Total Synthesis of Achaetolide from D-Mannitol

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Abstract: A highly convergent stereoselective total synthesis of achaetolide, a ten-membered lactone is described. The ring-closing metathesis reaction was used to construct the macrocycle and *E*-olefinic moiety in the molecule. The key acid and alcohol fragments were synthesized from a single chiral pool material D-mannitol.

Key words: *Achaetominum cristalliferum*, *Ophiobolus sp*., achaetolide, D-mannitol, ring-closing metathesis

Due to their important biological activities and interesting structure, naturally occurring ten-membered lactones have attracted considerable attention of the synthetic organic chemists as well biologists.[1] Representative examples of this class of molecules are achaetolide,[2] aspinolide B,[3] microcarpalide,[4] and lethaloxin[5] (Figure 1). Achaetolide was initially isolated by Bodo et al. in 1983[2a] from the cultures of *Achaetominum cristalliferum*. In 2009, the same compound was isolated by Tanaka and co-workers from a fermentation broth of *Ophiobolus sp*.[2b] The absolute stereochemistry of the molecule was established by detailed ^{1}H NMR studies as well as by Mosher method.[6] The unknown biological activity along with interesting structural features, have attracted considerable attention from synthetic organic chemists, and as a result three syntheses have appeared in the literature.[7]

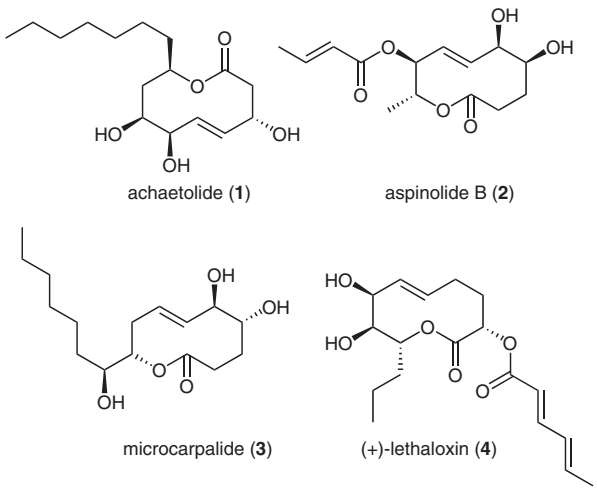
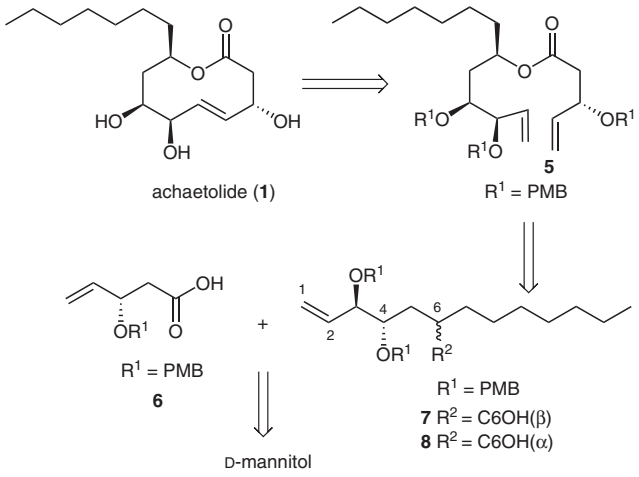


Figure 1

As part of our continuing interest in stereoselective synthesis of naturally occurring ten-membered lactones from the chiral pool D-mannitol;[8] herein, we wish to report a convergent approach for the total synthesis of achaetolide.

Inspection of the structure of achaetolide revealed that the ten-membered lactone with *E*-olefinic moiety of the molecule could be constructed via ring-closing metathesis reaction of the bisolefinic compound **5**, which would be obtained either through esterification reaction between the olefinic acid **6** and olefinic alcohol **7** or via Mitsunobu inversion of the alcohol **8** with the acid **6**. Finally, the olefinic alcohol fragments **7** and **8** as well as acid fragment **6**, in turn could be obtained from D-mannitol (Scheme 1).



