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First total synthesis of achaetolide

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ABSTRACT

The first total synthesis of achaetolide, a 10-membered macrolactone was achieved using Mitsunobu reaction and Grubbs ring-closing metathesis reaction as the key steps for ring construction. The desired stereo centres were generated by Jacobsen hydrolytic kinetic resolution, dihydroxylation and Sharpless asymmetric epoxidation reactions.

In 1983, Bodo et al. reported the isolation of achaetolide (**1**, Fig. 1) from the culture broth of *Achaetomium crisalliferum*.[1] However, the stereochemistry of **1** was unknown until recently. In 2009, Takada and co-workers established the stereochemistry of **1** after isolating it from a different species, *Ophiobolus* sp.[2] achaetolide is a 10-membered macrolide having four stereo centres, three hydroxyl groups and a trans-olefin functionality. The biological activity of **1** was also unknown. The structural features of achaetolide combined with our interest on synthesis of macrolides[3] prompted us for the synthesis of achaetolide. Further, its chemical synthesis would allow to evaluate the biological activity.

Our retrosynthetic plan was to construct the complete skeleton through the assembly of the fragments: secondary alcohol **2** and acid **3** through a Mitsunobu esterification followed by ring closing metathesis (RCM) reaction. The fragment **2** was envisioned from epichlorohydrin (**6**) using Jacobsen hydrolytic kinetic resolution and dihydroxylation for the generation of stereo centres and the acid fragment **3** can be obtained from the known epoxy alcohol which in turn is prepared from 1,3-propane diol (Scheme 1).

The synthesis of alcohol **2** began from the commercially available epichlorohydrin (**6**), regioselective ring opening of the epoxide ring by *n*-hexylmagnesium bromide in the presence of CuCN followed by intramolecular substitution using NaOH to give nonene oxide **8** in 70% (for two steps). The epoxide was enantioselectively resolved using (*S,S*)-Jacobsen's catalyst (**I**) by hydrolytic kinetic resolution to give **9** in 43% yield.[4] Next, ring opening of the epoxide with lithium salt of ethyl propiolate gave the homopropargylic alcohol **10** (80%).[5] To make a six-membered unsaturated lactone, a two-step sequence was followed; partial hydrogenation of the alkyne using Lindlar's catalyst (palladium on $CaCO_3$, poisoned with Pb, quinoline) followed by lactonisation using catalytic *p*-TSA afforded the lactone **12** in 82% yield (for two steps). Dihydroxylation of **12** using catalytic OsO_4 and NMO was highly diasteroselective. The diol **13** was obtained as a sole product in 58% yield, which was protected as its acetonide using 2,2-DMP and cat. PPTS to afford the lactone **14** in 72% yield.[6] The lactone was then reduced to lactol **15** (78%) using DIBAL-H which on homologation using $PPh_3^+ CH_3Br^-$ gave the alcohol **2** in 77% yield (Scheme 2).

The synthesis of acid **3** (Scheme 3) began with 1,3-propane diol **7** which was transformed to epoxy alcohol **5** using a known sequence.[7] The epoxy alcohol **5** was then iodinated using TPP, iodine and imidazole, which on refluxing in ethanol in the presence of zinc transforms to secondary allylic alcohol followed by the

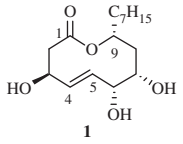

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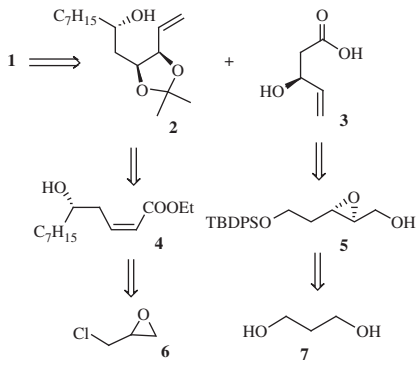
Figure 1. Structure of achaetolide.



Scheme 1. Retrosynthetic analysis.

