Advance Publication Cover Page

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Synthesis of β-Hydroxy-α,α-disubstituted Amino Acids through the Orthoamide-Type Overman Rearrangement of an α,β-Unsaturated Ester and Stereodivergent Intramolecular S_N2' Reaction: Development and Application to the Total Synthesis of Sphingofungin F

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Synthesis of β-Hydroxy-α,α-disubstituted Amino Acids through the Orthoamide-Type Overman Rearrangement of an α,β-Unsaturated Ester and Stereodivergent Intramolecular S_N2' Reaction: Development and Application to the Total Synthesis of Sphingofungin F

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Abstract

The development of a two-step synthesis for β-hydroxy-α,α-disubstituted amino acid derivatives from cyclic orthoamide is reported. The first step is the orthoamide-type Overman rearrangement of an α,β-unsaturated ester to give a sterically hindered α,α-disubstituted amidoester. The α,β-unsaturated ester is known to be a challenging substrate in the conventional Overman rearrangement due to the competitive aza-Michael reaction. However, suppression of the aza-Michael reaction is realized by two factors; 1) the high reaction temperature, and 2) an alkyl substituent at the α-position. The second step is stereodivergent intramolecular S_N2' reaction for the installation of a hydroxy group at the β-position. Either *syn*- or *anti*-type S_N2' reaction is possible by simply changing the reaction conditions. The developed method can provide all four possible stereoisomers of the β-hydroxy-α,α-disubstituted amino acid, and is successfully applied to the total synthesis of sphingofungin F.

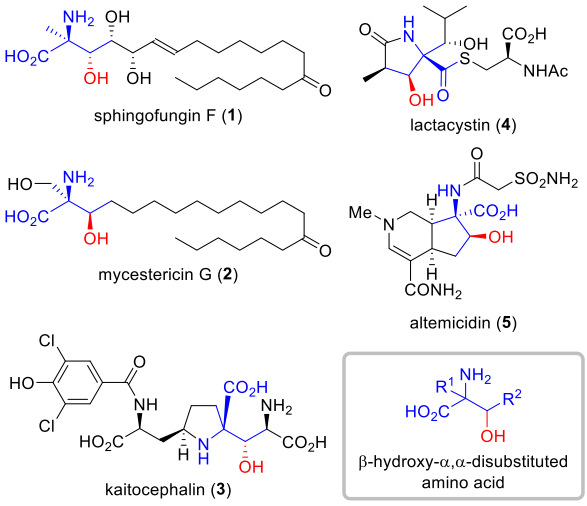


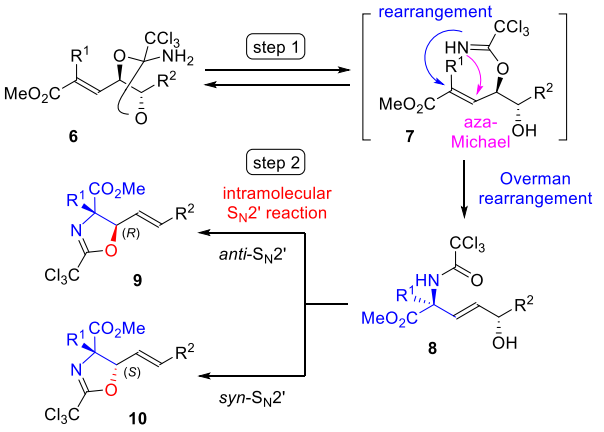
Figure 1. Representative natural products with a β-hydroxy-α,α-disubstituted amino acid

1. Introduction

β-Hydroxy-α,α-disubstituted amino acid[1] is a widely distributed structural motif embedded in a number of biologically active natural products such as sphingofungin F (**1**)[2], mycestericin G (**2**)[3] and kaitocephalin (**3**)[4] (Figure 1). This motif containing two contiguous stereocenters constitutes a variety of stereoisomers seen in natural products. Therefore, the synthetic method that can provide all four possible diastereomers would be significant. However, the development of such approach is highly challenging due to the motif's densely functionalized structure.

To develop a versatile approach for β-hydroxy-α,α-disubstituted amino acids, we planned a two-step synthesis involving the orthoamide-type Overman rearrangement[5-7] of α,β-unsaturated ester **6**, and subsequent intramolecular S_N2' reaction of trichloroacetamide **8** (Scheme 1). Heating cyclic orthoamide **6** at high temperature would initiate the ring opening of the cyclic orthoamide. The

generated imidate **7** under equilibrium conditions would undergo the Overman rearrangement. In spite of its high utility, no successful example of the Overman rearrangement has been reported on a substrate containing an α,β-unsaturated ester due to the competing aza-Michael reaction. If successful, the rearrangement would enable direct access to α,α-disubstituted amidoesters **8** via chirality transfer. The next stereodivergent intramolecular S_N2' reaction of trichloroacetamide **8** would install either (*R*)- or (*S*)-hydroxy group from the same allylic alcohol. While *anti*-type S_N2' reaction would afford oxazoline **9** with the (*R*)-hydroxy group, *syn*-type S_N2' reaction would give oxazoline **10** with the (*S*)-hydroxy group. In this full paper, we provide full details on the development of the two-step approach to β-hydroxy-α,α-disubstituted amino acid derivatives.[8] The developed method afforded all four possible stereoisomers by properly selecting both stereochemistry of 1,2-diols embedded in cyclic orthoamides **6**, and reaction conditions of the S_N2' reaction. The two-step method was successfully applied to the concise total synthesis of sphingofungin F (**1**).



Scheme 1. Synthetic plan for β-hydroxy-α,α-disubstituted amino acid derivatives by the Overman rearrangement of an α,β-unsaturated ester and stereodivergent intramolecular S_N2' reaction

2. Experimental

General Details. Reactions were performed in oven-dried glassware fitted with rubber septa under argon atmosphere. Toluene and *t*-BuPh were distilled from CaH_2. MeOH was distilled from $CaSO_4$. Pyridine was distilled from sodium hydroxide. All distilled solvents, CH_2Cl_2 and MeCN were dried over activated 3Å molecular sieves. THF (dehydrated, stabilizer free) was purchased from KANTO CHEMICAL CO., INC. Other commercial reagents were used without further purification. Thin-layer chromatography was performed on Merck TLC silica gel 60 F_{254}, which were visualized by exposure to UV (254 nm) or stained by submersion in aquatic ceric ammonium molybdate, ethanolic ninhydrin or ethanolic phosphomolybdic acid solution followed by heating on a hot plate. Flash column chromatography was performed on silica gel (Silica Gel 60 N; 63–210 or 40–50 mesh, KANTO CHEMICAL CO., INC.). Preparative layer chromatography was performed on Merck PLC silica gel 60 F_{254}. ^{1}H NMR spectra were recorded at 500 MHz with JEOL ECA-500 spectrometer or 400 MHz with JEOL ECS-400 spectrometer. ^{13}C NMR spectra were recorded at 125 MHz with JEOL ECA-500 spectrometer or 100 MHz with JEOL ECS-400 spectrometer or BRUKER AVANCE III 500 equipped with CRYO PLATFORM. Chemical shifts are reported in ppm with reference to solvent signals [^{1}H NMR: $CDCl_3$ (7.26), CD_3OD (3.31), C_6D_6 (7.16)]; ^{13}C NMR: $CDCl_3$ (77.16), CD_3OD (49.00), C_6D_6 (128.06)]. Signal patterns are indicated as br, broad peak; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Infrared spectra were recorded using a BRUKER ALPHA FT-IR spectrometer. Mass spectra (ESI-TOF) were measured with a Waters, LCT Premier XE. Melting points were measured with a Mitamura-Riken microhot stage. Optical rotations were measured with a JASCO P-2100 polarimeter.

[General procedure A: the Overman rearrangement]

(*S*,*E*)-Methyl 2-(2,2,2-trichloroacetamido)pent-3-enoate (19a): Reaction at 140 °C: A sealed tube was charged with imidate **18a**[9] (>99%ee, 26.0 mg, 94.7 μmol) and *t*-BuPh (5.9 mL). The solution was heated to 140 ºC for 4 d. After cooling to room temperature, the resulting mixture was filtrated through a pad of silica gel to separate *t*-BuPh. The filtrate was then concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:40) to give 11.9 mg of trichloroacetamide **19a** (46%), 7.9 mg of *trans*-oxazoline **20a** (31%) and 0.8 mg of *cis*-oxazoline **21a** (3%). trichloroacetamide **19a**: >99%ee by HPLC (CHIRALPAK OD-H, 250×4.6 mm, UV 254 nm, *i*-PrOH/hexane 1:24, 1.0 mL/min, **19a**: T_R= 6.5 min, ***ent*-19a**: T_R= 8.0 min); a colorless oil; $[\alpha]^{25}_D$ +72.5 (*c* 0.94, $CHCl_3$); IR (film) 3348, 2955, 1747, 1712, 1510, 1207, 966, 822 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, *J* = 7.2 Hz, 1H), 5.87 (dqd, *J* = 15.5, 6.6, 1.2 Hz, 1H), 5.50 (ddq, *J* = 15.5, 6.6, 1.7 Hz, 1H), 4.98 (ddd, *J* = 7.2, 6.6, 1.2 Hz, 1H), 3.81 (s, 3H), 1.75 (dd, *J* = 6.6, 1.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5 (C), 161.2 (C), 131.7 (CH), 123.4 (CH), 92.3 (C), 55.8 (CH), 53.2 (CH_3), 17.9 (CH_3); HRMS (ESI), calcd for $C_8H_{11}NO_3Cl_3^+$ $(M+H)^+$ 273.9805, found 273.9796. *trans*-oxazoline **20a**: colorless oil; $[\alpha]^{20}_D$ –48.0 (*c* 0.96, $CHCl_3$); IR (film) 2981, 2955, 1737, 1658, 1021, 892, 794, 666 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.78 (dq, *J* = 6.3, 6.3 Hz, 1H), 4.21 (ddd, *J* = 9.7, 6.3, 4.3 Hz, 1H), 3.72 (s, 3H), 2.89 (dd, *J* = 16.6, 4.3 Hz, 1H), 2.54 (dd, *J* = 16.6, 9.7 Hz, 1H), 1.49 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0 (C), 162.4 (C), 86.8 (C), 85.8 (CH), 69.7 (CH), 52.1 (CH_3), 38.6 (CH_2), 20.6 (CH_3); HRMS (ESI), calcd for $C_8H_{11}NO_3Cl_3^+$ $(M+H)^+$ 273.9805, found 273.9796. *cis*-oxazoline **21a**: a colorless oil; $[\alpha]^{21}_D$ –6.6 (*c* 0.20, $CHCl_3$); IR (film) 2988, 2954, 1737, 1657, 1011, 888, 795, 669 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.25 (dq, *J* = 8.9, 6.6 Hz, 1H), 4.72 (ddd, *J* = 10.0, 8.9, 5.2 Hz, 1H), 3.73 (s, 3H), 2.92 (dd, *J* = 17.2, 5.2 Hz, 1H), 2.66 (dd, *J* = 17.2, 10.0 Hz, 1H), 1.30 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5 (C), 162.6 (C), 86.9 (C), 83.0 (CH), 65.1 (CH), 52.3 (CH_3), 34.4 (CH_2), 14.7 (CH_3); HRMS (ESI), calcd for $C_8H_{10}NO_3Cl_3Na^+$ $(M+Na)^+$ 295.9624, found 295.9624.

Reaction at 180 °C: A sealed tube was charged with imidate **18a** (>99%ee, 22.7 mg, 83.7 μmol) and *t*-BuPh (5.2 mL). The solution was heated to 180 ºC for 3 h. After cooling to room temperature, the resulting mixture was filtrated through a pad of silica gel to separate *t*-BuPh. The filtrate was then concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:40) to give 21.7 mg of trichloroacetamide **19a** (96%): >99%ee by HPLC (CHIRALPAK OD-H, 250×4.6 mm, UV 254 nm, *i*-PrOH/hexane 1:24, 1.0 mL/min, **19a**: T_R= 6.5 min, ***ent*-19a**: T_R= 8.0 min).

