Synthesis of musclide-A1 diastereomers; Confirmation of absolute stereochemistry

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Abstract

(2*R*,5*R*)-Musclide-A1 and (2*S*,5*R*)-musclide-A1 were synthesized from L-valine and their diastereomers from D-valine in order to determine the structure of natural musclide-A1 isolated from musk. Comparisons of spectral data of synthetic, natural, and previously synthesized musclide-A1 confirmed the structure suggested previously; *i.e.*, natural musclide-A1 is a mixture of (2*R*)-hydroxy-6-methyl-(5*R*)-heptyl hydrogen sulfate and (2*R*)-hydroxy-6-methyl-(5*S*)-heptyl hydrogen sulfate.

Key words Musk, musclide-A1, absolute configuration, synthesis, *Moschus moschiferus*, Mosher's method.

Abbreviations Bzl-Br, benzyl bromide; e.e., enantiomeric excess; HPLC, high performance liquid chromatography; IR, infrared; LAH, lithium aluminum hydride; MEM, (2-methoxyethyloxy)methyl; MTPA, α-methoxy-α-trifluoromethylphenylacetic acid; NMR, nuclear magnetic resonance; *p*-TsOH, *para*-toluensulfonic acid; TLC, thin layer chromatography.

Introduction

Musk, a dried secretion from the preputial follicles of a male musk deer (*Moschus moschiferus* L.), is one of the most famous traditional Chinese medicines and it is used for resuscitation and as an agent to activate blood flow, remove blood stasis, and to expedite delivery.[1,2] Pharmacological studies have indicated that musk exhibits cardiotonic, sedative, anti-inflammatory, male hormonal, and β-adrenergic activities.[3-6] Several groups of authors examined the contituents of musk and reported the presence of muscone, steroidal hormones, muscopyridine, hydroxymuscopyridines, and peptides.[7-10] We previously reported three aliphatic sulfates, musclides-A1 (**1**), -A2 (**2**), and -B (**3**) (Chart 1), as cardiotonic potentiating principles.[11] Their structures were presented through the analyses of their spectral data and the syntheses of authentic samples. Our recent synthetic work on musclides-A2 and -B, however, indicated that the absolute structure of musclide-A2 should be revised from (4*R*)-**2** to (4*S*)-**2** and that of musclide-B from (2*R*,5*R*)-**3** to (2*R*,5*S*)-**3**.[12] Thus, we synthesized all diastereomers of musclide-A1 from L-or D-valine in order to clarify whether the structure of musclide-A1 is correct or not. This paper deals with the synthesis and structure confirmation of musclide-A1.

Materials and Methods

General : Optical rotations were measured on a JASCO DIP-140 digital polarimeter at 26°C. IR spectra were obtained on a JASCO IRA-2 spectrophotometer in $CHCl_3$ solutions otherwise noted and NMR spectra were with a JEOL JNM-GX400 spectrometer in $CDCl_3$ solutions otherwise noted. Column chromatography was carried out over silica gel (Merck, Art. 7734 or Fuji Silysia, BW-820MH), and analytical and preparative TLC were on precoat-

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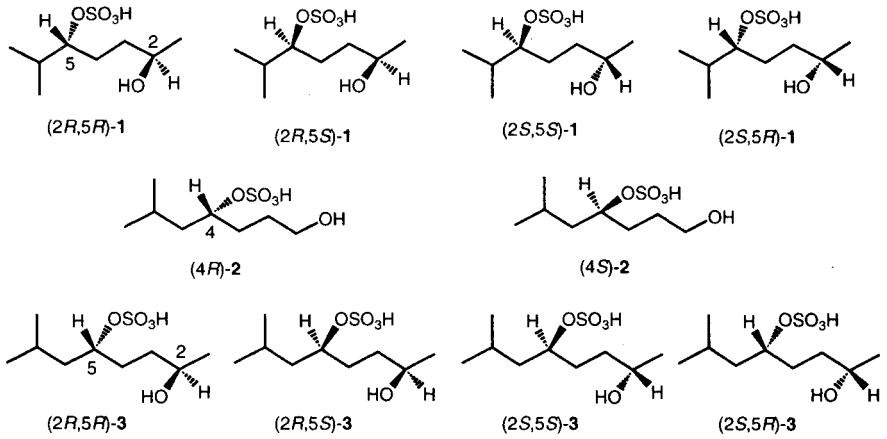

Fig. 1 Diastereomers of musclides-A1, -A2, and -B.
Natural musclide-A1 is a diastereomeric mixture of (2*R*,5*R*)-**1** and (2*R*,5*S*)-**1**.
The structure of natural musclide-A2 has been revised from (4*R*)-**2** to (4*S*)-**2** and that of natural musclide-B from (2*R*,5*R*)-**3** to (2*R*,5*S*)-**3**.

ed Merck Kieselgel $60F_{254}$ plates (0.25, 0.5, and 1.0 mm).

Preparation of (2S)-(+)-Ethyl Valate (4): (2*S*)-(+)-Ethyl valate (2*S*-**4**) were prepared from L-valine by the same manner as the preparation of ethyl leucate[13] as colorless oil, bp 75°/65 mmHg, $[\alpha]_D$+8.1° (*c*=1.15, $CHCl_3$).[14] (2*R*)-**4**: bp 75-83°/54 mmHg, $[\alpha]_D$ −7.9° (*c*=1.09, $CHCl_3$).

