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SYNTHESIS AND SYNTHESIS-BASED STRUCTURAL ELUCIDATION OF (–)-MACROSPHELIDES J AND K

Hongchan An,[a] Seung-Hee Kim,[a] Heegyu Kim,[b] Kyeojin Kim,[a] Jaehoon Sim,[a] Jaebong Jang,[a] Seung-Mann Paek,[c] Young-Ger Suh,[a] and Hwayoung Yun[b]*

[a]College of Pharmacy, Seoul National University, 1 Gwanak-ro, Gwanak-gu, Seoul 151-742, Korea; [b]College of Pharmacy, Pusan National University, Geumjeong-gu, Busan 609-735, Korea; [c]College of Pharmacy, Research Institute of Pharmaceutical Science, Gyeongsang National University, Jinju daero, Jinju, 660-751, Korea

E-mail: hyun@pusan.ac.kr

Abstract – The structures of (–)-macrosphelides J and K have been elucidated via asymmetric total syntheses. Key points of the structure elucidation include an initial prediction of the stereochemistries of (–)-macrosphelides J and K based on the structural relationship of the macrosphelides and molecular modeling of macrosphelide B. Our synthetic approach features an isoxazoline-based route involving a diastereoselective olefin-nitrile oxide cycloaddition, an intricate reductive *N*-*O* bond cleavage of an isoxazoline and *O*-alkylation of the labile β-hydroxy ketone intermediate.

INTRODUCTION

Natural products are frequently promising candidates for drug discovery.[1] In addition, the total syntheses of biologically active natural products play an important role in the elucidation of their intriguing molecular structure as well as their structure-activity relationships. Although structural analyses utilizing spectrometry efficiently allow the structural determination of complex molecules, the final structures have occasionally been confirmed via extensive synthetic studies.[2] Indeed, the originally reported structures of many natural products have been revised based on the results of total syntheses, although a number of structures of bioactive natural products remain to be elucidated.[2b]

The stereochemistries of the macrosphelides, which are considered novel lead compounds for the development of anticancer and immunosuppressant agents, have not been completely elucidated thus

far.[3b-d] Thirteen macrosphelides have been reported over the past two decades (Figure 1).[3,4] Macrosphelides A, B, C, D, J and K were discovered by Ōmura et al. from the fermentation broth of *Microsphaeropsis* sp. FO-5050.[3] Macrosphelides E, F, G, H, I, L and M were isolated by Numata et al. from a strain of *Periconia byssoides*, which was originally separated from the sea hare *Aplysia kurodai*.[4] Macrosphelides are unique polyketides consisting of a 16-membered macrolactone backbone with the exception of macrosphelides D and M,[4d,5t] which are 15-membered macrocyclic polyketides. They commonly consist of three core fragments including a γ-keto- or γ-hydroxy-*trans*-α,β-unsaturated acid moiety connected via an ester linkage.[3,4] Macrolides possess four or five stereocenters, and the number of stereocenters depends on the presence of a secondary alcohol.[3,4] Since the initial isolation and structural elucidation of macrosphelides in the 1990s, these unique polyketides have attracted interest from synthetic[5] and medicinal[6] chemists due to their potent tumor metastasis-suppressing and immune-modulating activities.[3-7] However, the stereochemistries of macrosphelides J and K had not been confirmed until we elucidated them.[3c]

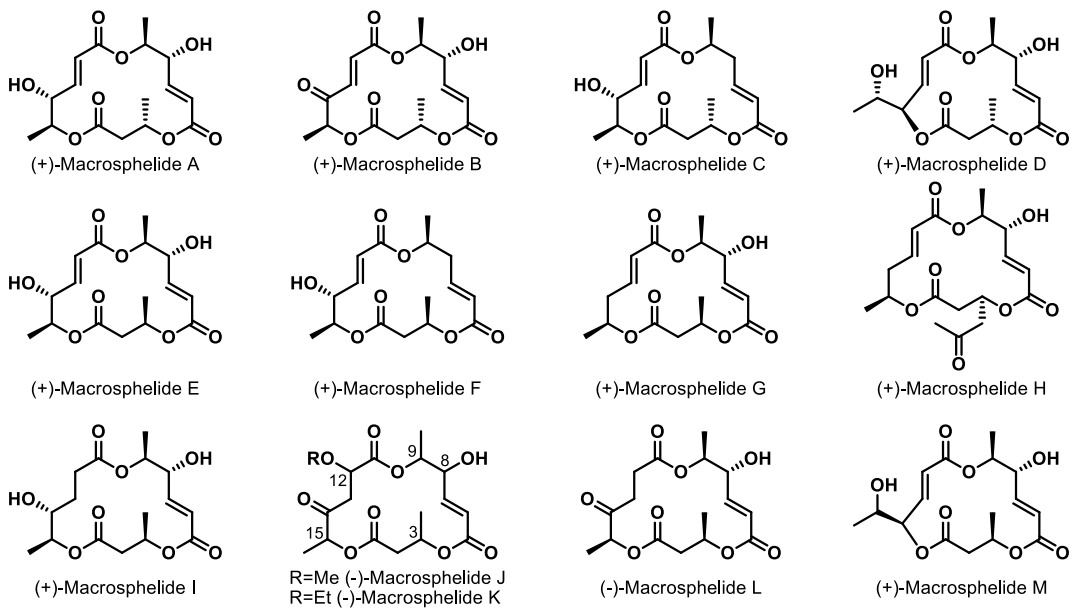


Figure 1. The macrosphelide family

Macrosphelides J and K are structurally unique compared to other macrosphelides.[3c] Notably, they possess a γ-keto-α-alkoxy ester moiety, which could be a challenge late in the total synthesis because the alkoxy unit is readily eliminated to form a favored conjugated system.[8] In this work, the first total syntheses of (–)-macrosphelides J (**1**) and K (**2**) via an isoxazoline-based route,[9] which we recently reported, is described.[5s] Moreover, the stereochemistries of the five stereocenters were elucidated for the first time through these syntheses.[5s] Throughout the synthetic studies, we took special note of the

structural similarities between macrosphelide B and macrosphelides J and K.[5p] With the assistance of a molecular modeling study, one isomer was rationally deduced from thirty-two possible diastereomers. In this paper, we provide a full account of the structural elucidation of (–)-macrosphelides J and K through total synthesis.

RESULT AND DISCUSSION

Structural prediction of (–)-macrosphelides J and K

Unlike all other macrosphelide isotypes, macrosphelides J and K possess an oxygenated C-12 carbon (Figure 2). Based on the common framework of this family, it was envisioned that macrosphelides J and K would be derived from conjugated addition process of C-12=C-13 alkene moiety of mother macrosphelide molecule. Actually this type of biological conjugated addition, as metabolism or small molecule-protein interaction or other processes *in vivo*, is prevailing in bioactive natural product.[10] Interesting was all of other macrosphelide molecules favor conjugated addition at C-13 position except for macrosphelide B which has C-14 ketone moiety to stay C-12 electron deficient. This hypothesis made to deduce absolute configuration of other chiral centers in macrosphelides J and K as identical as those in macrosphelide B, except for C-12 chiral center. It also meant, instead of 32 possible stereoisomers, just 2 suspicious stereoisomers were necessary to confirm our hypothesis and full structure of natural product macrosphelides J and K.