(*S*,*E*)-Methyl 2-methyl-2-(2,2,2-trichloroacetamido)pent-3-enoate (19b): Reaction at 140 °C: Following the general procedure A at 140 °C, imidate **18b**[9] (>99%ee, 25.5 mg, 88.4 μmol) was converted to **19b** (21.2 mg, 83%) over 2.5 d: >99%ee by HPLC (CHIRALPAK AD-H, 250×4.6 mm, UV

254 nm, *i*-PrOH/hexane 1:49, 1.0 mL/min, **19b**: T_R= 6.5 min, ***ent*-19b**: T_R= 6.0 min), a colorless oil; $[\alpha]^{26}_D$ +27.9 (*c* 1.07, $CHCl_3$); IR (film) 3373, 2954, 1720, 1499, 1449, 1269, 1132, 821, 684 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.63 (brs, 1H), 5.77 (dq, *J* = 15.5, 6.6 Hz, 1H), 5.63 (dq, *J* = 15.5, 1.4 Hz, 1H), 3.80 (s, 3H), 1.75 (s, 3H), 1.74 (dd, *J* = 6.6, 1.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.8 (C), 160.2 (C), 128.8 (CH), 128.5 (CH), 92.8 (C), 61.4 (C), 53.5 (CH_3), 21.7 (CH_3), 18.0 (CH_3); HRMS (ESI), calcd for $C_9H_{12}NO_3Cl_3K^+$ $(M+K)^+$ 325.9520, found 325.9527.

Reaction at 180 °C: Following the general procedure A at 180 °C, allylic alcohol **18b** (>99%ee, 24.8 mg, 85.9 μmol) was converted to **19b** (22.1 mg, 89%) over 6 h: >99%ee by HPLC (CHIRALPAK AD-H, 250×4.6 mm, UV 254 nm, *i*-PrOH/hexane 1:49, 1.0 mL/min, **19b**: T_R= 6.5 min, ***ent*-19b**: T_R= 6.0 min).

(*S*,*E*)-Methyl 2-(3-((4-methoxybenzyl)oxy)propyl)-2-(2,2,2-trichloroacetamido)pent-3-enoate (19c): Reaction at 140 °C: Following the general procedure A at 140 °C, imidate **18c**[9] (96%ee, 21.2 mg, 46.8 μmol) was converted to **19c** (16.9 mg, 80%) over 2.5 d: >96%ee by HPLC (CHIRALPAK AD-H, 250×4.6 mm, UV 254 nm, *i*-PrOH/hexane 1: 24, 1.0 mL/min, **19c**: T_R= 11.0 min, ***ent*-19c**: T_R= 13.5 min); a colorless oil; $[\alpha]^{23}_D$ +11.8 (*c* 1.08, $CHCl_3$); IR (film) 3375, 3248, 2952, 2859, 1722, 1513, 1248, 821 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.24 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 5.69 (dq, *J* = 15.6, 5.9 Hz, 1H), 5.63 (dq, *J* = 15.6, 1.0 Hz, 1H), 4.42 (s, 2H), 3.80 (s, 3H), 3.79 (s, 3H), 3.44 (ddd, *J* = 9.4, 6.2, 6.2 Hz, 1H), 3.39 (ddd, *J* = 9.4, 7.1, 6.2 Hz, 1H), 2.45 (ddd, *J* = 14.3, 10.6, 5.0 Hz, 1H), 2.12 (ddd, *J* = 14.3, 10.6, 5.0 Hz, 1H), 1.73 (dd, *J* = 5.9, 1.0 Hz, 3H), 1.63–1.55 (m, 1H), 1.44–1.36 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.6 (C), 160.1 (C), 159.3 (C), 130.4 (C), 129.4 (CH), 128.1 (CH), 127.5 (CH), 113.9 (CH), 92.9 (C), 72.7 (CH_2), 69.2 (CH_2), 65.0 (C), 55.4 (CH_3), 53.5 (CH_3), 31.5 (CH_2), 24.3 (CH_2), 18.0 (CH_3); HRMS (ESI), calcd for $C_{19}H_{24}NO_5NaCl_3^+$ $(M+Na)^+$ 474.0618, found 474.0606.

Reaction at 180 °C: Following the general procedure A at 180 °C, imidate **18c** (96%ee, 21.9 mg, 48.4 μmol) was converted to **19c** (19.7 mg, 90%) over 6 h: 96%ee by HPLC (CHIRALPAK AD-H, 250×4.6 mm, UV 254 nm, *i*-PrOH/hexane 1: 24, 1.0 mL/min, **19c**: T_R= 11.0 min, ***ent*-19c**: T_R= 13.5 min).

(*S*,*E*)-2,2,2-Trichloro-*N*-(2-oxo-3-(prop-1-en-1-yl)tetrahydro-2H-pyran-3-yl)acetamide (19d): Reaction at 140 °C: Following the general procedure A at 140 °C, imidate **18d**[9] (96%ee, 16.1 mg, 53.2 μmol) was converted to a mixture of **19d** (2.9 mg, 18%), **20d** (major diastereomer, 6.9 mg, 43%) and **20d** (minor diastereomer, 4.7 mg, 29%) over 8 h. For analytical samples, the mixture was separated by HPLC (PEGASIL Silica 120–5 250×10 mm, UV 210 nm, *i*-PrOH/hexane 1:20, 3 mL/min, **19d**: T_R= 13.0 min, **20d (major)**: T_R= 22.0 min, **20d (minor)**: T_R= 20.0 min). **19d**: 96%ee by HPLC (CHIRALPAK AD-H, 250×4.6 mm, UV 254 nm, *i*-PrOH/hexane 1: 14, 1.0 mL/min, **19d**: T_R= 8.0 min, ***ent*-19d**: T_R= 7.5 min); an amorphous solid; $[\alpha]^{25}_D$ +94.9 (*c* 0.04, $CHCl_3$); IR (film) 3324, 2971, 1723, 1699, 1495, 1167, 968, 821 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.65 (s, 1H), 5.93 (dq, *J* = 15.6, 6.6 Hz, 1H), 5.75 (dq, *J* = 15.6, 1.4 Hz, 1H), 4.48–4.41 (m, 2H), 2.64 (ddd, *J* = 13.7, 5.8, 5.2 Hz, 1H), 2.31 (ddd, *J* = 13.7, 10.8, 5.7 Hz, 1H), 2.11–2.02 (m, 1H), 1.99–1.92 (m, 1H), 1.79 (dd, *J* = 6.6, 1.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5 (C), 160.8 (C), 132.2 (CH), 128.3 (CH), 92.3 (C), 69.8 (CH_2), 61.0 (C), 30.1 (CH_2), 20.7 (CH_2), 18.2 (CH_3); HRMS (ESI), calcd for $C_{10}H_{12}NO_3Cl_3Na^+$ $(M+Na)^+$ 321.9780, found 321.9775. **20d (major diastereomer)**: an amorphous solid; $[\alpha]^{23}_D$ –37.6 (*c* 1.11, $CHCl_3$); IR (film) 2976, 2934, 1735, 1657, 1164, 795 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.80 (dq, *J* = 6.0, 6.0 Hz, 1H), 4.53 (dd, *J* = 6.0, 3.1 Hz, 2H), 4.36–4.28 (m, 2H), 3.13 (ddd, *J* = 12.6, 7.5, 3.7 Hz, 1H), 2.03–1.91 (m, 3H), 1.59–1.53 (m, 1H), 1.52 (d, *J* = 6.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2 (C), 162.8 (C), 86.7 (C), 83.3 (CH), 72.5 (CH), 68.5 (CH_2), 42.9 (CH), 21.8 (CH_2), 21.2 (CH_3), 18.7 (CH_2); HRMS (ESI), calcd for $C_{10}H_{13}NO_3Cl_3^+$ $(M+H)^+$ 321.780, found 321.9786. **20d (minor diastereomer)**: an amorphous solid; $[\alpha]^{22}_D$ –94.5 (*c* 1.19, $CHCl_3$); IR (film) 2992, 2940, 1733, 1657, 1166, 1020, 928, 817 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.90 (dq, *J* = 6.3, 5.7 Hz, 1H), 4.37–4.28 (m, 2H), 4.11 (dd, *J* = 8.6, 5.7 Hz, 1H), 2.59 (ddd, *J* = 11.5, 8.6, 8.6 Hz, 1H), 2.40–2.32 (m, 1H), 2.03–1.89 (m, 2H), 1.74 (dddd, *J* = 13.8, 11.5, 7.5, 7.5 Hz, 1H), 1.53 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.7 (C), 162.5 (C), 86.9 (C), 85.8 (CH), 74.1 (CH), 68.3 (CH_2), 44.3 (CH), 21.8 (CH_2), 21.5 (CH_2), 20.7 (CH_3); HRMS (ESI), calcd for $C_{10}H_{12}NO_3Cl_3Na^+$ $(M+Na)^+$ 321.9780, found 321.9773.

Reaction at 180 °C: Following the general procedure A at 180 °C, imidate **18d** (96%ee, 16.5 mg, 54.5 μmol) was converted to a mixture of **19d** (6.5 mg, 39%), **20d** (major diastereomer, 5.5 mg, 33%) and **20d** (minor diastereomer, 2.6 mg, 16%) over 2 h. For analytical samples, the mixture was separated by HPLC (PEGASIL Silica 120–5 250×10 mm, UV 210 nm, *i*-PrOH/hexane 1:20, 3 mL/min, **19d**: T_R= 13.0 min, **20d (major)**: T_R= 22.0 min, **20d (minor)**: T_R= 20.0 min). **19d**: 96%ee by HPLC (CHIRALPAK AD-H, 250×4.6 mm, UV 254 nm, *i*-PrOH/hexane 1: 14, 1.0 mL/min, **19d**: T_R= 8.0 min, ***ent*-19d**: T_R= 7.5 min).

Attempted retro-aza-Michael Reaction of oxazoline 20a

A sealed tube was charged with *trans*-oxazoline **20a** (24.3 mg, 88.5 μmol) and *t*-BuPh (5.5 mL). The solution was heated to 180 ºC for 34 h. After cooling to room temperature, the resulting mixture was directly purified by silica gel column chromatography (EtOAc/hexane 1:29 to 1:19) to give 18.9 mg of *trans*-oxazoline **20a** (78%).

Attempted retro-aza-Michael Reaction of oxazoline 21a

A sealed tube was charged with *cis*-oxazoline **21a** (17.9 mg, 65.2 μmol) and *t*-BuPh (4.1 mL). The solution was heated to 180 ºC for 36 h. After cooling to room temperature, the resulting mixture was directly purified by silica gel column chromatography (EtOAc/hexane 1:29 to 1:19) to give 16.9 mg of *cis*-oxazoline **21a** (94%).

[General procedure B: *anti*-type S_N2' reaction]

(4*R*,5*R*)-4-((Benzyloxy)methyl)-5-((*E*)-3-(methoxymethoxy)prop-1-en-1-yl)-2-(trichloromethyl)-4,5-dihydrooxazole (23): Trifluoromethanesulfonic anhydride (12 μL, 75 μmol) was added to a solution of allylic amino alcohol **22**[9] (21.3 mg, 49.9 μmol), pyridine (81 μL, 1.0 mmol) and CH_2Cl_2 (5.0 mL) at –40 °C. The solution was maintained for 5 h at –40 °C, quenched with saturated aqueous $NaHCO_3$ (2.5 mL), and diluted with hexane (3 mL). The mixture was extracted with EtOAc (3x 5 mL). The combined organic extracts were washed with brine (1 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:9) to give 15.7 mg of oxazoline **23** (77%, dr = 10:1): a colorless oil; $[\alpha]^{26}_D$ +101.0 (*c* 1.04, $CHCl_3$); IR (film) 2931, 2886, 1661, 1151, 1117, 1039, 923, 793 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36–7.27 (m, 5H), 5.94 (dtd, *J* = 15.5, 5.0, 0.9 Hz, 1H), 5.85 (ddt, *J* = 15.5, 6.6, 1.4 Hz, 1H), 5.27 (ddd, *J* = 7.0, 6.6, 0.9 Hz, 1H), 4.64 (s, 2H), 4.61 (d, *J* = 12.0 Hz, 1H), 4.56 (d, *J* = 12.0 Hz, 1H), 4.19 (ddd, *J* = 7.0, 6.0, 4.0 Hz, 1H), 4.10 (dd, *J* = 5.0, 1.4 Hz, 2H), 3.74 (dd, *J* = 10.0, 4.0 Hz, 1H), 3.65 (dd, *J* = 10.0, 6.0 Hz, 1H), 3.37 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.7 (C), 137.9 (C), 130.8 (CH),

128.5 (CH), 128.4 (CH), 127.9 (CH), 127.7 (CH), 96.0 (CH_2), 86.7 (C), 86.3 (CH), 73.5 (CH_2), 72.6 (CH), 70.2 (CH_2), 66.6 (CH_2), 55.5 (CH_3); HRMS (ESI), calcd for $C_{17}H_{21}Cl_3NO_4^+$ $(M+H)^+$ 408.0536, found 408.0527.