Preparation of (2S)-[(2-Methoxyethyloxy)methyloxy]-3-methylbutanol (2S-5): A mixture of NaH (containing ca. 60 % of mineral oil, 10.2 g) and (2*S*)-**4** (25.5 g) in dry tetrahydrofuran (THF, 270 ml) was stirred under Ar (0°C, 30 min). 2-Methoxyethoxymethyl (MEM) chloride (MEMCl, 23.3 ml) was added to the mixture and the stirring continued (0°C, overnight). The reaction mixture was poured over ice-cold sat. NH_4Cl aq. and extracted with ether. The ether layer was washed (sat. NaCl aq.), dried (K_2CO_3), and evaporated to give crude MEM ether (57 g). A solution of the crude MEM ether and $LiAlH_4$ (6.0 g) in dry ether (545 ml) was stirred under Ar (0°C, 10 min). After excess $LiAlH_4$ was destroyed with aqueous ether, the ether layer was dried (K_2CO_3) and evaporated, and the residue was chromatographed using AcOEt-hexane (10 : 90) to give (2*S*)-**5** (26.9 g, 80 %) as a colorless oil, $[\alpha]_D$+66.6°C (*c*=1.05, $CHCl_3$). IR ν_{max} (neat) cm^{-1}: 3350, 1450, 1380, 1355, 1090, 1030, 850, 830. ^{1}H-NMR δ: 0.92, 0.93 (each 3H, d, *J*= 7 Hz, 4-H_3, 5-H_3), 1.84 (1H, qqd, *J*= 7, 7, 6 Hz, 3-H), 3.31 (1H, ddd, *J*= 7, 6, 2.5 Hz, 2-H), 3.40 (3H, s, OMEM), 3.54-3.91 (6H, m, 1-H_2, OMEM), 4.73, 4.86 (each 1H, d, *J*= 7.5 Hz, OMEM). ^{13}C-NMR δ: 18.3 (q), 18.8 (q), 30.2 (d), 59.0 (q), 63.6 (t), 67.5 (t), 71.7 (t), 88.1 (d), 96.6 (t). (2*R*)-**5**: $[\alpha]_D$-68.4° (*c*=1.24, $CHCl_3$).

Preparation of (5S)-[(2-Methoxyethyloxy)methyloxy]-6-methylhept-(3E)-en-2-one (5S-6): A solution of dimethyl sulfoxide (DMSO, 3.75 ml) and $(COCl)_2$ (3.40 ml) in dry CH_2Cl_2 (60 ml) was stirred under Ar (-80°C, 10 min) and a solution of (2*S*)-**5** (5.07 g) in dry CH_2Cl_2 (50 ml) was added to the mixture. After additional stirring (-75°C, 1 h), Et_3N (16.3 ml) was added and the reaction mixture was allowed to warm to -30°C (30 min). To the reaction mixture, a solution of Ph_3P=$CHCOCH_3$ (24 g) in dry CH_2Cl_2 (100 ml) was added and the mixture was allowed to warm to room temperature (3 h). After additional stirring (1.5 h), the reaction mixture was poured onto sat. NaCl aq. and extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed (water, sat NaCl aq.), dried ($MgSO_4$), and evaporated. The residue was chromatographed using AcOEt-hexane (5 : 95) to give (2*S*)-**7** (1.3 g, 26 %) and (5*S*)-**6** (3.5 g, 58 %) in this order.

(5*S*)-**6**: Colorless oil, $[\alpha]_D$-76.2° (*c*=0.98, $CHCl_3$). *Anal.* Calcd for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63. Found: C, 62.42: H, 9.64. IR ν_{max} (neat) cm^{-1}: 1670, 1620, 1460, 1355, 1250, 1100, 1030, 980. ^{1}H-NMR δ: 0.92, 0.96 (each

3H, d, J=7 Hz, 7-H_3, 8-H_3), 1.88 (1H, qqd, J=7, 7, 6 Hz, 6-H), 2.28 (3H, s, 1-H_3), 3.38 (3H, s, OMEM), 3.54, 3.65, 3.79 (total 4H, m, OMEM), 4.00 (1H, ddd, J=7, 6, 1 Hz, 5-H), 4.70 (2H, s, OMEM), 6.21 (1H, dd, J=16, 1 Hz, 3-H), 6.63 (1H, dd, J=16, 7 Hz, 4-H). ^{13}C-NMR δ : 18.2 (q), 18.3 (q), 27.3 (q), 32.6 (d), 59.0 (q), 67.2 (t), 71.7 (t), 80.6 (d), 93.8 (t), 131.9 (d), 145.2 (d), 198.0 (s). (5*R*)-**6** : $[\alpha]_D$+75.6°(c=1.12, $CHCl_3$).

(2*S*)-**7** : Colorless oil, $[\alpha]_D$-27.0°(c=1.33, $CHCl_3$. IR ν_{max} (neat) cm^{-1} : 1725, 1470, 1390, 1365. ^{1}H-NMR δ : 0.96, 0.98 (each 3H, d, J=7 Hz, 4-H_3, 5-H_3), 1.82 (1H, octet, J=7 Hz, 3-H), 3.39 (3H, s, OMEM), 3.36-3.42, 3.53-3.60, 3.69-3.75 (total 5H, m, OMEM, 2-H), 4.78 (2H, s, OMEM), 9.70 (1H, d, J=6 Hz, 1-H). (2*R*)-**7**: $[\alpha]_D$+46.1°(c=1.03, $CHCl_3$).

