Optical Resolution of 3-(Silyloxy)glutaric Acid Half Esters and Their Utilization for Enantioconvergent Synthesis of a HMG-CoA Reductase Inhibitor

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Useful chiral synthons, (3*R*)- and (3*S*)-[(*tert*-butyldimethylsilyl)oxy]pentanedioic acid monomethyl ester, (*R*)-**1** and (*S*)-**1**, were obtained by optical resolution of a racemic mixture of **1**. Sulfoxide **8** has been developed from (*S*)-**1** as a new building block for preparing HMG-CoA reductase inhibitors. Two alternate chiral synthons **2** and **8**, synthesized from (*R*)-**1** and (*S*)-**1**, respectively, were employed for enantioconvergent synthesis of potent inhibitor **15** containing a pyrrole moiety.

Introduction

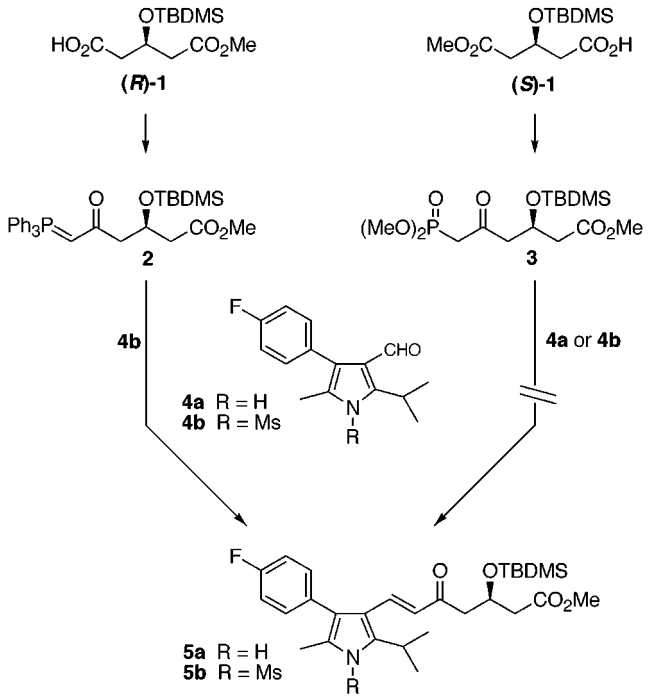
Success with three HMG-CoA reductase (HMGR) inhibitors for treating hypercholesterolemia,[1] lovastatin, pravastatin, and simvastatin, led to a surge in novel HMGR inhibitors[2] that are more potent and synthesized by simple chemical processes. A number of synthetic approaches[3,4] have been reported for the preparation of HMGR inhibitors, and two useful chiral synthons[5−7] have been developed for their synthesis.

We previously reported[7] a practical synthesis of enantiomerically pure 3-[(*tert*-butyldimethylsilyl)oxy]pentanedioic acid monomethyl ester in either of these enantiomeric forms by desymmetrization of 3-[(*tert*-butyldimethylsilyl)oxy]pentanedioic anhydride by means of chiral benzyl mandelate. Two chiral synthons for HMG-CoA reductase inhibitors, Wittig reagent **2** and Horner−Wadsworth−Emmons (HWE)-type synthon **3**, were derived from these chiral half esters, and Wittig reagent **2** was converted to pyrrole-containing potent HMGR inhibitor **15**[8] by way of **5b** (Scheme 1). The desymmetrization approach was also employed for synthesis of (+)-6-*epi*-mevinolin.[4]

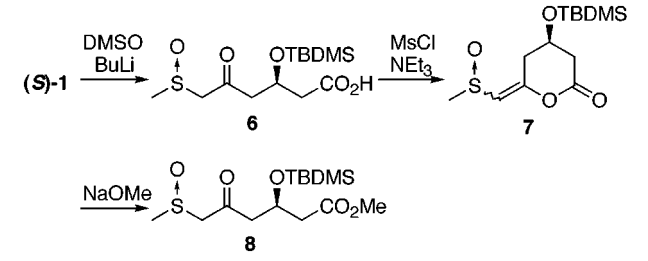
Results and Discussion

To supply a large amount of drug candidate **15** (Scheme 3) for biological evaluation, the sequence of the synthesis was optimized from an economical point of view. This led us to develop an optical resolution method for racemic monomethyl ester **1**[9] by salt formation of **1** with enantiopure amines, which is more practical and less expensive than the desymmetrization methods.[5−7] Racemic **1** was prepared from dimethyl acetonedicarboxylate in three steps. Sodium borohydride reduction, TBDMS protection, and subsequent partial hydrolysis of methyl ester gave **1** in 72% yield. Optical resolution was

Scheme 1



Scheme 2



(1) For reviews, see: Endo, A. *J. Med. Chem.* **1985**, *28*, 401. Endo, A.; Hasumi, K. *Nat. Prod. Rep.* **1993**, *10*, 541.