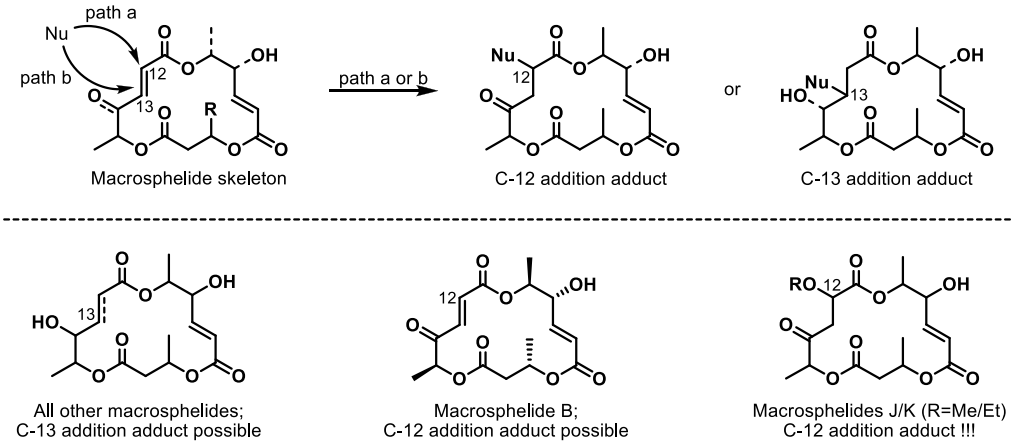


Figure 2. Conjugated addition to macrosphelides J and K from other macrosphelide

In addition, a preliminary molecular modeling study revealed that addition of the alkoxy unit to the γ-keto-*trans*-α,β-unsaturated ester moiety from the α-face was favored (Figure 3).[11] The two axial methyl substituents may hinder attack from the β-face.

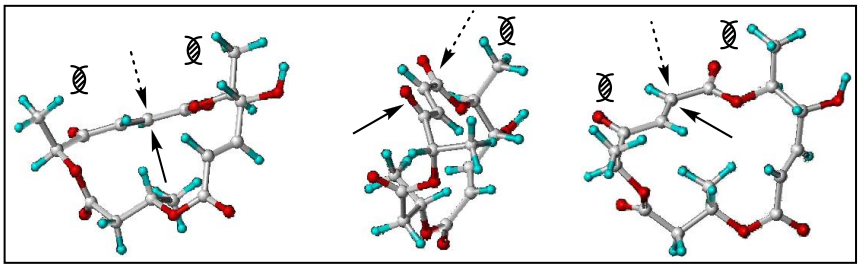
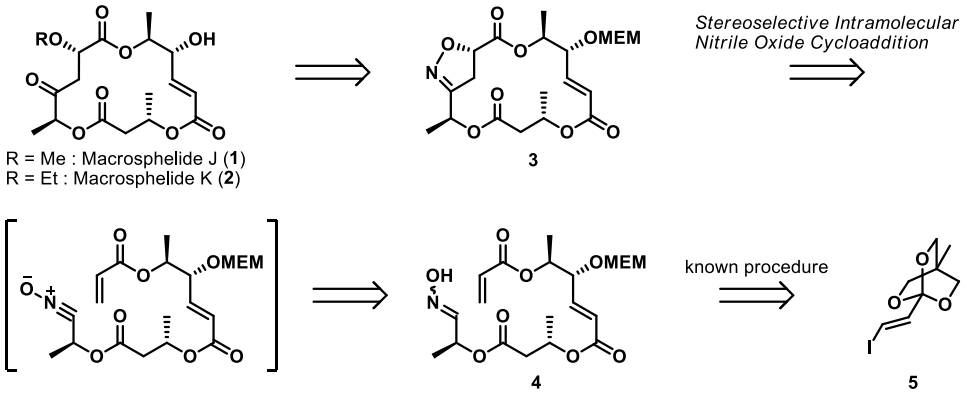


Figure 3. Preliminary molecular modeling shown from different angles

We then commenced the syntheses of predicted structures **1** and **2** to confirm the structures of macrosphelides J and K, respectively. The syntheses of the C-12 epimers of **1** and **2** were also carried out to confirm our hypothesis regarding facial selectivity on C-12 carbon.

*Synthetic strategy for **1** and **2***

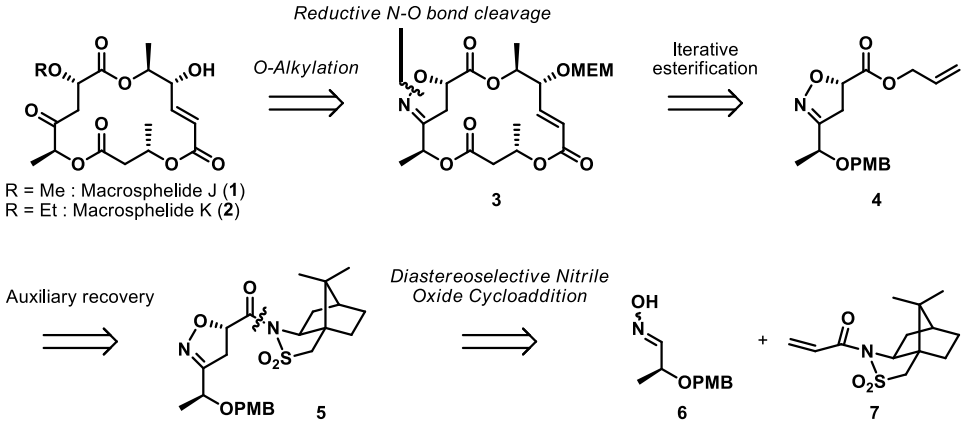
The synthetic strategy for **1** and **2** is illustrated in Scheme 1. Our previous synthetic strategy for (+)-macrosphelide B was employed for the initial synthetic approach because of the structural similarities between the compounds.[5o,r] An intramolecular olefin-nitrile oxide cycloaddition (INOC) was utilized for the key macrocyclization step in the synthesis of (+)-macrosphelide B. In this particular case, the diastereoselectivity of the INOC was not crucial for the synthesis of (+)-macrosphelide B because the newly formed stereogenic center is not present in the natural product. However, the moderate diastereoselectivity of the INOC was not sufficient for stereoselective introduction of the C-12 alkoxy group in the syntheses of (–)-macrosphelides J and K.[3c] We extensively investigated other reaction conditions to increase the stereoselectivity of the INOC, including utilization of a metal catalyst[12] or a phase transfer catalyst (PTC). Sufficiently high stereoselectivities were not obtained in spite of isolating the isoxazoline products in high yields.[13] Therefore, alternative routes for the stereoselective introduction of the alkoxy unit were investigated.



Scheme 1. Initial synthetic approach for macrosphelides J and K

*Revised synthetic strategy for **1** and **2***

We intended to maximize the diastereoselectivity by performing the intramolecular cycloaddition at an early stage in the syntheses of macrosphelides J and K. As shown in Scheme 2, the revised synthetic strategy for macrosphelides J and K focused on the stereoselective elaboration of a sensitive β-alkoxy ketone.[5s] The C-12 alkoxy group would be installed in a high diastereoselective procedure though reductive *N*-*O* bond cleavage of the isoxazoline, which would be prepared by a chiral auxiliary-assisted cycloaddition[14] and subsequent *O*-alkylation of the resulting secondary alcohol.

