Furan Ring Oxidation Strategy for the Synthesis of Macrosphelides A and B

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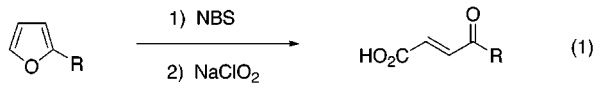
By using the convenient protocol for conversion of 2-substituted furans into 4-oxo-2-alkenoic acids ((i) NBS, (ii) $NaClO_2$), macrosphelide B (**2**) was synthesized from furyl alcohol **5** (>98% ee) and acid **6** (99% ee). The protocol was first applied to the PMB ether of **5** to afford acid **13b**. On the other hand, DCC condensation of acid **6** with **5** gave **16** after deprotection of the TBS group. Condensation was again carried out between **13b** and **16** to furnish the key ketone **17**, which upon reduction with $Zn(BH_4)_2$ afforded anti alcohol **18** stereoselectively (15:1). After protection/deprotection steps, the furan **18** was converted to seco acid **3** by using the furan oxidation protocol mentioned above, and lactonization of **3** with $Cl_3C_6H_2COCl$, Et_3N, and DMAP afforded **22** (MOM ether of **2**), which upon deprotection with TFA produced **2**. Transformation of **22** to macrosphelide A (**1**) was then investigated. Although the chelation-controlled reduction of **22** should afford the desired anti alcohol **24**, $Zn(BH_4)_2$ at <−90 °C gave a 2∼1:1 mixture of anti/syn alcohols. On the contrary, reduction with $NaBH_4$ in MeOH at −15 °C produced the syn isomer **23** with >10:1 diastereoselectivity. Mitsunobu inversion of the resulting C(14)-hydroxyl group and deprotection of the MOM group with TFA afforded **1**. Similarly, reduction of **2** with $NaBH_4$ afforded the C(14)-epimer of **1** stereoselectively. The observed stereoselectivity in the reductions of **22** and **2** could be explained on the basis of computer-assisted calculation, which showed presence of the low-energy conformers responsible for the stereoselective reduction. In addition, conversion of **2** to **1** was established, for the first time.

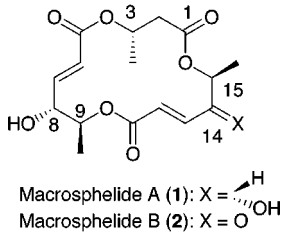
Introduction

Recently, we published a convenient two-step transformation of 2-alkylfurans into 4-oxo-2-alkenoic acids (eq 1).[1] This oxidative conversion proceeds under mild conditions and is compatible with functional groups such as carbonyl groups, acid labile protecting groups, and a free hydroxyl group at a distal position. In addition to these synthetic advantages, furans with a substituent at C(2) are prepared by several methods quite easily. Consequently, there is no doubt that this transformation provides an attractive method for the synthesis of biologically important molecules with 4-oxo- as well as 4-hydroxy-2-alkenoic acid moieties.[2]



(1)

Among these molecules are macrosphelides A and B, produced by *Microsphaeropsis* sp. FO-5050, in which 4,5-dihydroxy- and 5-hydroxy-4-oxo-2-alkenoic acid moieties constitute the major part of the lactone backbones.[3] These



natural products strongly inhibit the adhesion of human-leukemia HL-60 cells to human-umbilical-vein endothelial cells, while they do not inhibit the growth of other mammalian cell lines or microorganisms.[3a] Accordingly, macrosphelides A and B would serve as valuable leads for development of a new drug against cancer,[4] and hence, a synthetic method for producing these molecules and their analogues is urgently required.

Recently, Omura and Smith published a total synthesis of **1**,[5] in which the vicinal hydroxyl groups were installed on the sorbic ester by using AD-mix-α[6] with 85% ee[7] and

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(1) Kobayashi, Y.; Nakano, M.; Kumar, G. B.; Kishihara, K. *J. Org. Chem.* **1998**, *63*, 7505−7515.

(2) (a) Boeckman, R. H., Jr.; Goldstein, S. W. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; Wiley: New York, 1988; Vol. 7, Chapter 1. (b) Asaoka, M.; Takei, H. *J. Synth. Org. Chem. Jpn.* **1986**, *44*, 819−828.

(3) (a) Hayashi, M.; Kim, Y.-P.; Hiraoka, H.; Natori, M.; Takamatsu, S.; Kawakubo, T.; Masuma, R.; Komiyama, K.; Omura, S. *J. Antibiot.* **1995**, *48*, 1435−1439. (b) Takamatsu, S.; Kim, Y.-P.; Hayashi, M.; Hiraoka, H.; Natori, M.; Komiyama, K.; Omura, S. *J. Antibiot.* **1996**, *49*, 95−98.

(4) (a) Omura, S.; Shiomi, K. *Baiosaiensu to Indasutori* **1996**, *54*, 633−635; *Chem. Abstr.* **1996**, *125*, 299445v. (b) Ishizuka, M. *Nippon Nogei Kagaku Kaishi* **1997**, *71*, 527−529; *Chem. Abstr.* **1997**, *127*, 12893x.

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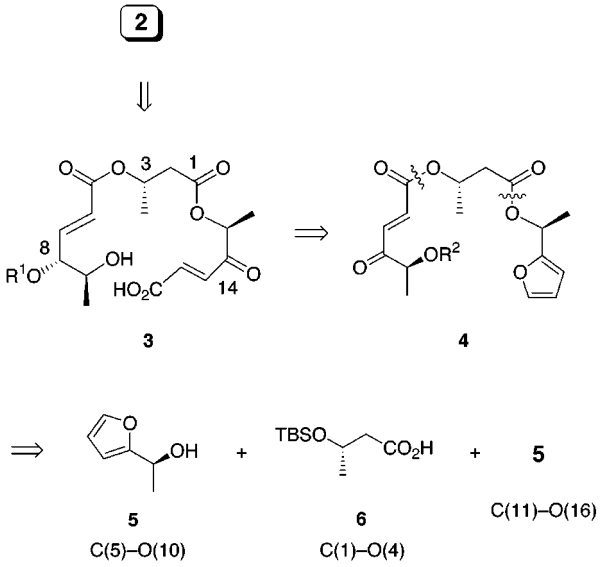
Scheme 1. Retrosynthesis of Macrosphelide B (2)

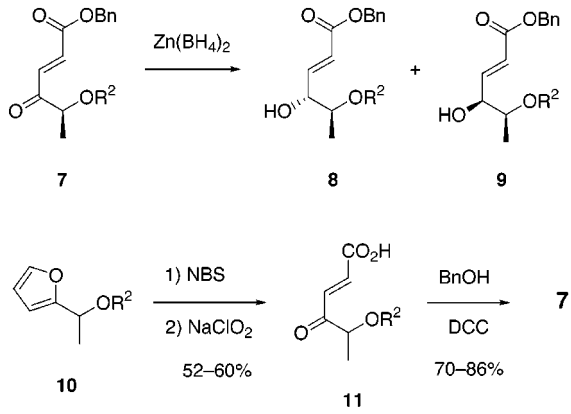


the subsequent inversion of one of the hydroxyl groups. They also attempted conversion of **1** into **2** by PDC oxidation, which resulted in rather low regioselectivity and efficiency. These results prompted us to conceive an alternative route involving a synthesis of **2** and subsequent hydride reduction of the intermediate to furnish **1**. Since **2** possesses one less chiral center than **1**, synthesis of **2** would be accomplished more easily than **1**. Moreover, we expected high diastereoselectivity in the reduction of **2** due to the conformational bias provided by the macrocycle, producing either the desired (14*R*) alcohol or the (14*S*) isomer. In practice, this idea has proved to be correct as was reported previously in a communication.[8] Herein, we disclose the synthesis of **1** and **2** in detail. In addition, the conversion of **2** to **1** is presented, and the stereoselective reduction of the macrocyclic ketones is discussed with the stable conformers obtained by a computer-assisted calculation.

Results and Discussion

Synthesis of Macrosphelide B. Keeping the furan methodology in mind, furan **4** was proposed as the key intermediate for synthesis of macrosphelide B (**2**) (Scheme 1) and was dissected into the two starting compounds **5** and **6**, both of which are easily produced by several methods. Furyl alcohol **5** serves as the C(5)−O(10) and C(11)−O(16) moieties (macrosphelide numbering), while acid **6** provides the C(1)−O(4) moiety. We envisioned that the chelation-controlled reduction of ketone **4** would produce the desired anti stereochemistry in the C(8)−C(9) region, and that subsequent oxidation of the furan ring would produce the C(11)−C(14) unit of seco acid **3**.

