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FORMAL TOTAL SYNTHESIS OF MACROSPHELIDE (+)-A, EFFECT ON MACROLACTONIZATION DEPENDED UPON THE LACTONE FORMATION POSITION

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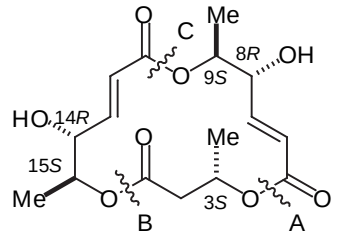
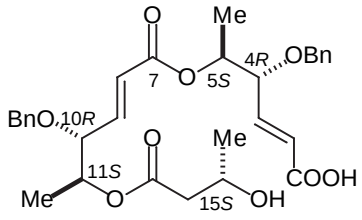
Abstract –Formal total synthesis of (+)-macrosphelide A (**1**) was achieved based on macrolactonization *via* path B from a seco-acid (**3**) and path C from a seco-acid (**4**). The yield of macrolactonization *via* paths B and C were 18 and 59%, respectively.

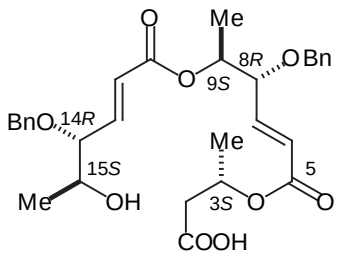
(+)-Macrosphelide A (**1**) isolated from the culture broth of *Microsphaeropsis* sp. FO-5050 by Omura and co-workers has been exhibited to strongly inhibit the adhesion of human leukemia HL-60 cells to human umbilical-vein endothelial cells (HUVEC) in dose-dependent fashion.[1] It is the first 16-membered ring antibiotics involving three lactone linkages.[1] We reported the total synthesis of (+)-macrosphelide A (**1**) *via* path A involving macrolactonization of a seco-acid (**2**).[2] Herein, we report the total synthesis of (+)-**1** *via* paths B and C in comparison with the synthesis *via* path A from a point of synthetic efficiency. The synthesis of (+)-**1** *via* paths B and C is required to prepare the seco-acids (**3**) and (**4**), respectively (Scheme 1).