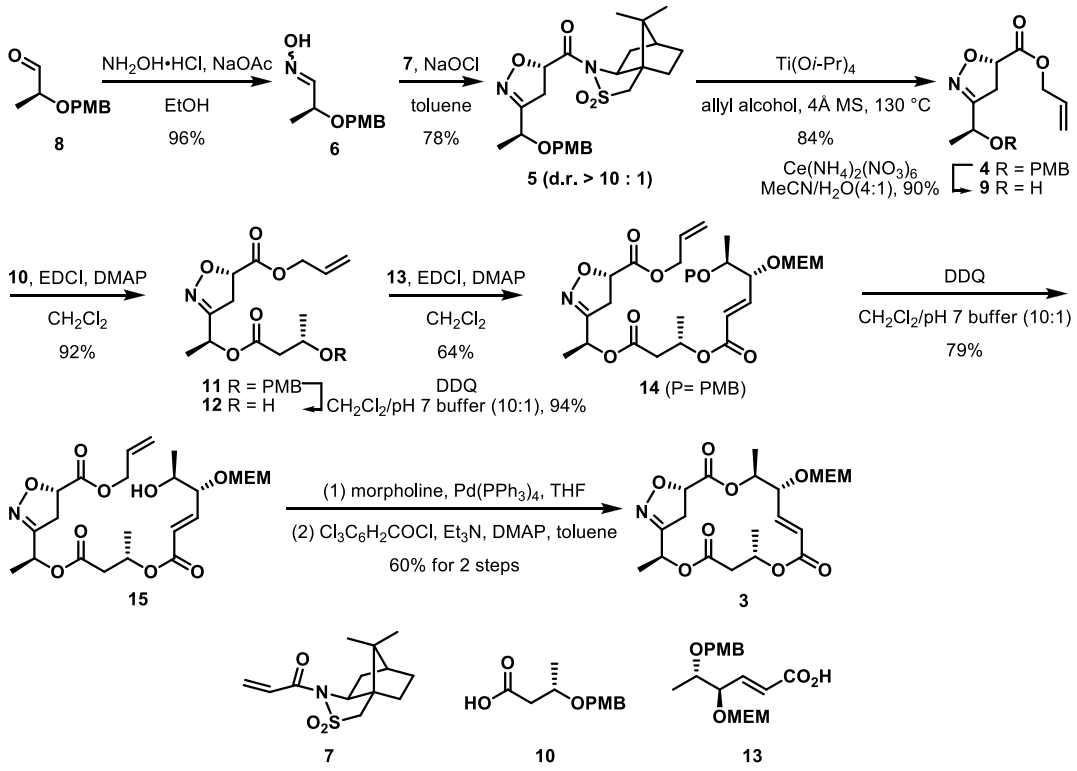


Scheme 2. Revised synthetic strategy

*Preparation of the isoxazoline intermediate **3***

Preparation of isoxazoline intermediate **3** is outlined in Scheme 3. The known aldehyde **8**[15] was condensed with hydroxylamine hydrochloride to afford oxime **6**.[16] The key intermolecular cycloaddition of oxime **6** and acrylate **7**[17] in the presence of aqueous NaOCl afforded isoxazoline **5** in 78% yield with high diastereoselectivity (>10:1).[14b] Only the desired regioisomer was observed. Upon reaction of

isoxazoline **5** with excess allyl alcohol in the presence of Ti(O*i*-Pr)$_4$, the desired ester **4** was obtained, and the sultam auxiliary could be recovered in 90% yield.[18] Diester **11** was obtained by PMB deprotection of **4** and esterification of the resulting alcohol with acid **10**. The lactonization precursor **15** was conveniently prepared by deprotection of **11** and esterification of the resulting alcohol with acid **13**. The deprotection of allyl ester **15** and subsequent macrolactonization of the resulting ω-hydroxy acid under Yamaguchi conditions afforded the 16-membered macrolide **3** in 60% yield for two steps.[19]

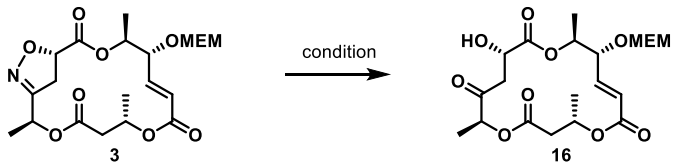


Scheme 3. Preparation of isoxazoline intermediate **3**

Reductive N-O bond cleavage of 3

Having accomplished the diastereoselective synthesis of isoxazoline **3**, we turned our attention to the intricate *N-O* bond cleavage[20] and *O*-alkylation[21] of the labile β-hydroxy ketone. Several metal-mediated reductions have been studied for cleavage of the *N-O* bond of isoxazolines. Numerous reductive conditions were examined to obtained the β-hydroxy ketone unit from the isoxazoline (Table 1). Reaction utilizing Zn, Sm, Cu and Ni (entries 1 - 4)[20a-d] did not result in a recognizable reaction. Treatment of isoxazoline **3** with molybdenum led to complete decomposition of the substrate (entries 5 and 6).[20e,f] Treatment of isoxazoline **3** with Pd/C afforded exclusively the olefin-reduced product in 80% yield (entry 7).[20g] Finally, reduction of isoxazoline **3** was accomplished with Ti(O*i*-Pr)$_4$/EtMgBr (entry 8).[20h] It should be noted that only the supernatant of the Kulinkovich reagent should be used for successful reduction.

Table 1. Reductive *N*-*O* bond cleavage



3 16

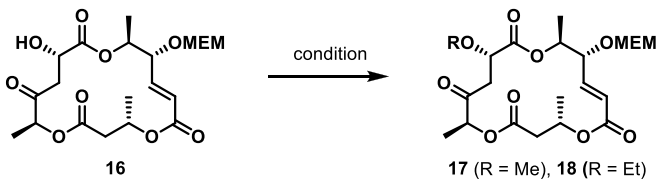
entry	condition	yield
1	Zn, AcOH, Ac_2O	no reaction
2	SmI_2, THF, 0 °C	no reaction
3	$CuSO_4$, EtOH	no reaction
4	Raney nickel[a], H_3BO_3, MeOH/H_2O(5:1)	no reaction
5	$Mo(CO)_6$, MeCN/H_2O(100:1), reflux	degradation
6	$Mo(CO)_3(MeCN)_3$, SiO_2, MeCN, reflux	degradation
7	H_2, Pd/C, MeOH	saturated product
8	Ti(O*i*-Pr)$_4$, EtMgBr, Et_2O	64%

[a] Raney 2400® nickel, Raney 2800® nickel also were used.

O-Alkylation of hydroxy ketone ***16*** *and completion of the syntheses*

For the final stage of the syntheses, *O*-alkylations of the γ-keto-α-hydroxy unit of intermediate **16** were carefully explored because of potential complications resulting from the presence of labile ester moieties (Table 2). Treatment of **16** with KO*t*-Bu or $KHCO_3$ as bases in the presence of MeI/EtI (entries 1 and 2) did not provide the desired product. Treatment of **16** with Ag_2O or NaH led to complete decomposition of the substrate (entries 3 and 4).[21a,b] Other methylations were not successful (entries 5 and 6).[21c,d] *O*-Alkylations of **16** were finally achieved with ROTf/2,6-di-*tert*-butylpyridine (DTBP) (entries 7 and 8).[21e] Interestingly, no epimerization or ester hydrolysis were observed when using DTBP as base.

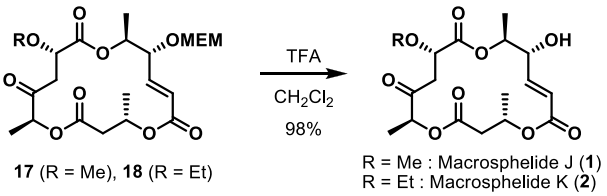
Table 2. *O*-Alkylation



16 **17** (R = Me), **18** (R = Et)

entry	condition	yield
1	MeI or EtI, KO*t*-Bu, THF	no reaction
2	MeI or EtI, $KHCO_3$, THF or DMF, 0 °C	no reaction
3	MeI, Ag_2O, DMF	degradation
4	MeI, NaH, DMF or MeCN	degradation
5	Me_2SO_4, THF	degradation
6	$TMSCHN_2$, CH_2Cl_2/MeOH	degradation
7	MeOTf, DTBP, $CHCl_3$, reflux	70%
8	EtOTf, DTBP, $CHCl_3$, reflux	50%