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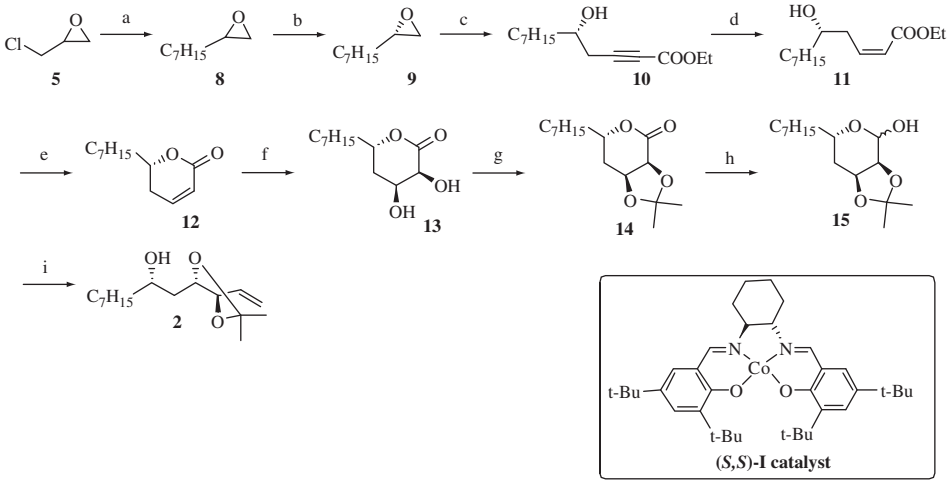
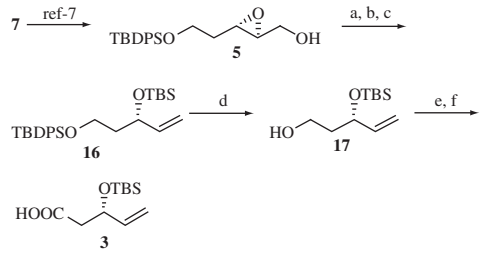
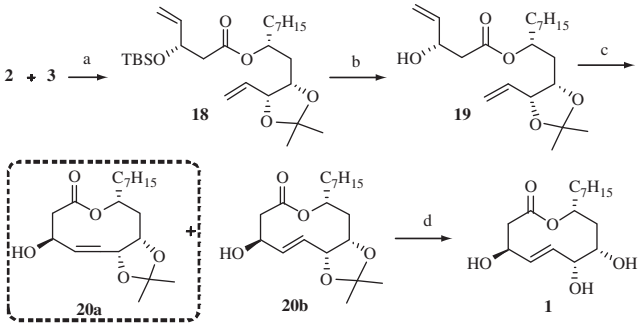


Scheme 2. Reagents and conditions: (a) (i) *n*-$C_6H_{13}MgBr$, CuCN, THF, −78 °C, 3 h; (ii) NaOH, THF, 0 °C to rt, 70% (for two steps), (b) (*S*,*S*)-*I*, H_2O AcOH, toluene. 0 °C to rt, 10 h, 43%; (c) ethyl propiolate, *n*-BuLi, $BF_3{\cdot}OEt_2$, THF, −78 °C, 80%; (d) Lindlar's catalyst, quinoline (cat), H_2, benzene, 1 h; (e) *p*-TSA (cat), benzene 82% (for two steps); (f) OsO_4, NMO, acetone/H_2O (7:3), rt, 58%, 12 h; (g) 2,2-DMP, PPTS (cat), CH_2Cl_2, 72%, 2 h; (h) DIBAL-H, CH_2Cl_2, −78 °C, 30 min, 78%; (i) $PPh_3{}^+CH_3Br^-$, *n*-BuLi, THF, 0 °C to rt, 4 h, 77%.



Scheme 3. Reagents and conditions: (a) TPP, I_2, imidiazole, Et_2O/CH_3CN (3:1), 0 °C to rt 30 min, 88%; (b) Zn, ethanol, reflux, 2 h, 85%; (c) TBSCl, imidiazole, CH_2Cl_2, 0 °C to rt, 95%; (d) $NH_4{}^+F^-$, CH_3OH, 10 h, 80%; (e) IBX, DMSO, THF, rt, 1 h; (f) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH/H_2O (7:3), 6 h, 76%.



Scheme 4. Reagents and conditions: (a) DIAD, PPh_3, benzene, 6 h, 0 °C to rt, 62%; (b) TBAF, 1 M solution, THF, 0 °C to rt, 1 h, 87%; (c) Grubbs' catalyst II, 3 h, 40 °C, 70% (mixture of cis and trans); (d) TFA, CH_2Cl_2, 0 °C to rt, 1 h, 65%.

protection as TBS ether **16** in 88% (for three steps). Selective deprotection of the TBDPS ether using $NH_4{}^+F^-$ gave the alcohol **17** in 80% yield. The alcohol on oxidation with IBX afforded the aldehyde, which on further oxidation using $NaClO_2$ and NaH_2PO_4 in the presence of 2-methyl-2-butene gave the acid **3** in 76% yield (two steps).

