A Convergent and Stereoselective Total Synthesis of Phomolides G and H

B. V. Subba Reddy,*[a] P. Sivaramakrishna Reddy,[a] B. Phaneendra Reddy,[a,b] J. S. Yadav[a]

[a] Natural Products Chemistry, CSIR-Indian Institute of Chemical Technology, Hyderabad 500007, India
Fax +91(40)27160512; E-mail: basireddy@iict.res.in

[b] Department of Chemistry, Yogi Vemana University, Kadapa 516003, Andhra Pradesh, India

Received: 20.09.2013; Accepted after revision: 13.11.2013

Abstract: A stereoselective total synthesis of phomolides G and H, a polyketide natural products is described. The synthesis involves organocatalytic enantioselective asymmetric epoxidation, C1-Wittig olefination, and ring-closing metathesis as key steps. The use of organocatalytic MacMillan asymmetric epoxidation for the construction of two chiral centers of phomolides G and H makes this approach more attractive.

Key words: MacMillan asymmetric epoxidation, ring-closing metathesis, decalactones

Polyhydroxy macrolides were isolated as secondary metabolites of terrestrial and marine organisms, such as bacteria, fungi, and plants. They are found to exhibit various biological activities such as antibacterial, antifungal, phytotoxic, or enzyme-inhibitory effects.[1] In particular, the ten-membered macrolides such as sonnerlactones,[2] decarestrictines,[3] modiolides,[4] and stagonolides[5] have received significant attention due to their interesting biological properties.

Phomolides G (**1**, Figure 1) and H (**2**), were isolated from the leaves of mangrove species, that is, Kandelia candel.[6] Due to their interesting biological activity and natural scarcity, these natural products have attracted immense interest to take up their total synthesis for further biological evaluation.[7]

In continuation of our efforts in the area of biologically active natural product synthesis,[8] we herein report a convergent and stereoselective total synthesis of phomolides G and H starting from a readily available dimethyl L-tartrate (Scheme 1).

Our retrosynthetic analysis of the target molecules **1** and **2** revealed that they could be synthesized by means of ring-closing metathesis of **18**, which could in turn be prepared through the esterification of the alkenol **11** derived from readily available dimethyl L-tartrate (**3**, Scheme 1).

Accordingly, oxidation of alcohol **4** with tetrapropylammonium perruthenate (TPAP) followed by Wittig olefination[9] afforded the *trans*-olefinic ester **5** in 80% overall yield. Reduction of **5** with diisobutylaluminum hydride (DIBAL-H) afforded the allylic alcohol **6** in 85% yield. Isomerization of **6** using **7** mol% of preactivated $Pd(OH)_2/C$ in benzene at room temperature gave the corresponding aldehyde **7** in 90% yield.[10] The aldehyde was then subjected to organocatalyzed asymmetric epoxidation using catalyst **A** to give the terminal epoxide **8** (93% de, by HPLC analysis) in 86% yield.[11] Regioselective ring opening of epoxide **8** with ethylmagnesium bromide in the presence of a catalytic amount of copper(I) iodide gave the corresponding alcohol **9** in quantitative yield. Debenzylation of compound **9** with Li/naphthalene in THF afforded the primary alcohol **10** in 84% yield. Oxidation of alcohol **10** with DMP in CH_2Cl_2 gave the corresponding lactol, which upon C-1 Wittig olefination, afforded the alkenol **11** in 75% yield (Scheme 2).

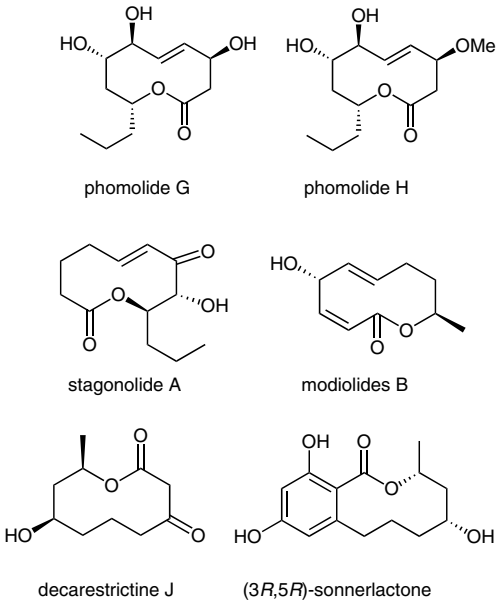

Figure 1 Examples of ten-membered macrolides

Next, we attempted the synthesis of another key intermediate **17** from butane-1,4-diol (**12**). Monoprotection of the diol **12** with BnBr in the presence of NaH in THF afforded the benzyl ether **13** in 88% yield. Oxidation of alcohol **13** with IBX gave the corresponding aldehyde, which was then subjected to organocatalyzed asymmetric epoxidation using catalyst **A**, and resulted in the formation of epoxide **14** (95% ee, by HPLC analysis) in 85% yield.[11] Treatment of epoxide **14** with trimethylsulfonium iodide in the presence of *n*-BuLi in THF at –20 °C gave the allylic alcohol in 88% yield,[12] which was then protected as its TBS ether **15** using TBSCl and imidazole. Debenzylation of **15** with Li/naphthalene afforded the alcohol **16** in 85% yield. One-pot oxidation of **16** with 2,2,6,6-tetramethylpi-

SYNLETT 2014, 25, 0501–0504
Advanced online publication: 10.01.2014
DOI: 10.1055/s-0033-1340348; Art ID: ST-2013-D0895-L