HETEROCYCLES, Vol. 77, No. 1, 2009, pp. 483 - 492. © The Japan Institute of Heterocyclic Chemistry
Received, 17th July, 2008, Accepted, 22nd August, 2008, Published online, 25th August, 2008.
DOI: 10.3987/COM-08-S(F)47

TOTAL SYNTHESIS OF 2-NOR-MACROSPHELIDES A AND B†

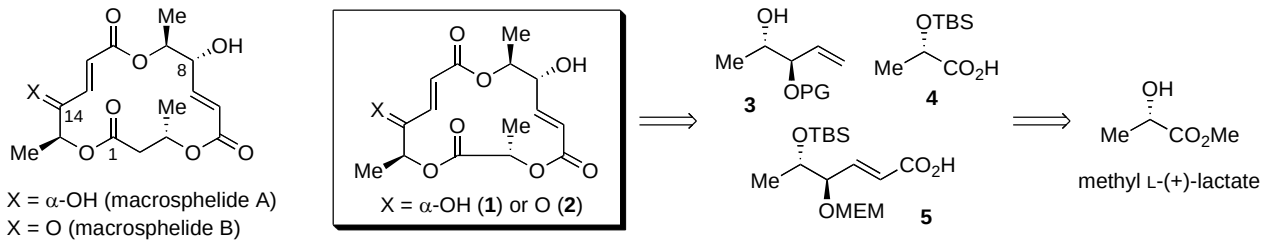
Yuji Matsuya,* Takashi Matsushita, Keiji Sakamoto, and Hideo Nemoto*

Graduate School of Medicine and Pharmaceutical Sciences, University of Toyama, 2630 Sugitani, Toyama 930-0194, Japan (matsuya@pha.u-toyama.ac.jp, nemotoh@pha.u-toyama.ac.jp)

Abstract – Total synthesis of 2-nor-macrosphelides, a 15-membered analogue of 16-membered natural macrosphelides, is described. The synthesis was accomplished starting from methyl L-(+)-lactate as a sole chiral source with a high efficiency.

INTRODUCTION

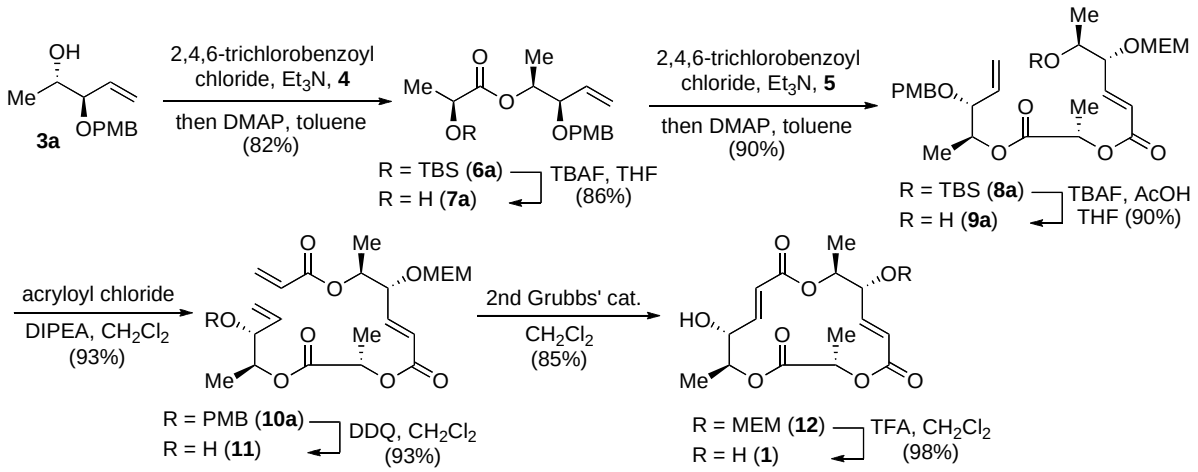
Macrosphelides are natural macrolides isolated from *Microsphaeropsis* sp. FO-5050 and *Periconia byssoides*, and characterized by a 16-membered tri-lactone framework.[1] This novel class of macrolide compounds has been reported to exhibit potent inhibitory activity against adhesion of human leukemia HL-60 cells to human-umbilicalvein endothelial cells (HUVECs).[2] Adhesion of tumor cells to the vessel wall endothelia of distant organs is a critical step in tumor metastasis, and it has been reported that macrosphelide B can suppress the metastasis of B16-BL6 mouse melanoma cells to the lung in vivo.[3] In addition, macrosphelide B and relating compounds have been found to exert inhibitory activity against tumor cell growth (colon 26-L5 adenocarcinoma cells).[4] We have recently first disclosed that several natural macrosphelides can induce apoptotic cell death of human lymphoma U937 cells,[5] and that these compounds also have a notable property as an effective sensitizer of hyperthermia-induced apoptosis.[6] These results have revealed that macrosphelides can be a potential lead compound for development of a new anticancer chemotherapeutic agent. We have been engaged in design, synthesis, and biological evaluation of macrosphelides and relating compounds,[7,8] and recently reported that several artificial macrosphelides (hybridized compounds with epothilones) exhibit significantly improved apoptosis-inducing activity compared with natural macrosphelides.[9] As a part of the structure-activity relationship studies of macrosphelides, we set about synthesizing novel 15-membered 2-nor-macrosphelides A and B (**1** and **2**, Scheme 1). Herein, we wish to report details of these synthetic studies.



