Pergamon

Tetrahedron: *Asymmetry* 13 (2002) 705–713

TETRAHEDRON: *ASYMMETRY*

New total syntheses of (+)-macrosphelides C, F and G

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Received 27 February 2002; accepted 11 April 2002

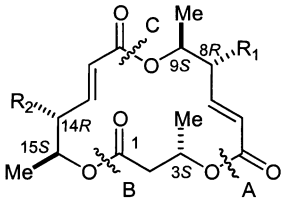
Abstract—The total synthesis of (+)-macrosphelide C **1** (25% overall yield in nine steps), (+)-macrosphelide F **2** (20% overall yield in nine steps) and (+)-macrosphelide G **3** (22% overall yield in nine steps) has been achieved from the chemoenzymatic reaction product (4*R*,5*S*)-4-benzyloxy-5-hydroxy-(2*E*)-hexenoate **7**. © 2002 Published by Elsevier Science Ltd.

1. Introduction

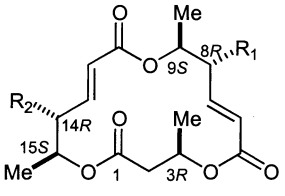
(+)-Macrosphelide C **1** was isolated from a cultured broth of *Macrosphaeropsis* sp. FO-5050, and the plane structure of (+)-**1** was determined as depicted **1**,[1] whereas (+)-macrosphelides F **2**, G **3** and C **1** were obtained from a strain of *Periconia byssoides* separated from the gastrointestinal tract of the sea hare *Aplysia kurodai* as minor products (Scheme 1).[2] These compounds were found to strongly inhibit the adhesion of human leukemia HL-60 cells to human umbilical-vein endothelial cells (HUVEC).[1,2] The absolute stereostructures of macrosphelides F **2** and G **3** have been elucidated on the basis of spectroscopic analysis using 1D and 2D NMR techniques and some chemical transformations.[2] In addition, the absolute configuration of **1** has been established by X-ray analysis and application of the modified Mosher method.[2] Recently, syntheses of macrosphelides (+)-A **4**[3a,b,c] and (+)-E **5**[3c] were carried out by three groups to investigate the biological properties and determine their stereochemistry. The asymmetric synthesis of macrosphelides C **1** and F **2** was achieved by lactonization of the chiral 14-oxo *seco*-acids at the O(10)–C(11) bond followed by reduction and Mitsunobu inversion of the resulting hydroxyl group,[4] while asymmetric synthesis of macrosphelide G **3** has not been reported so far. On the other hand, we reported that the enantioselective hydrolysis of (±)-(4,5)-*anti*-5-acetoxy-4-benzyloxy-(2*E*)-hexenoate **6** using the lipase 'Amano P' from *Pseudomonas* sp. in phosphate buffer solution gave the (4*R*,5*S*)-5-acetoxy ester **6** (>99% e.e., 48% yield) and the (4*S*,5*R*)-5-hydroxy ester **7** (>99% e.e., 44% yield), and methanolysis of (4*R*,5*S*)-**6** provided (4*R*,5*S*)-**7** in 84% yield (Scheme 2).[5] These enzymatic products were effectively applied to the synthesis of macrosphelides (+)-A **4**,[3c] (−)-A **4**[3c] and (+)-E **5**[3c] as useful chiral synthons. Herein, we report a new synthesis of macrosphelides (+)-C **1**, (+)-F **2** and (+)-G **3** from the above-mentioned enzymatic products.

2. Results and discussion

We reported previously the total synthesis of (+)-macrosphelide A **4** via paths A, B and C (Scheme 1)



R_1 = H, R_2 = OH : (+)-Macrosphelide C **1**
R_1 = R_2 = OH : (+)-Macrosphelide A **4**



R_1 = H, R_2 = OH : (+)-Macrosphelide F **2**
R_1 = OH, R_2 = H : (+)-Macrosphelide G **3**
R_1 = R_2 = OH : (+)-Macrosphelide E **5**

Scheme 1.

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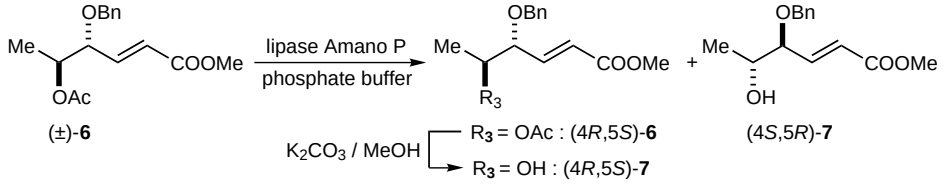
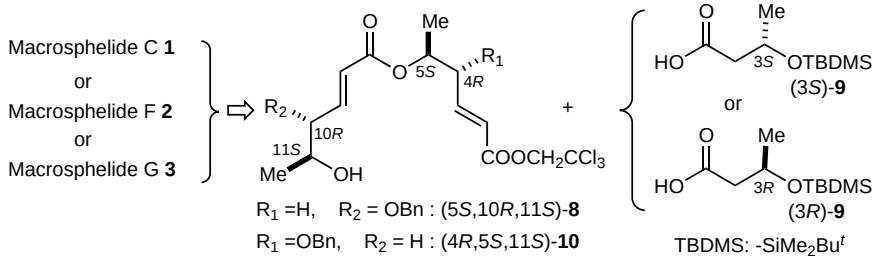
PII: S0957-4166(02)00180-5

involving macrolactonization. The synthesis via path A was found to give the best result from the viewpoint of synthetic efficiency.[6] The common synthetic intermediate in the synthesis of **1** and **2** via path A is considered to be the diester (5*S*,10*R*,11*S*)-**8**, which is coupled with (3*S*)-butanoic acid derivative **9** or (3*R*)-**9** to lead to the synthesis of C **1** or F **2**, respectively. On the other hand, the synthetic intermediate via path A in the synthesis of macrosphelide G **3** can be regarded as the diester (4*R*,5*S*,11*S*)-**10**, which is connected with (3*R*)-**9** to enable the synthesis of G **3** (Scheme 3). As a preliminary experiment, ester formation between (4*R*,5*S*,2*E*)-hexenoic acid congener **11** derived from (4*R*,5*S*)-**7**[5] and (±)-5-hydroxy-(2*E*)-hexenoate **12** in the presence of 4-*N*,*N*-dimethylaminopyridine (DMAP) and camphorsufonic acid (CSA) in CH_2Cl_2 (method a) gave a diastereomeric mixture (29%) of diester **13** and diester **14**, while in the absence of CSA (method b) a diastereomeric mixture (38%) of diester **13** and diester **14** was afforded. When 2,2,2-trichloroethyl 5-hydroxy-(2*E*)-hexenoate instead of methyl ester (±)-**12** was applied to the above esterification reaction using method a, a diastereomeric mixture (44%) of the diester corresponding to a mixture of **13** and **14** along with 2,4-hexadienoate (12%) was produced. In order to circumvent the low yield and the undesired generation of 2,4-hexadienoate in this process, the macrolactonization process was changed to path C from path A (Scheme 4).

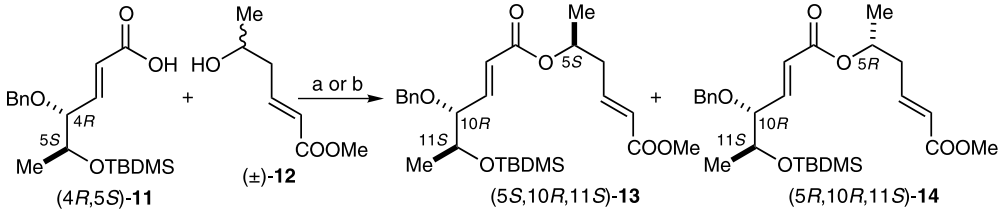
First, (5*S*)-*tert*-butyldimethylsiloxy-(2*E*)-hexenoic acid **15** was synthesized from the enzymatic reaction product (4*R*,5*S*)-**7** (Scheme 5). Debenzylation of (4*R*,5*S*)-**7** by the reported method gave (4*R*,5*S*)-dihydroxy ester **16**[7] which was treated with *tert*-butyldimethylsilyl chloride (TBDMSCl) to provide (4*R*,5*S*)-**17** (12%) and (4*R*,5*S*)-**18** (65%). In order to confirm the position of silylation, both **17** and **18** were subjected to mesylation with methanesulfonic anhydride (Ms_2O) to afford the corresponding mesylates (4*R*,5*S*)-**19** (87%) and (4*R*,5*S*)-**20** (96%), respectively. The structures of both (4*R*,5*S*)-**19** and (4*R*,5*S*)-**20** were confirmed by the fact that chemical shift due to the C(5) hydrogen of (4*R*,5*S*)-**19** appeared at lower field (δ 4.74, dq, $J=4$, 6 Hz) in comparison with that due to C(5) hydrogen of (4*R*,5*S*)-**20** (δ 4.02, dq, $J=4$, 6 Hz). Treatment of (4*R*,5*S*)-**20** with $NaBH_4$ in the presence of 1,1,1-tris(dibenzylideneacetone)dipalladium(0)–chloroform adduct ($Pd_2(dba)_3{\cdot}CHCl_3$) and Bu_3P according to the procedure of Tsuji[8] gave (5*S*)-*tert*-butyldimethylsiloxy-(2*E*)-hexenoate **21** in 78% yield. Alkaline hydrolysis of **21** afforded the corresponding carboxylic acid (5*S*)-**15** (95% crude yield), which was used for the next reaction without further purification.