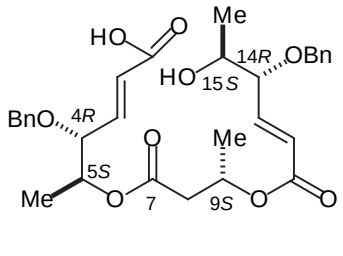
(+)-Macrosphelide A **1**



(4*R*,5*S*,10*R*,11*S*,15*S*)-**2**



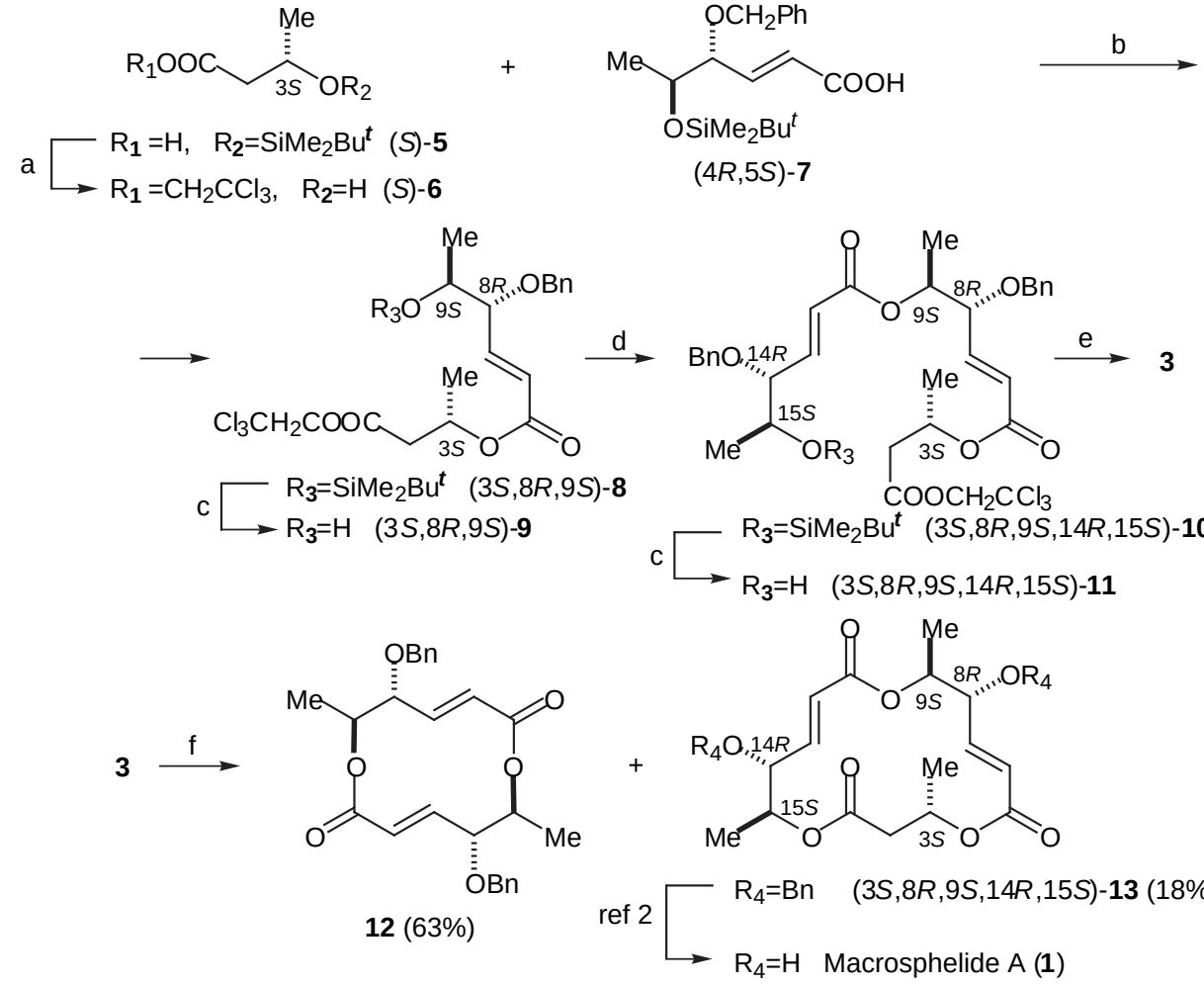
(3*S*,8*R*,9*S*,14*R*,15*S*)-**3**



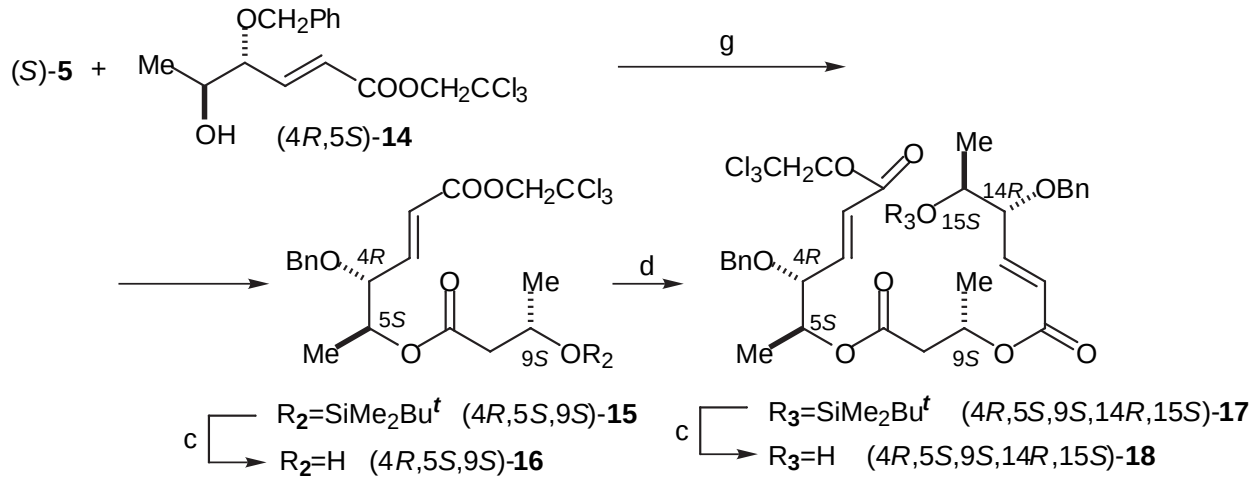
(4*R*,5*S*,9*S*,14*R*,15*S*)-**4**

Scheme 1.

Synthesis of (+)-**1** *via* path B



Synthesis of (+)-**1** *via* path C



(4*R*,5*S*,9*S*,14*R*,15*S*)-**18** → (e) **4** → (f) **13** (59%) → (ref 2) (+)-**1**

a: 1) CCl_3CH_2OH / DCC / DMAP / CSA 2) AcOH / H_2O / THF b: DCC / DMAP / CSA

c: AcOH / H_2O / THF d: (4*R*,5*S*)-**7** / DCC / DMAP / CSA e: Zn / THF / AcOH-AcONa

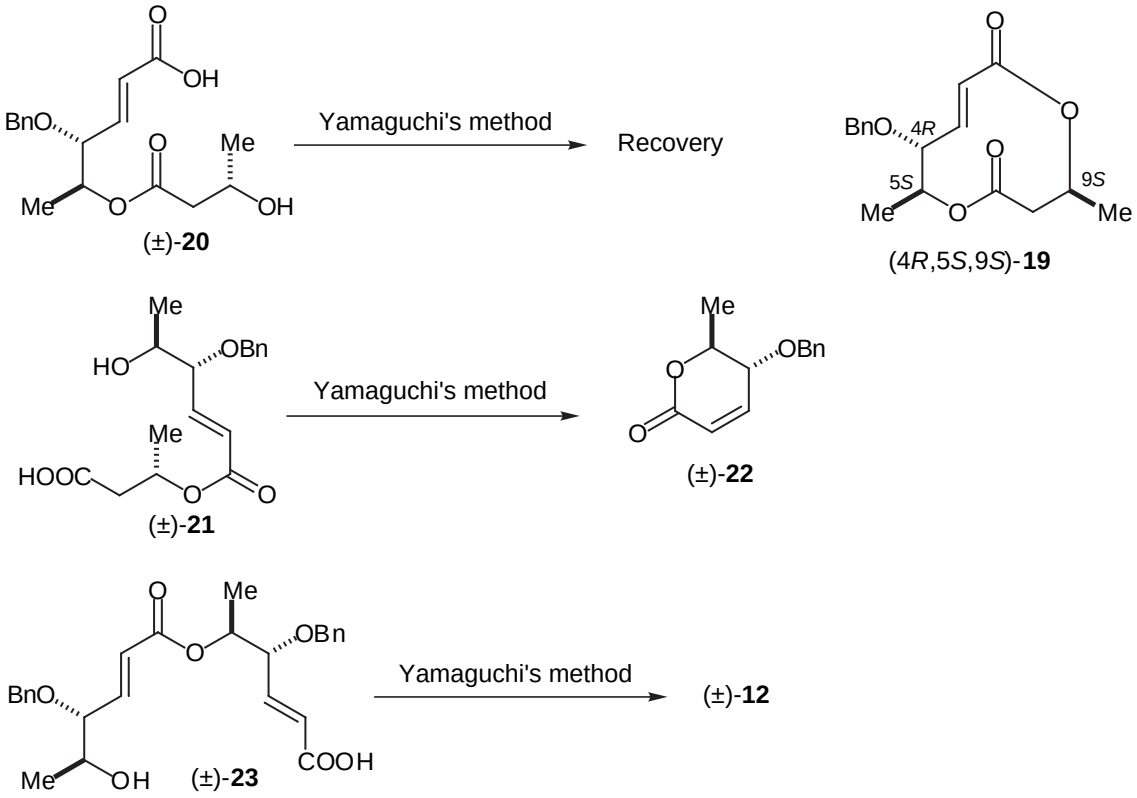
f: 2,4,6-trichlorobenzoyl chloride / Et_3N / DMAP / toluene g: DCC / DMAP

Scheme 2.

