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First stereoselective total synthesis of Phomolide G and H via RCM protocol

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ABSTRACT

A first total synthetic route has been reported for the synthesis of Phomolide G and H. The syntheses of fragments were initiated from commercially available and inexpensive starting material (*R*)-epichlorohydrin. The synthesis involves a key Sharpless epoxidation, stereoselective epoxide opening, lactonization and ring closing metathesis (RCM).

Many natural products pose considerable synthetic challenge because of their stereochemical complexity. Therefore the development of new and efficient methods for the regio and stereoselective synthesis of biologically active compounds is an active area of research. Nature provides many biologically active metabolites. The genus *Cordyceps* is an abundant source of biologically active secondary metabolite, for example erythrostominones,[1] cordypyridones[2] antimalarial and sterols as antitumor agents.[3] In addition, some metabolites are widely used as food and herbal medicine in Asia. Among the metabolites Phomolide G (**1**) and Phomolide H (**2**)[4] (Fig. 1) have attracted attention because of the medicinal properties. The Phomolides were endophytic fungal stain *Phomopsis* sp. A123, a isolated from leaves of the mangrove species, *Kandelia candel*, collected in the Fugong Mangrove Conservation Area, Fujian (China).

Recently, we initiated a research programme for the total synthesis of bioactive natural products from a chiral source.[5] Our approach to the total synthesis of Phomolide G and H and its diastereomer involves the use of commercially available (*R*)-epichlorohydrin as a starting material. The retro synthetic analysis of Phomolide G (**1**) is shown in Scheme 1. The crucial 10-membered lactones was to be prepared by ring closing metathesis (RCM). The hydrolysis of the lactone gave the PMB protected olefinic acid **5** and the acetonide protected olefinic alcohol **4.** Precursors **4** and **5** would be constructed from commercially available chiral (*R*)-epichlorohydrin.

Synthesis of fragment **5** started from the (*R*)-epichlorohydrin and the anion derived from 1,3-dithane to give epoxide **7**.[6] The epoxide **7** was regioselectively opened with $(Me)_3S^+I^-$, *n*-BuLi in THF at −10 °C to afford secondary allylic alcohol **11** in 76% yield.[7] Protection of alcohol **11** with *p*-methoxybenzyl bromide (PMB-Br) in the presence of NaH gave **6** in 82% yield. The dithane **6** on hydrolysis provided aldehyde which was converted into olefinic acid fragment **5** by using NaH_2PO_4, $NaClO_2$, 2-methyl-2-butene in CH_3CN:H_2O (1:1), rt, 74% (Scheme 2).[8]

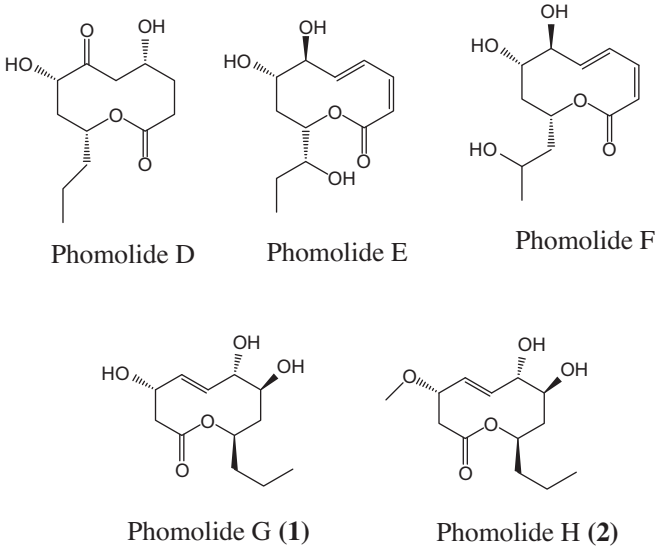

Figure 1. Structure of Phomolide D–H.

