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Synthesis of macrosphelides H and G

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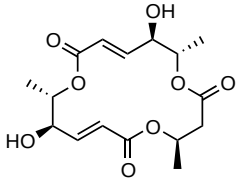
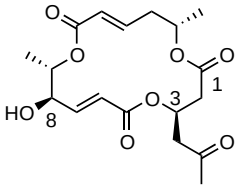
Abstract—A compound with furyl and vinyl groups was designed as an intermediate for synthesis of macrosphelide H. The furyl group was oxidatively transformed into the key C(5)–O(10) part by a two-step conversion of (1) NBS, H_2O; (2) $NaClO_2$ without affecting the free hydroxyl group at C(3), thus furnishing the seco acid, while the Wacker oxidation at the final step was used to convert the vinyl group into acetyl group to afford macrosphelide H. This strategy was applied successfully to synthesis of macrosphelide G as well.

Macrosphelides A–L are 16-membered macrocyclic triesters recently isolated from different sources by the Omura[1] and Numata groups.[2] Macrosphelide A (**1**)[1a] and, quite recently, several other macrosphelides[2b,c] have been shown to inhibit adhesion of human-leukemia HL-60 cells to human-umbilical-vein endothelial cells strongly and cell-selectively. Macrosphelides H (**2**) and L are those which show the strongest activity. Consequently, macrosphelides have received much attention as lead compounds for the development of new anti-cancer drugs. In addition to the biological interest, the multi-chiral centers and the three ester linkages present in macrospelides evoke interest in organic synthesis as target molecules. Construction of the key 4-hydroxyl-2-alkenoic acid part(s) with the correct stereochemistry, differentiation of one acid moiety from the other two for preparation of a seco acid, and macrocyclization are the key steps of the synthesis. Two groups have reported the synthesis of macrosphelides A, B, and E with conventional reactions,[3,4] while we achieved a synthesis of macrosphelides A and B[5] in which the furan ring is built in as the masked 4-oxo-2-alkenoic acid moiety. The furan ring is later unmasked for macrocyclization by the two-step oxidation [(1) NBS, H_2O; (2) $NaClO_2$] without affecting the free hydroxyl group present in another side of the molecule.[6] The specificity of the reagents for the furan oxidation and the chemical stability of the furan ring provide plenty of flexibility in the synthesis of macrosphelide, and this advantage was shown in the recent synthesis of macrosphelides C and F.[7]



macrosphelide A (**1**)



macrosphelide H (**2**)

After the above synthesis, the Numata group has determined the absolute structure of macrosphelide H (**2**), the molecule of the highest inhibitory activity.[2c] Being different from other macrosphelides, the side chain at C(3) is the acetonyl ($AcCH_2$) group, which is highly reactive toward nucleophiles and unstable under acidic and basic conditions. One synthetic equivalent of the acetyl (Ac) group is the vinyl group, which transformed into the acetyl group by Wacker oxidation under mild conditions.[8,9] In consideration of the Wacker oxidation and the furan ring as the masked 4-oxo-2-alkenoic acid part, we designed compound **3** as a key intermediate, which is depicted in Fig. 1 with a sequence leading to **2**. Herein, we describe a result of this investigation. In addition, we accomplished synthesis of macrosphelide G,[2a,b] a formally de-acetylated compound of **2** (structure is shown in Scheme 2), by using the same method.

First, a synthetic route to the intermediate **3** through acid **6** with the TBS group was studied. According to the literature,[10] alcohol **4** of >99% ee was converted into **5**, which was hydrolyzed to **6** in 70% yield. On the

