Pergamon

Tetrahedron Letters 43 (2002) 9159–9161

TETRAHEDRON LETTERS

The total synthesis of macrosphelides A and E from carbohydrate precursors†

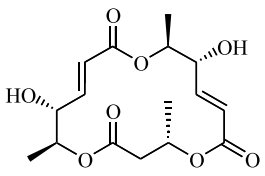
G. V. M. Sharma* and Ch. Chandra Mouli

D-211, Discovery Laboratory, Organic Chemistry Division-III, Indian Institute of Chemical Technology, Hyderabad 500 007, India

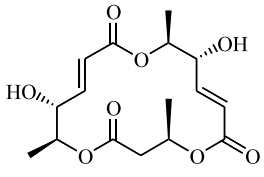
Received 3 September 2002; revised 27 September 2002; accepted 4 October 2002

Abstract—The total synthesis of macrolide antibiotics, macrosphelide A and E has been achieved starting from carbohydrate precursors.

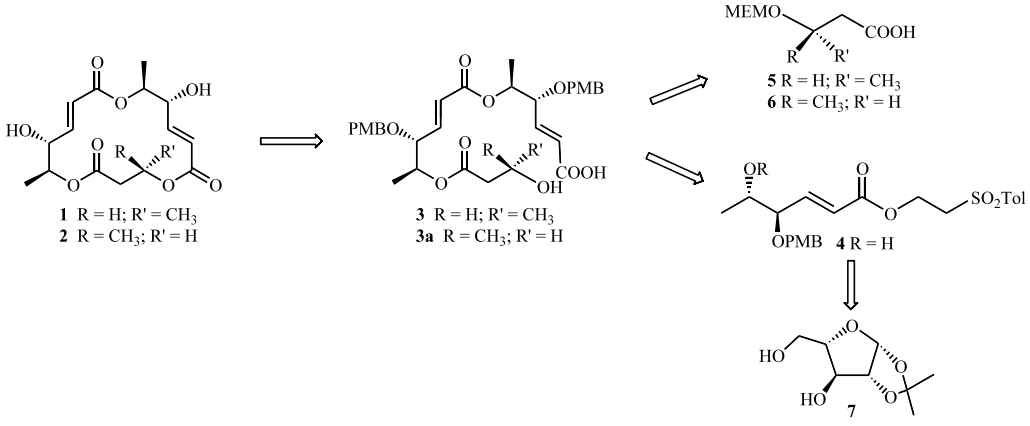
Macrosphelides A–L are 16-membered macrolide antibiotics having three lactone bridges in the ring structure. Macrosphelide A, isolated from the culture broth of *Microsphaeropsis* sp FO-5050, was found to inhibit strongly the adhesion of human leukemia HL-60 cells to an LPS-activated human-umbilical-vein endothelial cells (HUVETC) monolayer (IC_{50}, 3.5 μm) in a dose dependent fashion.[1] Macrosphelide E, the C(3) stereoisomer of macrosphelide A, was isolated from a strain of *Periconia byssoides* separated from the gastrointestinal tract of the sea hare *Aplysia* kurodai.[2] It was also found to inhibit the adhesion of human-leukemia HL-60 cells to human-umbilical-vein endothelial cells as potently as macrosphelide A. Consequently, macrosphelides have received much attention as valuable lead compounds for the development of new anticancer chemotherapeutical drugs, thus resulting in synthetic routes for generating these molecules and their analogues. Recently, the syntheses of macrosphelides A **1**[3–5] and E **2**[5] has been reported. Herein, we report the first carbohydrate based total synthesis of macrosphelides A **1** and E **2** from L (+)-arabinose.



Macrosphelide A **1**



Macrosphelide E **2**



Scheme 1. Retrosynthesis of macrosphelide A **1** and E **2**.

* Corresponding author. E-mail: esmvee@iict.ap.nic.in

† IICT Communication No. 020807.

0040-4039/02/$ - see front matter
PII: S0040-4039(02)02284-0

The synthetic strategy presented here involved the preparation of *trans* (4*R*,5*S*)-5-hydroxy-4-*p*-methoxybenzyloxy-2-hexenoate **4**, condensation with commercially available 3*S*- or 3*R*-hydroxy butanoic acid unit **5** or **6**, respectively, and recoupling with one more unit of *trans* **4**, to give *seco* acids **3** and **3a**, respectively, which on Yamaguchi macrolactonisation afford the target molecules **1** and **2**. The retrosynthesis of macrosphelides A and E is presented in Scheme 1.

