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Total synthesis of aspinolide B: a ring-closing metathesis approach☆

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Abstract—A highly convergent stereoselective total synthesis of aspinolide B, a 10-membered lactone is described. The key step includes a ring-closing metathesis reaction to construct the 10-membered ring and the *E*—olefinic moiety. D-Mannitol was used as a chiral pool material for the construction of the key fragments—the olefinic acid and the olefinic alcohol moieties.

In recent years naturally occurring 10-membered lactones, commonly known as decanolides have attracted considerable attention from synthetic, as well as bioorganic chemists, because of their interesting structures and important biological activities.[1] Representative examples of this class of molecules are (Fig. 1) aspinolide B (**1**),[2] microcarpalide (**2**),[3] lethaloxin (**3**)[4] and decarestrictine D (**4**).[5] Aspinolide B was isolated from cultures of *Aspergillus ochraceus*, whose relative stereochemistry was established by X-ray analysis. The absolute stereochemistry was established on the basis of Helmchen's method,[6] followed by total synthesis.[7] As part of our continuing interest on stereoselective syntheses of natural products from the chiral pool,[8] herein we report a convergent approach for the total synthesis of aspinolide B (**1**) starting from the cheap and easily available starting material, D-mannitol.

Retrosynthetically (Scheme 1), aspinolide B could be obtained via esterification of crotonic acid with alcohol **5**, which in turn could be obtained from bis-alkene **6** via ring closing metathesis,[9] an important reaction, which has been widely used for the synthesis of natural products having similar decanolide frameworks.[10]

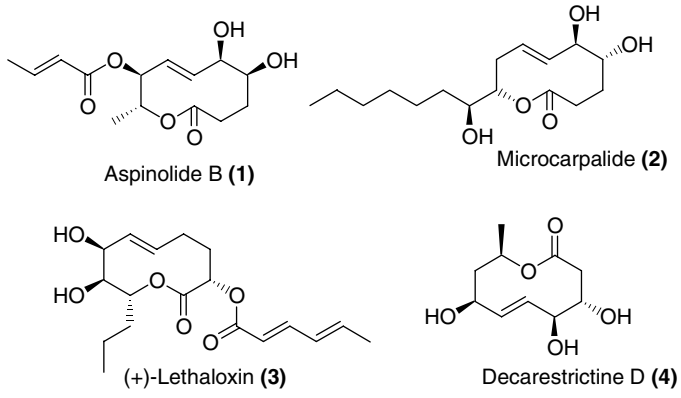

Figure 1.

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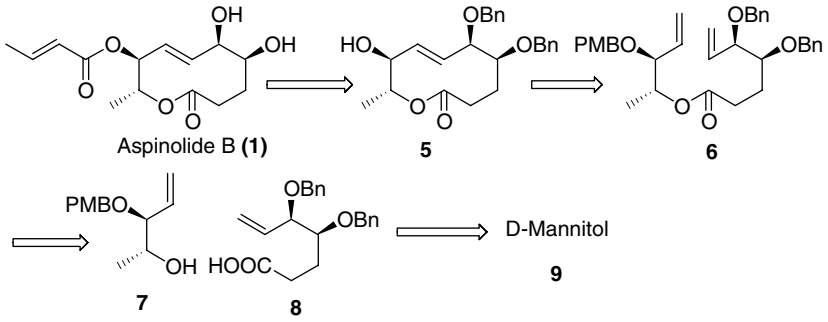
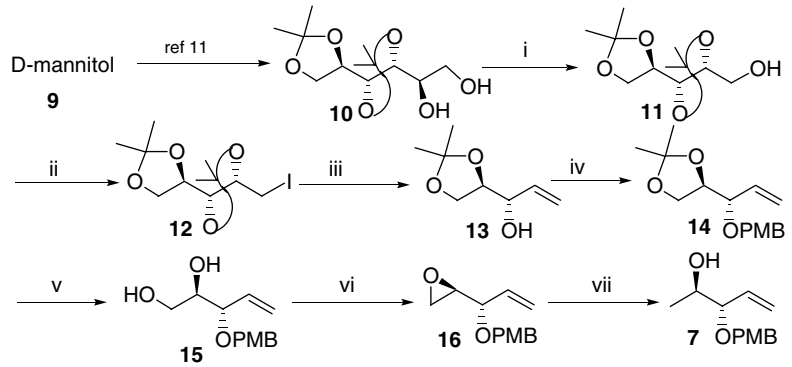


Scheme 1. Retrosynthetic analysis of **1**.

