Toward Leiodermatolide: Synthesis of the Core Structure

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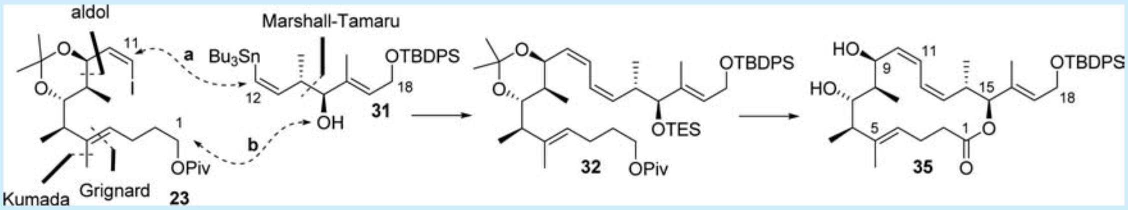
Ⓢ *Supporting Information*



ABSTRACT: The macrocyclic core (**35**) of the marine natural product leiodermatolide (**1**) was synthesized from two key fragments, vinyl iodide **23** (C1−C11 part) and vinyl stannane **31** (C12−C18 part). A Stille coupling led to conjugated *Z*,*Z*-diene **32**. The derived seco acid **34** was cyclized using a Yamaguchi macrolactonization. Key steps in the assembly of vinyl iodide **23** were a Paterson aldol reaction, and a Kumada coupling on a triflate derivative to create the C4−C5 trisubstituted double bond. The two stereocenters in fragment **31** were established by a Marshall−Tamaru reaction. The longest linear sequence comprises 20 steps.

The macrolide (−)-leiodermatolide (**1**) was discovered by the Wright group in a screening program aimed at the discovery of antimitotic agents from marine sponges (Figure 1).

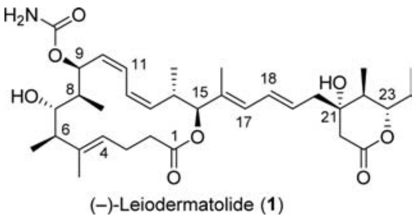
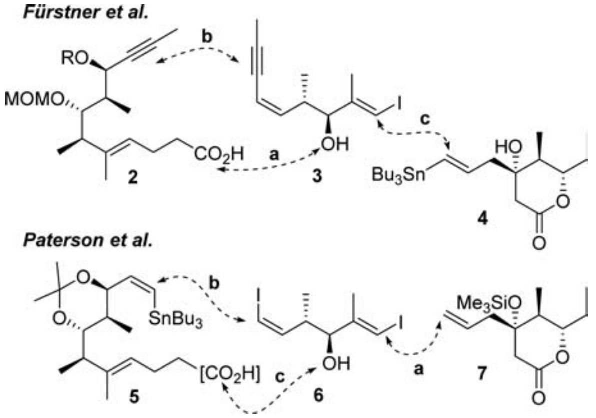


Figure 1. Structure of (−)-leiodermatolide (**1**).

It was isolated from the listhed sponge *Leiodermatium*. Cells treated with leiodermatolide showed abnormal spindle formation, even though tubulin was not affected. The IC_{50} values for several cancer cell lines were in the low nanomolar range. In a patent application from 2008 only the flat structure (constitution) was reported.[1] Later a tentative stereostructure appeared on a webpage.[2] However, in this structure C6 and C8 were inverted. In 2011 an almost complete structure assignment was achieved through NMR spectroscopie analysis, NMR shift calculations, and molecular modeling.[3] However, the relative configurations of the macrolactone part and the δ-lactone remained open.

The structure of **1** is characterized by a 16-membered macrolactone ring, with a diene-containing side chain with a δ-lactone at its terminus. The macrolactone contains a conjugated *Z*,*Z*-diene and one trisubstituted double bond. In addition, there are eight stereocenters. Our group had contributed to the chemistry of leiodermatolide with the synthesis of key fragments and a macrolactonization approach to the macrolactone core, both based on the C6,C8-epimer.[4] The exact structure was finally secured through the first total synthesis of (−)-leiodermatolide by the Fürstner group.[5] In this elegant synthesis, acid **2**, prepared by aldol technology, was esterified with enynol **3** followed by ring-closing alkyne metathesis. Finally, the δ-lactone part was attached via a Suzuki coupling (Scheme 1). Later, the Fürstner group refined some steps of their first synthesis.[6] In the total synthesis by Paterson et al. the C17−C18 bond was early on established by a Heck coupling between vinyl iodide **6** and δ-lactone **7**.[7] This was followed by Stille coupling with stannane **5** to form the C11−C12 bond. A Yamaguchi macrolactonization on a deprotected seco acid essentially completed this route. Prior to their total synthesis,

Scheme 1. Fragments and Order of Assembly in the Total Syntheses of Leiodermatolide



