Formal Total Synthesis of (+)-Macrosphelide A Based on Regioselective Hydrolysis Using Lipase

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Three kinds of seco-macrosphelide A congeners, (4*R*,5*S*,10*R*,11*S*,15*S*)-6, (4*R*,5*S*,9*S*,14*R*,15*S*)-7 and (3*S*,8*R*, 9*S*,14*R*,15*S*)-8 were chemically synthesized, and they were exposed to the lipase OF-360 from *Candida rugosa* to give three hydroxy carboxylic acids, respectively. Macrolactonization of the hydroxy acid (4*R*,5*S*,10*R*,11*S*)-18 derived from (4*R*,5*S*,10*R*,11*S*,15*S*)-6 gave 12-membered lactone (19) in 47% overall yield from 6, while that of the seco-acid (4) derived from (4*R*,5*S*,9*S*,14*R*,15*S*)-7 afforded (−)-dibenzyl macrosphelide A (25) in 27% overall yield from 7. Macrolactonization of the hydrolysis product, seco-acid (5) derived from (3*S*,8*R*,9*S*,14*R*,15*S*)-8, provided (−)-dibenzyl macrosphelide A (25) (5% overall yield from 8) and 12-membered lactone (19) (20% overall yield from 8) concurrently.

Key words macrosphelide A; enzymatic hydrolysis; total synthesis; Keck condensation

(+)-Macrosphelide A (**1**), isolated from the culture broth of *Microsphaeropsis* sp. FO-5050 by Omura and co-workers, has been shown to strongly inhibit the adhesion of human leukemia HL-60 cells to human umbilical-vein endothelial cells (HUVEC) in a dose-dependent fashion.[1,2] It is the first 16-membered ring antibiotic involving three lactone linkages.[1,2] We reported the total synthesis of (+)-macrosphelide A (**1**) involving macrolactonization of a seco-acid (**2**) derived from the corresponding 2,2,2-trichloroethyl ester (4*R*,5*S*,10*R*,11*S*,15*S*)-**3**.[3] In this synthesis, a three ester moiety in the substrate **3** was differentiated, and a 2,2,2-trichloroethyl group was deprotected in the presence of Zn in acetic acid buffer solution to afford a seco-acid (**2**). Now we have examined whether the synthesis of three kinds of seco-acids, (**2**), (**4**) and (**5**), from three corresponding triesters (4*R*,5*S*,10*R*,11*S*,15*S*)-**6**, (3*S*,8*R*,9*S*,14*R*,15*S*)-**7** and (4*R*,5*S*,9*S*, 14*R*,15*S*)-**8**, respectively, under a lipase-catalysed hydrolysis condition and formal synthesis of (+)-macrosphelide A (**1**) from a seco-acid (**2** or **4** or **5**) *via* macrolactonization is possible.

In addition, we reported that the enantioselective hydrolysis of (±)-(4,5)-*anti*-5-acetoxy-4-benzyloxy-2(*E*)-hexenoate (**9**) using the lipase "Amano P" from *Pseudomonas* sp. in phosphate buffer solution gave the (4*R*,5*S*)-5-acetoxy ester (**9**) (>99% ee, 48% yield) and the (4*S*,5*R*)-5-hydroxy ester (**10**) (>99% ee, 44% yield), and methanolysis of (4*R*,5*S*)-**9** provided the (4*R*,5*S*)-**10** in 84% yield.[4] Silylation (98% yield) of (4*R*,5*S*)-**10** using *tert*-butyldimethylsilyl chloride (TBDMSCl), followed by hydrolysis (99% yield), gave the desired carboxylic acid (4*R*,5*S*)-**11** in 97% overall yield.[3]

Model Experiments for Lipase-Catalysed Hydrolysis of Diesters (4*R*,5*S*,10*R*,11*S*)-12, (4*R*,5*S*,9*S*)-13 and (3*S*,8*R*,9*S*)-14 As model experiments, lipase-catalyzed hydrolyses of diesters **12**, **13** and **14** were carried out in order to check the hydrolysis site of two ester moieties in the substrate. Condensation of a secondary alcohol (4*R*,5*S*)-**10**[4] and carboxylic acid (4*R*,5*S*)-**11**[3] *via* the Keck procedure[5] (dicyclohexylcarbodiimide (DCC), 4-(dimethylamino)pyridine (DMAP), cam-