(2) Connolly, P. J.; Westin, C. D.; Loughney, D. A.; Minor, L. K. *J. Med. Chem.* **1993**, *36*, 3674 and references therein.

(3) For a review on synthetic work, see: Chapleur, Y. The Chemistry and Total Synthesis of Mevinic Acids. In *Recent Progress in the Chemistry of Antibiotics*; Lukacs, G., Ueno, S., Eds.; Springer: New York, 1993; Vol. 2; pp 829−937.

(4) Araki, Y.; Konoike, T. *J. Org. Chem.* **1997**, *62*, 5299.

(5) Theisen, P. D.; Heathcock, C. H. *J. Org. Chem.* **1993**, *58*, 142 and references therein.

(6) Karanewsky, D. S.; Malley, M. F.; Gougoutas, J. Z. *J. Org. Chem.* **1991**, *56*, 3744.

(7) Konoike, T.; Araki, Y. *J. Org. Chem.* **1994**, *59*, 7849.

(8) (a) Watanabe, M.; Koike, H.; Ishiba, T.; Okada, T.; Seo, S.; Hirai, K. *Bioorg. Med. Chem.* **1997**, *5*, 437. (b) Hirai, K.; Ishiba, T.; Koike, H.; Watanabe, M. European Application EP-A-0464845, 1992; *Chem. Abstr.* **1992**, *116*, 173999z. (c) Hirai, K.; Ishiba, T.; Koike, H.; Watanabe, M. Jpn. Kokai Tokkyo Koho JP 04-352767 [92-352767], 1992.

(9) Hirai, K.; Okada, T. Jpn. Kokai Tokkyo Koho JP 05-32680 [93-32680], 1993; *Chem. Abstr.* **1993**, *119*, 138753e.

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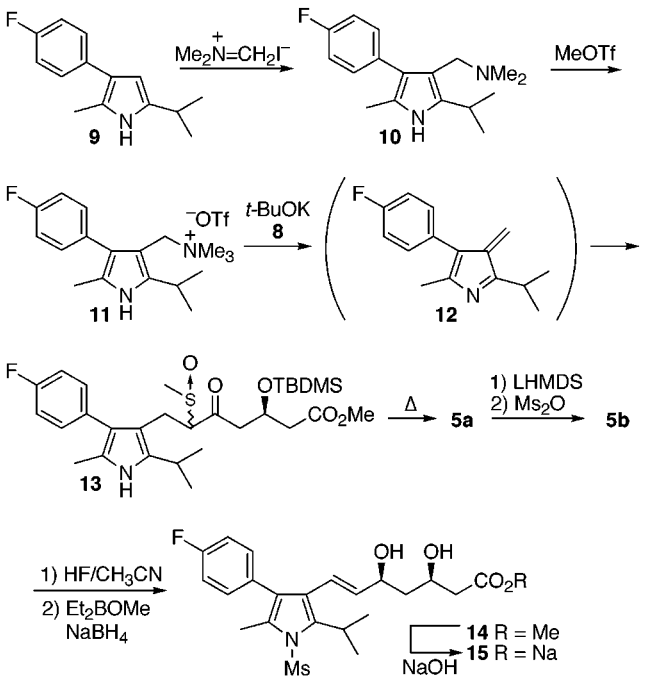
Scheme 3



achieved as follows. Racemic **1** was treated with an equimolar amount of (+)-dehydroabietylamine, and the (+)-dehydroabietylamine salt of (*R*)-**1** was obtained as a crystalline powder in 43% yield (>96% ee). The mother liquor was acidified to remove (+)-dehydroabietylamine, and the resulting (*S*)-rich **1** was treated with an equimolar amount of (*S*)-(−)-1-phenethylamine to give a salt of (*S*)-**1** and (*S*)-(−)-1-phenethylamine in 46% yield (98% ee). Acidic treatment of the salts of (*R*)- and (*S*)-**1** followed by chromatographic purification afforded (*R*)-**1** and (*S*)-**1** of high optical purity. This separation process was optimized in cooperation with Ube Industries, Ltd., and both (*R*)-**1** and (*S*)-**1** are now commercially available.[10]

