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Published on Web 05/04/2002

Asymmetric Total Synthesis of (−)-Laulimalide: Exploiting the Asymmetric Glycolate Alkylation Reaction

Michael T. Crimmins,* Matthew G. Stanton, and Shawn P. Allwein

Department of Chemistry, Venable and Kenan Laboratories of Chemistry, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599-3290

Received March 21, 2002

Laulimalide **1** is a potent cell growth inhibitor with low nanomolar IC_{50} values that was isolated from *Cacospongia mycofijiensis*,[1] *Hyatella* sp.,[2] and *Fasciospongia rimosa*.[3] Laulimalide stimulates tubulin polymerization by a mechanism similar to that of taxol, but unlike taxol, inhibits proliferation of SKVLB-1, a multidrug-resistant cell line.[4] The promising biological activity of laulimalide has inspired substantial effort toward its synthesis, culminating in the first total synthesis from the Ghosh laboratory,[5] and subsequent syntheses by Paterson,[6] Mulzer,[7] and Wender.[8] Reports of partial syntheses by Davidson,[9] Nishayama,[10] and Lee[11] have also appeared.

Strategically, our synthetic design focused on hydroxy acid **2** as the macrolactonization substrate since the 2,3-*Z*-enoate was known to isomerize during standard based induced macrolactonizations.[5] Thus, exploiting a Mitsunobu macrolactonization[12,6] of hydroxy acid **2** would obviate a base-catalyzed lactonization. A diastereoselective allylstannane addition[13] was envisioned to connect the two advanced synthetic fragments **3** and **4**. The observation that homoallylic (or latent homoallylic) C−O bonds are present at C5, C9, C15, C19, and C23 led to the strategic decision to rely heavily on the glycolate variation[14] of the Evans asymmetric alkylation[15] to construct both the C1−C14 fragment and the C15−C27 subunit. The C1−C14 fragment **4** of laulimalide was constructed as shown in Scheme 1. Treatment of (*S*)-citronellal with the Brown chiral borane[16] produced the homoallylic alcohol **5**. The alcohol **5** was alkylated with bromoacetic acid to provide the substituted glycolic acid, which was acylated with the D-valine-derived oxazolidinone to produce the acyloxazolidinone **6**. The alkylation of glycolyl oxazolidinone **6** with the *Z*-allylic iodide **7** proceeded with excellent diastereoselectivity (>97:3). The diastereoselectivity of complex glycolate alkylations of this type are apparently unaffected by adjacent or nearby stereogenic centers.[17] Direct reduction[18] of the glycolate alkylation product from **6** delivered the alcohol **8**, which was efficiently processed to the tetraene **9** by Swern oxidation[19] and Wittig olefination. The tetraene **9** was exposed to the Grubbs catalyst,[20] leading to exclusive formation of the dihydropyran **10**. Selective cleavage of the trisubstituted alkene, α-methylenation of the resultant aldehyde, and immediate reduction of the unsaturated aldehyde gave the allylic alcohol **11**. The alcohol was readily transformed to the tributylstannane **4** under standard conditions.

The C22−C27 subunit was also prepared by taking advantage of the asymmetric glycolate alkylation (see Scheme 2). The *O*-allylglycolyl-oxazolidinone **12** was alkylated with methylallyl iodide to provide the oxazolidinone **13** (96:4 dr). Ring-closing metathesis of the diene with the Grubbs catalyst,[20] reductive removal of the auxiliary, and Swern oxidation of the alcohol provided the required aldehyde **14**. The extreme sensitivity of the aldehyde dictated that it be prepared immediately prior to its use in the next transformation.

