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SIMPLE SYNTHESIS OF ALL OF THE FOUR STEREOISOMERS OF 5-HYDROXY-4-DECANOLIDE (L-FACTORS), THE PROPOSED AUTOREGULATORS FROM *STREPTOMYCES GRISEUS*†

KENJI MORI* and **TATSUYA OTSUKA**

Department of Agricultural Chemistry, The University of Tokyo,
Yayoi 1-1-1, Bunkyo-ku, Tokyo 113, Japan

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Abstract---All of the four possible stereoisomers (ca. 95 % e.e.) of 5-hydroxy-4-decanolide (L-factors), the proposed autoregulator from *Streptomyces griseus*, were synthesized from (±)-1-octen-3-ol in two or four steps employing the Sharpless asymmetric epoxidation as the key-step

Khokhlov's discovery of A-factor as the autoregulator of *Streptomyces griseus* to induce the streptomycin production and the formation of aerial mycelium[1] made us to undertake further synthetic and stereochemical studies on A-factor culminating to the assignment of its (3*R*)-absolute configuration as depicted in the formula[2,3] At the same time when we were working on A-factor, two new autoregulators were isolated from cultures of *Streptomyces griseus*.[4] Owing to their promotive effects on the biosynthesis of leukaemomycin (an anthracycline antibiotic), the autoregulators were termed L-factors To them were assigned the structures (4*S*,5*R*)-5-hydroxy-4-decanolide **1** and its (4*S*,5*S*)-isomer based on their spectral (IR, ^{1}H- and ^{13}C-NMR, MS and CD) data[4] The proposed structures as δ-hydroxy-γ-lactones coupled with their remarkable bioactivity prompted us to devise a simple synthetic method for preparing all of the stereoisomers of **1**. Obviously the synthesis of all the stereoisomers was the prerequisite to study the stereochemistry-bioactivity relationship In the course of our investigation, however, Grãfe and Eritt retracted the claim of autoregulatory activities for **1** after testing the bioactivity of the synthetic (4*S**,5*R**)- and (4*S**,5*S**)-**1**[5] The previously observed activity of **1** was due to its contamination by trace amounts of A-factor[5]

In spite of the withdrawal of Grafe's original claim, the status of (4*S*,5*R*)- and (4*S*,5*S*)-5-hydroxy-4-decanolide **1** as novel natural products remains secure with full description of their physical properties such as spectral data.[4] We therefore continued our work and completed a chiral synthesis of the four stetreoisomers of **1** Meanwhile, Pougny *et al* reported a synthesis of (4*S*,5*R*)-**1** from triacetyl-D-glucal by a twelve-step sequence[6] followed by some modifications on that route[7] Wightman *et al* also published in a preliminary form a synthesis of (4*S*,5*R*)-**1** as well as that of (4*S*,5*S*)-**1** starting from D-ribose in six or eight steps, respectively[8] Our synthesis as shown in the Scheme yielded the lactone stereoisomers **1** in only two or four steps from a simple racemic starting material **2**.

The structure **1** as a lactonic alcohol reminded us of our previous syntheses of hydroxy-lactones from epoxy alcohols[9,10] The strategy employed in those earlier syntheses must again be useful in synthesizing **1**. An attack at C-1 of an epoxy alcohol (2*S*,3*R*)-**3a** with an appropriate two-carbon nucleophile will lead to (4*S*,5*R*)-**1**, with retention of configurations at the two chiral centers In connection with our pheromone synthesis, we had the experience in preparing (2*S*,3*R*)-