Each enantiomer was successfully converted to chiral synthon **2** or **3**[5,6,11] (Scheme 1) as shown in our previous paper.[7] Each chiral synthon was considered to undergo olefination with a suitable aldehyde to give an optically pure hydroxy heptenoate moiety such as **5a** or **5b**, which would be a precursor of HMGR inhibitor **15**. Wittig reagent **2** underwent condensation with *N*-(methanesulfonyl) pyrrole aldehyde **4b** (methanesulfonyl = mesyl) to give unsaturated ketone **5b**.[7] However, HWE reagent **3** did not condense with either pyrrole aldehyde **4a** or **4b** under various conditions. Pyrrole **4a** was recovered unchanged, while **4b** was hydrolyzed to the parent pyrrole **4a** in most cases employing a variety of bases. These results led to the conclusion that only one enantiomer (*R*)-**1** could contribute to the synthesis of pyrrole-containing HMGR inhibitor **15**, and the other (*S*)-**1** is useless unless it can be converted to (*R*)-**1** or another chiral synthon for **15**. To fully utilize both enatiomeric forms of **1** obtained by optical resolution, we developed a novel chiral synthon, sulfoxide **8**,[12] from (*S*)-**1**. We describe herein the preparation of sulfoxide **8** derived from (*S*)-**1** and its application for the synthesis of HMGR inhibitor **15**.

Novel chiral synthon **8** was developed from (*S*)-**1** in a similar way to that of HWE reagent **3** (Scheme 2). Enantioenriched (*S*)-**1** (98% ee) was treated with an excess of lithium anion of DMSO to give a diastereomeric mixture (1:1) of hexanoic acid **6**, whose additional chiral center was derived from the sulfoxide. Diazomethane treatment of **6** led to methyl ester **8**, although this was a drawback to large-scale preparation. Therefore, we developed an alternative way to obtain enantiopure **8** via cyclic enol lactone **7**, which is safe and applicable for large-scale preparation. Hexanoic acid **6** was converted to enol lactone **7** by treatment with methanesulfonyl chloride and triethylamine. Three isomers of **7** were detected by ^{1}H NMR. Subsequent lactone cleavage by sodium methoxide in methanol gave a mixture of diastereomeric methyl ester **8**.

Our synthesis of HMGR inhibitor **15** from sulfoxide **8** was accomplished by a judicious choice of a pyrrole counterpart (Scheme 3). After several unsuccessful attempts to condense **8** with pyrroles that have reactive functional groups at the 3-position such as the chloromethyl group, we finally obtained Mannich base **10**.[13] [(Dimethylamino)methyl]pyrrole **10** was prepared from **9**[14] using Eschenmoser's salt;[15] however, this gramine-type intermediate did not undergo condensation with **8**. Methylation of **10** by methyl triflate gave quaternary ammonium salt **11**, which in turn showed effective condensation with **8**. Treatment of activated species **11** and **8** with *t*-BuOK afforded a diastereomeric mixture of condensed product **13** in a good yield, presumably via the intermediate enimine **12**. The diastereomeric mixture of **13** underwent thermal sulfenate elimination to exclusively give (*E*)-heptenoic acid methyl ester **5a** (98% ee).[16] This was mesylated to **5b** and further converted to syn dihydroxy methyl ester **14** by the conventional pathway of deprotection and stereoselective hydride reduction. Sodium salt **15** was prepared from **14** by ester hydrolysis for biological evaluation.

In conclusion, we were able to achieve optical resolution of racemic **1**, and both enantiomers (*R*)-**1** and (*S*)-**1** were obtained with high optical purity from the racemate in high yield. Enantioenriched **1** is a versatile chiral building block, and one example of its synthetic application is the enantioconvergent synthesis of HMGR inhibitor **15**. Each enantiomeric **1** was converted to a chiral synthon for HMGR inhibitor, Wittig reagent **2**, and sulfoxide **8**, from which a single enantiomeric HMGR inhibitor **15** can be prepared.

Experimental Section

General Methods. Reactions were carried out under a nitrogen atmosphere in anhydrous solvents (dried over molecular sieves type 4A). Organic extracts were dried over anhydrous $MgSO_4$. Solvent removal was accomplished at aspirator pressure using a rotary evaporator. TLC was

(10) Both enantiomers (99% ee) are now available through the cooperation of Shionogi & Co., Ltd. and Ube Industries, Ltd. For samples of (*R*)-**1** and (*S*)-**1**, send inquiries to T. Hashimoto at Ube Industries, Ltd., 2-3-11, Higashi-Shinagawa, Shinagawa-ku, Tokyo 140, Japan.

(11) Okada, T.; Konoike, T. Jpn. Kokai Tokkyo Koho JP 07-118233 [95-118233], 1995; *Chem. Abstr.* **1995**, *123*, 286068h.