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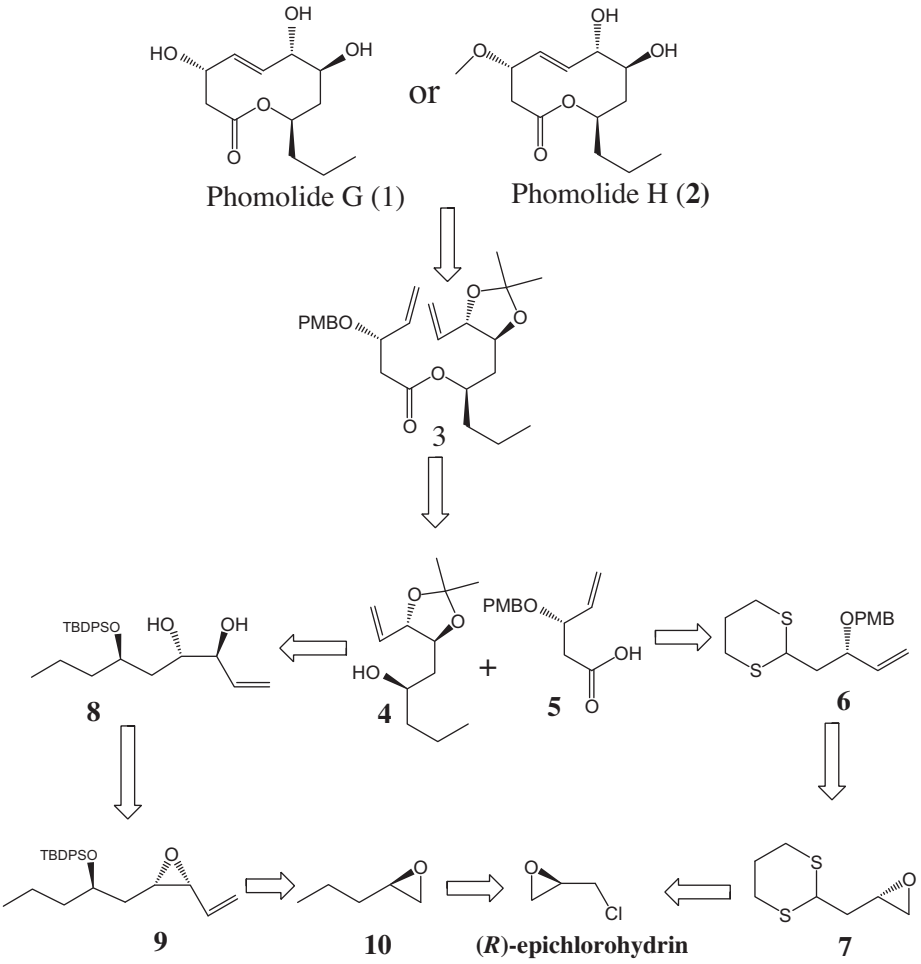
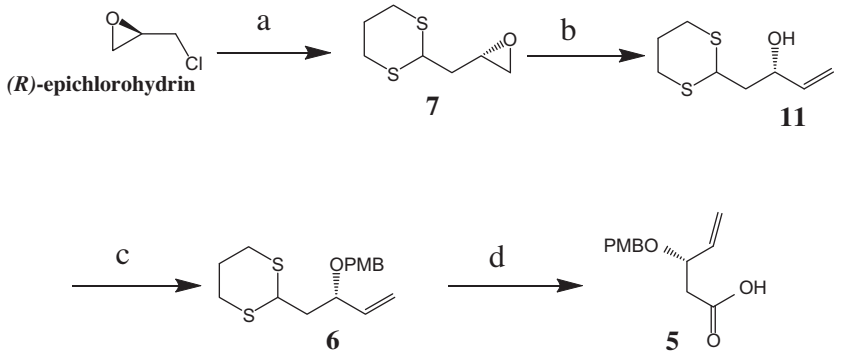