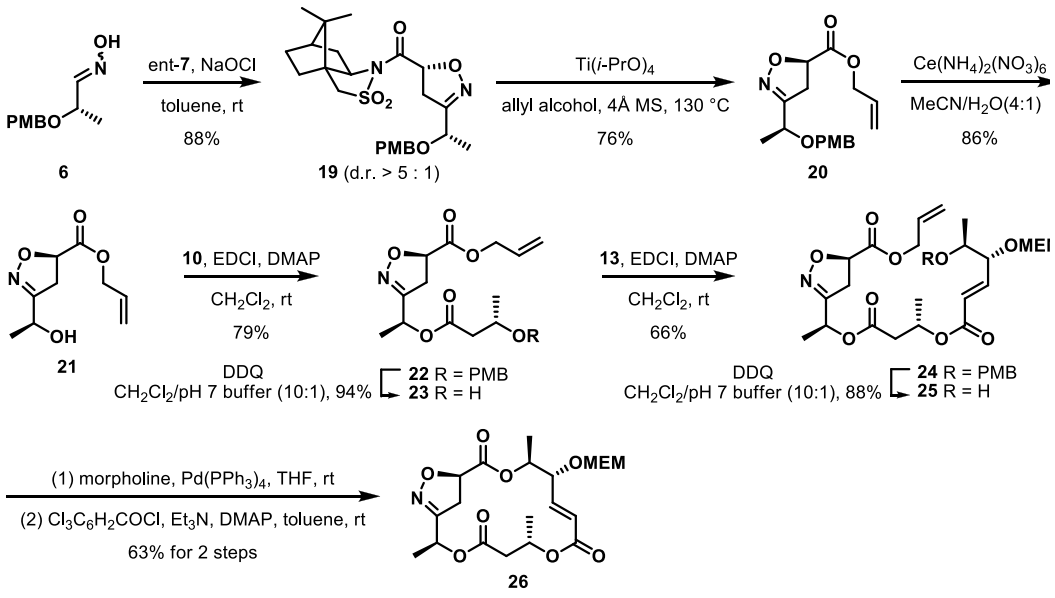
The final deprotection of MEM ethers **17** and **18** proceeded smoothly to give the synthetic (–)-macrosphelides J (**1**) and K (**2**) in excellent yields (Scheme 4). Their spectral data (^{1}H NMR, ^{13}C NMR, HR-MS and IR) and optical rotations were identical to the reported data for the natural products.[5s]



Scheme 4. Completion of the total syntheses of **1** and **2**

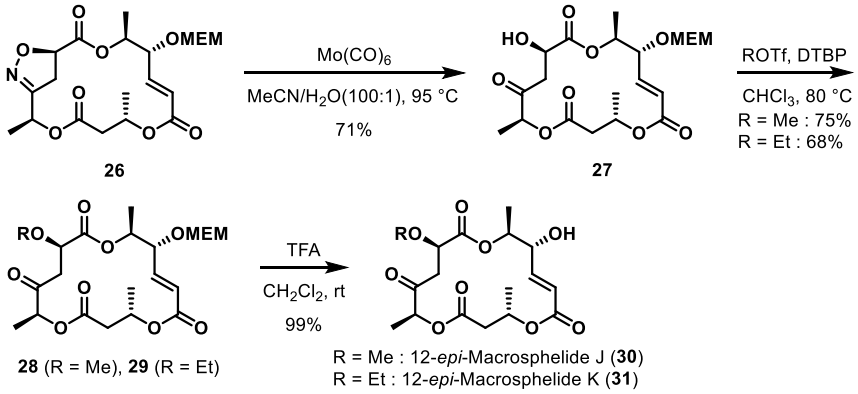
*Total syntheses of 12-epi-macrosphelides J (epi-1, **30**) and K (epi-2, **31**)*

The structures of (–)-macrosphelides J (**1**) and K (**2**) were further confirmed by the total syntheses of 12-*epi*-macrosphelides J (**30**) and K (**31**) (Schemes 5 and 6). The syntheses of 12-*epi*-macrosphelides J and K were achieved via intermolecular olefin-nitrile oxide cycloaddition using *ent*-**7**.[14] The well-established isoxazoline synthesis efficiently provided the C-12 stereocenters. The moderate stereoselectivity (>5:1) is likely due to the mismatch of oxime ether **6** and *ent*-**7** in the cycloaddition. The 16-membered macrolactone **26** was conveniently prepared in high yield using the previously described procedure.[5s]



Scheme 5. Preparation of 16-membered lactone **26**

With the desired isoxazoline **26** available, transformation of **26** into β-hydroxy ketone **27** was carried out using excess $Mo(CO)_6$.[20e] In the case of substrate **26**, reduction of the Kulinkovich reagent was unsuccessful. Again, the β-hydroxy group of **27** was alkylated with ROTf in the presence of DTBP.[21e] Treatment of the resulting ether intermediates with TFA in CH_2Cl_2 afforded 12-*epi*-macrosphelides J (**30**) and K (**31**). As anticipated, the spectral data for **30** and **31** did not match the reported spectral data for natural macrosphelides J and K. Thus, the absolute configurations of (–)-macrosphelides J (**1**) and K (**2**) were clearly elucidated.

