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Total Synthesis of (−)-Laulimalide

Paul A. Wender,* Sayee G. Hegde, Robert D. Hubbard, and Lei Zhang

Department of Chemistry, Stanford University, Stanford, California 94305-5080

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Laulimalide (**1**) is a structurally novel cancer therapeutic lead, recently isolated in trace quantities from Pacific marine sponges.[1] Laulimalide promotes abnormal tubulin polymerization and apoptosis in vitro, with a mode of action similar to that of Taxol® but with potentially less susceptibility to multidrug resistance.[2] Its significant clinical potential and unique molecular structure has attracted considerable interest,[3] resulting in impressive syntheses from the groups of Ghosh, Paterson, and Mulzer.[4] The instability of **1** coupled with the view that superior analogues could be more readily accessed and advanced through pre-clinical development prompted our efforts described herein to develop a concise, flexible, and enantioselective synthesis of **1**.

For maximum convergency, our synthetic strategy (Figure 1) called for connection of similarly complex precursors **2** and **3** through formation of the $C_{14}-C_{15}$ bond followed by C_3 homologation and lactonization. Formation of the $C_{14}-C_{15}$ bond was designed to explore an unprecedentedly complex asymmetric Sakurai reaction, coupling allyl silane **2** with aldehyde **3**.[5] Subsequent regioselective macrolactonization of an unprotected C_{19},C_{20}-diol was envisioned to provide the target 18-membered ring. This plan drew additional advantage from the expectation that **3** could be derived from a pseudo-symmetrical precursor whose chirality would originate in C_2-symmetric tartaric acid while the chirality of **2** would be traced to (*R*)-citronellic acid.

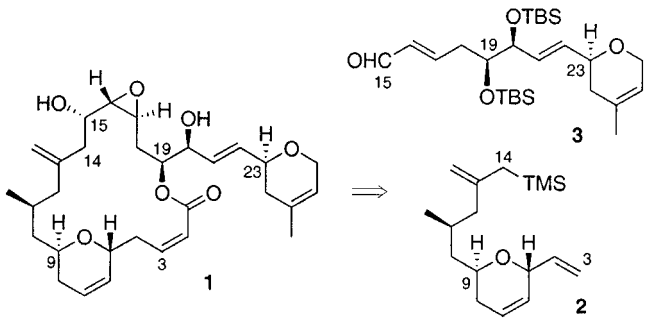
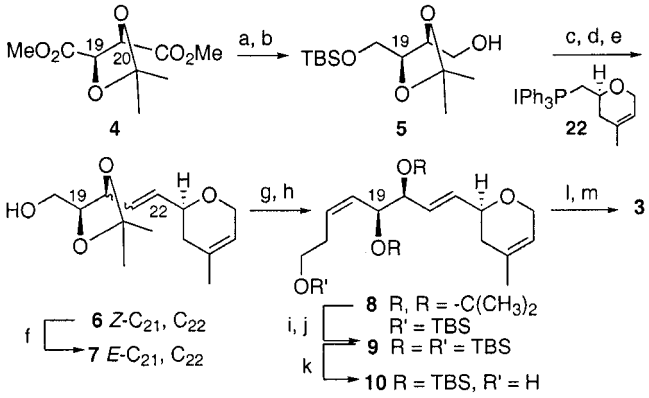


Figure 1. Retrosynthetic analysis.

The synthesis of aldehyde **3** started with LAH reduction of commercial tartrate **4** (Scheme 1). The resultant diol was monoprotected as silyl ether **5** (97%, 2 steps).[6] Swern oxidation,[7] Wittig olefination with phosphonium salt **22**,[8] and subsequent TBAF deprotection yielded a 4.5:1 mixture of *Z*,*E*-isomers **6** and **7** in a combined yield of 67%. Conversion of **6** to **7** using a range of conventional procedures[9] gave low yields or complex mixtures. However, using a previously unprecedented procedure, irradiation (300 nm) of a benzene solution of **6** and hexabutyldistannane (20 mol %) at room temperature gave **7** in remarkably high yield (92%; 100% BORSM). Swern oxidation of **7** followed by Wittig olefination with phosphonium salt **23**[10] generated diene **8** (92%, 2 steps). Global deprotection and subsequent silylation afforded the tris-TBS ether **9** (>99%, 2 steps). While numerous conditions were tested,[11] selective cleavage of the primary TBS group in **9** to give alcohol **10** (86%) was achieved only by using the procedure of Hwu.[12] Oxidation of **10** to the corresponding β,γ-unsaturated aldehyde (92%) followed by isomerization with 10 mol % DBU[13] led without epimerization or elimination to the aldehyde **3** (91%).

