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A total synthesis of macrosphelides C and F from L-(+)-arabinose☆

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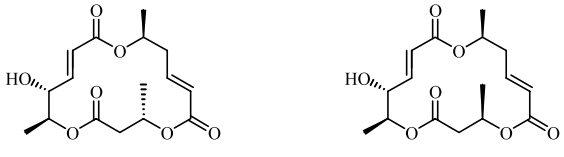
Abstract—A total synthesis of the 16-membered macrolides, macrosphelides C and F has been achieved starting from L-(+)-arabinose.

Macrosphelides A–L were isolated as inhibitors of the adhesion of HL-60 cells to a monolayer of LPS-activated human-umbilical-vein endothelial cells. Macrosphelide C (**1**) was isolated from the culture broth of *Microsphaeropsis* sp. FO-5050,[1] whereas macrosphelide F (**2**) was obtained from a strain of *Periconia byssoides* separated from the gastrointestinal tract of the sea hare *Aplysia* kurodai.[2a] The absolute stereostructures of macrosphelides C (**1**) and F (**2**) have been described by the Numata group.[2] These compounds were found to inhibit strongly the adhesion of human-leukemia HL-60 cells to human-umbilical-vein endothelial cells (HUVETC). Consequently these are highly attractive compounds for use as the next generation chemotherapeutical drugs against cancer and hence different synthetic methods for producing these molecules and their analogues is urgently required. In addition to their biological interest, the four chiral centres and the three ester linkages present in macrosphelides evoke interest for the synthesis of these target molecules. Earlier syntheses of macrosphelides C and F have been reported by three groups,[3,4] while we have recently reported a total synthesis of macrosphelides A and E.[5] Herein, we report the first 'chiron approach' based total synthesis of **1** and **2** (Fig. 1) from L-(+)-arabinose.

Our approach to the construction of **1** and **2** (Scheme 1), entailed the preparation of *trans*-(5*S*)-5-hydroxy-*p*-toluenesulfonylethyl-2-hexenoate (**4**) and *trans*-(4*R*,5*S*)-5-*tert*-butyldimethylsilyloxy-4-*p*-methoxybenzyloxy-2-hexenoic acid (**5**). Esterification of **4** and **5** and further condensation with commercially available 3*S*- or 3*R*-hydroxybutanoic acid units **6** or **7**, respectively would give *seco* acids **3** and **3a**. Yamaguchi macrolactonisation of *seco* acids **3** and **3a**, would thus afford the target molecules **1** and **2**. Both segments **4** and **5** were to be derived from a common synthon **8**.

Accordingly, 5-deoxy-1,2-*O*-isopropylidene-L-arabinofuranose[6] (**8**) was treated with CS_2, MeI, NaH in THF to give **9** (90% yield), which on deoxygenation using *n*-Bu_3SnH (toluene) afforded **10** in 61% yield. Hydrolysis of the 1,2-acetonide (cat. HCl in 60% aq. AcOH) furnished **11** in 75% yield. Oxidative cleavage of **11** ($NaIO_4$, CH_2Cl_2) and subsequent olefination of the unstable aldehyde **12** with (*p*-toluenesulfonylethoxy carbonylmethylene)triphenylphosphorane[7] gave **13** in 70% yield. Finally, de-*O*-formylation of **13** with catalytic HCl (1, 4 dioxane:water, 1:1) afforded the key intermediate **4** in 78% yield, $[\alpha]_D$ −5.15 (*c* 1.1, $CHCl_3$) (Scheme 2).

Trans-(4*R*,5*S*)-5-hydroxy-4-*p*-methoxybenzyloxy-2-hexenoate[5] **14** (Scheme 3) which was reported earlier by our group, was silylated (TBDMSCl, Et_3N, CH_2Cl_2) to



Macrosphelide C (**1**) Macrosphelide F (**2**)

Figure 1.