Scheme 1 Retrosynthetic analysis

Thus our synthesis started from the known compound **9** (Scheme 2), which was prepared from D-mannitol according to the reported procedure.[9] PMB protection of the secondary alcohol and separation of the minor isomer via standard silica gel column chromatography gave the pure stereoisomer **10**, in good yield. Dihydroxylation of the olefinic compound **10** gave a diol compound, which on oxidative cleavage with $NaIO_4$ followed by $NaBH_4$ reduction of the resultant aldehyde afforded the primary alcohol **11** in 55% yield over three steps. TBDPS protection of the primary alcohol followed by acetonide deprotection furnished diol compound **13** in 72% yield over two steps. The diol compound **13** was converted to the epoxide **14** in two steps in good yield. The epoxide was then opened with Me_3SI–*n*-BuLi[10] to give a secondary allylic alcohol, which was protected as its PMB ether to give the fully protected olefinic compound **15**. TBDPS deprotection of **15**

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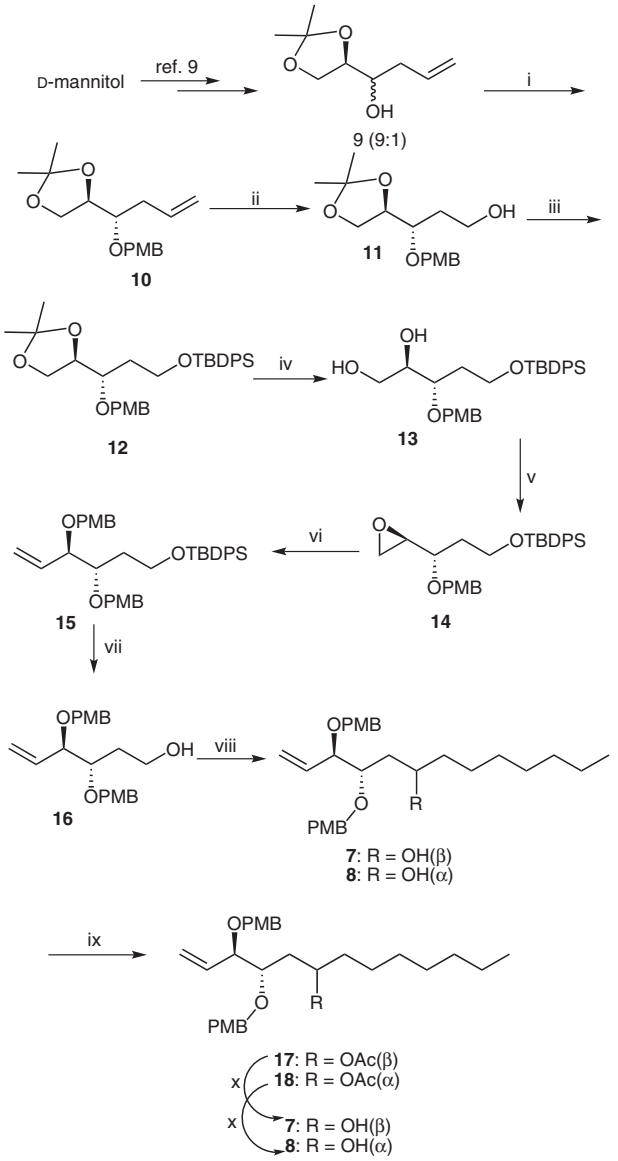
gave primary alcohol, which on oxidation followed by Grignard (heptyl magnesium bromide) addition afforded an inseparable mixture of compounds **7** and **8** (1.5:1). However diastereomerically pure alcohols **7** and **8** were obtained via their acetate protection, chromatographic separation through silica gel and acetate deprotection.



Scheme 2 *Reagents and conditions*: (i) PMBCl, NaH, TBAI, THF, 0 °C to r.t., 2 h, 85%; (ii) (a) OsO_4, NMO, THF–H_2O, 0 °C to r.t., overnight, 80%; (b) $NaIO_4$, $NaBH_4$, MeOH–H_2O, 1 h, 80%; (iii) TBDPSCl, Et_3N, DMAP, CH_2Cl_2, 0 °C to r.t., 4 h, 90%; (iv) PTSA, MeOH, 15 min, r.t., 80%; (v) (a) TsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C to r.t., 1 h; (b) K_2CO_3, MeOH, r.t., 5 h, 70% (over 2 steps); (vi) (a) Me_3SI, *n*-BuLi, THF, –20 °C to r.t., 2 h; (b) PMBCl, NaH, TBAI, THF, 0 °C to r.t., 2 h, 80% (over 2 steps); (vii) TBAF, THF, 0 °C to r.t., 3 h, 87%; (viii) (a) DMP, $NaHCO_3$, CH_2Cl_2, 0 °C to r.t.; (b) heptyl magnesium bromide, Et_2O, 0 °C to r.t., 30 min, 78%(over 2 steps); (ix) Ac_2O, Et_3N, CH_2Cl_2, DMAP, 0 °C to r.t., 2 h; (x) K_2CO_3, MeOH, 0 °C to r.t., 5 h, 54%; (**7**), 36% (**8**) over two steps.

