Tetrahedron Letters 55 (2014) 913–915

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Stereoselective synthesis of the C3–C12 subunit of laulimalide

Sadagopan Raghavan, Pradip Kumar Samanta *

Division of Natural Product Chemistry, Indian Institute of Chemical Technology, Hyderabad 500007, India

ARTICLE INFO

Article history:
Received 4 October 2013
Revised 10 December 2013
Accepted 14 December 2013
Available online 18 December 2013

Keywords:
Laulimalide
Organocatalysis
Ferrier type rearrangement

ABSTRACT

A stereoselective synthesis of the C3–C12 subunit of the tumor growth inhibitors laulimalide is disclosed. The key steps of the synthesis include asymmetric alkylation using Oppolzer's protocol and an asymmetric hetero-Diels–Alder reaction using Jacobsen's catalyst. Substrate controlled diastereoselective Luche reduction followed by Ferrier type reactions are other key steps.

Laulimalide (**1**), also known as figianolide B, a 20-membered macrolide isolated from the Indonesian sponge *Hyattella* sp., has shown remarkable antitumor activities.[1] It promotes abnormal tubulin polymerization and apoptosis in vitro and has a mode of action similar to that of taxol **2**. The structure of **1** was initially established by NMR studies. Subsequently, its absolute configuration was established by X-ray analysis by Higa et al.[2] (Fig. 1).

Initially it was shown that laulimalide displayed potent cytotoxicity against the KB cell line with an IC50 value of 15 ng/mL but it did not attract the attention of synthetic chemists until Mooberry et al.[3] discovered that laulimalide displays microtubule stabilizing activity similar to that of paclitaxel and the epothilones. Furthermore, it has been shown to possess cytotoxicity against P388, A549, HT29, and MEL28 cell lines with IC50 values in the range of 10–50 ng/mL. The significant clinical potential of laulimalide **1**, insufficient material for preclinical development and novel structure has stimulated considerable interest in its synthesis and several groups have disclosed the total synthesis of natural laulimalide[4] and its analogues.[5] In a period of twelve years, five syntheses of laulimalide have been reported in the literature. Owing to its potential as an anticancer lead, its restricted natural supply and unique structure the total synthesis of **1** and the preparation of analogues are a hot topic.

Herein, we describe the synthesis of the C3–C12 subunit **3** of laulimalide utilizing organocatalytic asymmetric reactions and a hetero Diels–Alder (HDA) as key intermediate for pyran ring formation. The retrosynthetic analysis of laulimalide is depicted in Scheme 1. Laulimalide **1** was envisaged to be synthesized via addition of sulfone anion subunit to aldehyde fragment that is by

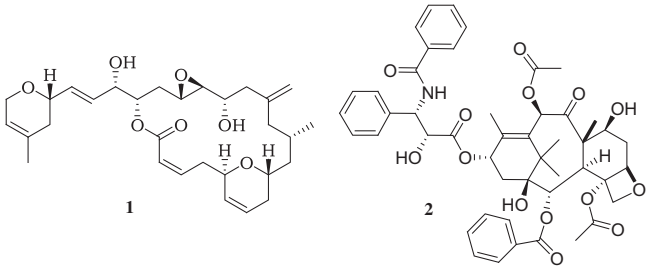


Figure 1. Tumor growth inhibitors laulimalide **1** and taxol **2**.