(12) A part of this work has been published in the patent. Konoike, T.; Araki, Y. PCT Int. Appl., WO 92/22560, 1992; *Chem. Abstr.* **1993**, *119*, 95827n.

(13) Kozikowski, A. P.; Ishida, H. *Heterocycles* **1980**, *14*, 55.

(14) Pyrrole **9** was prepared by a slight modification of Watanabe's method[8a] using 3-methyl-2-butanone instead of ethyl 4-methyl-3-oxoheptanoate as a starting material.

(15) Schreiber, J.; Maag, H.; Hashimoto, N.; Eschenmoser, A. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 330.

(16) Enatiomeric excess was determined by HPLC; see ref 8.

performed with Merck precoated TLC plates silica gel 60 F_{254}, and compound visualization was effected with 10% H_2SO_4 containing 5% of ammonium molybdate and 0.2% of ceric sulfate. Gravity chromatography was done with Merck silica gel 60 (70−230 mesh). Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were determined as $CDCl_3$ solutions at 200 and 50.3 MHz, unless specified otherwise. *J* values are given in hertz. High-resolution mass spectra (HR-LSIMS) were recorded on a Hitachi M-90 instrument.

Optical Resolution of 1. Racemic **1** was treated with an equimolar amount of (+)-dehydroabietylamine in methanol, and the solvent was evaporated. The residue was dissolved in pentane and stored at 0 °C overnight. Crystals were collected, and the complex of (*R*)-**1** and (+)-dehydroabietylamine was obtained in 43% yield (>96% ee). The mother liquor was concentrated, dissolved in Et_2O, and treated with 4 N HCl/EtOAc. The insoluble materials were filtered, and the filtrate was concentrated and purified by silica gel chromatography to give (*S*)-rich **1** (93% ee). This compound was dissolved in Et_2O and treated with an equimolar amount of (*S*)-(−)-1-phenethylamine. Pentane was added, and the mixture was stored at room temperature for 1 h. Crystals were collected, and the complex of (*S*)-**1** and (*S*)-(−)-1-phenethylamine was obtained in 46% yield (98% ee). Acidic treatment of both amine complexes gave crude half esters, and further chromatographic purification afforded (*R*)-**1** and (*S*)-**1**, respectively.

(3*R*)-[(*tert*-Butyldimethylsilyl)oxy]-6-(methanesulfinyl)-5-oxohexanoic Acid (6). To a solution of DMSO (7.66 mL, 108 mmol) in THF (120 mL) was added BuLi (65.4 mL of 1.56 M hexane solution, 102 mmol) dropwise at −30 °C. The mixture was stirred at 2 °C for 40 min, and after being cooled to −66 °C, (*S*)-**1** (8.29 g, 30 mmol) in THF (60 mL) was added dropwise over 10 min. The mixture was stirred at −30 °C for 45 min and then poured into ice and 1 N HCl (110 mL). The mixture was extracted with EtOAc (2 × 300 mL), and the organic phase was washed with brine (4 × 200 mL), dried, and concentrated to give a 1:1 diastereomeric mixture of acid **6** (9.87 g, quant): IR ($CHCl_3$) 3507, 1714 cm^{-1}; ^{1}H NMR δ 0.08 (s, 3), 0.10 (s, 3), 0.85 (s, 9), 2.56 (d, 2, J = 6.0), 2.73 (s, 1.5), 2.74 (s, 1.5), 2.88 (dd, 1, J = 6.0, 16.8), 2.93 (dd, 1, J = 6.0, 16.8), 3.8−4.0 (m, 2), 4.57 (quintet, 1, J = 6.6); ^{13}C NMR δ −4.8, −4.8, 17.9, 25.7, 38.6, 41.7, 51.8, 51.8, 64.5, 64.6, 65.1, 65.2, 174.4, 174.4, 200.6, 200.8; TLC (EtOAc/AcOH/H_2O = 30/1/1) R_f 0.35.