i) Synthesis of (+)-**1** *via* path B: Condensation of carboxylic acid ((*S*)-**5**)[2] and 2,2,2-trichloroethanol *via* the Keck procedure[3] (DCC, DMAP, CSA) followed by desilylation provided a hydroxy trichloroethyl ester ((+)-**6**) ($[\alpha]_D$ +15.7° (c=0.7, $CHCl_3$)) in 87% yield (Scheme 2), which was subjected to the condensation with (4*R*,5*S*)-**7**[2] under the above Keck conditions to afford diester ((3*S*,8*R*,9*S*)-**8**) ($[\alpha]_D$ –8.8° (c=0.77, $CHCl_3$)) in 87% yield (Scheme 2). Desilylation of (3*S*,8*R*,9*S*)-**8** gave an alcohol ((3*S*,8*R*,9*S*)-**9**) ($[\alpha]_D$ –33.0° (c=0.58, $CHCl_3$)) in 78% yield, which was again subjected to the condensation with (4*R*,5*S*)-**7** under the above Keck conditions to provide triester ((3*S*,8*R*,9*S*,14*R*,15*S*)-**10**) ($[\alpha]_D$ –23.5° (c=0.68, $CHCl_3$)) in 66% yield. Removal of the silyl group of (-)-**10** afforded the desilylated alcohol ((-)-**11**) ($[\alpha]_D$ –40.1° (c=0.51, $CHCl_3$)) in 67% yield. Deprotection of (-)-**11** using Zn in acetic acid buffer solution gave the seco-acid (**3**), which was subjected to Yamaguchi macrolactonization[4] (2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP) to provide 12-membered lactone ((-)-**12**) ($[\alpha]_D$ –153.6° (c=0.45, $CHCl_3$), 63% overall yield from (-)-**11**) and (-)-dibenzyl macrosphelide A ((**13**)) ($[\alpha]_D$ –81.2° (c=0.25, $CHCl_3$)) in 18% overall yield from (-)-**11**. The spectral data (^{1}H-NMR, ^{13}C-NMR) and specific rotation ($[\alpha]_D$) of (-)-**13** were identical with those ($[\alpha]_D$ –75.9° (c=0.34, $CHCl_3$)) of the reported (-)-**13**.[2] Finally, deprotection of benzyl group in (-)-**13** using $AlCl_3$ in the presence of *m*-xylene[5] was reported to give (+)-macrosphelide A (**1**).[2]

ii) Synthesis of (+)-**1** *via* path C: Condensation of carboxylic acid ((*S*)-**5**)[2] and an alcohol ((4*R*,5*S*)-**14**)[2] by the Keck procedure providd diester ((4*R*,5*S*,9*S*)-**15**) ($[\alpha]_D$ –20.1° (c=0.71, $CHCl_3$)) in 88% yield. Desilylation of (4*R*,5*S*,9*S*)-**15** afforded an alcohol ((4*R*,5*S*,9*S*)-**16**) ($[\alpha]_D$ –34.1° (c=0.35, $CHCl_3$)) in 87% yield. Condensation of carboxylic acid ((4*R*,5*S*)-**7**) with (4*R*,5*S*,9*S*)-**16** by the Keck procedure provided diester ((4*R*,5*S*,9*S*,14*R*,15*S*)-**17**) ($[\alpha]_D$ –28.6° (c=0.85, $CHCl_3$)) in 41% yield, which was subjected to desilylation to provide an alcohol ((4*R*,5*S*,9*S*,14*R*,15*S*)-**18**) ($[\alpha]_D$ –52.2° (c=0.53, $CHCl_3$)) in 84% yield. Deprotection of (-)-**18** using Zn in acetic acid buffer solution gave the seco-acid (**4**), which was subjected to Yamaguchi macrolactonization (2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP) provided (-)-dibenzyl macrosphelide A (**13**) ($[\alpha]_D$ –85.4° (c=0.51, $CHCl_3$)) in 59% overall yield from (-)-**18**. The spectral data (^{1}H-NMR, ^{13}C-NMR) and specific rotation ($[\alpha]_D$) of (-)-**13** were identical with those ($[\alpha]_D$ –75.9° (c=0.34, $CHCl_3$)) of the reported (-)-**13**.[2]

In case of Yamaguchi's macrolactonization of (4*R*,5*S*,10*R*,11*S*,15*S*)-**2**, in spite of the possible formation of 10-membered lactone (4*R*,5*S*,9*S*)-**19** (Scheme 3.) by the attack of C_{15}-hydroxyl group to the α,β-unsaturated ester carbonyl group, 10-membered lactone (4*R*,5*S*,9*S*)-**19** was not obtained actually.[2] The construction of (±)-**19** by means of Dreiding Stereomodels was found to be extremely difficult. Generally, the formation of 10-membered ring structure including lactone is one of the most difficult reaction.[6] As preliminary experiments, Yamaguchi's macrolactonization of (±)-**20** gave the starting material while that of (±)-**21** afforded δ-lactone ((±)-**22**) as a major product accompanied by the *trans* to *cis* double bond isomerization.[7] On the other hand, Yamaguchi's macrolactonization of (±)-**23** provided the 12-membered lactone (±)-**12** in 90% yield. From these preliminary experiments (Scheme 3.), the present results of macrolactonization of the seco-acids (**3**) and (**4**) could be understood. The formation of **12** could be explained by the attack of C_{15}-hydroxyl group to the C_5-position (carbonyl group) in the seco-acid (**3**), while the attack of C_{15}-hydroxyl group to the C_7-position (carbonyl group)



Scheme 3.

in the seco-acid (**4**) hardly occurred.

In conclusion, Formal total synthesis of (+)-macrosphelide A (**1**) was achieved based on macrolactonization *via* path B from a seco-acid (**3**) and path C from a seco-acid (**4**). The yield of macrolactonization *via* paths B and C were 18 and 59%, respectively, in comparison with that (70%) *via* path A from a seco-acid (**2**).

EXPERIMENTAL

^{1}H- and ^{13}C-NMR spectra were recorded on JEOL AL 400 spectrometer in $CDCl_3$. Carbon substitution degrees were established by DEPT pulse sequence. The FAB MS and ESI MS spectra were obtained with JEOL JMS-DX 303 spectrometer and ThermoQuest LCQ , respectively. IR spectra were recorded a JASCO FT/IR-300 spectrophotometer. Optical rotations were measured with a JASCO DIP-370 digital polarimeter. All evaporations were performed under reduced pressure. For column chromatography, silica gel (Kieselgel 60) was employed.

