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Synthetic studies of antitumor macrolide laulimalide: a stereoselective synthesis of the C_{17}–C_{28} segment

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Abstract

A stereoselective synthesis of the C_{17}–C_{28} 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 C_{20}-hydroxyl stereochemistry, and elaboration of the C_{21}–C_{22} *trans*-olefin geometry.

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 (IC_{50} 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 C_3–C_{14} segment of laulimalide has been previously reported by us.[4] More recently, we have reported an efficient enantioselective route to the C_2–C_{16} segment.[5] Our synthetic strategy of laulimalide is convergent and involves the assembly of fragments **2** (C_2–C_{16} segment) and **3** (C_{17}–C_{28}) by Julia olefination and subsequent macrolactonization between the C_{19}-hydroxyl group and the C_1-carboxylic acid. In continuation of our on-going studies, we now report a stereocontrolled route to the C_{17}–C_{28} 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

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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 CH_2Cl_2 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 CH_2Cl_2 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).

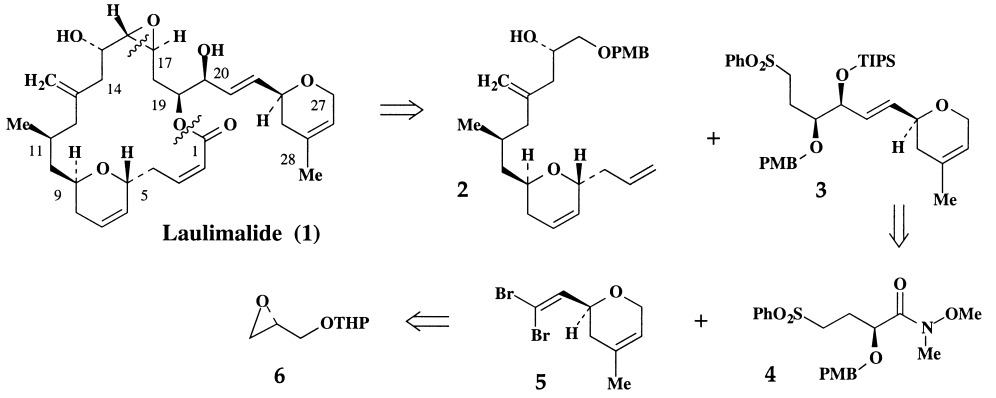
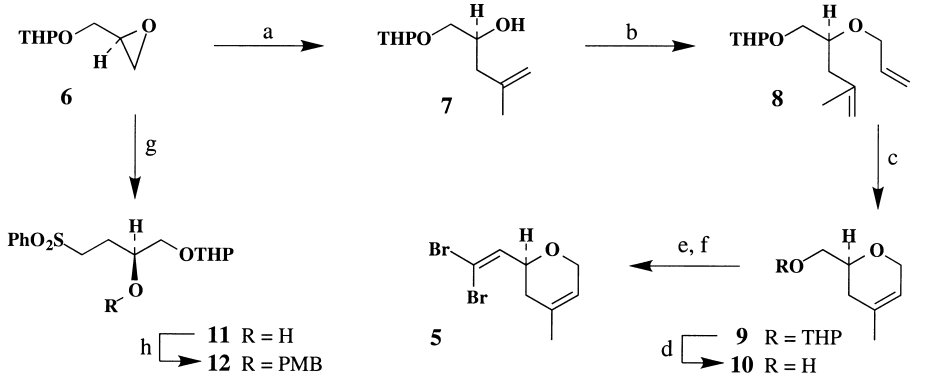
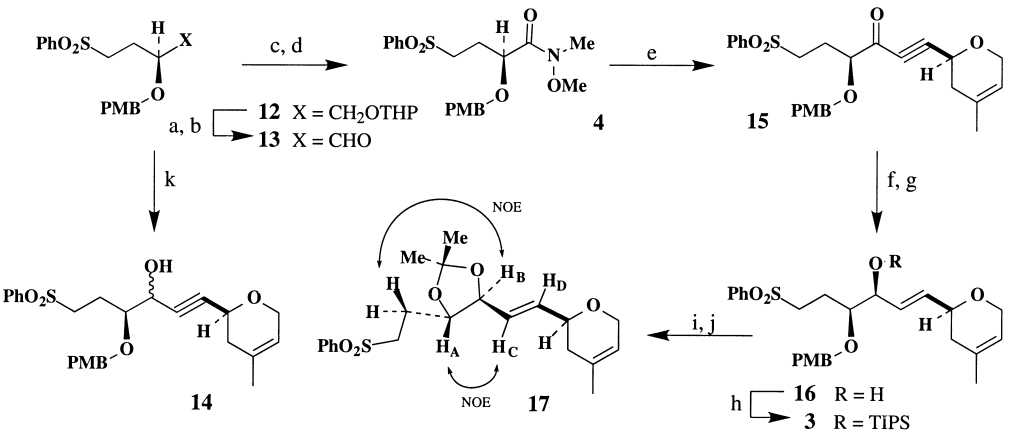


Figure 1.



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) $Cl_2(PCy_3)_2Ru{=}CHPh$ (2 mol%), CH_2Cl_2, 23°C; (d) CSA, MeOH (81%); (e) Swern oxidation; (f) CBr_4, PPh_3, CH_2Cl_2, 0 to 23°C (67%); (g) $PhSO_2CH_3$, *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 $NaClO_2$ in the presence of 2-methyl-2-butene and NaH_2PO_4 in *t*BuOH; and (2) reaction of the resulting acid with isobutyl chloroformate, *N*,*O*-dimethylhydroxylamine and *N*-methylpiperidine in CH_2Cl_2 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 C_{20}-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 C_{20}-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 ^{13}C NMR analysis) in 87% yield.[12] The C_{21}–C_{22} *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 CH_2Cl_2 at 0 to 23°C for 2 h (92%). In order to establish the C_{20}-hydroxyl stereochemistry as well as the C_{21}–C_{22} *trans*-olefin geometry, the alcohol **16** was converted to the isopropylidene derivative **17** by removal of the PMB–ether with trifluoroacetic acid in CH_2Cl_2 followed by the exposure of the resulting diol with CSA and dimethoxypropane in CH_2Cl_2 (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) $NaClO_2$, 2-methyl-2-butene, NaH_2PO_4, *t*BuOH; (d) MeONHMe·HCl, *N*-methylpiperidine, isobutyl chloroformate, CH_2Cl_2, 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, CH_2Cl_2, 0 to 23°C (92%); (i) CF_3CO_2H, CH_2Cl_2, 23°C; (j) $Me_2C(OMe)_2$, CSA, CH_2Cl_2, 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 correponds to *trans*-olefin geometry.

Thus, a stereocontrolled synthesis of the C_{17}–C_{28} 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 C_{20}. Further work toward the total synthesis of laulimalide is in progress.

Acknowledgements

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13. All new compounds gave satisfactory spectral data. Compound **3**: $[\alpha]_D^{23}$ –66 (*c* 1.21, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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.