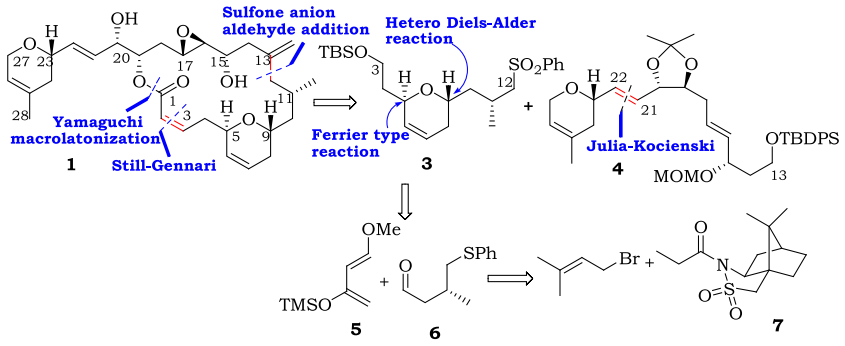
reaction between fragments **3** and **4**.[4p] Fragment **3** can be obtained by a diastereoselective hetero Diels–Alder reaction utilizing Jacobsen's protocol to form the enone followed by a Ferrier reaction.

The synthesis of the pyran **3** commenced from the (*R*)-sultam **8** that on treatment with propionyl chloride yielded auxiliary **7**. Alkylation of the lithio anion of **7** generated using LDA as the base and prenyl bromide as the alkylating agent furnished compound **10** via enolate intermediate **9**.[6] Alcohol **11** was obtained in 83% yield along with the auxiliary by the reduction of **10** using $LiAlH_4$, Scheme 2.

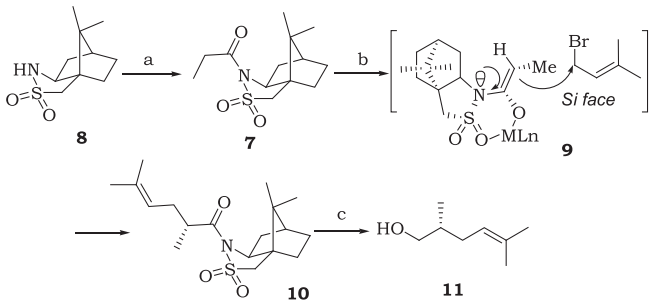
Sulfide **12** was prepared from **11** following Hata's protocol[7] using Bu_3P and diphenyl disulfide. Sulfide **12** on ozonolysis in CH_2Cl_2 under standard reaction conditions furnished sulfone aldehyde **13** in 52% yield along with an epimeric mixture of sulfoxide aldehyde **14**. Compounds **13** and **14** were confirmed by corresponding alcohol. Thus, compounds **13** and **14** exposed to $NaBH_4$ furnished sulfone alcohol **15** in 50% yield along with an epimeric mixture of sulfoxide alcohol **16**, Scheme 3.

* Corresponding author. Tel.: +91 124 4885456.
E-mail address: pch.sam@gmail.com (P.K. Samanta).

0040-4039/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2013.12.040



Scheme 1. Retrosynthetic analysis of (−)-laulimalide **1**.



Scheme 2. Synthesis of alcohol **11**. Reagents and conditions: (a) NaH, CH_3CH_2COCl, toluene, rt, 3 h, 95%; (b) prenyl bromide, *n*BuLi, DIPA, HMPA, THF, −78 °C, 1 h, 83%; (c) LAH, THF, 0 °C, 1 h, 83%.

Attempted hetero Diels–Alder reaction[8] of aldehydes **13**/**14**, with Danishefsky diene[9] **5** failed to afford any desired pyran product **17**/**18**, Scheme 4.

Hence, alcohol **11** was protected as its acetate **20** and further subjected to ozonolysis to afford aldehyde **21**. Attempted hetero Diels–Alder reaction of aldehyde **21** with Danishefsky diene **5** afforded the desired pyran **22**, (Scheme 5). Substrate controlled chemoselective reduction of the carbonyl group using Luche's protocol[10] afforded *cis*-2,4-disubstituted pyran derivative **23** exclusively. Acetylation under standard conditions yielded compound **24** that on reaction with TBS-vinyl ether in the presence of $TiCl_2(OiPr)_2$ as a Lewis acid afforded aldehyde **25**. Thus the trans configuration in the pyran ring was introduced stereoselectively,[13] Scheme 5. Reduction of aldehyde **25** using $NaBH_4$ in MeOH at 0 °C yielded the primary alcohol **26** that was protected as its PMB ether **27** by reaction with the *p*-methoxybenzyl imidate in the presence of $Ln(OTf)_3$.