Scheme 2



for **7**–**11**: **a**, R^2 = THP; **b**, R^2 = MOM; **c**, R^2 = PMB ($CH_2C_6H_4OMe$-*p*)

Although the most reliable reagent for the anti selective reduction in general is $Zn(BH_4)_2$,[9] rather low diastereoselectivities have been reported for α-alkoxy- (or α-hydroxy-)ethyl alkyl ketones.[10] Ketone **4** is one such compound. Consequently, reduction of the model ketones **7a**−**c** with R = THP, MOM, PMB (*p*-$MeOC_6H_4CH_2$) was investigated (Scheme 2) in order to obtain practical information about the protective group R^2 in the real ketone **4**. The choice of R^2 is expected to be crucial in order to realize high stereoselectivity. In addition, R^2 should be appropriate for the subsequent routine transformation to **3** involving protection of the alcohol at C(8) and deprotection at C(9).

Racemic ketones **7a**−**c**, prepared in reasonable yields by the sequence summarized in Scheme 2, were used for the reduction. When an ethereal solution of $Zn(BH_4)_2$ was added to THP ether **7a** in Et_2O at −78 °C or even below −90 °C, a mixture of **8a** and **9a** was produced in a 1:1 ratio.[11] However, MOM and PMB ethers **7b** and **7c** furnished **8b** and **8c** with acceptable ratios of ca. 10:1 in 83% and 91% yields, respectively.[12] Next, protection of the resulting hydroxyl group in **8b** and **8c** was examined. Attempted protection of **8b** with PMBCl and NaH in THF afforded many products, whereas reaction of **8c** with MOMCl and *i*-Pr_2NEt furnished the corresponding MOM ether in good yield. On the basis of these results and with the expectation that PMB can be removed by DDQ

(5) Sunazuka, T.; Hirose, T.; Harigaya, Y.; Takamatsu, S.; Hayashi, M.; Komiyama, K.; Omura, S.; Sprengeler, P. A.; Smith, A. B., III. *J. Am. Chem. Soc.* **1997**, *119*, 10247−10248.

(6) (a) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem*. **1992**, *57*, 2768−2771. (b) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev*. **1994**, *94*, 2483−2547.

(7) In theory, this selectivity lowers yield and the product ratio of the desired stereoisomer over the other isomers in the step of joining the two diol parts, though details are not given in their communication.

(8) Kobayashi, Y.; Kumar, B. G.; Kurachi, T. *Tetrahedron Lett*. **2000**, *41*, 1559−1563.

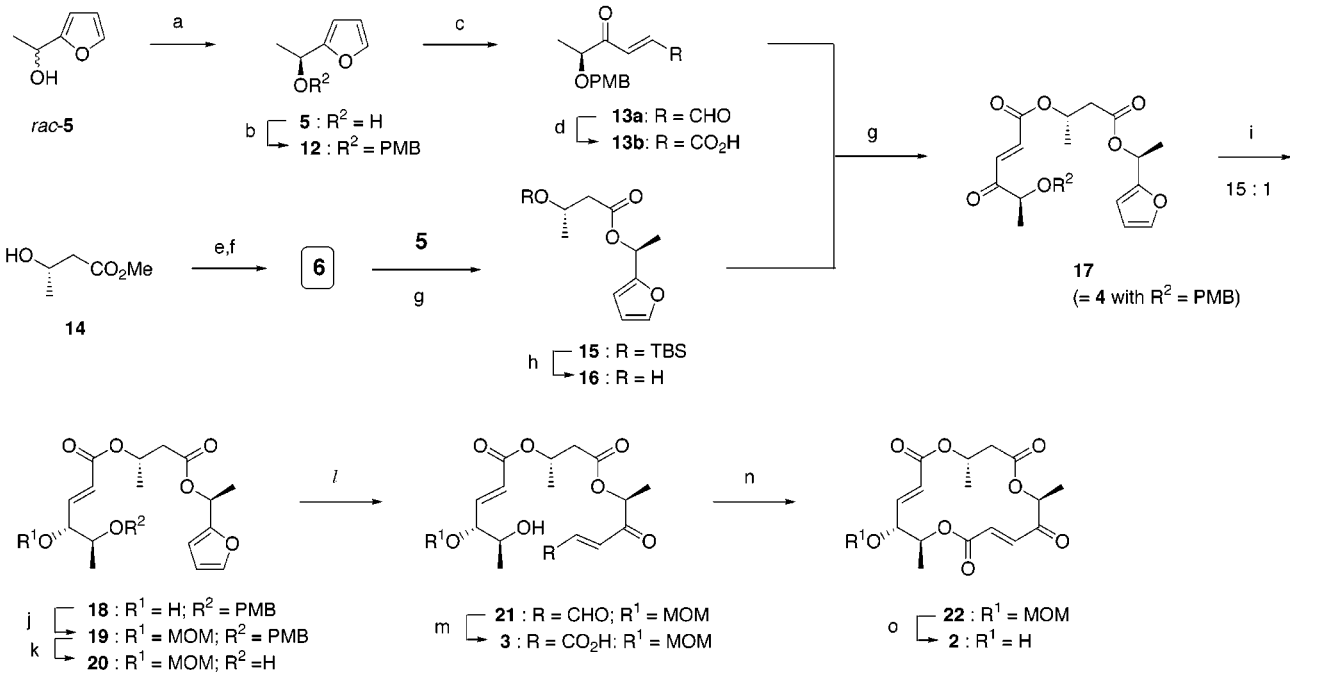
(9) (a) Nakata, T.; Tani, Y.; Hatozaki, M.; Oishi, T. *Chem. Pharm. Bull*. **1984**, *32*, 1411−1415. (b) Oishi, T.; Nakata, T. *Acc. Chem. Res*. **1984**, *17*, 338−344.

(10) (a) Reduction of α-hydroxyethyl and α-alkoxyethyl alkyl ketones $MeCH(OR^1)$-C(=O)-R^2 with $Zn(BH_4)_2$ has been reported occasionally,[10b,c] where selectivity of anti and syn alcohols is somewhat lower than that of other ketones of $R^3CH(OR^1)$-C(=O)-R^2 (R^3 > Me). (b) Nakata, T.; Tanaka, T.; Oishi, T. *Tetrahedron Lett*. **1983**, *24*, 2653−2656. (c) Takahashi, T.; Miyazawa, M.; Tsuji, J. *Tetrahedron Lett*. **1985**, *26*, 5139−5142.

(11) To indicate the relative stereochemistry in the compounds, one enantiomer for each compound is shown for convenience.

(12) The anti stereochemistry of **8c** was confirmed by the ^1H NMR spectra (300 MHz, $CDCl_3$) of ethyl 4,5-dihydroxy-2*E*-hexenoate derived from **8c** [(1) DDQ, CH_2Cl_2/H_2O (19:1), rt; (2) NaH (cat.), EtOH, rt]. The authentic sample and its syn isomer were prepared by epoxidation of ethyl sorbate followed by acid hydrolysis (Hirama, M.; Shigemoto, T.; Yamazaki, Y.; Ito, S. *Tetrahedron Lett*. **1985**, *26*, 4133−4136) or OsO_4-catalyzed dihydroxylation of ethyl sorbate (Hirama, M.; Shigemoto, T.; Ito, S. *Tetrahedron Lett*. **1985**, *26*, 4137−4140). The ^1H NMR signals (in $CDCl_3$) characteristic of the anti diol are as follows: δ 3.93−4.02 (m, 1H), 4.32−4.38 (m, 1 H), 6.12 (dd, *J* = 16, 2 Hz, 1 H), 6.94 (dd, *J* = 16, 5 Hz, 1 H). Those of the syn diol are: δ 3.66−3.77 (m, 1 H), 4.03−4.11 (m, 1 H), 6.14 (dd, *J* = 16, 2 Hz, 1 H), 6.92 (dd, *J* = 16, 5 Hz, 1 H).

Scheme 3. Synthesis of Macrosphelide B (2)[a]



[a] Reagents and conditions: (a) *t*-BuOOH, $Ti(OPr)_4$, D-(−)-DIPT, 38% based on *rac*-**5**; (b) NaH, PMBCl, 93%; (c) NBS, acetone/H_2O, 10:1, −15 °C, 1 h then furan, C_5H_5N, rt, 6 h, 74%; (d) $NaClO_2$, $MeC(H)=CMe_2$, 70%; (e) TBSCl, imidazole, 98%; (f) 1 N NaOH, MeOH, 93%; (g) DCC, DMAP, CSA, rt, overnight, 98% for **15** and 92% for **17**; (h) TBAF, THF, 0 °C, 24 h, 73%; (i) $Zn(BH_4)_2$, Et_2O, <−90 °C, 70%; (j) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 88%; (k) DDQ, CH_2Cl_2/H_2O, 93%; (l) and (m) conditions similar to (c) and (d); (n) $Cl_3C_6H_2COCl$, NEt_3 then DMAP, toluene, 40 °C, 5 h, 40% from **20**; (o) TFA/CH_2Cl_2, 1:1, rt, 1.5 h, 92%.

without affecting the MOM-oxy group, the MOM and PMB groups were chosen as the R^1 and R^2 groups, respectively, in the synthesis (Scheme 1).