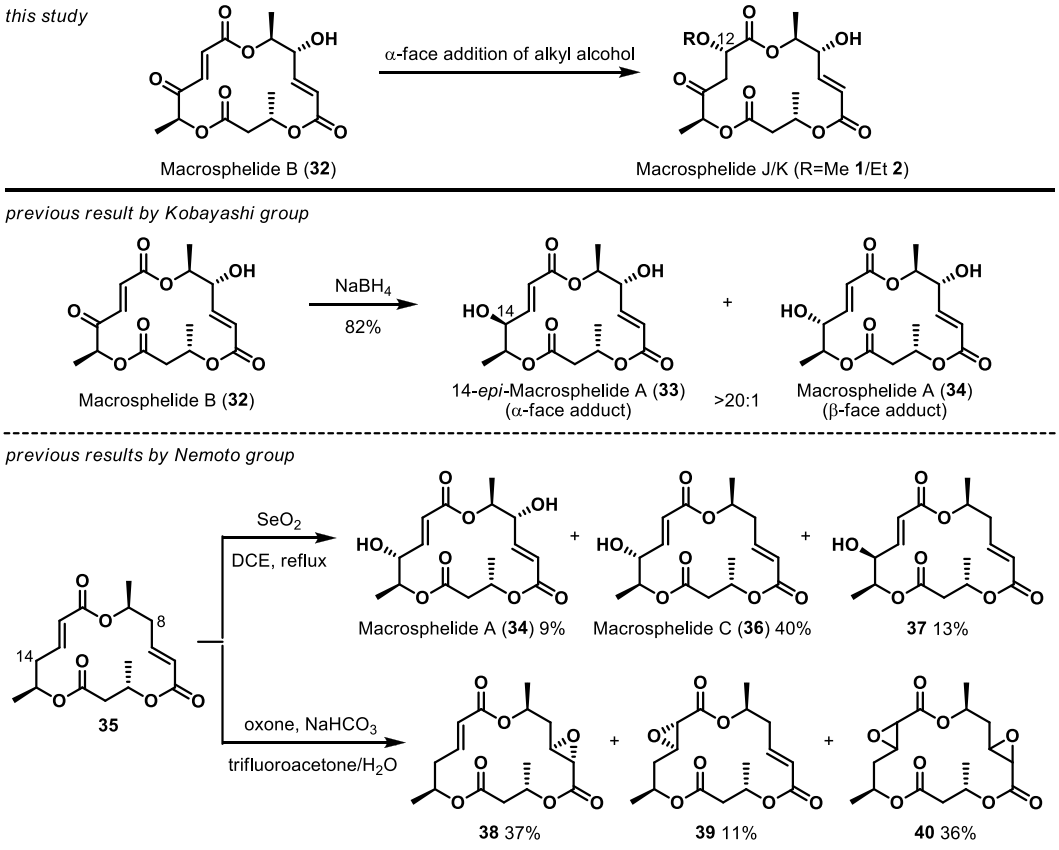


Scheme 6. Completion of the total syntheses of **30** and **31**

Plausible biosynthetic pathway

Hypothesis on biosynthetic pathway of macrosphelides J and K is suggested below (Scheme 7). Because of sterically demanding C-15 and C-9 methyl group, β-face of the C-12=C-13 olefin is thought to be totally hindered. Consequently, conjugate addition of alkoxide or alcohol moiety induces stereoselective formation of C-12 chiral center. This hypothesis matches well with the previous report by Kobayashi group and Nemoto group. During the synthesis of macrosphelide A from macrosphelide B, Kobayashi group tried to induce C-14 hydroxyl group from stereoselective reduction of C-14 ketone group.[5d] Unfortunately, treatment of $NaBH_4$ afforded a trace amount of desired macrosphelide A (**34**), whereas 14-*epi*-macrosphelide A (**33**) was obtained as a major isomer. This unexpected result shows to what extent the β-face of macrosphelide framework is blocked. Similar results were also observed in allylic oxidation strategy for macrosphelide derivatives synthesis. Nemoto group planned to prepare macrosphelide derivatives directly via allylic oxidation of simply substituted macrosphelide skeleton **35**.[6c] After extensive reaction screening and X-ray crystallography analysis of **35**, it was possible to produce macrosphelide A (**34**) and macrosphelide C (**36**) in high yield, along with 14-*epi* macrosphelide C (**37**) as

a minor product. During epoxidation strategy for macrosphelide-derivatives synthesis, similar facial selectivity was also observed. Introduction of epoxide group to the conjugated alkene in macrosphelide skeleton afforded α-face addition product **38** and its isomer **39** as major products. These stereoselectivities are regarded as results from steric hindrance of β-face in macrosphelide skeleton and concomitant nucleophilic addition from α-face, which is more open than β-face. Our study also shows macrosphelides J and K might be prepared from β-face addition of alcohol to the mother molecule **32** as usually observed in reactions of macrosphelide framework. This hypothesis is valuable as it can be applied to further research such as development of more advanced immunomodulator or preparation of chemical probes for target protein identification.



Scheme 7. Structural environment of macrosphelide skeleton and its synthetic features

CONCLUSION

In summary, the convergent syntheses of (–)-macrosphelides J and K from the acrylated camphorsultam **7** were achieved in 12 linear steps. In addition, the predicted stereochemistries of both macrosphelides were confirmed by the total syntheses of natural (–)-macrosphelides J and K as well as their C12-epimers. The key part of the syntheses involved diastereoselective preparation of the isoxazoline intermediates, which

were later transformed into the requisite β-hydroxy ketones. Specifically, intricate *N*-*O* bond cleavage of the isoxazoline intermediates was successfully achieved utilizing the in-situ generated Kulinkovich reagent. Appropriate reaction conditions for *O*-alkylation of the labile β-hydroxy ketones were also found. (12*S*)-Alkoxy-12,13-dihydromacrosphelide B, which seem conjugated addition products of macrosphelide B were proved to be real structure of these natural products. It can be also deduced that conjugated addition of biomolecules, such as proteins, nucleic acids or other constituents, triggers pharmacological pathway of macrosphelide B, as simple alcohol generates macrosphelides J and K. Overall, the structural elucidation of (–)-macrosphelides J and K based on their hypothetical biosynthetic routes greatly facilitates our current work regarding their mode of action.

EXPERIMENTAL

Unless noted otherwise, all starting materials and reagents were obtained from commercial suppliers and were used without further purification. Tetrahydrofuran and Et_2O were distilled from sodium benzophenone ketyl. Dichloromethane, chloroform, triethylamine, acetonitrile and pyridine were freshly distilled from calcium hydride. All solvents used for routine isolation of products and chromatography were reagent grade and glass distilled. Reaction flasks were dried at 100 °C. Air and moisture sensitive reactions were performed under argon atmosphere. Flash column chromatography was performed using silica gel 60 (230-400 mesh, Merck) with the indicated solvents. Thin-layer chromatography was performed using 0.25 mm silica gel plates (Merck). Optical rotations were measured with JASCO DIP-1000 digital polarimeter at ambient temperature using 100 nm cell of 2 mL capacity. Infrared spectra were recorded on a Perkin-Elmer 1710 FT-IR spectrometer. Mass spectra were obtained with VG Trio-2 GC-MS instrument. High resolution mass spectra were obtained with JEOL JMS-AX 505WA instrument. ^{1}H-and ^{13}C-NMR spectra were recorded on either a JEOL JNM-GCX 400 or JEOL JNM-LA 300 spectrometer as solutions in deuteriochloroform ($CDCl_3$). Chemical shifts are expressed in parts per million (ppm, δ) downfield from tetramethylsilane and are referenced to the deuterated solvent ($CHCl_3$). ^{1}H-NMR data were reported in the order of chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet and/or multiple resonance), number of protons, and coupling constant in hertz (Hz).

Preliminary molecular modeling: The study was carried out using SYBYL 6.8. (+)-Macrosphelide B was minimized using Tripos forcefield parameters and the conjugate gradient algorithm with a gradient convergence value of 0.005 kcal/mol Å. Low energy conformation was searched by a systematic conformational search.

*Isoxazoline (**19**).* To a solution of aldoxime **6** (2.80 g, 13.4 mmol) and acrylate *ent*-**7** (3.0 g, 11.1 mmol) in toluene (120 mL) were added aqueous NaOCl (13.2 mL, 22.2 mmol, c.a. 10%) at ambient temperature. The reaction mixture was stirred for 1 h at the same temperature and diluted with H_2O. The aqueous layer was extracted with EtOAc and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc : *n*-hexane = 1 : 2) to afford 4.66 g (88%) of isoxazoline **19** (d.r. > 5 : 1) as pale yellow and foamy solid: $[\alpha]_D^{25}$ -249 (c 0.373, $CHCl_3$); FT-IR (thin film, neat) ν_{max} 2959, 1699, 1612, 1514, 1335 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.23 (d, 2H, *J* = 8.8 Hz), 6.85 (d, 2H, *J* = 8.6 Hz), 5.47 (dd, 1H, *J* = 11.1, 6.9 Hz), 4.44 (q, 1H, *J* = 6.6 Hz), 4.38 (m, 2H), 3.90 (dd, 1H, *J* = 7.7, 5.0 Hz), 3.78 (s, 3H), 3.48 (m, 2H), 3.27 (m, 2H), 2.15 (m, 1H), 2.05 (m, 2H), 1.90 (m, 2H), 1.40 (m, 2H), 1.37 (d, 3H, *J* = 6.6 Hz), 1.17 (s, 3H), 0.96 (s, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 168.3, 159.4, 159.3, 129.6, 129.6, 129.6, 113.8, 113.8, 77.0, 70.6, 69.2, 65.3, 55.2, 52.9, 49.0, 47.8, 44.6, 38.1, 36.8, 32.9, 26.4, 20.9, 19.8, 19.2; LR-MS (FAB+) *m*/*z* 477 ($M+H^+$); HR-MS (FAB+) calcd for $C_{24}H_{33}N_2O_6S$ ($M+H^+$) 477.2059; found 477.2051.

