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Synthesis of the Macrocyclic Core of Laulimalide

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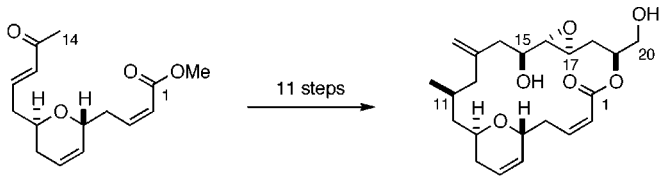
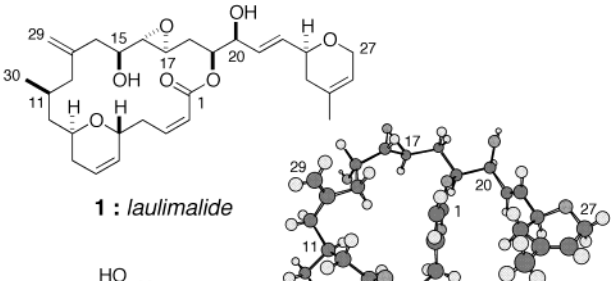
ABSTRACT



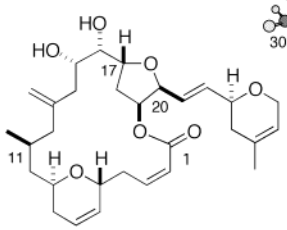
5 **3 :** *laulimalide core*

A stereoselective synthesis of 3, corresponding to the fully functionalized macrocyclic core of the novel microtubule-stabilizing agent, laulimalide, has been completed. Efficient macrolactonization was achieved by a Mitsunobu reaction, installing the sensitive (*Z*)-enoate, and macrocyclic stereocontrol was then exploited to introduce the methyl group and *trans*-epoxide.

Laulimalide,[1a] also known as fijianolide B,[1b] is a potent cytotoxic macrolide with IC_{50} values in the nanomolar range and is isolated from the Indonesian sponge *Hyattella* sp. and the Okinawan sponge *Fasciospongia rimosa*.[1c] Its full structure and absolute stereochemistry were determined to be **1** by X-ray crystallographic analysis.[1c] Laulimalide has a 20-membered macrolide ring with two dihydropyran rings and an acid-labile epoxide and contains nine stereogenic centers and five double bonds. It co-occurs with the less active, tetrahydrofuran-containing metabolite, isolaulimalide (**2**), which is derived from **1** via epoxide opening at C_{17} by the C_{20} hydroxyl group.



1 : *laulimalide*



2 : *isolaulimalide*

Recent studies[2] have shown that laulimalide shares the same mechanism of action[3] as the anticancer drug Taxol (paclitaxel) and, notably, is both more effective in stimulating tubulin polymerization and in circumventing P-glycoprotein-mediated drug resistance. Previously, only three other nontaxane classes of natural products (the epothilones,[4] discodermolide,[5] and the eleutherobins[6a]/sarcodictyins[6b]) have been identified that possess properties similar to those of Taxol. Hence, laulimalide represents an entirely new class

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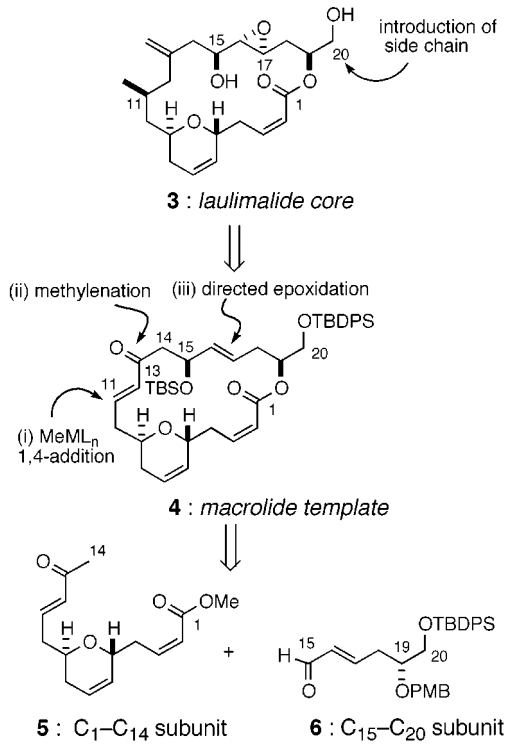
of microtubule-stabilizing anticancer agents with activities that may provide therapeutic utility. As the natural supply from the sponge source is restricted, an efficient and flexible synthesis of laulimalide is required in order to provide material to further evaluate its anticancer activity, together with that of novel structural analogues. To date, several synthetic approaches to fragments of laulimalide have been reported,[7a−g,8] including a completed total synthesis by Ghosh and Wang.[7h] Herein, we report a stereocontrolled synthesis of **3**, which corresponds to the fully functionalized macrocyclic core of laulimalide, employing a novel strategy.