*Preparation of (5S)-[(2-Methoxyethyloxy)methyloxy]-6-methylhept-(3E)-en-2-ol (2R,5S-**8** and 2S,5S-**9**)*: A solution of (5*S*)-**6** (3.5 g) and $NaBH_4$ (567 mg) in MeOH (75 ml) was stirred under Ar (rt, 1 h). After concentration to 1/3 and addition of water, the mixture was extracted with CH_2Cl_2, and the CH_2Cl_2 layer was washed (sat. NaCl ap.), dried (K_2CO_3), evaporated, and chromatographed using ether-hexane (40 : 60) to give (2*R*,5*S*)-**8** (1.3 g, 37 %) and (2*S*,5*S*)-**9** (1.7 g, 48 %).

(2*R*,5*S*)-**8**: Colorless oil, $[\alpha]_D$-50.3°(c=1.15, $CHCl_3$). *Anal.* Calcd for $C_{12}H_{24}O_4$: C, 62.04 ; H, 10.41. Found : C, 61.66 ; H, 10.49. IR ν_{max} (neat) cm^{-1} : 3600, 3450, 1470, 1365, 1260, 1100, 1035, 980, 850, 700. ^{1}H-NMR δ : 0.88, 0.94 (each 3H, d, J=6.5 Hz, 7-H_3, 8-H_3), 1.27 (3H, d, J=6.5 Hz, 1-H_3), 1.78 (1H, qqd, J=6.5, 6.5, 6.5 Hz, 6-H), 3.39 (3H, s, OMEM), 3.56, 3.67, 3.75 (total 4H, m, OMEM), 3.74 (1H, dd, J=8, 6.5 Hz, 5-H), 4.33 (1H, br qd, J=6.5, 6 Hz, 2-H), 4.65, 4.75 (each 1H, d, J=7 Hz, OMEM), 5.53 (1H, ddd, J=15.5, 8, 1.5 Hz, 4-H), 5.72 (1H, ddd, J=15.5, 6, 1 Hz, 3-H). ^{13}C-NMR δ : 18.4 (q), 18.6 (q), 23.4 (q), 32.7 (d), 59.0 (q), 66.9 (t), 68.1 (d), 71.9 (t), 82.0 (d), 93.2 (t), 128.0 (d), 138.2 (d). (2*S*,5*R*)-**8** : $[\alpha]_D$+63.2°(c=0.97, $CHCl_3$).

(2*S*,5*S*)-**9**: Colorless oil, $[\alpha]_D$-44.0°(c=1.00, $CHCl_3$). *Anal.* Calcd for $C_{12}H_{24}O_4$: C, 62.04 ; H, 10.41. Found : C, 61.72 ; H, 10.86. IR ν_{max} (neat) cm^{-1} : 3600, 3430, 1460, 1365, 1260, 1100, 1040, 980, 850, 700. ^{1}H-NMR δ : 0.87, 0.94 (each 3H, d, J=6.5 Hz, 7-H_3, 8-H_3), 1.27 (3H, d, J=6.5 Hz, 1-H_3), 1.76 (1H, qqd, J=6.5, 6.5, 6.5 Hz, 6-H), 3.39 (3H, s, OMEM), 3.51-3.78 (4H, m, OMEM), 3.71 (1H, dd, J=8, 7 Hz, 5-H), 4.31 (1H, br qd, J=6.5, 6 Hz, 2-H), 4.66, 4.77 (each 1H, d, J=7 Hz, OMEM), 5.50 (1H, ddd, J=15.5, 8, 1 Hz, 4-H), 5.70 (1H, ddd, J=15.5, 6, 0.5 Hz, 3-H). ^{13}C-NMR δ : 18.4 (q), 18.6 (q), 23.4 (q), 32.7 (d), 59.0 (q), 66.9 (t), 68.3 (d), 71.9 (t), 82.6 (d), 93.5 (t), 128.5 (d), 138.1 (d). (2*R*,5*R*)-**9** : $[\alpha]_D$+55.6°(c=1.08, $CHCl_3$).

*Preparation of (5R)-[(2-Methoxyethyloxy)methyloxy]-6-methyl-(2R)-heptanol (2R,5R-**10**)* : (a) H_2-PtO_2 Reduction : The allyl alcohol (2*R*,5*R*)-**8** (749 mg) in MeOH (60 ml) was hydrogenated (overnight) with prereduced (overnight) PtO_2 (108 mg). After PtO_2 was filtered off, the filtrate was chromatographed using AcOEt-hexane (20 : 80) to give (2*R*,5*R*)-**10** (254 mg, 34 %) and (5*S*)-[(2-methoxyethyloxy)-ethyloxy]-6-methylheptane (408 mg, 58 %).

(2*R*, 5*R*)-**10** : Colorless oil, $[\alpha]_D$+5.4°(c=1.03, $CHCl_3$). *Anal.* Calcd for $C_{12}H_{26}O_4$: C, 61.50 ; H, 11.18. Found : C, 61.00 ; H, 11.19. IR ν_{max} (neat) cm^{-1} : 3400, 1460, 1365, 1100, 1040, 980, 925. ^{1}H-NMR δ : 0.89, 0.91 (each 3H, d, J=6.5 Hz, 7-H_3, 8-H_3), 1.19 (3H, d, J=6 Hz, 1-H_3), 1.47-1.81 (4H, m, 3-H_2, 4-H_2), 1.86 (1H, qqd, J=6.5, 6.5, 5.5 Hz, 6-H), 3.39 (3H, s, OMEM), 3.57, 3.67, 3.82 (total 4H, m, OMEM), 3.79 (1H, m, 5-H), 4.75, 4.77 (each 1H, d, J=7 Hz, OMEM), ^{13}C-NMR δ : 17.9 (q), 18.4 (q), 23.5 (q), 26.9 (t), 30.9 (d), 35.0 (t), 59.1 (q), 67.3 (t), 68.1 (d), 71.9 (t), 83.2 (d), 95.4 (t). (2*S*,5*S*)-**10**: $[\alpha]_D$-7.0°(c=1.11, $CHCl_3$).