[General procedure C: *syn*-type S_N2' reaction]

(4*R*,5*S*)-4-((Benzyloxy)methyl)-5-((*E*)-3-(methoxymethoxy)prop-1-en-1-yl)-2-(trichloromethyl)-4,5-dihydrooxazole (24): Tributylphosphine (31 µL, 130 µmol) was added to a solution of allylic amino alcohol **22** (20.6 mg, 48.3 µmol), DEAD (40wt% in toluene, 110 µL, 260 µmol) and toluene (4.8 mL) at –20 °C. This solution was maintained for 1 h at –20 °C, quenched with H_2O (2.5 mL), and extracted with EtOAc (4x 5 mL). The combined organic extracts were washed with brine (1 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:29 to 1:14) to give 16.4 mg of oxazoline **24** (83%, dr = >20:1): a colorless oil; $[\alpha]^{23}_D$ +69.4 (*c* 0.99, $CHCl_3$); IR (film) 2932, 2885, 1660, 1150, 1104, 1041, 921, 793 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36–7.27 (m, 5H), 6.00–5.99 (m, 2H), 5.41 (ddd, *J* = 9.7, 2.9, 2.9 Hz, 1H), 4.63 (s, 2H), 4.54–4.49 (m, 3H), 4.09 (d, *J* = 2.9 Hz, 2H), 3.72 (dd, *J* = 9.9, 4.0 Hz, 1H), 3.59 (dd, *J* = 9.9, 7.2 Hz, 1H), 3.35 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.0 (C), 137.9 (C), 132.0 (CH), 128.5 (CH), 127.9 (CH), 127.8 (CH), 125.2 (CH), 96.0 (CH_2), 86.8 (C), 86.1 (CH), 73.6 (CH_2), 69.3 (CH), 68.5 (CH_2), 66.8 (CH_2), 55.5 (CH_3); HRMS (ESI), calcd for $C_{17}H_{21}Cl_3NO_4^+$ $(M+H)^+$ 408.0536, found 408.0532.

Methyl (2*S*,5*R*,*E*)-5-hydroxy-6-(methoxymethoxy)-2-methyl-2-(2,2,2-trichloroacetamido)hex-3-enoate (26): A sealed tube was charged with cyclic orthoamide **25**[9] (32.8 mg, 86.6 µmol), 2,6-di-*tert*-butylhydroxytoluene (1.0 mg, 4.3 µmol) and *t*-BuPh (5.4 mL). The solution was heated to 220 ºC for 13 h. After cooling to room temperature, the resulting mixture was directly purified by silica gel column chromatography (EtOAc/hexane 1:4) to give 24.7 mg of allylic amino alcohol **26** (75%): a yellow oil; $[\alpha]^{25}_D$ +26.5 (*c* 1.09, $CHCl_3$); IR (film) 3371, 2953, 2891, 1742, 1718, 1506, 1115, 1037, 823 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.71 (s, 1H), 6.01 (d, *J* = 15.8 Hz, 1H), 5.76 (dd, *J* = 15.8, 5.2 Hz, 1H), 4.67 (d, *J* = 8.0 Hz, 1H), 4.65 (d, *J* = 8.0 Hz, 1H), 4.39–4.35 (m, 1H), 3.81 (s, 3H), 3.67 (dd, *J* = 10.6, 2.9 Hz, 1H), 3.45 (dd, *J* = 10.6, 7.5 Hz, 1H), 3.39 (s, 3H), 2.95 (d, *J* = 3.7 Hz, 1H), 1.78 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5 (C), 160.2 (C), 130.9 (CH), 129.3 (CH), 97.3 (CH_2), 92.7 (C), 72.9 (CH_2), 70.6 (CH), 61.2 (C), 55.7 (CH_3), 53.7 (CH_3), 22.1 (CH_3); HRMS (ESI), calcd for $C_{12}H_{18}Cl_3NO_6Na^+$ $(M+Na)^+$ 400.0097, found 400.0098.

Methyl (4*S*,5*R*)-5-((*E*)-3-(methoxymethoxy)prop-1-en-1-yl)-4-methyl-2-(trichloromethyl)-4,5-dihydrooxazole-4-carboxylate (27): Following the general procedure B, allylic amino alcohol **26** (20.2 mg, 53.4 µmol) was converted to 15.6 mg of oxazoline **27** (81%, dr = >20:1): a colorless oil; $[\alpha]^{26}_D$ +58.7 (*c* 1.10, $CHCl_3$); IR (film) 2953, 2888, 1737, 1655, 1242, 1149, 1038, 934, 794 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.06 (dtd, *J* = 15.5, 5.2, 0.9 Hz, 1H), 5.82 (ddt, *J* = 15.5, 6.9, 1.7 Hz, 1H), 5.58 (dd, *J* = 6.9, 0.9 Hz, 1H), 4.65 (s, 2H), 4.15 (dd, *J* = 5.2, 1.7 Hz, 2H), 3.82 (s, 3H), 3.37 (s, 3H), 1.43 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 172.2 (C), 162.7 (C), 133.2 (CH), 123.6 (CH), 96.0 (CH_2), 88.9 (CH), 87.4 (C), 77.3 (C), 66.4 (CH_2), 55.0 (CH_3), 52.5 (CH_3), 19.9 (CH_3); HMRS (ESI) calcd for $C_{12}H_{16}Cl_3NO_5Na^+$ $(M+Na)^+$ 381.9992, found 381.9986.

Methyl (4*S*,5*S*)-5-((*E*)-3-(methoxymethoxy)prop-1-en-1-yl)-4-methyl-2-(trichloromethyl)-4,5-dihydrooxazole-4-carboxylate (28): Following the general procedure C, allylic amino alcohol **26** (18.4 mg, 48.6 µmol) was converted to 15.7 mg of oxazoline **28** (90%, dr = >20:1): a colorless oil; $[\alpha]^{24}_D$ +46.9 (*c* 0.53, $CHCl_3$); IR (film) 2952, 2888, 1743, 1661, 1258, 1118, 1037, 947 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.99 (dt, *J* = 15.5, 5.2 Hz, 1H), 5.74 (ddt, *J* = 15.5, 7.5, 1.4 Hz, 1H), 5.01 (d, *J* = 7.5 Hz, 1H), 4.62 (s, 2H), 4.08 (dd, *J* = 5.2, 1.4 Hz, 2H), 3.72 (s, 3H), 3.35 (s, 3H), 1.66 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2 (C), 163.4 (C), 133.3 (CH), 124.0 (CH), 95.9 (CH_2), 92.1 (CH), 86.4 (C), 78.4 (C), 66.3 (CH_2), 55.5 (CH_3), 52.7 (CH_3), 24.0 (CH_3); HRMS (ESI), calcd for $C_{12}H_{16}Cl_3NO_5Na^+$ $(M+Na)^+$ 381.9992, found 381.9982.

Methyl (2*R*,5*R*,*E*)-5-hydroxy-6-(methoxymethoxy)-2-methyl-2-(2,2,2-trichloroacetamido)hex-3-enoate (30): A sealed tube was charged with cyclic orthoamide **29**[9] (35.7 mg, 94.2 µmol, dr = 2.4:1), 2,6-di-*tert*-butylhydroxytoluene (1.0 mg, 4.7 µmol) and *t*-BuPh (5.9 mL). The solution was heated to 220 ºC for 1.5 d. After cooling to room temperature, the resulting mixture was directly purified by silica gel column chromatography (EtOAc/hexane 1:4 to 1:2) to give 19.8 mg of allylic amino alcohol **30** (56%): a colorless oil; $[\alpha]^{24}_D$ –28.0 (*c* 1.00, $CHCl_3$); IR (film) 3467, 3368, 2952, 1740, 1718, 1503, 1114, 1038, 823 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.73 (s, 1H), 6.00 (d, *J* = 15.8 Hz, 1H), 5.75 (dd, *J* = 15.8, 5.2 Hz, 1H), 4.66 (d, *J* = 8.0 Hz, 1H), 4.65 (d, *J* = 8.0 Hz, 1H), 4.40–4.35 (m, 1H), 3.81 (s, 3H), 3.67 (dd, *J* = 10.6, 2.9 Hz, 1H), 3.44 (dd, *J* = 10.6, 7.5 Hz, 1H), 3.38 (s, 3H), 2.95 (d, *J* = 3.8 Hz, 1H), 1.78 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4 (C), 160.2 (C), 131.0 (CH), 129.5 (CH), 97.3 (CH_2), 92.7 (C), 72.9 (CH_2), 70.7 (CH), 61.2 (C), 55.7 (CH_3), 53.7 (CH_3), 22.0 (CH_3); HMRS (ESI) calcd for $C_{12}H_{18}Cl_3NO_6Na^+$ $(M+Na)^+$ 400.0097, found 400.0112.

Methyl (4*R*,5*R*)-5-((*E*)-3-(methoxymethoxy)prop-1-en-1-yl)-4-methyl-2-(trichloromethyl)-4,5-dihydrooxazole-4-carboxylate (*ent*-28): Following the general procedure B, allylic amino alcohol **30** (15.6 mg, 41.2 µmol) was converted to 12.4 mg of oxazoline ***ent*-28** (84%, dr = 4:1). For analytical samples, the mixture was separated by HPLC (PEGASIL Silica 120–5 250×20 mm, UV 210 nm, *i*-PrOH/hexane 1:20, 10 mL/min, ***ent*-28**: T_R= 15.0 min, ***ent*-27**: T_R= 14.0 min). oxazoline ***ent*-28**: a colorless oil; $[\alpha]^{26}_D$ −48.6 (*c* 0.53, $CHCl_3$). The spectral data of ***ent*-28** was identical to oxazoline **28**.

Methyl (4*R*,5*S*)-5-((*E*)-3-(methoxymethoxy)prop-1-en-1-yl)-4-methyl-2-(trichloromethyl)-4,5-dihydrooxazole-4-carboxylate (*ent*-27): Following the general procedure C, allylic amino alcohol **30** (18.1 mg, 47.8 µmol) was converted to 14.4 mg of oxazoline ***ent*-27** (84%, dr = >20:1): a colorless oil; $[\alpha]^{22}_D$ −56.5 (*c* 0.98, $CHCl_3$). The spectral data of ***ent*-27** was identical to oxazoline **27**.

(3a*S*,6a*S*)-2,2-Dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-ol (36): Sodium borohydride (3.18 g, 84.0 mmol) was divided into four portions, and added to a solution of **31** and MeOH (21 mL) at 0 °C every 15 min. The resulting mixture was stirred for more 15 min, quenched with H_2O (21 mL) and 1 M HCl aq. (80 mL), and allowed to warm to room temperature. Sodium periodate (4.49 g, 21.0 mmol) was added to the mixture at room temperature. After stirring for 10 min at room temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (30 mL). The resulting mixture was filtrated to remove white solid, which was washed with EtOAc (50 mL). The combined filtrate was extracted with EtOAc (12x 50 mL). The combined organic extracts were washed with brine (200 mL), dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:3) to give 1.60 g of lactol **36** (95%), which was identical to reported data.[10]

(4*R*, 5*S*, *E*)-Methyl 6-((benzyloxy)methoxy)-4,5-dihydroxy-2 -methylhex-2-enoate (38): Sodium hydroxide aq. (2 M, 85 mL, 170 mmol) was added to a solution of carbomethoxy methyl triphenylphosphonium bromide (5.15 g,

12.0 mmol) and CH_2Cl_2 (20 mL) at room temperature. After stirring for 15 min at room temperature, the solution was extracted with $CHCl_3$ (2x 15 mL), washed with brine (15 mL), dried over Na_2SO_4 and concentrated. The resulting ylide was used without further purification.