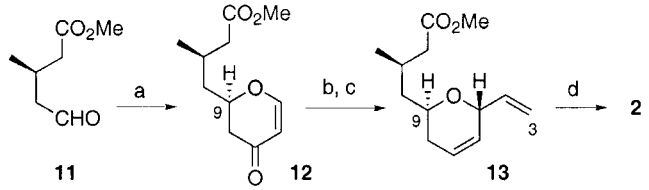
Scheme 1 [a]



[a] Conditions: (a) $LiAlH_4$, THF, reflux; (b) 1 equiv of NaH, TBSCl, DMF (97%, 2 steps); (c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C; (d) **22**, *n*-BuLi, THF/HMPA (2:1), −78 °C to 0 °C; (e) TBAF, THF (67%, **6**:**7** 4.5:1, 2 steps); (f) $Bu_3SnSnBu_3$, *hν* 300 nm, benzene (92%, 100% BORSM); (g) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C; (h) $TBSO(CH_2)_3PPh_3I$ (**23**), NaHMDS, THF, −30 °C to room temperature (92%, 2 steps); (i) 2 N HCl, THF; (j) TBSOTf, Et_3N, CH_2Cl_2 (>99%, 2 steps); (k) CAN, *i*-PrOH, (86%); (l) Dess−Martin periodinane, CH_2Cl_2 (92%); (m) 10 mol % DBU, $CHCl_3$ (91%).

For the construction of allyl silane **2** (Scheme 2), known aldehyde **11**[14] (3 steps from commercial (*R*)-citronellic acid) was treated with Danishefsky's diene and Jacobsen's (*S*,*S*)-Cr-salen[15] catalyst to yield under nonstandard conditions[16] pyranone **12** (87%, 82% de).

Scheme 2 [a]



[a] Conditions: (a) (1) 4 mol % (*S*,*S*)-Cr-Salen, 4Å MS, TBME, −78 °C. (2) Danishefsky's diene, −78 to −20 °C. (3) TFA, CH_2Cl_2 (87%, 82% de); (b) (1) CuCN, MeLi, tributylvinyltin, **12**, THF, −78 °C. (2) Comins' reagent, THF, −78 °C (74%, 82% de); (c) LiCl, Bu_3SnH, $Pd(PPh_3)_4$, THF (88%); (d) (1) $TMSCH_2MgCl$, $CeCl_3$, THF, −78 °C to room temperature. (2) Silica gel, CH_2Cl_2 (85%).

* Corresponding author. E-mail: wenderp@stanford.edu.

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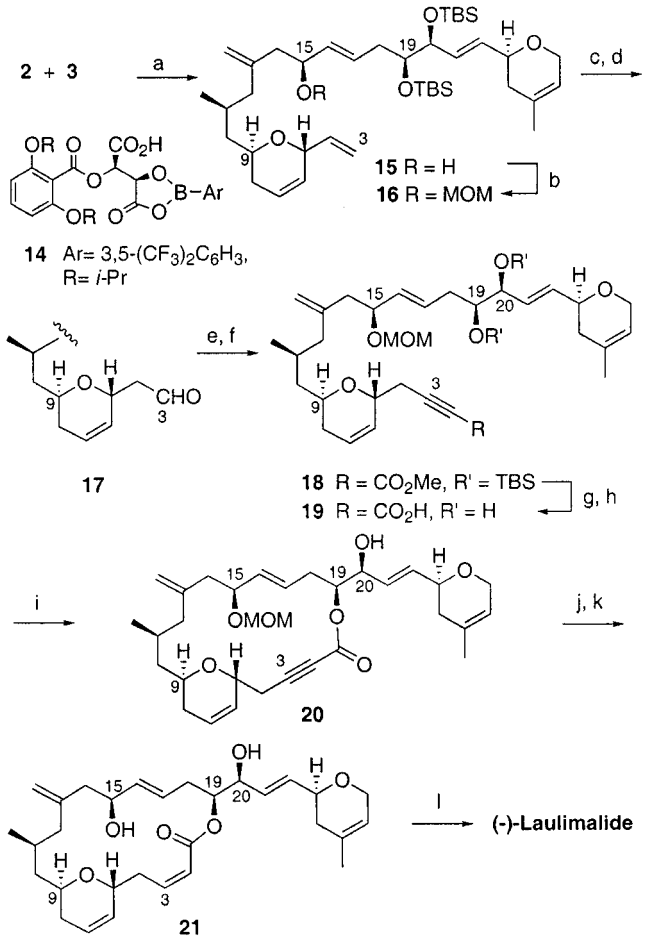
Cuprate addition using Lipshutz's procedure[17] and trapping of the resultant enolate with Comins' reagent[18] afforded an enol-triflate (74%, 82% de) that upon reduction[19] yielded olefin **13** (88%). Treatment of **13** with excess $TMSCH_2MgCl$ and $CeCl_3$[20] and in situ Peterson olefination generated allyl silane **2** (85%).