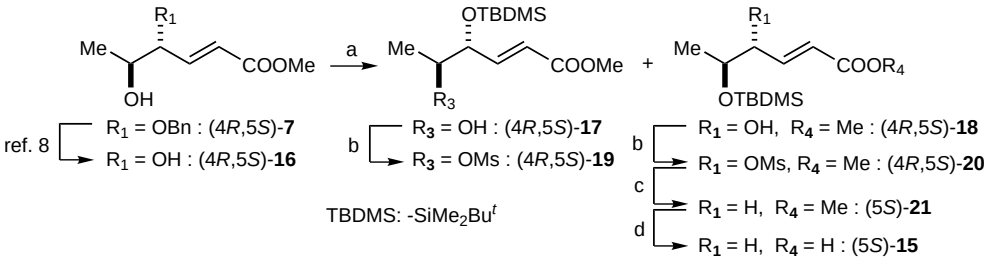
Scheme 2.



Scheme 3.



Scheme 4. *Reagents*: (a) DCC/DMAP/CSA/CH_2Cl_2; (b) DCC/DMAP/CH_2Cl_2.



Scheme 5. *Reagents*: (a) TBDMSCl/imidazole/DMF; (b) Ms_2O/pyridine; (c) $NaBH_4/Pd_2(dba)_3{\cdot}CHCl_3/Bu_3P$/dioxane–$H_2O$; (d) (1) 2 M NaOH aq./MeOH (2) 2 M HCl aq.

2.1. Synthesis of (+)-macrosphelide C 1

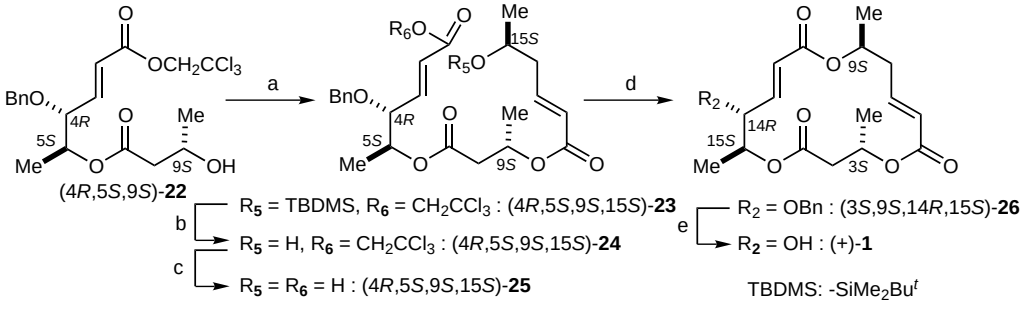
Ester formation between the carboxylic acid (5*S*)-**15** and the reported hydroxy-diester (4*R*,5*S*,9*S*)-**22**[6] via the Steglich procedure[9] gave a triester (4*R*,5*S*,9*S*,15*S*)-**23** in 86% yield, which was subjected to desilylation to provide a secondary alcohol (4*R*,5*S*,9*S*,15*S*)-**24** in 88% yield. Deprotection of (4*R*,5*S*,9*S*,15*S*)-**24** using Zn in acetic acid buffer solution followed by Yamaguchi macrolactonization[10] (2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP) provided (3*S*,9*S*,14*R*,15*S*)-benzyl macrosphelide C **26** ($[\alpha]_D$ −43.7 ($c=0.22$, $CHCl_3$)) in 69% overall yield from (−)-**24**. Finally, deprotection of the benzyl group in (−)-**26** using $AlCl_3$ in the presence of *m*-xylene[5] gave the synthetic (+)-macrosphelide C **1** (mp 152–155°C, $[\alpha]_D$ +53.3 ($c=0.08$, EtOH)) in 77% yield. Physical data ($[\alpha]_D$, ^1H and ^{13}C NMR) of synthetic (+)-**1** were identical with those of the natural (+)-**1** (mp 156–158°C, $[\alpha]_D$ +46.3 ($c=0.54$, EtOH)) (Scheme 6).[1,2]

2.2. Synthesis of (+)-macrosphelide F 2

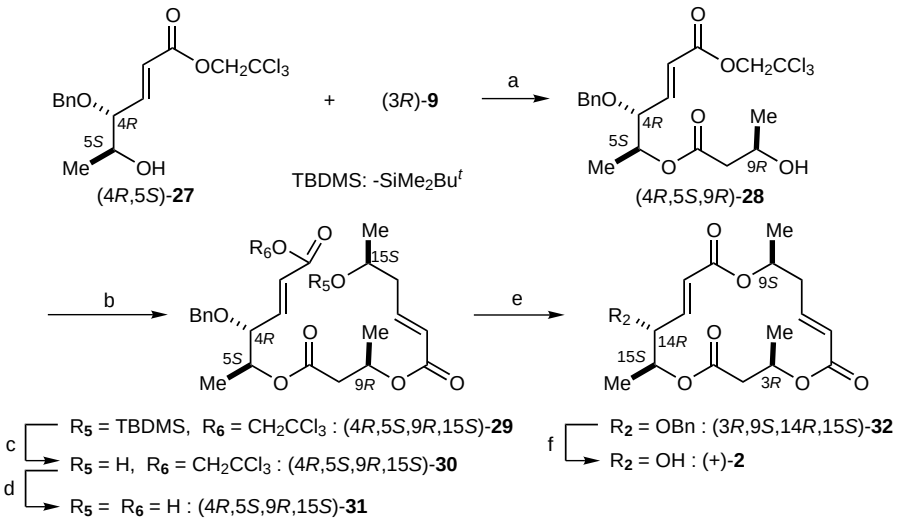
Ester formation between the carboxylic acid (3*R*)-**9** (>99% e.e.)[3c] and the reported hydroxy ester (4*R*,5*S*)-**27**[3c] via the Steglich procedure followed by desilylation gave a diester (4*R*,5*S*,9*R*)-**28** in 76% yield. The second ester formation between (5*S*)-**15** and the diester (4*R*,5*S*,9*R*)-**28** again via the Steglich procedure provided a triester (4*R*,5*S*,9*R*,15*S*)-**29** in 55% yield, which was subjected to desilylation to provide the secondary alcohol (4*R*,5*S*,9*R*,15*S*)-**30** (86% yield, $[\alpha]_D$ −27.9 ($c=0.27$, $CHCl_3$)). Deprotection of (4*R*,5*S*,9*R*,15*S*)-**30** using Zn in acetic acid buffer solution followed by Yamaguchi macrolactonization provided (3*S*,9*S*,14*R*,15*S*)-benzyl macrosphelide F **32** ($[\alpha]_D$ −19.7 ($c=0.16$, $CHCl_3$)) in 79% overall yield from (−)-**30** (Scheme 7). Finally, deprotection of the benzyl group in (−)-**32** using $AlCl_3$ in the presence of *m*-xylene gave synthetic (+)-macrosphelide F **2** ($[\alpha]_D$ +42.8 ($c=0.50$, EtOH) in 89% yield. Physical data ($[\alpha]_D$, ^1H and ^{13}C NMR) of synthetic (+)-**2** were identical with those of the natural (+)-**2** ($[\alpha]_D$ +23.3 ($c=0.09$, EtOH)).[2]