A solution of the ylide and CH_2Cl_2 (30 mL) was added to a solution of lactol **36** (1.00 g, 5.98 mmol) and CH_2Cl_2 (30 mL) at room temperature. After maintaining for 19 h at room temperature, diisopropylethylamine (5.2 mL, 30 mmol) and BOMCl (3.3 mL, 24 mmol) were added to the yellow solution at room temperature. The solution was maintained for 2 d at room temperature, quenched with H_2O (40 mL) and extracted with $CHCl_3$ (3x 30 mL). The combined organic extracts were washed with brine (30 mL), dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:24 to 1:7) to give 2.27 g of a mixture of the unsaturated methylester **37** and benzyl alcohol, which was used in the next step without further purification. For analytical sample, the mixture was purified by HPLC (PEGASIL Silica 120–5 250×20 mm, UV 254 nm, EtOAc/hexane 1:3, 10 mL/min, T_R= 12 min) to afford pure the unsaturated methylester **37**: a colorless oil; $[\alpha]^{24}_D$ –6.5 (*c* 1.06, $CHCl_3$); IR (film) 2988, 2936, 2885, 1719, 1248, 1048, 1028 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36–7.27 (m, 5H), 6.69 (dq, *J* = 8.9, 1.7 Hz, 1H), 4.98 (dd, *J* = 8.9, 6.6 Hz, 1H), 4.77 (d, *J* = 8.1 Hz, 1H), 4.75 (d, *J* = 8.1 Hz, 1H), 4.60 (d, *J* = 14.9 Hz, 1H), 4.58 (d, *J* = 14.9 Hz, 1H), 4.42 (ddd, *J* = 7.5, 6.6, 4.6 Hz, 1H), 3.72 (s, 3H), 3.57 (dd, *J* = 10.6, 7.5 Hz, 1H), 3.51 (dd, *J* = 10.6, 4.6 Hz, 1H), 1.90 (d, *J* = 1.7 Hz, 3H), 1.53 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.7 (C), 137.8 (C), 136.4 (CH), 131.0 (C), 128.6 (CH), 128.0 (CH), 127.9 (CH), 109.7 (C), 95.1 (CH_2), 77.2 (CH), 73.9 (CH), 69.7 (CH_2), 67.2 (CH_2), 52.2 (CH_3), 28.0 (CH_3), 25.5 (CH_3), 13.2 (CH_3); HMRS (ESI) calcd for $C_{19}H_{26}O_6Na^+$ $(M+Na)^+$ 373.1627, found 373.1618.

A mixture of unsaturated methylester **37** (2.27 g) was dissolved in AcOH/H_2O (4:1, 20 mL) at room temperature. This solution was warmed to 40 °C, and stirred for 1 d at 40 °C. The solution was cooled to room temperature, and concentrated. Acetic acid and H_2O were azeotropically removed from EtOH (4x 40 mL) and toluene (20 mL) under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane 3:1) to give 1.62 g of allylic vicinal diol **38** (87%, 2 steps): a colorless oil; $[\alpha]^{27}_D$ +9.6 (*c* 1.16, $CHCl_3$); IR (film) 3435, 2951, 2886, 1715, 1245, 1122, 1042, 750 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39–7.28 (m, 5H), 6.71 (dd, *J* = 8.6, 1.5 Hz, 1H), 4.79 (d, *J* = 8.9 Hz, 1H), 4.78 (d, *J* = 8.9 Hz, 1H), 4.64 (d, *J* = 12.1 Hz, 1H), 4.61 (d, *J* = 12.1 Hz, 1H), 4.57 (ddd, *J* = 8.6, 5.2, 5.2 Hz, 1H), 3.82 (dddd, *J* = 6.3, 5.2, 4.6, 3.8 Hz, 1H), 3.74 (s, 3H), 3.72 (dd, *J* = 10.6, 3.8 Hz, 1H), 3.70 (dd, *J* = 10.6, 6.3 Hz, 1H), 3.02 (d, *J* = 4.6 Hz, 1H), 2.67 (d, *J* = 5.2 Hz, 1H), 1.90 (d, *J* = 1.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.1 (C), 138.7 (CH), 137.5 (C), 130.8 (C), 128.6 (CH), 128.1 (CH), 128.0 (CH), 95.5 (CH_2), 72.5 (CH), 70.1 (CH_2), 69.9 (CH), 69.7 (CH_2), 52.2 (CH_3), 13.3 (CH_3); HMRS (ESI) calcd for $C_{16}H_{22}O_6Na^+$ $(M+Na)^+$ 333.1314, found 333.1313.

Methyl (*E*)-3-((2*S*,5*R*)-2-amino-5-(((benzyloxy)methoxy) methyl)-2-(trichloromethyl)-1,3-dioxolan-4-yl)-2-methylacr ylate (32): A solution of DBU (290 μL, 2.0 mmol) and CH_2Cl_2 (10 mL) was added to a mixture of allylic vicinal diol **38** (2.02 g, 6.51 mmol), $ZnCl_2$ (88.9 mg, 651 μmol), CCl_3CN (850 μL, 8.5 mmol) and CH_2Cl_2 (120 mL) at 0 °C. The resulting solution was maintained at 0 °C for 17 h, quenched with H_2O (40 mL) and extracted with $CHCl_3$ (2x 40 mL). The combined organic extracts were washed with brine (30 mL), dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:2) to give 2.65 g of cyclic orthoamide **32** (90%): a colorless oil; $[\alpha]^{27}_D$ –21.8 (*c* 1.12, $CHCl_3$); IR (film) 3417, 3337, 2950, 2887, 1718, 1251, 1200, 1113, 1046, 805 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37–7.27 (m, 5H), 6.77 (dq, *J* = 8.9, 1.5 Hz, 1H), 5.45 (dd, *J* = 10.9, 8.9 Hz, 1H), 4.84 (ddd, *J* = 10.9, 7.7, 4.6 Hz, 1H), 4.75 (d, *J* = 8.3 Hz, 1H), 4.74 (d, *J* = 8.3 Hz, 1H), 4.61 (d, *J* = 11.8 Hz, 1H), 4.56 (d, *J* = 11.8 Hz, 1H), 3.78 (dd, *J* = 10.6, 7.7 Hz, 1H), 3.74 (s, 3H), 3.51 (dd, *J* = 10.6, 4.6 Hz, 1H), 2.58 (s, 2H), 1.92 (d, *J* = 1.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.4 (C), 137.7 (C), 134.0 (CH), 132.4 (C), 128.6 (CH), 128.1 (CH), 127.9 (CH), 114.7 (C), 102.3 (C), 94.9 (CH_2), 79.4 (CH), 75.9 (CH), 69.7 (CH_2), 66.2 (CH_2), 52.3 (CH_3), 13.5 (CH_3); HMRS (ESI) calcd for $C_{18}H_{22}Cl_3NO_6Na^+$ $(M+Na)^+$ 476.0410, found 476.0408.

Methyl (2*S*,5*R*,*E*)-6-((benzyloxy)methoxy)-5-hydroxy-2-methyl-2-(2,2,2-trichloroacetamido)hex-3-enoate (33): A sealed tube was charged with cyclic orthoamide **32** (438 mg, 963 μmol), 2,6-di-*tert*-butylhydroxytoluene (10.6 mg, 48.1 μmol) and *t*-BuPh (9.6 mL). The solution was heated to 220 ºC for 13 h. After cooling to room temperature, the resulting mixture was directly purified by silica gel column chromatography (EtOAc/hexane 1:3 to 1:2) to give 295 mg of allylic amino alcohol **33** (67%): a yellow oil; $[\alpha]^{27}_D$ +25.1 (*c* 1.15, $CHCl_3$); IR (film) 3469, 3427, 3373, 2952, 2885, 1721, 1499, 1040, 822 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.38–7.28 (m, 5H), 6.00 (dd, *J* = 15.8, 1.5 Hz, 1H), 5.76 (dd, *J* = 15.8, 5.2 Hz, 1H), 4.80 (d, *J* = 8.6 Hz, 1H), 4.79 (d, *J* = 8.6 Hz, 1H), 4.64 (d, *J* = 13.2 Hz, 1H), 4.61 (d, *J* = 13.2 Hz, 1H), 4.40–4.34 (m, 1H), 3.80 (s, 3H), 3.71 (dd, *J* = 10.6, 3.2 Hz, 1H), 3.49 (dd, *J* = 10.6, 7.8 Hz, 1H), 2.82 (d, *J* = 3.8 Hz, 1H), 1.78 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5 (C), 160.2 (C), 137.5 (C), 130.9 (CH), 129.3 (CH), 128.7 (CH), 128.1 (CH), 128.1 (CH), 95.4 (CH_2), 92.7 (C), 72.9 (CH_2), 70.6 (CH), 70.0 (CH_2), 61.2 (C), 53.7 (CH_3), 22.1 (CH_3); HMRS (ESI) calcd for $C_{18}H_{22}Cl_3NO_6Na^+$ $(M+Na)^+$ 476.0410, found 476.0395.

Direct dihydroxylation of allylic alcohol 33: *N*-Methylmorpholine *N*-oxide (5.6 mg, 47.6 μmol) was added to a solution of allylic amino alcohol **33** (10.8 mg, 23.8 μmol), osmium tetroxide (0.1 M in CH_2Cl_2, 12 μL, 1.2 μmol) and CH_2Cl_2 saturated with H_2O (2.4 mL) at 40 °C. After stirring at 40 °C for 2.5 d, the reaction was quenched with saturated aqueous $NaHSO_3$ (4 mL) and extracted with $CHCl_3$ (3x 10 mL). The combined organic extracts were washed with brine (3 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:2) to give 7.6 mg of lactone **47** (70%): white crystals, mp 155.0–156.0 °C; $[\alpha]^{26}_D$ –25.3 (*c* 1.00, $CHCl_3$); IR (film) 3371, 2960, 2944, 1770, 1709, 1197, 1095, 1022, 817 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37–7.29 (m, 5H), 7.24 (brs, 1H), 4.89 (dd, *J* = 7.9, 3.2 Hz, 1H), 4.84 (s, 2H), 4.78 (dd, *J* = 8.5, 7.9 Hz, 1H), 4.67 (d, *J* = 11.5 Hz, 1H), 4.63 (d, *J* = 11.5 Hz, 1H), 4.19–4.14 (m, 1H), 4.15 (d, *J* = 3.2 Hz, 1H), 3.90 (dd, *J* = 11.0, 2.9 Hz, 1H), 3.84 (dd, *J* = 11.0, 7.5 Hz, 1H), 3.65 (d, *J* = 4.0 Hz, 1H), 1.62 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.2 (C), 162.9 (C), 137.5 (C), 128.7 (CH), 128.2 (CH), 128.1 (CH), 95.5 (CH_2), 91.3 (C), 77.8 (CH), 74.1 (CH), 70.1 (CH_2), 69.7 (CH), 69.3 (CH_2), 61.6 (C), 18.6 (CH_3); HRMS (ESI), calcd for $C_{17}H_{20}Cl_3NO_7Na^+$ $(M+Na)^+$ 478.0203, found 478.0208.