Conjunction of **2** and **3** (Scheme 3) with Yamamoto's (acyloxy)-borane **14**[21] gratifyingly resulted in a uniquely complex intermolecular asymmetric Sakurai reaction affording **15** (86%) as the only detectable diastereomer ^1H and ^{13}C-NMR. Protection of the C_{15}-hydroxyl as a MOM ether (99%) and chemo- and regioselective hydroboration[22] of the resultant hexaene **16** yielded upon Dess−Martin oxidation[23] aldehyde **17** (78%, 2 steps).

Scheme 3 [a]



[a] Conditions: (a) 100 mol % **14**, EtCN, −75 °C (86%, >90% de); (b) MOMCl, DIPEA, CH_2Cl_2 (99%); (c) (1) BH_3·DMS, cyclohexene, THF. (2) H_2O_2, 3 M NaOH, EtOH (92%); (d) Dess−Martin periodinane, CH_2Cl_2, H_2O (85%); (e) $MeC(=O)C(=N_2)P(=O)(OMe)_2$, K_2CO_3, MeOH, 4 °C (80%); (f) *n*-BuLi, $ClCO_2Me$, THF (75%, 86% BORSM); (g) HF·pyridine, THF (98%); (h) LiOH, H_2O, THF (88%); (i) 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, benzene (55%); (j) Lindlar's catalyst, quinoline, H_2, EtOAc (91%); (k) Me_2BBr, Et_3N, CH_2Cl_2, −78 °C (76%); (l) (+)-DIPT, *t*-BuOOH, $Ti(OiPr)_4$, CH_2Cl_2, −20 °C (70%).

Homologation of **17** under carefully controlled thermal conditions, using the Bestmann modification[24] of the Seyferth−Gilbert reaction, followed by lithiation of the resultant alkyne and trapping with $ClCO_2Me$ afforded alkynoate **18** (60%, 2 steps). Desilylation with HF·pyridine and subsequent saponification yielded diol acid **19** (86%, 2 steps). Macrolactonization under Yamaguchi conditions[25] proceeded exclusively at the C_{19}-hydroxyl of the diol to give macrolide **20** (55%), which upon reduction, with Lindlar's catalyst,[26] yielded the *Z*-enoate (91%). Cleavage of the MOM ether[27] afforded allylic alcohol **21** (76%). Finally, Sharpless asymmetric epoxidation of the reagent matched allylic alcohol in **21**[28] chemoselectively afforded (−)-laulimalide (**1**, 70%).

In summary, a convergent asymmetric synthesis of (−)-laulimalide has been achieved in 25 steps (longest linear; 36 overall) and in 3.5% overall yield, providing a uniquely short and efficient route to **1** and flexible access to its analogues. Structure−activity studies on analogues will be reported separately.

