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Synthesis of the Macrocyclic Core of Leiodermatolide

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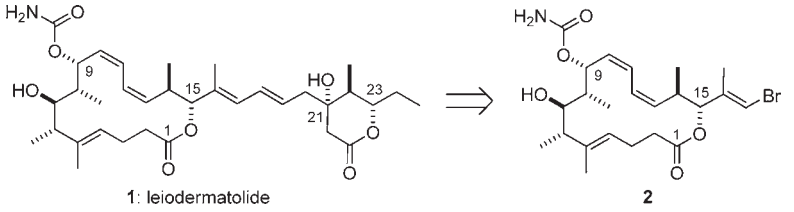
ABSTRACT



The macrocyclic core (2) of the marine macrolide leiodermatolide (1) has been synthesized in 19 steps through a convergent strategy exploiting boron aldol methodology to install the requisite stereochemistry and a selective Stille coupling reaction for controlled fragment assembly, followed by a Yamaguchi macrolactonization and carbamate introduction at the C9-OH.

Marine natural products continue to represent an important source of lead compounds for the development of novel cancer chemotherapeutics,[1] highlighted by the recent FDA approval of Halaven (eribulin mesylate) for the treatment of advanced breast cancer.[1a] Leiodermatolide (**1**, Scheme 1) has recently emerged as a promising new anticancer polyketide, isolated by the Wright group in 2008 from the lithistid sponge *Leiodermatium sp.*, collected off the coast of Florida.[2] Crude sponge extracts displayed activity in an antimitotic assay, and subsequent bioassay-guided fractionation identified leiodermatolide as the active component, which exhibited low nanomolar (< 10 nM) cytotoxicity against a range of human cancer cell lines. This antimitotic activity appears to be mediated through the disruption of tubulin dynamics, leading to cell-cycle arrest in the G2/M phase. While the exact mechanism of action is presently unknown, it is clearly distinct from other important antimitotic drugs such as the epothilones, taxanes, and Vinca alkaloids,[3] marking out leiodermatolide as a potential lead compound for the development of new anticancer agents.

From a structural perspective, leiodermatolide features a 16-membered macrolactone appended with a carbamate and an unsaturated side chain terminating in a δ-lactone ring, which together incorporate five alkenes, including a (*Z*,*Z*)-diene and an (*E*,*E*)-diene, and nine stereocenters.[2] Recently, we have used a combination of homo- and heteronuclear NMR analysis, molecular modeling, and DP4 NMR prediction methodology to determine the stereostructure **1** for leiodermatolide,[2a] where the full configuration of the C1−C16 macrocyclic and C20−C33 δ-lactone stereoclusters remains undefined. Synthetic studies by Maier and co-workers directed toward an earlier, tentative stereostructure for leiodermatolide revealed inconsistencies with this assignment.[4] Herein, we report the convergent synthesis of the C1−C16 macrocyclic core **2** of leiodermatolide corresponding to stereostructure **1**, whose NMR homology with the natural product fully supports our relative configurational assignment for this region of the macrolide.

Our approach is outlined retrosynthetically in Scheme 1. In order to resolve the remaining stereochemical ambiguities, we aimed for late-stage incorporation of the δ-lactone **3**, enabling facile divergence to both possible diastereomers (enantiomers) for comparison with the natural product.