(5*S*)-[(2-Methoxyethyloxy)ethyloxy]-6-methylheptane : Colorless oil. IR ν_{max} (neat) cm^{-1} : 1470, 1385, 1365, 1100, 1040, 975, 930, 850. ^{1}H-NMR δ : 0.89, 0.90 (each 3H, d, J=7 Hz, 7-H_3, 8-H_3), 0.91 (3H, t, J=6.5 Hz, 1-H_3), 1.23-1.51 (6H, m, 2-H_2, 3-H_2, 4-H_2), 1.86 (1H, qqd, J=7, 6.5, 4.5 Hz, 6-H), 3.36 (1H, q, J=4.5 Hz, 5-H), 3.40 (3H, s, OMEM), 3.57, 3.82 (each 2H, m, OMEM), 4.77 (2H, s, OMEM).

(b) H_2-Pd/C Reduction : The allyl alcohol (2*R*,5*R*)-**8** (708 mg) in benzene (60 ml) was hydrogenated (overnight) with 5 % Pd/C (71 mg). After Pd/C was filtered off, the filtrate was chromatographed using AcOEt-hexane (20 : 80) to give (2*R*,5*R*)-**10** (460 mg, 64 %) and (5*S*)-[(2-methoxyethyloxy)ethyloxy]-6-methyl-2-heptanone (225 mg, 32 %).

(5*S*)-[(2-methoxyethyloxy)ethyloxy]-6-methyl-2-heptanone : Colorless oil. IR ν_{max} (neat) cm^{-1} : 1705, 1470, 1355, 1100, 1035. ^{1}H-NMR δ : 0.89, 0.91 (each 3H,

d, J=6.5 Hz, 7-H_3, 8-H_3), 1.61-1.72, 1.75-1.90 (total 3H, m, 4-H_2, 6-H), 2.15 (3H, s, 1-H_3), 2.50 (1H, ddd, J=17, 8.5, 6.5 Hz, 3-H), 2.57 (1H, ddd, J=17, 9, 5.5 Hz, 3-H), 3.33 (1H, ddd, J=8, 4.5, 3.5 Hz, 5-H), 3.39 (3H, s, OMEM), 3.56, 3.72 (each 2H, m, OMEM), 4.72 (2H, s, OMEM).

(c) Diimide Reducton : To a stirred solution of (2*R*,5*S*)-**8** (14.2 mg) in MeOH (0.3 ml), $N_2H_4 \cdot H_2O$ (0.89 ml), AcOH (0.44 ml), saturated $CuSO_4$ (0.49 ml) were added (under Ar). The mixture was maintained at 25°C while a solution of $NaIO_4$ (770 mg) in water (6 ml) was added dropwise (1 h). After cmpletion of the addition, stirring was continued (3 days). To the reaction mixture, the same amounts of $N_2H_4 \cdot H_2O$, AcOH, saturated $CuSO_4$, and $NaIO_4$ were added and the stirring was continued (3 days). After concentration *in vacuo,* the residue was dissolved in ether, washed (sat. NaCl aq.), dried (K_2CO_3), and concentrated. The residue was chromatographed with AcOEt-hexane (10 : 40) to give (2*R*,5*R*)-**10** (11.6 mg, 81 %).

Preparation of (5R)-[(2-Methoxyethyloxy)methyloxy]-6-methyl-(2S)-heptanol (2S,5R-11) : This was prepared from (2*S*,5*S*)-**9** in the same manner as the preparation of (2*R*,5*R*)-**10**. Colorless oil, $[\alpha]_D$+18.9°(c=1.03, $CHCl_3$). *Anal.* Calcd for $C_{12}H_{26}O_4$: C, 61.50 ; H, 11.18. Found : C, 61.02 ; H, 11.15. IR ν_{max} (neat) cm^{-1} : 3400, 1460, 1365, 1100, 1040, 980, 925. ^{1}H-NMR δ : 0.895, 0.902 (each 3H, d, J=7 Hz, 7-H_3, 8-H_3), 1.19 (3H, d, J=6 Hz, 1-H_3), 1.48-1.61 (4H, m, 3-H_2, 4-H_2), 1.86 (1H, qqd, J=7, 7, 5 Hz, 6-H), 3.37 (1H, m, 2-H), 3.39 (3H, s, OMEM), 3.57, 3.69, 3.79 (total 4H, m, OMEM), 3.81 (1H, m, 5-H), 4.75, 4.77 (each 1H, d, J=7Hz, OMEM). ^{13}C-NMR δ : 17.8 (q), 18.2 (q), 23.4 (q), 26.5 (t), 30.9 (d), 35.1 (t), 59.1 (q), 67.3 (t), 68.2 (d), 71.9 (t), 83.3 (d), 95.2 (t). (2*R*,5*S*)-**11** :$[\alpha]_D$−21.4°(c=1.15, $CHCl_3$).