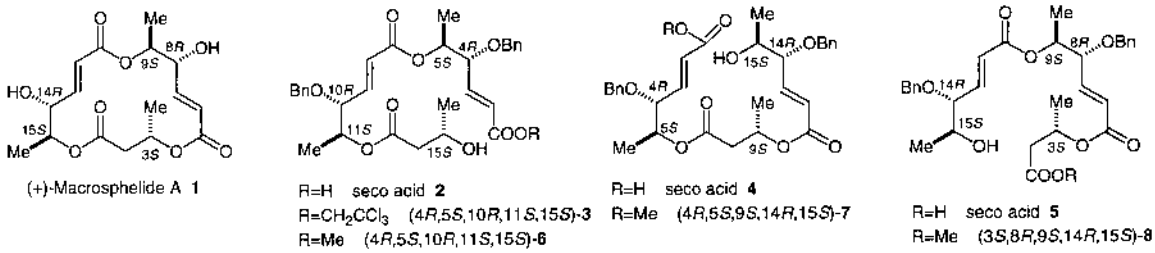

Fig. 1

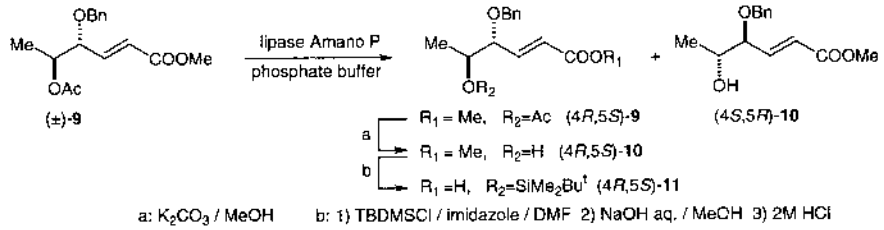

Chart 1

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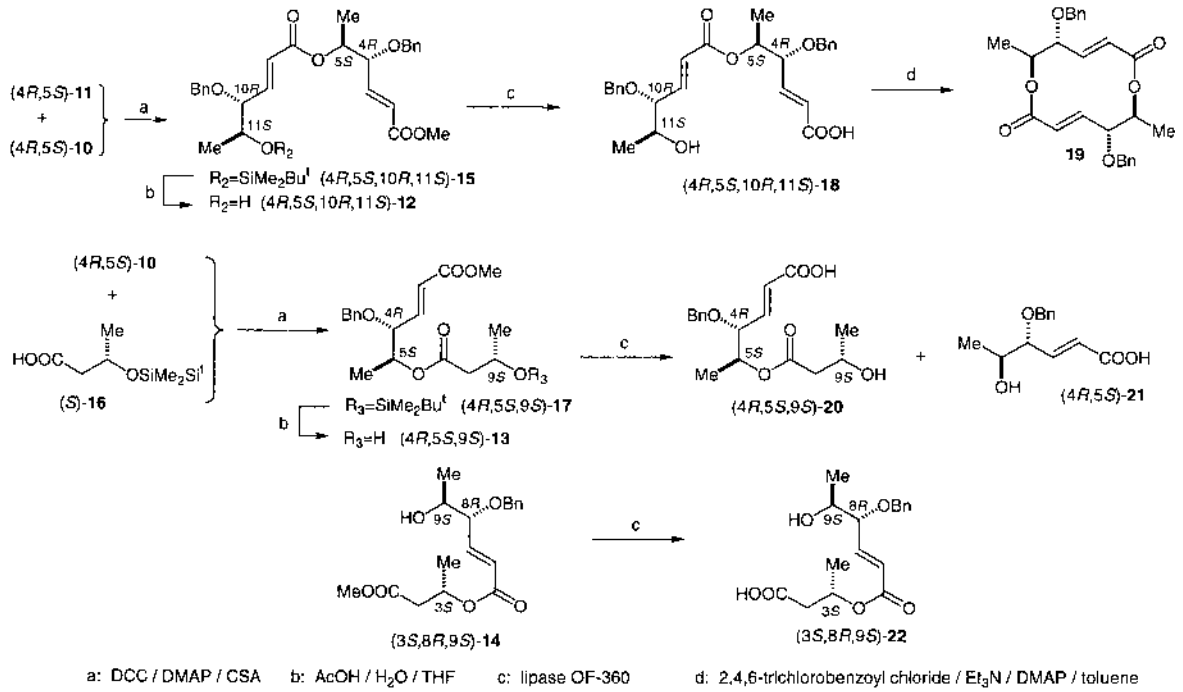

Chart 2

phorsulfonic acid (CSA)) provided diester (4*R*,5*S*,10*R*,11*S*)-**15** in 57% yield, which was desilylated to yield hydroxy-diester (4*R*,5*S*,10*R*,11*S*)-**12** in 67% yield. A second condensation of carboxylic acid (*S*)-**16**[3] and (4*R*,5*S*)-**10** *via* the Keck procedure afforded diester (4*R*,5*S*,9*S*)-**17** in 83% yield, which was desilylated to yield hydroxy-diester (4*R*,5*S*,9*S*)-**13** in 69% yield. In order to find the most effective lipase for the hydrolysis of the α,β-unsaturated ester moiety, compound (±)-**10** was selected as a model substrate, and screening experiments using several kinds of lipases were carried out. Among them, lipase OF-360 from *Candida rugosa* was found to be effective. The exposure of (4*R*,5*S*,10*R*,11*S*)-**12** with lipase OF-360, followed by subjection to Yamaguchi macrolactonization[6] (2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP) provided a 12-membered lactone (**19**) in 62% overall yield, of which the physical data were identical with those (^{1}H-NMR) of the reported **19**.[7] Ester cleavage in the substrate **12** was found to occur at the outer ester moiety. The second substrate, (4*R*,5*S*,9*S*)-**13**, was treated with the lipase OF-360 to give the desired hydroxy carboxylic acid (4*R*,5*S*,9*S*)-**20**, along with hydroxy carboxylic acid (4*R*,5*S*)-**21**. The preparation of (*S*)-3-hydroxybutanoic acid was not observed from the organic layer because this acid could be easily soluble in the water layer. This result showed that ester cleavage occurred at both outer and inner ester moieties. The third substrate, (3*S*,8*R*,9*S*)-**14**,[8] was again treated with the lipase OF-360 to afford the corresponding acid (3*S*,8*R*,9*S*)-**22**, and ester cleavage was found to occur at the outer ester moiety. In the case of diesters (4*R*,5*S*,10*R*,11*S*)-**12** and (3*S*,8*R*,9*S*)-**14**, selective hydrolysis of the methyl ester occurred in the presence of lipase OF-360.

Lipase-Catalysed Hydrolysis of Triesters (4*R*,5*S*,10*R*,11*S*,15*S*)-6, (4*R*,5*S*,9*S*,14*R*,15*S*)-7 and (3*S*,8*R*,9*S*,14*R*,15*S*)-8 The condensation of secondary alcohol (4*R*,5*S*,10*R*,11*S*)-**12** and carboxylic acid (*S*)-**16** *via* the Keck procedure provided triester (4*R*,5*S*,10*R*,11*S*,15*S*)-**23** in 70% yield, which was desilylated to yield hydroxy-triester (4*R*,5*S*,10*R*,11*S*,15*S*)-**6** in 82% yield. A second condensation of secondary alcohol (4*R*,5*S*,9*S*)-**13** and (4*R*,5*S*)-**11** *via* the Keck procedure afforded triester (4*R*,5*S*,9*S*,14*R*,15*S*)-**24** in 53% yield, which was desilylated to yield a hydroxy-triester (4*R*,5*S*,9*S*,14*R*,15*S*)-**7** in 56% yield. An exposure of (4*R*,5*S*,10*R*,11*S*,15*S*)-**6** with lipase OF-360, followed by subjection to Yamaguchi macrolactonization, provided a 12-membered lactone (**19**) in 47% overall yield from **6**, of which the physical data (^{1}H-NMR and $[\alpha]_D$) were identical with those reported for **19**.[7] In this case, no preparation of (*S*)-3-hydroxybutanoic acid was observed from the organic layer. The second substrate, (4*R*,5*S*,9*S*,14*R*,15*S*)-**7**, was treated with the lipase OF-360 to give a mixture of seco-acid (**4**) , hydroxy-acid (**21**) and the starting material **7**. No preparation of (*S*)-3-hydroxybutanoic acid was observed from the organic layer, and preparation of the hydroxy acid (3*S*,8*R*,9*S*)-**22** was not clear. This mixture was subjected to Yamaguchi macrolactonization to give (−)-dibenzyl macrosphelide A (**25**) ($[\alpha]_D$ −93.6° (c=0.47, $CHCl_3$)) in 27% overall yield from (4*R*,5*S*,9*S*,14*R*,15*S*)-**7**), along with starting material **7** (14% recovery). The spectral data (^{1}H-, ^{13}C-NMR and $[\alpha]_D$) of (−)-**25** were identical with those ($[\alpha]_D$ −75.9° (c=0.34, $CHCl_3$)) reported for (−)-**25**.[3] Finally, deprotection of the benzyl group in (−)-**25** using $AlCl_3$ in the presence of *m*-xylene[4] was reported to give (+)-macrosphelide A (**1**).[3] The third substrate, (3*S*,8*R*,9*S*,14*R*,15*S*)-**8**,[8] was treated with the lipase OF-360 to afford a mixture of seco-acid (**5**) and starting material **8**. This mixture was subjected to Yamaguchi macrolactonization to give 12-membered lactone (**19**) (20% overall yield from **8**), (−)-dibenzyl macrosphelide A (**25**) ($[\alpha]_D$ −82.9° (c=0.25, $CHCl_3$) in 5% overall yield from **8**), along with starting material **8** (27% recovery). The preparation of **19** could be explained by the fact that chemically synthesized seco-acid (**5**)