Scheme 1. Natural Macrosphelides and 2-Nor-Analogues

RESULTS AND DISCUSSION

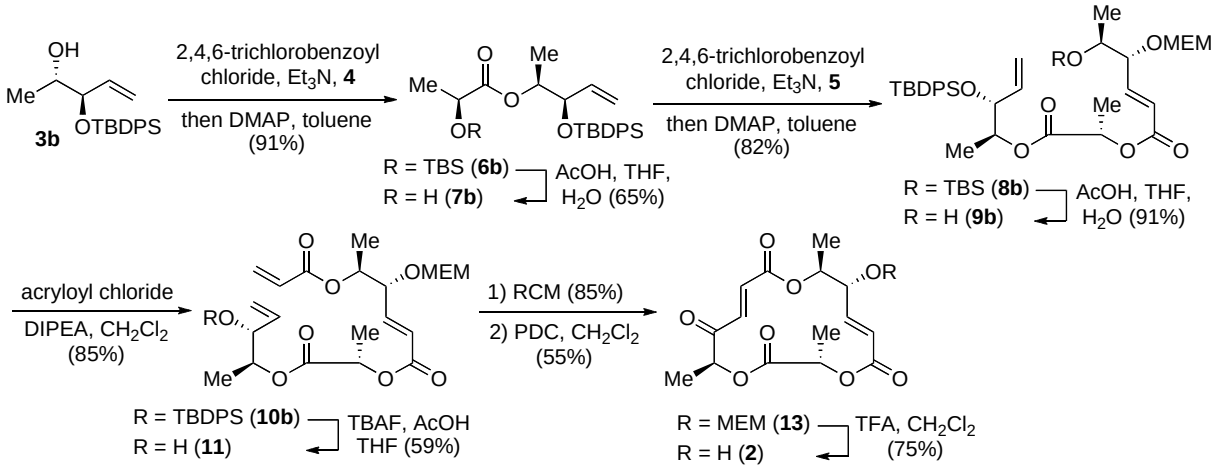
Because the macrocyclic core of macrosphelides is composed of three esters, protected hydroxy-acids possessing a suitable stereocenter are required as a synthetic block. For the synthesis of 2-nor-macrosphelides A and B (**1** and **2**), we chose the chiral blocks **3**, **4**, and **5** which are all derived from methyl L-(+)-lactate (Scheme 1). Ring-closing metathesis (RCM) is our choice for macrocyclization, as we have previously demonstrated its usefulness for macrosphelide syntheses.[8]



Scheme 2. Synthesis of 2-Nor-Macrosphelide A (**1**)

Preparation of the compounds **3**, **4**, and **5** from methyl L-(+)-lactate has already been reported in our previous studies.[8] Initially, the alcohol **3a** and the carboxylic acid **4** were connected using a Yamaguchi's esterification protocol[10] to give the ester **6a**, which was then treated with TBAF to form desilylated alcohol **7a** in satisfactory yields. The second esterification with the carboxylic acid **5** was carried out under the same condition. After desilylation of **8a**, the third esterification of **9a** was performed using acryloyl chloride to afford ω-diene compound **10a**. Prior to the RCM, the PMB group needs to be removed, because steric congestion around the reaction site seriously interferes progress of the RCM reaction.[8] After removal of the PMB group, RCM of the substrate **11** using Grubbs' second-generation catalyst[11] proceeded smoothly to provide the 15-membered macrocycle **12** in 85% yield. Finally, the

MEM group was eliminated by acid treatment to complete the synthesis of 2-nor-macrosphelide A (**1**). Above synthesis seems to be very efficient and high yielding. In practice, however, there is a serious problem that bulk preparation of the starting chiral alcohol **3a** is difficult, because *p*-methoxybenzylation of 4-(*tert*-butyldimethylsilyloxy)-1-penten-3-ol is a troublesome process as reported before.[8] On the other hand, preparation of the chiral alcohol **3b**, which appends a TBDPS group instead of the PMB group, was found to be much more convenient to realize large quantity synthesis. Thus, we decided to continue further synthetic study using **3b** as a starting material. Following the above synthetic pathway (Scheme 2), successive esterification–deprotection sequence led to the same RCM substrate **11** after removal of the TBDPS group (Scheme 3). Selective desilylation of the TBS group could be achieved under AcOH–THF–H_2O condition (**8b**→**9b**). The compound **12** obtained by RCM of **11** was subjected to PDC oxidation to give the corresponding ketone **13**. The synthesis of 2-nor-macrosphelide B (**2**) was accomplished by TFA treatment of **13**.



Scheme 3. Synthesis of 2-Nor-Macrosphelide B (**2**)

In this paper, we described total synthesis of 2-nor-macrosphelides A and B. All of the stereogenic centers bearing methyl group originate from an inexpensive chiral source, methyl L-(+)-lactate. These artificial macrosphelide analogues preserve the functional group arrangement, but may have different three-dimensional features from 16-membered natural macrosphelides. Bioactivities of these compounds are now under investigation, and will be reported in due course.

EXPERIMENTAL

All nonaqueous reactions were carried out under an Ar atmosphere. Reagents were purchased from commercial sources and used as received. Anhydrous solvents were prepared by distillation over CaH_2, or purchased from commercial sources. ^1H and ^{13}C NMR spectra were obtained on a Varian Gemini 300

instrument, using chloroform peak as an internal reference. Mass spectra were measured on a JEOL D-200 or a JEOL AX 505 mass spectrometer, and the ionization method was electron impact (EI, 70 eV). IR spectra were recorded on a JASCO FT/IR-460Plus spectrometer. Column chromatography was carried out by employing Cica Silica Gel 60N (spherical, neutral, 40-50 μm or 63-210 μm). Preparative methods of the compounds **3**, **4**, and **5** have already been reported.[8]

(–)-3-(4-Methoxybenzyloxy)pent-1-en-4-yl 2-(*tert*-Butyldimethylsilyloxy)propanoate (6a)