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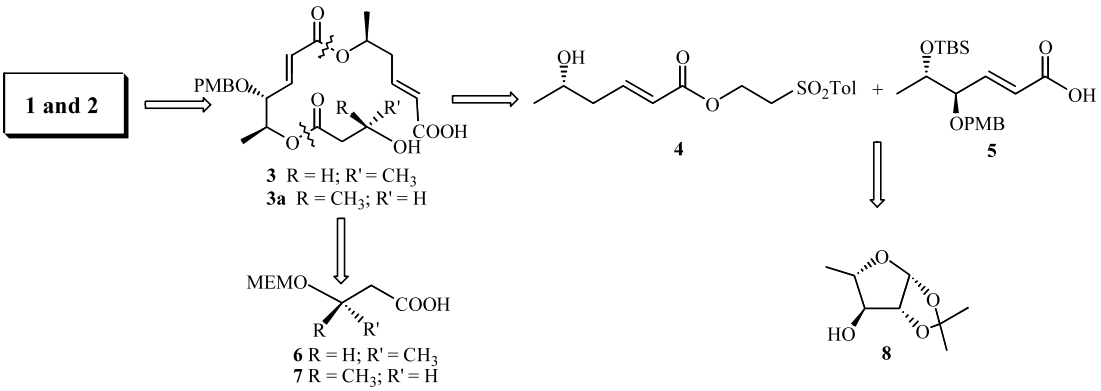
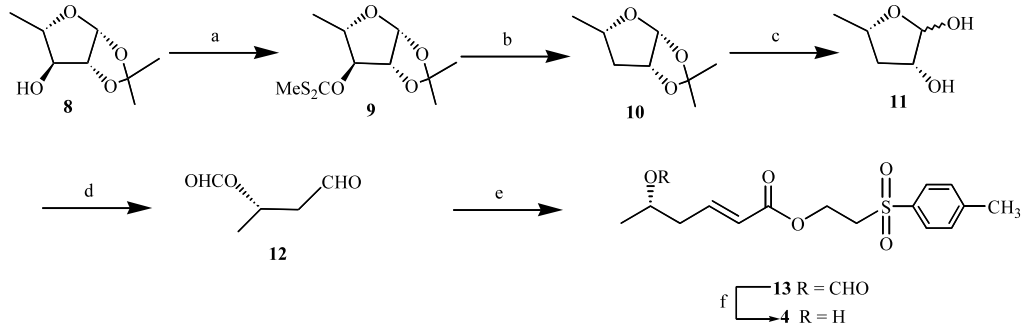
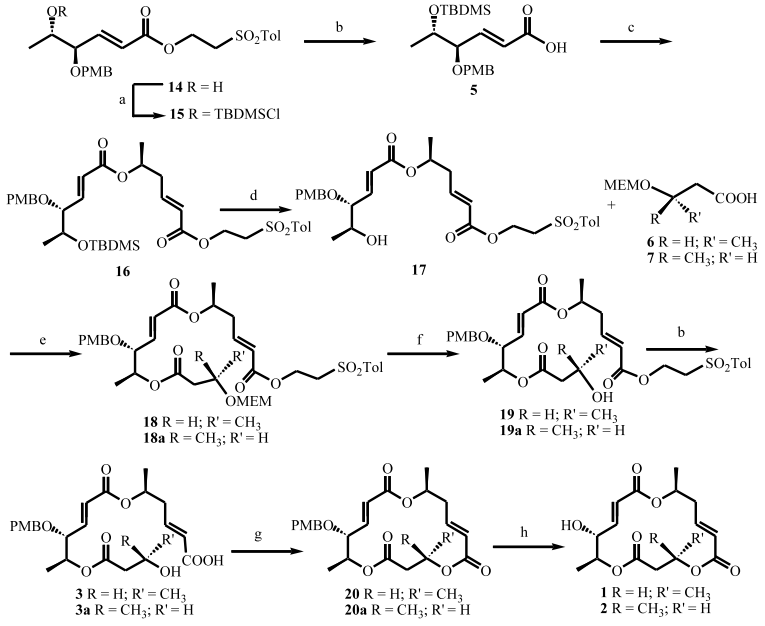


Scheme 1. Retrosynthesis of macrosphelide C **1** and F **2**.