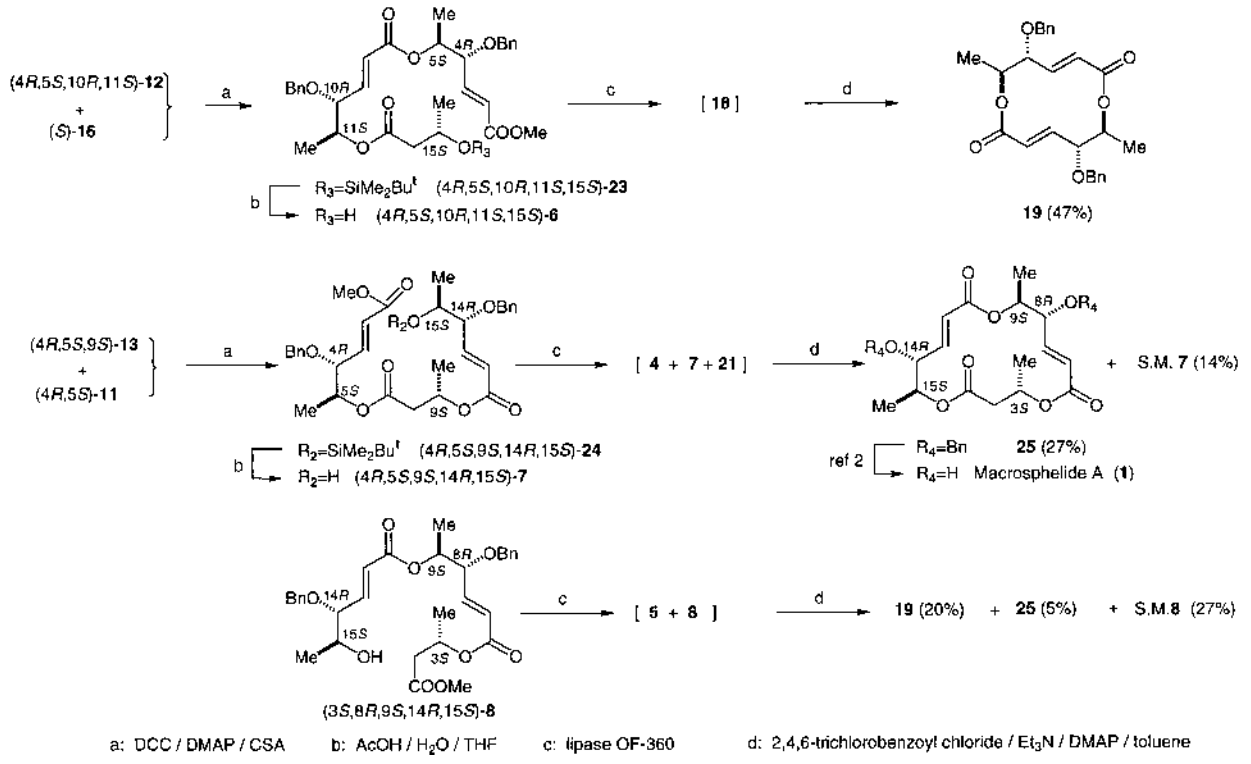

Chart 3

was subjected to Yamaguchi macrolactonization to give (−)-dibenzyl macrosphelide A (**25**) (18%) and 12-membered lactone (**19**) (63%).[7]

In conclusion, the lipase-catalysed hydrolysis of three kinds of seco-macrosphelide A congeners, (4*R*,5*S*,10*R*,11*S*,15*S*)-**6**, (4*R*,5*S*,9*S*,14*R*,15*S*)-**7** and (3*S*,8*R*,9*S*,14*R*,15*S*)-**8**, gave hydroxy carboxylic acids, respectively. The results were different in all cases. Macrolactonization of the hydroxy acid (4*R*,5*S*,10*R*,11*S*)-**18** derived from (4*R*,5*S*,10*R*,11*S*,15*S*)-**6** gave a 12-membered lactone (**19**) in 47% overall yield from **6**, while that of the seco-acid (**4**) derived from (4*R*,5*S*,9*S*,14*R*,15*S*)-**7** afforded (−)-dibenzyl macrosphelide A (**25**) in 27% overall yield from **7**. Macrolactonization of the hydrolysis products, seco-acid (**5**) derived from (3*S*,8*R*,9*S*,14*R*,15*S*)-**8**, provided (−)-dibenzyl macrosphelide A (**25**) (5% overall yield from **8**) and 12-membered lactone (**19**) (20% overall yield from **8**), concurrently.

Experimental

All melting points were measured on a Yanaco MP-3S micro melting point apparatus and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were recorded on a JEOL AL 400 spectrometer in $CDCl_3$. Carbon substitution degrees were established by DEPT pulse sequence. The fast atom bombardment mass spectra (FAB-MS) and electrospray ionization mass spectra (ESI-MS) were obtained with a JEOL JMS-DX 303 spectrometer and ThermoQuest LCQ , respectively. IR spectra were recorded on a JASCO FT/IR-300 spectrometer. 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.