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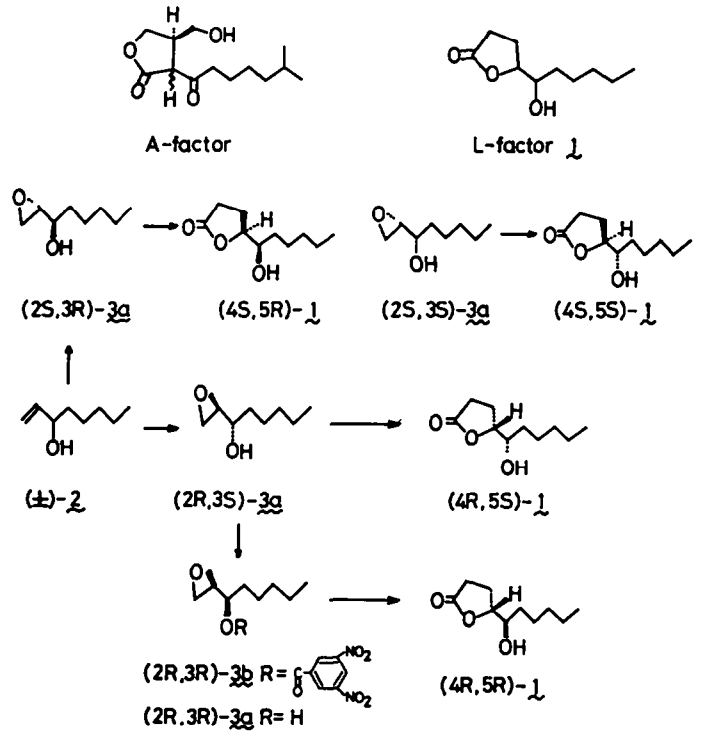
and (2S,3S)-**3a**.[11] The epoxide (2S,3R)-**3a** was obtained by the kinetic resolution of the commercially available (±)-1-octen-3-ol **2** by enantioselective epoxidation.[12] The Walden inversion at C-3 of (2S,3R)-**3a** under the Mitsunobu condition[13] afforded (2S,3S)-**3a** After several unsuccessful trials we found $LiCH_2CO_2Li$[14] to be a convenient two-carbon nucleophile to prepare **1**. Treatment of (2S,3R)-**3a** with a large excess of $LiCH_2CO_2Li$ in DME was followed by acidification to give (4S,5R)-**1**, $[\alpha]_D^{21}$+9 8°(CCl_4) [lit [6] $[\alpha]_D$ +11°(CCl_4); lit [8] $[\alpha]_D$ +8 6°(CCl_4)], in 42 % yield Similarly (2S,3S)-**3a** furnished (4S,5S)-**1**, m p. 42~44°, $[\alpha]_D^{21}$+33.2°($CHCl_3$) [lit.[8] oil, $[\alpha]_D$ +24 8° ($CHCl_3$)], in 40 % yield. Their spectral properties including the ^{13}C-NMR data were in good accord with those reported previously for both the natural[4] and synthetic[6,8] materials.

For the preparation of the antipodes of the natural lactones, (2R,3S)- and (2R,3R)-**3a** were required as the key-intermediates (±)-1-Octen-3-ol **2** was epoxidized with t-BuOOH and $Ti(i\text{-}PrO)_4$ in the presence of diisopropyl L-(+)-tartrate for 12 h at -20°to give (2R,3S)-**3a** in 41 2 % yield.[cf.11,12] This was treated with $LiCH_2CO_2Li$ to give (4R,5S)-**1**, $[\alpha]_D^{20}$-9.5°($CHCl_3$), in 39 % yield Then the Walden inversion at C-3 of (2R,3S)-**3a** was effected with Ph_3P, 3,5-dinitrobenzoic acid and diethyl azodicarboxylate to yield (2R,3R)-**3b** as an oil [11,13] Alkaline hydrolysis of (2R,3R)-**3b** afforded (2R,3R)-**3a**. Treatment of (2R,3R)-**3a** with $LiCH_2CO_2Li$ furnished (4R,5R)-**1**, m.p 42~44°, $[\alpha]_D^{21}$-33.1°($CHCl_3$), in 26 % yield.

In this way the synthesis of (4S,5R)-**1** and its antipode (4R,5S)-**1** was achieved in two steps from **2** in 27 % and 16 % overall yield, respectively The overall yield of the four-step synthesis of (4S,5S)-**1** from **2** was 11 %, and that of (4R,5R)-**1** was 10 %. Determination of the optical purities of our synthetic isomers of **1** was carried out by the measurement of the 400 MHz ^1H-NMR spectra of their respective (S)-α-methoxy-α-trifluoromethylphenylacetates (MTPA esters).[15] The intensities of the signals due to the diastereotopic OCH_3 protons of the MTPA esters were precisely estimated, which allowed the determination of the optical purity of (4S,5R)-**1** as 94 7 % e e., while that of (4R,5S)-**1** was 95.2 % e e (4S,5S)-**1** was of 95.5 % e.e and the antipode (4R,5R)-**1** was shown to be of 94.8 % e e Thus all the stereoisomers of **1** prepared by us were of ca. 95 % e e.