2.3. Synthesis of (+)-macrosphelide G 3

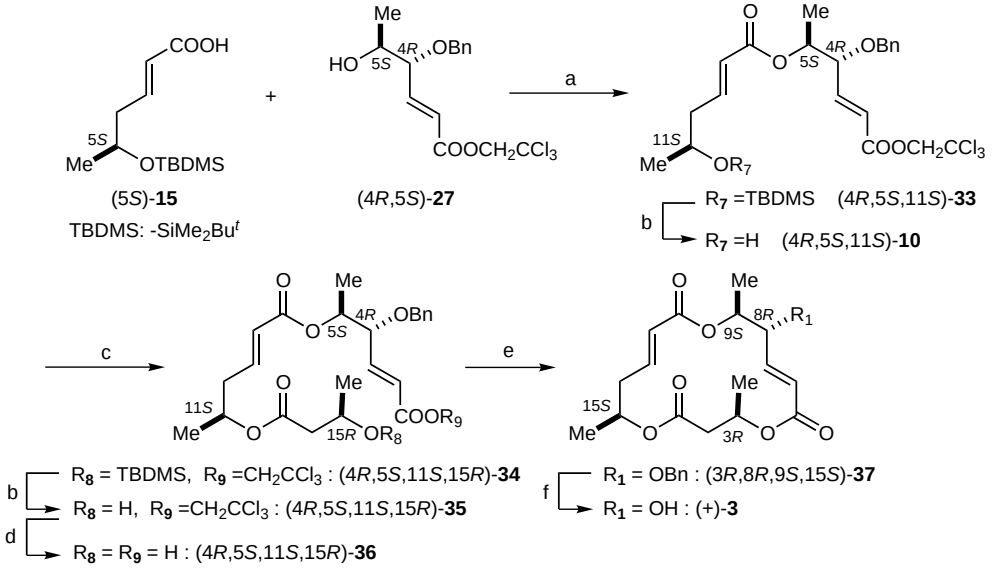
Ester formation between (5*S*)-**15** and (4*R*,5*S*)-**27** via the Steglich procedure gave diester (4*R*,5*S*,11*S*)-**33** in 67% yield, which was subjected to desilylation to provide the secondary alcohol (4*R*,5*S*,11*S*)-**10** in 93% yield. The second ester formation between the carboxylic acid (3*R*)-**9** and the alcohol (4*R*,5*S*,11*S*)-**10** via the Steglich procedure resulted in the recovery of the staring material. On the other hand, the above-mentioned reaction via the Keck procedure[11] provided a triester (4*R*,5*S*,11*S*,15*R*)-**34** in 88% yield, which was subjected to desilylation to give a secondary alcohol (4*R*,5*S*,11*S*,15*R*)-**35** (93% yield, $[\alpha]_D$ −37.8 ($c=0.50$, $CHCl_3$)). Deprotection of (4*R*,5*S*,11*S*,15*R*)-**35** using Zn in acetic acid buffer solution followed by Yamaguchi macrolactonization provided (3*R*,8*R*,9*S*,15*S*)-benzyl macrosphelide G **37** ($[\alpha]_D$ −22.1 ($c=0.35$, $CHCl_3$)) in 68% overall yield from (−)-**35**. Finally, deprotection of the benzyl group of (−)-**37** using $AlCl_3$ in the presence of *m*-xylene gave (+)-synthetic macrosphelide G **3** ($[\alpha]_D$ +51.7 ($c=0.35$, EtOH) in 78% yield. Physical data ($[\alpha]_D$, ^1H and ^{13}C NMR) of synthetic (+)-**3** were identical with those ($[\alpha]_D$ +66.7 ($c=0.48$, EtOH)) of the natural (+)-**3**.[2] This synthetic route represents the first synthesis of macrosphelide G **3** (Scheme 8).



Scheme 6. *Reagents*: (a) (5*S*)-**15**, DCC/DMAP/CH_2Cl_2; (b) AcOH:H_2O:THF (2:1:1); (c) Zn/THF/AcOH–AcONa buffer; (d); 2,4,6-trichlorobenzoyl chloride/Et_3N/DMAP/toluene; (e) *m*-xylene/$AlCl_3/CH_2Cl_2$.



Scheme 7. *Reagents*: (a) (1) DCC/DMAP/CH_2Cl_2; (2) AcOH:H_2O:THF (2:1:1); (b) (5*S*)-**15**, DCC/DMAP/CH_2Cl_2; (c) AcOH:H_2O:THF (2:1:1); (d) Zn/THF/AcOH–AcONa buffer; (e); 2,4,6-trichlorobenzoyl chloride/Et_3N/DMAP/toluene; (f) *m*-xylene/$AlCl_3$/CH_2Cl_2.



Scheme 8. *Reagents*: (a) DCC/DMAP/CH_2Cl_2; (b) AcOH:H_2O:THF (2:1:1); (c) (3*R*)-**9**, DCC/DMAP/CSA/CH_2Cl_2; (d) Zn/THF/AcOH–AcONa buffer; (e) 2,4,6-trichlorobenzoyl chloride/Et_3N/DMAP/toluene; (f) *m*-xylene/$AlCl_3$/CH_2Cl_2.

3. Conclusion

In conclusion, the total synthesis of (+)-macrosphelide C **1** (25% overall yield in nine steps), (+)-macrosphelide F **2** (20% overall yield in nine steps) and (+)-macrosphelide G **3** (22% overall yield in nine steps) has been achieved from the chemoenzymatic reaction product (4*R*,5*S*)-4-benzyloxy-5-hydroxy-(2*E*)-hexenoate **7**.

4. Experimental

4.1. General

All melting points were measured on a Yanaco MP-3S micro melting point apparatus and are uncorrected. ^1H 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) were obtained with a JEOL JMS-600H spectrometer. 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.

4.2. Silylation of (4*R*,5*S*)-4,5-dihydroxy-(2*E*)-hexenoate, 16

To a solution of (4*R*,5*S*)-**16**[8] (3.692 g, 23 mmol) and imidazole (6.28 g, 92 mmol) in dimethylformamide

(DMF, 40 mL) was added TBDMSCl (4.17 g, 28 mmol) at 0°C and the reaction mixture was stirred for 1 h at 0°C and for 3 h at room temperature. The reaction mixture was diluted with H_2O and extracted with Et_2O. The organic layer was washed with saturated brine and dried over $MgSO_4$. The organic layer was evaporated to give a crude residue, which was chromatographed on silica gel (200 g, *n*-hexane:AcOEt = 20:1) in elution order to give the less polar (4*R*,5*S*)-**18** (4.107 g, 65%) as a colorless oil and the more polar (4*R*,5*S*)-**17** (0.783 g, 12%) as a colorless oil. (4*R*,5*S*)-**17**: IR (neat): 3477, 1725, 1658 (sh) cm^{-1}; $[\alpha]_D^{29}$ −14.1 (c = 0.40, $CHCl_3$); ^1H NMR: δ 0.03 (3H, s), 0.07 (3H, s), 0.90 (9H, s), 1.11 (3H, d, J = 6 Hz), 2.14 (1H, br. s), 3.72 (3H, s), 3.80 (1H, dq, J = 4, 6 Hz), 4.21 (1H, ddd, J = 2, 4, 6 Hz), 6.00 (1H, dd, J = 2, 16 Hz), 6.91 (1H, dd, J = 6, 16 Hz). Anal. calcd for $C_{13}H_{26}O_4Si$: C, 56.90; H, 9.55. Found: C, 56.85; H, 9.69%. FAB MS m/z: 275 (M^++1). (4*R*,5*S*)-**18**: IR (neat): 3480, 1727, 1666 (sh) cm^{-1}; $[\alpha]_D^{28}$ +26.1 (c = 0.10, $CHCl_3$); ^1H NMR: δ 0.04 (6H, s), 0.85 (9H, s), 1.05 (3H, d, J = 6 Hz), 2.56 (1H, br. s), 3.70 (3H, s), 3.87 (1H, dq, J = 4, 6 Hz), 4.16–4.20 (1H, m), 6.06 (1H, dd, J = 2, 16 Hz), 6.86 (1H, dd, J = 4, 16 Hz). Anal. calcd for $C_{13}H_{26}O_4Si$: C, 56.90; H, 9.55. Found: C, 56.71; H, 9.60%. FAB MS m/z: 275 (M^++1).

4.3. Mesylation of (4*R*,5*S*)-17 and (4*R*,5*S*)-18

(i) To a solution of (4*R*,5*S*)-**17** (0.100 g, 0.37 mmol) in pyridine (0.15 g) and benzene (2 mL) was added Ms_2O (0.10 g, 0.57 mmol) and the mixture was heated at 50°C for 2 h with stirring. The reaction mixture was diluted with H_2O and extracted with Et_2O. The organic layer was washed with 7% aqueous $NaHCO_3$, saturated brine 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 = 20:1) to give a colorless oil of (4*R*,5*S*)-**19** (0.113 g, 87%). IR (neat): 1727, 1662 (sh) cm^{-1}; ^1H NMR: δ 0.03 (3H, s), 0.08 (3H, s), 0.89 (9H, s), 1.31 (3H, d, J = 6 Hz), 2.98 (3H, s), 3.72 (3H, s), 4.46 (1H, ddd, J = 2, 4, 6 Hz), 4.74 (1H, dq, J = 4, 6 Hz), 6.05 (1H, dd, J = 2, 16 Hz), 6.84 (1H, dd, J = 6, 16 Hz). Anal. calcd for $C_{14}H_{28}O_6SSi$: C, 47.70; H, 8.01. Found: C, 48.00; H, 8.22%. FAB MS m/z: 353 (M^++1).