Accordingly, 1,2-*O*-isopropylidene-β-L-arabinofuranose[6] **7** was selectively tosylated (*p*-TsCl, pyridine, CH_2Cl_2) to give **8** in 75% yield, which on subsequent reduction with $LiAlH_4$ afforded **9** in 80% yield, $[\alpha]_D$ −12.6 (*c* 0.65, $CHCl_3$). Protection of hydroxy group in **9** with *p*-methoxybenzyl bromide (NaH, THF) afforded **10** (95%), which on hydrolysis of the 1,2-acetonide (cat. H_2SO_4 in 60% aq. AcOH) furnished **11** (75%). Oxidative cleavage of **11** ($NaIO_4$, MeOH–H_2O) and subsequent olefination of the unstable aldehyde **12** with (*p*-toluenesulfonylethoxy carbonylmethylene) triphenylphosphorane[7] gave **13** in 75% yield. Finally, de-*O*-formylation of **13** with catalytic HCl (1,4-dioxane:water, 1:1) afforded the key intermediate **4** in 80% yield, $[\alpha]_D$ −39.1 (*c* 2.2, $CHCl_3$), in enantiopure form (Scheme 2).

Total synthesis of macrosphelide A (1)

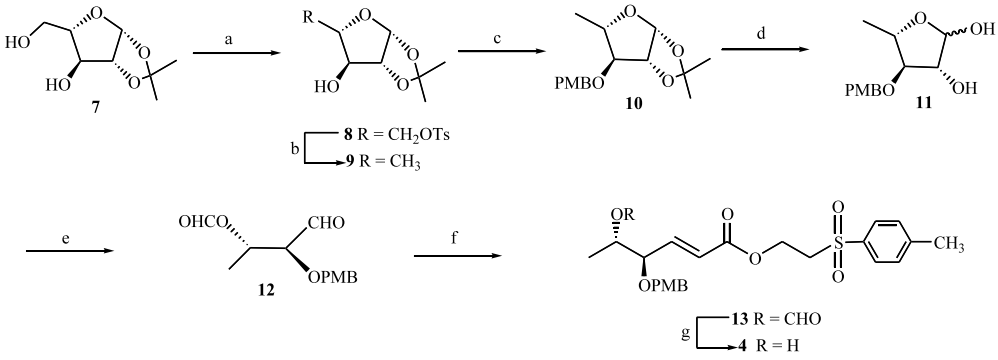
Condensation of alcohol **4** with acid **5** (Scheme 3) through the mixed anhydride prepared on reaction of **5** with 2,4,6-trichlorobenzoyl chloride (Et_3N, THF), in the presence of DMAP in toluene, afforded the ester **14** in 84% yield, $[\alpha]_D$ −39.3 (*c* 0.95, $CHCl_3$). Selective hydrolysis of the *p*-toluenesulfonylethyl group in **14** was effected with DBN[7] (C_6H_6, rt) to furnish **15** in 81% yield. Esterification of carboxylic acid **15** with alcohol **4** using 2,4,6-trichlorobenzoyl chloride (Et_3N, THF) and DMAP in toluene gave **16** in 82% yield. Reaction of **16** with TMSCl and NaI in CH_3CN (−20°C) afforded **17** in 77% yield, which on selective hydrolysis with DBN in C_6H_6 provided *seco* acid **3** in 79% yield. Finally, macrolactonisation of **3** under Yamaguchi conditions[8] (2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, toluene) gave **18** in 67% yield, $[\alpha]_D$ −90.4 (*c* 0.215, $CHCl_3$), which on reaction with DDQ in CH_2Cl_2/H_2O gave **1** (90%), $[\alpha]_D$ +83.8 (*c* 0.10, MeOH); lit.[1b] $[\alpha]_D$ +84.1 (*c* 0.59, MeOH); lit.[3] $[\alpha]_D$ +82 (*c* 0.10, MeOH); mp 139–141°C; lit.[1b] mp 141–142°C.

Total synthesis of macrosphelide E (2)