By exploiting macrocyclic control,[9] our planned route is based around the sequential elaboration of the macrolide template **4** (Scheme 1). We need to introduce into **4**, in turn,

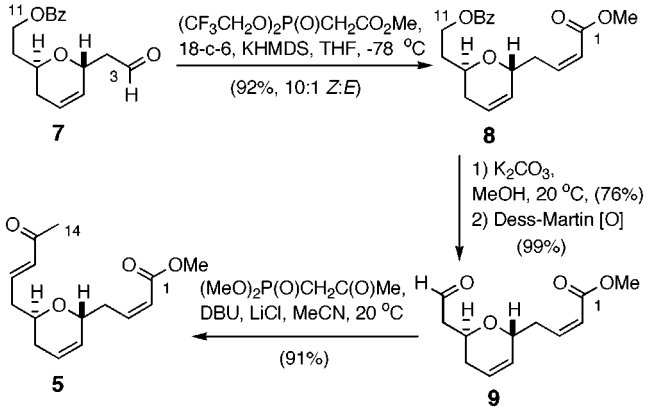
Scheme 1



(i) the isolated methyl-bearing stereocenter at C_{11} by conjugate addition, (ii) the exocyclic methylene at C_{13}, and (iii) the sensitive $C_{16}-C_{17}$ *trans*-epoxide. An aldol disconnection at the $C_{14}-C_{15}$ bond in **4** and opening of the macrolactone (with inversion at C_{19}) leads back to the C_1-C_{14} and $C_{15}-C_{20}$ subunits **5** and **6**, respectively. In this modular approach, the two building blocks **5** and **6** selected are relatively simple with one or two stereocenters and, as such, should be readily prepared in multigram quantities. Key concerns throughout were avoiding opening of the epoxide to generate a tetrahydrofuran, as occurs in isolaulimalide (**2**), and maintaining the *cis*-geometry of the enoate, as well as securing the correct configuration at several of the stereocenters.

The synthesis of the C_1-C_{14} subunit **5** is outlined in Scheme 2. This makes use of the enantiopure dihydropyran

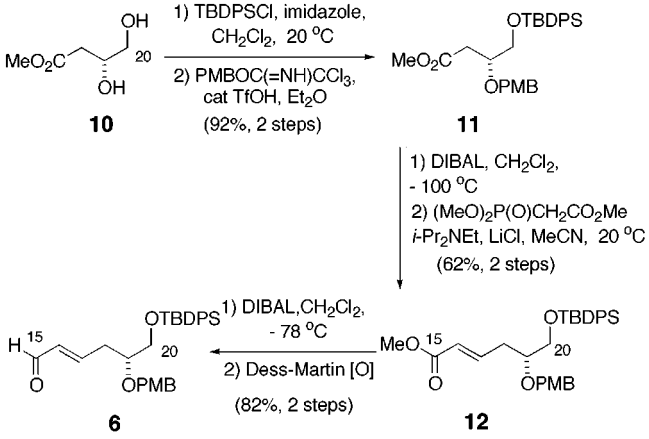
Scheme 2



7 (used previously in the total synthesis of swinholide A[10a,b] and scytophycin C[10c]), prepared by asymmetric aldol methodology.[11] Aldehyde **7** was converted directly into the (*Z*)-enoate **8** using the Still−Gennari HWE variant[12] in 92% yield (*Z*/*E* 10:1). A marked decrease in *Z*:*E* selectivity was observed if more than 1 equiv of KHMDS was used and if the reaction temperature was not maintained at −78 °C throughout. Presumably, this was due to base-mediated isomerization of the enoate in **8**. Benzoyl deprotection with K_2CO_3 in MeOH, followed by Dess−Martin oxidation, gave aldehyde **9** (75%, 2 steps). Homologation of aldehyde **9** in a further HWE reaction[13] provided the required subunit **5**.

The preparation of the $C_{15}-C_{20}$ subunit is shown in Scheme 3 and commences with the known diol **10**,[14] obtained