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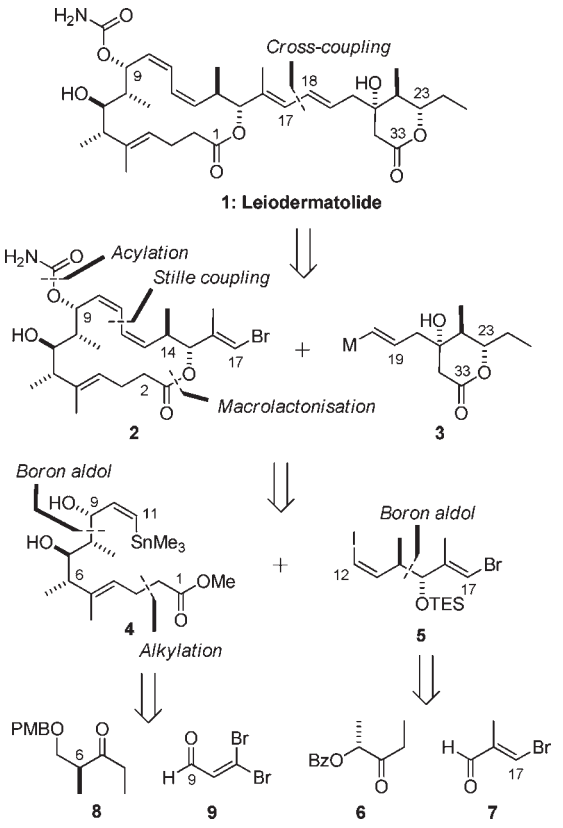
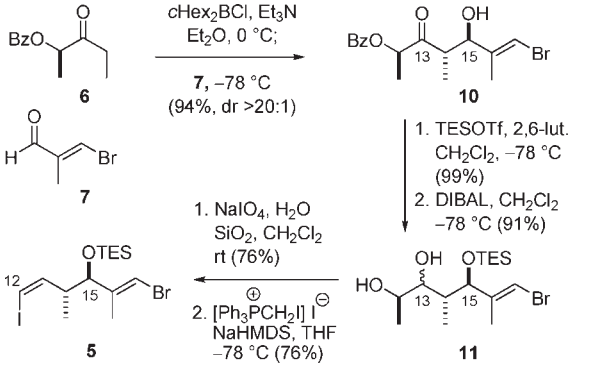
Accordingly, leiodermatolide would arise through cross-coupling of macrocyclic vinyl bromide **2** with the suitably functionalized vinyl metallic species **3**/***ent*-3**, forming the C16−C19 diene.