2,2,2-Trichloroethyl (*S*)-3-hydroxybutanoate (6)

i) To a mixture of DCC (4.18 g, 20.3 mmol), DMAP (3.3 g, 27.0 mmol) and (+)-CSA (3.14 g, 13.5 mmol) in CH_2Cl_2 (70 mL) was added a solution of (*S*)-**5** (2.965 g, 13.5 mmol) and CCl_3CH_2OH (4.06 g, 27.2 mmol) in CH_2Cl_2 (10 mL) and the reaction mixture was stirred for 1 d at rt. After the precipitate was filtered off and the filtrate was washed with 2M aqueous HCl and 7% aqueous $NaHCO_3$. The organic

layer was dried over $MgSO_4$ and evaporated to give a crude residue, which was chromatographed on silica gel (200 g, *n*-hexane:AcOEt=50:1) to give 2,2,2-trichloroethyl (*S*)-3-*tert*-butyldimethylsiloxybutanoate (3.844 g, 81%) as a colorless oil. IR (neat): 1758, 1460 cm^{-1}; NMR: δ 0.03 (3H, s), 0.06 (3H, s), 0.84 (9H, s), 1.22 (3H, d, *J*=7 Hz), 2.51 (1H, dd, *J*=7, 16 Hz), 2.61 (1H, dd, *J*=7, 16 Hz), 4.31 (1H, quintet, *J*=7 Hz), 4.68, 4.73 (each 1H, d, *J*=12 Hz). Anal. Calcd for $C_{12}H_{23}O_3Cl_3Si$: C, 41.21; H, 6.63. Found: C, 41.13; H, 6.64. FAB MS *m/z*; 349 (M^++1), 351. ii) A mixture of 2,2,2-trichloroethyl (*S*)-3-*tert*-butyldimethylsiloxybutanoate (3.844 g, 11 mmol) in the mixed solvent (AcOH (15 mL), H_2O (10 mL) and THF (10 mL)) was stirred for 12 h at 80 ℃. The reaction mixture was evaporated and the residue was diluted with H_2O, extracted with Et_2O. The organic layer was washed with 7% aqueous $NaHCO_3$ and dried over $MgSO_4$. The organic layer was evaporated to give a crude residue, which was chromatographed on silica gel (90 g, *n*-hexane:AcOEt=5:1) to give (*S*)-**6** (2.25 g, 87%) as a homogeneous oil. (*S*)-**6**; IR (neat): 3417, 1752, 1378 cm^{-1}; $[\alpha]_D^{22}$ +15.7° (c=0.7, $CHCl_3$); NMR: δ 1.27 (3H, d, *J*=6 Hz), 2.59 (1H, dd, *J*=8, 17 Hz), 2.64 (1H, dd, *J*=4, 14 Hz), 2.80 (1H, br s), 4.22-4.31 (1H, m), 4.74, 4.78 (each 1H, d, *J*=12 Hz). Anal. Calcd for $C_6H_9O_3Cl_3$: C, 30.60; H, 3.85. Found: C, 30.64; H, 3.91. FAB MS *m/z*; 235 (M^++1), 237.

Ester formation between (4*R*, 5*S*)-7 and (*S*)-6

To a mixture of DCC (1.80 g, 8.7 mmol), DMAP (1.41 g, 11.5 mmol) and (+)-CSA (1.35 g, 5.8 mmol) in CH_2Cl_2 (36 mL) was added a solution of (4*R*,5*S*)-**7** (2.017 g, 5.8 mmol) and (*S*)-**6** (1.90 g, 8.12 mmol) in CH_2Cl_2 (4 mL) and the reaction mixture was stirred for 2 d at rt. After the precipitate was filtered off and the filtrate was washed with 2M aqueous HCl and 7% aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$ and evaporated to give a crude residue, which was chromatographed on silica gel (110 g) to give (3*S*,8*R*,9*S*)-**8** (2.852 g, 87%) as a homogenous oil from *n*-hexane:AcOEt=30:1 eluate and recovery (*S*)-**6** (0.329 g) from *n*-hexane:AcOEt=20:1 eluate. (3*S*,8*R*,9*S*)-**8**; IR (neat): 1759, 1723 cm^{-1}; $[\alpha]_D^{23}$ –8.8° (c=0.77, $CHCl_3$); NMR: δ 0.02 (3H, s), 0.04 (3H, s), 0.87 (9H, s), 1.20 (3H, d, *J*=6 Hz), 1.39 (3H, d, *J*=6 Hz), 2.70 (1H, dd, *J*=6, 16 Hz), 2.86 (1H, dd, *J*=6, 16 Hz), 3.77 (1H, dt, *J*=2, 6 Hz), 3.83 (1H, quintet, *J*=6 Hz), 4.44, 4.60 (each 1H, d, *J*=12 Hz), 4.73, 4.77 (each 1H, d, *J*=12 Hz), 5.41 (1H, sixtet, *J*=6 Hz), 6.01 (1H, dd, *J*=2, 16 Hz), 6.91 (1H, dd, *J*=6, 16 Hz), 7.26-7.37 (5H, m). Anal. Calcd for $C_{25}H_{37}O_6Cl_3Si$: C, 52.68; H, 6.57. Found: C, 51.75; H, 6.44. FAB MS *m/z*; 459 (M^+-$PhCH_2O$), 461.

Desilylation of (3*S*, 8*R*, 9*S*)-8

A mixture of (3*S*,8*R*,9*S*)-**8** (2.486 g, 4.4 mmol) in the mixed solvent (AcOH (8 mL), H_2O (5 mL) and THF (5 mL) was stirred for 12 h at 80 ℃. The reaction mixture was evaporated and the residue was diluted with H_2O, extracted with Et_2O. The organic layer was washed with 7% aqueous $NaHCO_3$ and dried over $MgSO_4$. The organic layer was evaporated to give a crude residue, which was chromatographed on silica gel (50 g, *n*-hexane:AcOEt=5:1) to give (3*S*,8*R*,9*S*)-**9** (1.558 g, 78%) as a homogeneous oil. (3*S*,8*R*,9*S*)-**9**; IR (neat): 3483, 1756, 1719 cm^{-1}; $[\alpha]_D^{25}$ –33.0° (c=0.58, $CHCl_3$);

