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A macrolactonization-based strategy to obtain microtubule-stabilizing agent (–)-laulimalide

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Abstract

An alternative synthesis of anti-tumor macrolide (–)-laulimalide is described. The synthesis was achieved utilizing Yamaguchi macrolactonization as the key step. The sensitive C₂–C₃ *cis*-olefin functionality has been installed by a macrolactonization of hydroxy alkynic acid and subsequent hydrogenation over Lindlar's catalyst.

Anti-tumor macrolide laulimalide (**1**), also known as figanolide B, has been isolated from both the Indonesian sponge *Hyattella* sp. and the Okinawan sponge *Fasciospongia rimosa*.¹ It displays remarkable anti-tumor activity against numerous NCI cell lines. It displayed cytotoxicity against the KB cell line with an IC₅₀ value of 15 ng/mL. Furthermore, it has shown cytotoxicity against P388, A549, HT29, and MEL28 cell lines in the range of 10–50 ng/mL (IC₅₀ values).² Laulimalide exhibits microtubule-stabilizing properties similar to paclitaxel (Taxol[™]).³ One of the intriguing properties of laulimalide is that it inhibits the P-glyco-protein that is responsible for multiple-drug resistance in tumor cells. Recently, it has been shown that it is as much as 100-fold more potent than Taxol in multidrug-resistant cell lines.³ Thus, laulimalide represents a new class of microtubule-stabilizing agents with significant clinical potential. The remarkable anti-tumor activity as well as its unique structural features has stimulated considerable interest in its synthesis and structure–function studies. Several synthetic approaches toward fragments of laulimalide have been reported by us⁴ and others.⁵ Recently we reported the first total synthesis of (–)-laulimalide (**1**).⁶ The key macrocyclization step in this synthesis involved an intramolecular Horner–Emmons reaction of the C-19 bis-(trifluoroethyl) phosphonoacetate and C-3 aldehyde which provided a 1:2 mixture of C₂–C₃ *cis/trans* macrolactones (Fig. 1). The isomers were separated and the major *trans*-isomer was photoisomerized to the *cis*-isomer.⁶ In an effort to install the C₂–C₃ *cis*-olefin geometry selectively, we now have investigated an alternative macrolactonization strategy. Herein, we wish to report a macrolactonization route to laulimalide in which the sensitive C₂–C₃ *cis*-olefin functionality has been incorporated by macrolactonization of a hydroxy alkynic acid followed by hydrogenation of the resulting alkyne derivative.

First, we explored the possibility of macrolactonization between the C-19 hydroxyl group and the C-1 alkenyl acid utilizing Yamaguchi protocol.⁷ Selective preparation of this type of

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sensitive *cis*-alkenyl acid was previously reported by Roush during the synthesis of verrucaric acid. ⁸ Therefore, we elected to use a 2-(trimethylsilyl)ethyl ester as the blocking group for the C-1 carboxylic acid as it can be removed under mild conditions. The corresponding precursor **5** for the synthesis was prepared by Julia reaction of sulphone **4** with aldehyde **2** as described previously (46% yield). ⁶ Protection of the C-20 alcohol as a THP ether with dihydropyran and a catalytic amount of PPTS in CH₂Cl₂, followed by removal of the TBS group by treatment with *n*Bu₄N⁺F⁻ in THF afforded primary alcohol **6** in 76% yield (Scheme 1). Dess–Martin oxidation ⁹ of the alcohol, followed by Ando's modified Horner–Emmons reaction ¹⁰ of the resulting aldehyde with (PhO)₂P(O)CH₂CO₂SEM, KN(TMS)₂ and 18-crown-6 at –78°C for 30 min provided the *cis*- α,β -unsaturated ester **7** as a single isomer in 64% yield (by ¹H NMR). ¹¹ Removal of the PMB-ether by DDQ and subsequent deprotection of the SEM ester by exposure to *n*Bu₄N⁺F⁻ in THF provided the hydroxy acid, the key macrolactonization precursor, in 60% yield. Yamaguchi lactonization ⁷ of the hydroxy acid at 23°C, however, resulted in a mixture of macrolactones **8** and **9** (65%, *E:Z* ratio 2:1). Evidently, olefin isomerization occurred during the macrolactonization reaction. Attempted cyclization under a variety of reaction conditions (base, acylating agent) did not improve the ratio of desired *Z*-isomer. Roush previously reasoned that such olefin isomerization is due to the reversible Michael addition of the acylating catalyst (DMAP) to the active acylating agent. ⁸