Ester Formation between (4*R*,5*S*)-11 and (4*R*,5*S*)-10 To a mixture of DCC (2.04 g, 9.9 mmol), DMAP (1.61 g, 13.2 mmol) and (+)-CSA (1.53 g, 6.6 mmol) in CH_2Cl_2 (50 ml) was added a solution of (4*R*,5*S*)-**11** (2.179 g, 6.6 mmol) and (4*R*,5*S*)-**10** (2.483 g, 9.9 mmol) in CH_2Cl_2 (15 ml), and this reaction mixture was stirred for 2 d at room temperature. After the generated precipitate was filtered off and the filtrate was washed with 2 M 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 (50 g) to give (4*R*,5*S*,10*R*,11*S*)-**15** (2.206 g, 57%) as a homogenous oil from *n*-hexane : AcOEt = 10 : 1 eluate, and (4*R*,5*S*)-**10** (1.007 g, 40% recovery) was recovered from *n*-hexane : AcOEt = 5 : 1 eluate. (4*R*,5*S*,10*R*,11*S*)-**15**; IR (neat): 2931, 1726, 1659 cm^{-1}; $[\alpha]_D^{22}$ −29.3° (*c* = 1.41, $CHCl_3$); ^{1}H-NMR: δ 0.05 (3H, s), 0.07 (3H, s), 0.89 (9H, s), 1.23 (3H, d, *J* = 6 Hz), 1.31 (3H, d, *J* = 6 Hz), 3.76 (3H, s), 3.79 (1H, ddd, *J* = 2, 6, 6 Hz), 3.88 (1H, quintet, *J* = 6 Hz), 4.13 (1H, ddd, *J* = 2, 4, 6 Hz), 4.47, 4.52, 4.63, 4.66 (each 1H, d, *J* = 12 Hz), 5.16 (1H, dq, *J* = 4, 6 Hz), 6.07 (1H, dd, *J* = 2, 16 Hz), 6.15 (1H, dd, *J* = 2, 16 Hz), 6.91 (1H, dd, *J* = 6, 16 Hz), 6.95 (1H, dd, *J* = 6, 16 Hz), 7.25—7.42 (10H, m). *Anal.* Found: C, 67.84; H, 8.15. Calcd for $C_{33}H_{46}O_7Si$: C, 68.01; H, 7.96%. ESI-MS *m/z*; 600 ($M^+ + NH_4^+$).

Desilylation of (4*R*,5*S*,10*R*,11*S*)-15 A mixture of (4*R*,5*S*,10*R*,11*S*)-**15** (2.206 g, 3.79 mmol) in the mixed solvent (AcOH (10 ml), H_2O (5 ml) and tetrahydrofuran (THF, 5 ml)), was stirred for 12 h at 80 °C. The reaction mixture was evaporated and the residue was diluted with H_2O, then 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*,10*R*,11*S*)-**12** (1.187 g, 67%) as a homogeneous oil. (4*R*,5*S*,10*R*,11*S*)-**12**; IR (neat): 3479, 1720, 1657 (sh) cm^{-1}; $[\alpha]_D^{21}$ −53.7° (*c* = 0.40, $CHCl_3$); ^{1}H-NMR: δ: 1.16 (3H, d, *J* = 6 Hz), 1.30 (3H, d, *J* = 6 Hz), 3.76 (3H, s), 3.92 (1H, ddd, *J* = 2, 4, 6 Hz), 3.96 (1H, dq, *J* = 4, 6 Hz), 4.10 (1H, ddd, *J* = 2, 4, 6 Hz), 4.41, 4.42, 4.63, 4.64 (each 1H, d, *J* = 12 Hz), 5.13 (1H, dq, *J* = 4, 6 Hz), 6.07 (1H, dd, *J* = 2, 16 Hz), 6.12 (1H, dd, *J* = 2, 16 Hz), 6.88 (1H, dd, *J* = 6, 16 Hz), 6.92 (1H, dd, *J* = 6, 16 Hz), 7.25—7.38 (10H, m). ^{13}C-NMR: δ 15.3 (q), 18.1 (q), 51.7 (q), 69.2 (d), 71.4 (t), 71.5 (t), 71.6 (d), 79.4 (d), 81.8 (d), 123.7 (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), 143.9 (d), 144.5 (d), 164.6 (s), 165.9 (s). *Anal.* Found: C, 69.18; H, 7.07. Calcd for $C_{27}H_{32}O_7$: C, 69.21; H, 6.88%. FAB MS *m/z*; 469 ($M^+ + 1$).

Ester Formation between (4*R*,5*S*)-10 and (*S*)-16 To a mixture of DCC (2.01 g, 9.7 mmol), DMAP (1.59 g, 13.0 mmol) and (+)-CSA (1.51 g, 6.5 mmol) in CH_2Cl_2 (50 ml), was added a solution of (4*R*,5*S*)-**10** (1.685 g, 6.7 mmol) and (*S*)-**16** (1.68 g, 7.7 mmol) in CH_2Cl_2 (5 ml) and the reaction mixture was stirred for 2 d at room temperature. Afterwards, the generated precipitate was filtered off and the filtrate was washed with 2 M 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*)-**17** (2.50 g, 83%) as a homogenous oil from *n*-

hexane : AcOEt=10 : 1 eluate. (4*R*,5*S*,9*S*)-**17**; IR (neat): 1733, 1660 cm^{-1}; $[\alpha]_D^{23}$ −24.8° (*c*=0.71, $CHCl_3$); ^{1}H-NMR: δ: 0.02 (3H, s), 0.04 (3H, s), 0.84 (9H, s), 1.16, 1.21 (each 3H, d, *J*=6 Hz), 2.32, 2.45 (each 1H, dd, *J*=6, 16 Hz), 3.74 (3H, s), 4.02 (1H, ddd, *J*=2, 4, 6 Hz), 4.22 (1H, sextet, *J*=6 Hz), 4.45, 4.60 (each 1H, d, *J*=12 Hz), 5.02 (1H, dq, *J*=4, 6 Hz), 6.08 (1H, dd, *J*=2, 16 Hz), 6.83 (1H, dd, *J*=6, 16 Hz), 7.21—7.37 (5H, m). *Anal.* Found: C, 63.86; H, 8.57. Calcd for $C_{24}H_{38}O_6Si$: C, 63.97; H, 8.50%. FAB MS *m*/*z*; 451 (M^++1).

Desilylation of (4*R*,5*S*,9*S*)-17 A mixture of (4*R*,5*S*,9*S*)-**17** (2.50 g, 5.55 mmol) in the mixed solvent (AcOH (15 ml), H_2O (10 ml) and THF (10 ml)) was stirred for 1 d at 80 °C. The reaction mixture was evaporated and the residue was diluted with H_2O, then 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*)-**13** (1.28 g, 69%) as a homogeneous oil. (4*R*,5*S*,9*S*)-**13**; IR (neat): 3498, 1727 cm^{-1}; $[\alpha]_D^{21}$ −47.5° (*c*=0.30, $CHCl_3$); ^{1}H-NMR: δ: 1.21, 1.25 (each 3H, d, *J*=6 Hz), 2.38 (1H, dd, *J*=6, 16 Hz), 2.47 (1H, dd, *J*=4, 16 Hz), 2.93 (1H, br s), 3.77 (3H, s), 4.03 (1H, ddd, *J*=2, 4, 6 Hz), 4.13—4.20 (1H, m), 4.45, 4.64 (each 1H, d, *J*=12 Hz), 5.11 (1H, dq, *J*=4, 6 Hz), 6.10 (1H, dd, *J*=2, 16 Hz), 6.86 (1H, dd, *J*=6, 16 Hz), 7.26—7.41 (5H, m). ^{13}C-NMR: δ 15.4 (q), 22.6 (q), 43.2 (t), 51.8 (q), 64.4 (d), 71.4 (d), 71.5 (t), 79.3 (d), 124.0 (d), 127.5 (d), 127.6 (d), 128.3 (d), 137.3 (s), 143.6 (d), 165.9 (s), 171.8 (s). *Anal.* Found: C, 63.83; H, 7.33. Calcd for $C_{18}H_{24}O_6$: C, 64.27; H, 7.19%. FAB MS *m*/*z*; 337 (M^++1).