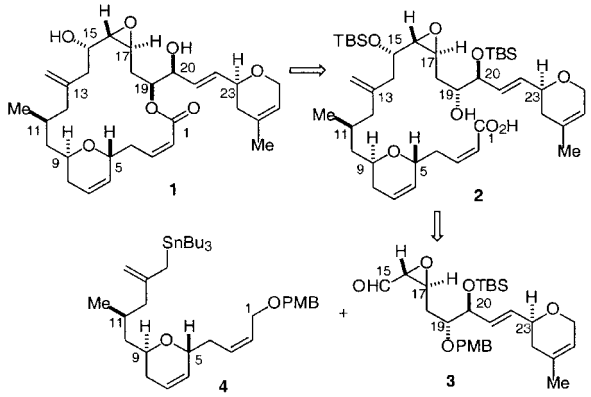
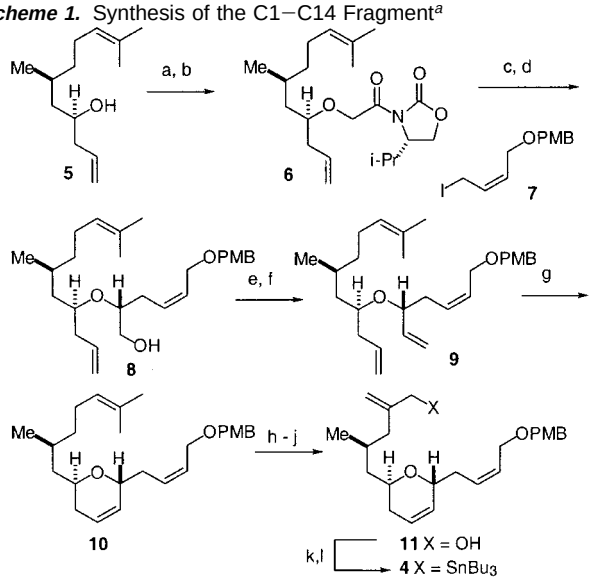


Figure 1. Retrosynthesis of (−)-laulimalide.

Scheme 1. Synthesis of the C1−C14 Fragment[a]



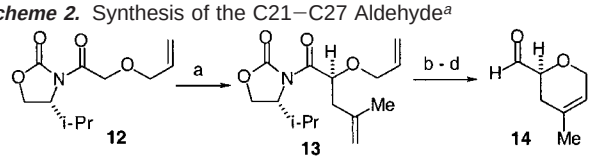
[a] a) NaH, $BrCH_2CO_2H$, THF, 97%; b) Me_3CCOCl, Et_3N, THF, −78 to 0 °C; (*S*)-5-lithio-4-isopropyl-oxazolidin-2-one, 89%; c) $NaN(SiMe_3)_2$, THF, −78 to −45 °C, iodide **7**, 86%; d) $LiBH_4$, MeOH, Et_2O, 0 °C; e) $(COCl)_2$, DMSO, Et_3N; f) $Ph_3P{=}CH_2$, 66% 3 steps; g) $(Cy_3P)_2Cl_2Ru{=}CHPh$, CH_2Cl_2, 40 °C, 85%; h) *m*-CPBA; $HClO_4$, $NaIO_4$; i) $Me_2N^+{=}CH_2$, 84%; 2 steps; j) $NaBH_4$, $CeCl_3$, 78%; k) MsCl, Et_3N, CH_2Cl_2, l) Bu_3SnLi, THF, 85% 2 steps.

The C15−C27 fragment was constructed as shown in Scheme 3. Again, the asymmetric glycolate alkylation was utilized, in this instance to establish the C19 stereocenter. Alkylation of the *p*-methoxybenzyl-protected glycolate **15** with allyl iodide **16** produced the oxazolidinone **17**. Hydrolytic cleavage of the auxiliary

* To whom correspondence should be addressed. E-mail: crimmins@email.unc.edu.

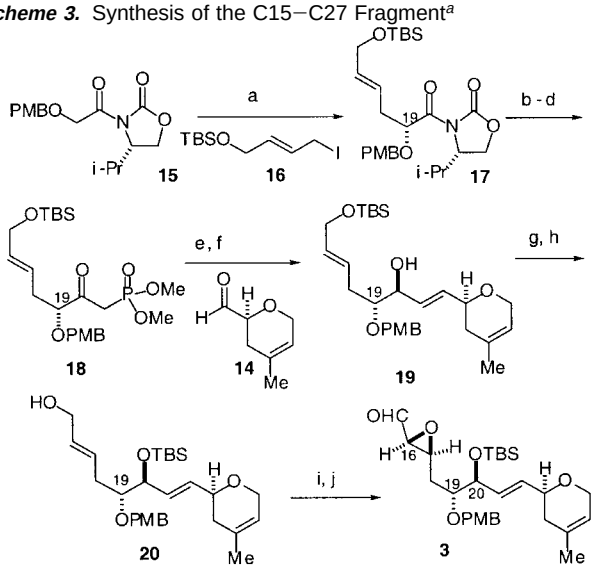
10.1021/ja026269v CCC: $22.00

Scheme 2. Synthesis of the C21−C27 Aldehyde[a]



[a] a) $NaN(SiMe_3)_2$, $CH_2{=}C(Me)CH_2I$, THF, 85%; b) $(Cy_2P)_2Cl_2Ru{=}CHPh$, CH_2Cl_2, 40 °C 86%; c) $NaBH_4$, H_2O, THF, 0 °C; 88% d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; 90%.

