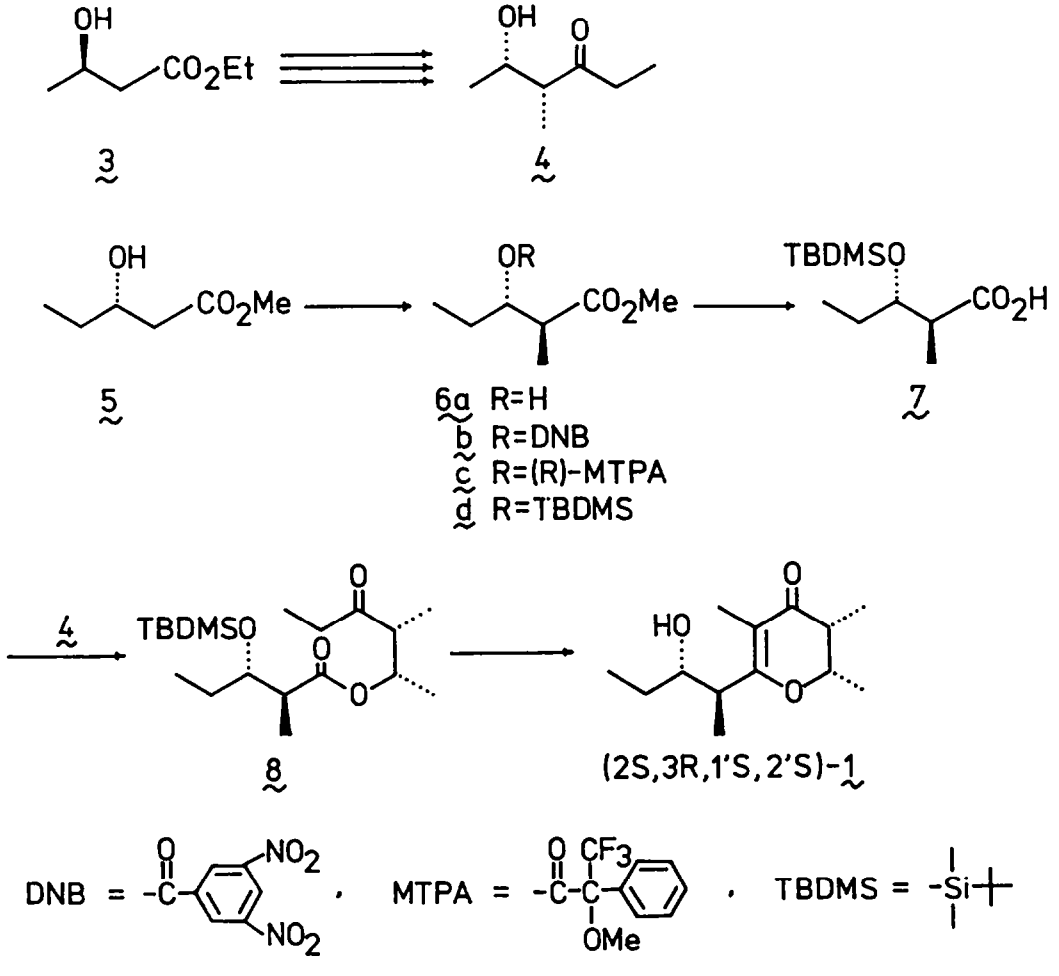

Fig.2. Synthesis of (2S,3R,1'S,2'S)-stegobiol.

The difference in polarity of **A** and **B** was thought to be the reflection of the ease of the formation of the intramolecular H bonding as shown in Fig.1. The stereoformulas of **A** and **B** clearly show that the isomer **B** should form the H bonding more easily due to the eq nature of the Et group attached to the chair-like six-membered ring resulting from the formation of the H bonding. In addition, a severe interaction may take place in the case of the isomer **A** between the Me group at C-5 and the Et group as shown in the formula. This of course destabilize the H bonding. The alcohol **B** was therefore thought to be less polar, and the natural stegobiol must have the structure **A** [=(2S*,3R*,1'S*,2'S*)-1]. As stegobiol **1** is the congener of (2S,3R,1'R)-stegobinone **2**, it seemed highly probable that the absolute configuration of natural stegobiol is 2S,3R,1'S,2'S. Consequently we decided to synthesize it [=(2S,3R,1'S,2'S)-1].