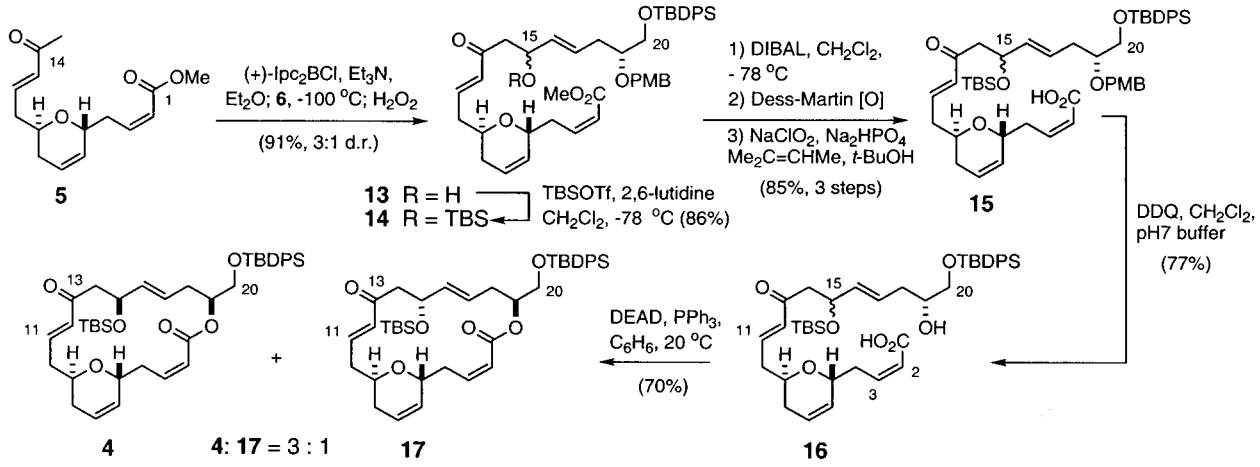
Scheme 3



from dimethyl (*R*)-malate. Differential bis-protection of the diol gave ether **11**. DIBAL-mediated reduction at −100 °C, followed directly by homologation of the resulting aldehyde using Masamune−Roush HWE conditions,[13] yielded the (*E*)-enoate **12** (62%). Final reduction/oxidation provided the required enal **6** in 82% yield.

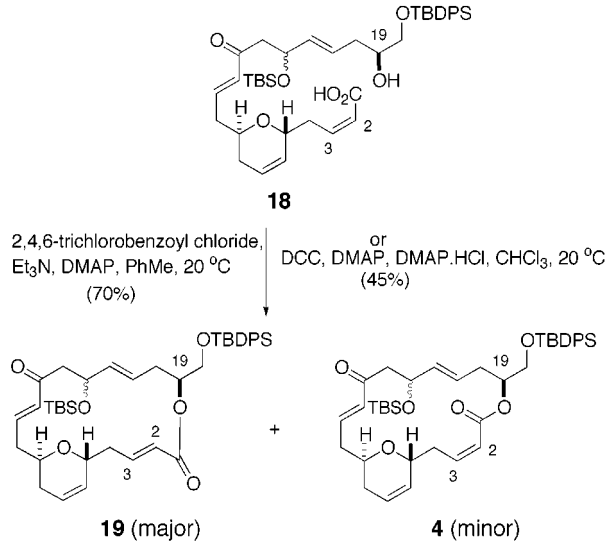
Having both major subunits in hand, we turned to coupling these together (Scheme 4). The aldol reaction between methyl

Scheme 4



ketone **5** and enal **6** required the correct introduction of the remote C_{15} stereocenter, necessitating the use of reagent control.[11a,b] Boron aldol coupling using (+)-Ipc_2BCl/Et_3N in Et_2O gave **13** as a 3:1 mixture in favor of the desired (15*S*)-adduct (91% combined yield), as confirmed by ^1H NMR analysis of the corresponding (*R*)- and (*S*)-MTPA esters using the advanced Mosher method.[15] Protection of the resultant secondary hydroxy group gave the TBS ethers **14**. Attempts to hydrolyze the methyl ester by standard means (viz. KOH/THF/MeOH, LiOH, $Ba(OH)_2$, etc.) failed. Thus, a three-step sequence of reduction with DIBAL, followed by Dess−Martin oxidation and subsequent $NaClO_2$ oxidation, was employed to reveal the acid **15** in 85% yield, followed by treatment with DDQ to cleave the PMB ether to give the alcohol **16** (77%). Mitsunobu macrolactonization[16] proceeded smoothly to deliver macrocycles **4** and **17** (70% combined yield after HPLC separation). This Mitsunobu protocol was essential, as attempts to macrolactonize the C_{19}-*epi* seco-acid **18** (prepared according to Schemes 3 and 4 starting with dimethyl (*S*)-malate), under both Yamaguchi[17] and Keck[18] conditions (Scheme 5), resulted in concomitant, base-induced, scrambling of the (*Z*)-enoate, leading to the undesired *trans*-macrocycle **19** and the required macrocycle **4** (6:1 ratio, respectively).

