ORGANIC LETTERS

2001
Vol. 3, No. 20
3149−3152

Total Synthesis of the Microtubule-Stabilizing Agent (−)-Laulimalide

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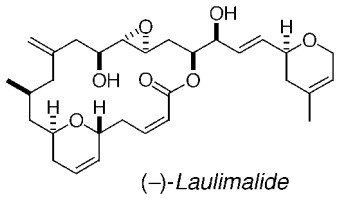
Received July 13, 2001

ABSTRACT

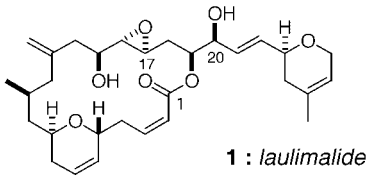


(−)-*Laulimalide*

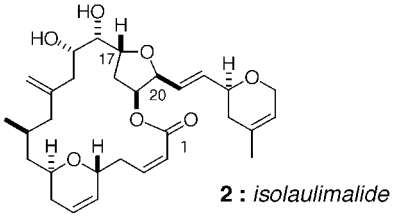
The total synthesis of the potent microtubule-stabilizing anticancer agent (−)-laulimalide has been achieved in 27 steps and 2.9% overall yield. Notable features are the use of Jacobsen HDA chemistry for the enantioselective construction of the side chain dihydropyran, a diastereoselective aldol coupling using chiral boron enolate methodology, a Mitsunobu macrolactonization, and a Sharpless AE to introduce the epoxide onto *des*-epoxy-laulimalide.

Laulimalide (**1**),[1a] also known as fijianolide B,[1b] is a unique antimitotic macrolide, isolated from the Pacific sponges *Hyatella* sp. and *Spongia mycofijiensis* and the Okinawan sponge *Fasciospongia rimosa*,[1c] which potently inhibits the proliferation of numerous cancer cell lines with IC_{50} values in the low nanomolar range, while retaining activity against multi-drug-resistant cancer cells. In the cell cycle, it initiates mitotic arrest, micronuclei formation, and ultimately apoptosis. The full configurational assignment was determined by X-ray crystallographic analysis.[1c] Laulimalide occurs with the less active congener isolaulimalide (**2**), having micromolar IC_{50} values, which arises from facile epoxide opening at C_{17} by the C_{20} hydroxyl group.

Recently, both laulimalide and isolaulimalide were identified as sharing the same microtubule-stabilizing mechanism of action[2] as the clinically validated anticancer drug Taxol (paclitaxel). Notably, laulimalide was found to be both superior to Taxol in its ability to circumvent P-glycoprotein-mediated drug resistance and more effective in stimulating tubulin polymerization.[3]



1 : *laulimalide*



2 : *isolaulimalide*

As with some other cytotoxic natural products (including the epothilones,[4] discodermolide,[5] and the eleutherobins[6]),

(1) (a) Corley, D. G.; Herb, R.; Moore, R. E.; Scheuer, P. J.; Paul, V. J. *J. Org. Chem.* **1988**, *53*, 3644. (b) Quinoa, E.; Kakou, Y.; Crews, P. *J. Org. Chem.* **1988**, *53*, 3642. (c) Jefford, C. W.; Bernardinelli, G.; Tanaka, J.; Higa, T. *Tetrahedron Lett.* **1996**, *37*, 159.

(2) Schiff, P. B.; Horwitz, S. B. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 1561.

(3) Mooberry, S. L.; Tien, G.; Hernandez, A. H.; Plubrukarn, A.; Davidson, B. S. *Cancer Res.* **1999**, *59*, 653.

(4) Bollag, D. M.; McQueney, P. A.; Zhu, J.; Hensens, O.; Koupal, L.; Liesch, J.; Goetz, M.; Lazirides, E.; Woods, C. M. *Cancer Res.* **1995**, *55*, 2325.