(4*R*)-[(*tert*-Butyldimethylsilyl)oxy]-6-[(methanesulfinyl)methylene]tetrahydropyran-2-one (7). To a solution of crude acid **6** (9.87 g, 30 mmol) in CH_2Cl_2 (100 mL) was added triethylamine (10.0 mL, 72 mmol) dropwise over 10 min followed by MsCl (2.79 mmol, 36 mmol) also added dropwise over 10 min at 0 °C. The cooling bath was then removed, and the reaction mixture was warmed to 15 °C over 15 min. Stirring was continued at that temperature for 30 min. The mixture was poured into ice and 1 N HCl and extracted twice with EtOAc. Each organic phase was washed with saturated $NaHCO_3$ and brine, dried, and concentrated. The resulting orange solid was crystallized from $CHCl_3$ (10 mL)−hexane (300 mL) to give **7** (6.50 g, 74% yield) as orange crystals: mp 99−100 °C; IR ($CHCl_3$) 1783, 1650 cm^{-1}; ^{1}H NMR δ 0.09 (s, 3), 0.10 (s, 3), 0.86 (s, 4.5), 0.88 (s, 4.5), 2.68 (s, 1.5), 2.70 (s, 1.5), 2.6−2.7 (m, 3), 2.7−2.8 (m, 2), 4.2−4.4 (m, 1), 5.5−5.6 (m, 1); ^{13}C NMR δ −4.9, −4.8, 18.0, 25.5, 25.6, 35.7, 35.8, 39.6, 39.7, 40.9, 40.9, 62.4, 62.5, 117.2, 117.4, 152.2, 152.8, 163.9; TLC ($CHCl_3$/MeOH = 10/1) R_f 0.39 and 0.43. Anal. Calcd for $C_{13}H_{24}O_4SSi$: C, 51.28; H, 7.95. Found: C, 51.22; H, 8.02.

(3*R*)-[(*tert*-Butyldimethylsilyl)oxy]-6-(methanesulfinyl)-5-oxohexanoic Acid Methyl Ester (8). To a solution of **7** (6.27 g, 20.6 mmol) in MeOH (60 mL) was added NaOMe (4.12 mL of 1 N MeOH solution, 4.12 mmol) dropwise over 2 min at 0 °C. After 30 min, the reaction mixture was poured into ice and 1 N HCl (10 mL), saturated with NaCl, and extracted with EtOAc (2 × 300 mL). Each organic layer was washed with brine (3 × 50 mL), dried, and concentrated. The residual oil was purified by silica gel chromatography ($CHCl_3$/MeOH = 50/1 to 10/1) to give **8** (6.77 g, 98% yield): IR ($CHCl_3$) 2954, 1731 cm^{-1}; ^{1}H NMR δ 0.07 (s, 3), 0.08 (s, 3), 0.85 (s, 9), 2.5−2.6 (m, 2), 2.69 (s, 3), 2.89 (t, 2, J = 5.4), 3.67 (s, 3), 3.75 (dd, 1, J = 5.1, 14.1), 3.85 (dd, 1, J = 6.6, 14.1), 4.5−4.6 (m, 1); ^{13}C NMR δ −4.9, −4.8, 17.9, 25.7, 39.1, 42.0, 42.0, 51.6, 52.1, 52.2, 65.1, 65.1, 65.2, 65.3, 171.2, 200.6, 200.8; TLC ($CHCl_3$/MeOH = 10/1) R_f 0.46. Anal. Calcd for $C_{14}H_{28}O_5SSi\cdot0.3H_2O$: C, 49.28; H, 8.43; S, 9.38. Found: C, 49.21; H, 8.20; S, 9.33.

[[4-(4-Fluorophenyl)-2-isopropyl-5-methyl-1*H*-pyrrol-3-yl]methyl]dimethylamine (10). To a solution of **9** (22.2 g, 102 mmol) in CH_2Cl_2 (200 mL) was added Eschenmoser's salt (18.9 g, 102 mmol) in one portion at room temperature. The mixture was refluxed for 1 h and quenched with H_2O. The aqueous NaOH was added, and the mixture was extracted with CH_2Cl_2. The organic phase was separated, washed with brine, dried, and concentrated. Obtained crude **10** was sufficiently pure and used without purification for the next step. Analytically pure sample was obtained by chromatography on neutral alumina (EtOAc/hexane = 1/4) and crystallization from cold hexane gave **10**: mp 87−89 °C; IR ($CHCl_3$) 3465, 2965, 1505 cm^{-1}; ^{1}H NMR δ 1.25 (d, 6, J = 7.0), 2.13 (s, 6), 2.23 (s, 3), 3.14 (s, 2), 3.19 (quintet, 1, J = 7.0), 7.03 (dd, 2, J = 9.0, 9.0), 7.43 (dd, 2, J = 6.0, 9.0), 7.58 (br s, 1); ^{13}C NMR δ 12.0, 23.2, 25.1, 44.8, 53.1, 113.2, 114.6 (J = 21.4), 121.4 (J = 55.1), 131.7 (J = 7.6), 132.8 (J = 2.9), 158.9, 161.1 (J = 244); TLC ($CHCl_3$/MeOH = 3/1) R_f 0.10. Anal. Calcd for $C_{17}H_{23}N_2F\cdot0.3H_2O$: C, 72.98; H, 8.50; N, 10.01; F, 6.79. Found: C, 72.95; H, 8.36; N, 9.90; F, 6.84.