(ii) To a solution of (4*R*,5*S*)-**18** (3.836 g, 14 mmol) in pyridine (5.53 g, 70 mmol) and benzene (50 mL) was added Ms_2O (4.87 g, 28 mmol) and the mixture was heated at 50°C for 2 h with stirring. The reaction mixture was worked up in the same way as for the preparation of (4*R*,5*S*)-**19** to give (4*R*,5*S*)-**20** as a colorless oil (4.71 g, 96%). IR (neat): 1727, 1666 (sh) cm^{-1}; $[\alpha]_D^{21}$ −17.7 (c = 0.91, $CHCl_3$); ^1H NMR: δ 0.05 (3H, s), 0.06 (3H, s), 0.86 (9H, s), 1.15 (3H, d, J = 6 Hz), 3.03 (3H, s), 3.74 (3H, s), 4.02 (1H, qd, J = 4, 6 Hz), 5.02 (1H, ddd, J = 2, 4, 6 Hz), 6.12 (1H, dd, J = 2, 16 Hz), 6.88 (1H, dd, J = 6, 16 Hz). Anal. calcd for $C_{14}H_{28}O_6SSi$: C, 47.70; H, 8.01. Found: C, 47.95; H, 8.05%. FAB MS m/z: 353 (M^++1).

4.4. (5*S*)-5-*tert*-Butyldimethylsiloxy-(2*E*)-hexenoic acid, 15

(i) To a solution of $Pd_2(dba)_3{\cdot}CHCl_3$ (0.32 g, 0.31 mmol), tributylphosphine (0.062 g, 0.31 mmol) and (4*R*,5*S*)-**20** (2.176 g, 6.1 mmol) in dioxane (50 mL) under an argon atmosphere was added a suspension of $NaBH_4$ (0.23 g, 6.1 mmol) in H_2O (4 mL) and the whole mixture was stirred for 2 h at room temperature. The reaction mixture was diluted with saturated brine and extracted with Et_2O. The organic layer was dried over $MgSO_4$ and evaporated to give a residue, which was chromatographed on silica gel (100 g, *n*-hexane:AcOEt = 100:1) to afford (5*S*)-**21** as a colorless oil (1.238 g, 78%). IR (neat): 2954, 1727 cm^{-1}; $[\alpha]_D^{21}$ +8.8 (c = 0.51, $CHCl_3$); ^1H NMR: δ 0.01 (3H, s), 0.02 (3H, s), 0.86 (9H, s), 1.13 (3H, d, J = 6 Hz), 2.25–2.34 (2H, m), 3.71 (3H, s), 3.90 (1H, tq, J = 6, 6 Hz), 5.82 (1H, dt, J = 2, 16 Hz), 6.93 (1H, dt, J = 8, 16 Hz). Anal. calcd for $C_{13}H_{26}O_3Si$: C, 60.42; H, 10.14. Found: C, 60.54; H, 10.33%. FAB MS m/z: 259 (M^++1).

(ii) To a solution of (5*S*)-**21** (2.754 g, 10.6 mmol) in MeOH (30 mL) was added dropwise 2 M aqueous NaOH (2 mL) and the reaction mixture was stirred for 12 h at room temperature. The reaction mixture was acidified with 2 M aqueous HCl and extracted with Et_2O. The ether layer was washed with saturated brine and dried over $MgSO_4$. The ether layer was evaporated to give a crude (5*S*)-**15** as a colorless oil (2.467 g, 95%). The crude (5*S*)-**15** was found to be a single product from ^1H NMR analysis. (5*S*)-**15**; $[\alpha]_D^{26}$ +13.7 (c = 0.67, $CHCl_3$); ^1H NMR: δ 0.02 (3H, s), 0.03 (3H, s), 0.86 (9H, s), 1.15 (3H, d, J = 6 Hz), 2.33 (2H, ddd, J = 2, 6, 8 Hz), 3.92 (1H, qt, J = 6, 6 Hz), 5.82 (1H, dt, J = 2, 16 Hz), 6.97–7.15 (1H, br. s), 7.05 (1H, dt, J = 8, 16 Hz).

4.5. Ester formation between (5*S*)-15 and (4*R*,5*S*,9*S*)-22

To a mixture of DCC (0.116 g, 0.56 mmol) and DMAP (0.021 g, 0.17 mmol) in CH_2Cl_2 (1 mL) was added a solution of (5*S*)-**15** (0.137 g, 0.56 mmol) and (4*R*,5*S*,9*S*)-**22**[6] (0.18 g, 0.4 mmol) in CH_2Cl_2 (3 mL) and the reaction mixture was stirred for 2 days at room temperature. The reaction mixture was filtered and the filtrate was evaporated to afford a residue, which was chromatographed on silica gel (20 g, *n*-hexane:AcOEt = 19:1) to give (4*R*,5*S*,9*S*,15*S*)-**23** as an oil (0.235 g, 86%). IR (neat): 1728, 1657 cm^{-1}; $[\alpha]_D^{25}$ −17.8 (c = 0.72, $CHCl_3$); ^1H NMR: δ 0.01 (3H, s), 0.02 (3H, s), 0.85 (9H, s), 1.12 (3H, d, J = 6 Hz), 1.20 (3H, d, J = 6 Hz), 1.28 (3H, d, J = 6 Hz), 2.19–2.32 (2H, m), 2.48 (1H, dd, J = 7, 16 Hz), 2.62 (1H, dd, J = 7, 16 Hz), 3.88 (1H, qt, J = 6, 6 Hz), 4.08 (1H, ddd, J = 2, 4, 6 Hz), 4.48, 4.61 (each 1H, d, J = 13 Hz), 4.80 (2H, s), 5.04 (1H, qd, J = 4, 6 Hz), 5.28 (1H, qt, J = 6, 7 Hz), 5.75 (1H, dt, J = 1, 16 Hz), 6.19 (1H, dd, J = 2, 16 Hz), 6.90 (1H, dt, J = 8, 16 Hz), 6.99 (1H, dd, J = 6, 16 Hz), 7.25–7.36 (5H, m). Anal. calcd for $C_{31}H_{45}O_8Cl_3Si$: C, 54.74; H, 6.67. Found: C, 54.60; H, 6.85%.

4.6. Desilylation of (4*R*,5*S*,9*S*,15*S*)-23

A mixture of (4*R*,5*S*,9*S*,15*S*)-**23** (0.235 g, 0.35 mmol) in a mixed solvent of AcOH (4 mL), H_2O (2 mL) and THF (2 mL) was stirred for 2.5 h at 80°C. The reaction mixture was evaporated to give a residue, which was diluted with ether. The organic layer was washed with 7% aqueous $NaHCO_3$ and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (25 g, *n*-hexane:AcOEt = 3:1) to give (4*R*,5*S*,9*S*,15*S*)-**24** as an oil (0.172 g, 88%). IR (neat): 3455, 1729, 1656 cm^{-1}; $[\alpha]_D^{22}$ −23.4 ($c = 0.35$, $CHCl_3$); ^1H NMR: δ 1.19 (3H, d, $J = 6$ Hz), 1.20 (3H, d, $J = 6$ Hz), 1.28 (3H, d, $J = 6$ Hz), 1.74–1.87 (1H, br. s), 2.30 (2H, dd, $J = 7.5$, 7.5 Hz), 2.49 (2H, dd, $J = 6$, 16 Hz), 2.61 (1H, dd, $J = 8$, 16 Hz), 3.90 (1H, qt, $J = 6$, 6 Hz), 4.07 (1H, ddd, $J = 2$, 4, 6 Hz), 4.48, 4.60 (each 1H, d, $J = 13$ Hz), 4.80 (2H, s), 5.05 (1H, qd, $J = 4$, 6 Hz), 5.28 (1H, qdd, $J = 6$, 6, 8 Hz), 5.81 (1H, dt, $J = 2$, 16 Hz), 6.19 (1H, dd, $J = 2$, 16 Hz), 6.91 (1H, dt, $J = 8$, 16 Hz), 6.99 (1H, dd, $J = 6$, 16 Hz), 7.25–7.36 (5H, m). ^{13}C NMR: δ 15.3 (q), 20.0 (q), 23.4 (q), 41.1 (t), 41.9 (t), 66.6 (d), 67.1 (d), 71.5 (d), 71.9 (t), 74.1 (t), 79.4 (d), 94.8 (s), 122.3 (d), 123.6 (d), 127.6 (d), 127.8 (d), 128.3 (s), 137.2 (s), 145.2 (d), 146.4 (d), 163.7 (s), 165.0 (s), 169.1 (s). Anal. calcd for $C_{25}H_{31}O_8Cl_3$: C, 53.06; H, 5.52. Found: C, 53.34; H, 5.78%. FAB MS m/z; 565, 567 (M^++1).