To establish the absolute stereochemistry of C6-OH, both (*R*)- and (*S*)-MTPA esters (**7a**, **7b**) of the major isomer **7** were synthesized. The ^{1}H NMR data of both the esters were analyzed and the $\Delta_{SR} = (\delta_S - \delta_R)$ value was calculated for all possible detectable protons and arranged in accordance with the rule.[11] The protons on the left side of the C6 stereocenter showed negative Δδ values, and hence were assigned as 6*R*, as per the proposed rule (Figure 2).

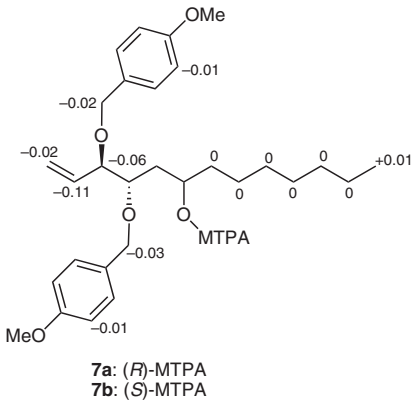
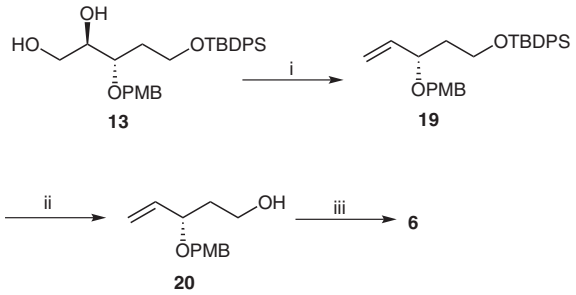


Figure 2

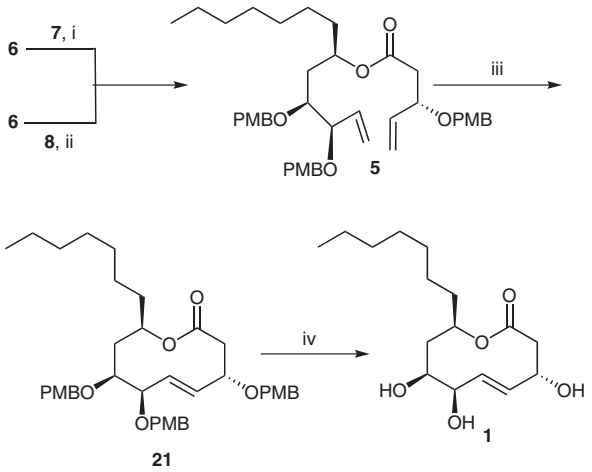
For the synthesis of acid fragment, we started with the diol compound **13** (Scheme 3), which on treatment with TPP, iodine and imidazole gave the olefinic compound **19** in 72% yield.[12] TBDPS deprotection of **19** gave primary alcohol **20**, which on two-step oxidation[13] provided the olefinic acid fragment **6**.



Scheme 3 *Reagents and conditions*: (i) I_2, TPP, imidazole, toluene, 60 °C, 15 min, 80%; (ii) TBAF, THF, 0 °C to r.t., 3 h, 90%; (iii) (a) DMP, $NaHCO_3$, CH_2Cl_2, 0 °C to r.t., 1 h; (b) $NaClO_2$, NaH_2PO_4, *t*-BuOH, H_2O, 2-methyl-2-butene, 0 °C to r.t., 1 h, 85% (over 2 steps).