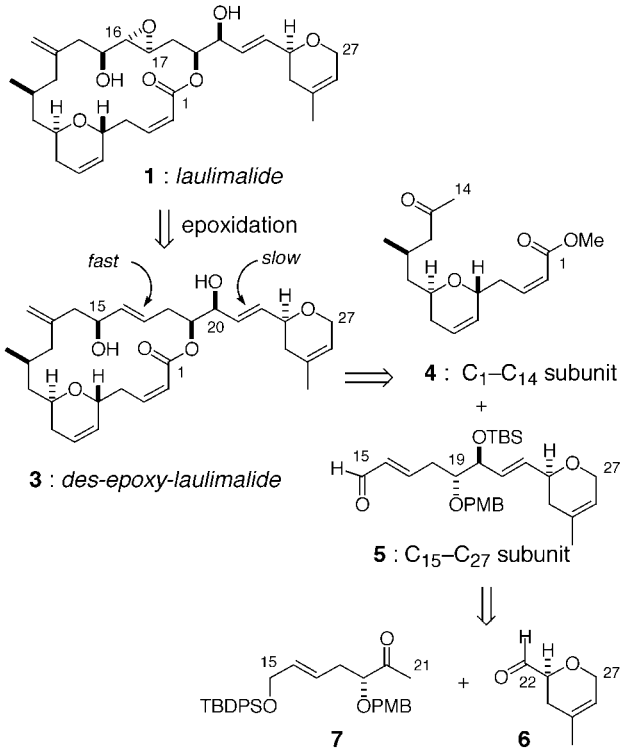
10.1021/ol010150u CCC: $20.00
Published on Web 09/06/2001

laulimalide constitutes an entirely novel class of microtubule-stabilizing antimitotic agent, with activities that may provide therapeutic utility, particularly against multi-drug-resistant cancers.

As the natural supply is restricted, an efficient and flexible synthesis is essential to provide further material for biological evaluation, along with access to novel analogues. Several synthetic endeavors toward laulimalide have been described,[7a−k] leading to various fragments, including an advanced macrolide core,[8] with the first total synthesis achieved recently by Ghosh and Wang.[7h] Herein, we report the second total synthesis of (−)-laulimalide (**1**), which follows an entirely different strategy.

Our synthetic plan (Scheme 1) relied on installing the sensitive *trans*-epoxide of laulimalide (**1**) in the final step,

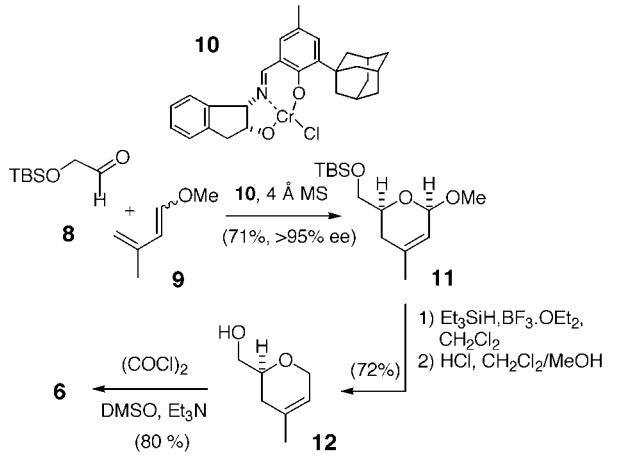
Scheme 1



without invoking protection of the C_{20} hydroxyl in the side chain and, importantly, avoiding concomitant formation of isolaulimalide (**2**). Recognizing that *des*-epoxy-laulimalide (**3**) possesses two allylic alcohols at C_{15} and C_{20}, which are *pseudo*-enantiomeric as well as being in different steric environments, discriminating between them by hydroxyl-directed asymmetric epoxidation (in a manner similar to a kinetic resolution of a racemic allylic alcohol) was proposed by using the Sharpless Ti(O^iPr)$_4$-tartrate protocol.[9] The 20-membered macrolide **3** would then be assembled from two fragments of similar complexity, i.e., the C_1-C_{14} subunit **4**, incorporating the *trans*-dihydropyran and (*Z*)-enoate, and the $C_{15}-C_{27}$ subunit **5**, incorporating the terminal dihydropyran and a protected 1,2-*anti* diol (where the C_{19} center would be inverted on Mitsunobu macrocyclization), which in turn would be derived from **6** and **7**.