We then turned our attention to the macrolactonization of the C-19 alcohol and C-1 alkynyl acid (Scheme 2). Thus, protection of alcohol **10** ⁶ as a THP ether, followed by removal of TBS by reaction with *n*Bu₄N⁺F⁻ in THF furnished the alcohol **11**. Dess–Martin oxidation of the alcohol provided the aldehyde which was subjected to Corey–Fuchs homologation conditions ¹² using carbon tetrabromide and triphenylphosphine in CH₂Cl₂ at 0°C for 30 min to afford the dibromo olefin. Treatment of the resulting dibromo olefin with *n*BuLi at –78°C for 10 min afforded the alkynyl anion, which upon treatment with methyl chloroformate at –78°C for 30 minutes afforded alkynyl ester **12** in 59% yield for the three-step sequence. Removal of the THP ether by treatment with CSA in methanol, followed by saponification of the methyl ester by exposure to aqueous lithium hydroxide provided the precursor hydroxy acid **13** in 74% yield. Yamaguchi macro-lactonization ⁷ of hydroxy acid **13** afforded lactone **14** in 68% isolated yield. ¹³ Hydrogenation of lactone **14** over Lindlar's catalyst in a mixture (1:1) of 1-hexene and EtOAc for 1.5 h afforded the *cis*-macrolactone **15** as a single isomer (94% yield). ¹⁴ The spectral properties of macrolactone **15** are in full agreement with reported values. ⁶ Macrolactone **15** was previously converted to synthetic (–)-laulimalide (**1**) by us. ⁶

In conclusion, a stereoselective synthesis of (–)-laulimalide via a macrolactonization strategy has been achieved. The key steps are alkylation of the dibromo olefin derived alkynyl anion with methyl chloroformate and Yamaguchi macrolactonization. Considering its clinical potential as an anti-tumor agent, the present synthesis will provide convenient access to the synthesis of analogues of laulimalide for biological evaluation.

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11. The reagent, (PhO)₂P(O)CH₂CO₂SEM was derived from benzyl (diphenylphosphono)acetate which was prepared by following the procedure of Ando.¹⁰ Catalytic hydrogenation followed by esterification of the resulting acid with trimethylsilylethyl alcohol in the presence of DCC and DMAP in CH₂Cl₂ provided the (diphenylphosphono)acetate derivative in near quantitative yield from the benzyl ester.
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13. All new compounds gave satisfactory spectral data. Compound **14**: [α]_D²³ -46 (c 0.92, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.23 (d, *J*=8.6 Hz, 2H), 6.86 (d, *J*=8.6 Hz, 2H), 5.89 (m, 1H), 5.86 (dd, *J*=15.6, 5.6 Hz, 1H), 5.63–5.57 (m, 3H), 5.51 (dd, *J*=15.6, 6.8 Hz, 1H), 5.43 (s, 1H), 5.10 (m, 1H), 4.85 (s, 1H), 4.78 (s, 1H), 4.63 (d, *J*=6.9 Hz, 1H), 4.59 (d, *J*=11.8 Hz, 1H), 4.47 (d, *J*=6.8 Hz, 1H), 4.43 (brd, *J*=11.0 Hz, 1H), 4.32 (d, *J*=11.8 Hz, 1H), 4.20 (brs, 2H), 4.08 (m, 1H), 3.85 (t, *J*=6.4 Hz, 1H), 3.80 (s, 3H), 3.69 (m, 1H), 3.30 (s, 3H), 2.71 (dd, *J*=17.4, 11.1 Hz, 1H), 2.37 (dd, *J*=17.4, 2.7 Hz, 1H), 2.34–1.79 (m, 12H), 1.71 (s, 3H), 1.58 (m, 1H), 1.08 (m, 1H), 0.82 (d, *J*=6.4 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 165.2, 159.1, 153.1, 144.7, 135.8, 134.9, 131.3, 130.1, 129.3, 127.6, 126.9, 126.7, 126.2, 119.7, 113.7, 113.5, 94.0, 86.8, 79.2, 76.2, 73.9, 73.2, 71.1, 70.1, 65.6, 65.1, 55.4, 55.2, 45.0, 43.2, 41.1, 35.7, 32.2, 31.3, 26.0, 24.0, 23.0, 18.5.
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Figure 1.

Scheme 1.

(a) Ref. 6; (b) dihydropyran, PPTS, CH_2Cl_2 ; (c) TBAF, THF (76%); (d) Dess–Martin, CH_2Cl_2 ; (e) $\text{KN}(\text{TMS})_2$, 18-crown-6, $(\text{PhO})_2\text{P}(\text{O})\text{CH}_2\text{CO}_2\text{SEM}$, THF, -78°C (64%); (f) DDQ, CH_2Cl_2 , pH 7 buffer; (g) TBAF, THF (60%); (h) Cl_3PhCOCl , $i\text{Pr}_2\text{NEt}$, THF then DMAP, benzene (65%).

Scheme 2.

(a) Dihydropyran, PPTS, CH₂Cl₂; (b) TBAF, THF (87%); (c) Dess–Martin, CH₂Cl₂; (d) CBr₄, PPh₃, CH₂Cl₂, 0°C; (e) *n*BuLi, THF, –78°C then ClCO₂Me, –78°C (59%); (f) CSA, MeOH; (g) LiOH, THF, H₂O (74%); (h) Cl₃PhCOCl, *i*Pr₂NEt, THF then DMAP, benzene (68%); (i) H₂, Lindlar’s catalyst, 1-hexene, EtOAc (94%).