Now esterification reaction between **6** and **7** using DCC and DMAP (cat.) in CH_2Cl_2 gave the bisolefinic compound **5**,[14a] which was also obtained via Mitsunobu inversion[15] of the alcohol **8** with the acid **6** (Scheme 4). The stage was set for the crucial ring-closing metathesis. Accordingly compound **5** was subjected to the ring-closing metathesis reaction[16] with Grubbs 2nd generation catalyst in refluxing toluene affording compound **21** as a mixture of conformers (1:1) with exclusive *E* geometry.[17] Finally global deprotection of PMB groups with TFA in CH_2Cl_2 afforded achaetolide as a white solid [(mixture of conformers (9:1)] in 80% yield, whose analytical data (^{1}H NMR and ^{13}CNMR)[14b] and specific rotation {synthetic $[\alpha]_D^{25}$ –22 (*c* = 0.1, MeOH), reported $[\alpha]_D^{25}$ –27 (*c* = 0.52,

MeOH)} were in good agreement with the literature values.[2a]



Scheme 4 *Reagents and conditions*: (i) DCC, DMAP, CH_2Cl_2, 0 °C to r.t., overnight, 70%; (ii) TPP, DEAD, benzene, 0 °C to r.t., 1 h, 75%; (iii) Grubbs 2nd generation catalyst (10 mol%), toluene, 110 °C, 24 h, 45% (80% based on recovered starting material); (iv) TFA, CH_2Cl_2, 0 °C to r.t., 0.5 h, 80%.

In conclusion we have achieved the total synthesis of achaetolide starting from a single chiral pool material D-mannitol using ring-closing metathesis as a key step. The synthesis of its analogues and their biological screening is under progress, which will be reported in due course.

Acknowledgment

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(14) (a) Analytical data for **5**: $[\alpha]^{25}_D$ –30.3 (*c* = 0.82, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.24–7.30 (m, 4 H), 7.19 (d, *J* = 8.4 Hz, 2 H), 6.84–6.90 (m, 4 H), 6.78 (d, *J* = 8.4 Hz, 2 H), 5.73–5.86 (m, 2 H), 5.23–5.36 (m, 5 H), 4.59 (d, *J* = 11.7 Hz, 1 H), 4.49 (d, *J* = 10.95 Hz, 1 H), 4.47 (d, *J* = 10.0 Hz, 1 H), 4.25–4.37 (m, 4 H), 3.82 (m, 1 H), 3.81 (s, 3 H), 3.80 (s, 3 H), 3.75 (s, 3 H), 3.48 (m, 1 H), 2.67 (dd, *J* = 15.3, 8.1 Hz, 1 H), 2.48 (dd, *J* = 15.3, 5.3 Hz, 1 H), 1.65–1.74 (m, 3 H), 1.45–1.56 (m, 2 H), 1.21–1.30 (br s, 9 H), 0.88 (t, *J* = 6.7 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.6, 159.2, 159.1, 137.5, 135.8, 130.9, 130.7, 130.4, 130.0, 129.3, 118.9, 118.1, 113.7, 81.1, 78.0, 77.5, 76.9, 72.9, 71.6, 70.2, 70.1, 55.3, 41.3, 35.9, 35.2, 31.8, 29.6, 29.2, 25.2, 22.7, 14.1. IR: 2926, 2858, 1730, 1512, 1246, 1034 cm^{-1}. MS (ESI): *m/z* = 711 $[M + Na]^+$. HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{42}H_{56}O_8Na$: 711.3872; found: 711.3884. (b) Analytical data of achaetolide (**1**): mp 122–124 °C; $[\alpha]^{25}_D$ –22 (*c* = 0.1, MeOH); {lit.[2a] $[\alpha]^{25}_D$ –27 (*c* = 0.52, MeOH)}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.02 (ddd, *J* = 15.8, 3.02, 2.26 Hz, 1 H), 5.68 (dd, *J* = 15.8, 2.3 Hz, 1 H), 4.82 (q, *J* = 6.8 Hz, 1 H), 4.75 (m, 1 H), 4.57 (m, 1 H), 3.77 (d, *J* = 9.8 Hz, 1 H), 2.62 (dd, *J* = 12.1, 3.0 Hz, 1 H), 2.57 (dd, *J* = 12.1, 3.7 Hz, 1 H), 2.34 (ddd, *J* = 15.1, 10.5, 8.3 Hz, 1 H), 2.17 (br s, 2 H, OH), 2.03 (br s, 1 H, OH), 1.53–1.68 (m, 2 H), 1.48 (d, *J* = 15.8 Hz, 1 H), 1.21–1.31 (m, 10 H), 0.87 (t, *J* = 6.7 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.0, 130.8, 125.1, 75.3, 73.2, 67.1, 43.8, 36.9, 36.8, 31.7, 29.6, 29.3, 29.1, 24.9, 22.6, 14.0. IR: 2923, 2854, 1739, 1709, 1647, 1513, 1372, 1171 cm^{-1}. MS (ESI): *m/z* = 323 $[M + Na]^+$.
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