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First total synthesis of macrosphelides C and F

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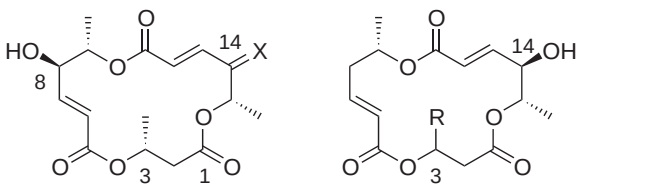
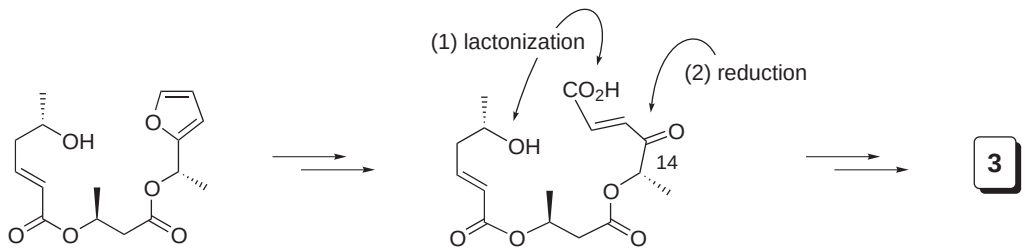
Abstract—Macrosphelides C and F were synthesized by lactonization of 14-oxo *seco* acids at the O(10)–C(11) bond followed by reduction and Mitsunobu inversion of the resulting hydroxyl group. The *seco* acids were prepared from the corresponding furans by furan ring-opening with NBS followed by further oxidation of the 4-oxo-2-alkenals with $NaClO_2$.

Macrosphelides A–L are a family of compounds isolated from the culture medium of *Microsphaeropsis* sp. FO-5050 and/or *Periconia byssoides* by the Omura group[1–3] and the Numata group,[4–6] and their planar structures have been determined by spectroscopic methods and by chemical transformations. Among them, macrosphelides A and B (**1** and **2**) have been shown to strongly inhibit the adhesion of human-leukemia HL-60 cells to human-umbilical-vein endothelial cells.[7] Discovery of this property is probably the reason that prompted elucidation of the stereochemistry and the first total synthesis of **1** and **2** shortly after the isolation.[8] Consequently, investigation of the biological property and determination of the stereochemistry of other macrosphelides should urgently be undertaken. However, it was quite recently that Numata elucidated the stereochemistry of macrosphelides C, F, G, I and L by X-ray analysis and/or chemical degradation.[6,9]



Macrosphelide A (**1**): X = OH, H
Macrosphelide B (**2**): X = O

Macrosphelide C (**3**): R = β-Me
Macrosphelide F (**4**): R = α-Me



5 **6**

Scheme 1. A sequence to macrosphelide C (**3**).

Keywords: asymmetric synthesis; furans; macrolides; macrosphelide C; macrosphelide F.

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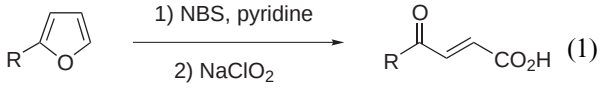
Macrosphelides are triesters possessing a 4-hydroxy (or 4-oxo)-2-hexenoic acid moiety (or moieties). With regard to this structural unit, we recently reported a simple method for conversion of the 2-alkylfurans into 4-oxo-2-alkenoic acids as illustrated in Eq. (1).[10]

