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Total synthesis of macrosphelides B and A

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Abstract

An efficient total synthesis of macrosphelide B has been developed in which the C(5)–O(10) and the C(11)–O(16) fragments were prepared from (*S*)-1-(2-furyl)ethanol of >98% ee via oxidation of the furan part. In addition, macrosphelide B was transformed stereoselectively into macrosphelide A by reduction followed by Mitsunobu inversion.

Keywords: biologically active compounds; macrosphelide B; macrosphelide A; macrolide; oxidation of furans; stereocontrol.

Macrosphelides A and B, which are produced by *Microsphaeropsis* sp. FO-5050, were isolated by Omura and co-workers[1] and have been shown to strongly inhibit the adhesion of human leukemia HL-60 cells to human umbilical-vein endothelial cells without inhibiting the growth of various mammalian cell lines and microorganisms; consequently, they are highly attractive compounds for use as next-generation chemotherapeutical drugs against cancer.[2] Recently, the 3D structures of macrosphelides A and B have been determined as depicted in **1** and **2**, respectively, and a total synthesis of **1** was accomplished by collaboration of Omura and Smith.[3] In their synthesis, the hydroxyl groups are installed on the sorbic ester by using the Sharpless AD reaction[4] with 85% ee,[5] and the conversion of **1** into **2** by PDC oxidation proceeds with low regioselectivity and efficiency, as expected. These results prompted us to investigate an alternative strategy whereby synthesis of **2** is carried out first, and hydride reduction of **2** or a macrocyclic intermediate thereof (ketone) follows to synthesize **1**. Advantages of this strategy are probably that: (1) synthesis of **2** would be accomplished more easily than that of **1** since there is one less chiral center in **2**; and (2) reduction of **2** would proceed with high diastereoselectivity due to the conformational bias provided by the macrocycle. Herein, we report a successful result of this strategy.

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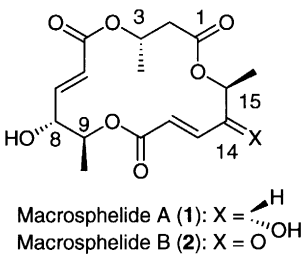
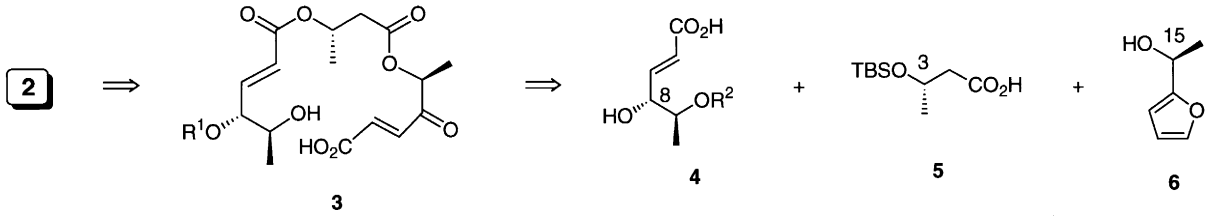
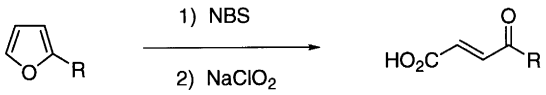


The target molecule **2** would be synthesized through macrocyclization of seco acid **3** (Scheme 1). Based on the fact that chemically stable 2-alkyl furans are a synthetic equivalent of the rather unstable γ-oxo-α,β-unsaturated carboxylic acids through the method developed by us (Eq. (1)),[6] **3** was dissected into pieces **4**–**6**. Acid **5** is available via the asymmetric reduction of acetoacetate,[7] while methods for the preparation of **6** have been published.[8] Concerning fragment **4**, the furan-ring oxidation (Eq. (1)) of an appropriately protected alcohol **6** followed by reduction of the resulting γ-keto acid would be an appropriate method.