As outlined in Scheme 2, the asymmetric synthesis of the dihydropyran unit **6**, for incorporation into the $C_{15}-C_{27}$

Scheme 2



subunit **5**, exploited Jacobsen's recently introduced hetero-Diels−Alder (HDA) reaction,[10] involving catalysis by the preformed chromium(III) Lewis acid **10**. Exposure of a neat mixture of diene **9** and aldehyde **8** (in the presence of molecular sieves) to catalyst **10** (5 mol %) gave the HDA adduct **11** in >95% ee and 71% yield.[11] Treatment of acetal **11** with Et_3SiH in the presence of $BF_3{\cdot}OEt_2$ displaced the anomeric methoxy group and deprotection gave the volatile alcohol **12**,[11] which on Swern oxidation generated aldehyde **6** (58% over three steps).

(5) (a) Hung, D. T.; Chen, J.; Schreiber, S. L. *Chem. Biol.* **1996**, *3*, 287. (b) ter Haar, E.; Kowalski, R. J.; Hamel, E.; Lin, C. M.; Longley, R. E.; Gunasekera, S. P.; Rosenkranz, H. S.; Day, B. W. *Biochemistry* **1996**, *35*, 243.

(6) Lindel, T.; Jensen, P. R.; Fenical, W.; Long, B. H.; Casazza, A. M.; Carboni, J.; Fairchild, C. R. *J. Am. Chem. Soc.* **1997**, *119*, 8744.

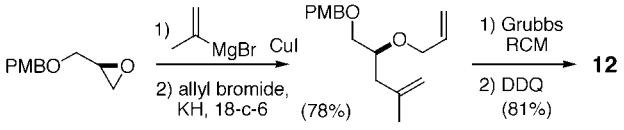
(7) (a) Shimizu, A.; Nishiyama, S. *Synlett* **1998**, 1209. (b) Shimizu, A.; Nishiyama, S. *Tetrahedron Lett.* **1997**, *38*, 6011. (c) Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron Lett.* **1997**, *38*, 2427. (d) Mulzer, J.; Hanbauer, M. *Tetrahedron Lett.* **2000**, *41*, 33. (e) Ghosh, A. K.; Wang, Y. *Tetrahedron Lett.* **2000**, *41*, 2319. (f) Ghosh, A. K.; Wang, Y. *Tetrahedron Lett.* **2000**, *41*, 4705. (g) Dorling, E. K.; Ohler, E.; Mulzer, J. *Tetrahedron Lett.* **2000**, *41*, 6323. (h) Ghosh, A. K.; Wang, Y. *J. Am. Chem. Soc.* **2000**, *122*, 11027. (i) Nadolski, G. T.; Davidson, B. S. *Tetrahedron Lett.* **2001**, *42*, 797. (j) Messenger, B. T.; Davidson, B. S. *Tetrahedron Lett.* **2001**, *42*, 801. (k) Ghosh, A. K.; Wang, Y. *Tetrahedron Lett.* **2001**, *42*, 3399.

(8) Paterson, I.; De Savi, C.; Tudge, M. *Org. Lett.* **2001**, *3*, 213.