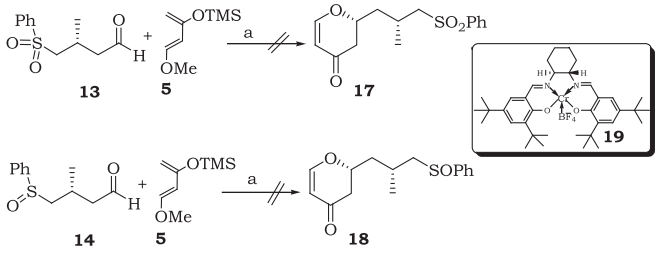
The acetate group in **27** was hydrolyzed to **28** and then exposed to diphenyldisulfide and tributyl phosphine in THF. Unfortunately, at ambient or at reflux temperatures no change was observed.

Mesylation of **28** using methanesulfonic acid in the presence of Et_3N afforded the mesylate **30**. Attempted displacement of the mesylate using thiophenol in the presence of DBU failed to furnish sulfide **29**, returning the starting material instead, (Scheme 6). The alcohol in **28** and mesylate **30** do not exhibit nucleophilic substitution reaction because of pyran ring.

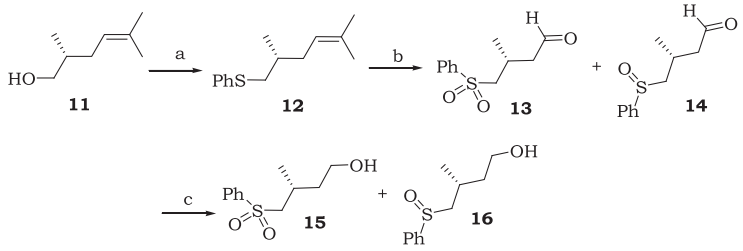
We were unsuccessful in synthesizing sulfide **29** by employing aldehydes **13** and **14** using the hetero Diels–Alder reaction and also from alcohol **11**. We chose to prepare the same from allyl acetate **33** which was obtained taking advantage of the hetero-Diels–Alder reaction as reported earlier by our group.[11] The unsaturated ketone **31** was prepared by a straightforward sequence of reactions beginning from α-chloro acetone, Scheme 7.

However, acetylation of **32** followed by Ferrier type reaction[12] with silyl enol ether yielded the *trans*-dihydropyran derivative **34** (dr = >95%). To the best of our knowledge, this is the first example of Ferrier type rearrangement using $TiCl_2(O^iPr)_2$ in the presence of sulfide. The *trans*-ring fusion of the pyran ring was confirmed by previous literature precedent[13] and for curiosity 2D-NOE NMR spectral data recorded. Reduction of the aldehyde **34** using sodium borohydride furnished alcohol **35** that was subsequently protected as its TBS ether **36** under standard conditions. Oxidation of the sulfide using ammonium molybdate and H_2O_2 yielded sulfone **3**, Scheme 7.

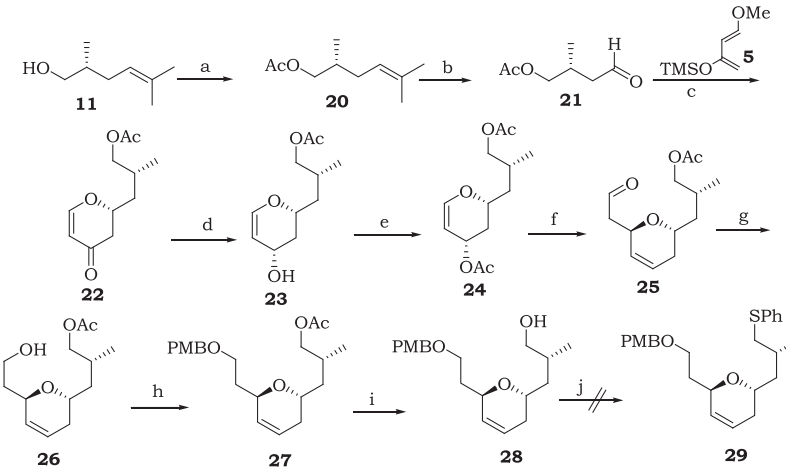
In conclusion, we have described a highly stereoselective convergent route to the C3–C12 subunit **3**, of laulimalide. The key steps in the successful route to the C3–C12 fragment include the