To a solution of the carboxylic acid **4** (790 mg, 3.87 mmol) and Et_3N (0.81 mL, 5.8 mmol) in toluene (35 mL) was added 2,4,6-trichlorobenzoyl chloride (0.6 mL, 3.87 mmol) at rt under Ar atmosphere, and the resulting mixture was stirred at rt for 1 h. The alcohol **3a** (430 mg, 1.93 mmol) and DMAP (284 mg, 2.32 mmol) were added, and the reaction mixture was stirred for 1 h. After the reaction completed (by TLC), the mixture was diluted with benzene, and washed with sat. aq. $NaHCO_3$ and brine, and dried over $MgSO_4$. The solvent was evaporated off to leave a residue, which was chromatographed on silica gel to afford the ester **6a** (648 mg, 82%) as a colorless oil. ^{1}H-NMR ($CDCl_3$): δ 7.14 (2H, d, *J* = 8.4 Hz), 6.80 (2H, d, *J* = 8.4 Hz), 5.19 (1H, d, *J* = 16 Hz), 5.24 (2H, d, *J* = 6.8 Hz), 5.60 (1H, m), 4.94 (1H, q, *J* = 5.1 Hz), 4.44 (1H, d, *J* = 12 Hz), 4.20 (2H, dd, *J* = 12, 7.0 Hz), 3.70 (3H, s), 3.63 (1H, s), 0.80 (9H, s), –0.02 (6H, s); ^{13}C-NMR ($CDCl_3$): δ 173.34, 159.09, 134.92, 129.21, 119.64, 113.67, 81.63, 71.98, 70.04, 68.35, 68.32, 55.21, 25.71, 25.67, 25.44, 21.31, 21.22, 18.27, 15.16, –4.88, –5.02; IR (neat): 1752, 1613 cm^{-1}; MS (EI): *m/z* 408 (M^+); HRMS Calcd for $C_{22}H_{36}O_5Si$: 408.2332 (M^+), found: 408.2299; $[\alpha]_D^{25}$ –29.96 (*c* 1.00, $CHCl_3$).

(–)-3-(4-Methoxybenzyloxy)pent-1-en-4-yl 2-Hydroxypropanoate (7a)

A 1 M solution of tetra-*n*-butylammonium fluoride (TBAF) in THF (1.39 mL, 1.39 mmol) was added to a stirred solution of the TBS ether **6a** (283 mg, 0.69 mmol) in THF (2 mL) at rt under Ar atmosphere, and the mixture was stirred for 0.5 h at rt. The solvent was evaporated off to leave a residue, which was dissolved in ether and the resulting organic layer was washed with water and brine, and dried over $MgSO_4$. Evaporation of the solvent left a residue, which was chromatographed on silica gel to give the alcohol **7a** (186 mg, 86%) as a colorless oil. ^{1}H-NMR ($CDCl_3$): δ 7.22 (2H, d, *J* = 8.4 Hz), 6.86 (2H, d, *J* = 8.4 Hz), 5.73 (1H, m), 5.32 (2H, m), 5.07 (1H, dt, *J* = 5.7, 4.9 Hz), 4.55 (1H, d, *J* = 12 Hz), 4.32 (1H, d, *J* = 12 Hz), 4.22 (1H, m), 3.80 (3H, s), 2.82 (1H, d, *J* = 5.4 Hz), 1.35 (3H, d, *J* = 6.9 Hz), 1.25 (3H, d, *J* = 6.3 Hz); ^{13}C-NMR ($CDCl_3$): δ 175.08, 159.17, 134.59, 130.12, 129.37, 129.27, 120.09, 113.80, 113.75, 81.47, 73.00, 70.02, 66.79, 55.25, 20.41, 15.61; IR (neat): 3470, 1737, 1613 cm^{-1}; MS (EI): *m/z* 294 (M^+); HRMS Calcd for $C_{16}H_{22}O_5$: 294.1467 (M^+), found: 294.1461; $[\alpha]_D^{26}$ –38.22 (*c* 1.00, $CHCl_3$).

(–)-1-[3-(4-Methoxybenzyloxy)pent-1-en-4-yloxycarbonyl]ethyl 5-(*tert*-Butyldimethylsilyloxy)-4-(methoxyethoxy)methoxyhex-2-enoate (8a)

According to the synthesis of **6a**, the carboxylic acid **5** (321 mg, 0.92 mmol) and the alcohol **7a** (135 mg, 0.46 mmol) gave the ester **8a** (259 mg, 90%) as a colorless oil. ^{1}H-NMR ($CDCl_3$): δ 7.20 (2H, d, *J* = 8.4 Hz), 6.83 (2H, d, *J* = 8.4 Hz), 6.03 (1H, dd, *J* = 16, 1.1 Hz), 5.70 (1H, m), 5.28 (2H, t, *J* = 9.2 Hz), 5.06 (1H, d, *J* = 7.0 Hz), 5.00 (1H, m), 4.69 (2H, q, *J* = 3.8 Hz), 4.50 (1H, dd, *J* = 12 Hz), 4.29 (1H, d, *J* = 12 Hz), 4.06 (1H, dq, *J* = 3.8 Hz), 3.76 (3H, s), 3.71 (1H, dq, *J* = 7.3, 3.2 Hz), 3.63 (1H,m), 3.50 (2H, t, *J* = 4.6 Hz), 3.34 (3H, s), 1.42 (3H, d, *J* = 6.9 Hz), 1.22 (3H, d, *J* = 6.6 Hz), 1.12 (3H, d, *J* = 6.3 Hz), 0.84 (9H, s), 0.04 (6H, s); ^{13}C-NMR ($CDCl_3$): δ 170.02, 165.12, 159.12, 147.01, 146.97, 134.77, 130.24, 129.23, 122.23, 119.81, 113.71, 81.53, 79.87, 72.62, 71.65, 70.64, 70.05, 68.65, 67.23, 58.99, 55.22, 25.75, 19.75, 18.00, 16.93, 15.58, –4.66, –4.83; IR (neat): 1730, 1656 cm^{-1}; MS (EI): *m/z* 624; HRMS Calcd for $C_{32}H_{52}O_{10}Si$: 624.3330 (M^+), found: 624.3307; $[\alpha]_D^{24}$ –56.3 (*c* 1.00, $CHCl_3$).