^{1}H-NMR: δ 1.15 (3H, d, *J*=6 Hz), 1.40 (3H, d, *J*=6 Hz), 2.25 (1H, br d, *J*=5 Hz), 2.72 (1H, dd, *J*=6, 16 Hz), 2.86 (1H, dd, *J*=8, 16 Hz), 3.90 (1H, ddd, *J*=2, 5, 7 Hz), 3.92-3.99 (1H, m), 4.40, 4.63 (each 1H, d, *J*=12 Hz), 4.73, 4.77 (each 1H, d, *J*=12 Hz), 5.40 (1H, ddq, *J*=6, 6, 8 Hz), 6.03 (1H, dd, *J*=2, 16 Hz), 6.90 (1H, dd, *J*=7, 16 Hz), 7.27-7.38 (5H, m). ^{13}C-NMR: δ 18.1 (q), 20.0 (q), 40.5 (t), 67.3 (d), 69.1 (d), 71.4 (t), 73.9 (t), 81.8 (d), 94.6 (s), 124.2 (d), 127.6 (d), 127.7 (d), 128.3 (d), 137.4 (s), 144.4 (d), 164.5 (s), 168.3 (S). Anal. Calcd for $C_{19}H_{23}O_6Cl_3$: C, 50.29; H, 5.11. Found: C, 50.06; H, 5.15. FAB MS *m/z*; 453 (M^++1), 455.

Ester formation between (4*R*, 5*S*)-7 and (3*S*, 8*R*, 9*S*)-9

To a mixture of DCC (0.92 g, 4.5 mmol), DMAP (0.72 g, 5.9 mmol) and (+)-CSA (0.69 g, 3 mmol) in CH_2Cl_2 (17 mL) was added a solution of (4*R*,5*S*)-**7** (1.171 g, 3.3 mmol) and (3*S*,8*R*,9*S*)-**9** (1.341 g, 3 mmol) in CH_2Cl_2 (3 mL) and the reaction mixture was stirred for 1 d at rt. After the precipitate was filtered off and the filtrate was washed with 2M aqueous HCl and 7% aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$ and evaporated to give a crude residue, which was chromatographed on silica gel (70 g) to give (3*S*,8*R*,9*S*,14*R*,15*S*)-**10** (1.554 g, 66%) as a homogenous oil from *n*-hexane:AcOEt=10:1 eluate and recovery (3*S*,8*R*,9*S*)-**9** (0.188 g, 14% recovery) from *n*-hexane:AcOEt=5:1 eluate. (3*S*,8*R*,9*S*,14*R*,15*S*)-**10**; IR (neat): 1759, 1721 cm^{-1}; $[\alpha]_D^{23}$ –23.5° (c=0.68, $CHCl_3$); NMR: δ 0.02 (3H, s), 0.04 (3H, s), 0.86 (9H, s), 1.21 (3H, d, *J*=6 Hz), 1.27 (3H, d, *J*=7 Hz), 1.40 (3H, d, *J*=6 Hz), 2.71 (1H, dd, *J*=6, 16 Hz), 2.85 (1H, dd, *J*=8, 16 Hz), 3.78 (1H, dt, *J*=2, 6 Hz), 3.85 (1H, quintet, *J*=6 Hz), 4.13 (1H, dt, *J*=2, 6 Hz), 4.45, 4.51, 4.62, 4.64 (each 1H, d, *J*=12 Hz), 4.73, 4.78 (each 1H, d, *J*=12 Hz), 5.12 (1H, dq, *J*=6, 7 Hz), 5.40 (1H, ddq, *J*=6, 6, 8 Hz), 6.04 (1H, dd, *J*=2, 16 Hz), 6.09 (1H, dd, *J*=2, 16 Hz), 6.88 (1H, dd, *J*=6, 16 Hz), 6.92 (1H, dd, *J*=6, 16 Hz), 7.24-7.37 (10H, m). Anal. Calcd for $C_{38}H_{51}O_9Cl_3Si$ C, 58.05; H, 6.54. Found: C, 58.09; H, 6.66.

Desilylation of (3*S*, 8*R*, 9*S*, 14*R*, 15*S*)-10

A mixture of (3*S*,8*R*,9*S*,14*R*,15*S*)-**10** (1.379 g, 1.8 mmol) in the mixed solvent (AcOH (5 mL), H_2O (3 mL) and THF (3 mL)) was stirred for 12 h at 80 ℃. The reaction mixture was evaporated and the residue was diluted with H_2O, extracted with Et_2O. The organic layer was washed with 7% aqueous $NaHCO_3$ and dried over $MgSO_4$. The organic layer was evaporated to give a crude residue, which was chromatographed on silica gel (40 g, *n*-hexane:AcOEt=5:1) to give (3*S*,8*R*,9*S*,14*R*,15*S*)-**11** (0.791 g, 67%) as a homogeneous oil. (3*S*,8*R*,9*S*,14*R*,15*S*)-**11**; IR (neat): 3504, 1715 cm^{-1}; $[\alpha]_D^{23}$ –40.1° (c=0.51, $CHCl_3$); ^{1}H-NMR: δ 1.16 (3H, d, *J*=6 Hz), 1.29 (3H, d, *J*=6 Hz), 1.39 (3H, d, *J*=6 Hz), 2.28 (1H, br s), 2.71 (1H, dd, *J*=6, 16 Hz), 2.85 (1H, dd, *J*=8, 16 Hz), 3.92 (1H, ddd, *J*=2, 4, 6 Hz), 3.96 (1H, dq, *J*=4, 6 Hz), 4.11 (1H, ddd, *J*=2, 4, 6 Hz), 4.42, 4.49, 4.63, 4.66 (each 1H, d, *J*=12 Hz), 4.73, 4.78 (each 1H, d, *J*=12 Hz), 5.11 (1H, dq, *J*=4, 6 Hz), 5.40 (1H, sextet, *J*=6 Hz), 6.07 (1H, dd, *J*=2, 16 Hz), 6.08 (1H, dd, *J*=2, 16 Hz), 6.87 (1H, dd, *J*=6, 16 Hz), 6.92 (1H, dd, *J*=6, 16 Hz), 7.26-7.38 (10H, m). ^{13}C-NMR: δ 15.1 (q), 18.2 (q), 19.9 (q), 40.4 (t), 67.3 (d), 69.1 (d), 71.3 (t),

71.6 (t), 71.6 (d), 73.9 (t), 79.3 (d), 81.9 (d), 94.6 (s), 123.8 (d), 124.2 (d), 127.4 (d), 127.6 (d), 127.6 (d), 127.7 (d), 128.2 (d), 128.3 (d), 137.4 (s), 137.4 (s), 144.1 (d), 144.5 (d), 164.5 (s), 164.6 (s), 168.2 (s). Anal. Calcd for $C_{32}H_{37}O_9Cl_3$: C, 57.20; H, 5.55. Found: C, 57.31; H, 5.70. FAB MS *m/z*; 671(M^++1), 673.