Methyl (4*S*,5*S*)-5-((*E*)-3-((benzyloxy)methoxy)prop-1-en-1-yl)-4-methyl-2-(trichloromethyl)-4,5-dihydrooxazole-4-ca rboxylate (34): Tributylphosphine (610 μL, 1.6 mmol) was added to a solution of allylic amino alcohol **33** (721 mg, 1.59 mmol), DEAD (40wt% in toluene, 2.5 mL, 6.4 mmol) and toluene (160 mL) at 0 °C. This solution was maintained for 20

min at 0 °C, quenched with H_2O (30 mL), and extracted with EtOAc (3x 20 mL). The combined organic extracts were washed with brine (60 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:7) to give 579 mg of oxazoline **34** (83%) and 39 mg of ***epi*-34** (6%). Oxazoline **34**: a colorless oil; $[\alpha]^{25}_D$ +33.4 (*c* 1.11, $CHCl_3$); IR (film) 2951, 2886, 1743, 1661, 1258, 1117, 1040, 947, 794 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40–7.27 (m, 5H), 6.00 (dtd, *J* = 15.8, 5.2, 0.9 Hz, 1H), 5.74 (ddt, *J* = 15.8, 7.4, 1.5 Hz, 1H), 5.01 (dd, *J* = 7.4, 0.9 Hz, 1H), 4.76 (s, 2H), 4.60 (s, 2H), 4.14 (dd, *J* = 5.2, 1.5 Hz, 2H), 3.71 (s, 3H), 1.66 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2 (C), 163.4 (C), 137.7 (C), 133.2 (CH), 128.6 (CH), 128.0 (CH), 127.9 (CH), 124.1 (CH), 94.0 (CH_2), 92.1 (CH), 86.4 (C), 78.4 (C), 69.6 (CH_2), 66.5 (CH_2), 52.7 (CH_3), 23.9 (CH_3); HMRS (ESI) calcd for $C_{18}H_{20}Cl_3NO_5Na^+$ $(M+Na)^+$ 458.0305, found 458.0321. Oxazoline ***epi*-34**: a colorless oil; $[\alpha]^{22}_D$ +49.4 (*c* 1.27, $CHCl_3$); IR (film) 2952, 2888, 1736, 1653, 1243, 1115, 1039, 935, 795 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39–7.27 (m, 5H), 6.07 (dt, *J* = 15.5, 5.2 Hz, 1H), 5.82 (ddt, *J* = 15.5, 7.2, 1.5 Hz, 1H), 5.58 (d, *J* = 7.2 Hz, 1H), 4.80 (s, 2H), 4.62 (s, 2H), 4.20 (dd, *J* = 5.2, 1.5 Hz, 2H), 3.83 (s, 3H), 1.43 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5 (C), 162.6 (C), 137.8 (C), 132.9 (CH), 128.6 (CH), 128.03 (CH), 127.95 (CH), 123.7 (CH), 94.2 (CH_2), 88.3 (CH), 86.4 (C), 77.4 (C), 69.7 (CH_2), 66.8 (CH_2), 53.4 (CH_3), 20.3 (CH_3); HMRS (ESI) calcd for $C_{18}H_{20}Cl_3NO_5Na^+$ $(M+Na)^+$ 458.0305, found 458.0305.

(3a*S*,6*R*,6a*R*)-6-((*S*)-2-((Benzyloxy)methoxy)-1-hydroxyethyl)-3a-methyl-2-(trichloromethyl)-6,6a-dihydrofuro[3,4-d]oxazol-4(3a*H*)-one (39): *N*-Methylmorpholine *N*-oxide (114 mg, 976 μmol) was added to a solution of oxazoline **34** (213 mg, 488 μmol), osmium tetroxide (0.1 M in CH_2Cl_2, 240 μL, 24.4 μmol) and CH_2Cl_2 saturated with H_2O (16 mL) at 40 °C. After stirring at 40 °C for 15 h, the reaction was quenched with saturated aqueous $NaHSO_3$ (15 mL) and extracted with $CHCl_3$ (3x 10 mL). The combined organic extracts were washed with brine (15 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:4) to give 65.2 mg of hydroxylactone **39** (30%) and 107 mg of hydroxylactone **40** (50%). Hydroxylactone **39**: white crystals, mp 146-147 °C; $[\alpha]^{23}_D$ +60.9 (*c* 0.80, $CHCl_3$); IR (film) 3428, 2927, 2871, 1757, 1644, 1101, 1016, 989, 813 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.43–7.27 (m, 5H), 5.08 (d, *J* = 5.7 Hz, 1H), 4.83 (s, 2H), 4.72 (dd, *J* = 5.7, 5.7 Hz, 1H), 4.67 (d, *J* = 12.0 Hz, 1H), 4.62 (d, *J* = 12.0 Hz, 1H), 4.14 (dddd, *J* = 5.7, 5.2, 4.9, 4.0 Hz, 1H), 3.89 (dd, *J* = 10.9, 4.9 Hz, 1H), 3.85 (dd, *J* = 10.9, 4.0 Hz, 1H), 2.67 (d, *J* = 5.2 Hz, 1H), 1.68 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.6 (C), 162.9 (C), 137.6 (C), 128.7 (CH), 128.1 (CH), 128.0 (CH), 95.8 (CH_2), 87.2 (CH), 85.5 (C), 80.6 (CH), 70.3 (CH_2), 69.2 (CH), 69.0 (C), 69.0 (CH_2), 20.7 (CH_3); HMRS (ESI) calcd for $C_{17}H_{18}Cl_3NO_6Na^+$ $(M+Na)^+$ 460.0097, found 460.0091. Hydroxylactone **40**: a colorless oil; $[\alpha]^{26}_D$ +43.1 (*c* 1.13, $CHCl_3$); IR (film) 3436, 2938, 2886, 1788, 1650, 1282, 1102, 1046, 800 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38–7.30 (m, 5H), 5.26 (d, *J* = 1.2 Hz, 1H), 4.82 (d, *J* = 6.9 Hz, 1H), 4.77 (d, *J* = 6.9 Hz, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.64 (dd, *J* = 1.4, 1.2 Hz, 1H), 4.62 (d, *J* = 12.0 Hz, 1H), 4.06 (dddd, *J* = 9.2, 8.1, 4.0, 1.4 Hz, 1H), 3.87 (dd, *J* = 10.9, 4.0 Hz, 1H), 3.69 (dd, *J* = 10.9, 8.1 Hz, 1H), 3.25 (d, *J* = 9.2 Hz, 1H), 1.71 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.2 (C), 162.9 (C), 137.2 (C), 128.7 (CH), 128.2 (CH), 128.1 (CH), 95.8 (CH_2), 89.3 (CH), 85.5 (C), 82.9 (CH), 70.9 (CH), 70.4 (CH_2), 70.1 (C), 70.1 (CH_2), 19.8 (CH_3); HMRS (ESI) calcd for $C_{17}H_{18}Cl_3NO_6Na^+$ $(M+Na)^+$ 460.0097, found 460.0096.

***N*-((4*S*,4a*S*,7*S*,7a*R*)-4-(((Benzyloxy)methoxy)methyl)-2,2,7-trimethyl-6-oxotetrahydro-4*H*-furo[3,2-d][1,3]dioxin-7-yl)-2,2,2-trichloroacetamide (41):** A solution of CCl_3CO_2H (14.4 mg, 88.4 μmol), H_2O (1.6 μL) and CH_2Cl_2 (4.4 mL) was added to a solution of hydroxylactone **39** (38.8 mg, 88.4 μmol) and CH_2Cl_2 (4.4 mL) at room temperature. The solution was maintained at room temperature for 19 h, and quenched with Et_3N (25 μL, 180 μmol) at room temperature. 2,2-Dimethoxypropane (430 μL, 3.5 mmol) and CSA (41.1 mg, 177 μmol) were then added to the solution of the diol at room temperature. The resulting solution was maintained at room temperature for 3 d, quenched with saturated aqueous $NaHCO_3$ (5 mL) and extracted with $CHCl_3$ (3x 5 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:9 to 1:7) to give 39.0 mg of cyclic acetal **41** (89%): a colorless oil; $[\alpha]^{27}_D$ +93.5 (*c* 1.02, $CHCl_3$); IR (film) 3409, 2942, 2888, 1789, 1722, 1512, 1163, 1119, 1045 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37–7.28 (m, 5H), 7.08 (s, 1H), 4.81 (s, 2H), 4.78 (d, *J* = 2.3 Hz, 1H), 4.64 (d, *J* = 11.8 Hz, 1H), 4.61 (d, *J* = 11.8 Hz, 1H), 4.40 (dd, *J* = 2.3, 2.3 Hz, 1H), 4.23 (ddd, *J* = 6.9, 6.9, 2.3 Hz, 1H), 3.84 (dd, *J* = 10.0, 6.9 Hz, 1H), 3.78 (dd, *J* = 10.0, 6.9 Hz, 1H), 1.64 (s, 3H), 1.44 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.6 (C), 161.3 (C), 137.8 (C), 128.6 (CH), 128.00 (CH), 127.98 (CH), 98.8 (C), 95.4 (CH_2), 92.0 (C), 71.6 (CH), 71.1 (CH), 70.0 (CH_2), 67.4 (CH), 66.8 (CH_2), 62.6 (C), 28.9 (CH_3), 19.2 (CH_3), 17.2 (CH_3); HMRS (ESI) calcd for $C_{20}H_{24}Cl_3NO_7Na^+$ $(M+Na)^+$ 518.0516, found 518.0511.

***N*-((4*S*,4a*S*,7*S*,7a*R*)-4-(Hydroxymethyl)-2,2,7-trimethyl-6-oxotetrahydro-4*H*-furo[3,2-d][1,3]dioxin-7-yl)acetamide (42):** Palladium on carbon (10 wt%, 10.2 mg) was added to a solution of cyclic acetal **41** (5.1 mg, 10.3 μmol), Et_3N (10 μL, 72 μmol) and MeOH (1.5 mL). The flask was purged with hydrogen. The mixture was stirred under hydrogen atmosphere (1 atm) at room temperature for 2.5 h, filtered through Celite, washed with MeOH and concetrated. The residue was purified by silica gel column chromatography (MeOH/$CHCl_3$ 1:19) to give 2.8 mg of primary alcohol **42** (100%): white crystals, mp 224–225 °C; $[\alpha]^{28}_D$ +157.7 (*c* 1.04, $CHCl_3$); IR (film) 3311, 2967, 2896, 1785, 1658, 1539, 1170, 1117, 1057 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.91 (s, 1H), 4.82 (d, *J* = 2.0 Hz, 1H), 4.37 (dd, *J* = 2.0, 1.7 Hz, 1H), 4.21 (ddd, *J* = 7.2, 5.5, 1.7 Hz, 1H), 3.92–3.79 (m, 2H), 2.05 (brs, 1H), 2.00 (s, 3H), 1.60 (s, 3H), 1.46 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.9 (C), 170.1 (C), 98.8 (C), 71.6 (CH), 71.5 (CH), 68.9 (CH), 62.3 (CH_2), 61.6 (C), 29.1 (CH_3), 23.5 (CH_3), 19.2 (CH_3), 18.0 (CH_3); HMRS (ESI) calcd for $C_{12}H_{19}NO_6Na^+$ $(M+Na)^+$ 296.1110, found 296.1104.

***N*-((4*S*,4a*R*,7*S*,7a*R*)-4-((*E*)-8-(2-Hexyl-1,3-dioxolan-2-yl)oct-1-en-1-yl)-2,2,7-trimethyl-6-oxotetrahydro-4*H*-furo[3,2-d][1,3]dioxin-7-yl)acetamide (44):** A solution of primary alcohol **42** (4.2 mg, 15.4 μmol) and CH_2Cl_2 (1.5 mL) was added to a mixture of Dess-Martin periodinane (32.7 mg, 77.0 μmol) and $NaHCO_3$ (32.3 mg, 385 μmol) and CH_2Cl_2 (1.1 mL) at 0 °C. The mixture was allowed to warm to room temperature and stirred at room temperature for 2.5 h. The resulting mixture was filtrated to remove white solid, which was washed with EtOAc (15 mL). The combined filtrate was then concentrated to give unstable aldehyde **43**, which was used in the next step without further purification.