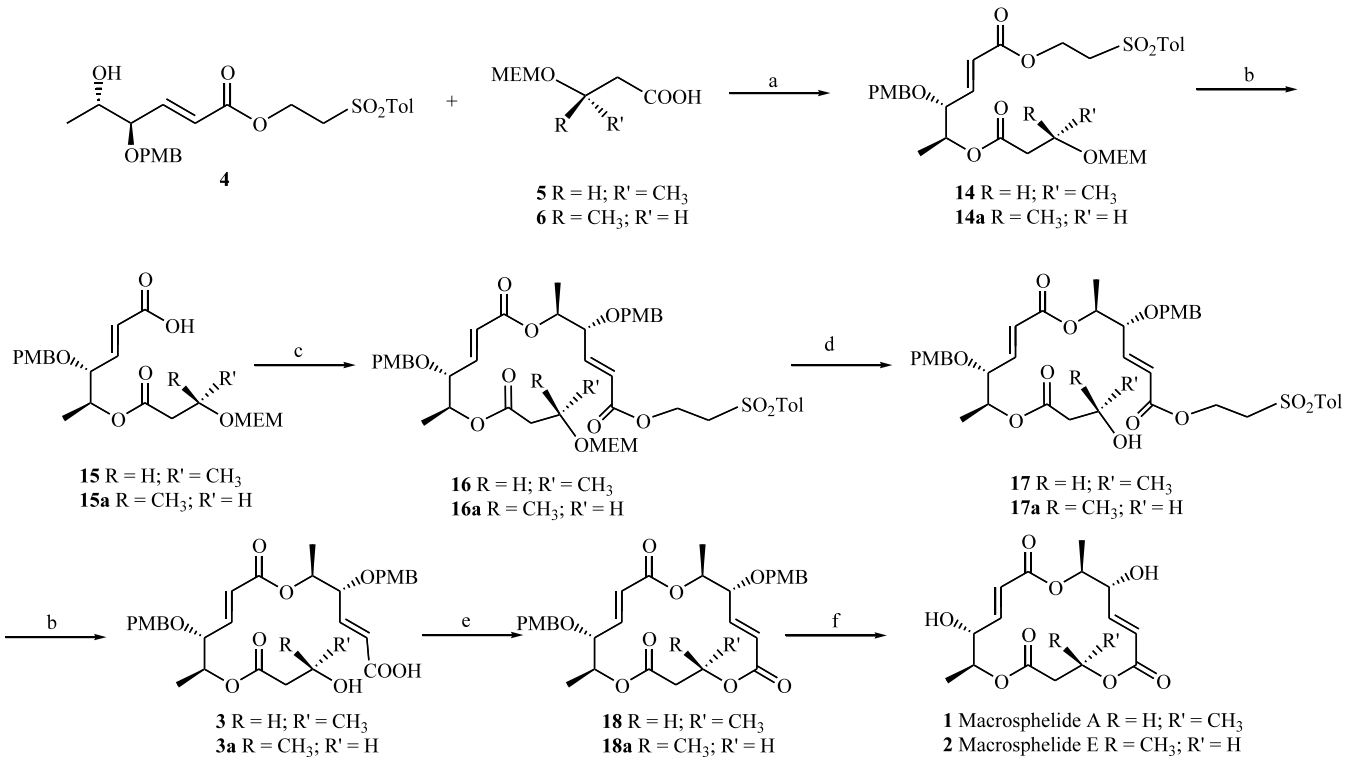
Similarly, esterification of acid **6** with alcohol **4** (Scheme 3) in the presence of 2,4,6-trichlorobenzoyl chloride (Et_3N, THF) and DMAP in toluene afforded the ester **14a** in 83% yield, $[\alpha]_D$ −13.13 (*c* 0.75, $CHCl_3$), which on selective hydrolysis with DBN in C_6H_6, furnished **15a** (80%). Esterification of carboxylic acid **15a** with alcohol **4** using 2,4,6-trichlorobenzoyl chloride (Et_3N, THF) and DMAP in toluene gave **16a** (84%), $[\alpha]_D$ −78.7 (*c* 0.25, $CHCl_3$). MEM deprotection of **16a** with TMSCl, NaI, in CH_3CN, afforded **17a** in 81% yield, which on selective hydrolysis with DBN in benzene gave **3a** (80%). Finally, **3a** under Yamaguchi macrolactonisation conditions (2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, toluene) gave **18a** in 70% yield. Deprotection of **18a** with DDQ in CH_2Cl_2/H_2O) gave **2** in 93% yield, $[\alpha]_D$ +54.9 (*c* 0.28, EtOH); lit.[2b] $[\alpha]_D$ +56.8 (*c* 0.46, EtOH); mp 104–106°C; lit.[2b] mp 105–107°C. The target molecules **1** and **2** were fully characterised[9,10] by ^1H, ^{13}C NMR, FAB MS and IR spectra.

Acknowledgements

Ch.C.M. is thankful to the UGC, New Delhi, India, for financial support.



Scheme 2. *Reagents and conditions*: (a) *p*-TsCl, pyridine, dry CH_2Cl_2, 0°C–rt, 14 h; (b) $LiAlH_4$, dry THF, 0°C–rt, 18 h; (c) NaH, PMBBr, dry THF, 0°C–rt, 4 h; (d) 60% aq. AcOH, cat. HCl, rt, 14 h; (e) $NaIO_4$, MeOH/H_2O (2:1), rt, 2 h; (f) $Ph_3P{=}CHCOO(CH_2)_2SO_2Tol$, 110°C, 1 h; (g) cat. HCl, dioxane/water (1:1), rt, 12 h.