As shown in Fig.2, the synthetic strategy for stegobiol **1** was the same as that employed previously for stegobinone **2**.[3] As intramolecular acylation (**8**→**1**) was the key-step. The starting materials were ethyl (R)-3-hydroxybutanoate **3** (100 % e.e.)[4] and methyl (S)-3-hydroxypentanoate **5** (98 % e.e.).[5] Both of these two esters **3** and **5** were of microbial origin.

The 13-steps conversion of **3** to a hydroxy ketone **4** was carried out as reported previously by us in 27.0 % overall yield.[3] The chemical purity of **4** was shown to be > 97 % with optical purity of 100 %. Conversion of **5** to **7** was executed as follows. Alkylation of a dianion derived from **4** according to Fráter[6] afforded **6a** as the major product contaminated with a small amount of the starting material **5** and the syn-isomer of **6a** (**5**:**6a**:the syn-isomer of **6a**=12:79:9).[7] This mixture was acylated to the corresponding mixture of 3,5-dinitrobenzoates which was recrystallized to give pure **6b**.[8] Saponification of **6b** with KOH aq gave pure **6a** in 86.0 % yield, whose GLC analysis showed its chemical purity to be 100 %. The optical purity of **6a** was also confirmed to be 100 % by the HPLC analysis of the corresponding (R)-α-methoxy-α-trifluoromethylphenylacetate (MTPA ester)[9] **6c**. Silylation of **6a** with t-butyldimethylsilyl chloride (TBDMS Cl) gave **6d** in 91.0 % yield. This ester **6d** was saponified with KOH aq to give **7** in 98.9 % yield. Esterification of **7** with **4** was carried out under the Yamaguchi condition,[10] using commercially available 2,6-dichlorobenzoyl chloride instead of 2,4,6-trichlorobenzoyl chloride in the original procedure, to give **8** in 91.9 % yield. Treatment of **8** with 2 eq of $(Me_3Si)_2$ NLi followed by acidification with $ClCH_2CO_2H$ aq and deprotection with HF aq afforded (2S,3R,1'S,2'S)-stegobiol **1** in 17.9 % yield after purification by prep TLC. Our synthetic stegobiol **1** showed IR, NMR and mass spectral properties identical to those of the natural pheromone.[1] The specific rotation of (2S,3R,1'S,2'S)-1, $[\alpha]_D^{19}$ -110°±6° ($CHCl_3$), was in agreement with the value reported for natural stegobiol, $[\alpha]_D$ -98.3° ($CHCl_3$).[1] As shown in Table 1, the CD spectral data of our synthetic (2S,3R,1'S,2'S)-**1** were in good accord with those of the natural pheromone. The absolute configuration of natural stegobiol was thus assigned as 2S,3R,1'S,2'S. The overall yield of (2S,3R,1'S,2'S)-1 was 4.4 % in 17 steps from **3** or 1.9 % in 9 steps from **5**.

Table 1. CD spectral data of natural and synthetic stegobiol **1**.

		Natural[1]	Synthetic* (2S,3R,1'S,2'S)
λ	355 nm	Δε -0.70	-0.80
	341	-1.46	-1.64
	329	-1.50	-1.69
	282	+0.25	+0.25
	254	-0.72	-0.82

* c=0.065 in n-hexane, 1 mm cell, room temp=21°

In summary, the first chiral synthesis of (-)-stegobiol was achieved. Our synthetic pheromone showed the same level of pheromone activity as that of the natural one when tested against the drugstore beetles.