(–)-1-[3-(4-Methoxybenzyloxy)pent-1-en-4-yloxycarbonyl]ethyl 5-Hydroxy-4-(methoxyethoxy)methoxyhex-2-enoate (9a)

A 1 M solution of TBAF in THF (0.83 mL, 0.83 mmol) was added to a stirred solution of the TBS ether **8a** (260 mg, 0.42 mmol) and acetic acid (47 μL, 0.83 mmol) in THF (3 mL) at rt under Ar atmosphere, and the mixture was stirred for 24 h at rt. The ethereal solution of the residue resulting from the evaporation of the solvent was washed with water, sat. aq. $NaHCO_3$, and brine, and dried over $MgSO_4$. Evaporation of the solvent left a residue, which was chromatographed on silica gel to give the alcohol **9a** (190 mg, 90%) as a colorless oil. ^{1}H-NMR ($CDCl_3$): δ 7.21 (2H, d, *J* = 8.9 Hz), 6.85 (2H, d, *J* = 8.9 Hz), 6.10 (1H, dd, *J* = 16, 1.6 Hz), 5.70 (1H, m), 5.08 (1H, d, *J* = 7.0 Hz), 5.03 (1H, m), 4.76 (1H, d, *J* = 7.0 Hz), 4.68 (1H, d, *J* = 7.0 Hz), 4.51 (1H, d, *J* = 11 Hz), 4.31 (1H, d, *J* = 11 Hz), 4.22 (1H, q, *J* = 1.0 Hz), 3.91 (1H, m), 3.78 (3H, s), 3.54 (1H, d, *J* = 4.6 Hz), 3.37 (3H, s), 1.44 (3H, d, *J* = 6.9 Hz), 1.24 (3H, d, *J* = 6.3 Hz), 1.11 (3H, d, *J* = 6.6 Hz); ^{13}C-NMR ($CDCl_3$): δ 194.71, 181.72, 145.13, 134.75, 130.26, 129.27, 129.24, 122.83, 113.74, 94.60, 81.54, 72.73, 71.66, 70.08, 68.99, 68.82, 67.60, 60.73, 58.97, 55.26, 31.26, 27.07, 17.54, 16.94, 15.55, 15.24; IR (neat): 3650, 1728, 1613 cm^{-1}; MS (EI): *m/z* 510 (M^+); HRMS Calcd for $C_{26}H_{38}O_{10}$: 510.2465 (M^+), found: 510.2498; $[\alpha]_D^{27}$ –47.76 (*c* 1.00, $CHCl_3$).

(–)-1-[3-(4-Methoxybenzyloxy)pent-1-en-4-yloxycarbonyl]ethyl 5-Acryloyloxy-4-(methoxyethoxy)methoxyhex-2-enoate (10a)

Acryloyl chloride (76 μL, 0.94 mmol) was added dropwise to a stirred solution of the alcohol **9a** (120 mg, 0.24 mmol) and *N,N*-diisopropylethylamine (200 μL, 1.18 mmol) in CH_2Cl_2 (3 mL) at 0 °C under Ar atmosphere. After continuous stirring for 1 h at rt, the reaction mixture was diluted with CH_2Cl_2, washed with water, 10% HCl, sat. aq. $NaHCO_3$, and brine successively, and dried over $MgSO_4$. Evaporation of the solvent afforded a residue, which was chromatographed on silica gel to give the ester **10a** (124 mg, 93%), as a colorless oil. ^{1}H-NMR ($CDCl_3$): δ 7.22 (2H, d, *J* = 8.9Hz), 6.85 (2H, d, *J* = 8.9 Hz), 6.39 (1H, dd, *J* = 17, 1.4 Hz), 6.15 (1H, dd, *J* = 17, 1.4 Hz), 6.08 (1H, d, *J* = 10 Hz), 5.82 (1H, dd, *J* = 10, 1.4 Hz),

5.72 (1H, dq, *J* = 7.0 Hz), 5.33 (1H, d, *J* = 10 Hz), 5.21 (1H, s), 5.10 (2H, m), 4.73 (2H, q, *J* = 9.2 Hz), 4.53 (2H, d, *J* = 12 Hz), 4.40 (1H, m), 4.32 (2H, d, *J* = 12 Hz), 3.79 (3H, s), 3.75 (1H, d, *J* = 4.9 Hz), 3.66 (1H, m), 3.52 (2H, d, *J* = 4.6 Hz), 3.37 (3H, d, *J* = 2.4 Hz), 2.05 (1H, dq, *J* = 5.9, 1.6 Hz), 1.44 (3H, d, *J* = 6.9 Hz), 1.24 (3H, d, *J* = 6.3 Hz), 1.11 (3H, d, *J* = 6.6 Hz); ^{13}C-NMR ($CDCl_3$): δ 169.95, 165.32, 164.89, 159.11, 144.48, 134.70, 131.03, 130.19, 129.20, 128.37, 123.23, 119.86, 113.70, 93.87, 81.48, 72.68, 71.56, 71.36, 70.02, 69.84, 67.22, 58.96, 55.21, 16.89, 15.56, 14.88; IR (neat): 3781, 1727, 1659 cm^{-1}; MS (EI): *m/z* 564; HRMS Calcd for $C_{29}H_{40}O_{11}$: 564.2571 (M^+), found: 564.2557; $[\alpha]_D^{25}$ –43.18 (*c* 1.00, $CHCl_3$).