Preparation of (2R)-Benzyloxy-(5R)-[(2-methoxyethyloxy)methyloxy]-6-methylheptane (2R,5R-12) : A mixture of NaH (containing ca. 60 % of mineral oil, 210 mg) and (2*R*,5*R*)-**10** (364 mg) in dry THF (6.3 ml) was stirred under Ar (0°C, 30 min). To the reaction mixture, benzyl bromide (BzlBr, 0.83 ml) and Bu_4NI (5.2 mg) were added and the stirring was continued (rt, overnight). The reaction mixture was poured over ice-cold sat. NH_4Cl aq. and extracted with ether. The ether layer was washed (sat. NaCl aq.), dried (K_2CO_3), and evaporated, and the residue was chromatographed using AcOEt-hexane (2 : 98) to give a benzyl ether (408 mg, 81 %) as a colorless oil, $[\alpha]_D$-10.9°(c=1.03, $CHCl_3$). *Anal.* Calcd for $C_{19}H_{32}O_4$: C, 70.33 ; H, 9.94. Found : C, 70.51 ; H, 10.10. IR ν_{max} (neat) cm^{-1} : 1455, 1365, 1100, 1040, 735, 695. ^{1}H-NMR δ : 0.887, 0.894 (each 3H, d, J=7 Hz, 7-H_3, 8-H_3), 1.20 (3H, d, J=6 Hz, 1-H_3), 1.39-1.68 (4H, m, 3-H_2, 4-H_2), 1.86 (1H, qqd, J=7, 7, 5 Hz, 6-H), 3.34 (1H, dt, J=6.5, 5 Hz, 5-H), 3.37 (3H, s, OMEM), 3.50 (1H, qdd, J=6, 6, 4 Hz, 2-H), 3.53, 3.72 (each 2H, m, OMEM), 4.46, 4.57 (each 1H, d, J=12 Hz, CH_2Ph), 4.74 (2H, s, OMEM), 7.23-7.37 (5H, m, CH_2Ph). ^{13}C-NMR δ : 17.9 (q), 18.2 (q), 19.7 (q), 26.5 (t), 30.8 (d), 32.6 (t), 59.0 (q), 67.1 (t), 70.3 (t), 71.8 (t), 75.2 (d), 83.0 (d), 95.0 (t), 127.4 (d), 127.6 (2C, d), 128.3 (2C, d), 136.3 (s). (2*S*,5*S*)-**12** : $[\alpha]_D$+13.6°(c=1.09, $CHCl_3$).

Preparation of (2S)-Benzyloxy-(5R)-[(2-methoxyethyloxy)methyloxy]-6-methylheptane (2S,5R-13) : This was prepared from (2*S*,5*R*)-**11** in the same manner as the preparation of (2*R*,5*R*)-**12**. Colorless oil, $[\alpha]_D$ +5.3°(c=1.20, $CHCl_3$). *Anal.* Calcd for $C_{19}H_{32}O_4$: C, 70.33 ; H, 9.94. Found : C, 70.59 ; H, 10.02. IR ν_{max} (neat) cm^{-1} : 1455, 1365, 1095, 1040, 730, 695. ^{1}H-NMR δ : 0.887, 0.890 (each 3H, d J=7 Hz, 7-H_3, 8-H_3), 1.20 (3H, d, J=6 Hz, 1-H_3), 1.42-1.73 (4H, m, 3-H_2, 4-H_2), 1.85 (1H, qdd, J=7, 7, 5 Hz, 6-H), 3.35 (1H, dt, J=7, 5 Hz, 5-H), 3.38 (3H, s, OMEM), 3.52 (1H, m, 2-H), 3.53, 3.72 (each 2H, m, OMEM), 4.45, 4.56 (each 1H, d, J=12 Hz, CH_2Ph), 4.74 (2H, s, OMEM), 7.23-7.37 (5H, m, CH_2Ph). ^{13}C-NMR δ : 18.0 (q), 18.1 (q), 19.6 (q), 26.1 (t), 30.8 (d), 32.2 (t), 59.0 (q), 67.1 (t), 70.3 (t), 71.8 (t), 74.7 (d), 82.6 (d), 95.0 (t), 127.4 (2C, d), 127.6 (d), 128.3 (2C, d), 139.1 (s). (2*R*,5*S*)-**13** : $[\alpha]_D$−9.7°(c=1.00, $CHCl_3$).

Preparation of (2R)-Benzyloxy-6-methyl-(5R)-heptanol (2R,5R-14) : A solution of (2*R*,5*R*)-**12** (466 mg) and *para*-toluensulfonic acid (*p*-TsOH, 847 mg) in EtOH (26 ml) was refluxed under Ar (1 h). After concentration, the reaction mixture was dissolved in CH_2Cl_2, washed (water, sat. $NaHCO_3$ aq., sat. NaCl aq.), dried ($MgSO_4$), and evaporated. The residue was chromatographed using AcOEt-hexane (3 : 97) to give (2*R*,5*R*)-**14** (316 mg, 93 %) as a colorless oil, $[\alpha]_D$ −8.3°(c=0.75, $CHCl_3$). *Anal.* Calcd for $C_{15}H_{24}O_2$: C, 76.22 ; H, 10.24. Found : C, 76.09 ; H, 10.51. IR ν_{max} (neat) cm^{-1} : 3350, 1450, 1370, 1055, 735, 695. ^{1}H-NMR δ :

0.906, 0.911 (each 3H, d, J=7Hz, 7-H_3, 8-H_3), 1.22 (3H, d, J=6 Hz, 1-H_3), 1.35-1.67 (4H, m, 3-H_2, 4-H_2), 1.71 (1H, qdd, J=7, 7, 5 Hz, 6-H), 3.33 (1H, ddd, J=9, 5, 2.5 Hz, 5-H), 3.57 (1H, qdd, J=6, 6, 4.5 Hz, 2-H), 4.46, 4.59 (each 1H, d, J=11.5 Hz, C$\underline{H_2}$Ph), 7.24-7.39 (5H, m, $CH_2\underline{Ph}$). ^{13}C-NMR δ: 17.4 (q), 18.9 (q), 19.5 (q), 30.1 (t), 33.2 (t), 33.6 (d), 70.4 (t), 75.1 (d), 76.7 (d), 127.5 (d), 127.8 (2C, d), 128.4 (2C, d), 138.8 (s). (2*S*,5*S*)-**14** : $[\alpha]_D$+9.4°(c=0.97, $CHCl_3$).

