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An enantioselective synthesis of the C_2–C_{16} segment of antitumor macrolide laulimalide[1]

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Abstract

An enantioselective synthesis of the C_2–C_{16} 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 IC_{50} 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 (IC_{50} 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 C_3–C_{14} 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 C_2–C_{16} 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 C_{13} *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 C_{19}

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hydroxyl group and the C_1 carboxylic acid group. We plan to introduce the sensitive epoxide between C_{16} and C_{17} at the final stage of the synthesis. The synthesis of the C_2–C_{16} segment commenced with the known optically active alcohol **4** (Scheme 1).[7] The alcohol **4** was mesylated with mesyl chloride and triethylamine in CH_2Cl_2 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 Et_3N in CH_2Cl_2 provided the acrylate ester **8** in 76% isolated yield. Exposure of the acrylate ester to Grubbs' catalyst (10 mol%) in CH_2Cl_2 in the presence of a catalytic amount (30 mol%) of $Ti(O^iPr)_4$ at 40°C for 5 h furnished the δ-lactone **9** in 72% yield after silica gel chromatography.

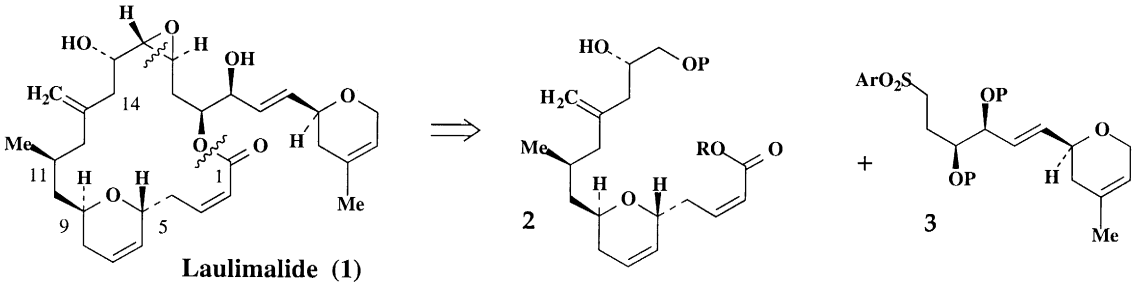
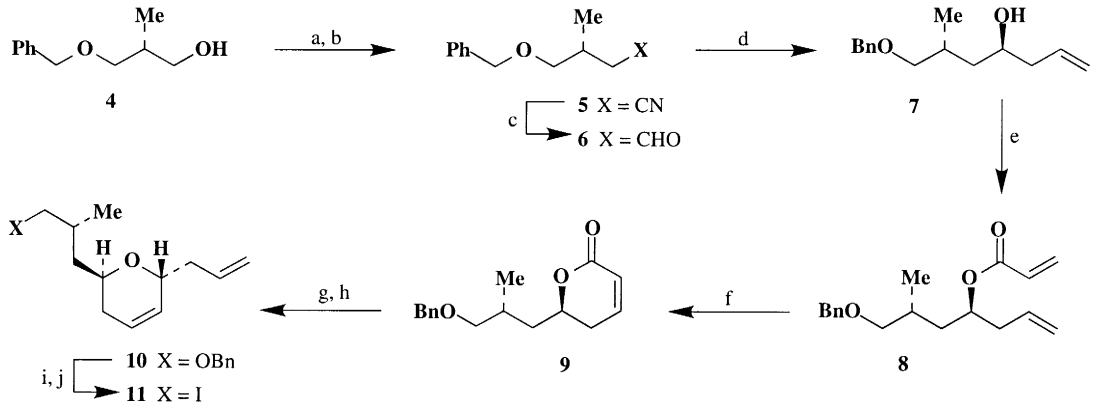


Fig. 1.