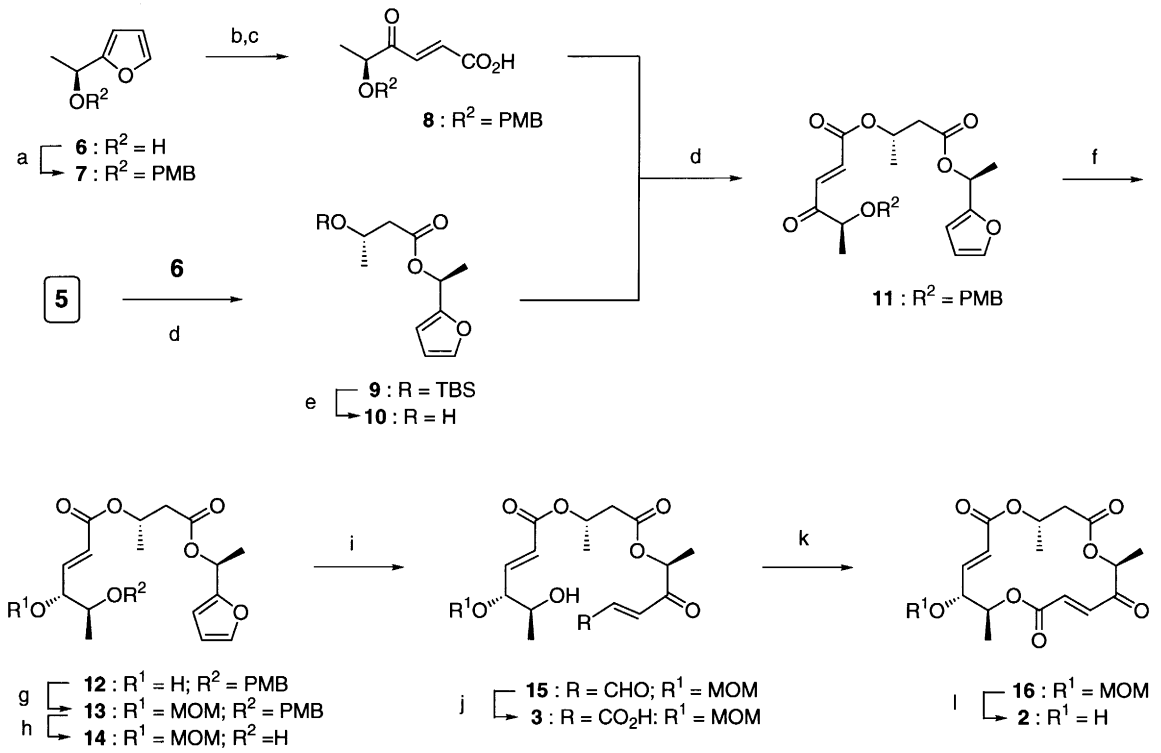
Scheme 1. Starting compounds and intermediates for synthesis of macrosphelide B (**2**)

Among possible sequences for assembling fragments **5** and **6**, the route presented in Scheme 2 was chosen on the basis of the number of reaction steps involved, in which chelation-controlled reduction of ketone **11** to afford the desired *anti* alcohol **12** is a crucial step in the synthesis. Alcohol **6** of >98% ee[9] was prepared by the kinetic resolution of the corresponding racemic alcohol[8a] using the Sharpless reagent[10] (38% yield based on the racemic alcohol). Conversion of **6** into the PMB ether **7** was carried out as usual, and **7** was then transformed into γ-keto acid **8** by the oxidative conversion shown in Eq. (1) (48% yield from **6**) (Scheme 2). On the other hand, condensation of acid **5**[11,12] (99% ee)[9] and alcohol **6** with DCC in the presence of DMAP and CSA[13] produced ester **9**, which upon desilylation furnished alcohol **10** in good yield. Condensation of acid **8** and alcohol **10** was also accomplished with DCC to afford **11** in 92% yield.



(1)

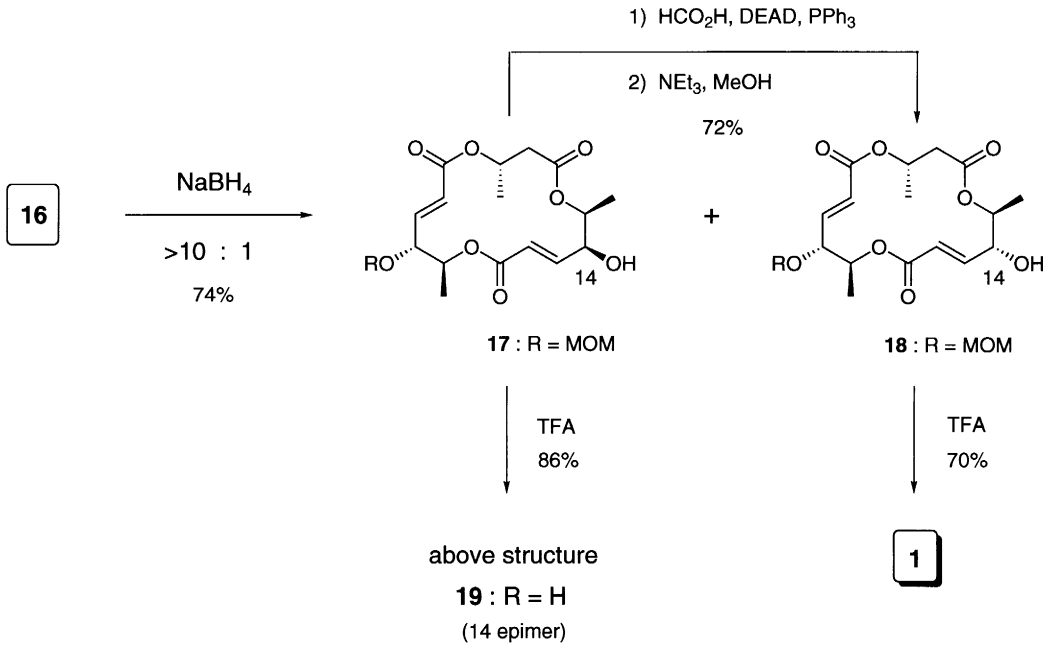
Next, reduction[14] of **11** with $Zn(BH_4)_2$ was investigated. Unfortunately, a mixture of **12** and its epimer was obtained in a ratio of 2:1 when **11** was added to an ethereal solution of $Zn(BH_4)_2$ even at ≤–90°C. It might be reasonable to assume that $Zn\{BH_n(OR)_{4-n}\}_2$, which was formed in the early stage of the reduction, participated in the reduction of the remaining ketone **11** without chelation due to the steric bulkiness of $Zn\{BH_n(OR)_{4-n}\}_2$, thus furnishing the diastereomeric mixture after aqueous work-up. After several unsuccessful trials, it was found that reverse addition could improve the ratio to a practical level of 15:1 in 70% yield. The result is consistent with the above assumption. Protection of alcohol **12** with MOMCl and subsequent deprotection of the PMB group with DDQ furnished alcohol **14** in 82% yield. Without protection of the hydroxyl group, **14** was converted into the key acid **3** by the two-step oxidation