Scheme 1. Retrosynthetic Analysis of Leiodermatolide

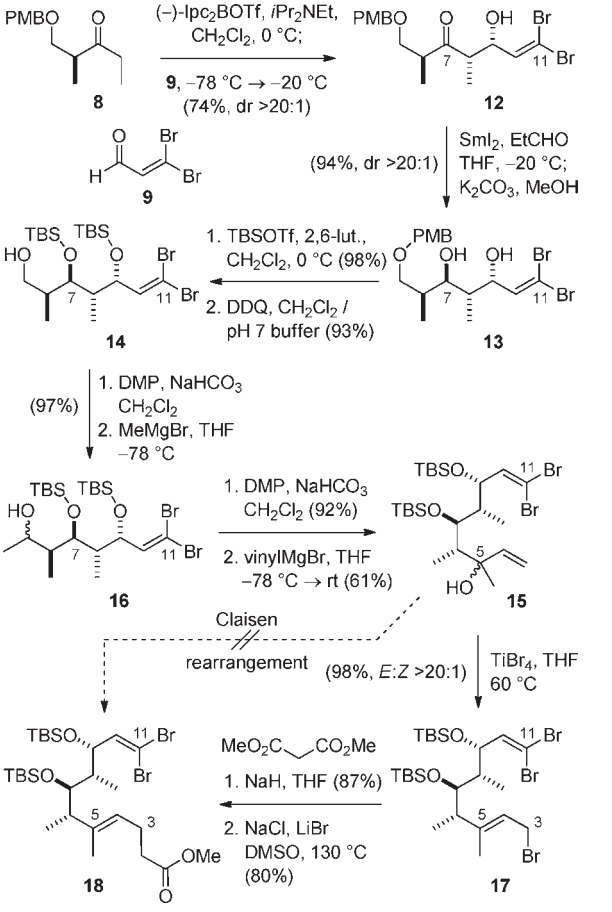


Macrocycle **2** would itself arise from vinyl stannane **4** and *bis*-vinyl halide **5**, exploiting a regioselective macrolactonization and a chemoselective Stille coupling reaction to differentiate the termini of **5** and generate the (10*Z*,12*Z*)-diene.[5] Notably, these maneuvers would be carried out without protection of the C7,C9 diol, demanding regioselective carbamate formation at C9. The preparation of both **4** and **5** would utilize our versatile boron aldol methodology to install the requisite stereochemistry. For *bis*-vinyl halide **5**, aldol coupling of lactate-derived ketone **6**[6] with aldehyde **7** would set the C14,C15-*anti*-relationship, while the conspicuous C6−C9 stereotetrad within **4** would be constructed through a boron aldol reaction of chiral ketone **8**[7,8] with aldehyde **9** containing a masked (*Z*)-vinyl stannane.[5] Subsequent chain extension through allylic rearrangement/alkylation would then install the (*E*)-γ, δ-unsaturated ester of **4**.

Scheme 2. Preparation of C12−C17 *Bis*-vinyl Halide **5**



Scheme 3. Preparation of C1−C11 Fragment **18**



As shown in Scheme 2, preparation of pivotal *bis*-vinyl halide **5** commenced with the aldol reaction[6] of the (*E*)-boron enolate of ethyl ketone **6** (*c*Hex$_2$BCl, Et$_3$N, Et$_2$O, 0 °C) with known aldehyde **7**,[9] which provided *anti* adduct **10** (94%, dr > 20:1).[10] Silylation of the newly formed C15

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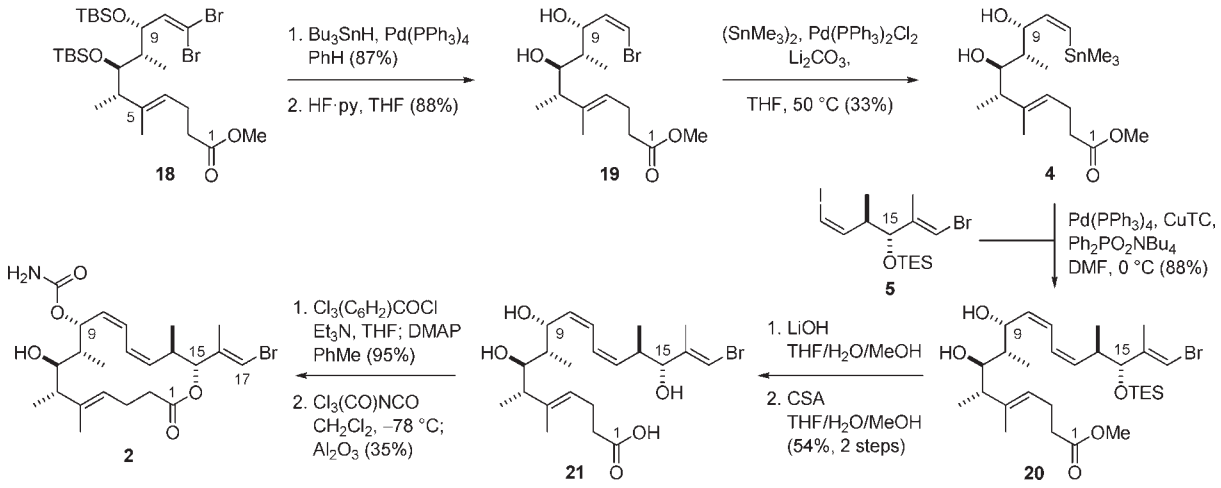
Scheme 4. Preparation of Macrolactone **2**



alcohol (TESOTf, 2,6-lutidine) followed by DIBAL-mediated reduction of the ketone and benzoate provided diol **11** (91%).