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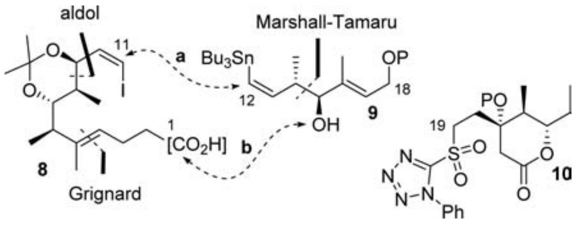
the Paterson group had published a synthesis of an enantiomer of the macrocyclic core featuring an (*E*)-(1-bromoprop-1-en-2-yl) side chain at C15.[8]

Biological studies confirmed that the cell cycle stops at the G2/M transition.[6] In addition, leiodermatolide induces formation of micronuclei, centrosome amplification, and tubuli disruption.[9] As a possible mode of action centrosome declustering was suggested. However, defined protein targets could not yet be identified. Testing of seven analogs that were also prepared showed that the 9-carbamate can be replaced by an acetate. The 7-OH has to be free for good activity. Moreover, the C18–C19 dihydro analog was less active. The δ-lactone in its correct configuration also seems to be crucial for good potency.

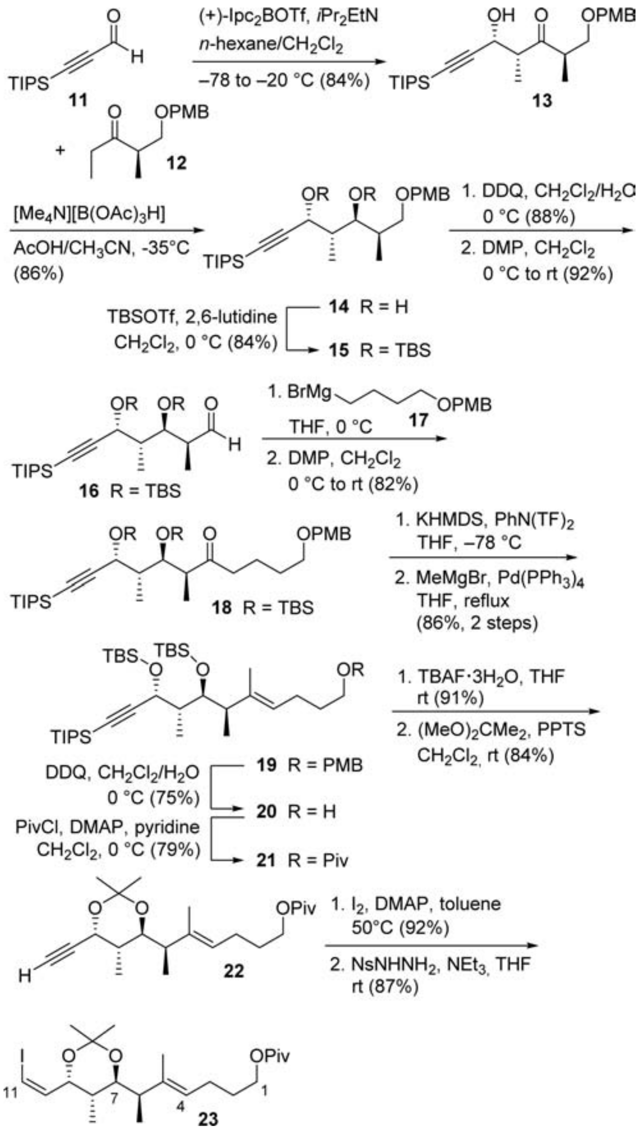
The novel mode of action together with the challenging structural features make leiodermatolide an interesting target for further synthetic studies. According to our previous retrosynthetic plan, leiodermatolide would be constructed from three fragments, a C1–C11 part **8**, the C12–C18 middle piece **9**, and a δ-lactone fragment **10** (Scheme 2).[3] Here the *Z,Z*-diene would be established by a Stille coupling and ring closure would be achieved by macrolactonization. Whether the planned C18–C19 olefination, for example by Julia–Kocienski olefination, was a good decision will have to be determined. In this paper we describe the synthesis of the macrolactone core according to this rough sketch. To introduce the stereocenters at C8 and C9 in fragment **8**, a boron-mediated aldol reaction was envisioned.[10] For chain extension, a C4 unit would be added by Grignard addition to a C3 aldehyde. Based on our previous studies the stereocenters on C14 and C15 would be created by a Marshall–Tamaru reaction.[11]