4.7. Deprotection of 2,2,2-trichloroethyl group of (4*R*,5*S*,9*S*,15*S*)-24

To a solution of (4*R*,5*S*,9*S*,15*S*)-**24** (0.143 g, 0.25 mmol) and AcOH–AcONa buffer solution (3 mL) in THF (3 mL) at 0°C was added Zn dust (0.099 g, 1.5 mmol) and the mixture was stirred for 8 h at room temperature. The reaction mixture was filtered and the filtrate was acidified with 2 M aqueous HCl and extracted with Et_2O. The organic layer was dried over $MgSO_4$ and evaporated to give crude *seco*-acid (4*R*,5*S*,9*S*,15*S*)-**25** (0.109 g, quantitative yield). (4*R*,5*S*,9*S*,15*S*)-**25**; ^1H NMR: δ 1.21 (3H, d, $J = 6$ Hz), 1.22 (3H, d, $J = 6$ Hz), 1.28 (3H, d, $J = 6$ Hz), 2.33 (2H, dd, $J = 7$, 7 Hz), 2.50 (1H, dd, $J = 5$, 16 Hz), 2.60 (1H, dd, $J = 8$, 16 Hz), 3.96 (1H, ddd, $J = 2$, 4, 7 Hz), 4.00 (1H, qt, $J = 6$, 6 Hz), 4.42, 4.60 (each 1H, d, $J = 12$ Hz), 5.04 (1H, qd, $J = 4$, 6 Hz), 5.30 (1H, qdd, $J = 5$, 6, 8 Hz), 5.83 (1H, dt, $J = 2$, 16 Hz), 6.06 (1H, dd, $J = 2$, 16 Hz), 6.80 (1H, br. s), 6.89 (1H, dd, $J = 7$, 16 Hz), 6.92 (1H, dt, $J = 7$, 16 Hz), 7.25–7.35 (5H, m).

4.8. Benzyl ether (3*S*,9*S*,14*R*,15*S*)-26

A solution of (4*R*,5*S*,9*S*,15*S*)-**25** (0.109 g, 0.26 mmol), Et_3N (0.065 g, 0.64 mmol) and 2,4,6-trichlorobenzoyl chloride (0.156 g, 0.64 mmol) in THF (3.5 mL) was stirred for 2 h at room temperature under an argon atmosphere and the mixture was diluted with toluene (160 mL). The resulting reaction mixture was added dropwise to a solution of DMAP (0.234 g, 1.91 mmol) in toluene (20 mL) at 100°C over 2 h and the mixture was stirred for 1 h at 100°C. The reaction mixture was washed with saturated aqueous citric acid solution 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 = 5:1) to give (3*S*,9*S*,14*R*,15*S*)-**26** as a colorless oil (0.073 g, 69% overall yield from (4*R*,5*S*,9*S*,15*S*)-**24**). IR ($CHCl_3$): 1720, 1521 cm^{-1}; $[\alpha]_D^{19}$ −43.7 ($c = 0.22$, $CHCl_3$); ^1H NMR: δ 1.28 (3H, d, $J = 6$ Hz), 1.28 (3H, d, $J = 6$ Hz), 1.35 (3H, d, $J = 6$ Hz), 2.30 (1H, ddd, $J = 10$, 10. 14 Hz), 2.47–2.52 (1H, m), 2.47 (1H, dd, $J = 8$, 16 Hz), 2.52 (1H, dd, $J = 4$, 16 Hz), 3.77 (1H, ddd, $J = 2$, 6, 6 Hz), 4.34, 4.59 (each 1H, d, $J = 11$ Hz), 4.99 (1H, qd, $J = 6$, 6 Hz), 5.11 (1H, qdd, $J = 4$, 6, 10 Hz), 5.28 (1H, qdd, $J = 4$, 6, 8 Hz), 5.74 (1H, dt, $J = 2$, 16 Hz), 6.01 (1H, dd, $J = 2$, 16 Hz), 6.78 (1H, dd, $J = 6$, 16 Hz), 6.82 (1H, ddd, $J = 7$, 10, 16 Hz), 7.25–7.35 (5H, m). ^{13}C NMR: δ 18.0 (q), 19.9 (q), 20.7 (q), 39.0 (t), 41.2 (t), 67.5 (d), 69.0 (d), 71.3 (t), 72.1 (d), 79.4 (d), 124.2 (d), 124.6 (d), 127.8 (d), 127.8 (d), 128.3 (d), 137.1 (s), 143.4 (d), 144.2 (d), 164.5 (s), 164.7 (s), 169.3 (s). Anal. calcd for $C_{23}H_{28}O_7$: C, 66.33; H, 6.78. Found: C, 66.83; H, 6.84%. FAB MS m/z; 417 (M^++1).

4.9. (+)-Macrosphelide C, 1

To a mixture of $AlCl_3$ (0.058 g, 0.43 mmol) in CH_2Cl_2 (3 mL) was added dropwise a solution of (3*S*,9*S*,14*R*,15*S*)-**26** (0.059 g, 0.14 mmol) and *m*-xylene (1.5 mL) in CH_2Cl_2 (3 mL) at −10°C and the reaction mixture was stirred for 3 h at room temperature. The reaction mixture was diluted with saturated brine and extracted with Et_2O. 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 = 2:1) to give (+)-**1** (0.035 g, 77%) as colorless solid. Recrystallization of (+)-**1** from *n*-hexane–CH_2Cl_2 gave colorless needles (+)-**1**. (+)-**1**; mp 152–155°C, IR ($CHCl_3$): 3456, 1718 cm^{-1}; $[\alpha]_D^{26}$ +53.3 ($c = 0.08$, EtOH). The NMR spectra (^1H and ^{13}C NMR) of the synthetic (+)-**1** were identical with those of natural (+)-**1**.[1] Anal. calcd for $C_{16}H_{22}O_7$: C, 58.89; H, 6.80. Found: C, 58.61; H, 6.81%. FAB MS m/z; 327 (M^++1).

4.10. Ester formation between (3*R*)-9 and (4*R*,5*S*)-27

(i) To a mixture of DCC (0.56 g, 2.71 mmol) and DMAP (0.10 g, 0.82 mmol) in CH_2Cl_2 (10 mL) was added a solution of (3*R*)-**9** (0.59 g, 2.7 mmol) and (4*R*,5*S*)-27[3c] (0.50 g, 1.36 mmol) in CH_2Cl_2 (3 mL) and the reaction mixture was stirred for 1 day at room temperature. The reaction mixture was worked up in the same way as for the preparation of (4*R*,5*S*,9*S*,15*S*)-**23** to give 2,2,2-trichloroethyl (4*R*,5*S*,9*R*)-4-benzyloxy-9-*tert*-butyldimethylsiloxy-5-methyl-7-oxo-6-oxadeca-(2*E*)-enoate as an oil (0.638 g, 82%). IR (neat): 1741, 1658 cm^{-1}; $[\alpha]_D^{23}$ −43.8 ($c = 0.78$, $CHCl_3$); ^1H NMR: δ 0.02 (3H, s), 0.04 (3H, s), 0.84 (9H, s), 1.15 (3H, d, $J = 6$ Hz), 1.24 (3H, d, $J = 6$ Hz), 2.30 (1H, dd, $J = 6$, 15 Hz), 2.46 (1H, dd, $J = 7$, 15 Hz), 4.08 (1H, ddd, $J = 2$, 4, 6 Hz), 4.23 (1H, qdd, $J = 6$, 6, 7 Hz), 4.49, 4.63 (each 1H, d, $J = 12$ Hz), 4.80 (2H, s), 5.05 (1H, dq, $J = 4$, 6 Hz), 6.19 (1H, dd, $J = 2$, 16 Hz), 7.01 (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, 52.92; H, 6.66%. FAB MS m/z; 567, 569 (M^++1).