(–)-1-(3-Hydroxypent-1-en-4-yloxycarbonyl)ethyl
5-Acryloyloxy-4-(methoxyethoxy)methoxyhex-2-enoate (11)

A mixture of the PMB ether **10a** (57 mg, 0.1 mmol) and DDQ (34 mg, 0.15 mmol) in CH_2Cl_2/H_2O (18 : 1, 1 mL) was stirred at rt for 1 h. The precipitate formed was removed by filtration, and the filtrate was concentrated to furnish a gummy mass, which was chromatographed on silica gel to give the alcohol **11** (42 mg, 93%) as a colorless oil. ^{1}H-NMR ($CDCl_3$): δ 6.94 (1H, dd, *J* = 16, 6.0 Hz), 6.40 (1H, dd, *J* = 17, 1.2 Hz), 6.17 (1H, dd, *J* = 16, 1.2 Hz), 6.09 (1H, d, *J* = 17 Hz), 5.84 (1H, d, *J* = 10 Hz), 5.78 (1H, m), 5.33 (1H, d, *J* = 17 Hz), 5.24 (1H, d, *J* = 10 Hz), 5.13 (1H, q, *J* = 3.6 Hz), 5.09 (1H, q, *J* = 7.2 Hz), 5.04 (1H, m), 4.74 (2H, q, *J* = 6.9 Hz), 4.43 (1H, q, *J* = 3.6 Hz), 4.19 (1H, m), 3.77 (1H, m), 3.67 (1H, m), 3.53 (2H, q, *J* = 4.8 Hz), 3.37 (3H, s), 1.89 (1H, br), 1.54 (3H, d, *J* = 7.2 Hz), 1.25 (3H, d, *J* = 1.5 Hz), 1.23 (3H, d, *J* = 6.6 Hz); ^{13}C-NMR ($CDCl_3$): δ 170.28, 165.52, 165.40, 145.11, 135.41, 131.27, 128.42, 123.13, 117.79, 94.09, 77.39, 74.64, 71.76, 71.54, 69.47, 67.61, 67.48, 59.24, 17.22, 15.27, 14.80; IR (neat): 3481, 1727, 1660 cm^{-1}; MS (EI): *m/z* 444 (M^+); HRMS Calcd for $C_{21}H_{32}O_{10}$: 444.1996 (M^+), found: 444.2046; $[\alpha]_D^{25}$ –28.80 (*c* 1.00, $CHCl_3$).

RCM of the Compound 11 (Synthesis of the Compound 12)

Grubbs' ruthenium catalyst (second generation) (7 mg, 7.9 μmol) was added to a solution of ω-diene compound **11** (35 mg, 0.079 mmol) in CH_2Cl_2 (80 mL) under Ar atmosphere. After continuous stirring for 24 h at rt, the solvent was evaporated to afford a residue, which was chromatographed on silica gel to give the compound **12** (28 mg, 85%) as a colorless oil. ^{1}H-NMR ($CDCl_3$): δ 6.75 (1H, dd, *J* = 16, 3.2 Hz), 6.69 (1H, dd, *J* = 16, 7.8 Hz), 5.98 (1H, dd, *J* = 16, 2.2 Hz), 5.95 (1H, d, *J* = 16 Hz), 4.98 (1H, dq, *J* = 7.3, 2.2 Hz), 5.05 (1H, q, *J* = 7.0 Hz), 4.69 (2H, td, *J* = 9.7, 3.0 Hz), 4.58 (1H, t, *J* = 4.2 Hz), 4.03 (2H, t, *J* = 8.9 Hz), 3.72 (1H, t, *J* = 5.1 Hz), 3.64 (1H, t, *J* = 4.3 Hz), 3.51 (2H, t, *J* = 4.3 Hz), 3.36 (3H, s), 1.38 (3H, d, *J* = 5.9 Hz), 1.47 (3H, d, *J* = 6.8 Hz), 1.41 (3H, d, *J* = 6.2 Hz); ^{13}C-NMR ($CDCl_3$): δ 198.60, 169.38, 165.05, 147.30, 146.07, 124.20, 120.60, 94.06, 80.49, 73.96, 71.49, 70.29, 69.55, 67.28, 58.96, 17.78, 17.17, 16.74, 2.36; IR (neat): 3447, 1737, 1661 cm^{-1}; MS (EI): *m/z* 416; HRMS Calcd for $C_{19}H_{28}O_{10}$: 416.1683 (M^+), found: 416.1660; $[\alpha]_D^{26}$ –131.11 (*c* 1.50, $CHCl_3$).

2-Nor-Macrosphelide A (1)

Trifluoroacetic acid (TFA, 1 mL) was added to a solution of the MEM ether **12** (28 mg, 0.13 mmol) in CH_2Cl_2 (1 mL) at 0 °C under Ar atmosphere. After continuous stirring for 24 h at rt, the solvent was evaporated to afford a residue, which was chromatographed on silica gel to give 2-nor-macrosphelide A (**1**, 22 mg, 98%) as a colorless solid. Mp 135–137 °C; ^{1}H-NMR ($CDCl_3$): δ 6.85 (1H, dd, *J* = 16, 8.1 Hz), 6.82 (1H, dd, *J* = 16, 8.1 Hz), 6.75 (1H, dd, *J* = 16, 5.4 Hz), 5.95 (1H, dd, *J* = 16, 5.4 Hz), 5.07 (1H, q, *J* = 7.0 Hz), 4.96 (1H, m), 4.68 (1H, m), 4.08 (2H, t, *J* = 7.0 Hz), 2.20 (1H, br), 4.03 (1H, t, *J* = 5.0 Hz), 1.50 (3H, d, *J* = 7.3 Hz), 1.46 (3H, d, *J* = 6.5 Hz), 1.38 (3H, d, *J* = 5.9 Hz); ^{13}C-NMR ($CDCl_3$): δ 169.50, 165.86, 164.91, 147.88, 146.29, 123.79, 122.24, 77.20, 74.55, 73.81, 73.44, 69.67, 17.74, 17.13, 16.78; IR (KBr): 3446, 1732, 1661 cm^{-1}; MS (EI): *m/z* 328; HRMS Calcd for $C_{15}H_{20}O_9$: 328.1158 (M^+), found: 328.1139; $[\alpha]_D^{28}$ +3.23 (*c* 1.00, $CHCl_3$).

