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Synthetic studies of antitumor macrolide laulimalide: a stereoselective synthesis of the C₁₇–C₂₈ segment

Arun K. Ghosh* and Yong Wang

Department of Chemistry, University of Illinois at Chicago, 845 West Taylor Street, Chicago, Illinois 60607, USA

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Abstract

A stereoselective synthesis of the C₁₇–C₂₈ segment of the potent antitumor macrolide, laulimalide has been accomplished. The key steps are a ring-closing olefin metathesis to construct the dihydropyran unit, nucleophilic addition of an alkynyl anion to the Weinreb amide, stereoselective reduction of the resulting ketone to set the C₂₀-hydroxyl stereochemistry, and elaboration of the C₂₁–C₂₂ *trans*-olefin geometry. © 2000 Elsevier Science Ltd. All rights reserved.

Laulimalide (**1**) is a 20-membered macrolide isolated from the Indonesian sponge *Hyattella* sp.¹ It has exhibited potent cytotoxicity in the range of 10–50 ng/mL (IC₅₀ values) against numerous human cancer cell lines.² The remarkable antitumor activities as well as its unique structural features have prompted considerable interest in the synthesis and structure–function studies of laulimalide.³ An asymmetric synthesis of the C₃–C₁₄ segment of laulimalide has been previously reported by us.⁴ More recently, we have reported an efficient enantioselective route to the C₂–C₁₆ segment.⁵ Our synthetic strategy of laulimalide is convergent and involves the assembly of fragments **2** (C₂–C₁₆ segment) and **3** (C₁₇–C₂₈) by Julia olefination and subsequent macrolactonization between the C₁₉-hydroxyl group and the C₁-carboxylic acid. In continuation of our on-going studies, we now report a stereocontrolled route to the C₁₇–C₂₈ segment (**3**) of laulimalide.

As depicted in Fig. 1, we planned to synthesize the fragment **3** by a nucleophilic addition of the dibromo olefin **5** derived alkynyl anion to the Weinreb amide **4** and subsequent stereoselective reduction of the resulting ketone. The synthesis of both Weinreb amide **4** and dihydropyran derivative **5** were planned from the readily available optically active glycidyl ether **6**.⁶ Thus, the synthesis of the dihydropyran derivative **5** was carried out as shown in Scheme 1. Opening of the epoxide **6** with isopropenylmagnesium bromide in the presence of a catalytic amount of CuCN (10 mol%) at –78 to 23°C for 2 h afforded the homoallylic alcohol **7** in 94% yield after silica gel chromatography. Allylation of alcohol **7** was carried out by treatment with potassium hydride

* Corresponding author. E-mail: arunghos@uic.edu

and allyl bromide in the presence of a catalytic amount of 18-Crown-6 in THF at 0 to 23°C for 1 h to provide allyl ether **8** in quantitative yield. For efficient elaboration of the functionalized dihydropyran ring, we relied upon a ring-closing metathesis protocol utilizing Grubbs' catalyst.⁷ Thus, exposure of the allyl ether **8** to Grubbs' catalyst (2 mol%) in CH₂Cl₂ at 23°C for 2 h furnished the dihydropyran derivative **9**. Treatment of **9** with camphorsulfonic acid in methanol at 23°C for 1 h resulted in the deprotection of THP-ether providing the alcohol **10** in 81% yield (two steps) after silica gel chromatography. Swern oxidation of **10** followed by subjection of the resulting aldehyde to Corey-Fuchs' homologation conditions using carbon tetrabromide and triphenylphosphine in CH₂Cl₂ at 0 to 23°C for 30 min afforded the dibromo olefin **5** in 67% yield (two steps).⁸ Dibromo olefin **5** is the precursor for the alkynyl anion; thus, it set the stage for coupling with Weinreb amide **4** which is also derived from the same glycidyl ether **6**. Thus, lithiation of phenyl methyl sulfone with 1 equiv. *n*BuLi in THF at 0°C for 1 h followed by addition of HMPA and reaction with epoxide **6** at -78 to 23°C for 2 h provided the alcohol **11** in 94% isolated yield.⁹ Alcohol **11** was subsequently protected as the PMB ether **12** by treatment with NaH and PMBCl in DMF at 0 to 23°C for 12 h (85% yield).