In summary we illustrated again the utility of the Sharpless asymmetric epoxidation in synthesizing hydroxylactones.[cf 9,10] Although the overall yields achieved by our method were not so excellent (10 27 %), it was still comparable to those reported by Pougny (13 % in twelve steps[6] or 4 % in eight steps[7] from triacetyl-D-glucal). Wightman's synthesis gave better overall yields than ours [68 % for (4S,5R)-**1** in five steps or 58 % for (4S,5S)-**1** in seven steps from isopropylidene D-ribose[8]]. The optical purities of their products, however, seemed to be lower than ours, judging from their reported values of specific rotation[8]

EXPERIMENTAL

All b.ps and m.ps were uncorrected. IR spectra were recorded on a Jasco A-102 spectrometer as a film. NMR spectra were measured on a Hitachi R-24A spectrometer at 60 MHz with TMS as an internal standard unless otherwise stated. Optical rotations were measured on a Jasco DIP-140 automatic polarimeter

(2S,3R)-(-)-1,2-Epoxy-3-octanol (2S,3R)-**3a**. This was prepared according to our published procedure.[11] Starting from 20.0 ml (16.6 g) of (±)-**2**, 6.0 g (63.8 %) of (2S,3R)-**3a** was obtained, b.p. 58°/0.2 Torr; $[\alpha]_D^{21}$ -22.3°(c=1.55, $CHCl_3$) [lit.[11] $[\alpha]_D^{20}$ -21.6° (c=1.43, $CHCl_3$)]

(2S,3S)-(+)-1,2-Epoxy-3-octanol (2S,3S)-**3a** According to the published procedure 6.90 g of the corresponding 3,5-dinitrobenzoate yielded 2.34 g (79.6 %) of (2S,3S)-**3a**, b.p. 81~82°/5 Torr; $[\alpha]_D^{21}$ +4.41° (c=1.48, $CHCl_3$) [lit.[11] $[\alpha]_D^{21}$ +4.40° (c=1.66, $CHCl_3$)].

(2R,3S)-(+)-1,2-Epoxy-3-octanol (2R,3S)-**3a**. To stirred and cooled (dry-ice-CCl_4 bath) dry CH_2Cl_2 (500 ml) at -20°under Ar were added Ti(i-PrO)$_4$ (19.3 ml, 64.8 mmol) and diisopropyl L-(+)-tartrate (16.2 ml, 77.8 mmol). After stirring for 5 min, (±)-**2** (18.0 ml=14.9 g, 116.7 mmol) and t-BuOOH (7.3 M in CH_2Cl_2, 18.1 ml, 132.5 mmol) were added to the mixture at -20°. The mixture was left to stand for 16 h at -20°in a freezer. It was then cooled with a dry ice-CCl_4 bath. To the stirred and cooled soln was added 10 % aq soln of L-(+)-tartaric acid (200 ml). The stirring was continued for 30 min at -20°, and for 2 h at room temp. The organic layer was separated, washed with water, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was diluted with ether (400 ml) and stirred with 1 N-NaOH (150 ml) for 1 h at room temp. The organic layer was separated, washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue resulting from three batches of the above epoxidation was chromatographed over SiO_2 (Merck Kieselgel 60, 1 kg). Elution with EtOAc-n-hexane (1 10~15 85) gave 16.9 g [67 % from (S)-**2**] of (2R,3S)-**3a**. This was distilled to give 10.4 g [41.2 % from (S)-**2**] of (2R,3S)-**3a**, b.p. 86~89°/10 Torr; $n_D^{19.5}$ 1.4376; $[\alpha]_D^{19.5}$ +24.7°(c=1.44, $CHCl_3$); νmax 3460 (s), 1070 (m), 945 (m), 850 (m) cm^{-1}; δ(CCl_4) 0.90 (3H, deformed t, J=7 Hz), 1.07~1.75 (8H, m), 2.61 (1H, dd, J=3.7, 7.0 Hz), 2.63 (1H, dd, J=3.7, 7.0 Hz), 2.82 (1H, ddd, J=3.7, 3.7, 7.0 Hz), 3.05 (1H, d, J=4.0 Hz, OH), 3.50 (1H, m) (Found C, 66.38, H, 11.17. Calc for $C_8H_{16}O_2$ C, 66.63; H, 11.18 %)