Scheme 2. *Reagents and conditions*: (a) NaH, CS_2, MeI, THF, 0°C–rt, 2 h; (b) *n*-Bu_3SnH, AIBN, toluene, 110°C, 12 h; (c) 60% aq. AcOH, cat. HCl, rt, 14 h; (d) $NaIO_4$, CH_2Cl_2, 0°C–rt, 6 h; (e) $Ph_3P{=}CHCOO(CH_2)_2SO_2Tol$, toluene 110°C, 1 h; (f) cat. HCl, 1:1 dioxane/water, rt, 12 h.

give **15** in 80% yield, $[\alpha]_D$ −73.80 (*c* 0.21, $CHCl_3$), which on ester cleavage with DBN[7] (C_6H_6) furnished acid **5** in 76% yield. Condensation of acid **5** with alcohol **4** through the mixed anhydride prepared on reaction of **5** with 2,4,6-trichlorobenzoyl chloride (Et_3N, THF) in the presence of DMAP in toluene afforded ester **16** in 88%



Scheme 3. Synthesis of macrosphelide C (**1**) and F (**2**). *Reagents and conditions*: (a) TBDMSCl, imidazole, CH_2Cl_2, rt, 24 h; (b) DBN, benzene, rt, 8 h; (c) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, **4**, DMAP, toluene, rt, 12 h; (d) TMSCl, H_2O, CH_3CN, rt, 8 h; (e) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, DMAP, toluene, rt, 24 h; (f) TMSCl, NaI, CH_3CN, −20°C, 6 h; (g) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, DMAP, toluene, 90°C, 24 h; (h) DDQ, aq CH_2Cl_2 (19:1), rt, 4 h.

yield, $[\alpha]_D$ −24.73 (*c* 0.31, $CHCl_3$). Desilylation of **16** with TMSCl and H_2O in CH_3CN afforded **17** in 84% yield, $[\alpha]_D$ −34.2 (*c* 0.91, $CHCl_3$), which on esterification (2,4,6-trichlorobenzoyl chloride (Et_3N, THF) in the presence of DMAP in toluene) independently with acids **6** and **7** furnished **18** (76% yield), $[\alpha]_D$ −10.80 (*c* 0.735, $CHCl_3$) and **18a** (75% yield), $[\alpha]_D$ −27.19 (*c* 0.815, $CHCl_3$), respectively. Exposure of **18** and **18a** to TMSCl and NaI in CH_3CN, facilitated removal of the MEM protection to afford **19** (80% yield), $[\alpha]_D$ −16.90 (*c* 0.56, $CHCl_3$) and **19a** (81% yield), respectively. Selective cleavage of the *p*-toluylsulphonylethyl group in **19** and **19a** was effected with DBN (C_6H_6) to furnish *seco* acids **3** (80% yield) and **3a** (84% yield), respectively. Macrolactonisation of **3** and **3a**, under Yamaguchi reaction conditions[8] (2,4,6-trichlorobenzoyl chloride Et_3N, THF, DMAP, toluene) furnished **20** in 62% yield and **20a** in 58% yield, respectively. Finally, oxidative deprotection of **20** and **20a** with DDQ in aq CH_2Cl_2 gave synthetic **1** (85% yield) as a white solid, mp 151–153°C, $[\alpha]_D$ +52.1 (*c* 0.10, MeOH); and **2** (80% yield), as a colourless oil, $[\alpha]_D$ +22.5 (*c* 0.10, MeOH). The target molecules **1** and **2** were fully characterised[9,10] by ^1H, NMR, FAB MS and IR spectra.