Synthesis of macrosphelide B (**2**) is presented in Scheme 3, in which alcohol **5** of >98% ee[13] was prepared by the kinetic resolution of the corresponding racemic alcohol *rac*-**5**[14a] using the Sharpless asymmetric epoxidation reagent[15] in 38% yield based on *rac*-**5**. The hydroxyl group of **5** was protected as PMB ether, and oxidation of the furan ring in the resulting ether **12** produced γ-keto acid **13b**, the C(5)−O(10) segment of **2**, in 48% yield. Intermediate **16** was prepared from alcohol **14**[16] of 99% ee.[13] Reaction of **14** with TBSCl followed by ester hydrolysis afforded acid **6** in 91% yield. Condensation of acid **6** and alcohol **5** with DCC in the presence of DMAP and CSA[5,17] produced ester **15**, which upon deprotection of the TBS group yielded ester alcohol **16** in 73% yield. Condensation was again performed with acid **13b** and alcohol **16** with DCC to afford **17** in 92% yield, which is the key intermediate **4** with R^2 = PMB proposed in Scheme 1.

On the basis of the results obtained with the model ketones **7** in Scheme 2 (vide supra), reduction of ketone **17** was carried out with $Zn(BH_4)_2$ in Et_2O at −78 °C. Unfortunately, a mixture of **18** and its C(8)-epimer *epi*-**18** (structure not shown) was produced in a ratio of 2:1. A lower temperature, below −90 °C, slightly improved the ratio (3:1). It is likely that $Zn\{BH_n(OR)_{4-n}\}_2$, which was probably formed in the early stage of the reduction, somehow participated in the reduction of **17**[18] without chelation to the oxygens present in the PMB-oxy and carbonyl groups, thus furnishing the mixture of **18** and *epi*-**18**. This hypothesis prompted us to examine the reduction with intact $Zn(BH_4)_2$. Thus, an ethereal solution of ketone **17** was slowly added to excess $Zn(BH_4)_2$ in Et_2O at <−90 °C, and this procedure was found to be successful, producing alcohol **18** and *epi*-**18** with a practical selectivity of 15:1 in 70% yield. The anti stereochemistry in the resulting diol part was tentatively assigned at this stage and was proved by the total synthesis of **2**. Reaction of alcohol **18** with MOMCl followed by deprotection of the PMB group with DDQ furnished alcohol **20** in 82% yield. Since a hydroxyl group has been shown to be compatible with the furan ring oxidation, **20** was submitted to this transformation to afford the key acid **3**. Lactonization of crude **3** was carried out under the conditions of Yamaguchi[19] at 40 °C to produce lactone **22** in 40% yield from the furan **20**. Finally, deprotection of the MOM group with TFA in CH_2Cl_2 furnished **2** in good yield: $[\alpha]^{24}_D = +9.1$ (*c* 0.154, MeOH) [lit.[3b] $[\alpha]^{23}_D = +4.10$ (*c* 0.99, MeOH); lit.[5] $[\alpha]^{24}_D = +10.0$ (*c* 0.39, MeOH)]. The ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra

(13) Enantiomeric excess (ee) was determined by ^1H NMR spectroscopy of the derived MTPA ester.

(14) (a) Kusakabe, M.; Kitano, Y.; Kobayashi, Y.; Sato, F. *J. Org. Chem.* **1989**, *54*, 2085−2091. Other methods: (b) Drueckhammer, D. G.; Barbas, C. F., III; Nozaki, K.; Wong, C.-H. *J. Org. Chem.* **1988**, *53*, 1607−1611. (c) Sammes, P. G.; Thetford, D. *J. Chem. Soc., Perkin Trans. 1* **1988**, 111−123.

(15) (a) Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237−6240. (b) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765−5780.

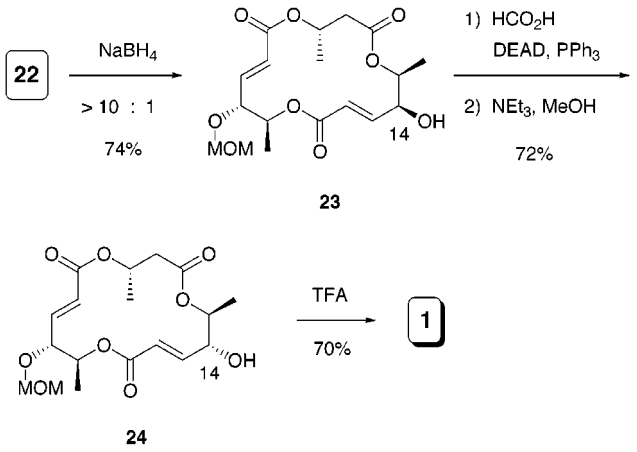
(16) Noyori, R.; Ohkuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1987**, *109*, 5856−5858.

(17) Boden, E. P.; Keck, G. E. *J. Org. Chem.* **1985**, *50*, 2394−2395.

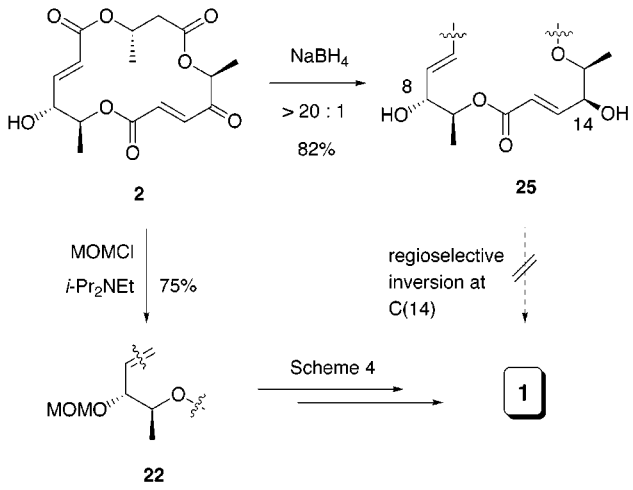
(18) Chelation of $Zn\{BH_n(OR)_{4-n}\}_2$ to the other oxygen(s) present in **17** perhaps accelerates the reduction, but nonstereoselectively, since the reverse mode did not change the selectivity in the reduction of the simple ketones shown in eq 2.

(19) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989−1993.

Scheme 4. Synthesis of Macrosphelide A (1)

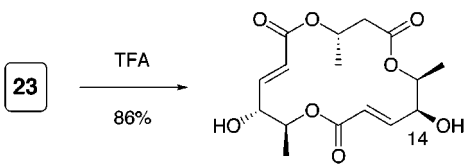


Scheme 5. Conversin of Macrosphelide B to A



of synthetic **2** were identical with the data reported in the literature.[3b,5]

Synthesis of Macrosphelide A from the MOM Ether of Macrosphelide B. In theory, reduction of MOM ether **22** with a hydride reagent which coordinates to the oxygen atoms in the *O*═(14)−C(15)−*O*(16) part should afford alcohol **24**, the precursor of macrosphelide A (**1**). However, attempted reduction of **22** with $Zn(BH_4)_2$ in Et_2O even at <−90 °C furnished **24** with a low stereoselection of 2∼1:1. In contrast, reduction with $NaBH_4$ in MeOH at −15 °C was found to produce the 14-*epi* alcohol **23** in 74% yield with high diastereoselectivity of >10:1 (Scheme 4). These results strongly indicate the existence of stable conformer(s) for **22** in which the undesired side of the carbonyl group (*re* face) is less congested, thus allowing the hydride attack to afford **23** selectively. The origin of the stereoselective reduction is discussed below with the stable conformer(s) of **22**, obtained by computer-assisted calculation. Finally, Mitsunobu inversion[20] of alcohol **23** followed by methanolysis of the resulting formate ester and deprotection of the MOM group with TFA afforded **1** in 70% yield. The ^{1}H NMR and ^{13}C NMR spectra of synthetic **1** were in good agreement with those reported:[3b,5] $[\alpha]^{30}_D = +85$ (*c* 0.046, MeOH) [lit.[3b] $[\alpha]^{23}_D = +84.1$ (*c* 0.59, MeOH); lit.[5] $[\alpha]^{27}_D = +82$ (*c* 0.10, MeOH)]. Similarly, treatment of 14-*epi* alcohol **23** with TFA furnished 14-*epi* macrosphelide A (i.e., **25**) in 86% yield (eq 2).



(2)

Next, macrosphelide B (**2**) as such was subjected to the reduction with $NaBH_4$, which resulted in production of the 14-epimer of **1** (i.e., **25**) with high stereoselectivity (>20:1) in 82% yield (Scheme 5), as was observed in the case of **22**. This result indicates that the stable and/or reactive conformer(s) of **2** is quite similar to that of **22**. A bias for the stereoselective reduction is discussed with the stable conformers of **2** below. Since differentiation of the two hydroxyl groups at C(8) and C(14) in **25** by the Mitsunobu inversion or by protection seems difficult, the route shown in Scheme 4 is definitely the best choice to obtain **1** from ketone **22**.