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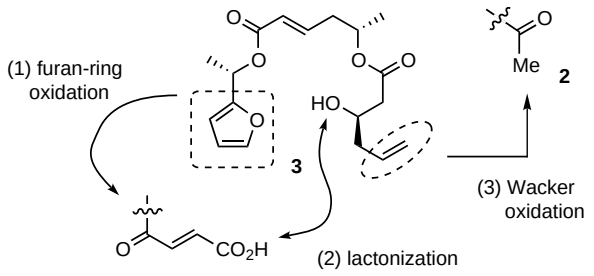
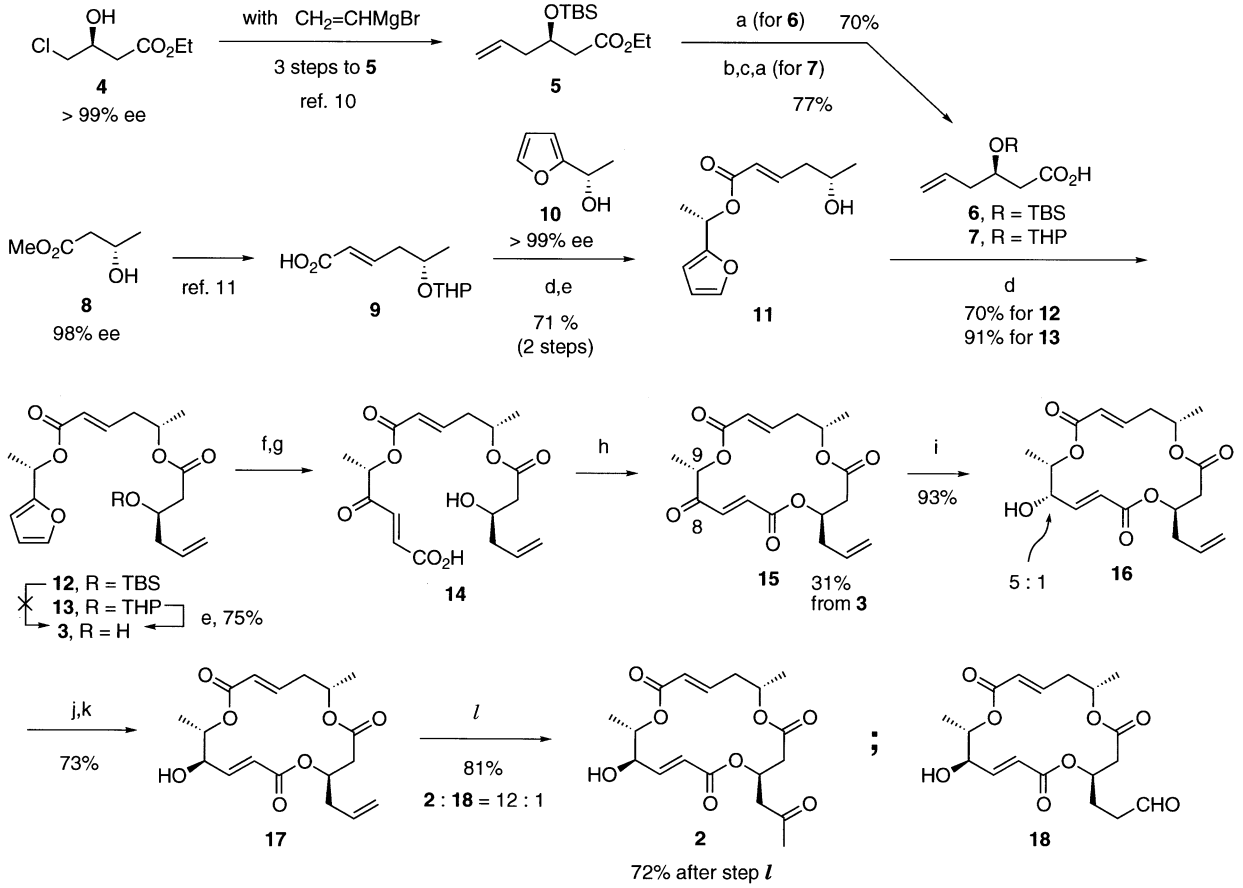


Figure 1. The key intermediate **3** and its transformation toward macrosphelide H (**2**).

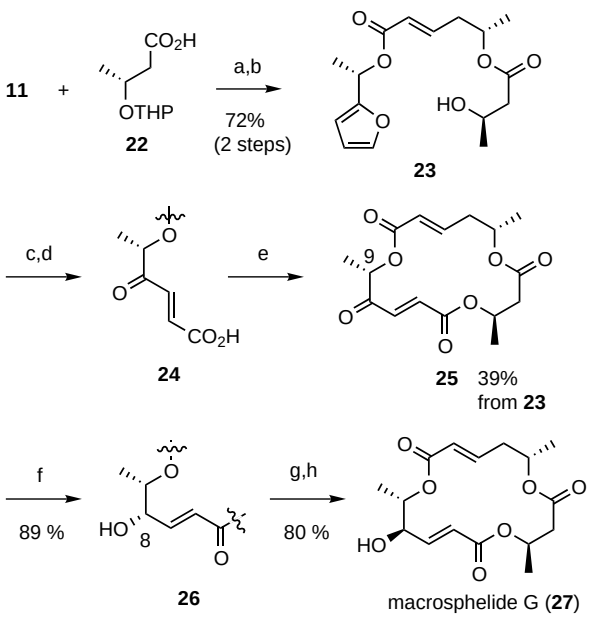
other hand, compound **11** was prepared in 71% yield by DCC condensation of acid **9**, derived[11] from alcohol **8**[12] of 98% ee, and furyl alcohol **10**[13] of >99% ee. Condensation of acid **6** and alcohol **11** using the DCC protocol produced ester **12** in 70% yield. Unfortunately, attempted desilylation of **12** with TBAF in THF and HF in CH_3CN at various temperatures for hours resulted in decomposition and/or recovery of **12**. Then, a sequence with the THP ether **7** was examined. Ether **7** was prepared from **5** by the three steps of b, c, and a in 77% yield,[14] and DCC condensation with **11** produced **13** in 91% yield. Deprotection of **13** was successful with PPTS in EtOH to furnish the key alcohol **3** in good yield.