Preparation of (2S)-Benzyloxy-6-methyl-(5R)-heptanol (2S,5R-15) : This was prepared from (2*S*,5*R*)-**13** in the same manner as the preparation of (2*R*,5*R*)-**14**. Colorless oil, $[\alpha]_D$+22.9°(c=1.00, $CHCl_3$). IR ν_{max} (neat) cm^{-1} : 3400, 1455, 1370, 1055, 735, 695. ^{1}H-NMR δ : 0.903, 0.905 (each 3H, d, J=7 Hz, 7-H_3, 8-H_3), 1.21 (3H, d, J=6 Hz, 1-H_3), 1.38-1.74 (4H, m, 3-H_2, 4-H_2), 1.74 (1H, qqd, J=7, 7, 2.5 Hz, 6-H), 3.32 (1H, ddd, J=9, 5, 2.5 Hz, 5-H), 3.55 (1H, qdd, J=6, 6, 4.5 Hz, 2-H), 4.45, 4.59 (each 1H, d, J=12 Hz, C$\underline{H_2}$Ph), 7.24-7.37 (5H, m, $CH_2\underline{Ph}$). ^{13}C-NMR δ : 17.3 (q), 18.8 (q), 19.5 (q), 29.9 (t), 33.1 (t), 33.6 (d), 70.3 (t), 74.8 (d), 76.6 (d), 127.5 (d), 127.8 (2C, d), 128.4 (2C, d), 138.8 (s). (2*R*,5*S*)-**15** : $[\alpha]_D$-35.3°(c=0.93, $CHCl_3$).

Preparation of (2R,5R)-Musclide-A1 (2R,5R-1) : To a solution of (2*R*,5*R*)-**14** (35.7 mg) in dry pyridine (333 μl), a solution of $ClSO_3H$ (15 μl) in dry $CHCl_3$ (79 μl) was added dropwise at 0°C. After stirring (0°C, 10 min), the reaction mixture was subjected to preparative TLC using AcOEt-acetone-MeOH (20 : 20 : 1) to give a sulfate (41.8 mg). The sulfate in MeOH (4 ml) was hydrogenated (overnight) with 10 % Pd/C (9.3 mg). After filtration followed by evaporation, the residue was subjected to preparative TLC using AcOEt-acetone-MeOH-H_2O (10 : 10 : 1 : 0.7) to give (2*R*,5*R*)-musclide-A1 (19.8 mg, 58 %) as a colorless amorphous powder, $[\alpha]_D$-2.1°(c=1.09, MeOH). IR ν_{max} (KBr) cm^{-1} : 3350, 1450, 1370, 1200-1250, 1050, 970, 905, 830, 805. ^{1}H-NMR (CD_3OD) δ : 0.94, 0.95 (each 3H, d, J=6.5 Hz, 7-H_3, 8-H_3), 1.16 (3H, d, J=6 Hz, 1-H_3), 1.45-1.67, 1.72-1.83 (total 4H, m, 3-H_2, 4-H_2), 2.07 (1H, qqd, J=6.5, 6.5, 5 Hz, 6-H), 3.72 (1H, qt, J=6, 5 Hz, 2-H), 4.16 (1H, dt, J=6.5, 5 Hz, 5-H). ^{13}C-NMR (CD_3OD) δ : 18.8 (q), 19.1 (q), 24.3 (q), 28.6 (t), 33.0 (d), 36.7 (t), 69.7 (d), 86.4 (d). (2*S*,5*S*)-Musclide-A1 (2*S*,5*S*-**1**) : $[\alpha]_D$+2.1°(c=0.90, MeOH).

Preparation of (2S,5R)-Musclide-A1 (2S,5R-1) : This was prepared from (2*S*,5*R*)-**15** in the same manner as the preparation of (2*R*,5*R*)-musclide-A1 (2*R*,5*R*-**1**). Colorless amorphous powder, $[\alpha]_D$+1.2° (c=1.31, MeOH). IR ν_{max} (KBr) cm^{-1} : 3400, 1470, 1380, 1200-1250, 1060, 980, 935, 830, 810. ^{1}H-NMR (CD_3OD) δ : 0.94, 0.95 (each 3H, d, J=6.5 Hz, 7-H_3, 8-H_3), 1.16