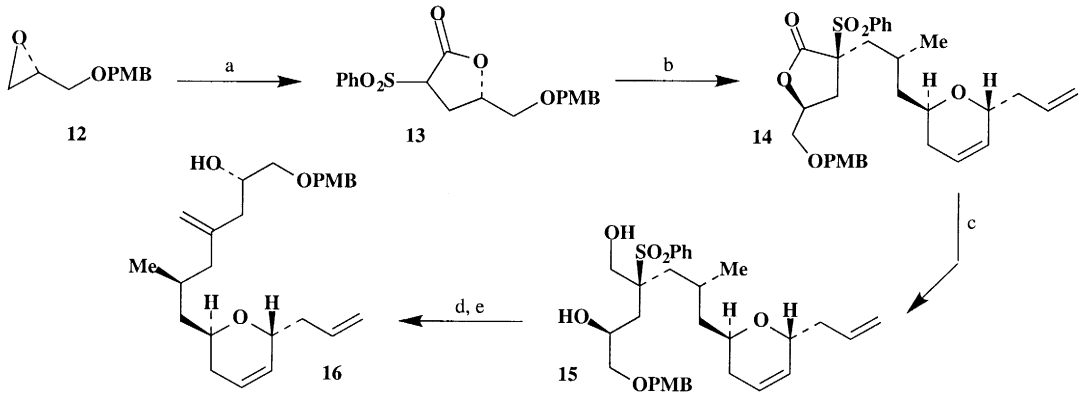


Scheme 1. (a) MsCl, Et_3N, CH_2Cl_2, 0°C; (b) NaCN, DMSO, 60°C (95%); (c) DIBAL-H, CH_2Cl_2, 0°C (93%); (d) $CH_2{=}CHCH_2B[(-)\text{-Ipc}]_2$, THF, −100°C (75%); (e) $CH_2{=}CHCOCl$, Et_3N, 0 to 23°C, CH_2Cl_2 (76%); (f) $Cl_2(PCy_3)_2Ru{=}CHPh$ (10 mol%), $Ti(O^iPr)_4$ (30 mol%), CH_2Cl_2, 40°C (72%); (g) DIBAL-H, CH_2Cl_2, −78°C then Ac_2O, pyridine, DMAP, −78 to 23°C; (h) $BF_3{\cdot}OEt_2$, CH_2Cl_2, $CH_2{=}CHCH_2SiMe_3$, −78°C (82%); (i) Li, NH_3, (78%); (j) I_2, PPh_3, imidazole, MeCN–Et_2O (97%)

To append the side chain, the unsaturated δ-lactone was reduced by reaction with DIBAL at −78°C in CH_2Cl_2. 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 $BF_3{\cdot}OEt_2$ in CH_2Cl_2 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 Et_2O and CH_3CN at 23°C for 30 min furnished the iodide **11** in 76% yield (two steps) after silica gel chromatography.

For installation of the C_{13} methylene unit and the C_{15} 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 C_{13} *exo*-methylene unit, the sulphonyl lactone **14** was treated with $LiBH_4$ in THF at 23°C for 12 h to provide the diol **15**. Treatment of the diol **15** with benzoyl chloride and Et_3N in the presence of a catalytic amount of DMAP in CH_2Cl_2 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]



12 13 14 15 16

Scheme 2. (a) NaH, $PhSO_2CH_2CO_2Me$, EtOH (83%); (b) NaH, DMF, iodide **11**, 60°C (91%); (c) $LiBH_4$, THF, 0 to 23°C; (d) PhCOCl, Et_3N, DMAP (cat), CH_2Cl_2; (e) Mg, $HgCl_2$ (cat), EtOH (44%)

In conclusion, the asymmetric synthesis of the C_2–C_{16} 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 C_{13} *exo*-methylene unit. Further work toward the total synthesis of laulimalide is in progress.

Acknowledgements

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References

1. This work has been presented at the 218th American Chemical Society National Meeting, New Orleans, August 22–26, 1999; contribution number: Medn 234.
2. Harris, C. R.; Danishefsky, S. J. *J. Org. Chem.* **1999**, *64*, 8434.
3. (a) Quinoa, E.; Kakou, Y.; Crews, P. *J. Org. Chem.* **1988**, *53*, 3642; (b) Corley, D. G.; Herb, R.; Moore, R. E.; Scheuer, P. J.; Paul, V. J. *J. Org. Chem.* **1988**, *53*, 3644.
4. (a) Jefford, C. W.; Bernardinelli, G.; Tanaka, J.-I.; Higa, T. *Tetrahedron Lett.* **1996**, *37*, 159; (b) Tanaka, J.-I.; Higa, T.; Bernardinelli, G.; Jefford, C. W. *Chem. Lett.* **1996**, 255.
5. Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron Lett.* **1997**, *38*, 2427.
6. (a) Shimizu, A.; Nishiyama, S. *Synlett* **1998**, 1209; (b) Mulzer, J.; Hanbauer, M. *Tetrahedron Lett.* **2000**, *41*, 33.
7. Keck, G. E.; Palani, A.; McHardy, S. F. *J. Org. Chem.* **1994**, *59*, 3113.
8. (a) Jadhav, P. K.; Bhat, K. S.; Perumal, T.; Brown, H. C. *J. Org. Chem.* **1986**, *51*, 432; (b) Racherla, U. S.; Brown, H. C. *J. Org. Chem.* **1991**, *56*, 401.
9. Keck, G. E.; Tarbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 8467.
10. (a) Ghosh, A. K.; Cappiello, J.; Shin, D. *Tetrahedron Lett.* **1998**, *39*, 4651; (b) Ghosh, A. K.; Liu, C. *Chem. Commun.* **1999**, 1743; (c) Nicolaou, K. C.; Rodriguez, R. M.; Mitchell, H. J.; van Delft, F. L. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1874.
11. For an excellent review, see: Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413.
12. Dahanukar, V. H.; Rychnovsky, S. D. *J. Org. Chem.* **1996**, *61*, 8317.
13. For related anomeric allylation, see: (a) Kozikowski, A. P.; Sorgi, K. L. *Tetrahedron Lett.* **1982**, *23*, 2281; (b) Danishefsky, S.; Kerwin, J. F. *J. Org. Chem.* **1982**, *47*, 3803.
14. Smith, A. B.; Zhuang, L.; Brook, C. S.; Boldi, A. M.; McBriar, M. D.; Moser, W. H.; Murase, N.; Nakayama, K.; Verhoest, P. R.; Lin, Q. *Tetrahedron Lett.* **1997**, *38*, 8667.
15. Lee, G. H.; Lee, H. K.; Choi, E. B.; Kim, B. T.; Pak, C. S. *Tetrahedron Lett.* **1995**, *36*, 5607.
16. All new compounds gave satisfactory spectral data. Compound **16**: $[\alpha]_D^{23}$ −35 (*c* 0.23, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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.