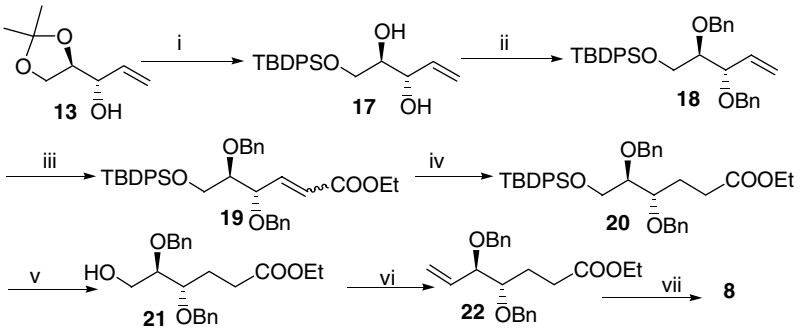
Bis-alkene **6** could be obtained via the esterification of **7** and **8**, which in turn could both be synthesized from D-mannitol.

The synthesis of olefinic alcohol **7** (Scheme 2) commenced from **10**, which was prepared from D-mannitol according to the reported procedure.[11] Oxidative cleavage of the diol in **10** with $NaIO_4$, followed by in situ reduction of the resulting aldehyde with $NaBH_4$ gave primary alcohol **11**. Compound **11** was converted to allylic alcohol **13**[12] in two steps, involving formation of iodide **12** with TPP, I_2 and imidazole in THF followed by activated Zn dust-mediated elimination to furnish allylic alcohol **13**. PMB protection of the resulting secondary alcohol afforded **14**, which on acetonide deprotection with AcOH–THF–H_2O (2:1:1) afforded diol **15**. Selective tosylation of the primary hydroxyl group gave the corresponding tosylate, which on treatment with K_2CO_3 in anhydrous methanol gave epoxide **16**. Finally, epoxide opening with DIBAL–H in CH_2Cl_2 afforded alcohol fragment **7** in 88% yield.

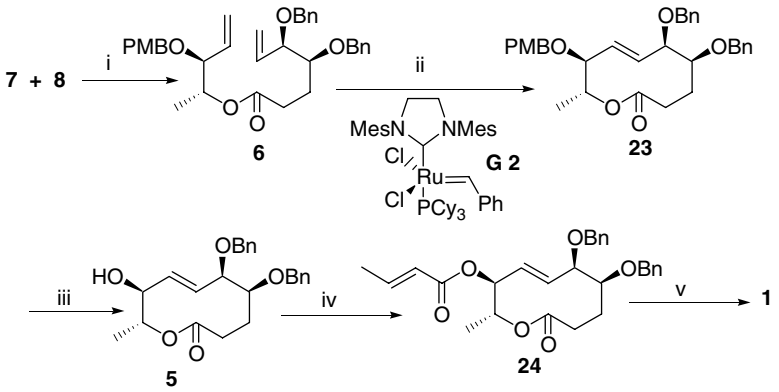
The synthesis of fragment **8** (Scheme 3) commenced from compound **13**. Acetonide deprotection followed by selective protection of the primary hydroxyl group as the TBDPS ether gave **17**. Benzylation of **17** with BnBr, NaH and TBAI (cat) in THF gave **18**. Dihydroxylation of **18** with OsO_4 gave a diol, which on oxidative cleavage with $NaIO_4$, followed by Wittig olefination with $Ph_3P{=}CHCOOEt$ in dichloromethane gave **19**



Scheme 2. Reagents and conditions: (i) $NaIO_4$, THF–H_2O (2:1), 0 °C, 1 h, then $NaBH_4$, 70%; (ii) TPP, I_2, imidazole, THF, 90 °C, 1 h; (iii) activated Zn dust, EtOH, reflux, 1 h, 75% over two steps; (iv) NaH, PMBBr, TBAI (cat), THF, 0 °C, 2 h, 90%; (v) AcOH–THF–H_2O (2:1:1), rt, 18 h, 90%; (vi) (a) TsCl, Et_3N, DMAP (cat), CH_2Cl_2, 0 °C, 2 h; (b) K_2CO_3, MeOH, 0 °C, 6 h, 75% over two steps; (vii) DIBAL–H, CH_2Cl_2, 0 °C, 2 h, 88%.



Scheme 3. Reagents and conditions: (i) (a) PTSA, MeOH, 0 °C, 6 h; (b) TBDPSCl, imidazole, DMF, rt, 12 h, 90% over two steps; (ii) NaH, BnBr, TBAI (cat), THF, 0 °C, 12 h, 80%; (iii) (a) NMO, OsO_4, acetone–water (2:1), rt, 24 h; (b) $NaIO_4$, THF–water (2:1), 0 °C , 1 h; (c) $Ph_3P{=}CHCOOEt$, CH_2Cl_2, rt, 6 h, 70% over three steps; (iv) H_2, Pd/C, *n*-$BuNH_2$, MeOH, rt, 2 h, 90%; (v) TBAF, THF, rt, 6 h, 90%; (vi) (a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 0.5 h; (b) $Ph_3P{=}CH_2$, ether, 0 °C, 75% over two steps; (vii) LiOH, THF–H_2O–MeOH (3:1:1), 0 °C, 2 h, 95%.