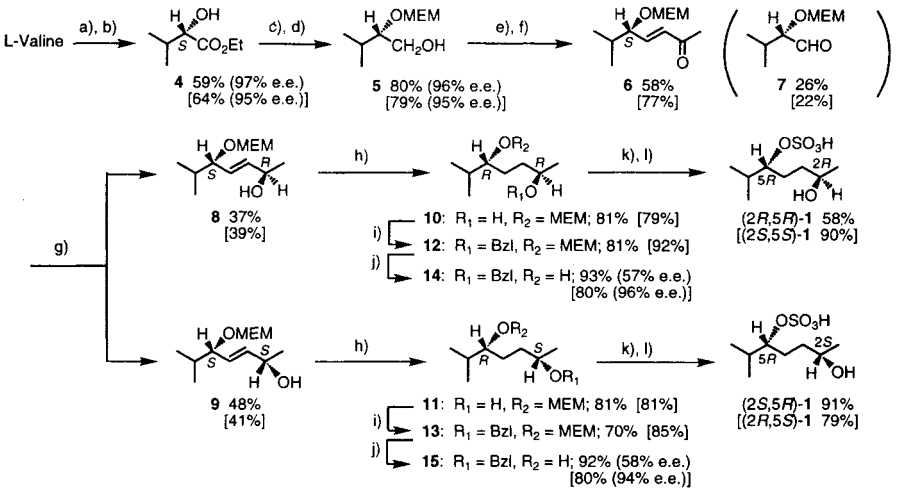

Fig. 2 Synthetic procedure of musclide-A1 diastereomers.
a) $NaNO_2$, c. H_2SO_4 ; b) EtOH, c. HCl ; c) NaH, MEM-Cl ; d) LAH ; e) DMSO, $(COCl)_2$, Et_3N ; f) Ph_3P=$CHCOCH_3$; g) $NaBH_4$; h) $N_2H_4 \cdot H_2O$, $NaIO_4$; i) NaH, Bzl-Br, Bu_4NI ; j) p-TsOH ; k) $ClSO_3H$; l) H_2, Pd/C.
The % values mean the yields, and enantiomer's yields are presented in parentheses. The e.e. values were obtained from the intensity ratio of the ^{1}H-NMR spectrum of (*R*)-MTPA esters.

(3H, d, J = 6 Hz, 1-H_3), 1.56, 1.69 (each 2H, m, 3-H_2, 4-H_2), 2.06 (1H, qqd, J=6.5, 6.5, 6 Hz, 6-H), 3.75 (1H, tq, J = 6.5, 6 Hz, 2-H), 4.18 (1H, q, J = 6 Hz, 5-H). ^{13}C-NMR (CD_3OD) δ : 18.9 (q), 19.2 (q), 24.3 (q), 28.2 (t), 32.8 (d), 36.1 (t), 69.2 (d), 86.0 (d). (2*R*,5*S*)-Musclide-A1 (2*R*,5*S*-**1**) : $[\alpha]_D$ −2.1° (c=0.90, MeOH).

Results and Discussion

Musclide-A1 (**1**) has the structure, one methylene less than musclide-B (**3**) prepared from D-leucine, and thus its synthesis is considered to be possible by the similar procedure to that of **3**, by using valine as a starting material (Fig. 2). First, we prepared (2*R*,5*R*)- and (2*S*,5*R*)-musclide-A1 from L-valine. Thus, (*S*)-ethyl valate [**4**, 97 % enantiomeric excess (e.e.)], prepared from L-valine by diazotization with sodium nitrite ($NaNO_2$) and concentrated sulfuric acid (H_2SO_4),[13] was transformed to MEM ether and then reduced with excess LAH to give an alcohol **5** in 80 % yield with 96 % e.e. The carbon chain of the alcohol **5** was elongated by Swern oxidation followed *in situ* Wittig olefination with acetylmethylenetriphenylphosphorane to give an α,β-unsaturated ketone **6** in 58 % yield together with 26 % of an aldehyde **7**. The α,β-unsaturated ketone **6** contains all carbon atoms present in musclide-A1, and thus the synthesis was focused on the modification of the functional groups. Then, the α,β-unsaturated ketone **6** was reduced to epimeric alcohols, **8** and **9**, with sodium borohydride ($NaBH_4$) in 37 % and 48 % yields, respectively, the C-2 configuration of which was determined by Mosher's method.[15] As can be seen in Fig. 3, the methyl protons (1-H_3) of (*R*)-α-methoxy-α-trifluoromethylphenylacetic acid (MTPA) ester of **8** resonated at higher field (δ 1.36) than those of (*R*)-MTPA ester of **9** (δ 1.42), due to shielding effect of the phenyl group of MTPA. On the other hand, the olefinic protons (3-H, 4-H) of (*R*)-MTPA ester of **8** appeared at lower field (δ 5.70, 5.65) than those of (*R*)-MTPA ester of **9** (δ 5.62, 5.53). Thus, the configuration at C-2 of **8** and **9** was determined to be *R* and *S*, respectively, which was confirmed by the advanced Mosher's method of Ohtani *et al.*; instead of the data for (*S*)-MTPA ester, data for (*R*)-MTPA ester of the corresponding enantiomer was used because they have the same chemical shift values.[16]

Although we could not selectively get the alcohol, **8** or **9**, each alcohol could be separated easily by column chromatography. The allyl alcohol, **8** or **9**, separated from the mixture, was hydrogenated with PtO_2, in the same procedure as the preparation of musclide-B isomers (**3**).[12] The hydrogenation of **8**, however, gave the desired saturated alcohol **10** in only