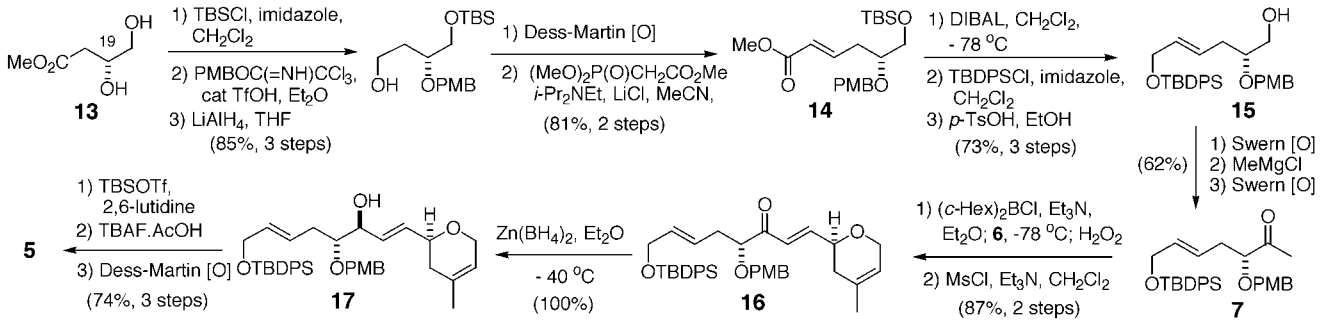
(9) (a) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765. (b) Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH Publishers: New York, 1993; p 103.

(10) Dossetter, A. G.; Jamison, T. F.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2398.

(11) The enantiomeric purity was determined by Mosher ester analysis of **12**, while the configuration predicted from Jacobsen's results was confirmed by correlation with material prepared from (*R*)-glycidol:



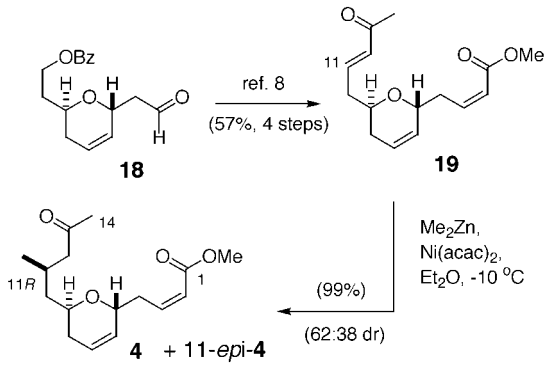
Scheme 3



The methyl ketone **7** required for assembly of the full side chain was prepared in a straightforward sequence (Scheme 3) on a multigram scale, starting from the diol **13**, derived from dimethyl (*R*)-malate.[12] This involved Horner−Wadsworth−Emmons (HWE) olefination to give **14**, followed by conversion via alcohol **15** into ketone **7**. Aldol coupling of ketone **7** with aldehyde **6** was best performed using the boron enolate, generated using $(c\text{-Hex})_2BCl$ in the presence of Et_3N, followed by base-induced elimination of the adduct via the corresponding mesylate, providing the (*E*)-enone **16** exclusively in 87% yield. Treatment of **16** with freshly prepared $Zn(BH_4)_2$ led to chelation-controlled reduction,[13] giving the allylic alcohol **17** cleanly with >97% diastereoselectivity.[14] Following protection of **17** as the TBS ether, the primary TBDPS ether was cleaved selectively using TBAF buffered with AcOH. Dess−Martin oxidation of the resulting alcohol then completed the $C_{15}-C_{27}$ subunit **5** (74% over three steps).

The corresponding C_1-C_{14} subunit **4** was conveniently prepared from the enantiomerically pure *trans*-dihydropyran **18** (Scheme 4), obtained by asymmetric boron aldol methodology and employed earlier in our syntheses of swinholide A[15a,b] and scytophycin C.[15c] Following sequential elaboration of the side chains using consecutive HWE reactions,[8] the (*E*)-enone **19** was submitted to reaction with Me_2Zn in the presence of catalytic $Ni(acac)_2$.[16] This resulted in clean conjugate attack at the enone, generating a separable mixture of adducts in 99% yield, favoring the desired (11*R*)-isomer **4** (62:38 dr).[17]

Scheme 4



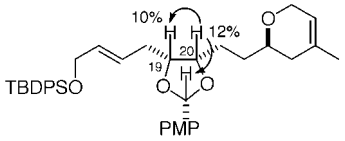
At this point, the controlled aldol coupling of the two subunits **4** and **5**, installing the remote C_{15} stereocenter, was addressed by use of a suitable chiral boron reagent (Scheme 5).[18] Enolization of the ketone **4** with (+)-Ipc_2BCl/Et_3N in Et_2O, followed by addition of the enal **5** gave **20**, as predominantly the desired (15*S*)-adduct (81:19 dr; 87% yield).