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.

Methyl (2S,3S)-3-hydroxy-2-methylpentanoate **6a**. A soln of LDA was prepared by the dropwise addition of n-BuLi soln (1.52 N in n-hexane, 99 ml, 150 mmol) to a stirred and cooled soln of $(i\text{-Pr})_2NH$ (15.2 g, 150 mmol) in dry THF (30 ml) at 0° under Ar. The mixture was stirred for 1 h at 0°. To a stirred and cooled (-60°) soln of LDA was added dropwise a soln of **5** (9 g, 68.2 mmol) in dry THF (6 ml). The mixture was stirred for 30 min at -30°. To this stirred and cooled (-30°) mixture was added dropwise a soln of MeI (11.6 g, 81.8 mmol) in HMPA (16 ml) at this temp. 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 and extracted with ether. The ether soln was washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was distilled to give 8.16 g (82.0 %) of **6a**, b.p. 86~88°/9 Torr, GLC (Column, OV-101, 50 m x 0.25 mm at 100°+2°/min; Carrier gas, N_2, 1.0 kg/cm^2): Rt 12.1 min (11.8 %, 5), 15.5 min (79.3 %, **6a**), 16.2 min (8.96 %, syn-isomer of **6a**).

Methyl (2S,3S)-3-(3',5'-dinitrobenzoyloxy)-2-methylpentanoate **6b**. To a stirred and ice-cooled soln of **6a** (8.40 g, 57.5 mmol), DCC (15.4 g, 74.8 mmol) and DMAP (912 mg, 74.8 mmol) in dry CH_2Cl_2 (140 ml) was added 3,5-dinitrobenzoic acid (15.9 g, 74.8 mmol). The mixture was stirred overnight at room temp, diluted with ether (300 ml) and filtered. The filtrate was washed with water, 5 % AcOH aq and water, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (Fuji Davison BW-820 MH, 300 g). Elution with C_6H_6-ether (10:1~5:1) gave crude **6b**. This was repeatedly recrystallized from n-hexane-C_6H_6 (7:1) to give 3.15 g (17.9 % recovery) of pure **6b** as colorless leaflets, m.p. 54~55°; $[\alpha]_D^{21}$ +16.0° (c=1.12, $CHCl_3$); vmax 3140 (w), 3105 (w), 1730 (s), 1720 (s), 1630 (m), 1550 (s), 1347 (s), 1295 (m), 1185 (m), 735 (m), 720 (m) cm^{-1}; δ ($CDCl_3$) 1.01 (3H, t, J=7 Hz), 1.29 (3H, d, J=7 Hz), 1.60~2.35 (1H, m), 3.00 (1H, dq, J=7, 7 Hz), 3.71 (3H, s), 5.15~5.70 (1H, m), 9.00~9.50 (3H, m). (Found: C, 49.41; H, 4.80; N, 8.13. Calc for $C_{14}H_{16}O_8N_2$: C, 49.42; H, 4.74; N, 8.23 %).

Methyl (2S,3S)-3-hydroxy-2-methylpentanoate **6a**. To a stirred and ice-cooled soln of **6b** (1.80 g, 5.29 mmol) in THF-MeOH (1:1, 20 ml) was added dropwise N KOH aq (5.82 ml, 5.82 mmol). The red-violet-colored reaction mixture was stirred for 2 h at 0° and diluted with sat $NaHCO_3$ aq (20 ml). The organic layer was separated and the aq layer was extracted with ether. The combined organic soln was washed wth brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (Fuji Davison BW-820 MH, 60 g). Elution with n-hexane-C_6H_6-ether (5:5:1) gave **6a**, which was distilled to give 665 mg (86.0 %) of pure **6a**, b.p. 69~70°/5 Torr; n_D^{22} 1.4254; $[\alpha]_D^{23}$ +12.2° (c=1.12, $CHCl_3$); vmax 3480 (br), 2980 (s), 2950 (s), 2890 (m), 1730 (s), 1460 (s), 1435 (s), 1260 (s), 1200 (s), 1170 (s), 1120 (s), 1080 (m), 1055 (m), 980 (s) cm^{-1}; δ (CCl_4) 0.93 (3H, t, J=7 Hz), 1.13 (3H, d, J=7 Hz), 1.20~1.75 (2H, m), 2.43 (1H, dq, J=7, 7 Hz), 2.75 (1H, d, J=7 Hz), 3.1~3.7 (4H, m, containing 3.62, 3H, s). GLC (Column, OV-101, 50 m x 0.25 mm at 100°+2°/min; Carrier gas, N_2, 1.1 kg/cm^2): Rt 14.4 min (single peak). (Found: C, 57.56; H, 9.66. Calc for $C_7H_{14}O_3$: C, 57.51; H, 9.65 %).