Lipase-Catalysed Hydrolysis of (4*R*,5*S*,10*R*,11*S*)-12 Followed by Macrolactonization A suspension of (4*R*,5*S*,10*R*,11*S*)-**12** (0.198 g, 0.42 mmol) and lipase OF-360 (400 mg) in 0.1 M phosphate buffer solution (20 ml) was stirred for 10 d at 35 °C, and the reaction mixture was filtered off with the aid of celite. The filtrate was acidified with 2 M aqueous HCl and extracted with ether. The ether layer was washed with saturated brine and dried over $MgSO_4$. The ether layer was evaporated to give a crude seco-acid (4*R*,5*S*,10*R*,11*S*)-**18** (0.181 g), which was subjected to NMR analysis. (4*R*,5*S*,10*R*,11*S*)-**18**; ^{1}H-NMR: δ: 1.17 (3H, d, *J*=7 Hz), 1.30 (3H, d, *J*=7 Hz), 3.93 (1H, ddd, *J*=2, 4, 6 Hz), 3.97 (1H, dq, *J*=4, 7 Hz), 4.13 (1H, ddd, *J*=2, 4, 6 Hz), 4.41, 4.51, 4.64, 4.66 (each 1H, d, *J*=12 Hz), 5.14 (1H, dq, *J*=4, 7 Hz), 6.07 (1H, dd, *J*=2, 16 Hz), 6.13 (1H, dd, *J*=2, 16 Hz), 6.92 (1H, dd, *J*=6, 16 Hz), 6.99 (1H, dd, *J*=6, 16 Hz), 7.27—7.39 (10H, m). To a solution of (4*R*,5*S*,10*R*,11*S*)-**18** (0.181 g, 0.4 mmol) in toluene (2 ml) was added triethylamine (0.05 g, 0.48 mmol) and 2,4,6-trichlorobenzoyl chloride (0.097 g, 0.4 mmol), and the reaction mixture was stirred for 3 h at room temperature. To a solution of DMAP (0.29 g, 2.39 mmol) in toluene (150 ml) was added dropwise a solution of the above-mentioned reaction mixture in toluene (20 ml) at 60 °C with stirring, and the whole mixture was stirred for 2 d at 60 °C. The reaction mixture was washed with 7% aqueous $NaHCO_3$, 2 M 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 (20 g, *n*-hexane : AcOEt=20 : 1) to give (−)-**19** (0.11 g, 62% overall yield from (4*R*,5*S*,10*R*,11*S*)-**12**) as a colorless solid. (−)-**19**; IR (neat): 1726, 1647 cm^{-1}; $[\alpha]_D^{27}$ −161.0° (*c*=0.36, $CHCl_3$); ^{1}H-NMR: δ: 1.43 (6H, d, *J*=6 Hz), 3.69 (2H, t, *J*=9 Hz), 4.35, 4.62 (each 2H, d, *J*=12 Hz), 5.11 (2H, qd, *J*=6, 9 Hz), 5.94 (2H, d, *J*=16 Hz), 6.52 (2H, dd, *J*=9, 16 Hz), 7.26—7.37 (10H, m). *Anal.* Found: C, 71.49; H, 6.57. Calcd for $C_{26}H_{28}O_6$: C, 71.54; H, 6.47%. FAB MS *m*/*z*; 437 (M^++1).

Lipase-Catalysed Hydrolysis of (4*R*,5*S*,9*S*)-13 A suspension of (4*R*,5*S*,9*S*)-**13** (0.217 g, 0.64 mmol) and lipase OF-360 (400 mg) in 0.1 M phosphate buffer solution (20 ml) was stirred for 7 d at 35 °C, and the reaction mixture was filtered off with the aid of celite. The filtrate was acidified with 2 M aqueous HCl and extracted with ether. The ether layer was washed with saturated brine and dried over $MgSO_4$. The ether layer was evaporated to give a 1 : 1.4 mixture (0.202 g) of seco-acid (4*R*,5*S*,9*S*)-**20** and (4*R*,5*S*)-acid **21**, which was subjected to NMR analysis. (4*R*,5*S*,9*S*)-**20**; ^{1}H-NMR: δ: 1.22 (3H, d, *J*=6 Hz), 1.25 (3H, d, *J*=6 Hz), 2.40 (1H, dd, *J*=8, 16 Hz), 2.46 (1H, dd, *J*=4, 16 Hz), 4.04 (1H, ddd, *J*=2, 4, 6 Hz), 4.18 (1H, ddq, *J*=4, 6, 8 Hz), 4.47, 4.64 (each 1H, d, *J*=12 Hz), 5.12 (1H, dq, *J*=4, 6 Hz), 6.10 (1H, dd, *J*=2, 16 Hz), 6.94 (1H, dd, *J*=6, 16 Hz), 7.28—7.37 (5H, m). **21**; ^{1}H-NMR: δ 1.15 (3H, d, *J*=7 Hz), 3.93 (1H, ddd, *J*=2, 4, 6 Hz), 3.97 (1H, dq, *J*=4, 6 Hz), 4.42, 4.64 (each 1H, d, *J*=12 Hz), 6.08 (1H, dd, *J*=2, 16 Hz), 7.01 (1H, dd, *J*=6, 16 Hz), 7.28—7.37 (5H, m).