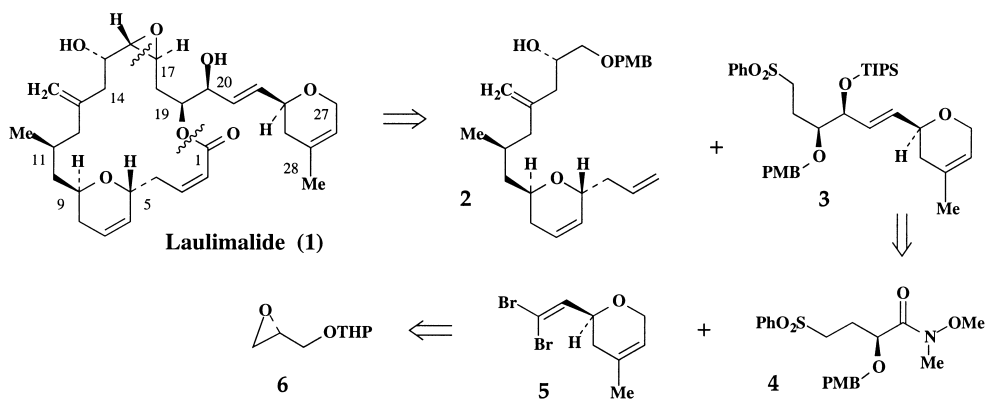
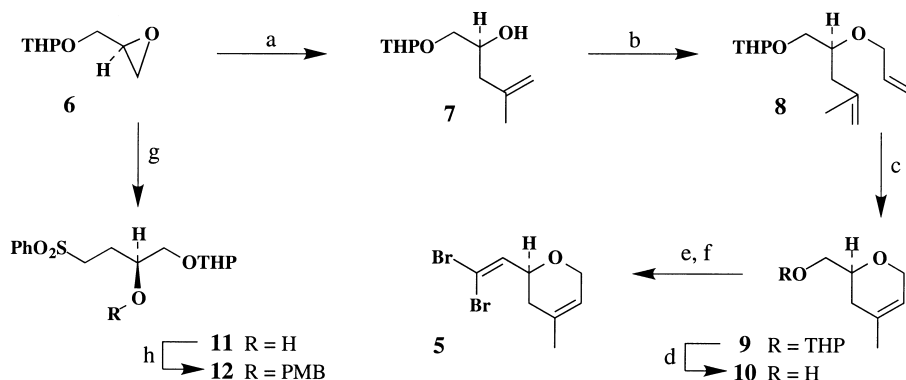
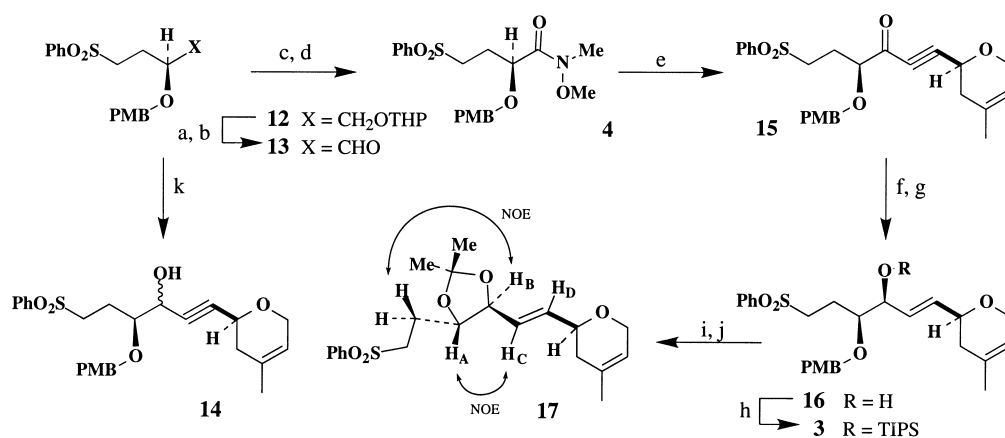


Figure 1.