Conversion of Macrosphelide B to Macrosphelide A. Reaction of macrosphelide B (**2**) with MOMCl in the presence of *i*-Pr_2NEt in CH_2Cl_2 at room temperature was somewhat slow, but was completed after 2.5 days to afford the MOM ether **22** in 75% yield (Scheme 5). The ^{1}H NMR spectrum of **22** showed no epimerization had occurred during the reaction. Since ether **22** was already converted into macrosphelide A (**1**) (see Scheme 4), this successful protection establishes the conversion of **2** to **1**. In the future, this conversion would be important when **2** is prepared by another method such as a biosynthetic one.

Conformational Analysis for the Stereoselective Reduction. Stable conformers of macrosphelide B (**2**) and the MOM ether **22** were calculated by using the software Conflex,[21,22] known as one of the most potent and efficient programs for automatic generation−optimization of low energy conformations. As listed in Table 1, 23 independent structures were eventually found within a range of 2 kcal/mol energy difference from the global minimum conformation.

The partial structures of the most and the second most stable conformers of macrosphelide B (**2**), MB-1 and MB-2, respectively, are shown in Figure 1 as representative examples for obtaining a clearer picture around the O═C(14) group where the diastereoselective reduction was experimentally observed.[23] In MB-1, the *re* and *si* faces are blocked efficiently by the macrocyclic ring and the

(20) Mitsunobu, O. *Synthesis* **1981**, 1−28.

(21) Conflex,[22] implemented in the CAChe Worksystem (version 4.1.1; Fujitsu Limited, Japan), was performed for generation of various conformers which were automatically optimized with Mechanics included in the same system until convergence to 0.00001 kcal/mol was attained. This sequence was carried out four times with the search limit of 0.001% to furnish 740 conformers.

(22) (a) Suginome, H.; Kondoh, T.; Gogonea, C.; Singh, V.; Goto, H.; Osawa, E. *J. Chem. Soc., Perkin Trans. 1* **1995**, 69−81. (b) Goto, H.; Kawashima, Y.; Kashimura, M.; Morimoto, S.; Osawa, E. *J. Chem. Soc., Perkin Trans. 2* **1993**, 1647−1654. (c) Goto, H.; Osawa, E. *THEOCHEM* **1993**, *285*, 157−168. (d) Shimazaki, K.; Mori, M.; Okada, K.; Chuman, T.; Kuwahara, S.; Kitahara, T.; Mori, K.; Goto, H.; Osawa, E.; Sakakibara, K.; Hirota, M. *J. Chem. Soc., Perkin Trans. 2* **1993**, 1167−1173. (e) Shimazaki, K.; Mori, M.; Okada, K.; Chuman, T.; Goto, H.; Osawa, E.; Sakakibara, K.; Hirota, M. *J. Chem. Soc., Perkin Trans. 2* **1992**, 811−818.

(23) Ball and stick models of MB-1 and MB-2 are shown in Figure 2 in the Supporting Information.

Table 1. Calculated Energies and Properties of Macrosphelide B (MB) within 2 kcal/mol from the Global Minimum Structure

conformer	ΔE (kcal/mol)	population[a] (%)	dihedral angles[b] (deg) A	B	C
MB-1	0.000	17.7	−131.1	−13.9	97.1
MB-2	0.157	13.3	37.3	157.9	−81.5
MB-3	0.247	11.2	−126.9	−9.9	100.9
MB-4	0.379	8.8	32.2	152.7	−86.4
MB-5	0.540	6.5	35.8	156.4	−82.7
MB-6	0.562	6.3	31.6	151.7	−87.0
MB-7	0.565	6.2	29.8	149.9	−89.6
MB-8	0.699	4.9	−95.3	24.1	142.9
MB-9	0.803	4.0	−6.0	112.4	−131.6
MB-10	0.810	4.0	25.5	145.2	−94.1
MB-11	0.905	3.3	26.2	146.3	−93.2
MB-12	1.049	2.6	−109.3	11.9	128.6
MB-13	1.095	2.4	16.7	135.9	−102.9
MB-14	1.293	1.6	−96.9	22.5	141.2
MB-15	1.364	1.4	−124.8	−3.2	112.3
MB-16	1.435	1.3	−137.8	−20.5	90.9
MB-17	1.446	1.2	29.8	149.6	−88.4
MB-18	1.707	0.8	30.2	150.3	−89.1
MB-19	1.888	0.5	8.8	129.8	−110.3
MB-20	1.909	0.5	29.9	149.8	−89.7
MB-21	1.948	0.5	−98.8	20.6	139.2
MB-22	1.952	0.5	−135.3	−18.1	93.1
MB-23	1.999	0.4	37.2	158.1	−82.0

[a] Calculated at 0 °C. [b] A: *O*═*C*(14)−*C*(15)−*C*H$_3$. B: *O*═*C*(14)−*C*(15)−H. C: *O*═*C*(14)−*C*(15)−*O*(16).

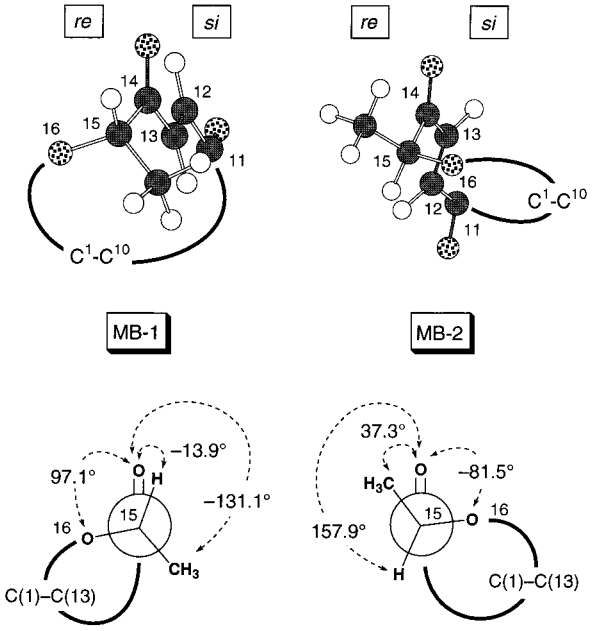


Figure 1. Partial structures of the most and the second most stable conformers of macrosphelide B (**2**).

Me group at C(15), respectively. On the other hand, the *re* face of MB-2 is sterically less congested, while the *si* face is encumbered by the ring (the Felkin−Anh-type conformation between C(14) and C(15), though slightly distorted). In other words, the O═C(14) group in MB-2 is susceptible to the hydride attack from the *re* face, while somewhat higher activation energy is required when the hydride attacks MB-1 from either face.[24−26] Consequently, MB-2 and the conformers of the MB-2 type in Table 1 (e.g., MB-4, -5, -6, -7, etc.) are consumed faster than other conformers with high stereoselectivity. On the contrary, conformer MB-1 and the other conformers of the MB-1 type (e.g., MB-3) first undergo conversion to the reactive conformers of the MB-2 type, thus furnishing overall stereoselective reduction to yield **25**, the epimer of **1**, as shown in Scheme 5.

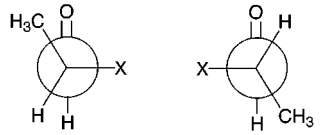
Because the MOM group at C(8) of **22** significantly increases the number of possible conformers, we have performed a rough conformational estimation for the MOM ether **22** to find 18 different conformers within a 2 kcal/mol range from the global minimum (data not shown). In this case, all of the low-energy conformers take Felkin−Anh-type conformations similar to MB-2 due to absence of the hydroxyl group at C(8). This computational result is consistent, at least qualitatively, with the stereoselective production of the epimeric alcohol **23** (Scheme 4).

As described above, $Zn(BH_4)_2$-mediated reduction of **22** resulted in the unexpectedly low diastereofacial selectivity of 2−1:1, though the *O*═C(14)−C(15)−*O*(16) moiety was, in principle, a site to form chelation with Zn^{2+}.[9] In the conformers with up to 10 kcal/mol higher energy levels from the global minimum, the two oxygen atoms were found to be placed separately, thus preventing the chelation. Instead, some conformers have approximately 3.3−3.4 Å distance[27] between the two carbonyl oxygen atoms *O*═C(14) and *O*═C(1), and this alignment is not suitable for providing a steric bias for the stereoselective reduction, thus furnishing a mixture of **24** and **23** in the 2∼1:1 ratio (vide supra).

Conclusion

In summary, we have established a stereoselective synthesis of macrosphelide A (**1**) and macrosphelide B (**2**). Since the furan ring-oxidation is not only independent of a substituent on the ring but also compatible with protective and/or functional groups, especially a free OH group, the method is amenable to synthesis of other macrosphelides.[28,29] For example, macrosphelide E[29] could be synthesized starting with methyl (*R*)-3-hydroxybutanoate, and other macrosphelides similarly. Furthermore, synthesis of analogues of **1** and **2** would spur biochemical research of these important compounds in development of a drug against cancer.