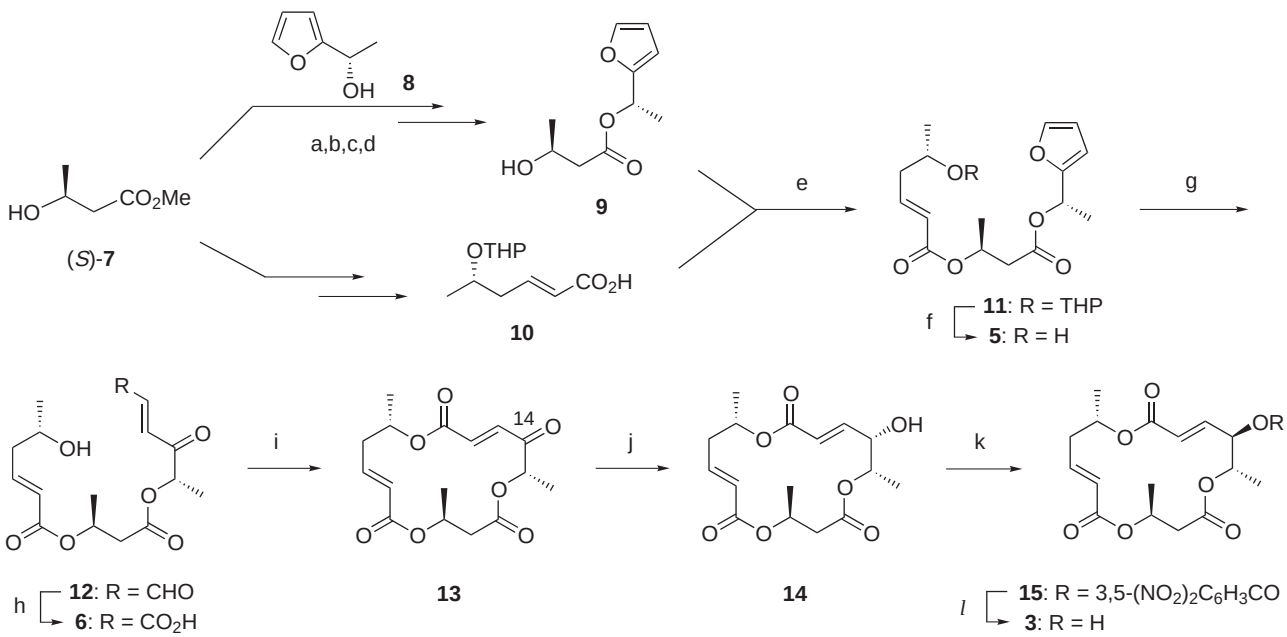


(1)

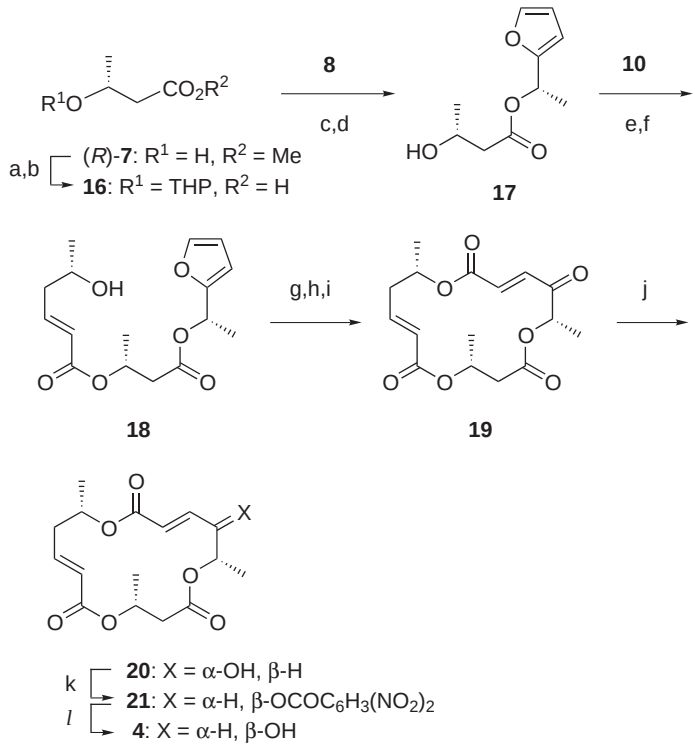
This transformation, though oxidation, is compatible with a free hydroxyl group. In addition, several methods are available for synthesis of 2-substituted furans. With the best use of these synthetic advantages, construction of the *seco* acid of **2** was accomplished quite efficiently.[11] Furthermore, reduction of the 14-oxo macrocyclic intermediate was found to proceed stereoselectively to yield 14-*epi* alcohol, and inversion of the hydroxyl group afforded **1**. The conformational bias provided by the macrocyclic lactone is probably responsible for the high stereoselectivity observed in the reduction. This result strongly suggests the feasibility of synthesis of other macrosphelides as well. Based on this concept, we report the first synthesis of macrosphelides C and F (**3** and **4**).