Determination of the optical purity of **6a**. Acylation of **6a** with MTPA-Cl prepared from either (R)-MTPA or (S)-MTPA gave two diastereomers of **6c** in the usual manner.[9] HPLC analysis of **6c** (Column, NUCLEOSIL®50-5, 25 cm x 4.6 mm; Solvent, n-hexane-THF-MeOH (6000:100:1), 0.8 ml/min; Detected at 254 nm) Rt 25.8 min [(S)-MTPA ester], 27.5 min [(R)-MTPA ester]. The optical purity of **6a** was estimated to be 100 %.

Methyl (2S,3S)-3-t-butyldimethylsilyloxy-2-methylpentanoate **6d**. Imidazole (627 mg, 9.22 mmol) and TBDMSCl (946 mg, 6.29 mmol) were added to a stirred soln of **6a** (612 mg, 4.19 mmol) in dry DMF (10 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 1.09 g (91.0 %) of **6d**, b.p. 83~84°/4 Torr; n_D^{24} 1.4374; $[\alpha]_D^{24}$ +38.5° (c=0.816, $CHCl_3$); vmax 2970 (s), 2940 (s), 2900 (m), 2870 (s), 1745 (s), 1460 (m), 1255 (s), 1195 (s), 1170 (s), 1120 (s), 1080 (s), 1055 (s), 1015 (s), 1005 (s), 835 (s), 775 (s) cm^{-1}; δ (CCl_4) -0.05 (6H, s), 0.83 (3H, t, J=7 Hz), 0.86 (9H, s), 1.03 (3H, d, J=7 Hz), 1.1~1.7 (2H, m), 2.54 (1H, dq, J=7, 7 Hz), 3.58 (3H, s), 3.65~4.10 (1H, m). (Found: C, 59.90; H, 10.84. Calc for $C_{13}H_{28}O_3Si$: C, 59.95; H, 10.84 %).