(24) It has been reported that nucleophilic reactions with 2-fluoro- (X = F)[25] or 2-chloropropionaldehyde (X = Cl)[26] were anticipated by ab initio calculations to occur predominantly via conformation A rather than conformer B.



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(27) Because the van der Waals radius of oxygen and the size of tetracoordinated Zn^{2+} were reported to be 1.52 and 0.6 Å, respectively, the distance of ca. 3.3−3.4 Å between two carbonyl oxygens would be sufficient for the bidentate interaction (seven-membered chelation). See, Bondi, A. *J. Phys. Chem.* **1964**, *68*, 441−451 for the van der Waals radii, and Dean, J. A. *Lange's Handbook of Chemistry*, 14th ed.; MacGraw-Hill, Inc.; New York, 1992 for the ionic radius.

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(29) Numata, A.; Iritani, M.; Yamada, T.; Minoura, K.; Matsumura, E.; Yamori, T.; Tsuruo, T. *Tetrahedron Lett.* **1997**, *38*, 8215−8218.

Experimental Section

General Methods. Infrared (IR) spectra are reported in wavenumbers (cm^{-1}). Unless otherwise noted, ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were measured in $CDCl_3$ using $SiMe_4$ ($\delta = 0$ ppm) and the center line of $CDCl_3$ triplet ($\delta = 77.1$ ppm) as internal standards, respectively. The following solvents were distilled before use: THF (from Na/benzophenone), Et_2O (from Na/benzophenone), and CH_2Cl_2 (from CaH_2). Methyl (*S*)-3-hydroxybutanoate was kindly offered by Takasago International Corporation, Japan. The phosphate buffer of pH 3.6 was prepared by mixing $Na_2HPO_4 \cdot 12H_2O$ (2.31 g), citric acid (1.31 g), and H_2O (98.6 g). Routinely, organic extracts were dried over $MgSO_4$ and concentrated using a rotary evaporator, and residues were purified by chromatography on silica gel.

(*S*)-1-(2-Furyl)ethanol (5). The title compound was prepared according to the literature procedure.[14a] Briefly, a solution of *t*-BuOOH in CH_2Cl_2 (5.67 mL, 4.72 M, 26.8 mmol) was added to a mixture of *rac*-**5** (5.00 g, 44.6 mmol), powdered 4 Å molecular sieves (1.5 g), $Ti(O\text{-}i\text{-}Pr)_4$ (2.64 mL, 8.93 mmol), D-(−)-DIPT (2.28 mL, 10.7 mmol), and CH_2Cl_2 (20 mL) at −30 °C. The mixture was stirred at −15 °C for 16 h and treated with Me_2S (1.99 mL, 27.2 mmol) at −15 °C for 30 min. Aqueous tartaric acid (5%, 10 mL), NaF (20 g), and Et_2O (100 mL) were added to the mixture. The resulting mixture was stirred vigorously at room temperature for 2 h and filtered through a pad of Celite. The filtrate was concentrated, and the crude product dissolved in Et_2O (100 mL) was treated with 3 N NaOH (50 mL) for 30 min at 0 °C with vigorous stirring to give **5** (1.92 g, 38% based on *rac*-**5**) after chromatography. The ^1H NMR spectrum of **5** was identical with that reported,[14b,c] and the enantiomeric excess (ee) was determined to be >98% by ^1H NMR spectroscopy of the corresponding MTPA ester. **5**: bp 75−80 °C (5 Torr); $[\alpha]^{28}_D = -22$ (*c* 0.506, $CHCl_3$) [lit.[14a] $[\alpha]^{25}_D = +20.8$ (*c* 1.27, $CHCl_3$)] for the enantiomer of >95% ee.

(*S*)-1-(2-Furyl)-1-(4-methoxybenzyloxy)ethane (12). To an ice-cold suspension of oil-free NaH, prepared from NaH (576 mg, 50% dispersion in mineral oil, 12 mmol) by washing with hexane, in DMF (10 mL) was added **5** (0.89 g, 8.0 mmol), and the reaction mixture was stirred at room temperature for 1 h. *p*-Methoxybenzyl chloride (1.41 mL, 10.4 mmol) was added to the mixture. After 2 h, brine was added to it and the product was extracted with Et_2O twice. The combined extracts were dried and concentrated to leave a residue, which was subjected to chromatography (hexane/EtOAc) to furnish **12** (1.73 g, 93%): bp 175 °C (1 Torr); $[\alpha]^{29}_D = -117$ (*c* 0.798, $CHCl_3$); IR (neat) 1612, 1585, 1514, 1248, 818, 742 cm^{-1}; ^1H NMR δ 1.52 (d, $J = 7$ Hz, 3 H), 3.79 (s, 3 H), 4.33 (d, $J = 11$ Hz, 1 H), 4.46 (d, $J = 11$ Hz, 1 H), 4.53 (q, $J = 7$ Hz, 1 H), 6.27 (d, $J = 3$ Hz, 1 H), 6.34 (dd, $J = 3$, 2 Hz, 1 H), 6.86 (d, $J = 9$ Hz, 1 H), 7.25 (d, $J = 9$ Hz, 1 H), 7.40 (br s, 1 H); ^{13}C NMR δ 159.3, 155.9, 142.2, 130.6, 129.5, 113.9, 110.1, 107.1, 69.9, 69.4, 55.3, 19.9. Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.36; H, 6.99.

(2*E*,5*S*)-5-(4-Methoxybenzyloxy)-4-oxo-2-hexenal (13a). To a mixture of **12** (1.01 g, 4.35 mmol) and $NaHCO_3$ (0.73 g, 8.7 mmol) in acetone/H_2O (10:1, 11 mL) was added NBS (851 mg, 4.78 mmol) dissolved in acetone/H_2O (10:1, 11 mL) at −15 °C, and the mixture was stirred for 1 h. Furan (0.32 mL, 4.4 mmol) and, after 30 min of stirring at −15 °C, pyridine (0.70 mL, 9.1 mmol) were added to the mixture. The resulting mixture was stirred at room temperature for 6 h and poured into 0.5 M $CuSO_4$ solution (20 mL). The product was extracted with Et_2O three times, and the combined extracts were dried and evaporated to furnish a residue, which on chromatography (hexane/EtOAc) afforded aldehyde **13a** (796 mg, 74%): $[\alpha]^{28}_D = -72$ (*c* 0.522, $CHCl_3$); IR (neat) 1693, 1612, 1514, 1250 cm^{-1}; ^1H NMR δ 1.39 (d, $J = 7$ Hz, 3 H), 3.80 (s, 3 H), 4.13 (q, $J = 7$ Hz, 1 H), 4.46 (d, $J = 11$ Hz, 1 H), 4.53 (d, $J = 11$ Hz, 1 H), 6.81−6.91 (m, 3 H), 7.22−7.29 (m, 3 H), 9.72 (d, $J = 8$ Hz, 1 H); ^{13}C NMR δ 201.4, 193.2, 159.9, 139.8, 138.2, 130.1, 129.1, 114.0, 79.9, 72.1, 55.2, 17.3. Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.65; H, 6.61.

(2*E*,5*S*)-5-(4-Methoxybenzyloxy)-4-oxo-2-hexenoic Acid (13b). To a solution of aldehyde **13a** (1.54 g, 6.20 mmol) and 2-methyl-2-butene (6.70 mL, 62.0 mmol) in *t*-BuOH (14 mL) and the phosphate buffer (7 mL, pH 3.6) was added a solution of $NaClO_2$ (841 mg, 80% purity, 7.44 mmol) in H_2O (2 mL). The reaction mixture was stirred at room temperature for 2 h. Most of the solvent was removed by using a vacuum pump, and the residue was diluted with EtOAc (10 mL) and brine (10 mL). The mixture was stirred vigorously, and the layers were separated. The aqueous layer was acidified to pH 4 with 1 N HCl and extracted with EtOAc several times. The combined extracts were dried and evaporated to furnish a mixture of acid **13** and $Me_2C(Cl)CHClMe$. The mixture was used for the next reaction without further purification (1.73 g, calculated yield of **13b** by ^1H NMR integration: 70%). The ^1H NMR signals for **13b**: δ 1.37 (d, $J = 7$ Hz, 3 H), 3.80 (s, 3 H), 4.10 (q, $J = 7$ Hz, 1 H), 4.47 (s, 2 H), 6.76 (d, $J = 16$ Hz, 1 H), 6.88 (d, $J = 9$ Hz, 2 H), 7.25 (d, $J = 9$ Hz, 2 H), 7.49 (d, $J = 16$ Hz, 1 H).