Deprotection of 2,2,2-trichloroethyl group of (3*S*, 8*R*, 9*S*, 14*R*, 15*S*)-11

To a mixture of Zn dust (0.06 g) and 1 M AcOH-AcONa buffer solution (15 mL) in THF (1 mL) was added a solution of (3*S*,8*R*,9*S*,14*R*,15*S*)-**11** (0.061 g, 0.09 mmol) in THF (2 mL) at 0 ℃ and the whole mixture was stirred for 2.5 h at rt. The reaction mixture was filtered off, and the filtrate was acidified with 2M aqueous HCl and extracted with Et_2O. The organic layer was dried over $MgSO_4$. The organic layer was evaporated to give crude seco-acid (**3**) (0.049 g) in quantitative yield. According to the SiO_2 TLC observation and NMR analysis of the crude seco-acid (**3**), it appeared to be almost single product. Therefore, it was used for the next reaction without further purification. **3**; NMR: δ 1.15 (3H, d, *J*=6 Hz), 1.29 (3H, d, *J*=6 Hz), 1.32 (3H, d, *J*=6 Hz), 2.54 (1H, dd, *J*=6, 16 Hz), 2.66 (1H, dd, *J*=6, 16 Hz), 3.85 (1H, ddd, *J*=2, 4, 6 Hz), 3.95 (1H, dq, *J*=4, 6 Hz), 4.02 (1H, ddd, *J*=2, 5, 6 Hz), 4.39, 4.44, 4.61, 4.62 (each 1H, d, *J*=12 Hz), 5.06 (1H, qd, *J*=5, 6 Hz), 5.32 (1H, sextet, *J*=6 Hz), 6.01 (1H, dd, *J*=2, 16 Hz), 6.05 (1H, dd, *J*=2, 16 Hz), 6.84 (1H, dd, *J*=6, 16 Hz), 6.85 (1H, dd, *J*=6, 16 Hz), 7.23-7.35 (10H, m).

Macrolactonization of seco-acid (3)

To a solution of seco-acid (**3**) (0.049 g, 0.09 mmol) and Et_3N (0.018 g, 0.18 mmol) in THF (1 mL) were added a solution of 2,4,6-trichlorobenzoyl chloride (0.044 g, 0.18 mmol) in THF (1 mL) and the reaction mixture (I) was stirred for 2 h at rt under argon atmosphere. A solution (II) of DMAP (0.066 g, 0.54 mmol) in toluene (10 mL) was heated at 100 ℃ for 1 h. A solution of the above-mentioned reaction mixture (I) in toluene (45 mL) was added to DMAP/toluene solution (II) and the whole mixture was stirred for 12 h at 100 ℃. The reaction mixture was washed with 7% aqueous $NaHCO_3$, 2M aqueous HCl and saturated brine. The organic layer was dried over $MgSO_4$ and evaporated to give a crude residue, which was chromatographed on silica gel (5 g, *n*-hexane:AcOEt=4:1) to give a colorless oil (**12**) (0.024 g, 63% overall yield from (3*S*,8*R*,9*S*,14*R*,15*S*)-**11**) and macrosphelide dibenzyl ether ((-)-**13**) (0.0086 g, 18% overall yield from (3*S*,8*R*,9*S*,14*R*,15*S*)-**11**) in elution order. **12**; IR ($CHCl_3$): 1726, 1647 cm^{-1}; $[\alpha]_D^{22}$ –153.6° (c=0.45, $CHCl_3$); NMR: δ 1.43 (6H, d, *J*=6 Hz), 3.69 (2H, dd, *J*=9, 9 Hz), 4.35, 4.63 (each 2H, d, *J*=12 Hz), 5.11 (2H, dq, *J*=6, 9 Hz), 5.94 (2H, dd, *J*=2, 16 Hz), 6.52 (1H, dd, *J*=9, 16 Hz), 7.26-7.38 (10H, m). Anal. Calcd for $C_{26}H_{28}O_6$: C, 71.54; H, 6.47. Found: C, 71.49; H, 6.57. FAB MS *m/z*; 437 (M^++1). The spectral data (^{1}H-NMR, ^{13}C-NMR) and specific rotation ($[\alpha]_D^{20}$ –81.2° (c=0.25, $CHCl_3$)) of (-)-**13** were identical with those ($[\alpha]_D$ –75.9° (c=0.34, $CHCl_3$)) of the reported (-)-**13**.[2]

Ester formation between (*S*)-5 and (4*R*, 5*S*)-14

To a mixture of DCC (2.41 g, 12 mmol), DMAP (0.36 g, 2.9 mmol) in CH_2Cl_2 (45 mL) was added a solution of (4*R*,5*S*)-**14**[2] (2.145 g, 5.8 mmol) and (*S*)-**5** (2.54 g, 12 mmol) in CH_2Cl_2 (5 mL) and the reaction mixture was stirred for 2 d at rt. After the precipitate was filtered off and the filtrate was washed with 2M aqueous HCl and 7% aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$ and evaporated to give a crude residue, which was chromatographed on silica gel (110 g) to give (4*R*,5*S*,9*S*)-**15** (2.914 g, 88%) as a homogenous oil from *n*-hexane:AcOEt=30:1 eluate. (4*R*,5*S*,9*S*)-**15**; IR (neat): 1733, 1660 cm^{-1}; $[\alpha]_D^{28}$ –20.1° (c=0.71, $CHCl_3$); NMR: δ 0.05 (3H, s), 0.07 (3H, s), 0.86 (9H, s), 1.19 (3H, d, *J*=7 Hz), 1.26 (3H, d, *J*=7 Hz), 2.36 (1H, dd, *J*=7, 16 Hz), 2.48 (1H, dd, *J*=7, 16 Hz), 4.13 (1H, ddd, *J*=2, 4, 6 Hz), 4.25 (1H, sextet, *J*=7 Hz), 4.53, 4.65 (each 1H, d, *J*=12 Hz), 4.82 (2H, s), 5.06 (1H, qd, *J*=4, 7 Hz), 6.22 (1H, dd, *J*=2, 16 Hz), 7.03 (1H, dd, *J*=6, 16 Hz), 7.27-7.39 (5H, m). Anal. Calcd for $C_{25}H_{37}O_6Cl_3Si$: C, 52.87; H, 6.57. Found: C, 52.89; H, 6.80. FAB MS *m/z*; 567 (M^++1), 569.

