Published in final edited form as:

Tetrahedron Lett. 2000 April 1; 41(14): 2319–2322. doi:10.1016/S0040-4039(00)00158-1.

An enantioselective synthesis of the C₂–C₁₆ segment of antitumor macrolide laulimalide¹

Arun K. Ghosh^{*} and Yong Wang

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

Abstract

An enantioselective synthesis of the C₂–C₁₆ segment of the novel antitumor agent laulimalide is described. The key steps involve a highly diastereoselective allylation, ring-closing olefin metathesis of a homoallylic alcohol derived acrylate ester, a stereoselective anomeric alkylation and an elaboration of an *exo*-methylene unit by a Julia olefination reaction.

Marine natural products containing macrocyclic features have been shown to exhibit anticancer properties with significant clinical potential.² One such compound is laulimalide (**1**), a 20-membered macrolide isolated from the Indonesian sponge *Hyattella* sp.³ More recently, laulimalide, also known as figianolide B, has been isolated from an Okinawan sponge *Fasciospongia rimosa*.⁴ Laulimalide represents a novel class of macrolide with remarkably potent antitumor activities. It has displayed potent cytotoxicity against the KB cell line with an IC₅₀ value of 15 ng/mL.^{3b} Furthermore, laulimalide has shown cytotoxicity against P388, A549, HT29 and MEL28 cell lines in the range of 10–50 ng/mL (IC₅₀ values).^{4b} Initially, the gross structure of laulimalide was established by NMR studies and its absolute configuration has now been elucidated by X-ray crystallographic analysis.^{4a} The unique structural features coupled with its significant antitumor activities have stimulated much interest in its synthesis and structure–function studies. We have earlier reported an asymmetric synthesis of the C₃–C₁₄ segment of laulimalide.⁵ More recently, Nishiyama and Mulzer have also constructed various fragments of laulimalide.⁶ As part of our continuing interest in the chemistry and biology of laulimalide, we have now constructed the C₂–C₁₆ segment of **1** in which the key steps involve a highly diastereoselective Brown's asymmetric allylboration, a ring-closing olefin metathesis of a homoallylic alcohol derived acrylate ester, a stereoselective anomeric alkylation with allyltrimethylsilane, and a novel Julia olefination reaction for the elaboration of the C₁₃ *exo*-methylene unit.

As shown in Fig. 1, we plan to synthesize laulimalide in a convergent manner from the fragment **2** and **3**. The fragments will be connected by Julia olefination followed by macrolactonization between the C₁₉ hydroxyl group and the C₁ carboxylic acid group. We plan to introduce the sensitive epoxide between C₁₆ and C₁₇ at the final stage of the synthesis. The synthesis of the C₂–C₁₆ segment commenced with the known optically active alcohol **4** (Scheme 1).⁷ The alcohol **4** was mesylated with mesyl chloride and triethylamine

^{*}Corresponding author. arunghos@uic.edu (A. K. Ghosh).

in CH₂Cl₂ at 0°C for 30 min. Displacement of the resulting mesylate with sodium cyanide furnished the cyanide **5** in 95% yield. DIBAL reduction of the cyanide afforded the aldehyde **6** which was subjected to Brown's asymmetric allylboration protocol to provide the homoallylic alcohol **7** (ratio 96:4) in 75% yield.⁸ Alternatively, the alcohol **7** has been prepared by utilizing Keck's allylation of **6** employing a catalytic amount (10 mol%) of (*S*)-BINOL and titanium isopropoxide to furnish **7** diastereoselectively (de 92%) in 46% yield.⁹ For the elaboration of the dihydropyran ring, we plan to form an α,β -unsaturated δ -lactone and then introduce the side chain functionality stereoselectively. For efficient elaboration of the corresponding δ -lactone, we relied on ring-closing metathesis protocol utilizing Grubbs' catalyst as described recently.^{10,11} Thus, reaction of the alcohol **7** with acryloyl chloride and Et₃N in CH₂Cl₂ provided the acrylate ester **8** in 76% isolated yield. Exposure of the acrylate ester to Grubbs' catalyst (10 mol%) in CH₂Cl₂ in the presence of a catalytic amount (30 mol %) of Ti(O^{*i*}Pr)₄ at 40°C for 5 h furnished the δ -lactone **9** in 72% yield after silica gel chromatography.