Methyl (*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]butanoate. A solution of methyl (*S*)-3-hydroxybutanoate (99% ee, 3.00 g, 25.4 mmol), imidazole (2.59 g, 38.1 mmol), and TBSCl (4.59 g, 30.5 mmol) in DMF (50 mL) was stirred at room temperature overnight and poured into saturated $NaHCO_3$ with Et_2O. The resulting mixture was stirred vigorously for 30 min. The layers were separated, and the aqueous layer was extracted with Et_2O twice. The combined extracts were dried and concentrated to give an oil, which was subjected to chromatography (hexane/EtOAc) to furnish the title compound (5.75 g, 98%): bp 100 °C (5 Torr); $[\alpha]^{29}_D = +31$ (*c* 0.674, $CHCl_3$); IR (neat) 1743, 1086, 837, 777 cm^{-1}; ^1H NMR δ 0.03 (s, 3 H), 0.05 (s, 3 H), 0.84 (s, 9 H), 1.18 (d, $J = 6$ Hz, 3 H), 2.37 (dd, $J = 15$, 5 Hz, 1 H), 2.47 (dd, $J = 15$, 8 Hz, 1 H), 3.64 (s, 3 H), 4.21−4.32 (m, 1 H); ^{13}C NMR δ 172.3, 65.9, 51.5, 44.8, 25.7, 23.9, 17.9, −4.6, −5.1. Anal. Calcd for $C_{11}H_{24}O_3Si$: C, 56.85; H, 10.41. Found: C, 56.47; H, 10.48.

(*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]butanoic Acid (6). A solution of the above ester (4.30 g, 18.5 mmol) and 1 N NaOH (93 mL, 93 mmol) in MeOH (160 mL) was stirred at room temperature for 3 h. Most of the MeOH was removed by evaporation, and the residue was extracted with Et_2O. The aqueous layer was acidified to pH 4 by addition of 1 N HCl, and the mixture was extracted with Et_2O three times. The combined extracts were dried and concentrated to afford an oil, which was subjected to chromatography (hexane/Et_2O) to afford **6** (3.76 g, 93%). The IR (neat) and ^1H NMR spectra of synthetic **6** were identical with those reported:[30a,b] $[\alpha]^{27}_D = +15$ (*c* 1.47, $CHCl_3$) [lit.[30a] $[\alpha]_D = +11.9$ (*c* 1.29, $CHCl_3$) for **6** of 85% ee; lit.[30b] $[\alpha]^{26}_D = +14.3$ (*c* 1.83, $CHCl_3$) for **6** of 80% ee]; ^{13}C NMR δ 177.0, 65.7, 44.2, 25.7, 23.6, 17.9, −4.6, −5.2.

(2*S*,6*S*)-6-[(*tert*-Butyldimethylsilyl)oxy]-2-(2-furyl)-3-oxa-4-heptanone (15). To a solution of acid **6** (3.27 g, 15.0 mmol) in CH_2Cl_2 (22 mL) were added alcohol **5** (>98% ee, 1.29 g, 11.5 mmol), DMAP (342 mg, 2.80 mmol), CSA (318 mg, 1.37 mmol), and DCC (3.56 g, 17.3 mmol). The reaction was continued overnight at room temperature and quenched with H_2O. The resulting mixture was extracted with CH_2Cl_2, and the extract was dried and concentrated to give a residue, which was purified by chromatography (hexane/EtOAc) to furnish **15** (3.52 g, 98%): bp 120 °C (1 Torr); $[\alpha]^{29}_D = -56$ (*c* 0.68, $CHCl_3$); IR (neat) 1738, 1178, 1005, 837, 777 cm^{-1}; ^1H NMR δ 0.02 (s, 3 H), 0.04 (s, 3 H), 0.84 (s, 9 H), 1.17 (d, $J = 6$ Hz, 3 H), 1.57 (d, $J = 7$ Hz, 3 H), 2.36 (dd, $J = 15$, 6 Hz, 1 H), 2.48 (dd, $J = 15$, 7 Hz, 1 H), 4.21−4.32 (m, 1 H), 5.95 (q, $J = 7$ Hz, 1 H), 6.29−6.33 (m, 2 H), 7.36 (dd, $J = 2$, 1 Hz, 1 H); ^{13}C NMR δ 171.0, 153.7, 142.6, 110.3, 107.9, 65.7, 65.0, 44.9, 25.7, 23.8, 18.3, 17.9, −4.6, −5.1. Anal. Calcd for $C_{16}H_{28}O_4Si$: C, 61.50; H, 9.03. Found: C, 61.77; H, 9.11.

(2*S*,6*S*)-2-(2-Furyl)-6-hydroxy-3-oxa-4-heptanone (16). To an ice-cold solution of **15** (2.55 g, 8.16 mmol) in THF (80 mL) was added a solution of Bu_4NF in THF (10.6 mL, 1 M,

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10.6 mmol) dropwise. The solution was stirred at 0 °C for 24 h and poured into saturated NH_4Cl with vigorous stirring. The mixture was extracted with EtOAc twice, and the combined extracts were dried and evaporated to give a residue, which was purified by chromatography (hexane/EtOAc) to yield **16** (1.18 g, 73%): $[\alpha]^{29}_D = -91$ (*c* 0.604, $CHCl_3$); IR (neat) 3431, 1736, 744 cm^{-1}; ^1H NMR δ 1.20 (d, $J = 6$ Hz, 3 H), 1.59 (d, $J = 7$ Hz, 3 H), 2.43 (dd, $J = 16$, 8 Hz, 1 H), 2.47 (dd, $J = 16$, 5 Hz, 1 H), 3.2 (br s, 1 H), 4.13−4.25 (m, 1 H), 6.00 (q, $J = 7$ Hz, 1 H), 6.33 (br s, 2 H), 7.38 (br s, 1 H); ^{13}C NMR δ 172.0, 153.2, 142.6, 110.2, 107.9, 65.2, 64.1, 42.9, 22.3, 18.0. Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.60; H, 7.18.

(2*S*,6*S*,9*E*,12*S*)-6,12-Dimethyl-2-(2-furyl)-14-(4-methoxyphenyl)-3,7,13-trioxa-9-tetradecene-4,8,11-trione (17). To a mixture of alcohol **16** (197 mg, 0.997 mmol), crude acid **13** (658 mg, obtained as a mixture with $Me_2C(Cl)CHClMe$, calculated amount of **13** by ^1H NMR integration: 429 mg, 1.62 mmol), DMAP (29 mg, 0.24 mmol), and CSA (30 mg, 0.13 mmol) in CH_2Cl_2 (15 mL) was added DCC (617 mg, 2.99 mmol) and the mixture was stirred overnight. The reaction was quenched by addition of H_2O. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined extracts were dried and evaporated to leave a residue, which was purified by chromatography (hexane/EtOAc) to furnish **17** (409 mg, 92%): $[\alpha]^{28}_D = -85$ (*c* 0.430, $CHCl_3$); IR (neat) 1736, 1705, 1612, 1514, 822, 750 cm^{-1}; ^1H NMR δ 1.34 (d, $J = 6$ Hz, 3 H), 1.36 (d, $J = 7$ Hz, 3 H), 1.56 (d, $J = 7$ Hz, 3 H), 2.57 (dd, $J = 16$, 6 Hz, 1 H), 2.70 (dd, $J = 16$, 8 Hz, 1 H), 3.80 (s, 3 H), 4.08 (q, $J = 7$ Hz, 1 H), 4.43 (d, $J = 11$ Hz, 1 H), 4.47 (d, $J = 11$ Hz, 1 H), 5.33−5.46 (m, 1 H), 5.97 (q, $J = 7$ Hz, 1 H), 6.31 (br s, 2 H), 6.72 (d, $J = 16$ Hz, 1 H), 6.87 (d, $J = 9$ Hz, 2 H), 7.24 (d, $J = 9$ Hz, 2 H), 7.37 (br s, 1 H), 7.40 (d, $J = 16$ Hz, 1 H); ^{13}C NMR δ 201.2, 169.4, 164.7, 159.8, 153.2, 142.8, 134.9, 132.0, 130.0, 129.3, 114.0, 110.3, 108.1, 79.8, 71.9, 68.5, 65.4, 55.3, 40.8, 19.7, 18.0, 17.3. Anal. Calcd for $C_{24}H_{28}O_8$: C, 64.85; H, 6.35. Found: C, 64.68; H, 6.19.