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

References

1. (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.
2. (a) Numata, A.; Iritani, M.; Yamada, T.; Minoura, K.; Matusumura, E.; Yamori, T.; Tsuruo, T. *Tetrahedron Lett*. **1997**, *38*, 8215–8218; (b) Yamada, T.; Iritani, M.; Doi, M.; Minoura, K.; Ito, T.; Numata, A. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3046–3053.
3. Sunazuka, T.; Hirose, T.; Harigaya, Y.; Takamatsu, S.; Hayashi, M.; Komiyama, K.; Omura, S.; Sprenpelet, P. A.; Smith, A. B., III *J. Am. Chem. Soc*. **1997**, *119*, 10247–10248.
4. (a) Kobayashi, Y.; Kumar, B. G.; Kurachi, T. *Tetrahedron Lett*. **2000**, *41*, 1559–1563; (b) Kobayashi, Y.; Kumar, B. G.; Kurachi, T.; Acharya, H. P.; Yamazaki, T.; Kitazuma, T. *J. Org. Chem*. **2001**, *66*, 2011–2018.
5. Ono, M.; Nakamura, H.; Konno, F.; Akita, H. *Tetrahedron: Asymmetry* **2000**, *11*, 2753–2764.
6. Rauter, A. P.; Ramoa-Ribeiro, F.; Fernandes, A.; Figueiredo, J. A. *Tetrahedron* **1995**, *51*, 6529–6540.
7. Colvin, E. W.; Purcell, T. A.; Raphael, R. A. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1718.
8. Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn*. **1979**, *52*, 1989–1993.
9. Spectral data of macrosphelide-A **1**: IR (KBr): 3435, 1718 cm^{-1}; ^1H NMR (500 Hz, $CDCl_3$) δ 1.33 (d, 3H, $J=6.6$ Hz), 1.37 (d, 3H, $J=6.3$ Hz), 1.40 (d, 3H, $J=6.6$ Hz), 2.43 (d, 1H, $J=6.9$ Hz), 2.57 (dd, 1H, $J=3.6$, 15.7 Hz), 2.68 (dd, 1H, $J=9.1$, 15.7 Hz), 2.81 (d, 1H, $J=7.4$ Hz), 4.16 (br d, 1H, $J=5.7$ Hz), 4.23 (br d, 1H, $J=5.2$ Hz), 4.86 (dq, 1H, $J=5.7$, 6.3 Hz), 4.95 (dq, 1H, $J=5.2$, 6.3 Hz), 5.39 (m, 1H), 6.03 (dd, 1H, $J=1.6$, 9.3 Hz), 6.06 (dd, 1H, $J=1.4$, 9.0 Hz), 6.85 (dd, 1H, $J=3.8$, 15.6 Hz), 6.88 (dd, 1H, $J=4.4$, 15.6 Hz); ^{13}C NMR (300 Hz, $CDCl_3$) δ 17.8, 18.0, 19.6, 40.9, 67.6, 73.1, 74.1, 74.8, 75.1, 122.3, 122.7, 144.9, 145.9, 164.4, 165.7, 170.1; FAB MS (m/z, %): 343 (M^++1, 2), 307 (28), 289 (17), 259 (8), 154 (57), 137 (100), 55 (58).
10. Spectral data of macrosphelide-E **2**: IR (KBr): 3456, 1715, 1662 cm^{-1}; ^1H NMR (400 Hz, $CDCl_3$) δ 1.33 (d, 3H, $J=6.1$ Hz), 1.39 (d, 3H, $J=6.1$ Hz), 1.44 (d, 3H, $J=6.7$ Hz), 2.61 (dd, 1H, $J=7.3$, 15.8 Hz), 2.73 (dd, 1H, $J=3.0$, 15.8 Hz), 3.11 (d, 1H, $J=6.7$ Hz), 3.39 (d, 1H, $J=7.9$ Hz), 4.14–4.25 (m, 1H), 4.39 (br s, 1H), 4.99 (dq, 1H, $J=4.2$, 6.7 Hz), 5.13 (dq, 1H, $J=2.0$, 6.7 Hz), 5.34 (ddq, 1H, $J=3.0$, 6.7, 6.7 Hz), 6.08 (dd, 1H, $J=1.2$, 15.8 Hz), 6.12 (dd, 1H, $J=1.2$, 15.3 Hz), 6.81 (dd, 1H, $J=4.8$, 15.2 Hz), 7.03 (dd, 1H, $J=4.3$, 15.9 Hz); ^{13}C NMR (300 Hz, $CDCl_3$) δ 17.3, 17.7, 19.5, 40.0, 66.6, 73.7, 75.1, 75.3, 75.9, 122.3, 122.9, 145.0, 145.3, 165.2, 166.6, 170.1; FAB MS (m/z, %): 343 (M^++1, 5), 307 (52), 289 (42), 259 (53), 221 (68), 207 (59), 176 (100).