Scheme 4. Reagents and conditions: (i) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF 0 °C, 3 h, then **8**, DMAP, toluene, rt, 1 h 90%; (ii) 20 mol % of Grubbs' second generation catalyst **G2**, toluene, 90 °C, 20 h, 35%; (iii) TFA, CH_2Cl_2, rt, 1 h, 95%; (iv) crotonic acid, DIC, DMAP (cat), 0 °C, 12 h, 80%; (v) $TiCl_4$, CH_2Cl_2, 0 °C, 0.5 h, 90%.

(*E*:*Z* = 70:30). Olefin reduction of **19** with H_2 over Pd–C in methanol gave **20**, which on treatment with TBAF in THF afforded primary alcohol **21**. Compound **21** was converted into alkene ester **22** in two steps. Swern oxidation of **21** gave an aldehyde, which on Wittig olefination with $Ph_3P{=}CH_2$ in ether gave alkene ester **22**. Finally, saponification of ester **22** with LiOH in THF–methanol–water (3:1:1) provided the desired acid fragment **8**.

Condensation of fragments **7** and **8** was achieved under Yamaguchi conditions[13] to furnish bis-olefinic ester **6** (Scheme 4). The crucial ring closing metathesis of **6** using Grubbs' 1st generation catalyst failed under various conditions. Gratifyingly, use of Grubbs' 2nd generation catalyst (20 mol %) in toluene under argon at 90 °C for 20 h, resulted in ring-closing metathesis of **6** to afford *E*-**23** as the only isolable product in 35% yield. Selective deprotection of the PMB group with TFA in CH_2Cl_2[14] furnished alcohol **5**. Finally, acylation of **5** with crotonic acid gave ester **24**, which on debenzylation with $TiCl_4$ afforded aspinolide B (**1**).[15,16] The spectroscopic and analytical data of compound **5** and other compounds were in good agreement with the literature data.[2,7]

In conclusion, we have achieved the highly convergent stereoselective total synthesis of aspinolide B from the commercially available, cheap starting material D-mannitol, using ring-closing metathesis as a key step. The synthesis of other natural products of this family and their analogues are underway and will be reported in due course.

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15. Analytical and spectral data of **24**: mp: 95–96 °C; $[\alpha]_D^{27}$ −60.5 (*c* 1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.34–7.14 (m, 10H, Ar–*H*), 6.93 (dq, 1H, $J = 15.5$, 6.8 Hz), 5.78 (dq, 1H, $J = 15.5$, 1.7 Hz), 5.59 (ddd, 1H, $J = 15.6$, 8.5, 2.1 Hz), 5.39 (dd, 1H, $J = 15.6$, 2.1 Hz), 5.05–4.87 (m, 2H), 4.64 (q, 2H, $J = 12.6$), 4.39 (q, 2H, $J = 12.4$ Hz), 4.33 (m, 1H), 3.25 (td, 1H, $J = 10.4$, 1.5 Hz), 2.64–2.41 (m, 2H), 2.1–1.88 (m, 2H), 1.81 (dd, 3H, $J = 6.8$, 1.7 Hz), 1.22 (d, 3H, $J = 6.2$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.1, 165.5, 146.5, 138.9, 138.2, 131.2, 128.3, 128.1, 127.5, 127.3, 127.1, 122.3, 83.8, 78.9, 76.2, 72.1, 70.8, 70.6, 33.8, 25.2, 17.9, 16.9; MS (LCMS): *m*/*z*: 487.2 $[M+Na]^+$; HRMS (ESI) calcd for $C_{28}H_{32}O_6Na[M + Na]^+$ 487.2096. Found: 487.2082.
16. Analytical and spectral data of aspinolide B (**1**): mp: 98–99 °C (reported 102–103)[7] $[\alpha]_D^{27}$ −43.1 (*c* 0.5, MeOH), reported −43.1 (*c* 1, MeOH);[7] ^1H NMR (300 MHz, $CDCl_3$): δ 7.01 (dq, 1H, $J = 15.8$, 6.8 Hz), 5.85 (dq, 1H, $J = 15.1$, 1.5 Hz), 5.68 (dd, 1H, $J = 15.8$, 2.2 Hz), 5.57 (ddd, 1H, $J = 15.8$, 8.3, 2.2 Hz), 5.09 (dq, 1H, $J = 9.1$, 6.0 Hz), 4.95 (dd, 1H, $J = 9.1$, 7.6 Hz), 4.52 (br m, 1H), 3.64 (td, 1H, $J = 10.6$, 2.2 Hz), 2.51–2.46 (m, 1H), 2.36–2.22 (m, 2H), 1.89 (dd, 3H, $J = 6.8$, 2.2 Hz), 1.81–1.71 (m, 1H), 1.32 (d, 3H, $J = 6.8$ Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 175.6, 165.6, 146.2, 131.3, 127.5, 121.9, 78.6, 75.1, 72.7, 71.8, 32.5, 27.1, 18.2, 16.7; MS (LCMS): *m*/*z*: 307.1 $[M+Na]^+$; HRMS (ESI) calcd for $C_{14}H_{20}O_6Na$-$[M+Na]^+$ 307.1157. Found: 307.1147.