Completion of fragment **5** was then achieved through oxidative cleavage of diol **11** using silica-supported $NaIO_4$[11] to avoid competing desilylation, followed by Stork–Wittig homologation ($Ph_3PCH_2I_2$, NaHMDS, THF, −78 °C) which proceeded to install the requisite (*Z*)-vinyl iodide **5** as a single detectable geometric isomer.[12]

Key to synthesizing the C1–C11 vinyl stannane coupling partner **4** for **5** would be efficient control over installing the C6–C9 *syn*,*anti*,*syn*-stereotetrad (Scheme 3). This was achieved through a chiral ligand-mediated ((−)-Ipc_2BOTf, iPr_2NEt) boron aldol reaction[7,8] of ethyl ketone **8** with aldehyde **9**,[5] which provided the desired *syn* adduct **12** (74%) as essentially a single diastereomer.[10] The newly formed C9 stereochemistry could then be relayed to C7 through 1,3-*anti* reduction under Evans–Tishchenko conditions (SmI_2, EtCHO, THF, −20 °C),[13] which, following *in situ* methanolysis of the ensuing propionate ester, afforded the requisite stereotetrad as part of diol **13** (94%, dr > 20:1). Protecting group manipulation involving *bis*-silylation (TBSOTf, 2,6-lutidine) and PMB ether cleavage (DDQ) then provided alcohol **14**.

At this point, we were able to contemplate incorporation of the Δ^4 (*E*)-trisubstituted alkene of leiodermatolide. Following the failure of the corresponding terminal alkyne to undergo Negishi carbometalation,[14] a revised strategy targeted tertiary allylic alcohol **15** as a potential substrate for Claisen rearrangement to complete the C1–C5 region. Accordingly, a sequence of oxidation and Grignard additions provided **15** via alcohol **16**. Unfortunately, neither **15** nor the corresponding acetate derivative could be coaxed into undergoing Claisen rearrangement under a range of Ireland or Johnson-type conditions.[15,16] Instead, rather facile allylic rearrangement to the corresponding primary allylic alcohol was generally observed, forming the Δ^4 alkene with good levels of (*E*)-selectivity (> 10:1). We were able to exploit this behavior, however, through conversion of allylic alcohol **15** to the corresponding primary allylic bromide **17** according to the method of Fuchter,[17] involving treatment of the magnesium alkoxide of **15** with $TiBr_4$, which proceeded with excellent yield and selectivity (98%, (*E*):(*Z*) > 20:1). Finally, displacement of the allylic bromide with the sodium anion of dimethylmalonate (87%) followed by Krapcho decarboxylation (80%)[18] smoothly afforded methyl ester **18**, representing the full C1–C11 sequence of leiodermatolide.

In preparation for coupling of the C1–C11 and C12–C17 fragments, the vinyl stannane would have to be revealed from vinyl dibromide **18**. As shown in Scheme 4, selective reductive debromination of the *trans*-bromide under palladium-catalyzed conditions ($Pd(PPh_3)_4$, Bu_3SnH)[19] provided the corresponding (*Z*)-vinyl bromide (87%). This was then subjected to desilylation with HF·py to alleviate

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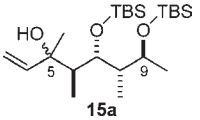
(16) These exploratory studies were carried out on the truncated model substrate **15a**:



15a

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steric hindrance that initially had prevented further functionalization of the vinyl bromide. After substantial investigation, vinyl bromide **19** could be converted to (*Z*)-vinyl stannane **4** in moderate yield (33%) under modified Wulff–Stille conditions ($Pd(PPh_3)_2Cl_2$, $(Me_3Sn)_2$, Li_2CO_3, THF, 50 °C).[20] This compound proved rather unstable with respect to proto-destannylation and was thus submitted immediately for Stille coupling with *bis*-vinyl halide **5**. Under conditions utilized recently in the context of our chivosazole synthesis[5] ($Pd(PPh_3)_4$, CuTC, $Ph_2PO_2NBu_4$, DMF, 0 °C),[21] a smooth and completely regioselective cross-coupling was achieved, generating the (10*Z*,12*Z*)-diene of **20** in high yield (88%).