To append the side chain, the unsaturated δ -lactone was reduced by reaction with DIBAL at -78°C in CH₂Cl₂. The resulting lactol was subjected to in situ acylation by reaction with acetic anhydride, pyridine and DMAP as described by Dahanukar and Rychnovsky.¹² Exposure of the resulting acetate to allyltrimethylsilane in the presence of BF₃·OEt₂ in CH₂Cl₂ at -78°C, afforded the anomeric allylation product **10** as a single isomer in 82% yield from lactone **9**.¹³ The next step in our synthetic plan was to convert the benzyl ether functionality into its corresponding iodide **11**. The removal of benzyl group was effected by exposure of **10** to lithium in liquid ammonia at -78°C for 10 min. Treatment of the resulting primary alcohol with iodine, triphenylphosphine and imidazole in a mixture (1:1) of Et₂O and CH₃CN at 23°C for 30 min furnished the iodide **11** in 76% yield (two steps) after silica gel chromatography.

For installation of the C₁₃ methylene unit and the C₁₅ hydroxyl group, we relied upon alkylation of α -sulphonyl- γ -lactone **13** with the iodide **11**, reduction of the resulting lactone followed by a Julia olefination reaction. For the synthesis of the lactone **13**, commercial (*R*)-(+)-glycidol was first protected as the *p*-methoxybenzyl ether **12** as described by Smith and co-workers.¹⁴ Reaction of the epoxide **12** with the sodium enolate of methyl phenylsulphonylacetate in EtOH at 23°C for 12 h afforded the α -sulphonyl- γ -lactone **13** as a 2.4:1 diastereomeric mixture in 83% yield after silica gel chromatography. Alkylation of lactone **13** with iodide **11** was carried out by treatment of **13** (1.7 equiv.) with NaH (1.7 equiv.) in DMF at 23°C for 15 min followed by reaction of the iodide **11** (1 equiv.) at 23°C for 15 min and then 60°C for 12 h. The alkylated sulfone **14** was isolated in 91% yield as a single diastereomer with stereochemistry as depicted in Scheme 2. For elaboration of the C₁₃ *exo*-methylene unit, the sulphonyl lactone **14** was treated with LiBH₄ in THF at 23°C for 12 h to provide the diol **15**. Treatment of the diol **15** with benzoyl chloride and Et₃N in the presence of a catalytic amount of DMAP in CH₂Cl₂ afforded the dibenzoate derivative. Exposure of the resulting dibenzoate to magnesium amalgam in ethanol as described by Pak and co-workers, furnished the olefin **16** with concomitant hydrolysis of the C-15 benzoate derivative in 44% overall yield (from **14**).^{15,16} The alkylation of α -sulfonyl- γ -lactone and

Julia olefination sequence may provide a convenient access to other *exo*-methylene units inherent to other biologically important macrolides.²

In conclusion, the asymmetric synthesis of the C₂–C₁₆ fragment of laulimalide has been achieved stereoselectively. The synthesis involved a number of important steps including a Brown's asymmetric allylboration, ring-closing olefin metathesis to form a δ -lactone, a highly stereoselective anomeric alkylation reaction to a functionalized dihydropyran and development of protocol for installation of the C₁₃ *exo*-methylene unit. Further work toward the total synthesis of laulimalide is in progress.

Acknowledgements

Financial support of this work by the National Institutes of Health (GM 55600) is gratefully acknowledged.