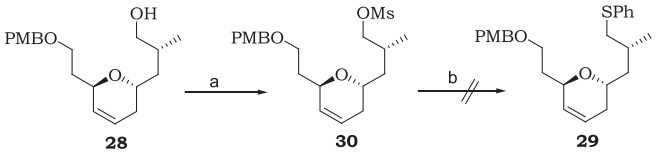
Scheme 4. Synthesis of pyran ring. Reagents and conditions: (a) **19** (4 mol %), TBME, −30 °C, 24 h, then TFA, 2 h.



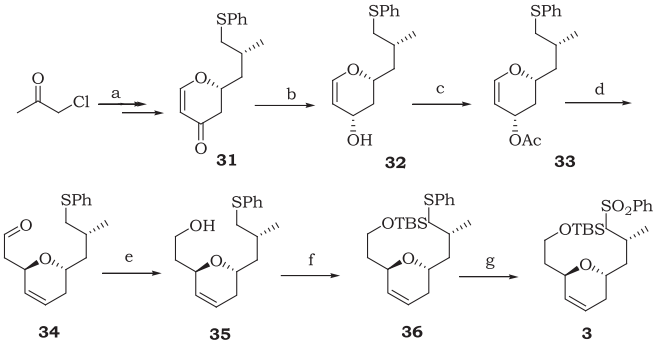
Scheme 3. Synthesis of sulfone aldehyde **13** and sulfoxide aldehyde **14**. Reagents and conditions: (a) $(PhS)_2$, Bu_3P, THF, rt, 24 h, 95%; (b) O_3, CH_2Cl_2, −78 °C, 20 min then Me_2S, rt, 2 h, (52% sulfone **13** and 36% sulfoxide **14**); (c) $NaBH_4$, MeOH, 0 °C, 30 min. (50% sulfone **15** and 35% sulfoxide **16**).



Scheme 5. Synthesis of sulfide **29**. Reagents and conditions: (a) TEA, Ac_2O, cat. DMAP, DCM, rt, 1 h, 95%; (b) O_3, CH_2Cl_2, −78 °C, 30 min then Me_2S, rt, 15 h, 88%; (c) **19** (4 mol %), TBME, −30 °C, 24 h, then TFA, 2 h, 75%; (d) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, −10 °C, 5 min, 95%; (e) Ac_2O, Et_3N, cat. DMAP, CH_2Cl_2, 0 °C, 5 min, 92%; (f) Vinyl-TBS ether, $TiCl_2(OiPr)_2$, toluene, −45 °C 2.5 h, 85%; (g) $NaBH_4$, MeOH, −10 °C, 5 min, 85%; (h) PMB-imidate, $Ln(OTf)_3$, toluene, 0 °C to rt, 5 min, 95%; (i) K_2CO_3, MeOH, rt, 30 min, 82%; (j) $(PhS)_2$, Bu_3P, THF, 60 °C, 20 h.



Scheme 6. Atempted synthesis of sulfide **29**. Reagents and conditions: (a) MsCl, Et_3N, CH_2Cl_2, 0 °C, 5 min, 64%; (b) PhSH, DBU, toluene, rt, 12 h.