Following hydroxyl protection, the TBS ethers **21** (88%) were converted readily into the corresponding *seco*-acids **22** (68%) by a sequence involving DIBAL reduction, Dess−Martin periodinane and $NaClO_2$ oxidation, and DDQ deprotection of the PMB ether. A Mitsunobu-type macrolactonization[19] of **22**, mediated by DEAD/PPh_3, then gave the 20-membered macrolide **23** (along with the separable (15*S*)-epimer in 68% combined yield) with inversion of the C_{19} configuration. Notably, this Mitsunobu protocol avoided any complications of isomerization of the (*Z*)-enoate geometry.[8] Introduction of the exocyclic methylene was then achieved by exposure of ketone **23** to a Takai reagent system (CH_2I_2,

(12) Saito, S.; Ishikawa, T.; Kuroda, A.; Koga, K.; Moriwake, T. *Tetrahedron* **1992**, *48*, 4067.

(13) Oishi, T.; Nakata, T. *Acc. Chem. Res.* **1984**, *17*, 338.

(14) The (19*R*,20*S*) configurational assignment was confirmed by NOE analysis of the PMP acetal obtained by DDQ treatment of **17**:



(15) (a) Paterson, I.; Smith, J. D.; Ward, R. A. *Tetrahedron* **1995**, *51*, 9413. (b) Paterson, I.; Cumming, J. G.; Ward, R. A.; Lamboley, S. *Tetrahedron* **1995**, *51*, 9393. (c) Paterson, I.; Watson, C.; Yeung, K. −S.; Wallace, P. A.; Ward, R. A. *J. Org. Chem.* **1997**, *62*, 452.

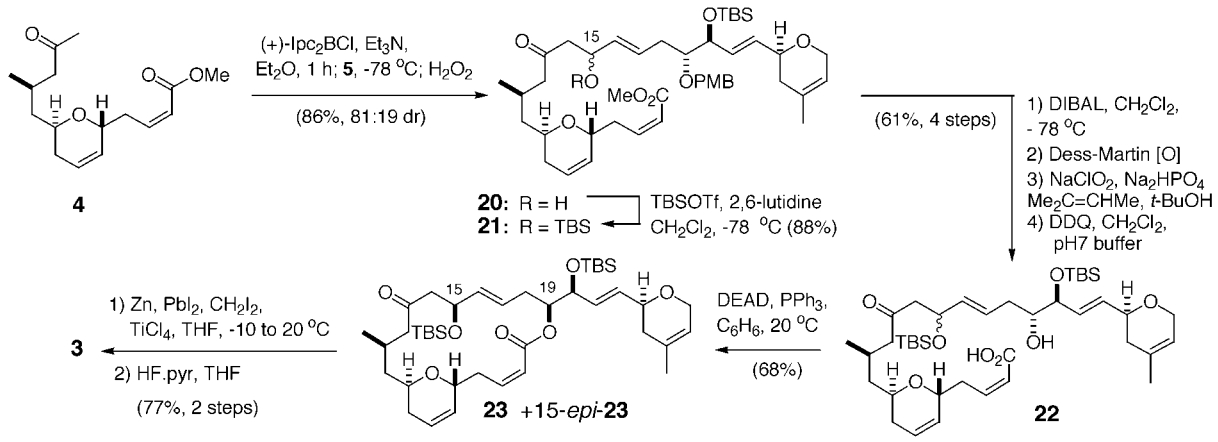
(16) Luche, J.-L.; Petrier, C.; Lansard, J.-P.; Greene, A. E. *J. Org. Chem.* **1983**, *48*, 3837 and references therein.