Lipase-Catalysed Hydrolysis of (3*S*,8*R*,9*S*)-14 A suspension of (3*S*,8*R*,9*S*)-**14**[8] (0.194 g, 0.57 mmol) and lipase OF-360 (300 mg) in 0.1 M phosphate buffer solution (20 ml) was stirred for 3 d at 35 °C, and the reaction mixture was filtered off with the aid of celite. The filtrate was acidified with 2 M aqueous HCl and extracted with ether. The ether layer was washed with saturated brine and dried over $MgSO_4$. The ether layer was evaporated to give a seco-acid (3*S*,8*R*,9*S*)-**22** (0.166 g), which was subjected to NMR analysis. (3*S*,8*R*,9*S*)-**22**; ^{1}H-NMR δ: 1.13 (3H, d, *J*=7 Hz), 1.33 (3H, d, *J*=6 Hz), 2.54 (1H, dd, *J*=6, 16 Hz), 2.70 (1H, dd, *J*=6, 16 Hz), 3.87 (1H, ddd, *J*=2, 4, 6 Hz), 3.92 (1H, dq, *J*=4, 7 Hz), 4.38, 4.60 (each 1H, d, *J*=12 Hz), 5.31 (1H, sextet, *J*=6 Hz), 6.02 (1H, dd, *J*=2, 16 Hz), 6.88 (1H, dd, *J*=6, 16 Hz), 7.24—7.35 (5H, m).

Ester Formation between (4*R*,5*S*,10*R*,11*S*)-12 and (*S*)-16 To a mixture of DCC (1.58 g, 7.7 mmol), DMAP (1.25 g, 10.2 mmol) and (+)-CSA (1.03 g, 4.4 mmol) in CH_2Cl_2 (50 ml) was added a solution of (4*R*,5*S*,10*R*,11*S*)-**12** (1.570 g, 3.4 mmol) and (*S*)-**16** (1.156 g, 7.19 mmol) in CH_2Cl_2 (20 ml), and the reaction mixture was stirred for 2 d at room temperature. Afterwards, the generated precipitate was filtered off and the filtrate was washed with 2 M 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 (80 g, *n*-hexane : AcOEt=10 : 1) to give (4*R*,5*S*,10*R*,11*S*,15*S*)-**23** (1.566 g, 70%) as a homogenous oil. (4*R*,5*S*,10*R*,11*S*,15*S*)-**23**; IR (neat): 1729, 1658 (sh) cm^{-1}; $[\alpha]_D^{26}$ −36.5° (*c*=0.46, $CHCl_3$); ^{1}H-NMR: δ: 0.04 (3H, s), 0.06 (3H, s), 0.86 (9H, s), 1.18 (3H, d, *J*=6 Hz), 1.22 (3H, d, *J*=6 Hz), 1.28 (3H, d, *J*=6 Hz), 2.37 (1H, dd, *J*=6, 15 Hz), 2.47 (1H, dd, *J*=6, 15 Hz), 3.75 (3H, s), 4.08 (1H, ddd, *J*=2, 4, 6 Hz), 4.10 (1H, ddd, *J*=2, 4, 6 Hz), 4.24 (1H, sextet, *J*=6 Hz), 4.44, 4.45, 4.61, 4.63 (each 1H, d, *J*=12 Hz), 5.03 (1H, dq, *J*=4, 6 Hz), 5.10 (1H, dq, *J*=4, 6 Hz), 6.08 (1H, dd, *J*=2, 16 Hz), 6.12 (1H, dd, *J*=2, 16 Hz), 6.83 (1H, dd, *J*=6, 16 Hz), 6.88 (1H, dd, *J*=6, 16 Hz), 7.24—7.39 (10H, m). *Anal.* Found: C, 66.03; H, 8.12. Calcd for $C_{37}H_{52}O_9Si$: C, 66.44; H, 7.84%. ESI-MS *m*/*z*; 669 (M^++1), 691 (M^++Na).

Desilylation of (4*R*,5*S*,10*R*,11*S*,15*S*)-23 A mixture of (4*R*,5*S*,10*R*,11*S*,15*S*)-**23** (1.566 g, 2.39 mmol) in the mixed solvent (AcOH (7.5 ml), H_2O (5 ml) and THF (5 ml)) was stirred for 12 h at 80 °C. The reaction mixture was evaporated and the residue was diluted with H_2O, then 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 (30 g, *n*-hexane : AcOEt=4 : 1) to give (4*R*,5*S*,10*R*,11*S*,15*S*)-**6** (1.063 g, 82%) as a homogeneous oil. (4*R*,5*S*,10*R*,11*S*,15*S*)-**6**; IR (neat): 3515, 1723, 1658 (sh) cm^{-1}; $[\alpha]_D^{22}$ −53.7° (*c*=0.40, $CHCl_3$); ^{1}H-NMR: δ: 1.18 (3H, d, *J*=6 Hz), 1.22 (3H, d, *J*=6 Hz), 1.27 (3H, d, *J*=6 Hz), 2.35 (1H, dd, *J*=8, 16 Hz), 2.42 (1H, dd, *J*=4, 16 Hz), 2.93 (1H, br s), 3.73 (3H, s), 4.01 (1H, ddd, *J*=2, 4, 6 Hz), 4.08 (1H, ddd, *J*=2, 4, 6 Hz), 4.12 (1H, m), 4.43, 4.46, 4.61, 4.63 (each 1H, d, *J*=12 Hz), 5.07 (1H, dq, *J*=4, 6 Hz), 5.10 (1H, dq, *J*=4, 6 Hz), 6.06 (1H, dd, *J*=2, 16 Hz), 6.11 (1H, dd, *J*=2, 16 Hz), 6.82 (1H, dd, *J*=6, 16 Hz), 6.87 (1H, dd, *J*=6, 16 Hz), 7.24—7.38 (10H, m). ^{13}C-NMR: δ 15.3 (q), 15.4 (q), 22.6 (q), 43.2 (t), 51.7 (q), 64.3 (d), 71.4 (d), 71.5 (t), 71.6 (t), 71.7 (d), 79.3 (d), 79.3 (d), 123.8 (d), 124.2 (d), 127.4 (d), 127.5 (d), 127.6 (d), 127.7 (d), 128.2 (d), 128.2 (d), 137.2 (d), 137.4 (d), 143.7 (d), 143.9 (d), 164.6 (s), 165.8 (s), 171.5 (s). *Anal.* Found: C, 67.20; H, 7.84. Calcd for $C_{31}H_{38}O_9$: C, 67.13; H, 6.91%. FAB MS *m*/*z*; 555 (M^++1).