[[4-(4-Fluorophenyl)-2-isopropyl-5-methyl-1*H*-pyrrol-3-yl]methyl]trimethylammonium Trifluoromethanesulfonate (11). To a solution of amine **10** (2.32 g, 8.46 mmol) in CH_2Cl_2 (20 mL) was added methyl trifluoromethanesulfonate (1.10 mL, 9.30 mmol) dropwise at room temperature. Stirring was continued for 30 min, and the mixture was concentrated to give crude ammonium salt **11**. Obtained crude **11** was sufficiently pure and used without purification for the next step. Analytically pure sample was obtained from pure **10**: mp 99−102 °C; IR ($CHCl_3$) 3322, 2969, 1507 cm^{-1}; ^{1}H NMR (CD_3OD) δ 1.31 (d, 6, J = 6.9), 2.15 (s, 3), 2.72 (s, 9), 3.1−3.2 (m, 1), 4.40 (s, 2), 7.16 (dd, 2, J = 9.0, 9.0), 7.25 (dd, 2, J = 5.4, 9.0); ^{13}C NMR (CD_3OD) δ 11.3, 23.2, 26.4, 52.2, 62.0, 103.3, 116.7 (J = 21.7), 121.1, 121.8 (J = 319), 126.7 (J = 11.7), 133.0 (J = 7.6), 133.9, 141.6 (J = 11.7), 162.9 (J = 244); TLC ($CHCl_3$/MeOH = 3/1) R_f 0.27. Anal. Calcd for $C_{19}H_{26}N_2O_3SF_4\cdot1.2H_2O$: C, 49.60; H, 6.22; N, 6.09. Found: C, 49.35; H, 5.82; N, 6.39.

(3*R*)-[(*tert*-Butyldimethylsilyl)oxy]-7-[4-(4-fluorophenyl)-2-isopropyl-5-methyl-1*H*-pyrrol-3-yl]-6-(methanesulfinyl)-5-oxoheptanoic Acid Methyl Ester (13). To a solution of sulfoxide **8** (2.22 g, 6.6 mmol) in *tert*-butyl alcohol (16 mL) and THF (4 mL) was added *t*-BuOK (741 mg, 6.6 mmol) in one portion at 0 °C. After being stirred at 0 °C for 15 min, **11** (2.63 mg, 6.0 mmol) was added, and the reaction mixture was stirred at 0 °C for 2 h. EtOAc and saturated NH_4Cl were added, and the organic phase was separated. The aqueous phase was extracted with EtOAc, and each organic layer was washed with brine, dried, and concentrated. Purification by silica gel chromatography (EtOAc/hexane = 1/1) gave a diastereomeric mixture of ester **13** (1.98 g, 58% yield from **9**): IR (KBr) 1738, 1505 cm^{-1}; ^{1}H NMR δ −0.05 (s, 3), −0.02 (s, 3), 0.7−0.8 (m, 9), 1.1−1.2 (m, 6), 2.11 (s, 3), 2.1−3.4 (m, 7), 3.60 (s, 3), 4.3−4.5 (m, 1), 7.0−7.3 (m, 4), 7.76 (br s, 1); TLC (EtOAc/hexane = 1/1) R_f 0.26−0.35. Anal. Calcd for $C_{29}H_{44}NO_5SSiF\cdot0.3H_2O$: C, 60.98; H, 7.87; N, 2.45. Found: C, 61.06; H, 7.69; N, 2.48.

(3*R*)-[(*tert*-Butyldimethylsilyl)oxy]-7-[4-(4-fluorophenyl)-2-isopropyl-5-methyl-1*H*-pyrrol-3-yl]-5-oxo-6-heptenoic Acid Methyl Ester (4a). A solution of **13** (484 mg, 0.855 mmol) in toluene (5 mL) was refluxed for 1 h and then concentrated. Purification by silica gel chromatography (EtOAc/hexane = 1/2) gave **4a** (389 mg, 91% yield): IR ($CHCl_3$) 3459, 2956, 1733 cm^{-1}; ^{1}H NMR δ −0.01 (s, 3), 0.02 (s, 3), 0.81 (s, 9), 1.30 (d, 6, J = 6.9), 2.11 (s, 3), 2.4−2.7 (m, 4), 3.33 (quintet, 1, J = 6.9), 3.64 (s, 3), 4.5−4.6 (m, 1), 5.92 (d, 1, J = 16.2), 7.07 (dd, 2, J = 9.0, 9.0), 7.21 (dd, 2, J = 5.4, 9.0), 7.60 (d, 1, J = 16.2), 8.38 (br s, 1); ^{13}C NMR δ −5.1, −4.7, 11.2, 17.9,