(17) We are currently investigating a reagent-controlled version of this conjugate addition reaction in the presence of suitable chiral ligand modifiers. The (11*R*) configuration of the methyl-bearing stereocentre in adduct **4** was established by conversion into laulimalide.

(18) (a) Paterson, I.; Goodman, J. M.; Lister, M. A.; Schumann, R. C.; McClure, C. K.; Norcross, R. D. *Tetrahedron* **1990**, *46*, 4663. (b) Paterson, I.; Oballa, R. M.; Norcross, R. D. *Tetrahedron Lett.* **1996**, *37*, 8581.

(19) Mitsunobu, O. *Synthesis* **1981**, 1.

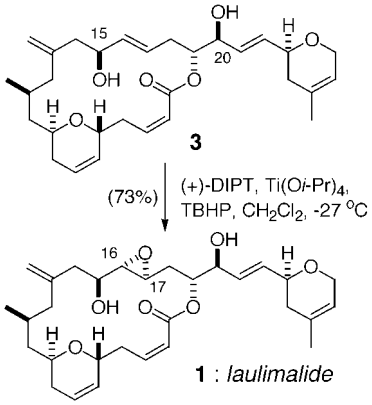
Scheme 5



Zn, $TiCl_4$, PbI_2),[20] leading on deprotection with HF·pyr to **3** (77%).

Completion of the total synthesis of laulimalide (Scheme 6) now required kinetic discrimination of the C_{15} and C_{20}

Scheme 6



allylic alcohols in **3**, with hydroxyl-directed epoxidation[9] of only the C_{16} alkene contained within the macrocyclic ring. Treatment of diol **3** with *t*BuOOH/Ti(O*i*Pr)$_4$ in the presence of (+)-DIPT in CH_2Cl_2 at −27 °C for 15 h resulted in controlled formation of a single epoxide product. On workup, this led to isolation of (−)-laulimalide in 73% yield, which had spectroscopic and physical data (^{1}H, ^{13}C NMR, MS, IR, HPLC, $[\alpha]^{20}_D$ −192 (*c* 0.2, $CHCl_3$); cf. $[\alpha]^{20}_D$ −200 (*c* 1.03, $CHCl_3$)[1c]) identical in all respects to a natural sample kindly provided by Professor Higa. Notably, the mild conditions of this final Sharpless epoxidation step prevented the formation of any detectable isolaulimalide (**2**). However, a sample of isolaulimalide was readily prepared by exposure of **1** to acid (CSA, $CDCl_3$).

In conclusion, this total synthesis of the potent microtubule-stabilizing anticancer agent (−)-laulimalide (**1**) proceeds in 27 steps and 2.9% overall yield (from diol **13**). Notable features are the novel use of Jacobsen HDA chemistry for the enantioselective construction of the side chain dihydropyran, a diastereoselective aldol coupling using our chiral boron enolate methodology, a Mitsunobu macrolactonization, and last, a highly effective Sharpless AE enabling the controlled introduction of the epoxide onto the unsaturated diol **3**. Further optimization of the synthesis, as well as application to the preparation of novel structural analogues of laulimalide, is underway.

Acknowledgment. We thank the EPSRC (GR/N08520), EC (HPRN-CT-2000-00018), and Queens' College, Cambridge (Research Fellowship to C.D.S), and Merck for support. We thank Prof. Tatsuo Higa (University of the Ryukyus) for an authentic sample of laulimalide and copies of NMR spectra.

Supporting Information Available: Spectroscopic data for diol **3** and synthetic and natural (−)-laulimalide **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) (a) Hibino, J.; Okazoe, T.; Takai, K.; Nozaki, H. *Tetrahedron Lett.* **1985**, *26*, 5579. (b) Takai, K.; Kakiuchi, T.; Kataoka, Y.; Utimoto, K. *J. Org. Chem.* **1994**, *59*, 2668.