Pergamon

Tetrahedron Letters 42 (2001) 3399–3401

TETRAHEDRON LETTERS

A macrolactonization-based strategy to obtain microtuble-stabilizing agent (−)-laulimalide

Arun K. Ghosh* and Yong Wang†

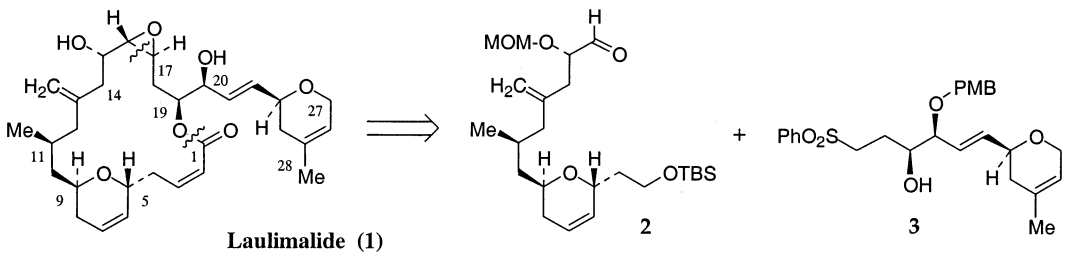
Department of Chemistry, University of Illinois at Chicago, 845 West Taylor Street, Chicago, IL 60607, USA

Received 8 March 2001; accepted 15 March 2001

Abstract—An alternative synthesis of anti-tumor macrolide (−)-laulimalide is described. The synthesis was achieved utilizing Yamaguchi macrolactonization as the key step. The sensitive C_2–C_3 *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 IC_{50} 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 (IC_{50} 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-glycoprotein 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 us[4] 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 C_2–C_3 *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 C_2–C_3 *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 C_2–C_3 *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 sensitive *cis*-alkenyl acid was previ-



Laulimalide (1)

Figure 1.

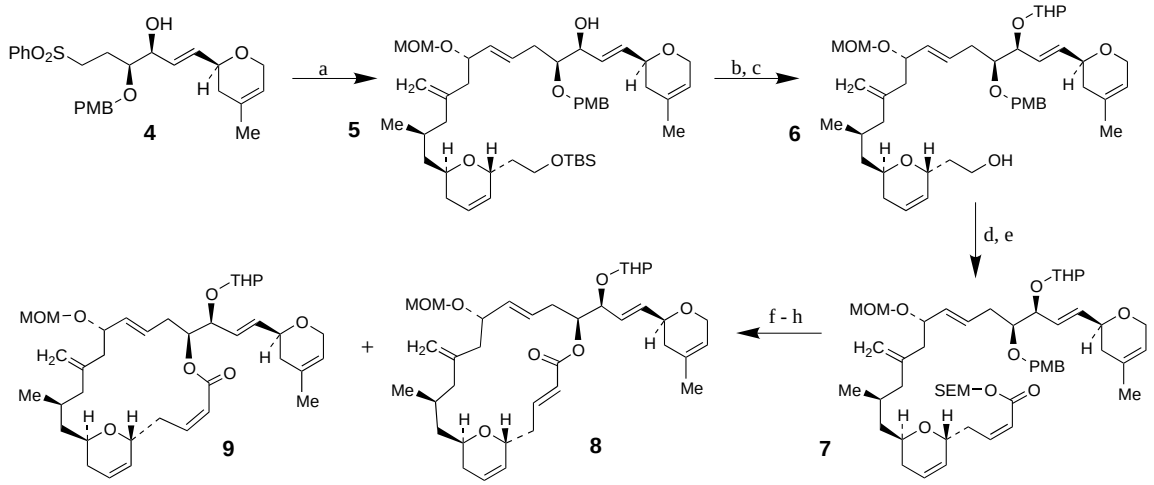
* Corresponding author.

† University Fellow (2000–2001), University of Illinois at Chicago.

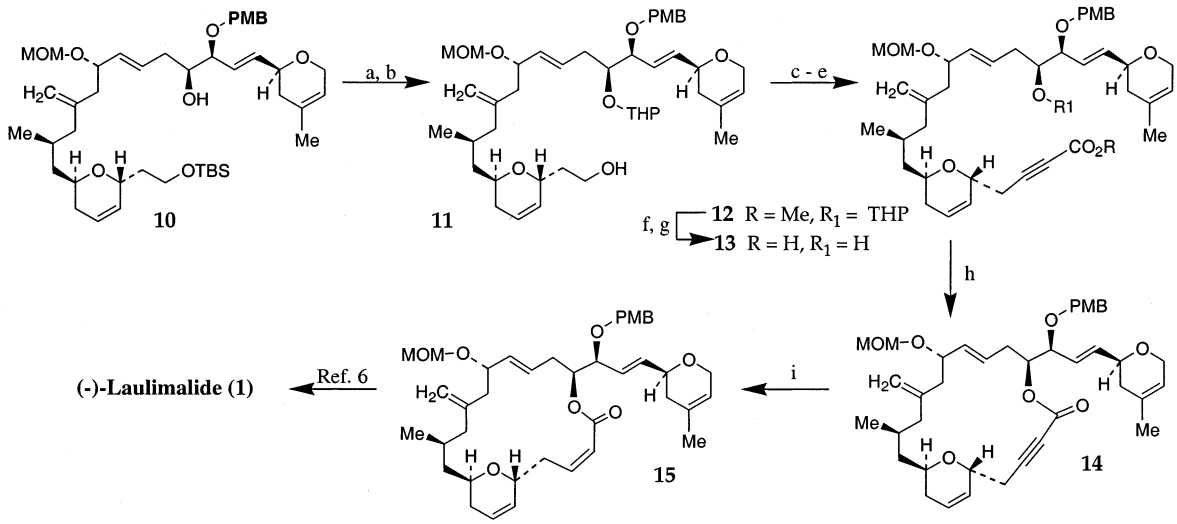
0040-4039/01/$ - see front matter
PII: S0040-4039(01)00436-1