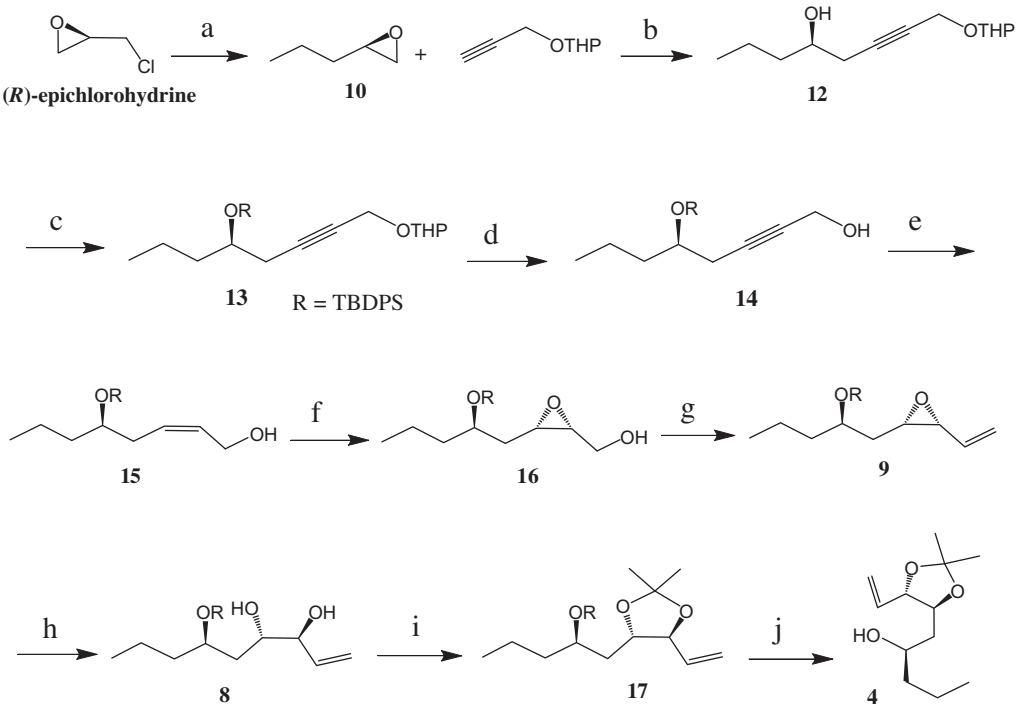
Scheme 1. Retrosynthesis of Phomolide G and H



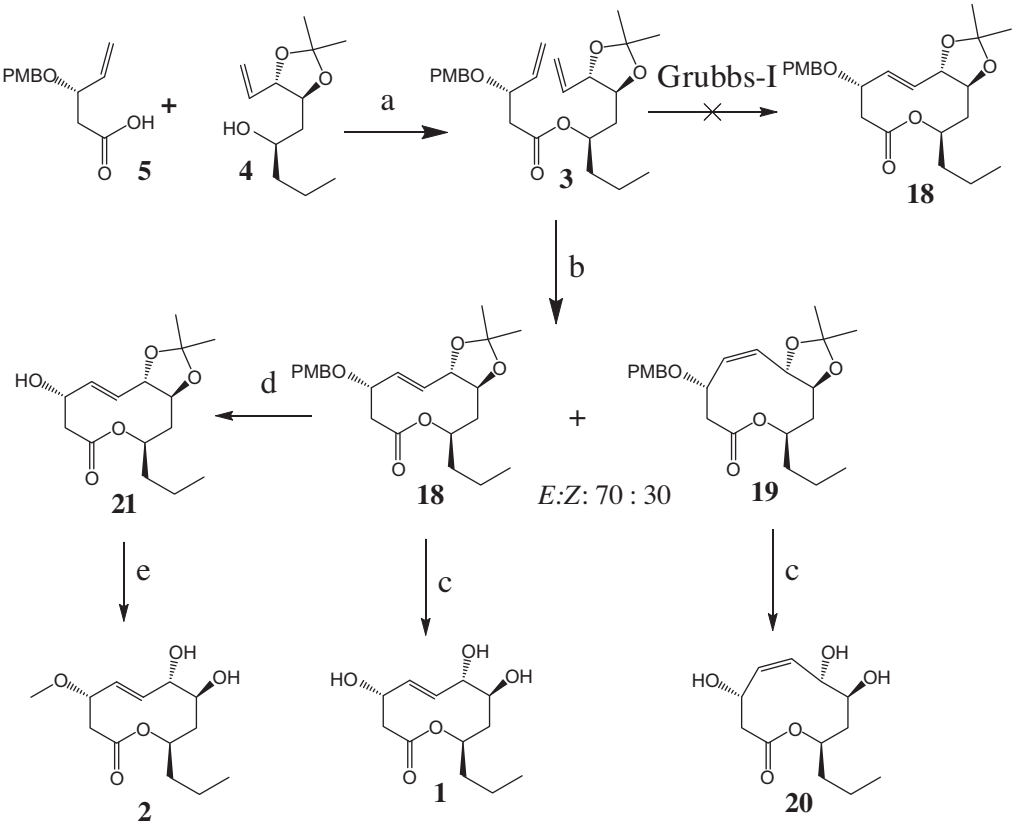
Scheme 2. Reagents and conditions: (a) Ref.[6]; (b) $(Me)_3S^+I^-$, *n*-BuLi, THF, −10 °C, 1 h, 76%; (c) NaH, PMB-Br, TBAI, THF, 0° to rt, 82%; (d) $CaCO_3$, MeI, CH_3CN:H_2O (9:1), 45 °C, 3 h; (ii) NaH_2PO_4, $NaClO_2$, MeCN, H_2O, 2-methyl-2-butene, rt, 6 h, 74% (for two steps).