Desilylation of (4*R*, 5*S*, 9*S*)-15

A mixture of (4*R*,5*S*,9*S*)-**15** (2.311 g, 4.1 mmol) in the mixed solvent (AcOH (15 mL), H_2O (10 mL) and THF (10 mL)) was stirred for 12 h at 80 ℃. The reaction mixture was evaporated and the residue was diluted with H_2O, extracted with Et_2O. The organic layer was washed with 7% aqueous $NaHCO_3$ and dried over $MgSO_4$. The organic layer was evaporated to give a crude residue, which was chromatographed on silica gel (40 g, *n*-hexane:AcOEt=5:1) to give (4*R*,5*S*,9*S*)-**16** (1.607 g, 87%) as a homogeneous oil. (4*R*,5*S*,9*S*)-**16**; IR (neat): 3450, 1735 cm^{-1}; $[\alpha]_D^{27}$ –34.1° (c=0.35, $CHCl_3$); ^{1}H-NMR: δ 1.19 (3H, d, *J*=7 Hz), 1.25 (3H, d, *J*=7 Hz), 2.36 (1H, dd, *J*=9, 16 Hz), 2.45 (1H, dd, *J*=4, 16 Hz), 2.82 (1H, br s), 4.08 (1H, ddd, *J*=2, 4, 6 Hz), 4.11-4.18 (1H, m), 4.48, 4.63 (each 1H, d, *J*=12 Hz), 4.80 (2H, s), 5.11 (1H, qd, *J*=4, 7 Hz), 6.19 (1H, dd, *J*=2, 16 Hz), 7.00 (1H, dd, *J*=6, 16 Hz), 7.26-7.36 (5H, m). ^{13}C-NMR: δ 15.4 (q), 22.6 (q), 43.2 (t), 64.3 (d), 71.4 (d), 71.9 (t), 74.1 (t), 79.3 (d), 94.8 (s), 122.4 (d), 127.6 (d), 127.8 (d), 128.3 (d), 137.1 (s), 146.2 (d), 163.7 (s), 171.7 (s). Anal. Calcd for $C_{19}H_{23}O_6Cl_3$: C, 50.29; H, 5.11. Found: C, 50.15; H, 5.26. FAB MS *m/z*; 453 (M^++1), 455.

Ester formation between (4*R*, 5*S*)-7 and (4*R*, 5*S*, 9*S*)-16

To a mixture of DCC (0.73 g, 3.5 mmol), DMAP (0.58 g, 4.7 mmol) and (+)-CSA (0.55 g, 2.4 mmol) in CH_2Cl_2 (25 mL) was added a solution of (4*R*,5*S*,9*S*)-**16** (1.033 g, 2.28 mmol) and (4*R*,5*S*)-**7** (1.166 g, 3.33 mmol) in CH_2Cl_2 (3 mL) and and the reaction mixture was stirred for 1 d at rt. After the precipitate was filtered off and the filtrate was washed with 2M aqueous HCl and 7% aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$ and evaporated to give a crude residue, which was chromatographed on silica gel (60 g) to give (4*R*,5*S*,9*S*,14*R*,15*S*)-**17** (0.739 g, 41%) as a homogenous oil from *n*-hexane:AcOEt=10:1 eluate and recovery (4*R*,5*S*,9*S*)-**16** (0.219 g, 12% recovery) from *n*-hexane:AcOEt=5:1 eluate. (4*R*,5*S*,9*S*,14*R*,15*S*)-**17**; IR (neat): 1735, 1650 cm^{-1}; $[\alpha]_D^{23}$ –28.6° (c=0.85, $CHCl_3$); NMR: δ 0.02 (3H, s), 0.04 (3H, s), 0.86 (9H, s), 1.19 (3H, d, *J*=6 Hz), 1.23 (3H,

d, *J*=7 Hz), 1.32 (3H, d, *J*=6 Hz), 2.50 (1H, dd, *J*=6, 16 Hz), 2.67 (1H, dd, *J*=6, 16 Hz), 3.75 (1H, ddd, *J*=2, 6, 6 Hz), 3.82 (1H, dq, *J*=6, 6 Hz), 4.10 (1H, ddd, *J*=2, 4, 6 Hz), 4.42, 4.49, 4.58, 4.63 (each 1H, d, *J*=12 Hz), 4.82 (2H, s), 5.07 (1H, qd, J=4, 7 Hz), 5.32 (1H, sextet, *J*=6 Hz), 5.99 (1H, dd, *J*=2, 16 Hz), 6.21 (1H, dd, *J*=2, 16 Hz), 6.99 (1H, dd, *J*=6, 16 Hz), 7.01 (1H, dd, *J*=6, 16 Hz), 7.24-7.37 (10H, m). Anal. Calcd for $C_{38}H_{51}O_9Cl_3Si$: C, 58.05; H, 6.54. Found: C, 58.40; H, 6.60.