(2S,3S)-t-Butyldimethylsilyloxy-2-methylpentanoic acid **7**. To a stirred soln of **6d** (963 mg, 3.70 mmol) in MeOH (10 ml) was added dropwise N KOH aq (4.8 ml, 4.8 mmol). The mixture was stirred for 6 h under reflux. After cooling, it was concentrated in vacuo to remove MeOH. The residue was extracted with ether. The aq layer was acidified (pH 5) by addition of AcOH. This was extracted with ether. The ether soln was washed with water, dried ($MgSO_4$) and concentrated in vacuo to give 901 mg (98.9 %) of **7**, vmax 3000 (br), 2970 (s), 2950 (s), 2900 (s), 2870 (s), 1710 (s), 1460 (m), 1250 (s), 1120 (s), 1080 (s), 1050 (s), 1015 (s), 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 (2S,3S)-3-t-butyldimethylsilyloxy-2-methylpentanoate **8**. 2,6-Dichlorobenzoyl chloride (577 mg, 2.76 mmol) was added to a mixture of **7** (678 mg, 2.76 mmol) and Et_3N (306 mg, 3.03 mmol) in dry THF (14 ml) under Ar. The mixture was stirred overnight at room temp. After the removal of Et_3N·HCl by filtration, the filtrate was concentrated under N_2, and the residue was dissolved in dry C_6H_6 (10 ml). To this soln were added a soln of **4** (358 mg, 2.76 mmol) in dry C_6H_6 (3 ml) and DMAP (370 mg, 3.03 mmol) in dry C_6H_6 (3 ml) at 0° under Ar. The resulting mixture was stirred for 5 h at 0°. It was then diluted with ether (15 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 (Fuji Davison BW-820 MH, 30 g). Elution with n-hexane-ether (20:1) gave 906 mg (91.9 %) of **8**, vmax 2980 (s), 2950 (s), 2900 (m), 2880 (m), 1740 (s), 1720 (s), 1460 (m), 1265 (s), 1185 (s), 1125 (s), 1115 (s), 1055 (s), 1015 (s), 835 (s), 775 (s) cm^{-1}; δ (CCl_4) 0.05 (6H, s), 0.6~1.7 (26H, m, containing 0.87, 9H, s), 2.2~2.9 (2H, m), 3.6~4.1 (1H, m), 5.03 (1H, dq, J=6, 6 Hz).

(2S,3R,1'S,2'S)-Stegobiol **1**. To a soln of **8** (100 mg, 0.28 mmol) in dry THF (5 ml) and TMEDA (1ml) 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, the soln 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 were added 3 drops of 46 % HF aq. After stirring for 5 h at room temp, the mixture was diluted with ether (10 ml). The ether soln was washed with water, dried ($MgSO_4$) and concentrated in vacuo. The residue (42 mg) was purified by preparative TLC (Merck Kieselgel 60 F_{254}, n-hexane-ether=1:3, Rf=0.23) to give 11.3 mg (17.9%) of **1**, $[\alpha]_D^{19}$ -110±6° (c=0.42, $CHCl_3$); νmax 3450 (br), 2995 (m), 2945 (m), 2895 (m), 1655 (s), 1605 (s), 1450 (m), 1385 (m), 1375 (m), 1345 (m), 1145 (s), 1115 (m), 995 (m) cm^{-1}; δ ($CDCl_3$, 500 MHz) 1.00 (3H, t, J=7.4 Hz), 1.04 (3H, d, J=7.3 Hz), 1.18 (3H, d, J=7.1 Hz), 1.33 (3H, d, J=6.6 Hz), 1.42 (1H, m), 1.60 (1H, ddq, J=14.0, 7.4, 3.8 Hz), 1.75 (3H, s), 1.89 (1H, d, J=7.4 Hz), 2.38 (1H, dq, J=7.3, 3.4 Hz), 2.86 (1H, dq, J=7.1, 6.8 Hz), 3.58 (1H, ddd, J=8.5, 6.8, 3.8 Hz), 4.49 (1H, dq, J=6.6, 3.4 Hz); MS m/z 227 (M^++1, 4 %), 226 (M^+, 27 %), 168 (100 %, base peak), 141 (21 %), 139 (14 %), 124 (16 %), 113 (91 %), 112 (90 %), 109 (18 %), 83 (51 %), 59 (26 %), 57 (37 %), 56 (23 %), 55 (21 %); ^{13}C-NMR δ ($CDCl_3$, 125 MHz) 9.3, 9.5, 10.2, 14.8, 16.0, 28.4, 41.0, 43.8, 75.5, 109.5, 172.7, 197.2. (Found: m/z 226.1581. Calc for $C_{13}H_{22}O_3$: 226.1569). In addition to **1**, C-3 epimer [Rf=0.29; 14.0 mg (22.2 %)] of **1** was also isolated, although it could not be purified completely. Other by-products were 4-methyl-4-hexen-3-one (νmax 1675 cm^{-1}) and 3-silyloxy-2-methylpentanoic acid (15 % recovery) generated by a retro-Michael process.

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