In a glove box, $CrCl_2$ (28.4 mg, 231 μmol) was dissolved in THF (1.0 mL) and DMF (18 μL, 230 μmol). Meanwhile, a mixture of above aldehyde **43** and diiodide **35** (24.6 mg, 48.4 μmol), which was dried by azeotroping with toluene (3x 500 μL) beforehand, was dissolved in THF (2.1 mL, dehydrated,

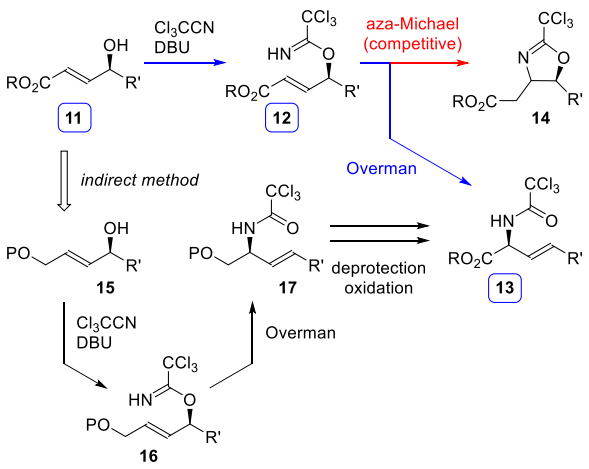
stabilizer free, Wako Pure Chemical Industries, Ltd.). The solution of **43** and **35** was added to the mixture of $CrCl_2$ at room temperature. The reaction vessel was removed from the glove box. The resulting deep green solution was heated to 35 °C, stirred for 1 d, quenched with H_2O (5 mL), and extracted with EtOAc (6x 5 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4, and concentrated. The residue was filtered through a pad of silica gel. The filtrate was then concentrated. The resulting residue was purified by silica gel column chromatography (EtOAc/hexane 1:3 to 2:1) and preparative TLC (EtOAc/hexane 1:1) to give 4.5 mg of ***E*-44** (58%) and 0.8 mg of the ***Z*-44** (10%). ***E*-44**: a colorless oil; $[\alpha]^{24}_D$ +121.2 (*c* 1.05, $CHCl_3$); IR (film) 3379, 2929, 2856, 1788, 1670, 1201, 1163 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.91 (s, 1H), 5.86 (dt, *J* = 15.5, 6.6 Hz, 1H), 5.65 (dd, *J* = 15.5, 7.7 Hz, 1H), 4.80 (d, *J* = 2.0 Hz, 1H), 4.47 (dd, *J* = 7.7, 1.5 Hz, 1H), 4.21 (dd, *J* = 2.0, 1.5 Hz, 1H), 3.91 (s, 4H), 2.10–2.03 (m, 2H), 2.00 (s, 3H), 1.70–1.14 (m, 20H), 1.58 (s, 3H), 1.46 (s, 3H), 1.36 (s, 3H), 0.87 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.0 (C), 170.1 (C), 136.8 (CH), 125.0 (CH), 112.0 (C), 98.6 (C), 74.4 (CH), 71.4 (CH), 70.1 (CH), 65.0 (CH_2), 61.8 (C), 37.3 (CH_2), 37.2 (CH_2), 32.4 (CH_2), 32.0 (CH_2), 29.9 (CH_2), 29.7 (CH_2), 29.34 (CH_2), 29.29 (CH_3), 28.8 (CH_2), 23.95 (CH_2), 23.89 (CH_2), 23.5 (CH_3), 22.7 (CH_2), 19.3 (CH_3), 17.9 (CH_3), 14.2 (CH_3); HMRS (ESI) calcd for $C_{28}H_{47}NO_7Na^+$ $(M+Na)^+$ 532.3250, found 532.3253. ***Z*-44**: a colorless oil; $[\alpha]^{21}_D$ +52.8 (*c* 0.37, $CHCl_3$); IR (film) 3380, 2928, 2856, 1789, 1671, 1201, 1164, 1110 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.91 (s, 1H), 5.72 (ddd, *J* = 11.2, 7.5, 7.5 Hz, 1H), 5.63 (dd, *J* = 11.2, 8.0 Hz, 1H), 4.86 (dd, *J* = 8.0, 1.7 Hz, 1H), 4.82 (d, *J* = 2.0 Hz, 1H), 4.17 (dd, *J* = 2.0, 1.7 Hz, 1H), 3.92 (s, 4H), 2.16–2.05 (m, 2H), 2.00 (s, 3H), 1.79–1.12 (m, 20H), 1.59 (s, 3H), 1.50 (s, 3H), 1.36 (s, 3H), 0.88 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.0 (C), 170.1 (C), 135.8 (CH), 124.5 (CH), 112.0 (C), 98.6 (C), 74.0 (CH), 71.4 (CH), 65.0 (CH_2), 64.6 (CH), 61.9 (C), 37.29 (CH_2), 37.26 (CH_2), 32.0 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.4 (CH_2), 29.4 (CH_3), 29.3 (CH_2), 28.2 (CH_2), 24.0 (CH_2), 23.9 (CH_2), 23.5 (CH_3), 22.7 (CH_2), 19.2 (CH_3), 17.9 (CH_3), 14.2 (CH_3); HMRS (ESI) calcd for $C_{28}H_{47}NO_7Na^+$ $(M+Na)^+$ 532.3250, found 532.3241.

***N*-((3*S*,4*R*,5*R*)-4-Hydroxy-5-((*S*,*E*)-1-hydroxy-10-oxohexadec-2-en-1-yl)-3-methyl-2-oxotetrahydrofuran-3-yl)acetamide (45):** *E*-olefin **44** (6.2 mg, 12.2 μmol) was dissolved in AcOH/H_2O (4:1, 1.2 mL) at room temperature. This solution was warmed to 40 °C, and stirred for 12 h at 40 °C. The solution was cooled to room temperature, and concentrated. Acetic acid and H_2O were azeotropically removed from EtOH (2x 10 mL) under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:1) to give 4.8 mg of diol **45** (92%): a colorless oil; $[\alpha]^{23}_D$ +21.0 (*c* 0.52, $CHCl_3$); IR (film) 3351, 2929, 2856, 1781, 1709, 1656, 1191 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.20 (s, 1H), 5.94 (dtd, *J* = 15.5, 6.6, 0.9 Hz, 1H), 5.57 (ddt, *J* = 15.5, 6.3, 1.4 Hz, 1H), 4.62–4.56 (m, 2H), 4.35 (dd, *J* = 6.9, 3.7 Hz, 1H), 3.47 (d, *J* = 4.9 Hz, 1H), 2.69 (brs, 1H), 2.38 (t, *J* = 7.2 Hz, 2H), 2.38 (t, *J* = 7.2 Hz, 2H), 2.23–1.90 (m, 2H), 2.07 (s, 3H), 1.83–1.03 (m, 16H), 1.51 (s, 3H), 0.87 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.0 (C), 176.1 (C), 171.6 (C), 135.6 (CH), 126.0 (CH), 84.7 (CH), 75.3 (CH), 70.8 (CH), 62.5 (C), 43.0 (CH_2), 42.9 (CH_2), 32.4 (CH_2), 31.8 (CH_2), 29.13 (CH_2), 29.08 (CH_2), 29.0 (CH_2), 28.8 (CH_2), 24.0 (CH_2), 23.9 (CH_2), 23.5 (CH_3), 22.6 (CH_2), 20.5 (CH_3), 14.2 (CH_3); HMRS (ESI) calcd for $C_{23}H_{39}NO_6Na^+$ $(M+Na)^+$ 448.2675, found 448.2672.

Sphingofungin F (1): Sodium hydroxide aq. (2 M, 180 μL, 360 μmol) was added to a solution of diol **45** (4.7 mg, 11.0 μmol) and MeOH (180 μL) at room temperature. This solution was warmed to 65 °C, and stirred for 1.5 h at 65 °C. The solution was cooled to room temperature. Amberlite IRC-76 resin (ca. 400 mg, pre-treated with 2 M HCl aq., H_2O and MeOH) was then added to the solution until pH 7 at room temperature. The resulting mixture was filtrated to remove the resin, which was washed with MeOH (200 mL). The combined filtrate was then concentrated. The residue was purified by silica gel column chromatography (pre-treated with MeOH, MeOH/$CHCl_3$ 1:1) to give 4.3 mg of sphingofungin F (**1**) (98%): white crystals, mp 141–143 °C; $[\alpha]^{24}_D$ +0.13 (*c* 0.09, MeOH); IR (film) 3319, 3194, 2928, 2856, 1713, 1624, 1464, 1404, 1108 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 5.78 (dt, *J* = 15.2, 6.6 Hz, 1H), 5.46 (dd, *J* = 15.2, 7.8 Hz, 1H), 4.11 (dd, *J* = 7.8, 7.2 Hz, 1H), 3.87 (s, 1H), 3.68 (d, *J* = 7.2 Hz, 1H), 2.45 (t, *J* = 7.2 Hz, 2H), 2.44 (t, *J* = 7.5 Hz, 2H), 2.06 (td, *J* = 6.9, 6.6 Hz, 2H), 1.63–1.50 (m, 4H), 1.49 (s, 3H), 1.48–1.20 (m, 12H), 0.90 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.4 (C), 175.2 (C), 135.7 (CH), 130.2 (CH), 76.2 (CH), 75.7 (CH), 72.5 (CH), 66.7 (C), 43.5 (CH_2), 43.5 (CH_2), 33.4 (CH_2), 32.8 (CH_2), 30.2 (CH_2), 30.2 (CH_2), 30.0 (CH_2), 30.0 (CH_2), 24.9 (CH_2), 24.9 (CH_2), 23.6 (CH_2), 21.8 (CH_3), 14.4 (CH_3); HMRS (ESI) calcd for $C_{21}H_{40}NO_6^+$ $(M+H)^+$ 402.2856, found 402.2856.

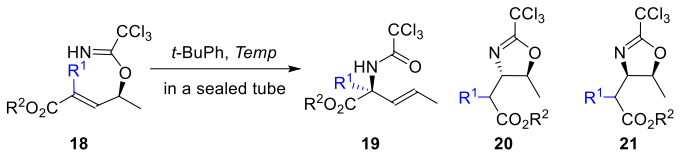
3. Results and Discussion

3.1 Overman Rearrangement of α,β-Unsaturated Esters. The allylic trichloroimidate rearrangement, the so-called Overman rearrangement, has been recognized as a promising C-N bond forming reaction.[5] The reaction is especially useful when subjected to an enantiopure allylic secondary alcohol, enabling the stereoselective installation of a trichloroacetamide group through chirality transfer.[11] Another conspicuous feature of the Overman rearrangement is the wide substrate scope. The rearrangement is known to be applicable to densely functionalized molecules. Therefore, the Overman rearrangement has been utilized in a number of enantioselective total synthesis of complex natural products. However, in spite of the extensive study, the Overman rearrangement has a longstanding problematic substrate; α,β-unsaturated ester **12** (Scheme 2).[12] In 1992, the Larchevêque group reported their attempt at the Overman rearrangement of unsaturated ester **12**. However, it did not provide amino acid derivative **13**, but instead resulted in the formation of oxazoline **14** due to the competitive aza-Michael addition.[12b] They finally synthesized

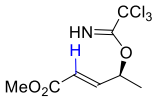
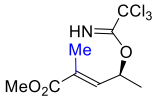
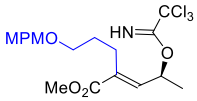
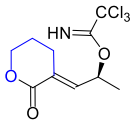


Scheme 2. Utility and limitation of the Overman rearrangement of an α,β-unsaturated ester

Table 1. The Overman rearrangement of α,β-unsaturated esters.[a)]



18 19 20 21

Entry	18	Temp (°C)	Time (h)	Yields [%][b)]		
				19[c)]	**20**	**21**
1	 **18a** (>99% ee)	140	96	46 (>99% ee)	31	3
2		160	14	54 (>99% ee)	7	11
3		180	3	96 (>99% ee)	0	0
4	 **18b** (>99% ee)	140	63	83 (>99% ee)	0	0
5		180	6	89 (>99% ee)	0	0
6	 **18c** (96% ee)	140	63	80 (96% ee)	0	0
7		180	6	90 (96% ee)	0	0
8	 **18d** (96% ee)	140	8	18 (96% ee)	72[d)]	0
9		180	2	39 (96% ee)	49[e)]	0

a) Imidate **18**, *t*-BuPh (0.015 M) in a sealed tube. b) Yields of isolated product after purification by column chromatography are given. c) The enantio excesses were determined by chiral HPLC. d) The diastereomeric ratio was 1.5:1. e) The diastereomeric ratio was 2.0:1.

amino acid derivative **13** by indirect method using protected primary alcohol **15**, which required a number of extra steps including protecting group manipulations[13] and redox reactions.[14] We believed that, if the direct Overman rearrangement of α,β-unsaturated ester **12** becomes possible, amino acid derivative **13** could be obtained in a step-economical fashion.[14b,15,16]