(–)-3-(*tert*-Butyldiphenylsilyloxy)pent-1-en-4-yl 2-(*tert*-Butyldimethylsilyloxy)propanoate (6b)

According to the synthesis of **6a**, the carboxylic acid **4** (790 mg, 3.87 mmol) and the alcohol **3b** (650 mg, 1.91 mmol) gave the ester **6b** (915 mg, 91%) as a colorless oil. ^{1}H-NMR ($CDCl_3$): δ 7.65 (4H, m), 7.37 (6H, m), 5.77 (1H, ddd, *J* = 17, 10, 7.3 Hz), 5.01 (1H, d, *J* = 10 Hz), 4.95 (1H, m), 4.87 (1H, dd, *J* = 17, 1.0 Hz), 4.19 (1H, m), 4.08 (1H, m), 1.30 (3H, d, *J* = 6.6 Hz), 1.14 (3H, d, *J* = 6.3 Hz), 1.04 (9H, s), 0.89 (9H, s), 0.07 (6H, s); ^{13}C-NMR ($CDCl_3$): δ 173.45, 136.33, 136.05, 136.01, 133.76, 133.58, 129.69, 129.58, 127.49, 127.39, 117.74, 77.24, 73.61, 68.32, 26.94, 25.75, 21.29, 19.36, 18.32, 15.32, –4.83, –5.25; IR (neat): 1751, 1579 cm^{-1}; MS (EI): *m/z* 469 (M^+–57); HRMS Calcd for $C_{26}H_{37}O_4Si_2$: 469.2231 (M^+–57), found: 469.2269; $[\alpha]_D^{29}$ –9.24 (*c* 1.05, $CHCl_3$).

(–)-3-(*tert*-Butyldiphenylsilyloxy)pent-1-en-4-yl 2-Hydroxypropanoate (7b)

A solution of the TBS ether **6b** (980 mg, 1.86 mmol) in AcOH/THF/H_2O (3 : 1 : 1, 15 mL) was stirred for 2 days at 50 °C. The reaction mixture was diluted with Et_2O, washed with sat. aq. $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting oil was purified by column chromatography on silica gel to afford the alcohol **7b** (499 mg, 65%) as a colorless oil. ^{1}H-NMR ($CDCl_3$): δ 7.66 (4H, m), 7.37 (6H, m), 5.77 (1H, ddd, *J* = 17, 10, 7.3 Hz), 5.05 (1H, d, *J* = 10 Hz), 4.99 (1H, m), 4.91 (1H, d, *J* = 17 Hz), 4.16 (1H, m), 4.09 (1H, m), 2.68 (1H, br), 1.34 (3H, d, *J* = 7.0 Hz), 1.17 (3H, d, *J* = 6.6 Hz), 1.05 (9H, s); ^{13}C-NMR ($CDCl_3$): δ 175.11, 136.00, 135.94, 135.88, 133.47, 133.45, 129.77, 129.65, 127.52, 127.37, 117.97, 77.04, 74.70, 66.81, 26.89, 20.44, 19.30, 15.21; IR (neat): 3451, 1731, 1644 cm^{-1}; MS (EI): *m/z* 413 (M^++1); HRMS Calcd for $C_{24}H_{33}O_4Si$: 413.2148 (M^++1), found: 413.2169; $[\alpha]_D^{27}$ –3.16 (*c* 1.150, $CHCl_3$).

(–)-1-[3-(*tert*-Butyldiphenylsilyloxy)pent-1-en-4-yloxycarbonyl]ethyl 5-(*tert*-Butyldimethylsilyloxy)-4-(methoxyethoxy)methoxyhex-2-enoate (8b)

According to the synthesis of **6a**, the carboxylic acid **5** (770 mg, 2.21 mmol) and the alcohol **7b** (790 mg,

1.91 mmol) gave the ester **8b** (1.16 g, 82%) as a colorless oil. ^{1}H-NMR ($CDCl_3$): δ 7.66 (2H, m), 7.61 (2H, m), 7.34 (6H, m), 6.92 (1H, dd, *J* = 16, 6.3 Hz), 6.05 (1H, dd, *J* = 16, 1.3 Hz), 5.73 (1H, ddd, *J* = 17, 10, 7.4 Hz), 5.02 (1H, m), 4.99 (1H, m), 4.96 (1H, m), 4.85 (1H, dd, *J* = 10, 1.1 Hz), 4.77 (1H, d, *J* = 6.9 Hz), 4.70 (1H, d, *J* = 6.9 Hz), 4.05 (2H, m), 3.82 (1H, m), 3.75 (1H, m), 3.64 (1H, m), 3.52 (2H, t, *J* = 4.6 Hz), 3.36 (3H, s), 1.40 (3H, d, *J* = 6.9 Hz), 1.15 (3H, d, *J* = 6.3 Hz), 1.14 (3H, d, *J* = 6.3 Hz), 1.03 (9H, s), 0.85 (9H, s), 0.02 (3H, s), 0.01 (3H, s); ^{13}C-NMR ($CDCl_3$): δ 170.10, 165.11, 146.93, 136.03, 136.00, 135.89, 133.65, 133.48, 129.72, 129.60, 127.21, 127.34, 122.32, 117.89, 94.11, 79.87, 77.15, 74.25, 71.66, 70.65, 68.68, 67.23, 59.01, 26.91, 25.76, 19.74, 19.31, 18.02, 16.97, 15.31, –4.64, –4.82; IR (neat): 1730, 1589 cm^{-1}; MS (EI): *m/z* 742 (M^+); HRMS Calcd for $C_{40}H_{62}O_9Si_2$: 742.3932 (M^+), found: 742.3936; $[\alpha]_D^{26}$ –5.920 (*c* 0.95, $CHCl_3$).