(ii) A mixture of 2,2,2-trichloroethyl (4*R*,5*S*,9*R*)-4-benzyloxy-9-*tert*-butyldimethylsiloxy-5-methyl-7-oxo-6-oxadeca-(2*E*)-enoate (0.577 g, 1.02 mmol) in a mixed solvent of AcOH (5 mL), H_2O (2.5 mL) and THF (2.5 mL) was stirred for 12 h at 80°C. The reaction mixture was worked up in the same way as for the preparation of (4*R*,5*S*,9*S*,15*S*)-**24** to give (4*R*,5*S*,9*R*)-**28** (0.431 g, 93%) as an oil. IR (neat): 3444, 1731 cm^{-1}; $[\alpha]_D^{26}$ −63.5 (c=0.15, $CHCl_3$); ^1H NMR: δ 1.18 (3H, d, J=6 Hz), 1.24 (3H, d, J=6 Hz), 2.38 (1H, dd, J=9, 16 Hz), 2.42 (1H, dd, J=5, 16 Hz), 2.86 (1H, br. s), 4.07 (1H, ddd, J=2, 4, 6 Hz), 4.12 (1H, qdd, J=5, 6, 9 Hz), 4.47, 4.64 (each 1H, d, J=12 Hz), 4.81 (2H, s), 5.11 (1H, qd, J=4, 6 Hz), 6.20 (1H, dd, J=2, 16 Hz), 7.00 (1H, dd, J=6, 16 Hz), 7.27–7.37 (5H, m). ^{13}C NMR: δ 15.5 (q), 22.5 (q), 43.3 (t), 64.3 (d), 71.3 (d), 71.8 (t), 74.1 (t), 79.3 (d), 94.8 (s), 122.5 (d), 127.7 (d), 127.9 (d), 128.4 (d), 137.1 (s), 146.2 (d), 163.7 (s), 171.6 (s). Anal. calcd for $C_{19}H_{23}O_6Cl_3$: C, 50.29; H, 5.11. Found: C, 50.24; H, 5.22%. FAB MS m/z; 453, 455 (M^++1).

4.11. Ester formation between (5*S*)-15 and (4*R*,5*S*,9*R*)-28

To a mixture of DCC (0.267 g, 1.29 mmol) and DMAP (0.03 g, 0.25 mmol) in CH_2Cl_2 (7 mL) was added a solution of (5*S*)-**15** (0.316 g, 1.29 mmol) and (4*R*,5*S*,9*R*)-**28** (0.414 g, 0.91 mmol) in CH_2Cl_2 (3 mL) and the reaction mixture was stirred for 1 day at room temperature. The reaction mixture was worked up in the same way as for the preparation of (4*R*,5*S*,9*S*,15*S*)-**23** to give (4*R*,5*S*,9*R*,15*S*)-**29** as an oil (0.34 g, 55%). IR (neat): 1741, 1656 cm^{-1}; $[\alpha]_D^{24}$ −22.3 (c=0.78, $CHCl_3$); ^1H NMR: δ 0.01 (3H, s), 0.02 (3H, s), 0.85 (9H, s), 1.12 (3H, d, J=7 Hz), 1.22 (3H, d, J=7 Hz), 1.27 (3H, d, J=7 Hz), 2.23 (1H, dddd, J=2, 7, 7, 14 Hz), 2.28 (1H, dddd, J=2, 7, 7, 14 Hz), 2.43 (1H, dd, J=6, 15 Hz), 2.64 (1H, dd, J=7, 15 Hz), 3.87 (1H, ddd, J=7, 7, 7 Hz), 4.09 (1H, ddd, J=2, 4, 6 Hz), 4.48, 4.61 (each 1H, d, J=12 Hz), 4.78 (1H, d, J=12 Hz), 4.81 (1H, d, J=12 Hz), 5.05 (1H, qd, J=4, 7 Hz), 5.27 (1H, qdd, J=6, 7, 7 Hz), 5.76 (1H, dt, J=2, 16 Hz), 6.19 (1H, dd, J=2, 16 Hz), 6.91 (1H, dt, J=7, 16 Hz), 6.98 (1H, dd, J=6, 16 Hz), 7.25–7.36 (5H, m). Anal. calcd for $C_{31}H_{45}O_8Cl_3Si$: C, 54.74; H, 6.67. Found: C, 54.46; H, 6.74%.

4.12. Desilylation of (4*R*,5*S*,9*R*,15*S*)-29

A solution of (4*R*,5*S*,9*R*,15*S*)-**29** (0.186 g, 0.27 mmol) in a mixed solvent of AcOH (2 mL), H_2O (1 mL) and THF (1 mL) was stirred for 12 h at 80°C. The reaction mixture was worked up in the same way as for the preparation of (4*R*,5*S*,9*S*,15*S*)-**24** to give (4*R*,5*S*,9*R*,15*S*)-**30** (0.133 g, 86%) as an oil. (4*R*,5*S*,9*R*,15*S*)-**30**; IR (neat): 3432, 1728 cm^{-1}; $[\alpha]_D^{23}$ −27.9 (c=0.27, $CHCl_3$); ^1H NMR: δ 1.19 (3H, d, J=7 Hz), 1.21 (3H, d, J=7 Hz), 1.28 (3H, d, J=7 Hz), 1.85 (1H, br s), 2.30 (2H, t, J=7 Hz), 2.45 (1H, dd, J=6, 16 Hz), 2.63 (1H, dd, J=7, 16 Hz), 3.90 (1H, qt, J=7, 7 Hz), 4.08 (1H, ddd, J=2, 4, 6 Hz), 4.48, 4.60 (each 1H, d, J=12 Hz), 4.78, 4.81 (each 1H, d, J=12 Hz), 5.05 (1H, qd, J=4, 7 Hz), 5.27 (1H, qdd, J=6, 7, 7 Hz), 5.82 (1H, dt, J=2, 16 Hz), 6.18 (1H, dd, J=2, 16 Hz), 6.92 (1H, dt, J=7, 16 Hz), 6.98 (1H, dd, J=6, 16 Hz), 7.26–7.37 (5H, m). ^{13}C NMR: δ 15.2 (q), 20.2 (q), 23.4 (q), 41.1 (t), 41.9 (t), 66.7 (d), 67.2 (d), 71.5 (d), 71.9 (t), 74.1 (t), 79.4 (d), 94.8 (s), 122.3 (d), 123.6 (d), 127.6 (d), 127.8 (d), 128.3 (d), 137.3 (s), 145.2 (d), 146.4 (d), 163.7 (s), 165.1 (s), 169.2 (s). Anal. calcd for $C_{25}H_{31}O_8Cl_3$: C, 53.06; H, 5.52. Found: C, 53.02; H, 5.67%. FAB MS m/z; 565, 567 (M^++1).

4.13. Deprotection of 2,2,2-trichloroethyl group of (4*R*,5*S*,9*R*,15*S*)-30

To a solution of (4*R*,5*S*,9*R*,15*S*)-**30** (0.114 g, 0.2 mmol) and AcOH–AcONa buffer solution (2 mL) in THF (2 mL) at 0°C was added Zn dust (0.08 g, 1.22 mmol) and the mixture was stirred for 3 h at room temperature. The reaction mixture was worked up in the same way as for the preparation of (4*R*,5*S*,9*S*,15*S*)-**25** to give the crude *seco*-acid (4*R*,5*S*,9*R*,15*S*)-**31** (0.088 g, quantitative yield). (4*R*,5*S*,9*R*,15*S*)-**31**; ^1H NMR: δ 1.20 (3H, d, J=7 Hz), 1.21 (3H, d, J=7 Hz), 1.28 (3H, d, J=7 Hz), 2.31 (2H, t, J=7 Hz), 2.48 (1H, dd, J=6, 16 Hz), 2.63 (1H, dd, J=8, 16 Hz), 3.93 (1H, qt, J=7, 7 Hz), 4.00 (1H, ddd, J=2, 4, 6 Hz), 4.44, 4.59 (each 1H, d, J=12 Hz), 5.05 (1H, qd, J=4, 7 Hz), 5.26 (1H, qdd, J=7, 7, 8 Hz), 5.83 (1H, dt, J=2, 16 Hz), 6.07 (1H, dd, J=2, 16 Hz), 6.35 (2H, br. s), 6.89 (1H, dd, J=6, 16 Hz), 6.92 (1H, dt, J=7, 16 Hz), 7.26–7.36 (5H, m).