Scheme 2. Reagents and conditions: (a) NaH, PMBCl, 93%. (b) NBS, acetone/H_2O, 10:1, −15°C, 1 h then furan, C_5H_5N, rt, 6 h, 74%. (c) $NaClO_2$, $MeC(H)=CMe_2$, 70%. (d) DCC, DMAP, CSA, rt, overnight, 98% for **9** and 92% for **11**. (e) TBAF, THF, 0°C, 24 h, 73%. (f) $Zn(BH_4)_2$, Et_2O, ≤–90°C, 70%. (g) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 88%. (h) DDQ, CH_2Cl_2/H_2O, 93%. (i and j) similar conditions to (b) and (c). (k) $Cl_3C_6H_2COCl$, NEt_3 then DMAP, toluene, 40°C, 5 h, 40% from **14**. (l) TFA/CH_2Cl_2, 1:1, rt, 1.5 h, 92%

via aldehyde **15**. Lactonization of crude seco acid **3** was carried out by the Yamaguchi method[15] to produce lactone **16**[16] in 40% yield from **14**. Finally, deprotection of the MOM group with TFA in CH_2Cl_2 furnished **2** in good yield: $[\alpha]_D^{24}$=+9.1 (*c* 0.154, MeOH); lit.[1b] $[\alpha]_D^{23}$=+4.10 (*c* 0.99, MeOH); lit.[3] $[\alpha]_D^{24}$=+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 literature.[1b,3]

Next, we examined a synthesis of macrosphelide A (**1**) (Scheme 3). Theoretically, chelation-controlled reduction[14] of ketone **16** should provide **18** of the desired stereochemistry at C(14). However, reduction of **16** with $Zn(BH_4)_2$ at −78°C resulted in a 1:1 mixture of **17** and **18**. On the contrary, $NaBH_4$ in MeOH at −15°C provided **17** highly selectively (>10:1). These results indicate that macrocycle **16** takes one stable conformer, where the undesired side of the carbonyl group at C(14) (pro-*S* face) is exposed to the outside of the macrocyclic ring, thus furnishing a bias for stereoselective reduction even with a simple reagent such as $NaBH_4$. The newly-formed hydroxyl group in **17** was inverted by Mitsunobu reaction[17] with HCO_2H, DEAD, and PPh_3, and methanolysis of the formate with NEt_3 in MeOH furnished **18** in 72% yield. Finally, deprotection with TFA afforded **1** in 70% yield: $[\alpha]_D^{30}$=+85 (*c* 0.046, MeOH); lit.[1b] $[\alpha]_D^{23}$=+84.1 (*c* 0.59, MeOH); lit.[3] $[\alpha]_D^{27}$=+82 (*c* 0.10, MeOH). Similarly, treatment of **17** with TFA furnished 14-epimer of **1** (i.e., **19**) in 86% yield.



Scheme 3. Synthesis of macrosphelide A (**1**)

Acknowledgements

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12. Acid **5** was prepared from methyl (*S*)-3-hydroxybutanoate[7] of 99% ee by silylation (*t*-BuMe_2SiCl, imidazole, DMF) followed by hydrolysis (1N NaOH, MeOH) in 91% yield.
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16. Compound **16**: $[\alpha]_D^{24}=-80$ (*c* 0.36, $CHCl_3$); IR (neat) 1735, 1718, 1708, 1265, 1182, 1055 cm^{-1}; ^1H NMR δ 1.37 (d, *J*=6 Hz, 3H), 1.42 (d, *J*=7 Hz, 3H), 1.44 (d, *J*=7 Hz, 3H), 2.63 (dd, *J*=16, 3 Hz, 1H), 2.75 (dd, *J*=16, 10 Hz, 1H), 3.39 (s, 3H), 4.20 (dt, *J*=1, 6 Hz, 1H), 4.65 (br s, 2H), 4.96-5.06 (m, 1H), 5.18 (q, *J*=7 Hz, 1H), 5.32–5.44 (m, 1H), 6.06 (dd, *J*=16, 1 Hz, 1H), 6.76 (d, *J*=16 Hz, 1H), 6.82 (dd, *J*=16, 6 Hz, 1H), 7.00 (d, *J*=16 Hz, 1H); ^{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.
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