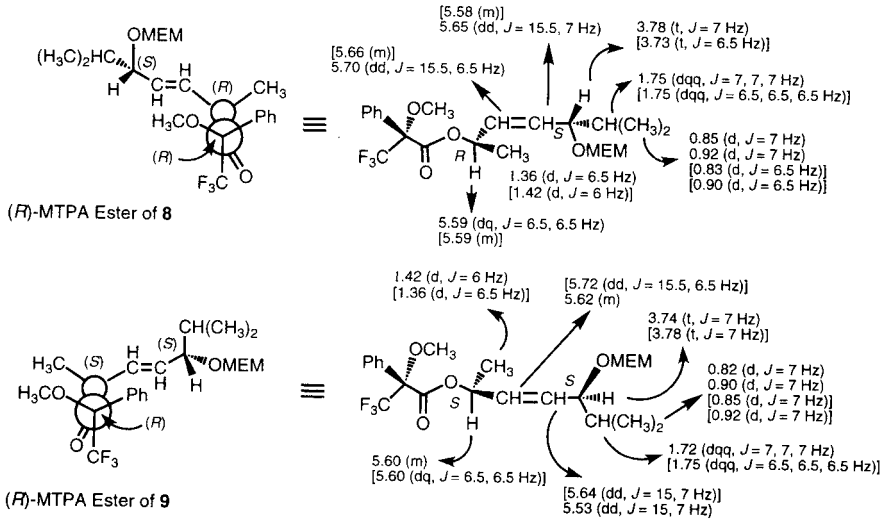

Fig. 3 Chemical shifts of (*R*)-MTPA esters of **8** and **9**.
[ ] : Values of the (*R*)-MTPA esters of enantiomers of **8** and **9**.

34 % yield and (5*S*)-[(2-methoxyethyloxy)ethyloxy]-6-methylheptane, due to hydrogenolysis, was produced in 54 % yield, while the hydrogenation of **9** yielded the desired alcohol **11** and the hydrogenolysis product in 76 % and 21 % yield, respectively. On the other hand, using 5 % Pd/C as a catalyst, **8** produced (5*S*)-[(2-methoxyethyloxy)ethyloxy]-6-methyl-2-heptanone, due to olefin migration, in 32 % yield together with the desired **11** (64 %), and **9** gave the olefin migration product and the desired **12** in 61 % and 34 % yield, respectively. The hydrogenolysis or olefin migration could be avoided by using diimide reduction ($N_2H_4 \cdot H_2O$, $NaIO_4$),[17,18] but the reduction needed long reaction time (6 days).

The saturated alcohol, **10** or **11**, was benzylated with benzyl bromide (Bzl-Br), sodium hydride (NaH), and tetrabutylammonium iodide (Bu_4NI),[19] followed hydrolysis of MEM ether with *para*-toluensulfonic acid (*p*-TsOH) to give an alcohol, **14** (57 % e.e.) or **15** (58 % e.e.). These low e.e. values were due to a partial racemization of the aldehyde **7** ($[\alpha]_D$ −27.0°, $CHCl_3$) ; in fact, on the synthesis of (2*S*,5*S*)- and (2*R*,5*S*)-musclide-A1 from D-valine, the $[\alpha]_D$ value of **7** was +46.1°($CHCl_3$) and the e.e. values for **14** and **15** were 96 % and 94 %, respectively. Sulfation of the alcohol, **14** or **15**, was done with chlorsulfonic acid ($ClSO_3H$) in dry chloroform ($CHCl_3$),[20] and the sulfate was debenzylated with 10 % Pd/C to give (2*R*,5*R*)-musclide-A1 and (2*S*,5*R*)-musclide-A1 (**1**). In the same manner, their enantiomers, (2*S*,5*S*)-musclide-A1 and (2*R*,5*S*)-musclide-A1, were also prepared from D-leucine.

Previously, optically active form of **14** and **15** had been synthesized, transformed to dicarbamates, and compared with the dicarbamate prepared from natural musclide-A1,[11] and a comparison by high performance liquid chromatography (HPLC) with a chiral column had led to the conclusion that the natural musclide-A1 was a mixture of (2*R*,5*R*)-**1** and (2*R*,5*S*)-**1**. The (2*R*,5*R*)-**14** and (2*R*,5*S*)-**15** obtained in this study showed the same spectral data as those of the previously synthesized (2*R*,5*R*)-**14** and (2*R*,5*S*)-**15**, which had been used for the determanation of the absolute stereochemistry of natural musclide-A1. Moreover, the newly synthesized (2*R*,5*R*)- and (2*R*,5*S*)-musclide-A1 (**1**) revealed the same spectral data, except optical rotation values, as the previously synthesized (2*R*,5*R*)- and (2*R*,5*S*)-musclide-A1 (**1**) and also of natural musclide-A1. Thus, the absolute configuration suggested previously has been confirmed ; *i.e.*, natural musclide-A1 is a mixture of (2*R*,5*R*)-**1** and (2*R*,5*S*)-**1**.

Conclusions

We synthesized all stereoisomers of musclide-A1 from L- or D-valine and confirmed the previously suggested absolute stereochemistry of musclide-A1 ; *i.e.*, a diastereomeric mixture of (2*R*,5*R*)-**1** and (2*R*,5*S*)-**1**. Kimura *et al.* reported that, among musclides, (2*R*,5*R*)-musclide-A1 activated protein kinase C most strongly.[21] However more detailed examination of the activity could not be done because the amounts obtained were little. The detailed pharmacological study using the synthetic samples is now under investigation and will be reported elsewhere.

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和文抄録

麝香から単離したムスクライドA1の構造を決定するために，L-バリンから (2*R*,5*R*)-ムスクライドA1及び (2*S*,5*R*)-ムスクライドA1を合成し，それらのジアステレオマーをD-バリンから合成した。合成品のスペクトルデータと天然ムスクライドA1のデータを比較することによって，以前に提出した構造，すなわち，天然ムスクライドA1が (2*R*)-hydroxy-6-methyl-(5*R*)-heptyl hydrogen sulfate 及び (2*R*)-hydroxy-6-methyl-(5*S*)-heptyl hydrogen sulfate の混合物であること，を確定した。

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