The synthesis of fragment **4** was initiated from the enantiomeric pure (*R*)-2-propyloxirane **10** which was also prepared from (*R*)-epichlorohydrin.[9] The epoxide **10** was subjected to regioselective ring opening with THP protected propargyl alcohol in the presence of *n*-BuLi, $BF_3{\cdot}OEt_2$ to furnish alcohol **12**.[10] The secondary hydroxyl group in **12** was protected with tert-butyldiphenylsilyl chloride (TBDPS-Cl) and imidazole to afford the silylether **13** in 86% yields. Depyranylation of compound **13** using PPTS (cat.) in methanol afforded compound **14** in 84% yield. The *cis*-allyl alcohol **15** was obtained by the reduction of **14** by using $Ni(OAc)_2{\cdot}2H_2O$, $NaBH_4$, EtOH, ethylene glycol in 92% yield.[11] The acetonide **4** was conveniently obtained from the allylic alcohol **8** in three steps-via allylic epoxide **9** through a sequence of reactions involving the Sharpless asymmetric epoxidation,[12] Swern oxidation[13] and one-carbon homologation with $PPh_3CH_3{}^+I^-$, (68% overall yield after 3 steps).[14]Treatment of olefinic epoxide **9** with $Sc(OTf)_3$ in THF and H_2O (10:1, 0.25 molar) cleanly afforded diol **8** in 79% yield.[15] Protection of diol **8** with 2,2-DMP, PPTS (cat.) in CH_2Cl_2 gave acetonide **17** in 86% yield and subsequent deprotection of TBDPS with TBAF afforded alcohol **4** in 82% yield (Scheme 3).

With the two key intermediates acid **5** and alcohol **4** in hand, the stage was set for their coupling to afford the macrolide