22.7, 25.5, 25.7, 42.7, 48.6, 51.4, 66.7, 113.2, 115.3 (J = 21.1), 120.3, 121.6, 125.1, 131.7, 131.9 (J = 7.6), 137.0, 141.6, 161.7 (J = 245), 171.7, 198.1; $[\alpha]^{25}_D$ +2.1 ± 0.4 (*c* 1.005, $CHCl_3$); TLC (EtOAc/hexane = 1/1) R_f 0.52. Anal. Calcd for $C_{28}H_{40}NO_4SiF \cdot 0.6H_2O$: C, 65.62; H, 8.10; N, 2.73. Found: C, 65.62; H, 7.93; N, 2.90.

(3*R*)-[(*tert*-Butyldimethylsilyl)oxy]-7-[4-(4-fluorophenyl)-2-isopropyl-1-(methanesulfonyl)-5-methyl-1*H*-pyrrol-3-yl]-5-oxo-6-heptenoic Acid Methyl Ester (4b). To a solution of **4a** (100 mg, 0.20 mmol) in THF (1.0 mL) was added LHMDS (0.22 mL of 1.0 M THF solution, 0.22 mmol) dropwise at −78 °C. After being stirred for 30 min, methanesulfonic anhydride (39 mg, 0.22 mmol) was added, and the mixture was stirred at −78 °C for 2 h and at 0 °C for 4 h. The reaction mixture was poured into a mixture of 1 N HCl and EtOAc, and the organic layer was separated. The aqueous phase was extracted with EtOAc, and each organic layer was washed with saturated $NaHCO_3$ and brine, dried, and concentrated. Purification by silica gel chromatography (EtOAc/toluene = 1/19−1/9) gave **4b** (72 mg, 62% yield): IR ($CHCl_3$) 2955, 2931, 1734, 1681 cm^{-1}; ^1H NMR δ −0.01 (s, 3), 0.02 (s, 3), 0.80 (s, 9), 1.46 (d, 6, J = 7.5), 2.22 (s, 3), 2.41 (dd, 1, J = 6.9, 15.0), 2.47 (dd, J = 6.9, 15.0), 2.47 (dd, 1, J = 6.3, 15.6), 2.58 (dd, 1, J = 6.3, 15.6), 3.25 (s, 3), 3.65 (s, 3), 3.95 (quintet, 1, J = 7.2), 4.48 (quintet, 1, J = 6.3), 5.53 (d, 1, J = 15.9), 7.0−7.2 (m, 4), 7.73 (d, 1, J = 15.9); ^{13}C NMR δ −5.0, −4.8, 13.6, 17.9, 23.3, 25.7, 26.5, 42.6, 43.8, 49.1, 51.5, 66.2, 115.7 (J = 22.4), 119.4, 124.6, 126.8, 129.6, 130.4 (J = 4.2), 134.5, 143.6, 162.4 (J = 247), 171.6, 197.4; $[\alpha]^{23}_D$ +5.9 (*c* 0.828, $CHCl_3$); TLC (EtOAc/toluene = 1/9) R_f 0.41; HR-LSIMS *m*/*z* 580.2562 $[M + H]^+$ (calcd for $C_{29}H_{42}NO_6SSiF$ 580.2563). Anal. Calcd for $C_{29}H_{42}NO_6SSiF$: C, 60.08; H, 7.30; N, 2.42; S, 5.53; F, 3.28. Found: C, 60.44; H, 7.44; N, 2.58; S, 6.06; F, 3.34.

(3*R*,5*S*)-7-[4-(4-Fluorophenyl)-2-isopropyl-1-(methanesulfonyl)-5-methyl-1*H*-pyrrol-3-yl]-3,5-dihydroxy-6-heptenoic Acid Methyl Ester (14). A 1:19 mixture of a 46% aqueous HF solution and CH_3CN (1.5 mL) was added to **4b** (106 mg, 0.183 mmol) at room temperature. The reaction mixture was stirred for 1 h, diluted with EtOAc, and poured into ice and saturated $NaHCO_3$. The organic phase was separated, and the aqueous phase was extracted with EtOAc. Each organic layer was washed with brine, dried, and concentrated. The residue was purified by silica gel chromatography (EtOAc/hexane = 1/1) to give the alcohol (69 mg, 81% yield): IR ($CHCl_3$) 3547, 1731 cm^{-1}; ^1H NMR δ 1.47 (d, 2, J = 7.2), 2.22 (s, 3), 2.48 (d, 2, J = 6.4), 2.53 (d, 2, J = 6.0), 3.26 (s, 3), 3.4−3.5 (m, 1), 3.70 (s, 3), 3.96 (quintet, 1, J = 7.2), 4.3−4.5 (m, 1), 5.51 (d, 1, J = 16.0), 7.0−7.2 (m, 4), 7.78 (d, 1, J = 16.0); $[\alpha]^{24}_D$ +14.5 (*c* 1.106, $CHCl_3$); TLC (EtOAc/hexane = 1/1) R_f 0.25.