(2*S*,6*S*,9*E*,11*R*,12*S*)-6,12-Dimethyl-2-(2-furyl)-11-hydroxy-14-(4-methoxyphenyl)-3,7,13-trioxa-9-tetradecene-4,8-dione (18). To a solution of $Zn(BH_4)_2$ (18 mL, 0.151 M in Et_2O, 2.71 mmol) maintained at −94 °C was added a solution of **17** (241 mg, 0.543 mmol) dissolved in Et_2O (10 mL) over 20 min. After the addition, the solution was stirred at the temperature below −90 °C for 1 h and poured into a mixture of brine and Et_2O. The layers were separated, and the aqueous layer was extracted with Et_2O. The combined extracts were dried and concentrated to give an oil, which was a 15:1 mixture of **18** and its epimer by ^1H NMR spectroscopy. Finally, chromatography (hexane/EtOAc) of the crude product furnished **18** (170 mg, 70%): IR (neat) 3464, 1737, 1720, 822, 746 cm^{-1}; ^1H NMR δ 1.13 (d, $J = 6$ Hz, 3 H), 1.31 (d, $J = 6$ Hz, 3 H), 1.55 (d, $J = 7$ Hz, 3 H), 2.37 (d, $J = 4.5$ Hz, 1 H), 2.54 (dd, $J = 15$, 6 Hz, 1 H), 2.68 (dd, $J = 15$, 8 Hz, 1 H), 3.65 (dq, $J = 3.5$, 6 Hz, 1 H), 3.82 (s, 3 H), 4.39−4.45 (m, 1 H), 4.45 (d, $J = 12$ Hz, 1 H), 4.56 (d, $J = 12$ Hz, 1 H), 5.28−5.38 (m, 1 H), 5.97 (q, $J = 7$ Hz, 1 H), 6.08 (dd, $J = 16$, 2 Hz, 1 H), 6.31 (br s, 2 H), 6.83−6.92 (m, 3 H), 7.23−7.30 (m, 2 H), 7.37 (dd, $J = 2$, 1 Hz, 1 H); ^{13}C NMR δ 169.6, 165.6, 159.6, 153.4, 146.0, 142.7, 130.2, 129.5, 122.0, 114.1, 110.3, 108.0, 76.3, 72.7, 70.6, 67.5, 65.3, 55.3, 41.1, 19.8, 18.1, 14.0. Anal. Calcd for $C_{24}H_{30}O_8$: C, 64.56; H, 6.77. Found: C, 64.60; H, 7.03.

(2*S*,6*S*,9*E*,11*R*,12*S*)-6,12-Dimethyl-2-(2-furyl)-11-(methoxymethoxy)-14-(4-methoxyphenyl)-3,7,13-trioxa-9-tetradecene-4,8-dione (19). To a solution of **18** (389 mg, 0.871 mmol) and $(i\text{-Pr})_2NEt$ (0.910 mL, 5.22 mmol) in CH_2Cl_2 (10 mL) was added MOMCl (0.264 mL, 3.48 mmol). The solution was stirred at room temperature for 16 h and diluted with saturated $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined extracts were dried and evaporated to leave an oil, which was purified by chromatography (hexane/EtOAc) to yield **19** (324 mg, 88%): $[\alpha]^{28}_D = -68$ (*c* 0.410, $CHCl_3$); IR (neat) 1738, 1720, 1658, 1612, 1514, 822, 746 cm^{-1}; ^1H NMR δ 1.19 (d, $J = 6$ Hz, 3 H), 1.31 (d, $J = 6$ Hz, 3 H), 1.55 (d, $J = 7$ Hz, 3 H), 2.54 (dd, $J = 15$, 6 Hz, 1 H), 2.69 (dd, $J = 15$, 7 Hz, 1 H), 3.38 (s, 3 H), 3.55−3.67 (m, 1 H), 3.80 (s, 3 H), 4.29 (ddd, $J = 6$, 4, 1.5 Hz, 1 H), 4.52 (s, 2 H), 4.64 (d, $J = 11$ Hz, 1 H), 4.66 (d, $J = 11$ Hz, 1 H), 5.29−5.41 (m, 1 H), 5.96 (q, $J = 7$ Hz, 1 H), 6.01 (dd, $J = 16$, 1.5 Hz, 1 H), 6.31 (br s, 2 H), 6.83−6.91 (m, 3 H), 7.25 (d, $J = 9$ Hz, 2 H), 7.37 (dd, $J = 2$, 1 Hz, 1 H); ^{13}C NMR δ 169.5, 165.3, 159.3, 153.3, 145.7, 142.7, 130.5, 129.4, 123.2, 113.9, 110.3, 108.0, 95.1, 77.5, 76.2, 70.8, 67.5, 65.3, 55.7, 55.3, 41.0, 19.8, 18.0, 15.6. Anal. Calcd for $C_{26}H_{34}O_9$: C, 63.66; H, 6.99. Found: C, 63.61; H, 7.10.

(2*S*,6*S*,9*E*,11*R*,12*S*)-2-(2-Furyl)-12-hydroxy-11-(methoxymethoxy)-3,7-dioxa-9-tridecene-4,8-dione (20). A solution of **19** (324 mg, 0.660 mmol) and DDQ (225 mg, 0.990 mmol) in CH_2Cl_2/H_2O (18:1, 7 mL) was stirred at room temperature for 30 min. The precipitate formed by the reaction was removed by filtration, and the filtrate was concentrated to furnish a gummy mass, which was purified by chromatography (hexane/EtOAc) to yield **20** (226 mg, 93%): $[\alpha]^{29}_D = -99$ (*c* 0.564, $CHCl_3$); IR (neat) 3464, 1738, 1720 cm^{-1}; ^1H NMR δ 1.16 (d, $J = 6$ Hz, 3 H), 1.31 (d, $J = 6$ Hz, 3 H), 1.56 (d, $J = 7$ Hz, 3 H), 2.50 (br s, 1 H), 2.55 (dd, $J = 15$, 6 Hz, 1 H), 2.69 (dd, $J = 15$, 7 Hz, 1 H), 3.41 (s, 3 H), 3.88−4.01 (m, 1 H), 4.17 (ddd, $J = 6$, 3.5, 1.5 Hz, 1 H), 4.67 (s, 2 H), 5.29−5.40 (m, 1 H), 5.97 (q, $J = 7$ Hz, 1 H), 6.02 (dd, $J = 16$, 1.5 Hz, 1 H), 6.30−6.35 (m, 2 H), 6.84 (dd, $J = 16$, 6 Hz, 1 H), 7.38 (dd, $J = 2$, 1 Hz, 1 H); ^{13}C NMR δ 169.5, 165.1, 153.4, 144.0, 142.7, 124.2, 110.3, 108.0, 95.5, 80.4, 69.2, 67.7, 65.4, 55.9, 41.0, 19.8, 18.1, 17.8. Anal. Calcd for $C_{18}H_{26}O_8$: C, 58.37; H, 7.08. Found: C, 58.31; H, 7.08.

MOM Ether of Macrosphelide B (22). To a mixture of **20** (129 mg, 0.334 mmol) and $NaHCO_3$ (56 mg, 0.67 mmol) in acetone/H_2O (10:1, 3.5 mL) was added NBS (77 mg, 0.43 mmol) dissolved in acetone/H_2O (10:1, 1.6 mL) at −15 °C. The mixture was stirred at −15 °C for 2 h, and excess NBS was quenched with furan (0.024 mL, 0.33 mmol) at −15 °C for 15 min. After addition of pyridine (0.054 mL, 0.67 mmol), the mixture was stirred at room temperature overnight and poured into 0.5 M $CuSO_4$ solution (5 mL). The product was extracted with EtOAc twice. The combined extracts were dried and evaporated to furnish a mixture of aldehyde **21** and succinimide, which was used without separation for the next reaction. The ^1H NMR signals of **21**: δ 1.17 (d, $J = 6$ Hz, 3 H), 1.37 (d, $J = 6$ Hz, 3 H), 1.47 (d, $J = 7$ Hz, 3 H), 2.61−2.85 (m, 3 H), 3.40 (s, 3 H), 3.90−4.00 (m, 1 H), 4.12−4.20 (m, 1 H), 4.68 (br s, 2 H), 5.31−5.47 (m, 2 H), 6.05 (dd, $J = 16$, 1 Hz, 1 H), 6.84−6.98 (m, 2 H), 7.04 (d, $J = 16$ Hz, 1 H), 9.79 (d, $J = 7$ Hz, 1 H).

To a solution of the above aldehyde **21** dissolved in *t*-BuOH (4 mL) were added the phosphate buffer (2 mL, pH 3.6), 2-methyl-2-butene (0.48 mL, 3.4 mmol), and $NaClO_2$ (60 mg, 80% purity, 0.53 mmol) dissolved in H_2O (1 mL). The reaction mixture was stirred at room temperature for 2 h. Most of the solvents were removed by using a vacuum pump, and the residue was diluted with EtOAc and brine. The layers were separated, and the aqueous layer, after acidification to pH 4 with 1 N HCl, was extracted with EtOAc several times. The combined extracts were dried and concentrated to yield a mixture of acid **3**, succinimide, and $Me_2C(Cl)CHClMe$, which was used for the next reaction without purification. The ^1H NMR signals of **3**: δ 1.19 (d, $J = 7$ Hz, 3 H), 1.38 (d, $J = 6$ Hz, 3 H), 1.45 (d, $J = 7$ Hz, 3 H), 2.60−2.85 (m, 2 H), 3.42 (s, 3 H), 3.93−4.02 (m, 1 H), 4.12−4.19 (m, 1 H), 4.69 (s, 2 H), 5.24−5.47 (m, 2 H), 6.06 (d, $J = 16$ Hz, 1 H), 6.5 (br peak, 2 H), 6.75−6.93 (m, 2 H), 7.23 (d, $J = 16$ Hz, 1 H).