ously reported by Roush during the synthesis of verrucarin B.[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 CH_2Cl_2, followed by removal of the TBS group by treatment with nBu$_4$N$^+$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 $(PhO)_2P(O)CH_2CO_2SEM$, $KN(TMS)_2$ 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 ^{1}H NMR).[11] Removal of the PMB-ether by DDQ and subsequent deprotection of the SEM ester by exposure to nBu$_4$N$^+$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 nBu$_4$N$^+$F$^-$ in THF furnished the alcohol **11**. Dess–Martin oxidation of the alcohol provided the aldehyde which was



Scheme 1. (a) Ref. 6; (b) dihydropyran, PPTS, CH_2Cl_2; (c) TBAF, THF (76%); (d) Dess–Martin, CH_2Cl_2; (e) $KN(TMS)_2$, 18-crown-6, $(PhO)_2P(O)CH_2CO_2SEM$, THF, −78°C (64%); (f) DDQ, CH_2Cl_2, pH 7 buffer; (g) TBAF, THF (60%); (h) $Cl_3PhCOCl$, iPr$_2$NEt, THF then DMAP, benzene (65%).



Scheme 2. (a) Dihydropyran, PPTS, CH_2Cl_2; (b) TBAF, THF (87%); (c) Dess–Martin, CH_2Cl_2; (d) CBr_4, PPh_3, CH_2Cl_2, 0°C; (e) nBuLi, THF, −78°C then $ClCO_2Me$, −78°C (59%); (f) CSA, MeOH; (g) LiOH, THF, H_2O (74%); (h) $Cl_3PhCOCl$, iPr$_2$NEt, THF then DMAP, benzene (68%); (i) H_2, Lindlar's catalyst, 1-hexene, EtOAc (94%).

subjected to Corey–Fuches homologation conditions[12] using carbon tetrabromide and triphenylphosphine in CH_2Cl_2 at 0°C for 30 min to afford the dibromo olfefin. 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 macrolactonization[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.

Acknowledgements

Financial support of this work by the National Institutes of Health (GM 55600) is gratefully acknowledged. We would also like to express our gratitude to Professor Higa for sending us a sample and NMR spectra of natural laulimalide.

References

1. (a) Quinoa, E.; Kakou, Y.; Crews, O. *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.
2. Jefford, C. W.; Bernardinelli, G.; Tanaka, J.; Higa, T. *Tetrahedron Lett.* **1996**, *37*, 159.
3. Mooberry, S. L.; Tien, G.; Hernandez, A. H.; Plubrukarn, A.; Davidson, B. S. *Cancer Res.* **1999**, *37*, 159.
4. (a) Ghosh, A. K.; Wang, Y. *Tetrahedron Lett.* **2000**, *41*, 4705; (b) Ghosh, A. K.; Wang, Y. *Tetrahedron Lett.* **2000**, *41*, 2319; (c) Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron Lett.* **1997**, *38*, 2427.
5. (a) Shimizu, A.; Nishiyama, S. *Synlett* **1998**, 1209; (b) Shimizu, A.; Nishiyama, S. *Tetrahedron Lett.* **1997**, *38*, 6011; (c) Mulzer, J.; Hanbauer, M. *Tetrahedron Lett.* **2000**, *41*, 33; (d) Mulzer, J.; Ohler, E.; Dorling, K. E. *Tetrahedron Lett.* **2000**, *41*, 6323; (e) Paterson, I.; Savi, C. D.; Tudge, M. *Org. Lett.* **2001**, *3*, 213; (f) Messenger, B. T.; Davidson, B. *Tetrahedron Lett.* **2001**, *42*, 797; (g) Nadolskir, G. T.; Davidson, B. *Tetrahedron Lett.* **2001**, *42*, 801.
6. Ghosh, A. K.; Wang, Y. *J. Am. Chem. Soc.* **2000**, *122*, 11027.
7. Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *53*, 1989.
8. (a) Roush, W. R.; Spada, A. P. *Tetrahedron Lett.* **1983**, *24*, 3693; (b) Roush, W. R.; Blizzard, T. A. *J. Org. Chem.* **1984**, *49*, 4332.
9. Meger, S. D.; Schreiber, S. L. *J. Org. Chem.* **1994**, *59*, 7549.
10. Ando, K. *J. Org. Chem.* **1999**, *64*, 8406 and references cited therein.
11. The reagent, $(PhO)_2P(O)CH_2CO_2SEM$ 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 CH_2Cl_2 provided the (diphenylphosphono)acetate derivative in near quantitative yield from the benzyl ester.
12. Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769.
13. All new compounds gave satisfactory spectral data. Compound **14**: $[\alpha]_D^{23}$ −46 (*c* 0.92, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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.
14. Ho, T.-L.; Liu, S. H. *Synth. Commun.* **1987**, *17*, 969.