(–)-1-[3-(*tert*-Butyldiphenylsilyloxy)pent-1-en-4-yloxycarbonyl]ethyl 5-Hydroxy-4-(methoxyethoxy)methoxyhex-2-enoate (9b)

According to the synthesis of **7b**, the TBS ether **8b** (1.10 g, 1.48 mmol) gave the alcohol **9b** (850 mg, 91%) as a colorless oil. ^{1}H-NMR ($CDCl_3$): δ 7.65 (2H, m), 7.61 (2H, m), 7.34 (6H, m), 6.90 (1H, dd, *J* = 16, 5.7 Hz), 6.10 (1H, dd, *J* = 16, 1.3 Hz), 5.73 (1H, ddd, *J* = 17, 10, 7.3 Hz), 5.02 (1H, m), 4.99 (1H, m), 4.95 (1H, m), 4.85 (1H, dd, *J* = 17, 1.0 Hz), 4.77 (1H, d, *J* = 6.8 Hz), 4.70 (1H, d, *J* = 6.8 Hz), 4.24 (1H, m), 4.04 (1H, m), 3.92 (1H, m), 3.81 (1H, m), 3.67 (1H, m), 3.53 (2H, t, *J* = 4.6 Hz), 3.36 (3H, s), 1.89 (1H, br), 1.40 (3H, d, *J* = 6.9 Hz), 1.14 (3H, d, *J* = 6.6 Hz), 1.12 (3H, d, *J* = 6.6 Hz), 1.03 (9H, s); ^{13}C-NMR ($CDCl_3$): δ 170.14, 165.01, 145.07, 136.01, 135.98, 133.62, 133.47, 129.73, 129.60, 127.51, 122.86, 117.90, 94.57, 80.94, 77.12, 74.38, 71.64, 68.97, 68.83, 67.56, 58.94, 26.91, 19.30, 17.52, 16.97, 15.27; IR (neat): 3460, 1728, 1658 cm^{-1}; MS (EI): *m/z* 571 (M^+–57); HRMS Calcd for $C_{30}H_{39}O_9Si$: 571.2363 (M^+–57), found: 571.2342; $[\alpha]_D^{25}$ –22.84 (*c* 1.55, $CHCl_3$).

(–)-1-[3-(*tert*-Butyldiphenylsilyloxy)pent-1-en-4-yloxycarbonyl]ethyl 5-Acryloyloxy-4-(methoxyethoxy)methoxyhex-2-enoate (10b)

According to the synthesis of **10a**, the alcohol **9b** (150 mg, 0.23 mmol) gave the ester **10b** (138 mg, 85%) as a colorless oil. ^{1}H-NMR ($CDCl_3$): δ 7.67 (2H, m), 7.63 (2H, m), 7.34 (6H, m), 6.90 (1H, dd, *J* = 16, 5.7 Hz), 6.40 (1H, dd, *J* = 17, 1.3 Hz), 6.16 (1H, dd, *J* = 17, 1.7 Hz), 6.10 (1H, m), 5.82 (1H, dd, *J* = 10, 1.3 Hz), 5.75 (1H, ddd, *J* = 17, 10, 7.3 Hz), 5.13 (1H, m), 5.04 (1H, m), 5.02 (1H, m), 4.99 (1H, m), 4.87 (1H, dd, *J* = 17, 1.3 Hz), 4.77 (1H, d, *J* = 6.9 Hz), 4.70 (1H, d, *J* = 6.9 Hz), 4.43 (1H, m), 4.05 (1H, m), 3.79 (1H, m), 3.65 (1H, m), 3.53 (2H, m), 3.37 (3H, s), 1.45 (3H, d, *J* = 6.8 Hz), 1.25 (3H, d, *J* = 6.8 Hz), 1.16 (3H, d, *J* = 6.4 Hz), 1.05 (9H, s); ^{13}C-NMR ($CDCl_3$): δ 170.02, 165.31, 164.86, 144.37, 135.95, 135.92, 133.50, 133.35, 131.06, 129.68, 129.56, 128.31, 127.46, 127.30, 123.25, 117.89, 93.79, 76.74, 76.46, 74.29, 71.51, 71.32, 68.84, 67.15, 58.94, 26.84, 19.24, 16.90, 15.26, 14.86; IR (neat): 3781, 1728, 1660 cm^{-1}; MS (EI): *m/z* 625 (M^+–57); HRMS Calcd for $C_{33}H_{41}O_{10}Si$: 625.2469 (M^+–57), found: 625.2450;

$[\alpha]_D^{26}$ –12.858 (*c* 1.10, $CHCl_3$).

Removal of the TBDPS group of the compound 10b

According to the synthesis of **9a**, the TBDPS ether **10b** (68 mg, 0.1 mmol) gave the alcohol **11** (261 mg, 59%) as a colorless oil. Spectral data of **11** have already been given.

PDC Oxidation of the Compound 12 (Synthesis of the Compound 13)

Pyridinium dichromate (PDC, 89 mg, 0.23 mmol) was added portionwise to a stirred solution of the alcohol **12** (22 mg, 0.053 mmol) and molecular sieves 4A (100 mg) in CH_2Cl_2 (5 mL) at 0 °C under Ar atmosphere. After continuous stirring for 3 h at rt, the reaction mixture was diluted with ether, and filtered through celite. The filtrate was evaporated to leave a residue, which was chromatographed on silica gel to give the ketone **13** (13 mg, 55%) as a colorless oil. ^{1}H-NMR ($CDCl_3$): δ 7.07 (1H, d, *J* = 16 Hz), 6.84 (1H, dd, *J* = 16, 8.9 Hz), 6.63 (1H, d, *J* = 16 Hz), 6.17 (1H, d, *J* = 16 Hz), 5.29 (1H, t, *J* = 7.3 Hz), 5.25 (1H, q, *J* = 6.9 Hz), 4.88 (1H, m), 4.74 (1H, d, *J* = 6.9 Hz), 4.67 (1H, d, *J* = 6.9 Hz), 4.17 (1H, t, *J* = 8.9 Hz), 3.74 (1H, m), 3.63 (1H, m), 3.51 (2H, t, *J* = 4.3 Hz), 3.35 (3H, s), 1.54 (3H, d, *J* = 6.9 Hz), 1.45 (3H, d, *J* = 6.3 Hz), 1.40 (3H, d, *J* = 6.9 Hz); ^{13}C-NMR ($CDCl_3$): δ 196.56, 168.99, 164.71, 164.25, 147.09, 133.75, 132.65, 124.40, 93.87, 79.72, 75.52, 72.21, 71.53, 69.01, 67.39, 59.00, 18.05, 16.94, 16.43; IR (neat): 1730, 1617 cm^{-1}; MS (EI): *m/z* 414 (M^+); HRMS Calcd for $C_{19}H_{26}O_{10}$: 414.1525 (M^+), found: 414.1537; $[\alpha]_D^{29}$ –122.692 (*c* 1.30, $CHCl_3$).