Ester Formation between (4*R*,5*S*,9*S*)-13 and (4*R*,5*S*)-11 To a mixture of DCC (1.18 g, 5.7 mmol), DMAP (0.93 g, 7.6 mmol) and (+)-CSA (0.88 g, 3.8 mmol) in CH_2Cl_2 (45 ml) was added a solution of (4*R*,5*S*)-**11** (1.601 g, 4.57 mmol) and (4*R*,5*S*,9*S*)-**13** (1.280 g, 3.81 mmol) in CH_2Cl_2 (10 ml), and the reaction mixture was stirred for 2 d at room temperature. Afterwards, the generated precipitate was filtered off and the filtrate was washed with 2 M 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 (50 g, *n*-hexane : AcOEt=10 : 1) to give (4*R*,5*S*,9*S*,14*R*,15*S*)-**24** (1.355 g, 53%) as a homogenous oil. (4*R*,5*S*,9*S*,14*R*,15*S*)-**24**; IR (neat): 1735, 1650 cm^{-1}; $[\alpha]_D^{27}$ −33.8° (*c*=1.07, $CHCl_3$); ^{1}H-NMR: δ: 0.02 (3H, s), 0.04 (3H, s), 0.86 (9H, s), 1.18 (3H, d, *J*=6 Hz), 1.21 (3H, d, *J*=6 Hz), 1.32 (3H, d, *J*=6 Hz), 2.50, 2.67 (each 1H, dd, *J*=6, 14 Hz), 3.74 (3H, s), 3.75 (1H, ddd, *J*=2, 6, 6 Hz), 3.82 (1H, dq, *J*=6, 6 Hz), 4.03 (1H, ddd, *J*=2, 4, 6 Hz), 4.41, 4.46, 4.58, 4.61 (each 1H, d, *J*=12 Hz), 5.04 (1H, dq, *J*=4, 6 Hz), 5.32 (1H, sextet, *J*=6 Hz), 5.99 (1H, dd, *J*=2, 16 Hz), 6.10 (1H, dd, *J*=2, 16 Hz), 6.84 (1H, dd, *J*=6, 16 Hz), 6.90 (1H, dd, *J*=6, 16 Hz), 7.32—7.40 (10H, m). *Anal.* Found: C, 66.63; H, 7.90. Calcd for $C_{37}H_{52}O_9Si$: C, 66.44; H, 7.84%.

Desilylation of (4*R*,5*S*,9*S*,14*R*,15*S*)-24 A mixture of (4*R*,5*S*,9*S*,14*R*,15*S*)-**24** (1.100 g, 1.56 mmol) in the mixed solvent (AcOH (8 ml), H_2O (5 ml) and THF (5 ml)) was stirred for 12 h at 80 °C. The reaction mixture was evaporated and the residue was diluted with H_2O, then 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*)-**7** (0.473 g, 56%) as a homogeneous oil. (4*R*,5*S*,9*S*, 14*R*,15*S*)-**7**; IR (neat): 3475, 1735 cm^{-1}; $[\alpha]_D^{24}$ −55.7° (c=0.38, $CHCl_3$); ^{1}H-NMR: δ: 1.12 (3H, d, J=6 Hz), 1.19 (3H, d, J=6 Hz), 1.32 (3H, d, J=6 Hz), 2.28 (1H, br s), 2.52, 2.65 (each 1H, dd, J=6, 16 Hz), 3.74 (3H, s), 3.86 (1H, ddd, J=2, 4, 6 Hz), 3.91 (1H, dq, J=4, 6 Hz), 4.01 (1H, ddd, J=2, 4, 6 Hz), 4.37, 4.43, 4.59, 4.60 (each 1H, d, J=12 Hz), 5.03 (1H, dq, J=4, 6 Hz), 5.31 (1H, sextet, J=6 Hz), 6.00 (1H, dd, J=2, 16 Hz), 6.08 (1H, dd, J=2, 16 Hz), 6.82 (1H, dd, J=6, 16 Hz), 6.87 (1H, dd, J=6, 16 Hz), 7.24—7.38 (10H, m). ^{13}C-NMR: δ: 15.2 (q), 18.2 (q), 19.8 (q), 41.0 (t), 51.8 (q), 67.6 (d), 69.0 (d), 71.2 (d), 71.4 (t), 71.6 (t), 79.3 (d), 81.9 (d), 123.8 (d), 124.2 (d), 127.5 (d), 127.5 (d), 127.6 (d), 127.7 (d), 128.2 (d), 128.3 (d), 137.3 (s), 137.4 (s), 143.6 (d), 144.2 (d), 164.6 (s), 165.8 (s), 169.0 (s). *Anal.* Found: C, 67.25; H, 7.04. Calcd for $C_{31}H_{38}O_9$: C, 67.13; H, 6.91%. FAB MS m/z; 555 (M^++1).

Lipase-Catalysed Hydrolysis of (4*R*,5*S*,10*R*,11*S*,15*S*)-6 Followed by Macrolactonization A suspension of (4*R*,5*S*,10*R*,11*S*,15*S*)-**6** (0.171 g, 0.3 mmol) and lipase OF-360 (300 mg) in 0.1 M phosphate buffer solution (40 ml) was stirred for 8 d at 35 °C, and the reaction mixture was filtered off with the aid of celite. The filtrate was acidified with 2 M aqueous HCl and extracted with ether. The ether layer was washed with saturated brine and dried over $MgSO_4$. The ether layer was evaporated to give a crude seco-acid (4*R*,5*S*,10*R*,11*S*)-**18** (0.14 g), which was subjected to NMR analysis. (4*R*,5*S*, 10*R*,11*S*)-**18**; ^{1}H-NMR: δ: 1.17 (3H, d, J=7 Hz), 1.30 (3H, d, J=7 Hz), 3.93 (1H, ddd, J=2, 4, 6 Hz), 3.97 (1H, dq, J=4, 7 Hz), 4.13 (1H, ddd, J=2, 4, 6 Hz), 4.41, 4.51, 4.64, 4.66 (each 1H, d, J=12 Hz), 5.14 (1H, dq, J=4, 7 Hz), 6.07 (1H, dd, J=2, 16 Hz), 6.13 (1H, dd, J=2, 16 Hz), 6.92 (1H, dd, J=6, 16 Hz), 6.99 (1H, dd, J=6, 16 Hz), 7.27—7.39 (10H, m).

To a solution of crude (4*R*,5*S*,10*R*,11*S*)-**18** (0.14 g, 0.31 mmol) in toluene (2 ml) was added triethylamine (0.03 g, 0.37 mmol) and 2,4,6-trichlorobenzoyl chloride (0.075 g, 0.31 mmol), and the reaction mixture was stirred for 2 h at room temperature under argon atmosphere. To a solution of DMAP (0.23 g, 1.85 mmol) in toluene (200 ml) was added dropwise a solution of the above-mentioned reaction mixture in toluene (30 ml) at 60 °C with stirring, and the whole mixture was stirred for 3 d at 60 °C. The reaction mixture was washed with 7% aqueous $NaHCO_3$, 2 M 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 (20 g, *n*-hexane : AcOEt= 10 : 1) to give (−)-**19** (0.063 g, 47% overall yield from (4*R*,5*S*,10*R*,11*S*,15*S*)-**6**, $[\alpha]_D^{25}$ −165.1° (c=0.24, $CHCl_3$)). The spectral data (^{1}H-NMR and $[\alpha]_D$) were identical with those of above-mentioned (−)-**19**.