Scheme 3. Synthesis of the C15−C27 Fragment[a]



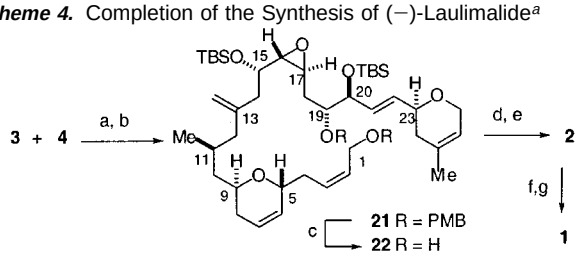
[a] a) $NaN(SiMe_3)_2$, THF, −40 °C; 98:2 dr 70%; b) LiOH, H_2O_2; THF, 96%; c) HClMeNHOMe, DCC, 85% d) $LiCH_2PO(OMe)_2$, 99%; e) NaH, aldehyde **14**, 93%; f) $Zn(BH_4)_2$, 77% g) TBSOTf, 2,6-lutidine, 94%; h) PPTS, MeOH; 89%; i) (+)-DET, Ti(*i*-OPr)$_4$, *t*-BuOOH, CH_2Cl_2, 95:5 dr; j) Dess−Martin, 91% 2 steps.

and subsequent conversion of the carboxylic acid to the ketophosphonate **18** was readily accomplished via the intermediate Weinreb's amide. Exposure of the aldehyde **14** to the sodium anion of ketophosphonate **18** delivered the unsaturated ketone in 93% yield. Chelation-controlled reduction of the enone with freshly prepared zinc borohydride[21] produced the allylic alcohol **19** (>98:2 dr). Protection of the secondary alcohol **19** and selective removal of the primary TBS ether generated the allylic alcohol **20** in excellent yield. The C16−C17 epoxide was introduced via a Sharpless asymmetric epoxidation[22] (95:5 dr), and the resultant epoxy alcohol was oxidized to the aldehyde **3** with the Dess−Martin periodinane.[23]

With the allylstannane **4** and the aldehyde **3** in hand, the critical fragment assembly was undertaken. Trimethylaluminum-mediated addition of allylstannane **4** to the aldehyde **3** resulted in good Felkin−Anh stereocontrol to give a 3:1 mixture of diastereomers favoring the laulimalide stereochemistry at C15. The major diastereomer was isolated in 72% yield after chromatography. Protection of the C15 alcohol as its TBS ether gave the silyl ether **21** in excellent yield.

Because of recent reports regarding the isomerization of the *Z*-enoate in laulimalide during Yamaguchi-type macrolactonizations,[24] a Mitsunobu-type macrolactonization was attempted. Thus, oxidative removal[25] of the two *p*-methoxybenzyl ethers resulted in isolation of the diol **22** in high yield (Scheme 4). Selective oxidation of the C1 allylic alcohol to an aldehyde with MnO_2 led to 9% isomerization to the *E*-enal. Immediate oxidation of the unsaturated aldehyde to the acid with buffered $NaClO_2$ provided the seco acid **2** needed for the Mistunobu lactonization. Treatment of the hydroxy acid under Mitsunobu conditions at −20 °C in THF led to the best results for the macrolactonization (46%). Careful exposure of the

Scheme 4. Completion of the Synthesis of (−)-Laulimalide[a]



[a] a) Me_3Al, CH_2Cl_2, 3:1 72% major isomer; b) TBSOTf, 2,6-lutidine 97%; c) DDQ, H_2O, CH_2Cl_2, 90%; d) MnO_2, 91:9 *Z*:*E*; e) $NaClO_2$, 75% 2 steps; f) DEAD, Ph_3P, THF, −20 °C, 46%; g) Et_3N-3HF, CH_3CN, 75%.

macrolactone to Et_3NHF[26] led to clean conversion to (−)-laulimalide without isomerization of the 2,3-*Z*-enoate or epoxide-opening to isolaulimalide. Synthetic (−)-laulimalide was identical in all respects to that reported previously by Ghosh,[5] Paterson,[6] and Mulzer.[7]

Acknowledgment. This work was supported by a research grant (CA63572) and a postdoctoral fellowship (GM20817 for S.P.A.) from the National Institutes of Health. A fellowship for M.G.S. from Merck and Co. is gratefully acknowledged. We thank Charles Ross, III, at Merck and Co. for obtaining mass spectral data.

Supporting Information Available: ^1H and ^{13}C spectra of synthetic laulimalide (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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JA026269V