The alcohol **2** and the acid **3** were coupled under Mitsunobu conditions to afford the diene **18** in 62% yield, with the inversion of configuration at the hydroxyl carbon.[8] Having the diene in hand, the stage is set for the RCM reaction. Though RCM reaction is an efficient method for the construction of macrolide core, it is well documented that the outcome of an RCM reaction depends upon the stereochemistry near the alkene, protecting group, catalyst etc.[9] The diene **18** on RCM reaction condition did not afford the expected product, therefore the TBS group was deprotected using 1 M solution of TBAF to afford the allylic alcohol **19** in 87% yield. This allylic alcohol underwent RCM reaction neatly under refluxing CH_2Cl_2 in 2 h. Though the reaction was successful, a mixture of *Z* (**20a**, 23%) and *E* alkenes (**20b**, 47%) was formed in 4:6 ratio, which was easily separated by column chromatography. Acetonide deprotection of **20b** using TFA gave achaetolide **1** (Scheme 4). The spectroscopic data of **1** were compared with that of the natural product data and were found to exist as a mixture of conformers as reported by Takada.[2,10]

In conclusion, for the first time, we have accomplished the total synthesis of achaetolide. The synthetic sequence demonstrates the application of Mitsunobu reaction and ring-closing metathesis for the construction of a macrolide as key steps.