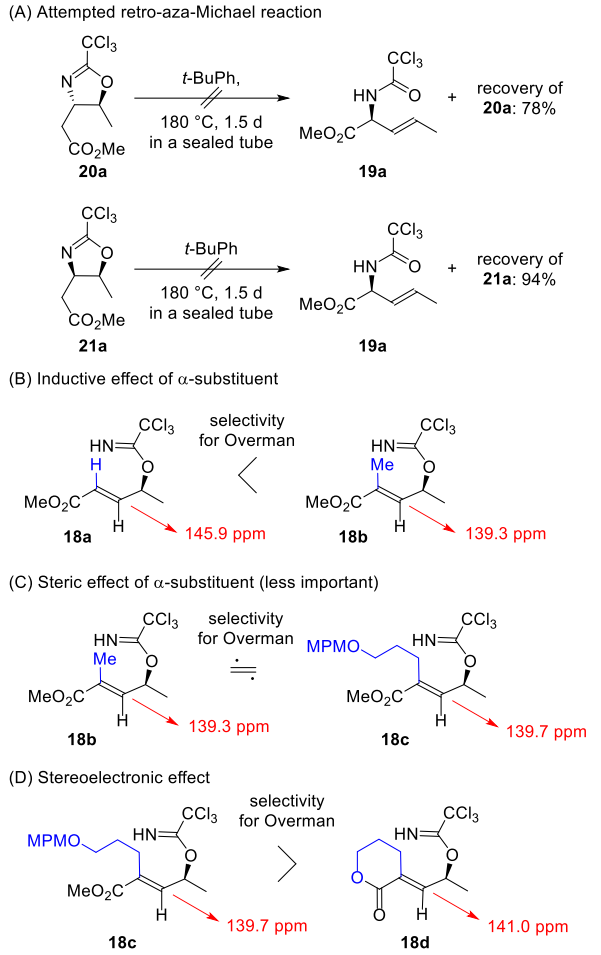
Our study began with the reinvestigation of the Overman rearrangement of α,β-unsaturated esters (Table 1). (*E*)-Unsaturated ester **18a**[9,17] (R^1 = H, >99% ee) was dissolved in *t*-BuPh, and was heated to 140 °C for 4 days in a sealed tube (Table 1, Entry 1). As reported by Larchevêque, oxazolines **20a** and **21a** were produced through the aza-Michael addition in 31% and 3% yields, respectively. However, the desired α-substituted amidoester **19a** was also obtained through the Overman rearrangement in 46% yield. The rearrangement proceeded via the complete chirality transfer of the allylic alcohol, giving α-substituted amidoester **19a** in >99% ee. We found that higher reaction temperature resulted in better selectivity, favoring the Overman rearrangement over the aza-Michael addition. The reaction of unsaturated ester **18a** at 160 °C provided amidoester **19a** in 54% yield, along with oxazolines **20a** and **21a** in 18% combined yield (Table 1, Entry 2). The best result was obtained at 180 °C with α-substituted amidoester **19a** isolated in 96% yield as a sole product (Table 1, Entry 3).

The effect of a substituent at the α-position of unsaturated esters proved to be crucial at 140 °C in term of the selectivity between the Overman rearrangement and the aza-Michael addition (Table 1). Initially, we were concerned that installation of an alkyl substituent at the α-position would increase the steric hindrance, resulting in inhibition of the Overman rearrangement (Table 1, Entry 4). However, use of unsaturated ester **18b**[9] (R^1 = Me) promoted the Overman rearrangement selectively, providing α,α-disubstituted amidoester **19b** in 83% yield with >99% ee as a sole product. A larger substituent (R^1 = $CH_2CH_2CH_2OMPM$) in **18c**[9] had no detrimental effect for it gave α,α-disubstituted amidoester **19c** in 80% yield (Table 1, Entry 6). In contrast, the aza-Michael addition became a dominant pathway when using α,β-unsaturated lactone **18d**,[9] affording α,α-disubstituted amino lactone **19d** in 18% yield, along with oxazoline **20d** in 72% yield (Table 1, Entry 8).

All substrates **18a-d** showed better results at 180 °C than 140 °C in terms of both yield and selectivity (Table 1). The

Overman rearrangement of three acyclic unsaturated esters **18a-c** took place in high yields without any detection of the aza-Michael products (Table 1, Entries 3, 5, and 7). Even unsaturated lactone **18d** provided α,α-disubstituted amino lactone **19d** in 39% yield, although the aza-Michael reaction was not completely suppressed (Table 1, Entry 9).

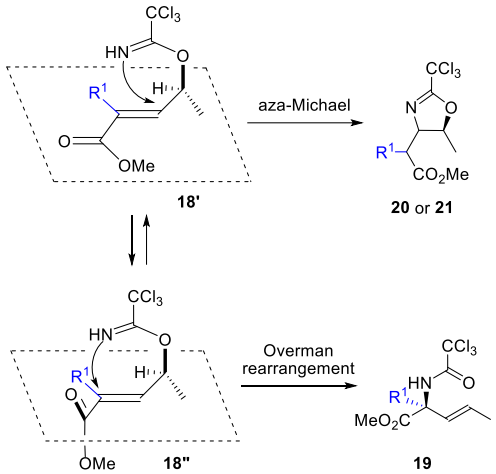
To elucidate the controlling factors favoring the Overman rearrangement, first we confirmed the reversibility of the aza-Michael reaction (Scheme 3A). Initially, we conceived that the Overman rearrangement showed higher selectivity at higher temperature because the aza-Michael reaction was reversible at 180 °C, while the Overman rearrangement was irreversible. However, re-exposure of isolated oxazolines **20a** and **21a** to high temperature at 180 °C for 1.5 days did not afford amidoester **19a**, but only resulting in the recovery of oxazolines **20a** and **21a**. The results clearly indicated that the selectivity was determined under kinetic control.



Scheme 3. Plausible mechanistic rationale for the selectivity between the Overman rearrangement and the aza-Michael reaction

We next supposed that the selectivity originated from both inductive and steric effects of the α-substituents in the unsaturated esters. The inductive effect of the methyl group was supported by the ^{13}C NMR spectra of α,β-unsaturated esters **18a** and **18b**, which consisted of peaks at 145.9 ppm and 139.3 ppm due to the β-carbons, respectively (Scheme 3B). Thus, **18a** is more electrophilic at the β-position than **18b**, and would promote the aza-Michael addition more than **18b**. In contrast, **18a** has a smaller hydrogen at the α-position than the methyl group of **18b**, and would sterically preferred the Overman rearrangement. Considering the experimental results that unsaturated ester **18b** showed a better selectivity favoring the Overman rearrangement, the inductive effect rather than the steric effect was seen to be a dominant factor in promoting the Overman rearrangement. This tendency was also observed between **18b** and **18c** (Scheme 3C). Unsaturated ester **18c** had a peak at the chemical shift similar to **18b** in the ^{13}C NMR spectrum (139.7 ppm VS. 139.3 ppm), but possesses a larger substituent than **18b**. However, the Overman rearrangement was predominant for both unsaturated esters **18b** and **18c**, regardless of the steric hindrance.

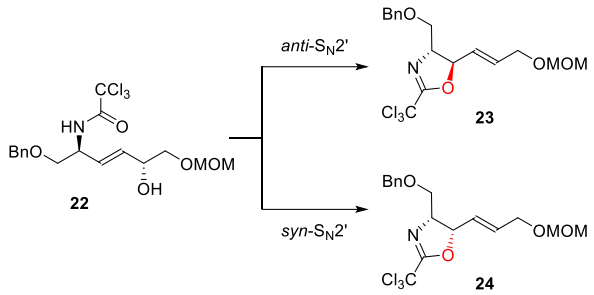
Unsaturated lactone **18d** had the inductive and steric effects similar to that of unsaturated ester **18c** (Scheme 3D), but exhibited much lower selectivity for the Overman rearrangement. We considered that the stereoelectronic effect might rationalize the low selectivity (Scheme 4). When the ester carbonyl group is located in the same plane as the olefin, the aza-Michael reaction (**18'→20 or 21)** might proceed dominantly over the Overman rearrangement. In contrast, the Overman rearrangement would be independent of the conformation of the ester carbonyl group (**18"→19**). The reaction of unsaturated lactone **18d** resulted in the low selectivity because the lactone moiety forced the carbonyl group to be located in the same plane as the double bond. The origin of the unique temperature-dependence was not elucidated, and further studies are necessary to account for the mechanism.[18]



Scheme 4. Plausible stereoelectronic effect in the Overman rearrangement and the aza-Michael reaction

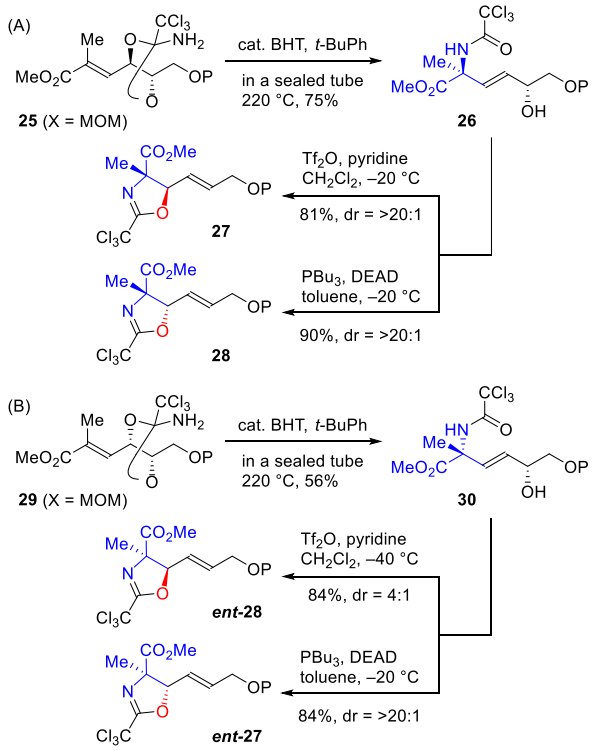
3.2 Stereodivergent intramolecular S_N2' reaction of trichloroacetamides. The next step was the stereodivergent intramolecular S_N2' reaction of the trichloroacetamides to install a β-hydroxy group (Table 2). We evaluated the optimized conditions of the S_N2' reaction using 1,4-amidoalcohol **22**.[9] Treatment of **22** with Tf_2O and pyridine at –40 °C initiated the *anti*-type S_N2' reaction to give oxazolines **23** and **24** in 77% yield with 10:1 diastereoselectivity (Table 2, Entry 1). On the contrary, change in stereoselectivity was observed under the Mitsunobu conditions (Table 2, Entries 2-4). Choice of phosphine reagents was crucial, and the *syn*-type S_N2' reaction took place selectively when PBu_3 and DEAD were used at –20 °C, providing oxazolines **23** and **24** in 83% combined yield with 1:>20 diastereoselectivity (Table 2, Entry 4). Thus, we developed the stereodivergent conditions to give either stereoisomer of oxazolines from a common trichloroacetamides.

Table 2. Stereodivergent S_N2' reaction of trichloroacetamides.



Entry	Conditions	Combined yield [%][a]	**23** : **24**[b]
1	Tf_2O, pyridine CH_2Cl_2, –40 °C	77	10:1
2	PPh_3, DEAD toluene, –20 °C	28	1.3:1
3	$P(OEt)_3$, DEAD toluene, –20 °C	27	3.3:1
4	PBu_3, DEAD toluene, –20 °C	83	<1: 20

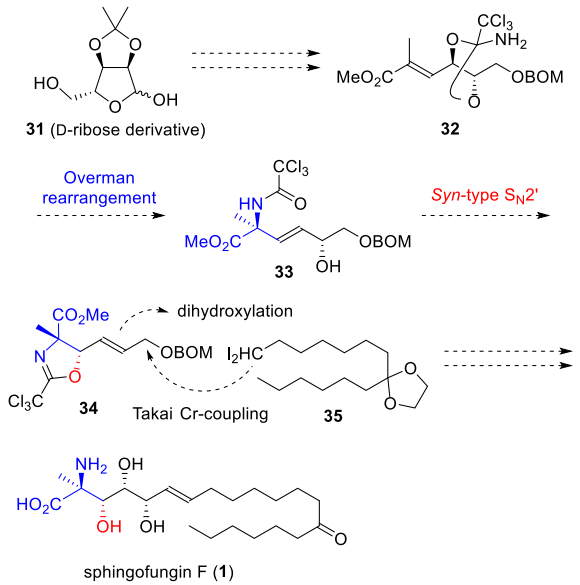
a) Yields of isolated product after purification by column chromatography are given. b) The ratio was determined by ^1H NMR.