(2R,3R)-(-)-1,2-Epoxy-3-octanol 3,5-dinitrobenzoate (2R,3R)-**3b**. To a stirred soln of (2R,3S)-**3a** (4.00 g, 27.8 mmol), 3,5-dinitrobenzoic acid (6.01 g, 28.3 mmol, 1.02 eq) and Ph_3P (7.43 g, 28.3 mmol) in THF (70 ml) was added dropwise over 15 min a soln of diethyl azodicarboxylate (4.93 g, 28.3 mmol) in THF (25 ml) under ice-cooling at 10°. The mixture was stirred overnight at room temp, and concentrated *in vacuo*. The residual brown oil was chromatographed over SiO_2 (Fuji Davison BW-820MH, 150 g). Elution with THF-$CHCl_3$ (1 10) gave crude **3b**, which was rechromatographed over SiO_2 (Fuji Davison BW-820MH, 150 g). Elution with EtOAc-n-hexane (1 10) gave 9.00 g (99.3 %) of (2R,3R)-**3b** as a yellow oil, n_D^{19} 1.5253; $[\alpha]_D^{19}$ -3.84° (c=2.77, $CHCl_3$); νmax 3125 (m), 1735 (s), 1630 (m), 1600 (w), 1550 (s), 1350 (s), 1280 (s), 1170 (s), 720 (s) cm^{-1}; δ($CDCl_3$) 0.88 (3H, deformed t, J= 7Hz), 1.05~1.65 (6H, m), 1.70~2.15 (2H, m), 2.73 (1H, dd, J=4.0, 4.7 Hz), 3.28 (1H, ddd, J=2.5, 4.0, 6.5 Hz), 5.00 (1H, dt, J=6.5, 6.5 Hz), 9.30 (3H, s) (Found C, 53.52; H, 5.47; N, 8.02. Calc for $C_{15}H_{18}O_7N_2$ C, 53.25, H, 5.36; N, 8.28 %)

(2R,3R)-(-)-1,2-Epoxy-3-octanol (2R,3R)-**3a**. To a stirred soln of (2R,3R)-**3b** (7.70 g, 22.8 mmol) in THF (50 ml) was added over 5 min a mixture of 1 N-KOH aq (25 ml) and MeOH (20 ml). The mixture was stirred for 1 h at room temp. It was then diluted with water and extracted with ether. The ether soln was washed with sat $NaHCO_3$ aq and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (BW-820MH, 30 g). Elution with EtOAc-n-hexane (1 5) gave 3.04 g (93 %) of (2R,3R)-**3a**, b.p. 80~84°/ 7 Torr; $n_D^{21.5}$ 1.4384; $[\alpha]_D^{21.5}$ -3.72°(c=1.50, $CHCl_3$); νmax 3455 (s), 1085 (m), 1060 (m), 1040 (m), 915 (m) cm^{-1}; δ(CCl_4) 0.90 (3H, deformed t, J=6 Hz), 1.05~1.65 (8H, m), 2.50~2.70 (2H, m), 2.75~2.95 (1H, m), 2.95 (1H, d, J=4 Hz, OH), 3.25 (1H, m) (Found C, 66.58; H, 11.14. Calc for $C_8H_{16}O_2$ C, 66.63; H, 11.18 %)