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Supporting Information Available: Experimental details and analytical data for all new compounds and data for synthetic laulimalide (**1**), including selected spectra (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (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.
(2) Mooberry, S. L.; Tien, G.; Hernandez, A. H.; Plubrukarn, A.; Davidson, B. S. *Cancer Res.* **1977**, *37*, 159.
(3) (a) Shimizu, A.; Nishiyama, S. *Synlett* **1998**, 1209. (b) Shimizu, A.; Nishiyama, S. *Tetrahedron Lett.* **1997**, *38*, 6011. (c) Messenger, B. T.; Davidson, B. S. *Tetrahedron Lett.* **2001**, *42*, 797. (d) Nadolski, G. T.; Davidson, B. S. *Tetrahedron Lett.* **2001**, *42*, 801.
(4) (a) Ghosh, A. K.; Wang, Y. *J. Am. Chem. Soc.* **2000**, *122*, 11027. (b) Ghosh, A. K.; Wang, Y.; Kim, J. T. *J. Org. Chem.* **2001**, *66*, 8973 and references therein. (c) Paterson, I.; De Savi, C.; Tudge, M. *Org. Lett.* **2001**, *3*, 213. (d) Paterson, I.; De Savi, C.; Tudge, M. *Org. Lett.* **2001**, *3*, 3149. (e) Mulzer, J.; Ohler, E. *Angew. Chem., Int. Ed.* **2001**, *40*, 3843. (f) Evev, V. S.; Kaehlig, H.; Mulzer, J. *J. Am. Chem. Soc.* **2001**, *123*, 10764 and references therein.
(5) Hosomi, A.; Sakurai, H. *Tetrahedron Lett.* **1976**, *16*, 1295.
(6) McDougal, P. G.; Rico, J. G.; Ph, Y.; Condon, B. D. *J. Org. Chem.* **1986**, *51*, 3388.
(7) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.
(8) Derived in 3 steps from the known hetero-Diels−Alder adduct of isoprene and methyl glyoxylate. See the Supporting Information and following reference: Terada, M.; Mikami, K. *J. Chem. Soc., Chem. Commun.* **1995**, 2391.
(9) Reagents such as Ph_2S_2, PhSH, and I_2, under various thermal and photochemical conditions, failed to promote the desired conversion.
(10) Molander, G. A.; Shakya, S. R. *J. Org. Chem.* **1996**, *61*, 5885.
(11) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; John Wiley & Sons: New York, 1999; pp 133−141.
(12) Hwu, J. R.; Jain, M. L.; Tsai, F.-Y.; Tsay, S.-C.; Balakumar, A.; Hakimelahi, G. H. *J. Org. Chem.* **2000**, *65*, 5077.
(13) Hanessian, S.; Dube, D.; Hodges, P. *J. Am. Chem. Soc.* **1987**, *109*, 7063.
(14) (a) Mori, K.; Kuwahara, S. *Tetrahedron* **1982**, *38*, 521. (b) Mori, K.; Kuwahara, S.; Ueda, H. *Tetrahedron* **1983**, *39*, 2439.
(15) Schaus, S. E.; Branalt, J.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 403.
(16) Other catalytic systems are inefficient. Use of standard Jacobsen's hetero-Diels−Alder conditions (−30 °C, 5.0 M) resulted in low yield (59%) and poor diastereoselectivity (72% de), which was improved by modified conditions (−78 to −20 °C, 3.0 M). Interestingly, the other diastereomer of **12** can be readily accessed with use of (*R,R*)-Cr-Salen catalyst in identical yield and diastereoselectivity (87%, 82% de).
(17) Behling, J. R.; Babiak, K. A.; Ng, J. S.; Campbell, A. L.; Moretti, R.; Koerner, M.; Lipshutz, B. H. *J. Am. Chem. Soc.* **1988**, *110*, 2641.
(18) Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, *33*, 6299.
(19) Scott, W. J.; Crisp, G. T.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 4630.
(20) Narayanan, B. A.; Bunnelle, W. H. *Tetrahedron Lett.* **1987**, *28*, 6261.
(21) Ishihara, K.; Mouri, M.; Gao, Q.; Maruyama, T.; Furuta, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *115*, 11490.
(22) Taber, D. F.; Song, Y. *J. Org. Chem.* **1996**, *61*, 7508.
(23) Meyer, S. D.; Schreiber, S. L. *J. Org. Chem.* **1994**, *59*, 7549.
(24) Muller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, 521.
(25) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *53*, 1989.
(26) Ho, T.-L.; Liu, S. H. *Synth. Commun.* **1987**, *17*, 969, and see ref 4b.
(27) Guindon, Y.; Therien, M.; Girard, Y.; Yoakim, C. *J. Org. Chem.* **1987**, *52*, 1680.
(28) For an analogous epoxidation strategy on **1**, see refs 4d and 4e.

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