An outline of the synthesis of macrosphelide C (**3**) is depicted in Scheme 1, which involves transformation of furan **5** into 14-oxo *seco* acid **6** followed by macrocyclization and reduction. A synthesis along this line is summarized in Scheme 2. Alcohol **9** was prepared from methyl (*S*)-3-hydroxybutanoate ((*S*)-**7**)[12] of 98% ee and furyl alcohol **8**[13,14] of 92–95% ee through DCC condensation, while acid **10** was synthesized through the Wittig reaction of the corresponding aldehyde derived from (*S*)-**7**.[15] Esterification of alcohol **9** and acid **10** with DCC in the presence of DMAP and CSA furnished ester **11**, and subsequent deprotection of the THP group yielded the key compound **5** in 53% yield from **9**. Furan **5** was converted into aldehyde **12** with NBS and then to the 14-oxo *seco* acid **6**, which, without purification, was subjected to the Yamaguchi lactonization.[16] The standard procedure[16] involving the following steps of (i) $Cl_3C_6H_2COCl$, Et_3N, THF; (ii) filtration; (iii) slow addition to DMAP in toluene, produced the 14-oxo lactone **13** in 35–42% yield, while a modified method (step i of Scheme 2), which is reported by Yonemitsu[17] and is known to be operationally simpler, furnished lactone **13** after chromatography in 61% yield from furan **5**. Higher temperatures of 40–50°C for the lactonization did not result in any further improvement in the yield of **13**.

Reduction of the carbonyl group at C(14) of **13** was investigated with $NaBH_4$ in MeOH at −70°C. The reaction proceeded stereoselectively to afford 14-*epi* macrosphelide C (i.e. **14**) with high stereoselectivity of 22:1 in 82% yield. Mitsunobu inversion of **14** with 3,5-$(NO_2)_2C_6H_3CO_2H$, PPh_3, and DEAD produced ester **15**. However, chromatographic separation of **15** and the co-produced dicyclohexylurea was unsuccessful due to the almost identical R_f values on TLC. Fortunately, the problem was averted with diisopropyl azodicarboxylate (DIAD), and ester **15** was isolated in 71% yield as the sole product. Finally, methanolysis of **15**



Scheme 2. (a) DHP, H^+, 97%; (b) 2N LiOH, THF, H_2O, 92%; (c) **8** (1 equiv.), acid from **7** (1.5 equiv.), DCC (1.2 equiv.), DMAP (0.3 equiv.), CSA (0.15 equiv.), 82%; (d) PPTS (cat.), MeOH, 80%; (e) **10**, DCC (1.5 equiv.), DMAP (0.3 equiv.), CSA (0.15 equiv.), CH_2Cl_2, rt, 8 h, 69%; (f) PPTS (0.2 equiv.), MeOH, 77%; (g) NBS (1.2 equiv.), $NaHCO_3$, acetone/H_2O (10:1), −15°C, 3 h then furan (5 equiv.), C_5H_5N (1.2 equiv.), rt, 12 h; (h) $NaClO_2$, $Me_2C{=}CHMe$, *t*-BuOH, buffer (pH 3.6); (i) $Cl_3C_6H_2COCl$, DMAP, toluene, rt, o.n., 61% from **5**; (j) $NaBH_4$, MeOH, −70°C, 82%; (k) DIAD (2 equiv.), $(NO_2)_2C_6H_3CO_2H$ (5 equiv.), PPh_3 (2 equiv.), THF, 71%; (l) Et_3N, MeOH, rt, 2 h, 84%.