Scheme 1. (a) Isopropenyl magnesium bromide, CuCN (10 mol%), THF, -78 to 23°C (94%); (b) KH, 18-Crown-6 (cat.), allyl bromide, THF, 0 to 23°C (quant); (c) Cl₂(PCy₃)₂Ru=CHPh (2 mol%), CH₂Cl₂, 23°C; (d) CSA, MeOH (81%); (e) Swern oxidation; (f) CBr₄, PPh₃, CH₂Cl₂, 0 to 23°C (67%); (g) PhSO₂CH₃, *n*BuLi, THF, 0°C, 1 h then HMPA, **6**, -78 to 23°C (94%); (h) NaH, PMBCl, DMF, 0 to 23°C (85%)

Our next synthetic plan involved the conversion of **12** into its corresponding Weinreb amide **4**. As outlined in Scheme 2, the removal of the THP ether with CSA in methanol followed by Swern oxidation of the resulting alcohol provided the aldehyde **13**. Aldehyde **13** was subsequently transformed into the Weinreb amide **4** in a two-step sequence involving: (1) oxidation of the aldehyde with NaClO₂ in the presence of 2-methyl-2-butene and NaH₂PO₄ in *t*BuOH; and (2) reaction of the resulting acid with isobutyl chloroformate, *N,O*-dimethylhydroxylamine and *N*-methylpiperidine in CH₂Cl₂ at 0 to 23°C for 2 h.¹⁰ Weinreb amide **4** was obtained in 83% isolated yield (from **12**). Our initial attempt to install the C₂₀-hydroxyl stereochemistry by addition of the dihydropyran **5** derived alkynyl anion to the aldehyde **13** resulted in the formation of alkynyl alcohol **14** in 64% yield. However, observed diastereoselectivity (*syn:anti* = 1:1.8 by ¹H NMR) was far from satisfactory for our synthesis. To set the C₂₀-hydroxyl stereochemistry, we therefore relied upon the addition of the dihydropyran **5**-derived alkynyl anion to the Weinreb amide **4** and then diastereoselective reduction of the resulting alkynyl ketone. The coupling of Weinreb amide **4** and dibromo olefin **5** was achieved by treatment of **5** with *n*BuLi at -78°C for 1 h followed by warming to 23°C for 1 h to form the corresponding alkynyl anion. The resulting anion was cooled to -78°C and reacted with the Weinreb amide **4** at -78°C to 0°C for 1 h to furnish the alkynyl ketone **15** in 59% isolated yield.¹¹ Diastereoselective reduction of **15** with L-Selectride in THF at -78°C for 1 h afforded the corresponding alkynyl alcohol as a single diastereomer (by ¹H NMR and ¹³C NMR analysis) in 87% yield.¹² The C₂₁-C₂₂ *trans*-olefin geometry was then set by reduction of the alkynyl group by Red-Al in THF at -20°C for 1 h to afford the *trans*-allylic alcohol **16** in 81% yield. The alcohol was subsequently protected as the TIPS-ether **3** by treatment with TIPSOTf and 2,6-lutidine in CH₂Cl₂ at 0 to 23°C for 2 h (92%). In order to establish the C₂₀-hydroxyl stereochemistry as well as the C₂₁-C₂₂ *trans*-olefin geometry, the alcohol **16** was converted to the isopropylidene derivative **17** by removal of the PMB-ether with trifluoroacetic acid in CH₂Cl₂ followed by the exposure of the resulting diol with CSA and dimethoxypropane in CH₂Cl₂ (70%).¹³ As shown in Scheme 2, an NOE was observed between the H_A and H_C. Also, NOEs were detected between the β-sulfonyl hydrogens and the H_B. Furthermore, a coupling