Desilylation of (4*R*, 5*S*, 9*S*, 14*R*, 15*S*)-17

A mixture of (4*R*,5*S*,9*S*,14*R*,15*S*)-**17** (0.655 g, 0.8 mmol) in the mixed solvent (AcOH (6 mL), H_2O (4 mL) and THF (4 mL)) was stirred for 12 h at 80 ℃. The reaction mixture was evaporated and the residue was diluted with H_2O, extracted with Et_2O. The organic layer was washed with 7% aqueous $NaHCO_3$ and dried over $MgSO_4$. The organic layer was evaporated to give a crude residue, which was chromatographed on silica gel (20 g, *n*-hexane:AcOEt=5:1) to give (4*R*,5*S*,9*S*,14*R*,15*S*)-**18** (0.472 g, 84%) as a homogeneous oil. (4*R*,5*S*,9*S*,14*R*,15*S*)-**18**; IR (neat): 3473, 1735 cm^{-1}; $[\alpha]_D^{21}$ –52.2° (c=0.53, $CHCl_3$); ^{1}H-NMR: δ 1.12 (3H, d, *J*=7 Hz), 1.21 (3H, d, *J*=6 Hz), 1.32 (3H, d, *J*=6 Hz), 2.19 (1H, br s), 2.52 (1H, dd, *J*=6, 16 Hz), 2.65 (1H, dd, *J*=6, 16 Hz), 3.86 (1H, ddd, *J*=2, 4, 6 Hz), 3.89-3.94 (1H, m), 4.08 (1H,ddd, *J*=2, 6, 6 Hz), 4.37, 4.48, 4.60, 4.61 (each 1H, d, *J*=12 Hz), 4.80 (2H, s), 5.06 (1H, qd, *J*=4, 6 Hz), 5.31 (1H, sextet, *J*=6 Hz), 6.00 (1H, dd, *J*=2, 16 Hz), 6.19 (1H, dd, *J*=2, 16 Hz), 6.87 (1H, dd, *J*=6, 16 Hz), 6.99 (1H, dd, *J*=6, 16 Hz), 7.25-7.36 (10H, m). ^{13}C-NMR: δ 15.2 (q), 18.2 (q), 19.5 (q), 41.0 (t), 67.5 (d), 69.1 (d), 71.3 (t), 71.4 (d), 71.8 (t), 74.0 (t), 79.3 (d), 81.9 (d), 94.8 (s), 122.3 (d), 124.3 (d), 127.5(d), 127.6 (d), 127.7 (d), 127.7 (d), 128.3 (d), 128.3 (d), 137.2 (s), 137.4 (s), 144.3 (d), 146.3 (d), 163.7 (s), 164.5 (s), 169.0 (s). Anal. Calcd for $C_{32}H_{37}O_9Cl_3$: C, 57.20; H, 5.55. Found: C, 56.95; H, 5.53. FAB MS *m/z*; 671(M^++1), 673.

Deprotection of 2,2,2-trichloroethyl group of (4*R*, 5*S*, 9*S*, 14*R*, 15*S*)-18

To a mixture of Zn dust (0.03 g, 0.9 mmol) and 1M AcOH-AcONa buffer solution (15 mL) in THF (6 mL) was added a solution of (4*R*,5*S*,9*S*,14*R*,15*S*)-**18** (0.10 g, 0.15 mmol) in THF (2 mL) at 0 ℃ and the whole mixture was stirred for 3.5 h at rt. The reaction mixture was filtered off, and the filtrate was acidified with 2M aqueous HCl and extracted with Et_2O. The organic layer was dried over $MgSO_4$. The organic layer was evaporated to give crude seco-acid (**4**) (0.078 g, 96%). According to the SiO_2 TLC observation and NMR analysis of the crude seco-acid (**4**), it appeared to be almost single product. Therefore, it was used for the next reaction without further purification. **4**; NMR: δ 1.13 (3H, d, *J*=6 Hz), 1.20 (3H, d, *J*=7 Hz), 1.32 (3H, d, *J*=6 Hz), 2.52 (1H, dd, *J*=6, 16 Hz), 2.65 (1H, dd, *J*=6, 16 Hz), 3.85 (1H, ddd, *J*=2, 4, 6 Hz), 3.92 (1H, dq, *J*=4, 6 Hz), 4.00 (1H, ddd, *J*=2, 4, 6 Hz), 4.37, 4.43, 4.59, 4.60 (each 1H, d, *J*=12 Hz), 5.05 (1H, qd, *J*=4, 6 Hz), 5.32 (1H, sextet, *J*=6 Hz), 6.00 (1H, dd, *J*=2, 16 Hz), 6.07 (1H, dd, *J*=2, 16 Hz), 6.88 (1H, dd, *J*=6, 16 Hz), 6.89 (1H, dd, *J*=6, 16 Hz), 7.23-7.35 (10H, m).

Macrolactonization of seco-acid (4)

To a solution of seco-acid (**4**) (0.078 g, 0.14 mmol) and Et_3N (0.03 g, 0.3 mmol) in THF (1 mL) was added a solution of 2,4,6-trichlorobenzoyl chloride (0.073 g, 0.3 mmol) in THF (1 mL) and the reaction mixture (III) was stirred for 2 h at rt under argon atmosphere. A solution (IV) of DMAP (0.109 g, 0.89 mmol) in toluene (15 mL) was heated at 100 ℃ for 1 h. A solution of the above-mentioned reaction mixture (III) in toluene (75 mL) was added to DMAP/toluene solution (IV) and the whole mixture was stirred for 12 h at 100 ℃. The reaction mixture was washed with 7% aqueous $NaHCO_3$, 2M aqueous HCl and saturated brine. The organic layer was dried over $MgSO_4$ and evaporated to give a crude residue, which was chromatographed on silica gel (25 g, *n*-hexane:AcOEt=10:1) to give macrosphelide dibenzyl ether ((-)-**13**) (0.046 g, 59% overall yield from (4*R*,5*S*,9*S*,14*R*,15*S*)-**18**) The spectral data (^{1}H-NMR, ^{13}C-NMR) and specific rotation ($[\alpha]_D^{21}$ –85.4° (c=0.51, $CHCl_3$)) of (-)-**13** were identical with those ($[\alpha]_D$ –75.9° (c=0.34, $CHCl_3$)) of the reported (-)-**13**.[2]

REFERENCES AND NOTE

1. a) M. Hayashi, Y.-P Kim, H. Hiraoka, M. Natori, S. Takamatsu, T. Kawakubo, R. Masuma, K. Komiyama, and S. Omura, *J. Antibiot.*, 1995, **48**, 1435. b) S. Takamatsu, Y.-P. Kim, M. Hayashi, H. Hiraoka, M. Natori, K. Komiyama, and S. Omura, *J. Antibiot.*, 1996, **49**, 95.
2. M. Ono, H. Nakamura, F. Konno, and H. Akita, *Tetrahedron:Asymmetry*, 2000, **11**, 2753.
3. E. P. Boden and G. E. Keck, *J. Org. Chem.*, 1985, **50**, 2394.
4. J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, and M. Yamaguchi, *Bull. Chem. Soc. Jpn.*, 1979, **52**, 1989.
5. M. Ono, C. Saotome, and H. Akita, *Tetrahedron:Asymmetry*, 1996, **7**, 2595.
6. G. Illuminati and L. Mandolini, *Acc. Chem. Res.*, 1981, **14**, 95.
7. The detailed study will be described elsewhere.