Scheme 3. For (a) and (b), see: (a) and (b) in Scheme 2, 90%; (c) **16**, **8**, DCC, DMAP, CSA, CH_2Cl_2; (d) PPTS, MeOH, 75%; (e) DCC, DMAP, CSA, CH_2Cl_2, 79%; (f) PPTS, MeOH, 73%; (g) NBS, $NaHCO_3$, acetone/H_2O (10:1), −15°C then furan, C_5H_5N, rt; (h) $NaClO_2$, $Me_2C{=}CHMe$, *t*-BuOH, buffer (pH 3.6); (i) $Cl_3C_6H_2COCl$, DMAP, toluene, rt, o.n., 56% from **18**; (j) $NaBH_4$, MeOH, −70°C, 80%; (k) DIAD, $(NO_2)_2C_6H_3CO_2H$, PPh_3, THF, 69%; (l) Et_3N, MeOH, rt, 79%.

furnished macrosphelide C (**3**) in good yield. The ^1H NMR spectrum and $[\alpha]_D$ value of synthetic **3** were in full agreement with the data reported: $[\alpha]_D^{26}=+31$ (*c* 0.065, MeOH); lit.[2] $[\alpha]_D^{20}=+29.5$ (*c* 0.10, MeOH).

Macrosphelide F (**4**) is a C(3) stereoisomer of macrosphelide C (**3**), and thence (*R*)-**7** (98% ee) was the starting compound. As illustrated in Scheme 3, (*R*)-**7** was converted into acid **16** by the standard transformation (Scheme 3). Condensation of **16** with furyl alcohol **8** and subsequent deprotection of the THP group produced alcohol **17** in 75% yield. Esterification of **17** with acid **10** followed by deprotection furnished the key intermediate **18**. Oxidative transformation of **18** and macrolactonization of the resulting 14-oxo *seco* acid again under the Yonemitsu conditions[17] produced lactone **19** in 56% yield from furan **18**. Reduction of **19** with $NaBH_4$ in MeOH at −70°C proceeded with somewhat lower selectivity than that of **13** (vide infra), and a mixture of **20** and **4** was obtained with a 4:1 ratio in 80% combined yield. Fortunately, the mixture underwent kinetic separation during the Mitsunobu inversion to furnish dinitrobenzoate **21** as the sole product, which upon methanolysis furnished **4** in 69% yield. The ^1H NMR spectrum and $[\alpha]_D$ value of **4**, thus synthesized, were in good agreement with the data reported: $[\alpha]_D^{26}=+21$ (*c* 0.02, EtOH); lit.[4] $[\alpha]_D=+23.3$ (*c* 0.09, EtOH).

The results described above clearly show that the *Re* face of the carbonyl group at C(14) in the stable conformers of **13** and **19** is exposed to the outside of the ring in the reduction with $NaBH_4$. On the basis of the present and previous results, this strategy, involving (1) convenient preparation of 14-oxo *seco* acid; (2) cyclization; (3) formation of the C(14)–OH by reduction followed by inversion, is undoubtedly applicable to the synthesis of other macrosphelides. In addition, we unexpectedly observed the product-selective formation of ester **21** from a 4:1 mixture of **20** and **4**. This result strongly indicates that alcohols **20** and **4** also take the same conformations as that of ketone **19**, in which the OH group at C(14) is projected into the inside and the outside of the macrocyclic ring, respectively, and that the benzoate anion attacked the PPh_3 complex of the major alcohol **20** from the outside of the ring to produce **21**, while the attack on the PPh_3 complex derived from the minor alcohol **4** was strongly prevented by the ring, thereby inducing other reaction(s) such as the elimination.

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