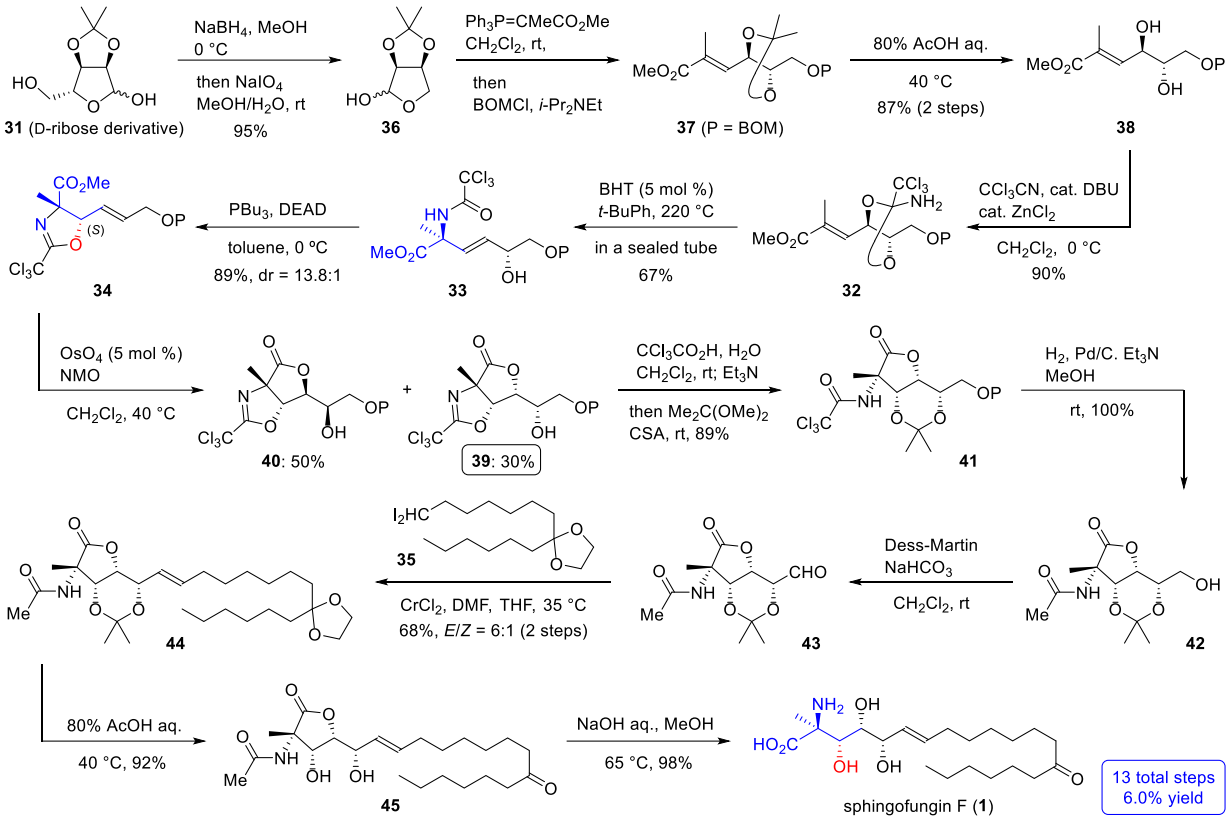
Scheme 5. Synthesis of all four possible diastereomers of a β-hydroxy-α,α-disubstituted amino acid derivative

3.3 Two-step synthesis of β-hydroxy-α,α-disubstituted amino acid derivatives. With the optimized conditions for both the Overman rearrangement and subsequent intramolecular S_N2' reaction in hand, we turned our attention to the synthesis of β-hydroxy-α,α-disubstituted amino acid derivatives (Scheme 5). The orthoamide-type Overman rearrangement of **25**[9] derived from the allylic 1,2-*anti*-diol was achieved at 220 °C in the presence of 2,6-di-*t*-butylhydroxytoluene (BHT, 5 mol%) in a sealed tube, giving α,α-disubstituted amidoester **26** in 75% yield (Scheme 5A). The resulting trichloroacetamide **26** smoothly underwent the stereodivergent intramolecular S_N2' reaction despite the large steric hindrance of the tetrasubstituted carbon center. While the *anti*-type S_N2' reaction of **26** with Tf_2O provided oxazoline **27** in 81% yield with >20:1 diastereoselectivity, the *syn*-type S_N2' reaction under the Mitsunobu conditions gave oxazoline **28** in 90% yield with >20:1 diastereoselectivity. The same sequence was applicable to cyclic orthoamide **29**[9] derived from the allylic 1,2-*syn*-diol, leading to the synthesis of oxazolines ***ent*-28** and ***ent*-27** (Scheme 5B). Thus, we achieved synthesis of all four possible diastereomers of the β-hydroxy-α,α-disubstituted amino acid derivative.

3.4 Total synthesis of sphingofungin F. The Merck Research Laboratories reported the isolation of sphingofungin F (**1**) from a fermentation of *Paecilomyces variotti* in 1992 (Scheme 6).[2] This sphingosine-like compound inhibited serinepalmitoyl transferase, an enzyme essential in the biosynthesis of sphingolipids, and has been expected as an antifungal agent.[19] Structurally, sphingofungin F (**1**) is comprised of the hydrophilic moiety including the β-hydroxy-α,α-disubstituted amino acid, and the hydrophobic side chain. Its important biological activity as well as the unique structure have inspired a number of synthetic chemists, resulting in the total syntheses of sphingofungin F (**1**)[20] and its congeners.[21,22] Our central strategy toward the total synthesis of **1** is based on the two-step sequence involving the Overman rearrangement (**32**→**33**) and subsequent *syn*-type S_N2' reaction (**33**→**34**). Cyclic orthoamide **32**, prepared from D-ribose derivative **31** in enantiomerically pure form, could be converted to β-hydroxy-α,α-disubstituted amino acid derivative **34** with our two-step procedure. The total synthesis of sphingofungin F (**1**) would be accomplished by dihydroxylation of **34**, and $CrCl_2$-mediated Takai coupling[23] with hydrophobic side chain **35**.



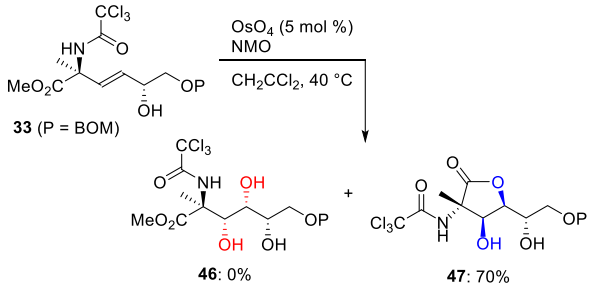
Scheme 6. Synthetic plan toward the total synthesis of sphingofungin F (**1**)



Scheme 7. Total synthesis of sphingofungin F (**1**) by the Overman rearrangement of the α,β-unsaturated ester, and S_N2' reaction

Our total synthesis of sphingofungin F (**1**) commenced with the reduction of D-ribose derivative **31**, and oxidative cleavage of the resulting diol (Scheme 7).[24] The Wittig reaction of the resulting lactol **36**, followed by one-pot protection of the primary alcohol provided BOM ether **37**, which was exposed to 80% AcOH aq to give allylic *anti*-1,2-diol **38**. Treatment of **38** with CCl_3CN (1.3 equiv) and catalytic amount of DBU (30 mol%) in the presence of $ZnCl_2$ (10 mol%) afforded cyclic orthoamide **32** in 90% yield as a single diastereomer.[6d] The orthoamide-type Overman rearrangement of α,β-unsaturated ester **32** was realized under optimized conditions, giving α,α-disubstituted amidoester **33** in 67% yield. It is noteworthy that this Overman rearrangement of **32** had a number of synthetic advantages during the course of the total synthesis. Firstly, sterically hindered α,α-disubstituted amidoester was constructed directly from the unsaturated ester without any detection of the aza-Michael byproduct. Secondly, the orthoamide-type conditions enabled the Overman rearrangement without protecting group manipulation of the homoallylic alcohol. In addition, the complete chirality transfer of the secondary alcohol was achieved to provide **33** as a single diastereomer.

The next stage was the construction of three consecutive hydroxy groups in the hydrophilic moiety of sphingofungin F (**1**) (Scheme 7). The *syn*-type intramolecular S_N2' reaction of allylic alcohol **33** under the Mitsunobu conditions[7b,7c,25] installed the desired (*S*)-hydroxy group at the β-position to give **34** in 89% yield with 13.8:1 diastereoselectivity. Subsequent dihydroxylation of the resulting olefin **34**, and concomitant formation of the lactone provided the triol derivative **39** with the desired stereochemistry in 30% yield, along with the unfavorable **40** in 50% yield.[26] As a control experiment, direct dihydroxylation of allylic alcohol **33** was attempted (Scheme 8). However, triol **46** with desired stereochemistry was not obtained under a variety of dihydroxylation conditions. For example, the dihydroxylation of **33** with OsO_4 (5 mol %) and NMO in CH_2Cl_2 at 40 °C, and subsequent formation of the lactone provided **47** in 70% yield.[20c,f] The dihydroxylation under Sharpless asymmetric conditions (AD-mix-α and β) resulted in no reaction probably due to the steric hindrance derived from the tetrasubstituted carbon center. Although the diastereoselectivity of the dihydroxylation was not sufficient, these results demonstrated the utility of our S_N2' reaction because the stereochemistry of the β-hydroxy group was established independent of the existing stereocenters.



Scheme 8. Attempted dihydroxylation of allylic alcohol **33**

The remaining issue toward the total synthesis was the coupling reaction between the hydrophilic moiety and the hydrophobic side chain (Scheme 7). Hydrolysis of oxazoline **39** in the presence of CCl_3CO_2H formed the 1,3-diol, which was protected as a cyclic acetal in 89% yield. The BOM group of **41** was removed by palladium-catalyzed hydrogenation, associated with dechlorination of the trichloroacetamide[27]. The Dess-Martin oxidation of the resulting alcohol **42**[28] provided aldehyde **43**, which underwent the $CrCl_2$-mediated Takai

coupling with alkyl diiodide **35**.[23] This convergent coupling strategy was originally developed by the Kan group for the total synthesis of a sphingofungin derivative.[21i] The method enabled the direct installation of hydrophobic side chain **35**, giving **44** in 68% yield (*E*/*Z* = 6:1). Finally, global deprotection afforded sphingofungin F (**1**) in two steps. Our synthetic sample was found to be indistinguishable from a natural sample based on ^{1}H NMR, ^{13}C NMR, HRMS, and IR, as well as its optical rotation.

4. Conclusion

We have developed a two-step synthesis of β-hydroxy-α,α-disubstituted amino acid derivatives. The first step was the Overman rearrangement of an β,α-unsaturated ester. The unsaturated ester has been recognized as a longstanding problematic substrate in the Overman rearrangement. However, we found that the temperature effect and the α-substituent could suppress the unfavorable aza-Michael side reaction. Combined with the orthoamide-type conditions, a α,α-disubstituted amidoester was obtained in a single step from a cyclic orthoamide. The next intramolecular S_N2' reaction of the trichloroacetamide could install a hydroxy group at the β-position with either stereochemistry. The developed method gave four possible stereoisomers of a β-hydroxy-α,α-disubstituted amino acid derivative by proper selection of the stereochemistry of the 1,2-diol, and the S_N2' conditions. The developed two-step sequence was successfully applied to the total synthesis of sphingofungin F. Our total synthesis of sphingofungin F (**1**) was accomplished in 13 steps with 6.0% total yield from the commercially available D-ribose derivative, and thus represents one of the most concise total syntheses to date. We believe that our method will be applicable to the synthesis of a number of amino acid natural products.

Acknowledgment

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17. The corresponding (*Z*)-unsaturated ester could not be synthesized due to formation of the lactone.
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stereoelectronic effect might be one of the reasons. At the higher temperature, the ester carbonyl group of **18** could undergo the quick free rotation to adopt conformation **18"** at the higher probability, which resulted in the selective Overman rearrangement. However, we do not have any direct evidence for the temperature dependence, and further studies are needed to account for the mechanism.

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Graphical Abstract

<Title>
Synthesis of β-Hydroxy-α,α-disubstituted Amino Acids through the Overman Rearrangement of an α,β-Unsaturated Ester and Stereodivergent S_N2' Reaction: Development and Application to the Total Synthesis of Sphingofungin F

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<Summary>
A two-step synthesis of β-hydroxy-α,α-disubstituted amino acid derivatives is developed. The orthoamide-type Overman rearrangement of an α,β-unsaturated ester and subsequent stereodivergent S_N2' provides all four possible stereoisomers, and is successfully applied to the total synthesis of sphingofungin F.

<Diagram>