2-Nor-Macrosphelide B (2)

According to the synthesis of **1**, the compound **13** (16 mg, 0.039 mmol) gave the 2-nor-macrosphelide B (**2**, 9 mg, 75%) as a colorless solid. Mp 100–102 °C; ^{1}H-NMR ($CDCl_3$): δ 7.16 (1H, d, *J* = 16 Hz), 6.99 (1H, dd, *J* = 16, 7.3 Hz), 6.64 (1H, d, *J* = 16 Hz), 6.13 (1H, dd, *J* = 16, 1.0 Hz), 5.28 (1H, q, *J* = 7.3 Hz), 5.25 (1H, m), 4.91 (1H, m), 4.25 (1H, t, *J* = 6.4 Hz), 1.56 (3H, d, *J* = 7.0 Hz), 1.51 (3H, d, *J* = 6.3 Hz), 1.43 (3H, d, *J* = 6.9 Hz); ^{13}C-NMR ($CDCl_3$): δ 196.67, 168.93, 164.94, 164.78, 147.82, 134.22, 132.31, 122.50, 75.99, 75.68, 74.68, 69.22, 17.88, 16.98, 16.60; IR (KBr): 3488, 1725, 1656 cm^{-1}; MS (EI): *m/z* 326 (M^+); HRMS Calcd for $C_{15}H_{18}O_8$: 326.1002 (M^+), found: 326.0987; $[\alpha]_D^{25}$ –45.84 (*c* 0.60, $CHCl_3$).

ACKNOWLEDGEMENTS

This work was supported by THE FUGAKU TRUST FOR MEDICINAL RESEARCH, and by Grant-in-Aid for Scientific Research (C) (No. 19590098) from Japan Society for the Promotion of Science (JSPS).

REFERENCES AND NOTES

† Dedicated to Professor Emeritus Keiichiro Fukumoto on the occasion of his 75th birthday.

1. M. Hayashi, Y.-P. Kim, H. Hiraoka, M. Natori, S. Takamatsu, T. Kawakubo, R. Masuma, K. Komiyama, and S. Ômura, *J. Antibiot*., 1995, **48**, 1435; T. Sunazuka, T. Hirose, Y. Harigaya, S. Takamatsu, M. Hayashi, K. Komiyama, S. Ômura, P. A. Sprengeler, and A. B. Smith III, *J. Am. Chem. Soc*., 1997, **119**, 10247; T. Yamada, M. Iritani, M. Doi, K. Minoura, T. Ito, and A. Numata, *J. Chem. Soc., Perkin Trans. 1*, 2001, 3046. For a review; Y. Matsuya and H. Nemoto, *Heterocycles*, 2005, **65**, 1741, and references cited therein.
2. S. Takamatsu, Y.-P. Kim, M. Hayashi, H. Hiraoka, M. Natori, K. Komiyama, and S. Ômura, *J. Antibiot*., 1996, **49**, 95.
3. A. Fukami, K. Iijima, M. Hayashi, K. Komiyama, and S. Ômura, *Biochem. Biophys. Res. Commun*., 2002, **291**, 1065.
4. K. Ishihara, T. Kawaguchi, Y. Matsuya, H. Sakurai, I. Saiki, and H. Nemoto, *Eur. J. Org. Chem*., 2004, 3973.
5. K. Ahmed, Q.-L. Zhao, Y. Matsuya, D.-Y. Yu, L. B. Feril Jr., H. Nemoto, and T. Kondo, *Chem. Biol. Interact*., 2007, **170**, 86.
6. K. Ahmed, Q.-L. Zhao, Y. Matsuya, D.-Y. Yu, T. L. Salunga, H. Nemoto, and T. Kondo, *Int. J. Hyperthermia*, 2007, **23**, 353.
7. Y. Matsuya, T. Kawaguchi, H. Nemoto, H. Nozaki, and H. Hamada, *Heterocycles*, 2003, **59**, 481; Y. Matsuya, T. Kawaguchi, and H. Nemoto, *Heterocycles*, 2003, **61**, 39; Y. Matsuya, K. Ishihara, N. Funamori, T. Kawaguchi, and H. Nemoto, *Heterocycles*, 2003, **61**, 59.
8. Y. Matsuya, T. Kawaguchi, and H. Nemoto, *Org. Lett*., 2003, **5**, 2939; T. Kawaguchi, N. Funamori, Y. Matsuya, and H. Nemoto, *J. Org. Chem*., 2004, **69**, 505.
9. Y. Matsuya, T. Kawaguchi, K. Ishihara, K. Ahmed, Q.-L. Zhao, T. Kondo, and H. Nemoto, *Org. Lett*., 2006, **8**, 4609.
10. J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, and M. Yamaguchi, *Bull. Chem. Soc. Jpn*., 1979, **52**, 1989.
11. M. Scholl, S. Ding, C. W. Lee, and R. H. Grubbs, *Org. Lett*., 1999, **1**, 953.