With the complete C1–C17 skeleton in place, attention now focused on closure of the macrolactone. Accordingly, basic ester hydrolysis (LiOH) followed by acid-mediated desilylation (CSA) provided the truncated *seco*-acid **21** (54%). In the event, we were delighted to observe completely regioselective macrolactonization under Yamaguchi conditions,[22] forming the desired 16-membered macrocycle in high yield (95%), presumably reflecting a favorable conformational preorganization of the substrate.

Completion of the macrocyclic portion of leiodermatolide finally required regioselective installation of the carbamate at C9. This was predicted based on our previous experience in derivatizing the natural product which had indicated a highly crowded environment about C7.[2a] In the event however, treatment of the macrocyclic diol with a slight excess (1.1 equiv) of $Cl_3C(O)NCO$ at −78 °C followed by hydrolytic workup[23] provided only a *ca.* 3:2 mixture (87% combined yield) of the C7 and C9 monoacylated products, from which the natural product-like C9 carbamate **2** was isolated in 35% yield after HPLC purification.

Detailed NMR comparisons for macrocycle **2** with the natural product data for the C1–C16 region[2a] were carried out (Figure 1). While some deviation at C15, C16, and C30 is to be expected for this macrocyclic truncate, all other ^1H resonances fell within ±0.03 ppm of the corresponding natural product values, and ^{13}C resonances within ±1.0 ppm, including particular homology for the C6–C9 region. Good correlation was also observed for the respective $^3J_{H,H}$ coupling constants about the macrocycle, and key NOE enhancements indicative of the proposed stereochemistry.[24] Together, these comparisons provide a strong indication of the validity of our stereochemical assignment for this region of leiodermatolide.[2a]

In conclusion, we have prepared the macrocyclic core of leiodermatolide in 19 steps from **8**. Notably, macrocycle **2** is appropriately functionalized for direct cross-coupling with either antipode of a C17–C33 δ-lactone side-chain fragment to complete the total synthesis. Spectroscopic and chiroptical comparisons of these diastereomers with the natural product data should finally unambiguously determine the complete stereochemistry of leiodermatolide. Work toward this end will be reported in due course.

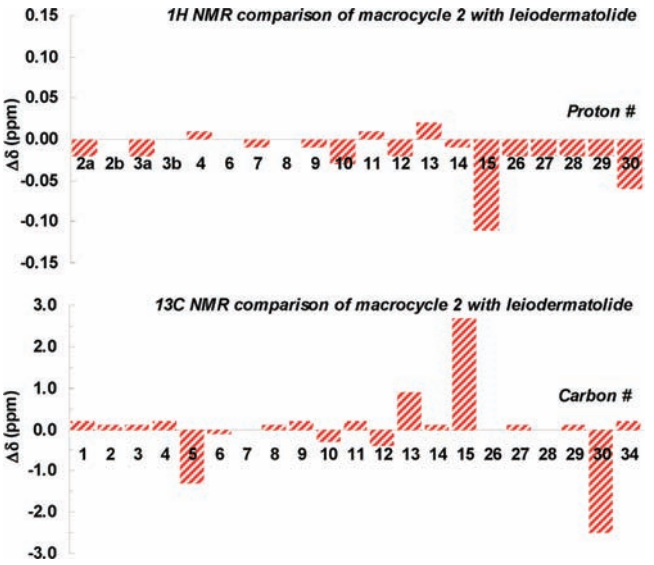

Figure 1. NMR comparison for macrocycle **2** with leiodermatolide (**1**).

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Supporting Information Available. Experimental details and spectroscopic data for new compounds, and details of NMR comparisons of synthetic macrocycle **2** with natural leiodermatolide. This material is available free of charge via the Internet at http://pubs.acs.org.

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(24) See the Supporting Information for detailed comparisons.