*Allyl ester (**20**).* To a solution of isoxazoline **19** (939 mg, 2.0 mmol) in the presence of 4 Å molecular sieves (493 mg, 250 mg/mmol) in allyl alcohol (39.4 mL, 0.05 M) was added Ti(O*i*-Pr)$_4$ (1.73 mL, 5.9 mmol) at 130 °C. The reaction mixture was vigorously stirred for 1 h at the same temperature and was quenched with saturated aqueous NH_4Cl. The mixture was extracted with EtOAc and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc : *n*-hexane = 1 : 3) to afford 479 mg (76%) of allyl ester **20** as a yellow oil: $[\alpha]_D^{25}$ -187 (c 2.25, $CHCl_3$); FT-IR (thin film, neat) ν_{max} 2937, 1744, 1613, 1514, 1444, 1375 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.22 (d, 2H, *J* = 8.6 Hz), 6.85 (d, 2H, *J* = 8.6 Hz), 5.90 (m, 1H), 5.32 (dd, 1H, *J* = 17.2, 1.5 Hz), 5.25 (dd, 1H, *J* = 10.4, 1.3 Hz), 4.96 (dd, 1H, *J* = 11.0, 7.3 Hz), 4.65 (dt, 2H, *J* = 5.9, 1.2 Hz), 4.45 (q, 1H, *J* = 6.6 Hz), 4.38 (m, 2H), 3.77 (s, 3H), 3.24 (m, 2H), 1.36 (d, 3H, *J* = 6.6 Hz) ; ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 169.6, 159.5, 159.3, 131.2, 129.4, 129.4, 129.4, 119.1, 113.8, 113.8, 77.2, 70.5, 69.3, 66.1, 55.2, 36.9, 19.1 ; LR-MS (FAB+) *m*/*z* 320 ($M+H^+$); HR-MS (FAB+) calcd for $C_{17}H_{22}NO_5$ ($M+H^+$) 320.1498; found 320.1494.

*Alcohol (**21**).* To a solution of allyl ester **20** (3.26 g, 10.2 mmol) in MeCN (120 mL) and H_2O (30 mL) was added ammonium cerium nitrate (8.39 g, 15.3 mmol) at ambient temperature. After stirring for 3 h at the same temperature, the reaction mixture was quenched with H_2O. The aqueous layer was extracted with EtOAc and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc : *n*-hexane = 1 : 1) to afford 1.75 g (86%) of alcohol **21** as a pale yellow oil: $[\alpha]_D^{25}$ -153 (c 1.15, $CHCl_3$); FT-IR (thin film, neat) ν_{max} 3419, 2982, 2938, 1743, 1649, 1438, 1375, 1330 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 5.88 (m, 1H), 5.31

(dd, 1H, *J* = 17.2, 1.1 Hz), 5.24 (dd, 1H, *J* = 10.4, 0.7 Hz), 5.01 (dd, 1H, *J* = 10.6, 7.5 Hz), 4.67 (m, 1H), 4.63 (d, 2H, *J* = 5.9 Hz), 3.31 (m, 2H), 2.92 (s, 1H), 1.39 (d, 3H, *J* = 6.6 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 170.0, 161.3, 131.1, 119.1, 77.4, 66.2, 63.4, 37.6, 20.8; LR-MS (FAB+) *m*/*z* 200 ($M+H^+$); HR-MS (FAB+) calcd for $C_9H_{14}NO_4$ ($M+H^+$) 200.0923; found 200.0918.

*Ester (**22**).* To a solution of alcohol **21** (2.63 g, 13.2 mmol) and acid **10** (4.44 g, 19.8 mmol) in CH_2Cl_2 (200 mL) were added EDCI (5.06 g, 26.4 mmol) and DMAP (3.23 g, 26.4 mmol) at ambient temperature. After stirring for 2 h at the same temperature, the reaction mixture was quenched with H_2O. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc : *n*-hexane = 1 : 3) to afford 4.22 g (79%) of ester **22** as a yellow oil: $[\alpha]_D^{25}$ -101 (c 1.35, $CHCl_3$); FT-IR (thin film, neat) ν_{max} 2937, 1742, 1613, 1514, 1454, 1377 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.19 (d, 2H, *J* = 8.6 Hz), 6.83 (d, 2H, *J* = 8.8 Hz), 5.89 (m, 1H), 5.71 (q, 1H, *J* = 6.6 Hz), 5.32 (dd, 1H, *J* = 17.1, 1.4 Hz), 5.25 (dd, 1H, *J* = 10.4, 1.2 Hz), 4.84 (dd, 1H, *J* = 11.6, 6.8 Hz), 4.63 (d, 2H, *J* = 5.9 Hz), 4.41 (m, 2H), 3.99 (m, 1H), 3.76 (s, 3H), 3.12 (m, 2H), 2.52 (m, 2H), 1.45 (d, 3H, *J* = 6.6 Hz), 1.23 (d, 3H, *J* = 6.1 Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 170.3, 169.4, 159.2, 158.0, 131.2, 130.4, 129.2, 129.2, 119.0, 113.8, 113.8, 77.6, 71.8, 70.6, 66.2, 65.5, 55.2, 42.1, 37.9, 19.6, 18.1; LR-MS (FAB+) *m*/*z* 428 ($M+Na^+$); HR-MS (FAB+) calcd for $C_{21}H_{27}NO_7Na$ ($M+Na^+$) 428.1685; found 428.1673.

*Alcohol (**23**).* To a solution of PMB ether **22** (3.48 g, 8.6 mmol) in CH_2Cl_2 (120 mL) and phosphate buffer solution (12 mL, pH 7.0) was added DDQ (5.83 g, 25.7 mmol) at ambient temperature. The reaction mixture was stirred for 3 h and diluted with CH_2Cl_2. The mixture was filtered under reduced pressure and washed with H_2O. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc : *n*-hexane = 1 : 1) to afford 2.30 g (94%) of alcohol **23** as a yellow oil: $[\alpha]_D^{25}$ -127 (c 1.39, $CHCl_3$); FT-IR (thin film, neat) ν_{max} 3444, 3088, 2977, 2938, 1739, 1649, 1453, 1377 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 5.86 (m, 1H), 5.68 (q, 1H, *J* = 6.7 Hz), 5.29 (dd, 1H, *J* = 17.1, 1.4 Hz), 5.22 (dd, 1H, *J* = 10.4, 1.2 Hz), 5.00 (dd, 1H, *J* = 11.2, 7.3 Hz), 4.62 (dt, 2H, *J* = 5.9, 1.3 Hz), 4.15 (m, 1H), 3.23 (m, 2H), 2.85 (s, 1H), 2.41 (m, 2H), 1.45 (d, 3H, *J* = 6.6 Hz), 1.18 (d, 3H, *J* = 6.4 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 171.4, 169.3, 157.6, 131.1, 119.0, 77.7, 66.2, 65.6, 64.3, 43.0, 38.0, 22.6, 17.9; LR-MS (FAB+) *m*/*z* 286 ($M+H^+$); HR-MS (FAB+) calcd for $C_{13}H_{20}NO_6$ ($M+H^+$) 286.1291; found 286.1286.

*Ester (**24**).* To a solution of alcohol **23** (1.02 g, 3.6 mmol) and acid **13** (1.78 g, 5.0 mmol) in CH_2Cl_2 (50 mL) were added EDCI (1.37 g, 7.16 mmol) and DMAP (875.0 g, 7.16 mmol) at ambient temperature. After stirring for 3 h at the same temperature, the reaction mixture was quenched with H_2O and the

aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc : *n*-hexane = 1 : 1) to afford 1.47 g (66%) of ester **24** as a yellow oil: $[\alpha]_D^{25}$ -80.0 (c 0.347, $CHCl_3$); FT-IR (thin film, neat) ν_{max} 2937, 1743, 1658, 1613, 1514, 1454, 1378 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.21 (d, 2H, *J* = 8.7 Hz), 6.85 (m, 1H), 6.84 (d, 2H, *J* = 8.4 Hz), 5.98 (dd, 1H, *J* = 16.1, 1.4 Hz), 5.90 (m, 1H), 5.68 (q, 1H, *J* = 6.5 Hz), 5.33 (dd, 1H, *J* = 17.1, 1.5 Hz), 5.33 (m, 1H), 5.26 (dd, 1H, *J* = 10.2, 0.9 Hz), 5.01 (dd, 1H, *J* = 11.4, 7.2 Hz), 4.71 (m, 2H), 4.66 (dt, 2H, *J* = 6.0, 1.2 Hz), 4.48 (s, 2H), 4.30 (m, 1H), 3.77 (s, 3H), 3.74 (m, 1H), 3.60 (m, 2H), 3.47 (m, 2H), 3.34 (s, 3H), 3.21 (m, 2H), 2.62 (m, 2H), 1.43 (d, 3H, *J* = 6.9 Hz), 1.32 (d, 3H, *J* = 6.6 Hz), 1.15 (d, 3H, *J* = 6.6 Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 169.4, 168.9, 165.0, 159.1, 157.5, 145.7, 131.2, 130.4, 129.2, 129.2, 123.0, 119.2, 113.7, 113.7, 94.0, 77.8, 77.6, 77.2, 76.0, 71.6, 70.8, 67.2, 66.3, 65.8, 59.0, 55.2, 40.8, 37.9, 19.9, 18.0, 15.6; LR-MS (FAB+) *m*/*z* 622 ($M+H^+$); HR-MS (FAB+) calcd for $C_{31}H_{44}NO_{12}$ ($M+H^+$) 622.2864; found 622.2869.

*Alcohol (**25**).* To a solution of PMB ether **24** (2.72 g, 4.4 mmol) in CH_2Cl_2 (80 mL) and phosphate buffer solution (8 mL, pH 7.0) was added DDQ (2.97 g, 13.1 mmol) at ambient temperature. The reaction mixture was stirred for 2 h, diluted with CH_2Cl_2 and filtered under reduced pressure. The organic layer was washed with H_2O and aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc : *n*-hexane = 3 : 2) to afford 1.93 g (88%) of alcohol **25** as a yellow oil: $[\alpha]_D^{25}$ -98.2 (c 0.747, $CHCl_3$); FT-IR (thin film, neat) ν_{max} 3464, 2929, 1741, 1652, 1453, 1376 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 6.83 (dd, 1H, *J* = 15.8, 6.2 Hz), 5.99 (dd, 1H, *J* = 15.8, 1.3 Hz), 5.90 (m, 1H), 5.69 (q, 1H, *J* = 6.5 Hz), 5.33 (d, 1H, *J* = 15.8 Hz), 5.31 (m, 1H), 5.26 (d, 1H, *J* = 10.4 Hz), 5.03 (dd, 1H, *J* = 11.2, 7.1 Hz), 4.72 (m, 2H), 4.66 (d, 2H, *J* = 5.7 Hz), 4.19 (m, 1H), 3.92 (m, 1H), 3.73 (m, 2H), 3.53 (t, 2H, *J* = 4.4 Hz), 3.36 (s, 3H), 3.24 (m, 2H), 2.62 (m, 2H), 2.20 (s, 1H), 1.45 (d, 3H, *J* = 6.6 Hz), 1.31 (d, 3H, *J* = 6.2 Hz), 1.12 (d, 3H, *J* = 6.6 Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 169.4, 169.0, 164.9, 157.5, 144.4, 131.2, 123.6, 119.3, 94.4, 80.8, 77.7, 71.6, 68.9, 67.5, 67.3, 66.4, 65.8, 59.0, 40.8, 38.0, 19.9, 18.0, 17.7; LR-MS (FAB+) *m*/*z* 502 ($M+H^+$); HR-MS (FAB+) calcd for $C_{23}H_{36}NO_{11}$ ($M+H^+$) 502.2288; found 502.2299.

*16-Membered lactone (**26**).* To a solution of alcohol **25** (91.2 mg, 0.2 mmol) in THF (3 mL) were added $Pd(PPh_3)_4$ (63.1 mg, 0.1 mmol) and morpholine (32 μL, 40 μmol) at ambient temperature. The mixture was stirred for 12 h at the same temperature, quenched with 1*N* HCl and extracted with EtOAc three times. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude acid was used for next step without further purification. To a solution of above acid in toluene (4 mL) were added Et_3N (166 μL, 1.1 mmol) and 2,4,6-trichlorobenzoyl chloride (142 μL, 0.9 mmol) at 0 °C. The mixture was warmed to ambient temperature and stirred for 2 h before removing THF under reduced

pressure. The residue was solved in toluene (30 mL) and the mixture was added slowly to a rapidly stirred solution of DMAP (556 mg, 4.6 mmol) in toluene (40 mL). The reaction mixture was stirred for 24 h and quenched with H_2O. The reaction mixture was extracted with EtOAc and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc : *n*-hexane = 2 : 1) to afford 80.7 mg (63%) of ester **26** as a pale yellow oil.

*β-Hydroxy ketone (**27**).* To a solution of macrolactone **26** (8.0 mg, 18 μmol) in MeCN (1 mL) and H_2O (10 μL) was added $Mo(CO)_6$ (47.8 mg, 180 μmol) at ambient temperature. The reaction mixture was refluxed for 12 h and cooled to room temperature. The reaction mixture was filtered through a pad of silica gel and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc : *n*-hexane = 3 : 2) to afford 5.8 mg (71%) of ester **27** as a pale yellow oil: $[\alpha]_D^{20}$ -30.5 (c 0.220, $CHCl_3$); FT-IR (thin film, neat) ν_{max} 3397, 2924, 2853, 1736, 1541, 1459 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 6.75 (dd, 1H, *J* = 15.7, 6.6 Hz), 6.02 (d, 1H, *J* = 15.9 Hz), 5.41 (m, 1H), 5.05 (q, 1H, *J* = 7.0 Hz), 4.87 (m, 1H), 4.71 (m, 2H), 4.56 (dd, 1H, *J* = 7.5, 1.9 Hz), 4.28 (t, 1H, *J* = 6.9 Hz), 3.75 (m, 1H), 3.64 (m, 1H), 3.52 (t, 2H, *J* = 4.5 Hz), 3.36 (s, 3H), 2.93 (dd, 1H, *J* = 18.2, 7.8 Hz), 2.72 (dd, 1H, *J* = 15.4, 10.8 Hz), 2.61 (m, 2H), 1.43 (d, 3H, *J* = 6.4 Hz), 1.38 (d, 3H, *J* = 7.0 Hz), 1.34 (d, 3H, *J* = 6.3 Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 205.4, 171.7, 170.3, 164.5, 144.2, 124.4, 94.0, 77.2, 75.1, 73.4, 71.6, 68.0, 67.5, 66.9, 59.0, 42.0, 40.8, 19.9, 17.3, 15.7; LR-MS (FAB+) *m*/*z* 469 ($M+Na^+$); HR-MS (FAB+) calcd for $C_{20}H_{30}O_{11}Na$ ($M+Na^+$) 469.1686; found 469.1685.