Scheme 5



The controlled elaboration of the 20-membered macrolide **4** into the laulimalide core was now investigated (Scheme

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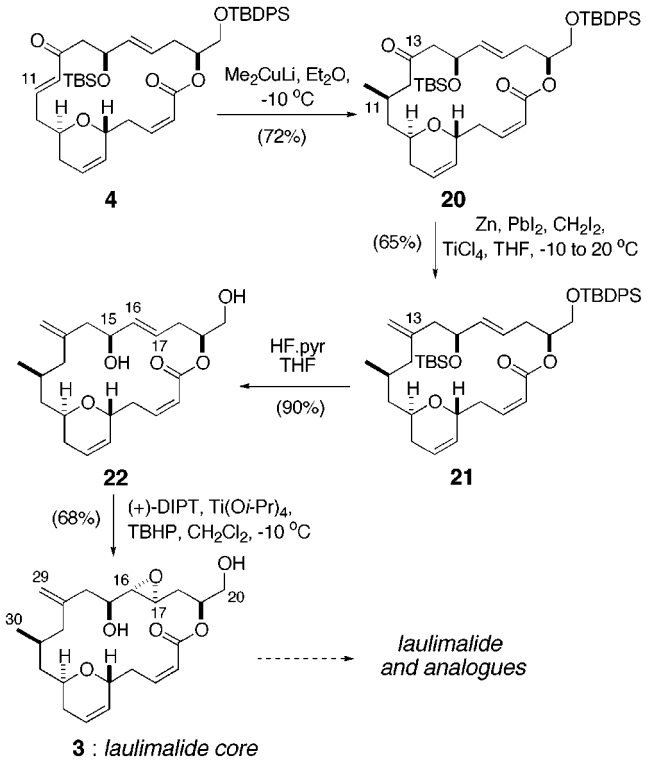
Scheme 6



6). First, the diastereoselective methylation at C_{11} by conjugate addition was required to proceed under macrocyclic stereocontrol to generate the desired (11*R*)-configuration. Notably, MM2 calculations (MacroModel v4.5,[19] Monte Carlo) on the bis-TMS protected version of macrolide **4** (Figure 1) show that in the global minimum conformation

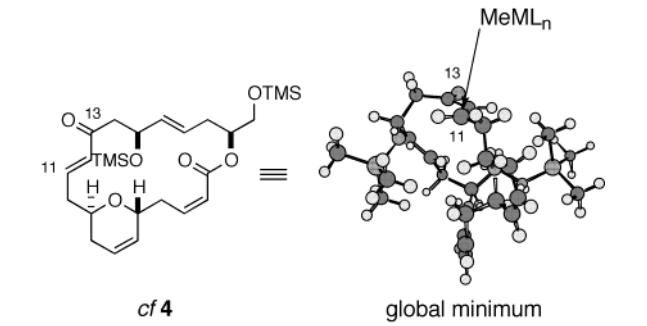


Figure 1.

one face of the *s-trans* enone double bond is exposed to external reagents. Assuming this same conformational bias extends to the reaction transition state, conjugate addition of an appropriate organometallic reagent would be expected to occur preferentially from the outer face of the alkene and deliver the required stereochemistry at C_{11}. In practice, treatment of macrocycle **4** with Me_2CuLi at −10 °C delivered a single adduct in a highly selective manner (72%). In contrast, the 15-*epi* macrolide **17** was relatively nonselective in addition of Me_2CuLi to the enone (1.7:1 mixture of diastereomers). While the stereochemistry at C_{11} has not been rigorously proven at this point, it is assigned in **20** as 11*R* on the basis of diagnostic ^1H and ^{13}C NMR resonances of the laulimalide core (**3**) (see Supporting Information). Introduction of the exocyclic methylene at C_{13} was achieved by employing the Takai reagent ($Zn/PbI_2/CH_2I_2/TiCl_4$).[20] Reaction of ketone **20** with excess reagent gave alkene **21** in 65% yield. Deprotection of both silicon protecting groups occurred using HF·pyr in THF, providing the macrocyclic diol **22** in 90% yield. The stage was now set for the controlled introduction of the $C_{16}-C_{17}$ *trans*-epoxide directed by the adjacent C_{15} hydroxyl group. Sharpless epoxidation[21] with (+)-DIPT gave solely epoxide **3** in 68% yield, achieved without any detectable epoxide opening by the C_{20} hydroxyl group (cf. **1** → **2**). In the ^1H (500 MHz, COSY) and ^{13}C NMR (125 MHz) spectra of **3**, the data for all diagnostic signals agreed with the corresponding data[1c] for laulimalide (**1**), providing support for the stereochemical assignments in Scheme 6.

In conclusion, the synthesis of the laulimalide core (**3**) has been achieved in a stereoselective manner, exploiting macrocyclic conformational bias in the installation of the remote methyl-bearing stereocenter at C_{11}. In addition, the sensitive C_2-C_3 (*Z*)-enoate has been preserved throughout the synthesis by careful selection of reagents and experimental protocols. The synthesis of the macrolide core serves a dual purpose of providing an advanced intermediate toward laulimalide and entry into an array of analogues through the attachment of various side chains at C_{20}. Studies toward this end are underway.

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Supporting Information Available: Spectroscopic data for diol **22** and epoxide **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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