Scheme 2. (a) CSA, MeOH (91%); (b) Swern oxidation; (c) NaClO₂, 2-methyl-2-butene, NaH₂PO₄, *t*BuOH; (d) MeONHMe·HCl, *N*-methylpiperidine, isobutyl chloroformate, CH₂Cl₂, 0 to 23°C (83%); (e) *n*BuLi, **5**, -78°C, 1 h and 23°C, 1 h then **4**, -78 to 0°C (59%); (f) L-Selectride, THF, -78°C (87%); (g) Red-Al, THF, -20°C (81%); (h) TIPSOTf, 2,6-lutidine, CH₂Cl₂, 0 to 23°C (92%); (i) CF₃CO₂H, CH₂Cl₂, 23°C; (j) Me₂C(OMe)₂, CSA, CH₂Cl₂, 23°C (70%); (k) *n*BuLi, **5**, -78 to 23°C, 1 h then **13**, -78°C (64%)

constant (J_{CD}) of 15.5 Hz was measured between the H_C and H_D protons of **17** which corresponds to *trans*-olefin geometry.

Thus, a stereocontrolled synthesis of the C₁₇–C₂₈ fragment of laulimalide has been achieved. The key steps are the ring-closing olefin metathesis to construct the dihydropyran side chain, nucleophilic addition of an alkynyl anion to the Weinreb amide and subsequent reduction to set the stereochemistry of C₂₀. Further work toward the total synthesis of laulimalide is in progress.

Acknowledgements

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- All new compounds gave satisfactory spectral data. Compound **3**: $[\alpha]_D^{23}$ –66 (c 1.21, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.85 (d, *J* = 7.4 Hz, 2H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.52 (t, *J* = 7.4 Hz, 2H), 7.19 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 5.78–5.68 (m, 2H), 5.40 (s, 1H), 4.47 (AB q, 2H, $\Delta\nu_{AB}$ = 51.2 Hz, *J*_{AB} = 11.4 Hz), 4.44 (m, 1H), 4.15 (br s, 2H), 4.00 (m, 1H), 3.79 (s, 3H), 3.48 (m, 1H), 3.20 (m, 1H), 3.02 (m, 1H), 1.99–1.91 (m, 2H), 1.85 (d, *J* = 14.5 Hz, 1H), 1.73 (m, 1H), 1.70 (s, 3H), 0.98 (s, 21H); ¹³C NMR (100 MHz, CDCl₃) δ 159.4, 139.1, 133.5, 132.4, 131.3, 130.1, 129.6, 129.1, 128.7, 128.0, 119.8, 113.8, 79.6, 73.3, 72.1, 72.0, 65.5, 55.3, 53.1, 35.6, 23.0, 22.8, 18.1, 12.2. Compound **17**: $[\alpha]_D^{23}$ –69 (c 0.32, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.92 (d, *J* = 7.9 Hz, 2H), 7.67 (t, *J* = 7.0 Hz, 1H), 7.58 (t, *J* = 7.6 Hz, 2H), 5.87 (dd, *J* = 15.5, 5.0 Hz, 1H), 5.66 (dd, *J* = 15.5, 7.6 Hz, 1H), 5.42 (s, 1H), 4.18 (s, 2H), 4.03 (m, 1H), 3.99 (t, *J* = 8.1 Hz, 1H), 3.67 (m, 1H), 3.32 (m, 1H), 3.15 (m, 1H), 2.10–1.99 (m, 2H), 1.93–1.88 (m, 2H), 1.70 (s, 3H), 1.34 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 139.5, 136.6, 134.2, 131.7, 129.8, 128.5, 126.8, 120.1, 109.6, 82.1, 79.0, 73.2, 66.1, 53.6, 36.0, 27.5, 27.3, 25.3, 23.3.