References

1. This work has been presented at the 218th American Chemical Society National Meeting, New Orleans, 8 22–26, 1999; contribution number: Medn 234.
2. Harris CR; Danishefsky SJ J. Org. Chem. 1999, 64, 8434.
3. (a)Quinoa E; Kakou Y; Crews P J. Org. Chem 1988, 53, 3642;(b)Corley DG; Herb R; Moore RE; Scheuer PJ; Paul VJ J. Org. Chem 1988, 53, 3644.
4. (a)Jefford CW; Bernardinelli G; Tanaka J-I; Higa T Tetrahedron Lett 1996, 37, 159;(b)Tanaka J-I; Higa T; Bernardinelli G; Jefford CW Chem. Lett 1996, 255.
5. Ghosh AK; Mathivanan P; Cappiello J Tetrahedron Lett 1997, 38, 2427. [PubMed: 30344352]
6. (a)Shimizu A; Nishiyama S Synlett 1998, 1209;(b)Mulzer J; Hanbauer M Tetrahedron Lett 2000, 41, 33.
7. Keck GE; Palani A; McHardy SF J. Org. Chem 1994, 59, 3113.
8. (a)Jadhav PK; Bhat KS; Perumal T; Brown HC J. Org. Chem 1986, 51, 432;(b)Racherla US; Brown HC J. Org. Chem 1991, 56, 401.
9. Keck GE; Tarbet KH; Geraci LS J. Am. Chem. Soc 1993, 115, 8467.
10. (a)Ghosh AK; Cappiello J; Shin D Tetrahedron Lett 1998, 39, 4651;(b)Ghosh AK; Liu C Chem. Commun 1999, 1743;(c)Nicolaou KC; Rodriguez RM; Mitchell HJ; van Delft FL Angew. Chem., Int. Ed. Engl 1998, 37, 1874.
11. For an excellent review, see: Grubbs RH; Chang S Tetrahedron 1998, 54, 4413.
12. Dahanukar VH; Rychnovsky SD J. Org. Chem 1996, 61, 8317. [PubMed: 11667826]
13. (a)For related anomeric allylation, see: Kozikowski AP; Sorgi KL Tetrahedron Lett 1982, 23, 2281; (b)Danishefsky S; Kerwin JF J. Org. Chem 1982, 47, 3803.
14. Smith AB; Zhuang L; Brook CS; Boldi AM; McBriar MD; Moser WH; Murase N; Nakayama K; Verhoest PR; Lin Q Tetrahedron Lett 1997, 38, 8667.
15. Lee GH; Lee HK; Choi EB; Kim BT; Pak CS Tetrahedron Lett 1995, 36, 5607.
16. All new compounds gave satisfactory spectral data. Compound **16**: [α]_D²³ –35 (*c* 0.23, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.25 (d, *J*=8.5 Hz, 2H), 6.87 (d, *J*=8.5 Hz, 2H), 5.87–5.80 (m, 2H), 5.68 (d, *J*=10.5 Hz, 1H), 5.08 (d, *J*=19.0 Hz, 1H), 5.04 (d, *J*=11.4 Hz, 1H), 4.86 (s, 1H), 4.84 (s, 1H), 4.47 (s, 2H), 4.18 (brs, 1H), 3.94 (m, 1H), 3.78 (s, 3H), 3.75 (m, 1H), 3.46 (dd, *J*=9.3, 3.4 Hz, 1H), 3.34 (dd, *J*=9.3, 7.1 Hz, 1H), 2.49 (brs, 1H), 2.40 (m, 1H), 2.24 (m, 1H), 2.16 (d, *J*=6.7 Hz, 2H), 2.05 (m, 1H), 1.96–1.83 (m, 4H), 1.60 (m, 1H), 1.08 (m, 1H), 0.86 (d, *J*=6.3 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 159.2, 144.4, 135.2, 130.1, 129.4, 129.4, 129.2, 124.6, 116.7, 113.9, 113.9, 113.8, 74.0, 73.0, 72.2, 68.2, 65.2, 55.2, 44.6, 42.6, 39.9, 38.8, 31.4, 26.7, 19.2.

Figure. 1.
Retrosynthetic Analysis.

Scheme 1.

(a) MsCl, Et₃N, CH₂Cl₂, 0°C; (b) NaCN, DMSO, 60°C (95%); (c) DIBAL-H, CH₂Cl₂, 0°C (93%); (d) CH₂=CHCH₂B[(-)-Ipc]₂, THF, -100°C (75%); (e) CH₂=CHCOCl, Et₃N, 0 to 23°C, CH₂Cl₂ (76%); (f) Cl₂(PCy₃)₂Ru=CHPh (10 mol%), Ti(O^{*i*}Pr)₄ (30 mol%), CH₂Cl₂, 40°C (72%); (g) DIBAL-H, CH₂Cl₂, -78°C then Ac₂O, pyridine, DMAP, -78 to 23°C; (h) BF₃·OEt₂, CH₂Cl₂, CH₂=CHCH₂SiMe₃, -78°C (82%); (i) Li, NH₃, (78%); (j) I₂, PPh₃, imidazole, MeCN–Et₂O (97%)

Scheme 2.

(a) NaH, PhSO₂CH₂CO₂Me, EtOH (83%); (b) NaH, DMF, iodide **11**, 60°C (91%); (c) LiBH₄, THF, 0 to 23°C; (d) PhCOCl, Et₃N, DMAP (cat), CH₂Cl₂; (e) Mg, HgCl₂ (cat), EtOH (44%)