Lipase-Catalysed Hydrolysis of (4*R*,5*S*,9*S*,14*R*,15*S*)-7 Followed by Macrolactonization A suspension of (4*R*,5*S*,9*S*,14*R*,15*S*)-**7** (0.165 g, 0.3 mmol) and lipase OF-360 (200 mg) in 0.1 M phosphate buffer solution (40 ml) was stirred for 14 d at 35 °C, and the reaction mixture was filtered off with the aid of celite. The filtrate was acidified with 2 M aqueous HCl and extracted with ether. The ether layer was washed with saturated brine and dried over $MgSO_4$. The ether layer was evaporated to give a mixture (0.148 g) of seco-acid (4*R*,5*S*,9*S*,14*R*,15*S*)-**4**, a small amount of starting material (4*R*,5*S*,9*S*,14*R*,15*S*)-**7** and **21**, which was subjected to NMR analysis. (4*R*,5*S*,9*S*,14*R*,15*S*)-**4**; ^{1}H-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, dq, 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). Other signals due to **7** (δ 3.75, 3H, s) and **21** (δ 7.01, 1H, dd, J=6, 16 Hz) were observed separately. To a solution of the above-mentioned mixture (0.148 g, 0.275 mmol) in THF (1 ml) was added triethylamine (0.06 g, 0.549 mmol) and 2,4,6-trichlorobenzoyl chloride (0.13 g, 0.549 mmol), and the reaction mixture was stirred for 2 h at room temperature under argon atmosphere. To a solution of DMAP (0.20 g, 1.65 mmol) in toluene (30 ml) was added dropwise a solution of the above-mentioned reaction mixture in toluene (110 ml) at 100 °C with stirring, and the whole mixture was stirred for 12 h at 100 °C. The reaction mixture was washed with 7% aqueous $NaHCO_3$, 2 M 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 (20 g, *n*-hexane : AcOEt=10 : 1) to give macrosphelide A dibenzyl ether (**25**) (0.042 g, 27% overall yield from (4*R*,5*S*,9*S*,14*R*,15*S*)-**7**, $[\alpha]_D^{22}$ −93.6° (c=0.47, $CHCl_3$)) from *n*-hexane : AcOEt=10 : 1 eluate and recovery (4*R*,5*S*,9*S*,14*R*,15*S*)-**7** (0.023 g, 14% recovery) from *n*-hexane : AcOEt=1 : 1 eluate. The spectral data (^{1}H-NMR and $[\alpha]_D$) of macrosphelide A dibenzyl ether (**25**) were identical with those ($[\alpha]_D^{22}$ −75.9° (c=0.34, $CHCl_3$)) of the reported (−)-**25**.[2)]

Lipase-Catalysed Hydrolysis of (3*S*,8*R*,9*S*,14*R*,15*S*)-8 Followed by Macrolactonization A suspension of (3*S*,8*R*,9*S*,14*R*,15*S*)-**8** (0.205 g, 0.37 mmol) and lipase OF-360 (400 mg) in 0.1 M phosphate buffer solution (40 ml) was stirred for 10 d at 35 °C, and the reaction mixture was filtered off with the aid of celite. The filtrate was acidified with 2 M aqueous HCl and extracted with ether. The ether layer was washed with saturated brine and dried over $MgSO_4$. The ether layer was evaporated to give a mixture (0.185 g) of seco-acid (3*S*,8*R*,9*S*,14*R*,15*S*)-**5** and starting material (3*S*,8*R*,9*S*, 14*R*,15*S*)-**8**, which was subjected to NMR analysis. **5** : **8**=2.5 : 1 (3*S*,8*R*,9*S*, 14*R*,15*S*)-**5**; ^{1}H-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, dq, 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). (3*S*,8*R*,9*S*,14*R*,15*S*)-**8**; ^{1}H-NMR δ 1.15 (3H, d, J=6 Hz), 1.30 (3H, d, J=6 Hz), 1.34 (3H, d, J=6 Hz), 2.28 (1H, br s, OH), 2.54, 2.70 (each 1H, dd, J=6, 16 Hz), 3.67 (3H, s), 3.93 (1H, ddd, J=2, 4, 6 Hz), 3.94—3.99 (1H, m), 4.11 (1H, ddd, J=2, 4, 6 Hz), 4.42, 4.49, 4.65, 4.65 (each 1H, d, J=12 Hz), 5.11 (1H, dq, J=4, 6 Hz), 5.35 (1H, sextet, J=6 Hz), 6.06 (1H, dd, J=2, 16 Hz), 6.08 (1H, dd, J=2, 16 Hz), 6.86 (1H, dd, J=6, 16 Hz), 6.91 (1H, dd, J=6, 16 Hz), 7.23—7.35 (10H, m). To a solution of the above-mentioned mixture (0.1851 g) in THF (1 ml) was added triethylamine (0.07 g, 0.67 mmol) and 2,4,6-trichlorobenzoyl chloride (0.17 g, 0.67 mmol), and the reaction mixture was stirred for 2 h at room temperature under argon atmosphere. To a solution of DMAP (0.25 g, 2.0 mmol) in toluene (35 ml) was added dropwise a solution of the above-mentioned reaction mixture in toluene (100 ml) at 100 °C with stirring, and the whole mixture was stirred for 12 h at 100 °C. The reaction mixture was washed with 7% aqueous $NaHCO_3$, 2 M 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 (20 g, *n*-hexane : AcOEt=10 : 1) to give (−)-**19** (0.032 g 20% yield from (3*S*,8*R*,9*S*,14*R*,15*S*)-**8**, $[\alpha]_D^{22}$ −156.6° (c=0.30, $CHCl_3$)), macrosphelide A dibenzyl ether (**25**) (0.01 g, 5% overall yield, from (3*S*,8*R*,9*S*,14*R*,15*S*)-**8**, $[\alpha]_D^{20}$ −82.9° (c=0.25, $CHCl_3$)) from *n*-hexane : AcOEt=10 : 1 eluate, and the recovery of (3*S*,8*R*,9*S*,14*R*,15*S*)-**8** (0.057 g, 27% recovery) from *n*-hexane : AcOEt=1 : 1 eluate. The spectral data (^{1}H-NMR and $[\alpha]_D$) of (−)-**19** and macrosphelide A dibenzyl ether (**25**) were identical with those of the above-mentioned (−)-**19** and the reported (−)-**25**,[2)] respectively.

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