The furan ring of **3** was converted into the 4-oxo-2-alkenoic acid moiety by the oxidation mentioned above[6] and the subsequent Yamaguchi lactonization[15] of the resulting seco acid **14** at 30°C furnished lactone **15**[16] in 31% yield from **3** with a minor diastereomer probably at C(9) as the result of the epimerization. At higher temperatures more than 30°C, the epimerization increased, thereby decreasing the yield of desired **15**. Reduction of **15** with $NaBH_4$ furnished a mixture of **16** and other diastereomer(s) in a ratio of 5:1 in 93% yield. The hydroxyl group at C(8) was inverted by the Mitsunobu inversion[17] with 3,5-$(NO_2)_2C_6H_3CO_2H$. As observed previously,[7] most of the minor diastereomer(s) was decomposed during the inversion reaction to furnish alcohol **17** with the desired stereochemistry for **2**.

Wacker oxidation of **17** under the standard conditions[8] ($PdCl_2$ (0.1 equiv.), CuCl (1 equiv.), DMF/H_2O = 10:1, O_2 atm, rt, overnight) encountered not only slow conversion but also poor regioselectivity to furnish the starting **17** in 33% recovery and production of macrosphelide H (**2**) and aldehyde **18** in a ratio of 5:1 in 53%



Scheme 1. Synthesis of macrosphelide H (**2**). (a) LiOH, THF/H_2O; (b) HF (1.5 equiv., 55% aqueous), CH_3CN; (c) DHP, *p*-TsOH, CH_2Cl_2; (d) DCC (1.4 equiv.), CSA (0.3 equiv.), DMAP (0.6 equiv.), CH_2Cl_2; (e) PPTS, EtOH; (f) NBS; then furan, pyridine, acetone/H_2O (5:1); (g) $NaClO_2$, phosphate buffer (pH 3.6), 2-methyl-2-butene, *t*-BuOH/H_2O (2:1); (h) $C_6H_3Cl_3COCl$, Et_3N; then DMAP, toluene, 30°C; (i) $NaBH_4$, MeOH, –78°C; (j) DIAD (2 equiv.), PPh_3 (2 equiv.), 3,5-dinitrobenzoic acid (5 equiv.), THF, rt; (k) Et_3N, MeOH; (l) $PdCl_2$ (5 equiv.), DMF/H_2O (7:1).



Scheme 2. Synthesis of macrosphelide G (**27**). (a) DCC (1.4 equiv.), CSA (0.3 equiv.), DMAP (0.6 equiv.), CH_2Cl_2; (b) PPTS, EtOH; (c) NBS, $NaHCO_3$; then furan, pyridine, acetone/H_2O (5:1); (d) $NaClO_2$, phosphate buffer (pH 3.6), 2-methyl-2-butene, *t*-BuOH/H_2O (2:1); (e) $C_6H_3Cl_3COCl$, Et_3N; then DMAP, toluene, 38°C; (f) $NaBH_4$, MeOH, –50°C; (g) DIAD (2 equiv.), PPh_3 (2 equiv.), 3,5-dinitrobenzoic acid (5 equiv.), THF; (h) Et_3N, MeOH.

combined yield. The formation of the aldehyde suggests chelation of the carbonyl oxygen to Pd^{2+} in the transition state.[18,19] To make matters worse, chromatographic separation of these products was unfortunately unsuccessful due to highly cross R_f values on TLC. Consequently, the Wacker reaction was re-investigated under conditions summarized in Table 1 using a model compound **19**, which under the standard conditions gave a 6:1 mixture of methyl ketone **20** and aldehyde **21** (entry 1). Lower temperature (entry 2) and use of another re-oxidizing metal ($Cu(OAc)_2$) in 0.2 and 2 equiv. quantities (entries 3 and 4) according to the literature[20] did not improve the situation. Fortunately, stoichiometric use of $PdCl_2$ (4.5 equiv.) was found to afford the ratio of 15:1 in 84% combined yield (entry 5), though the reason for the better ratio is not clear.[21]