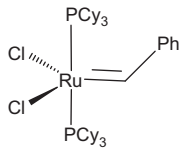


Scheme 3. Reagents and conditions: (a) Ref.[9]; (b)(i) *n*-BuLi, $BF_3{\cdot}OEt_2$, THF, −78 °C, 2 h, 90%;(c) TBDPS-Cl, imidazole, CH_2Cl_2, 0 °C to rt, 86%; (d) *p*-TSA(cat.), MeOH, 0 °C to rt; 84%; (e) $Ni(OAc)_2.2H_2O$, $NaBH_4$, EtOH, ethylene glycol, rt, 6 h, 92%; (f) (+)−DIPT, $Ti(Oipr)_4$, 4A° MS, TBHP, CH_2Cl_2, −20 °C, 12 h, 82%; (g) (i) $(COCl)_2$, DMSO, CH_2Cl_2, NEt_3, −78 °C; (ii) $PPh_3CH_3{}^+I^-$, NaHMDS, THF, 0 °C to rt, (72% overall yield after 2 steps); (h) $Sc(OTf)_3$, THF:H_2O (9:1), rt, 12 h, 79%; (i) 2,2-DMP, CSA (cat.), CH_2Cl_2, 0 °C to rt, 86%; (j) TBAF, THF, 0 °C to rt, 82%.

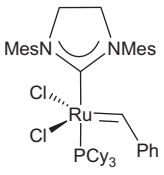


Scheme 4. Reagents and conditions: (a) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, 0 °C to rt, 4 h, then DMAP, toluene, 0 °C to rt, 12 h, 80%; (b) 10 mol % Grubb's 2nd generation catalyst, CH_2Cl_2 reflux, 70%; (c) TFA/ CH_2Cl_2, 0 °C to rt, 48 h, 70%; (d) DDQ, CH_2Cl_2:H_2O(9:1), 0 °C to rt, 2 h, 90%; (e) (i) NaH, MeI, THF, 0 °C to rt, 6 h; (ii) TFA, CH_2Cl_2, 0 °C to rt, 4 h, 58% (for two steps).

skeleton. The coupling of acid **5** and alcohol **4** was achieved under Yamaguchi conditions[16] (2,4,6-trichlorobenzoyl chloride–Et_3N–THF then DMAP–toluene) to afford the dienoic ester **3** in 80% yield (Scheme 4). The RCM of compound **3** was attempted with (10 mol %) Grubbs first generation catalyst in dry CH_2Cl_2 under reflux conditions, but the reaction did not proceed. Reaction of **3** with Grubb's second-generation catalyst (10 mol %) in CH_2Cl_2 at reflux afforded mixture of *E*:*Z* ratio 70:30 (**18** and **19**) as the sole product in 70% yield.[17,18] The *E*:*Z* isomers were separated by column chromatography. The geometry of the olefin in **18** was established as '*E*' from its coupling constants.[19] The removal of acetonide and PMB-protect of groups using trifluoroacetic acid (TFA) in CH_2Cl_2 afforded the target molecule Phomolide G (**1**) and its *Z*-isomer **20**. Deprotection of the PMB group present in **18** with DDQ in CH_2Cl_2/water (9:1) system furnished **21** in 90% yield. The methoxylation of alcohol **21** with methyl iodide (MeI) in the presence of NaH followed by deprotection of acetonide by using TFA in CH_2Cl_2 afforded the required Phomolide H (**2**) in 58% yield (for two steps) (Scheme 4). Synthetic Phomolide G (**1**) and Phomolide H (**2**) exhibited identical spectral data (IR, ^1H NMR, ^{13}C NMR and Mass) to that of the natural product.[4]



Grubbs 1st generation



Grubbs 2nd generation

In conclusion, we described the stereoselective total synthesis of Phomolide G, H and its *Z*-isomer (**20**) via an RCM of the respective dienoic esters. Phomolide G, H and its *Z*-isomer was achieved using inexpensive and commercially available starting material (*R*)- epichlorohydrin. The synthesis highlights Sharpless epoxidation and ring closing metathesis (RCM) reactions as key steps.

Acknowledgments

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19. While one of the olefinic proton signal appeared at δ 5.40 ppm as a dd (J = 9.82, 15.86 Hz) and the signal due to other double proton appeared at δ 5.82 ppm as a dd (J = 9.82, 15.86 Hz). And the geometry of the olefin in **19** was established as '*Z*' from its coupling constants, while one of the olefinic proton signal appeared at δ 5.78 ppm as a dd (J = 2.26, 7.55 Hz) and the signal due to other double proton appeared at δ 5.82 ppm as a dd (J = 2.26, 7.55 Hz).