Scheme 7. Synthesis of sulfone **3**. Reagents and conditions: (a) see: Ref. [11]; (b) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, −10 °C, 5 min, 96%; (c) Ac_2O, Et_3N, cat. DMAP, CH_2Cl_2, 0 °C, 5 min, 95%; (d) Vinyl-TBS ether, $TiCl_2(OiPr)_2$, toluene, −45 °C, 2.5 h, 85%; (e) $NaBH_4$, MeOH, −10 °C, 5 min, 75%; (f) TBSCl, Imidazole, CH_2Cl_2, rt, 1 h, 95%; (g) $(NH_4)_6Mo_7O_{24}$, H_2O_2, EtOH, 0 °C, 3 h, 97%.

reduction by utilizing organocatalysis and stereoselective hetero-Diels–Alder reaction using (*S,S*)-Cr-salen-BF_4^+ catalyst.

Acknowledgments

P.K.S. is thankful to the CSIR, New Delhi, for a fellowship. Financial assistance from the DST, New Delhi is gratefully acknowledged. We thank Dr. B. Jagadeesh, Head, NMR center, for NMR spectra and Dr. R. Srinivas, Head, NCMS division, for mass spectra.

References and notes

1. (a) Quinoa, E.; Kakou, Y.; Crews, P. *J. Org. Chem.* **1988**, *53*, 3642–3644; (b) Corley, D. G.; Herb, R.; Moore, R. E.; Scheuer, P. J.; Paul, V. J. *J. Org. Chem.* **1988**, *53*, 3644–3646.
2. (a) Higa, T.; Tanaka, J.-I.; Bernardinelli, G.; Jefford, C. W. *Chem. Lett.* **1996**, 255–256; (b) Higa, T.; Tanaka, J.-I.; Garcia Gravalos, D. WO 9710242, 1997.
3. (a) Mooberry, S. L.; Tien, G.; Hernandez, A. H.; Plubrukarn, A.; Davidson, B. S. *Cancer Res.* **1999**, *59*, 653; For a review, see: (b) Gallagher, B. M. *Curr. Med. Chem.* **2007**, *14*, 2959–2967.
4. Total synthesis of **1**: (a) Ghosh, A. K.; Wang, Y. *J. Am. Chem. Soc.* **2000**, *122*, 11027–11028; (b) Ghosh, A. K.; Wang, Y.; Kim, J. T. *J. Org. Chem.* **2001**, *66*, 8973–8982; (c) Mulzer, J.; Ohler, E. *Angew. Chem., Int. Ed.* **2001**, *113*, 3961–3964. *Angew. Chem., Int. Ed.* **2001**, *40*, 3842–3846.; (d) Paterson, I.; De Savi, C.; Tudge, M. *Org. Lett.* **2001**, *3*, 3149–3152; (e) Mulzer, J.; Enev, V. S.; Kaehlig, H. *J. Am. Chem. Soc.* **2001**, *123*, 10764–10765; (f) Wender, P. A.; Hegde, S. G.; Hubbard, R. D.; Zhang, L. *J. Am. Chem. Soc.* **2002**, *124*, 4956–4957; (g) Williams, D. R.; Liang, M.; Mullins, R. J.; Stites, R. E. *Tetrahedron Lett.* **2002**, *43*, 4841–4844; (h) Mulzer, J.; Ahmed, A.; Hoegenauer, E. K.; Enev, V. S.; Hanbauer, M.; Kaehlig, H.; Ohler, E. *J. Org. Chem.* **2003**, *68*, 3026–3042; (i) Crimmins, M. T.; Stanton, M. G.; Allen, S. P. *J. Am. Chem. Soc.* **2002**, *124*, 5958–5959; (j) Nelson, S. G.; Cheung, W. S.; Kassick, A. J.; Hilfiker, M. A. *J. Am. Chem. Soc.* **2003**, *125*, 655; (k) Gallagher, B. M., ; Fang, F. G., Jr.; Johannes, C. W.; Pesant, M.; Tremblay, M. R.; Zhao, H.; Akasaka, K.; Li, X. Y.; Liu, J.; Littlefield, B. A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 575–579; (l) Uenishi, J.; Ohmi, M. *Angew. Chem., Int. Ed.