4.14. Benzyl ether (3*R*,9*S*,14*R*,15*S*)-32

A solution of (4*R*,5*S*,9*R*,15*S*)-**31** (0.088 g, 0.2 mmol), Et_3N (0.043 g, 0.43 mmol) and 2,4,6-trichlorobenzoyl chloride (0.104 g, 0.43 mmol) in THF (2 mL) was stirred for 2 h at room temperature under argon atmosphere and the mixture was diluted with toluene (110 mL). The above-mentioned reaction mixture was added dropwise to a solution of DMAP (0.156 g, 1.28 mmol) in toluene (15 mL) at 100°C over 2 h and the mixture was stirred for 1.5 h at 100°C. The reaction mixture was worked up in the same way as for the preparation of (3*S*,9*S*,14*R*,15*S*)-**26** to give (3*R*,9*S*,14*R*,15*S*)-**32** as a colorless oil (0.067 g, 79% overall yield from (4*R*,5*S*,9*R*,15*S*)-**30**). (3*R*,9*S*,14*R*,15*S*)-**32**; IR (neat): 1712, 1666 cm^{-1}; $[\alpha]_D^{24}$ −19.7 (c=0.16, $CHCl_3$); ^1H NMR: δ 1.22 (3H, d, J=7 Hz), 1.37 (3H, d, J=7 Hz), 1.38 (3H, d, J=7 Hz), 2.36 (1H, dddd, J=2, 7, 7, 15 Hz), 2.49 (1H, dd, J=7, 14 Hz), 2.65 (1H, dd, J=4, 14 Hz), 2.68 (1H, dddd, J=2, 7, 7, 15 Hz), 3.83 (1H, ddd, J=2, 7, 7 Hz), 4.39, 4.58 (each 1H, d, J=12 Hz), 4.98 (1H, qd, J=7, 7 Hz), 5.12 (1H, qdd, J=7, 7, 7 Hz), 5.21 (1H, qdd, J=4, 7, 7 Hz), 5.78 (1H, dt, J=2, 16 Hz), 6.03 (1H, dd, J=2, 16 Hz), 6.78 (1H, dd, J=7, 16 Hz), 6.85 (1H, dt, J=7, 16 Hz), 7.25–7.36 (5H, m). ^{13}C NMR: δ 17.6 (q), 19.4 (q), 20.0 (q), 37.9 (t), 40.5 (t), 67.0 (d), 69.0 (d), 71.4 (t), 72.4 (d), 79.3 (d), 124.2 (d), 124.8 (d), 127.7 (d), 127.8 (d), 128.3 (d), 137.2 (s), 143.2 (d), 143.7 (d), 164.9 (s), 164.9 (s), 169.1 (s). Anal. calcd

for $C_{23}H_{28}O_7$: C, 66.33; H, 6.78. Found: C, 66.44; H, 6.77%. FAB MS m/z; 417 (M^++1).

4.15. (+)-Macrosphelide F, 2

To a mixture of $AlCl_3$ (0.063 g, 0.47 mmol) in CH_2Cl_2 (3 mL) was added dropwise a solution of (4*R*,5*S*,9*R*,15*S*)-**32** (0.067 g, 0.16 mmol) and *m*-xylene (1.5 mL) in CH_2Cl_2 (3 mL) at −0°C and the reaction mixture was stirred for 3 h at room temperature. The reaction mixture was worked up in the same way as for the preparation of macrosphelide C **1** to give (+)-**2** (0.046 g, 89%) as a colorless oil. IR (neat): 3440, 1712 cm^{-1}; $[\alpha]_D^{27}$ +42.8 ($c=0.50$, EtOH). The NMR spectra (^1H and ^{13}C NMR) of the synthetic (+)-**2** were identical with those of natural (+)-**2**.[2] Anal. calcd for $C_{16}H_{22}O_7$: C, 58.89; H, 6.80. Found: C, 58.61; H, 6.99%. FAB MS m/z; 327 (M^++1).

4.16. Ester formation between (5*S*)-15 and (4*R*,5*S*)-27

To a mixture of DCC (0.42 g, 2 mmol) and DMAP (0.1 g, 0.82 mmol) in CH_2Cl_2 (10 mL) was added a solution of (5*S*)-**15** (500 mg, 2.05 mmol) and (4*R*,5*S*)-**27**[3c] (0.5 g, 1.36 mmol) in CH_2Cl_2 (3 mL) and the reaction mixture was stirred for 1 day at room temperature. The reaction mixture was worked up in the same way as for the preparation of (4*R*,5*S*,9*S*,15*S*)-**23** to give (4*R*,5*S*,11*S*)-**33** (0.543 g, 67%) as an oil. IR (neat): 1727, 1452 cm^{-1}; $[\alpha]_D^{23}$ +2.8 ($c=0.18$, $CHCl_3$); ^1H NMR: δ 0.02 (3H, s), 0.03 (3H, s), 0.85 (9H, s), 1.14 (3H, d, $J=6$ Hz), 1.26 (3H, d, $J=6$ Hz), 2.24–2.36 (2H, m), 3.91 (1H, tq, $J=6$, 6 Hz), 4.15 (1H, ddd, $J=2$, 4, 6 Hz), 4.52, 4.63 (each 1H, d, $J=12$ Hz), 4.78, 4.82 (each 1H, d, $J=13$ Hz), 5.11 (1H, dq, $J=4$, 6 Hz), 5.81 (1H, dt, $J=2$, 16 Hz), 6.21 (1H, dd, $J=2$, 16 Hz), 6.92 (1H, dt, $J=7$, 16 Hz), 7.03 (1H, dd, $J=6$, 16 Hz), 7.26–7.36 (5H, m). Anal. calcd for $C_{27}H_{39}O_6SiCl_3$: C, 54.59; H, 6.62. Found: C, 54.88; H, 6.67%.

4.17. Desilylation of (4*R*,5*S*,11*S*)-33

A mixture of (4*R*,5*S*,11*S*)-**33** (0.494 g, 0.83 mmol) in a mixed solvent of AcOH (4 mL), H_2O (2 mL) and THF (2 mL) was stirred for 5 h at 80°C. The reaction mixture was worked up in the same way as for the preparation of (4*R*,5*S*,9*S*,15*S*)-**24** to give (4*R*,5*S*,11*S*)-**10** (370 mg, 93%) as an oil. IR (neat): 3455, 1727, 1656 (sh) cm^{-1}; $[\alpha]_D^{25}$ −14.0 ($c=0.56$, $CHCl_3$); ^1H NMR: δ 1.22 (3H, d, $J=7$ Hz), 1.27 (3H, d, $J=7$ Hz), 1.83 (1H, br s), 2.34 (2H, ddd, $J=1$, 7, 7 Hz), 3.94 (1H, qt, $J=7$, 7 Hz), 4.13 (1H, ddd, $J=2$, 5, 6 Hz), 4.51, 4.63 (each 1H, d, $J=12$ Hz), 4.78, 4.82 (each 1H, d, $J=12$ Hz), 5.10 (1H, dq, $J=5$, 7 Hz), 5.86 (1H, dt, $J=1$, 16 Hz), 6.20 (1H, dd, $J=2$, 16 Hz), 6.93 (1H, dt, $J=7$, 16 Hz), 7.02 (1H, dd, $J=6$, 16 Hz), 7.26–7.35 (5H, m). ^{13}C NMR: δ 15.4 (q), 23.4 (q), 41.9 (t), 66.7 (d), 71.2 (d), 72.0 (t), 74.1 (t), 79.5 (d), 94.8 (s), 122.1 (d), 123.5 (d), 127.6 (d), 127.7 (d), 128.3 (d), 137.3 (s), 145.5 (d), 146.7 (d), 163.8 (s), 165.1 (s). Anal. calcd for $C_{21}H_{25}O_6Cl_3$: C, 52.57; H, 5.25. Found: C, 52.86; H, 5.54%. FAB MS m/z; 479, 481 (M^++1).

4.18. Ester formation between (4*R*,5*S*,11*S*)-10 and (3*R*)-9

To a mixture of DCC (0.266 g, 1.29 mmol), DMAP (0.024 g, 0.2 mmol) and (+)-CSA (0.046 g, 0.2 mmol) in CH_2Cl_2 (5 mL) was added a solution of (4*R*,5*S*,11*S*)-**10** (0.31 g, 0.65 mmol) and (3*R*)-**9** (0.298 g, 1.37 mmol) in CH_2Cl_2 (1 mL) and the reaction mixture was stirred for 1 day at room temperature. The reaction mixture was worked up in the same way as for the preparation of (4*R*,5*S*,9*S*,15*S*)-**23** to give (4*R*,5*S*,11*S*,15*R*)-**34** as an oil (0.385 g, 88%). IR (neat): 1734, 1656 (sh) cm^{-1}; $[\alpha]_D^{27}$ −35.6 ($c=0.55$, $CHCl_3$); ^1H NMR: δ 0.02 (3H, s), 0.04 (3H, s), 0.84 (9H, s), 1.15 (3H, d, $J=7$ Hz), 1.22 (3H, d, $J=7$ Hz), 1.26 (3H, d, $J=7$ Hz), 2.31 (1H, dd, $J=6$, 15 Hz), 2.44 (1H, dd, $J=8$, 15 Hz), 2.36–2.51 (2H, m), 4.13 (1H, ddd, $J=2$, 4, 6 Hz), 4.23 (1H, ddd, $J=6$, 7, 8 Hz), 4.51, 4.63 (each 1H, d, $J=12$ Hz), 4.78, 4.81 (each 1H, d, $J=12$ Hz), 4.99 (1H, tq, $J=7$, 7 Hz), 5.09 (1H, dq, $J=4$, 7 Hz), 5.83 (1H, dt, $J=1$, 16 Hz), 6.20 (1H, dd, $J=2$, 16 Hz), 6.85 (1H, dt, $J=7$, 16 Hz), 7.01 (1H, dd, $J=7$, 16 Hz), 7.25–7.35 (5H, m). Anal. calcd for $C_{31}H_{45}O_8SiCl_3$: C, 54.70; H, 6.67. Found: C, 54.76; H, 6.89%.