A solution of the above acid **3** and NEt_3 (0.068 mL, 0.49 mmol) in THF (1 mL) was stirred at room temperature for 20 min, and a solution of $Cl_3C_6H_2COCl$ (0.070 mL, 0.45 mmol) in THF (1 mL for dilution and 1 mL for washing) was added. The resulting mixture was stirred at room temperature for 2 h and concentrated by using a rotary evaporator to afford the mixed anhydride, which was diluted with toluene. The cloudy solution was filtered quickly through a pad of Celite with toluene (total volume used for this operation was 120 mL). To a solution of DMAP (65 mg, 0.53 mmol) in toluene (10 mL) at 40 °C was added the above toluene solution over 3 h. After the addition, the solution was stirred at 40 °C further for 2 h and directly evaporated to leave an oil, which was purified by chromatography (hexane/EtOAc) to afford lactone **22** (55 mg,

40% from the furan **20**): $[\alpha]^{24}_D = -80$ (*c* 0.36, $CHCl_3$); IR (neat) 1735, 1718, 1708, 1265, 1182, 1055 cm^{-1}; ^1H NMR δ 1.37 (d, *J* = 6 Hz, 3 H), 1.42 (d, *J* = 7 Hz, 3 H), 1.44 (d, *J* = 7 Hz, 3 H), 2.63 (dd, *J* = 16, 3 Hz, 1 H), 2.75 (dd, *J* = 16, 10 Hz, 1 H), 3.39 (s, 3 H), 4.20 (dt, *J* = 1, 6 Hz, 1 H), 4.65 (br s, 2 H), 4.96−5.06 (m, 1 H), 5.18 (q, *J* = 7 Hz, 1 H), 5.32−5.44 (m, 1 H), 6.06 (dd, *J* = 16, 1 Hz, 1 H), 6.75 (d, *J* = 16 Hz, 1 H), 6.82 (dd, *J* = 16, 6 Hz, 1 H), 7.00 (d, *J* = 16 Hz, 1 H); ^{13}C NMR δ 196.2, 170.5, 164.6, 164.0, 144.2, 133.3, 132.6, 124.4, 95.2, 78.1, 75.4, 72.4, 68.3, 56.0, 40.9, 19.8, 17.7, 15.8. Anal. Calcd for $C_{18}H_{24}O_9$: C, 56.24; H, 6.29. Found: C, 55.99; H, 6.23.

Macrosphelide B (2). To a solution of **22** (16 mg, 0.042 mmol) in CH_2Cl_2 (0.5 mL) was added CF_3CO_2H (0.5 mL). The solution was stirred at room temperature for 1.5 h and concentrated to leave an oil, which was subjected to chromatography to furnish **2** (13 mg, 92%): $[\alpha]^{26}_D = +9.1$ (*c* 0.154, MeOH) [lit.[5] $[\alpha]^{24}_D = +10.0$ (*c* 0.39, MeOH)]. The ^1H NMR and ^{13}C NMR spectra of synthetic **2** were identical with the data reported in the literatures.[3b,5]

8-MOM Ether of 14-*epi*-Macrosphelide A (23). To a solution of **22** (19 mg, 0.049 mmol) in MeOH (2 mL) was added $NaBH_4$ (2 mg, 0.053 mmol) at −15 °C, and the solution was stirred at −15 °C for 20 min. Brine was added to the solution, and the resulting mixture was extracted with EtOAc twice. The combined extracts were dried and concentrated to give a residue. The ratio of **23** and **24** was >10:1 by ^1H NMR spectroscopy. Finally, purification by chromatography (hexane/EtOAc) afforded **23** (14 mg, 74%): IR ($CHCl_3$) 1728 cm^{-1}; ^1H NMR δ 1.28 (d, *J* = 6 Hz, 3 H), 1.37 (d, *J* = 7 Hz, 3 H), 1.40 (d, *J* = 6 Hz, 3 H), 1.9 (br s, 1 H), 2.48 (dd, *J* = 16, 1.5 Hz, 1 H), 2.61 (dd, *J* = 16, 11 Hz, 1 H), 3.39 (s, 3 H), 4.02 (t, *J* = 8 Hz, 1 H), 4.27 (br s, 1 H), 4.58 (d, *J* = 7 Hz, 1 H), 4.66 (d, *J* = 7 Hz, 1 H), 4.92−5.03 (m, 1 H), 5.17−5.25 (m, 1 H), 5.32−5.44 (m, 1 H), 5.88 (d, *J* = 16 Hz, 1 H), 6.02 (dd, *J* = 16, 2 Hz, 1 H), 6.71 (dd, *J* = 16, 8 Hz, 1 H), 6.87 (dd, *J* = 16, 4 Hz, 1 H).

Macrosphelide A (1). To a solution of **23** (25 mg, 0.065 mmol), DEAD (0.016 mL, 0.10 mmol), and PPh_3 (26 mg, 0.099 mmol) in THF (1.5 mL) was added HCO_2H (0.044 mL, 1.1 mmol), and the mixture was stirred at room temperature for 1.5 h. The phosphate buffer (2 mL, pH 3.6) was added, and the resulting mixture was extracted with EtOAc. The extract was dried and concentrated to give a residue, which was passed through a short column of silica gel with hexane/EtOAc to afford the semipurified formate ester.

A solution of the above formate and NEt_3 (1 drop) in MeOH (2 mL) was stirred at room temperature for 1 h and concentrated to leave a residue, which was purified by chromatography (hexane/EtOAc) to afford the 8-MOM ether **24** (18 mg, 72%).

A solution of the above MOM ether **24** in CH_2Cl_2 (0.7 mL) and CF_3CO_2H (0.7 mL) was stirred at room temperature for 2 h and concentrated to afford a residue, which was purified by chromatography to furnish macrosphelide A (**1**) (12 mg, 70%), whose ^1H NMR and ^{13}C NMR spectra were identical with those reported:[3b,5] $[\alpha]^{30}_D = +85$ (*c* 0.046, MeOH) [lit.[3b] $[\alpha]^{23}_D = +84.1$ (*c* 0.59, MeOH); lit.[5] $[\alpha]^{27}_D = +82$ (*c* 0.10, MeOH)].

14-*epi* Macrosphelide A (25). (a) From the MOM Ether 23. According to the procedure for preparation of macrosphelide B (**2**), a reaction involving **23** (11 mg, 0.028 mmol), CF_3CO_2H (0.7 mL), and CH_2Cl_2 (0.7 mL) at room temperature for 2 h afforded **25** (8 mg, 86%) after purification by chromatography: IR (THF) 3393, 1745, 1730 cm^{-1}; ^1H NMR (DMSO-d_6)[31] δ 1.19 (d, *J* = 6 Hz, 3 H), 1.22 (d, *J* = 7 Hz, 3 H), 1.32 (d, *J* = 6 Hz, 3 H), 2.4−2.7 (m), 3.94−4.04 (m, 1 H), 4.22−4.29 (m, 1 H), 4.61−4.74 (m, 1 H), 5.04−5.20 (m, 2 H), 5.43 (d, *J* = 6 Hz, 1 H), 5.69 (d, *J* = 6 Hz, 1 H), 5.78 (dd, *J* = 16, 1 Hz, 1 H), 5.92 (dd, *J* = 16, 2 Hz, 1 H), 6.65 (dd, *J* = 16, 6 Hz, 1 H), 6.78 (dd, *J* = 16, 4 Hz, 1 H).

(b) From Macrosphelide B (2). According to the procedure for preparation of **23** from ketone **22**, a reaction involving macrosphelide B (**2**) (7.7 mg, 0.023 mmol), $NaBH_4$ (1 mg, 0.026 mmol), and MeOH (1 mL) at 0 °C for 1 h afforded **25** (6.3 mg, 82%) with a >20:1 ratio of **25** and **1**.

MOM Protection of Macrosphelide B (2). According to the procedure for preparation of **19**, a solution of **2** (6.2 mg, 0.018 mmol), MOMCl (0.007 mL, 0.094 mmol), and *i*-Pr_2NEt (0.032 mL, 0.18 mmol) in CH_2Cl_2 (0.5 mL) was stirred at room temperature for 2.5 d to afford **22** (5.2 mg, 75%) after purification by chromatography. The ^1H NMR spectrum of synthetic **22** was identical with that obtained by the macrocyclization of seco acid **3** (vide supra).

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Supporting Information Available: ^1H NMR spectra of compounds lacking elemental analyses (**23** and **25**) and ball and stick models of MB-1 and MB-2. This material is available free of charge via the Internet at http://pubs.acs.org.

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(31) Compound **25** was sufficiently dissolved in $CDCl_3$.