Thus, in conclusion, an enantioselective synthesis of **1** and **2** has been achieved very efficiently from L-(+)-arabinose. Both the requisite segments with three asymmetric centres were prepared from a common chiral intermediate. The flexible strategy adopted in the present report will help in the design and synthesis of a variety of new chemical entities based on **1** and **2**, by the replacement of the 3-hydroxybutyric acid unit.

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9. Spectral data of macrosphelide-C (**1**): white solid, mp 151–153°C; lit.[3] mp 152–155°C, $[\alpha]_D$ +52.1 (*c* 0.10, MeOH); lit.[3] $[\alpha]_D$ +53.3 (*c* 0.08, EtOH); IR (KBr): 3458, 1725 cm^{-1}; ^1H NMR (500 Hz, $CDCl_3$) δ 1.33 (d, 3H, $J=6.5$ Hz), 1.36 (d, 3H, $J=6.5$ Hz), 1.38 (d, 3H, $J=6.8$ Hz), 2.0 (br. d, 1H, $J=6.3$ Hz), 2.36 (dd, 1H, $J=8.6$, 13.7 Hz), 2.51 (dd, 1H, $J=8.5$, 14.6 Hz), 2.56 (m, 1H), 2.63 (dd, 1H, $J=3.0$, 14.6 Hz), 4.16 (br d, 1H, $J=4.8$ Hz), 4.92 (q, 1H, $J=6.3$ Hz), 5.1 (m, 1H), 5.3 (m, 1H), 5.8 (dd, 1H, $J=1.5$, 15.6 Hz), 6.06 (dd, 1H, $J=1.5$, 15.5 Hz), 6.85 (dd, 1H, $J=6.2$, 9.3 Hz), 6.89 (dd, 1H, $J=4.8$, 15.5 Hz); ^{13}C NMR (300 Hz, $CDCl_3$) δ 17.5, 19.5, 20.5, 38.8, 40.9, 67.4, 69.0, 72.9, 73.7, 123.0, 124.7, 143.7, 144.8, 164.9, 165.0, 170.0; FAB MS (*m*/*z*, %): 327 (M^++1, 3), 309 (2), 289 (3), 154 (40), 107 (33), 83 (39), 69 (100), 55 (95).
10. Spectral data of macrosphelide-F (**2**): colourless oil, $[\alpha]_D$ +22.5 (*c* 0.10, MeOH); lit.[2] $[\alpha]_D$ +23.3 (*c* 0.09, EtOH); IR (neat): 3442, 1719 cm^{-1}; ^1H NMR (500 Hz, $CDCl_3$) δ 1.31 (d, 3H, $J=6.4$ Hz), 1.35 (d, 3H, $J=6.4$ Hz), 1.38 (d, 3H, $J=6.4$ Hz), 2.39 (dd, 1H, $J=6.4$, 14.3 Hz), 2.58 (dd, 1H, $J=7.9$, 15.8 Hz), 2.66 (dd, 1H, $J=3.2$, 15.8 Hz), 2.7 (m, 1H), 4.21 (dddd, 1H, $J=1.7$, 3.8, 4.0, 7.9 Hz), 4.93 (qd, 1H, $J=3.8$, 6.4 Hz), 5.14 (dqd, 1H, $J=5.0$, 6.4, 11.4 Hz), 5.30 (dqd, 1H, $J=3.2$, 6.4, 7.6 Hz), 5.79 (dd, 1H, $J=1.7$, 15.8 Hz), 6.09 (dd, 1H, $J=1.7$, 15.8 Hz), 6.85 (dd, 1H, $J=4.1$, 15.5 Hz), 6.89 (dd, 1H, $J=7.6$, 15.8 Hz); FAB MS (*m*/*z*, %): 327 (M^++1, 18), 309 (30), 289 (4), 154 (32), 137 (52), 83 (43), 69 (74), 55 (100).