* **2005**, *117*, 2816–2820. *Angew. Chem., Int. Ed.* **2005**, *44*, 2756–2760.; For a review, see: (m) Mulzer, J.; Ohler, E. *Chem. Rev.* **2003**, *80*, 3753–3786; (n) Gollner, A.; Altmann, K.-H.; Gertsch, J.; Mulzer, J. *Chem. Eur. J.* **2009**, *15*, 5979; (o) Trost, B. M.; Amans, D.; Seganish, W. M.; Chung, C. K. *J. Am. Chem. Soc.* **2009**, *131*, 17087; Synthesis of fragment **4**, see: (p) Raghavan, S.; Samanta, P. K. *Synlett* **2013**, 1983.
5. Synthesis of analogues of **1**: (a) Wender, P. A.; Hegde, S. G.; Hubbard, R. D.; Zhang, L.; Mooberry, S. L. *Org. Lett.* **2003**, *5*, 3507–3509; (b) Paterson, I.; Bergmann, H.; Menche, D.; Berkessel, A. *Org. Lett.* **2004**, *6*, 1293–1295; (c) Mooberry, S. L.; Randall-Hlubek, D. A.; Leal, R. M.; Hegde, S. G.; Hubbard, R. D.; Zhang, L.; Wender, P. A. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 8803–8804; (d) Gallagher, B. M., Jr.; Zhao, H.; Pesant, M.; Fang, F. G. *Tetrahedron Lett.* **2005**, *46*, 923–926; (e) Paterson, I.; Menche, D.; Hakansson, A. E.; Longstaff, A.; Wong, D.; Barasoain, I.; Buey, R. M.; Diaz, J. F. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2243–2247; (f) Wender, P. A.; Hilinski, M. K.; Soldermann, N. G.; Mooberry, S. L. *Org. Lett.* **2006**, *8*, 1507–1510; (g) Wender, P. A.; Hilinski, M. K.; Skaanderup, P. R.; Soldermann, N. G.; Mooberry, S. L. *Org. Lett.* **2006**, *8*, 4105–4108; (h) Faveau, C.; Mondon, M.; Gesson, J. P.; Mahnke, T.; Gebhardt, S.; Koert, U. *Tetrahedron Lett.* **2006**, *47*, 8305–8308.
6. Oppolzer, W.; Moretti, R.; Thomi, S. *Tetrahedron Lett.* **1989**, *30*, 5603.
7. Nakagawa, I.; Hata, T. *Tetrahedron Lett.* **1975**, *16*, 1409–1412.
8. Schaus, S. E.; Branalt, J.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 403.
9. For reviews, see: (a) Danishefsky, S. J. *Chemtracts* **1989**, 273; (b) Danishefsky, S. J.; De Ninno, M. P. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 15; (c) Danishefsky, S. J. *Aldrichim. Acta* **1986**, *19*, 59.
10. Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.
11. Raghavan, S.; Samanta, P. K. *Org. Lett.* **2012**, *14*, 2346.
12. (a) Ferrier, R. J. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1455–1458; (b) Ferrier, R. J.; Zubkov, O. A. *Org. React.* **2003**, 62; (c) Gleason, M. M.; McDonald, F. E. *J. Org. Chem.* **1997**, *62*, 6432.
13. The total synthesis of swinholide A-II. A stereoselective synthesis of a C1–C15 segment. (a) Paterson, I.; Smith, J. D.; Ward, R. A. *Tetrahedron-London* **1995**, *51*, 9413 (ISSN: 0040–4020); (b) Mulzer, J.; Ohler, E. *Chem. Rev.* **2003**, *80*, 3753–3786; (c) Ansari, A. A.; Lahiri, R.; Vankar, Y. D. *ARKIVOC* **2013**, *ii*, 316–362.