*β-Methoxy ketone (**28**).* To a solution of β-hydroxy ketone **27** (9.0 mg, 20 μmol) in $CHCl_3$ (1 mL) were added 2,6-di-*t*-butylpyridine (136 μL, 0.6 mmol) and MeOTf (67 μL, 0.6 mmol) at ambient temperature. The mixture was warmed to 80 °C and stirred for 12 h. The mixture was quenched with saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc : *n*-hexane = 1 : 1) to afford 7 mg (75%) of β-methoxy ketone **28** as a colorless oil: $[\alpha]_D^{20}$ -34.6 (c 0.067, CH_3OH); FT-IR (thin film, neat) ν_{max} 2927, 2855, 1739, 1660, 1453, 1373 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 6.71 (dd, 1H, *J* = 15.9, 7.9 Hz), 6.00 (d, 1H, *J* = 15.9 Hz), 5.38 (m, 1H), 4.93 (q, 1H, *J* = 6.4 Hz), 4.90 (m, 1H), 4.70 (m, 2H), 4.28 (dd, 1H, *J* = 10.3, 1.7 Hz), 4.18 (t, 1H, *J* = 8.5 Hz), 3.69 (m, 2H), 3.52 (t, 2H, *J* = 4.6 Hz), 3.36 (s, 3H), 3.34 (s, 3H), 2.90 (dd, 1H, *J* = 17.6, 10.3 Hz), 2.72 (dd, 1H, *J* = 14.7, 11.2 Hz), 2.54 (dd, 1H, *J* = 14.7, 2.2 Hz), 2.21 (dd, 1H, *J* = 17.6, 1.6 Hz), 1.44 (d, 3H, *J* = 6.4 Hz), 1.36 (d, 3H, *J* = 7.1 Hz), 1.33 (d, 3H, J = 6.3 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 204.3, 171.0, 171.0, 164.1, 145.5, 124.9, 93.9, 78.0, 71.5, 71.1, 68.8, 67.4, 59.0, 58.7, 51.7, 41.1, 40.1, 29.7, 20.1, 17.5, 15.7; LR-MS (FAB+) *m*/*z* 461 ($M+H^+$); HR-MS (FAB+) calcd for $C_{21}H_{33}O_{11}$ ($M+H^+$) 461.2023; found 461.1997.

*β-Ethoxy ketone (**29**).* To a solution of β-hydroxy ketone **27** (12 mg, 26 μmol) in $CHCl_3$ (1 mL) were added 2,6-di-*t*-butylpyridine (0.18 mL, 0.9 mmol) and EtOTf (0.10 mL, 0.8 mmol) at ambient temperature. The mixture was warmed to 80 °C and stirred for 12 h. The mixture was quenched with saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc : *n*-hexane = 1 : 1) to afford 8 mg (68%) of β-ethoxy ketone **29** as a colorless oil: $[\alpha]_D^{25}$ -34.9 (c 1.67, $CHCl_3$); FT-IR (thin film, neat) ν_{max} 2978, 2925, 2855, 1739, 1662, 1452, 1371 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 6.71 (dd, 1H, *J* = 15.9, 8.0 Hz), 6.00 (d, 1H, *J* = 15.7 Hz), 5.37 (m, 1H), 4.91 (m, 1H), 4.86 (q, 1H, *J* = 7.2 Hz), 4.70 (q, 2H, *J* = 7.2 Hz), 4.36 (dd, 1H, *J* = 10.4, 1.7 Hz), 4.19 (t, 1H, *J* = 8.6 Hz), 3.68 (m, 2H), 3.52 (t, 2H, *J* = 4.8 Hz), 3.52 (m, 2H), 3.36 (s, 3H), 2.92 (dd, 1H, *J* = 17.3, 10.5 Hz), 2.72 (dd, 1H, *J* = 14.7, 11.2 Hz), 2.53 (dd, 1H, *J* = 14.6, 2.2 Hz), 2.15 (dd, 1H, *J* = 17.3, 1.8 Hz), 1.42 (d, 3H, *J* = 6.2 Hz), 1.36 (d, 3H, *J* = 7.1 Hz), 1.32 (d, 3H, *J* = 6.2 Hz), 1.13 (t, 3H, *J* = 7.1 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 204.5, 171.4, 171.1, 164.1, 145.5, 124.9, 93.9, 78.0, 74.5, 71.5, 71.1, 68.8, 67.4, 66.7, 59.0, 41.1, 39.9, 30.2, 20.1, 17.5, 15.7, 15.0; LR-MS (FAB+) *m*/*z* 475 ($M+H^+$); HR-MS (FAB+) calcd for $C_{22}H_{35}O_{11}$ ($M+H^+$) 475.2179; found 475.2150.

*12-epi-Macrosphelide J (**30**).* To a solution of β-methoxy ketone **28** (7 mg, 15 μmol) in CH_2Cl_2 (0.5 mL) was added trifluoroacetic acid (0.5 mL) at ambient temperature. After stirring for 12 h, the reaction mixture was concentrated *in vacuo* and purified by flash column chromatography on silica gel (EtOAc : *n*-hexane = 1 : 1) to afford 6 mg (99%) of 12-*epi*-macrosphelide J **30** as a colorless oil: $[\alpha]_D^{24}$ 10.9 (c 0.373, $CHCl_3$); FT-IR (thin film, neat) ν_{max} 3471, 2927, 2854, 1737, 1662, 1452, 1375, 1336 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 6.83 (dd, 1H, *J* = 15.8, 5.5 Hz), 6.04 (dd, 1H, *J* = 15.8, 1.5 Hz), 5.42 (m, 1H), 4.93 (q, 1H, *J* = 6.9 Hz), 4.87 (m, 1H), 4.26 (m, 1H), 4.25 (dd, 1H, *J* = 10.1, 1.8 Hz), 3.34 (s, 3H), 2.95 (dd, 1H, *J* = 17.6, 10.3 Hz), 2.76 (dd, 1H, *J* = 15.3, 11.1 Hz), 2.66 (s, 1H), 2.57 (dd, 1H, *J* = 15.3, 2.5 Hz), 2.21 (dd, 1H, *J* = 17.6, 1.8 Hz), 1.48 (d, 3H, *J* = 6.4 Hz), 1.36 (d, 3H, *J* = 7.1 Hz), 1.33 (d, 3H, *J* = 6.6 Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 204.3, 172.0, 170.8, 164.3, 145.4, 123.2, 76.2, 76.1, 74.8, 74.3, 68.5, 58.7, 40.9, 40.0, 20.0, 17.7, 15.8; LR-MS (FAB+) *m*/*z* 373 ($M+H^+$); HR-MS (FAB+) calcd for $C_{17}H_{25}O_9$ ($M+H^+$) 373.1499; found 373.1511.

*12-epi-Macrosphelide K (**31**).* To a solution of β-ethoxy ketone **29** (3 mg, 7 μmol) in CH_2Cl_2 (0.5 mL) was added trifluoroacetic acid (0.5 mL) at ambient temperature. After stirring for 12 h, the reaction mixture was concentrated *in vacuo* and purified by flash column chromatography on silica gel (EtOAc : *n*-hexane = 1 : 1) to afford 3 mg (99%) of 12-*epi*-macrosphelide K **31** as a colorless oil: $[\alpha]_D^{20}$ 31.6 (c 0.140, CH_3OH); FT-IR (thin film, neat) ν_{max} 3471, 2980, 2933, 2877, 2856, 1737, 1663, 1450, 1373, 1335 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 6.82 (dd, 1H, *J* = 15.6, 5.5 Hz), 6.05 (dd, 1H, *J* = 15.7, 1.0 Hz), 5.42

(m, 1H), 4.90 (q, 1H, *J* = 7.1 Hz), 4.85 (m, 1H), 4.34 (dd, 1H, *J* = 10.4, 1.6 Hz), 4.25 (m, 1H), 3.49 (m, 2H), 2.97 (dd, 1H, *J* = 17.3, 10.4 Hz), 2.77 (dd, 1H, *J* = 15.2, 11.4 Hz), 2.66 (s, 1H), 2.56 (dd, 1H, *J* = 15.2, 2.2 Hz), 2.16 (dd, 1H, *J* = 17.2, 1.7 Hz), 1.47 (d, 3H, *J* = 6.4 Hz), 1.36 (d, 3H, *J* = 7.5 Hz), 1.33 (d, 3H, *J* = 7.0 Hz), 1.13 (t, 3H, *J* = 7.1 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 204.5, 172.5, 170.9, 164.2, 145.3, 123.2, 76.3, 75.0, 74.6, 74.4, 68.5, 66.8, 40.8, 39.9, 20.0, 17.7, 15.7, 15.0; LR-MS (FAB+) *m*/*z* 387 ($M+H^+$); HR-MS (FAB+) calcd for $C_{18}H_{27}O_9$ ($M+H^+$) 387.1655; found 387.1674.

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