(4S,5R)-(+)-5-Hydroxy-4-decanolide (4S,5R)-**1**. To a stirred and cooled soln of i-Pr_2NH (4.85 ml, 34.5 mmol) in 1,2-dimethoxyethane (DME, 18 ml) at -55°under Ar, a soln of n-BuLi in n-hexane (1.65 M, 20.9 ml, 34.5 mmol) was added dropwise keeping the reaction temp below -43°. To the stirred soln of LiN(i-Pr)$_2$ was added a soln of AcOH (0.99 ml, 17.3 mmol) in DME (4 ml). The temp was allowed to rise gradually. The stirring was continued for 1 h at 23°and another 1 h at 43°. The resulting soln of $LiCH_2CO_2Li$ was taken into a syringe and added in one portion to a stirred soln of (2S,3R)-**3a** (302.5 mg, 2.1 mmol) in DME (5 ml) under Ar. The mixture was stirred and heated at 55°for 48 h, and then cooled in an ice-bath. The reaction was quenched by the addition of water (6 ml). The mixture was concentrated *in vacuo* to remove DME. The residual aq soln was acidified with dil H_2SO_4 to pH 2, and thoroughly extracted with ether. The ether soln was dried ($MgSO_4$), and concentrated *in vacuo* to give 669 mg of a brown oil. This was chromatographed over SiO_2 (Kieselgel 60, 35 g). Elution with EtOAc-n-hexane (1 5~1 2) gave 165 mg (42.3 %) of (4S,5R)-**1** as a viscous oil. An analytical sample was further purified by chromatography over SiO_2 (BW-820MH) to give pure (4S,5R)-**1**, n_D^{21} 1.4600; $[\alpha]_D^{21}$ +9.8°(c=1.50, CCl_4); νmax 3475 (s), 2950 (s), 2875 (s), 1775 (s), 1470 (m), 1425 (w), 1385 (w), 1340 (w), 1300 (w), 1190 (s), 1140 (w), 1075 (w), 1030 (m), 1000 (w), 930 (m), 910 (m), 890 (w), 840 (w), 730 (w) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.895 (3H, t, J=7.0 Hz), 1.25~1.37 (5H, m), 1.38~1.45 (2H, m), 1.49~1.58 (1H, m), 2.145 (1H, dddd, J=5.5, 7.4, 10.0, 12.3 Hz), 2.275 (1H, dddd,

J=7.0, 7 5, 10 0, 12.3 Hz), 2.503 (1H, ddd, J=7.5, 10.0, 17.9 Hz), 2.597 (1H, ddd, J=5 5, 10.0, 17.9 Hz), 3 095 (1H, s, OH), 3.902 (1H, m), 4.448 (1H, ddd, J=3.3, 7.4, 7.5 Hz); ^{13}C-NMR (25 MHz, $CDCl_3$) δ 14.01, 21.12, 22.55, 25.36, 28.75, 31.74, 31 94, 71.43, 82.93, 177 58 (Found C, 64 50; H, 9.95 Calc for $C_{10}H_{18}O_3$ C, 64.49; H, 9.74 %)

(4S,5S)-(+)-5-Hydroxy-4-decanolide (4S,5S)-**1**. In the same manner as described above, a soln of $LiCH_2CO_2Li$ was prepared from $(i\text{-Pr})_2NH$ (17.1 ml, 122 mmol), n-BuLi (1.52 M soln in n-hexane, 80.0 ml, 122 mmol) and AcOH (3.50 ml, 61.0 mmol) in DME (85 ml). This was added to a soln of (2S,3S)-**3a** (1.00 g, 6.94 mmol) in DME (20.0 ml) with stirring under Ar. The mixture was stirred overnight at 45° It was then cooled in an ice-bath and the reaction was quenched by the addition of sat NH_4Cl aq (60 ml). The mixture was acidified with conc HCl to pH 2 and thoroughly extracted with ether. The ether soln was dried ($MgSO_4$) and concentrated in vacuo. The residual brown oil was chromatographed over SiO_2 (Merck Kieselgel 60, 100 g). Elution with $CHCl_3$-MeOH (50 1) gave 510 mg (40 %) of (4S,5S)-**1** as crystals. An analytical sample was further purified by chromatography over SiO_2 and decolorization with activated charcoal to give pure (4S,5S)-**1**, m.p. 42~44°; $[\alpha]_D^{21}$+33.2° (c=1.11, $CHCl_3$); νmax 3470 (s), 2950 (s), 2875 (s), 1770 (s), 1460 (m), 1415 (w), 1375 (w), 1290 (w), 1265 (w), 1190 (s), 1130 (m), 1050 (m), 1025 (m), 925 (m), 820 (w), 725 (w) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.894 (3H, t, J=7.0 Hz), 1.25~1.44 (5H, m), 1.45~1.61 (3H, m), 2.148 (1H, dddd, J=7.5, 8.3, 10.0, 12.3 Hz), 2.247 (1H, dddd, J=5.5, 7.5, 9.5, 13.3 Hz), 2.510 (1H, ddd, J=8.3, 9.5, 17.5 Hz), 2 608 (1H, ddd, J=5.5, 10.0, 17 5 Hz), 3.264 (1H, s, OH), 3 568 (1H, dt, J=4.2, 8.4 Hz), 4.446 (1H, ddd, J=4.2, 7.5, 7 5 Hz); ^{13}C-NMR (25 MHz, $CDCl_3$) δ 14.01, 22.55, 24 02, 25.24, 28 70, 31.74, 32.94, 73.36, 83.16, 177.88. (Found C, 64.75, H, 9.79. Calc for $C_{10}H_{18}O_3$ C, 64.49; H, 9.74 %).