Acknowledgement

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10. *Spectral data of representative compounds*: Compound **11**: colourless liquid: $[\alpha]_D^{32}$ 4.7 (*c* 0.69, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.3–6.4 (1H, m), 5.89 (1H, td, *J* = 11.3, 1.5 Hz), 4.16 (2H, q, *J* = 6.7 Hz), 3.66–3.79 (1H, m), 2.76 (2H, ddd, *J* = 8.3, 6.0, 1.5 Hz), 1.98 (1H, d, *J* = 4.5 Hz), 1.20–1.52 (15H, m), 0.85 (3H, t, *J* = 6.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): 166.8, 146.2, 121.5, 71.1, 60.0, 37.4, 36.4, 31.7, 29.5, 29.1, 25.5, 22.5, 14.1, 13.9. IR ν_{max} (KBr): 3426, 2927, 2858, 1715, 1177 cm^{-1}; (ESI-MS): *m/z* 243 (M+H). Compound **12**: colourless liquid: $[\alpha]_D^{33}$ 88.5 (*c* 0.51, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.79–6.86 (1H, m), 5.99 (1H, td, *J* = 9.8, 1.5 Hz), 4.33–4.43 (1H, m), 2.28–2.34 (2H, m), 1.73–1.86 (1H, m), 1.22–1.68 (11 H, m), 0.89 (3H, t, *J* = 6.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.6, 145, 121.4, 78.0, 34.8, 31.7, 29.4, 29.3, 29.1, 24.8, 22.6, 14.0.; IR ν_{max} (KBr): 2926, 2857, 1718, 1638 cm^{-1}; (ESI-MS): *m/z* 197 (M+H) HRMS: calcd for $C_{12}H_{20}NaO_2$: 219.1356 (M+Na), found: 219.1354. Compound **13**: white solid; mp: 90–92 °C; $[\alpha]_D^{33}$ −32.0 (*c* 0.18, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.67–4.78 (1H, m), 4.27–4.31 (1H, m), 4.0 (1H, m), 3.43 (1H, br s), 2.7 (1H, br s) 2.2 (1H, td, *J* = 14.3, 3.7 Hz), 1.2–1.85 (13H, m), 0.89 (3H, t, *J* = 6.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.2, 78.3, 70.4, 65.9, 35.5, 33.8, 31.6, 29.2, 29.0, 24.7, 22.5, 14.0; IR ν_{max} (KBr): 3390, 2920, 2851, 1728, 1229, 1109 cm^{-1}; (ESI-MS): *m/z* 231 (M+H). Compound **15**: colourless liquid; $[\alpha]_D^{33}$ −45.3 (*c* 0.91, $CHCl_3$); 4.6 (1H, d, *J* = 5.8 Hz), 4.29–4.33 (1H, m), 3.67 (1H, t, *J* = 5.8 Hz), 3.57–3.64 (1H, m), 2.9 (1H, br s), 1.88–1.93 (1H, m), 1.64 (1H, ddd, *J* = 14.6, 10.9, 3.9 Hz), 1.1–1.5 (18H, m), 0.82 (3H, t, *J* = 6.8 Hz) 109.1, 96.4, 76.5, 70.5, 72.8, 35.4, 32.6, 31.7, 29.5, 29.1, 27.9 25.8, 25.4, 22.6, 14.0.; IR ν_{max} (KBr): 3422, 2926, 2856, 1051 cm^{-1}; (ESI-MS): *m/z* 295 (M+Na) HRMS: calcd for $C_{15}H_{28}NaO_4$: 295.1880 (M+Na) found: 295.1877. Compound **2**: colourless liquid; $[\alpha]_D^{32}$ −14.0 (*c* 0.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.76 (1H, ddd *J* = 17.3, 9.8, 7.5 Hz), 5.20–5.34 (2H, m), 4.52 (1H, td, *J* = 7.5, 0.8 Hz), 4.31 (1H, ddd, *J* = 9.8, 6.0, 3.7 Hz), 3.69–3.79 (1H, m), 3.0 (1H, br s), 1.23–1.53 (20H, m), 0.89 (3H, t, *J* = 6.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 133.8, 118.6, 108.2, 79.8, 78.4, 71.3, 37.5, 37.2, 31.7, 29.5, 29.2, 28.0, 25.5, 25.4, 22.6, 14.0; IR ν_{max} (KBr): 3468, 2926, 2857, 1045 cm^{-1}; (ESI-MS): *m/z* 293 (M+Na); HRMS: calcd for $C_{16}H_{30}NaO_3$: 293.2089 (M+Na), found: 293.2087. Compound **19**: colourless liquid; $[\alpha]_D^{32}$ −19.8 (*c* 0.53, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.67–5.91 (2H, m), 5.31–5.35 (1H, m), 5.25–5.29 (1H, m), 5.19–5.25 (1H, m), 5.09–5.16 (1H, m), 5.01–5.09 (1H, m), 4.43–4.54 (2H, m), 4.15 (1H, dd, *J* = 6.2, 2.8 Hz), 3.0 (1H, br s), 2.54 (1H, dd, *J* = 15.8, 3.7 Hz), 2.44 (1H, dd, *J* = 15.8, 8.3 Hz), 1.46–1.70 (2H, m), 1.45 (3H, s), 1.24–1.34 (15H, m), 0.89 (3H, t, *J* = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.8, 138.7, 134.0, 118.5, 115.3, 108.4, 79.4, 74.4, 72.5, 68.9, 41.4, 34.9, 34.6, 31.7, 29.6, 29.3, 29.1, 28.1, 25.6, 22.6, 14.0; IR ν_{max} (KBr): 3449, 2926, 2856, 1731, 1375, 1217, 1044 cm^{-1}; (ESI-MS): *m/z* 391 (M+Na). Compound **20a**: colourless liquid; $[\alpha]_D^{32}$ 13.5 (*c* 0.25, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3/C_6D_6$, 1:1): δ 5.59–5.65 (1H, dd, *J* = 11.8, 10.5 Hz), 5.50–5.56 (2H, m), 5.05–5.12 (1H, m), 4.54–4.59 (1H, m), 4.20–4.25 (1H, m) 2.53 (1H, dd, *J* = 11.8, 5.2 Hz), 2.31–2.35 (1H, m), 2.29 (1H, br s), 1.88–1.96 (2H, m), 1.51–1.60 (1H, m), 1.46–1.49 (4H, m), 1.20–1.33 (13H, m), 0.88 (3H, t, *J* = 6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$: C_6D_6, 1:1): δ 169.0, 131.5, 130.3, 106.8, 76.1, 73.6, 67.9, 71.4, 40.7, 35.1, 35.0, 31.0, 28.8, 28.6, 28.0, 25.2, 22.1, 24.8, 13.3; IR ν_{max} (KBr): 3458, 2926, 2858, 1728, 1253, 1166, 1044 cm^{-1}; (ESI-MS): *m/z* 363 (M+Na). Compound **1**: solid; mp: 122–124 °C; $[\alpha]_D^{30}$ −24 (*c* 0.23, MeOH); [lit.[1] mp 122 °C; $[\alpha]_D^{23}$ −27 (*c* 0.52, MeOH)]; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.02 (1H, dd, *J* = 15.6, 2.9 Hz), 5.68 (1H, d, *J* = 15.6 Hz), 4.82 (1H, dt, *J* = 7.8, 6.8 Hz), 4.76 (1H, m), 4.57 (1H, m), 3.6 (1H, d, *J* = 9.7 Hz), 2.62 (1H, dd, *J* = 11.7, 3.9 Hz), 2.58 (1H, dd, *J* = 11.7, 3.9 Hz), 2.34 (1H, m), 2.25 (1H, br s), 1.63 (2H, br s), 1.55 (2H, m), 1.48 (1H, d, *J* = 15.6 Hz), 1.26 (10H, m), 0.88 (3H, t, *J* = 7.8 Hz) (peaks corresponding to minor conformer are omitted); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.0, 130.8, 125.1, 75.3, 73.3, 67.2, 43.8, 36.9, 36.8, 31.7, 29.7, 29.4, 29.1, 25.03, 22.6, 14.1; IR ν_{max} (KBr): 3455, 2927, 2857, 1713, 1171 cm^{-1}; (ESI-MS): *m/z* 323 (M+Na); HRMS: calcd for $C_{16}H_{28}O_5Na$: 323.1834 (M+Na), found: 323.1830.