The conditions of entry 5 were applied to the macrosphelide synthesis, which not only accelerated the reaction but also improved the ratio of **2** and **18** to 12:1 in 81% combined yield.[22] Moreover, we succeeded in a facile isolation of **2** from the mixture by submitting the mixture to the oxidation with $NaClO_2$ in *t*-BuOH and H_2O at pH 3.6, the conditions opted for the conversion of the aldehyde to the corresponding acid **14** (vide supra). Under the conditions, aldehyde **18** was selectively converted to acid (structure not shown), thus furnishing **2** ($[\alpha]_D^{29}$ +41 (*c* 0.034, EtOH); lit.[2a,b] $[\alpha]_D$ +41.7 (*c* 0.22, EtOH)] in 72% yield from **17** after chromatography on silica gel. Spectral data (^1H, ^{13}C NMR, IR spectra) of synthetic **2** were identical with those reported.[2a,b]

Because of the structural similarity of macrosphelide G (**27**) to macrosphelide H (**2**), the strategy used for the synthesis of **2** was applied to synthesis of **27** (Scheme 2). No epimerization at C(9) during the conversion of furan **23** to lactone **25**[16] was observed, thus indicating the unusually unstable nature of the intermediate **15** (and **14**) in Scheme 1. Reduction of keto lactone **25** with $NaBH_4$ to alcohol **26**, 8-epimer of **27**, proceeded with a 5:1 diastereoselectivity that was similar to that obtained above in the reduction of **15** of Scheme 1. Although the selectivity was not excellent, kinetic decomposition of the minor diastereomer took place during the subsequent Mitsunobu inversion to afford macrosphelide G (**27**) as the sole product in 80% yield: $[\alpha]_D^{29}$ +67 (*c* 0.087, EtOH); reported.[2a,b] $[\alpha]_D$ +66.7 (*c* 0.48, EtOH). The spectral data (^1H and ^{13}C NMR spectra) of synthetic **27** were coincident with those reported.[2a,b]

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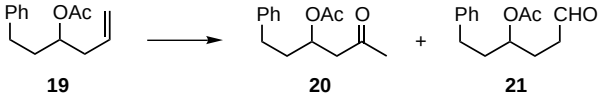
Table 1. Wacker oxidation of **19** under various conditions



Entry	Catalyst (equiv.)	Conditions	Ratio of **20**:**21**	Combined yield (%)
1	$PdCl_2$ (0.1) CuCl (1)	DMF/H_2O (10:1) rt, overnight	6:1	91
2	$PdCl_2$ (0.1) CuCl (1)	DMF/H_2O (10:1) 0°C, 24 h	6:1	65[a]
3	$PdCl_2$ (0.1) $Cu(OAc)_2$ (0.2)	$AcNMe_2$/H_2O (7:1) rt, 24 h	6:1	93
4	$PdCl_2$ (0.1) $Cu(OAc)_2$ (2)	$AcNMe_2$/H_2O (7:1) rt, 24 h	6:1	95
5	$PdCl_2$ (4.5)	DMF/H_2O (7:1) rt, 4 h	15:1	84

[a] Some of **19** was recovered.

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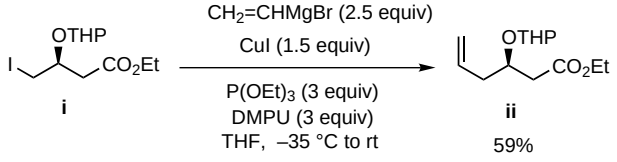
14. Reaction of THP ether **i** and CH_2=CHMgBr under the conditions used for synthesis of **5** (in 78–84% yield) produced olefin **ii** (in ca 60% calculated yield) which was contaminated with $P(OEt)_3$ even after careful separation of $P(OEt)_3$ by chromatography on silica gel.



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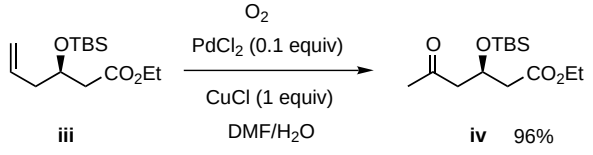
18. Wacker oxidation of olefin **iii** furnished methyl ketone **iv** exclusively.[2c]



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22. The use of 5 equiv. of $PdCl_2$ at the last step in the synthesis of **2** would be acceptable.