4.19. Desilylation of (4*R*,5*S*,11*S*,15*R*)-34

A mixture of (4*R*,5*S*,11*S*,15*R*)-**34** (0.319 g, 0.47 mmol) in a mixed solvent of AcOH (4 mL), H_2O (2 mL) and THF (2 mL) was stirred for 3 h at 80°C. The reaction mixture was worked up in the same way as for the preparation of (4*R*,5*S*,9*S*,15*S*)-**24** to give (4*R*,5*S*,11*S*,15*R*)-**35** as a an oil (0.247 g, 93%). IR (neat): 3465, 1722, 1656 (sh) cm^{-1}; $[\alpha]_D^{28}$ −37.8 ($c=0.50$, $CHCl_3$); ^1H NMR: δ 1.19 (3H, d, $J=7$ Hz), 1.24 (3H, d, $J=7$ Hz), 1.25 (3H, d, $J=7$ Hz), 2.37 (1H, dd, $J=9$, 16 Hz), 2.43 (1H, dd, $J=4$, 16 Hz), 2.43–2.48 (2H, m), 2.88 (1H, br. s), 4.13 (1H, ddd, $J=2$, 4, 6 Hz), 4.12–4.20 (1H, m), 4.51, 4.63 (each 1H, d, $J=12$ Hz), 4.78, 4.81 (each 1H, d, $J=12$ Hz), 5.04 (1H, qt, $J=7$, 7 Hz), 5.10 (1H, dq, $J=4$, 7 Hz), 5.84 (1H, dt, $J=1$, 16 Hz), 6.19 (1H, dd, $J=2$, 16 Hz), 6.84 (1H, dt, $J=7$, 16 Hz), 7.02 (1H, dd, $J=6$, 16 Hz), 7.26–7.36 (5H, m). ^{13}C NMR: δ 15.3 (q), 19.8 (q), 22.6 (q), 38.4 (t), 43.1 (t), 64.2 (d), 69.4 (d), 71.3 (d), 71.9 (t), 74.0 (t), 79.5 (d), 94.8 (s), 122.1 (d), 123.8 (d), 127.6 (d), 127.8 (d), 128.3 (d), 137.2 (s), 143.9 (d), 146.5 (d), 163.7 (s), 165.0 (s), 171.9 (s). Anal. calcd for $C_{25}H_{31}O_8Cl_3$: C, 53.06; H, 5.52. Found: C, 52.78; H, 5.66%. FAB MS m/z; 565, 567 (M^++1).

4.20. Deprotection of 2,2,2-trichloroethyl group of (4*R*,5*S*,11*S*,15*R*)-35

To a solution of (4*R*,5*S*,11*S*,15*R*)-**35** (0.212 g, 0.38 mmol) and AcOH–AcONa buffer solution (4 mL) in THF (4 mL) at 0°C was added Zn dust (240 mg, 3.7 mmol) and the whole mixture was stirred for 3 h at room temperature. The reaction mixture was worked up in the same way as for the preparation of (4*R*,5*S*,9*S*,15*S*)-**25** to give the crude *seco*-acid (4*R*,5*S*,11*S*,15*R*)-**36** (0.147 g, 90%). ^1H NMR: δ 1.19 (3H, d, $J=7$ Hz), 1.23 (3H, d, $J=7$ Hz), 1.24 (3H, d,

$J=7$ Hz), 2.39 (1H, dd, $J=7$, 16 Hz), 2.42 (1H, dd, $J=4$, 16 Hz), 2.45 (2H, ddd, $J=1$, 7, 7 Hz), 4.07 (1H, ddd, $J=2$, 4, 6 Hz), 4.12–4.19 (1H, m), 4.47, 4.61 (each 1H, d, $J=12$ Hz), 5.04 (1H, qt, $J=7$, 7 Hz), 5.08 (1H, dq, $J=4$, 7 Hz), 5.80–6.00 (2H, br s), 5.84 (1H, dt, $J=1$, 16 Hz), 6.08 (1H, dd, $J=2$, 16 Hz), 6.84 (1H, dt, $J=7$, 16 Hz), 6.94 (1H, dd, $J=6$, 16 Hz), 7.25–7.35 (5H, m).

4.21. Benzyl ether (3*R*,8*R*,9*S*,15*S*)-37

To a solution of (4*R*,5*S*,11*S*,15*R*)-**36** (0.146 g, 0.33 mmol) and Et_3N (0.068 g, 0.68 mmol) in THF (3 mL) were added a solution of 2,4,6-trichlorobenzoyl chloride (0.165 g, 0.67 mmol) in THF (3 mL) and the reaction mixture was stirred for 1.5 h at room temperature. To a solution of DMAP (0.248 g, 2.03 mmol) in toluene (20 mL) at 100°C was added dropwise the above-mentioned reaction mixture diluted with toluene (170 mL) over 2 h and the whole mixture was stirred for 1 h at 100°C. The reaction mixture was worked up in the same way as for the preparation of (3*S*,9*S*,14*R*,15*S*)-**26** to give (3*R*,8*R*,9*S*,15*S*)-**37** as a colorless oil (0.107 g, 76%). IR ($CHCl_3$): 1716, 1660 (sh) cm^{-1}; $[\alpha]_D^{29}$ −22.1 ($c=0.35$, $CHCl_3$); ^1H NMR: δ 1.20 (3H, d, $J=7$ Hz), 1.29 (3H, d, $J=7$ Hz), 1.43 (3H, d, $J=7$ Hz), 2.32 (1H, ddt, $J=1$, 8, 16 Hz), 2.50–2.57 (1H, m), 2.51 (1H, dd, $J=7$, 16 Hz), 2.76 (1H, dd, $J=4$, 16 Hz), 3.95 (1H, ddd, $J=2$, 4, 6 Hz), 4.47, 4.58 (each 1H, d, $J=12$ Hz), 4.96–5.02 (1H, m), 5.18 (1H, dq, $J=4$, 7 Hz), 5.25 (1H, ddq, $J=4$, 7, 7 Hz), 5.75 (1H, dt, $J=1$, 16 Hz), 6.14 (1H, dd, $J=2$, 16 Hz), 6.75 (1H, dt, $J=7$, 16 Hz), 6.90 (1H, dd, $J=6$, 16 Hz), 7.25–7.35 (5H, m). ^{13}C NMR: δ 17.6 (q), 19.4 (q), 20.0 (q), 37.9 (t), 40.2 (t), 67.4 (d), 70.2 (d), 70.5 (d), 70.9 (t), 80.5 (s), 124.0 (d), 124.3 (d), 127.5 (d), 127.7 (d), 128.3 (d), 137.2 (s), 143.5 (d), 143.7 (d), 164.3 (s), 164.9 (s), 169.1 (s). Anal. calcd for $C_{23}H_{28}O_7$: C, 66.33; H, 6.78. Found: C, 66.40; H, 6.79%. FAB MS m/z; 417 (M^++1).

4.22. (+)-Macrosphelide G, 3

To a mixture of $AlCl_3$ (0.043 g, 0.32 mmol) in CH_2Cl_2 (3 mL) was added dropwise a solution of (3*R*,8*R*,9*S*,15*S*)-**37** (0.066 g, 0.16 mmol) and *m*-xylene (1.5 mL) in CH_2Cl_2 (3 mL) at −5°C and the reaction mixture was stirred for 2 h at 0°C. The reaction mixture was worked up in the same way as for the preparation of macrosphelide C **1** to give (+)-**3** as a colorless oil (0.040 g, 78%). (+)-**3**; IR ($CHCl_3$): 3465, 1714 cm^{-1}; $[\alpha]_D^{26}$ +51.7 ($c=0.35$, EtOH). The NMR spectra (^1H and ^{13}C NMR) of the synthetic (+)-3**2** were identical with those of natural (+)-**3**.[2] Anal. calcd for $C_{16}H_{22}O_7$: C, 58.89; H, 6.80. Found: C, 59.01; H, 6.94%. FAB MS m/z; 327 (M^++1).

Acknowledgements

The authors are grateful to Professor A. Numata at Osaka University of Pharmaceutical Sciences, for generously providing the spectral data (^1H and ^{13}C NMR) of natural products (+)-**1**, (+)-**2** and (+)-**3**.

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