To a solution of the ketone (67 mg, 0.14 mmol) in THF (1.2 mL) and MeOH (0.3 mL) was added Et_2BOMe (0.160 mL of 1.0 M THF solution, 0.160 mmol) at −78 °C. The mixture was stirred at −78 °C for 20 min, and $NaBH_4$ (6.0 mg, 0.16 mmol) was added. The reaction mixture was stirred at −78 °C for 1.5 h, diluted with EtOAc, and poured into ice and saturated $NaHCO_3$. The organic phase was separated, and the aqueous phase was extracted with EtOAc. Each organic layer was washed with brine, dried, and concentrated. The residual oil was dissolved in MeOH and concentrated. This operation was repeated three times. Purification by silica gel chromatography (EtOAc/hexane = 1/1) gave syn-diol **14** (61 mg, 91% yield): IR ($CHCl_3$) 3486, 2952, 1720 cm^{-1}; ^1H NMR δ 1.2−1.5 (m, 2), 1.32 (d, 6, J = 7.2), 2.16 (s, 3), 2.3−2.4 (m, 2), 2.91 (br s, 1), 3.10 (s, 3), 3.56 (br s, 1), 3.64 (s, 3), 3.75 (quintet, 1, J = 7.2), 3.9−4.1 (m, 1), 4.1−4.3 (m, 1), 4.93 (dd, 1, J = 6.3, 16.0), 6.48 (dd, 1, J = 1.1, 16.0), 6.9−7.1 (m, 4); ^{13}C NMR δ 13.7, 22.5, 22.6, 26.4, 41.4, 42.5, 43.2, 51.8, 68.0, 72.5, 115.0, 115.2, 121.2, 125.5, 128.2, 131.0 (J = 2.6), 132.5 (J = 45.6), 135.0, 137.8, 161.9 (J = 247), 172.9; $[\alpha]^{24}_D$ +10.9 (*c* 1.14, $CHCl_3$); TLC (EtOAc/hexane = 1/1) R_f 0.21.

(3*R*,5*S*)-7-[4-(4-Fluorophenyl)-2-isopropyl-1-(methanesulfonyl)-5-methyl-1*H*-pyrrol-3-yl]-3,5-dihydroxy-6-heptenoic Acid Sodium Salt (15). To a solution of **14** (48 mg, 0.10 mmol) in MeOH (0.5 mL) was added 2 N NaOH (77 μL, 0.15 mmol) dropwise at 0 °C. After being stirred at 0 °C for 2 h, solvent was removed, and the residue was purified by column chromatography on Diaion CHP-20P resin (40% aq MeOH) and freeze-dried to give **15** (29 mg, 59% yield): mp 187−189 °C; IR ($CHCl_3$) 3367, 1580 cm^{-1}; ^1H NMR (CD_3OD) δ 1.2−1.4 (m, 1), 1.40 (d, 6, J = 7.2), 1.4−1.6 (m, 1), 2.1−2.3 (m, 2), 2.21 (s, 3), 3.35 (s, 3), 3.8−4.0 (m, 2), 4.18 (q, 1, J = 6.6), 5.03 (dd, 1, J = 6.6, 16.2), 6.57 (dd, 1, J = 0.9, 16.2), 7.0−7.2 (m, 4); ^{13}C NMR (CD_3OD) δ 13.8, 22.7, 23.0, 27.5, 45.0, 45.0, 68.3, 72.1, 116.0 (J = 21.0), 122.4, 122.6, 126.7, 129.3, 132.7 (J = 3.9), 133.8 (J = 7.9), 136.6, 138.9, 163.3 (J = 245), 180.5; $[\alpha]^{25}_D$ +29 (*c* 0.86, CH_3OH); TLC (EtOAc/AcOH/H_2O = 30/1/1) R_f 0.59. Anal. Calcd for $C_{22}H_{27}NO_6SFNa \cdot 1.7H_2O$: C, 52.21; H, 6.05; N, 2.77. Found: C, 52.11; H, 5.68; N, 3.07.

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