(4R,5S)-(-)-5-Hydroxy-4-decanolide (4R,5S)-**1**. In the same manner as described for the preparation of (4S,5R)-**1**, a soln of $LiCH_2CO_2Li$ was prepared from $(i\text{-Pr})_2NH$ (9.73 ml, 69.4 mmol), n-BuLi (1.60 M in n-hexane, 43.4 ml, 69.4 mmol) and AcOH (1.98 ml, 34.7 mmol) in DME (28 ml). This was added to a stirred soln of (2R,3S)-**3a** (1.0 g, 6.94 mmol) in DME (10 ml) under Ar. The mixture was stirred at 40~45° for 24 h. It was then poured into ice-water, acidified with conc HCl to pH 1~2, stirred for 30 min at 0° and thoroughly extracted with CH_2Cl_2. The CH_2Cl_2 soln was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by SiO_2 chromatography to give 500 mg (38.7 %) of (4R,5S)-**1**, n_D^{21} 1.4604; $[\alpha]_D^{20}$ -9.5° (c=1.13, CCl_4). The IR and NMR spectra of (4R,5S)-**1** were identical with those of (4S,5R)-**1**. (Found C, 64.13; H, 9.76. Calc for $C_{10}H_{18}O_3$ C, 64.49; H, 9.74 %).

(4R,5R)-(-)-5-Hydroxy-4-decanolide (4R,5R)-**1**. In the same manner as described for the preparation of (4S,5R)-**1**, a soln of $LiCH_2CO_2Li$ was prepared from $(i\text{-Pr})_2NH$ (24.3 ml, 17.3 mmol), n-BuLi (1.52 M in n-hexane, 114 ml, 173 mmol) and AcOH (5.20 g, 87 mmol) in DME (39 ml). A portion of this soln containing 33 mmol of $LiCH_2CO_2Li$ was added to a stirred soln of (2R,3R)-**3a** (1.00 g, 6.94 mmol) in DME (15 ml) under Ar. The mixture was stirred at 55° for 36 h. It was then cooled in an ice-bath and the reaction was quenched by the addition of sat NH_4Cl aq (80 ml). The mixture was acidified with conc HCl to pH 2 and thoroughly extracted with ether. The ether soln was dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by SiO_2 chromatography (twice) to give 340 mg (26.3 %) of crystalline (4R,5R)-**1**, m.p. 42~44°; $[\alpha]_D^{21}$ -33.1° (c=1.64, $CHCl_3$). The IR and NMR spectra of (4R,5R)-**1** were identical with those of (4S,5S)-**1** (Found C, 64.61; H, 9.75. Calc for $C_{10}H_{18}O_3$ C, 64.49; H, 9.74 %).

Determination of the optical purities of four isomers of **1**

Each of the isomers was converted to the corresponding (S)-MTPA ester in the usual manner,[15] and its 400 MHz ^{1}H-NMR spectrum ($CDCl_3$ soln) was measured to know the δ-values and intensities of the diastereotopic OCH_3 protons of the MTPA ester.

A signal due to OCH_3 protons of (S)-MTPA ester of (4S,5R)-**1** appeared at δ 3.552, while that of (S)-MTPA ester of (4R,5S)-**1** appeared at δ 3.492. The optical purity of (4S,5R)-**1** was 94.7 % e.e., while that of (4R,5S)-**1** was 95.2 % e.e.

A signal due to OCH_3 protons of (S)-MTPA ester of (4S,5S)-**1** appeared at δ 3.576, while that of (S)-MTPA ester of (4R,5R)-**1** appeared at δ 3.520. The optical purity of (4S,5S)-**1** was 95.5 % e.e., while that of (4R,5R)-**1** was 94.8 % e.e.

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