Scheme 2. Plan for the Synthesis of Leiodermatolide



The known aldehyde[12] **11** and chiral ketone[13] **12** were used in a boron-mediated aldol reaction using (+)-Ipc_2BOTf at −78 °C (Scheme 3).[10] A similar aldol reaction was used by the Paterson group to construct the stereotetrad of leiodermatolide although with a different aldehyde as a precursor to a *Z*-vinylstannane.[8] The resulting β-hydroxyketone **13** was treated with $[NMe_4][B(OAc)_3H]$ in an *anti* selective reduction to give *anti* diol **14** in good yield (86%) and a high diastereomeric ratio of 16:1.[14] The diol **14** was protected as a TBS ether, and after cleaving the PMB ether with DDQ and oxidation of the resulting alcohol with Dess-Martin periodinane (DMP) at 0 °C, aldehyde **16** was obtained. Diol **14** was initially protected as acetonide. However, during the oxidative cleavage of the PMB ether and oxidation to the corresponding aldehyde, epimerization at C9 to the 7,9-*syn*-isomer was observed (see Supporting Information (SI)). For chain extension aldehyde **16** was treated with the Grignard reagent **17**.[15] The resulting secondary alcohol was directly oxidized with DMP to ketone **18** in good yield (82% over two steps). For the formation of the trisubstituted double bond at C4, ketone **18** was enolized with KHDMS in THF at −80 °C and the enolate was trapped with $PhNTf_2$. The methyl group was introduced by a Kumada coupling[16] with MeMgBr in refluxing THF in the presence of $Pd(PPh_3)_4$ which gave enyne **19** in 86% yield over two steps and an *E*/*Z* ratio of 4:1 (determined by ^1H NMR).

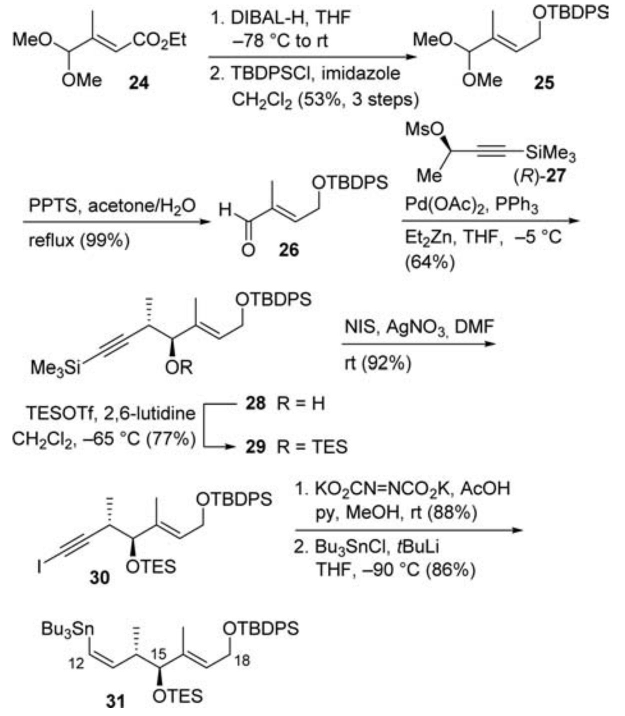
Scheme 3. Synthesis of C1–C11 Fragment 23 via Aldol Technology, Chain Extension via Grignard Reaction and Kumada Coupling To Form the Trisubstituted Double Bond



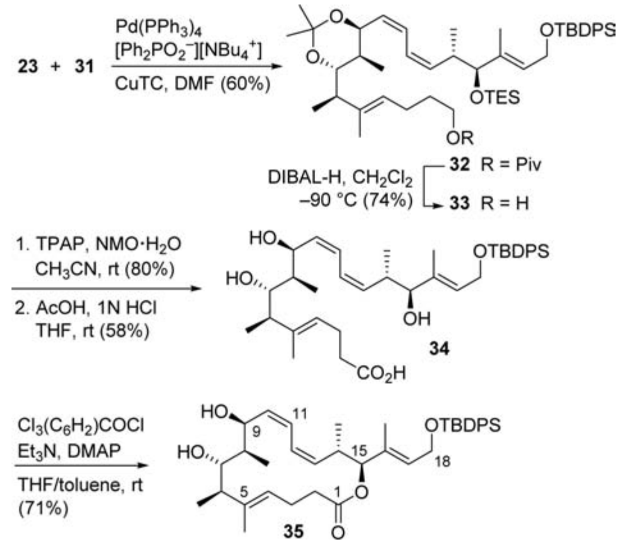
Exchange of the protecting group at C1 led to pivaloate **21**. For the iodination of the triple bond the TIPS group had to be removed since the direct iodination[17] (NIS, $AgNO_3$, AgF, MeCN) did not work in our hands. For the desilylation of **21**, $TBAF{\cdot}3H_2O$ in THF at room temperature was used, but under these conditions the TBS groups also were cleaved. The resulting diol was then protected as acetal **22**. After introducing the iodine using I_2 and DMAP in toluene at 50 °C,[18] the triple bond was reduced with $NsNHNH_2$ to give the *cis* vinyl iodide **23** in 87% yield.[19] The observed coupling constant $^3J(10H/11H)$ of 7.6 Hz indicated the required *cis*-double bond.

The other coupling partner, stannane **31**, was prepared from enoate[20] **24**, which itself was obtained by a Horner–Wadsworth–Emmons reaction (Scheme 4). Thus, the crude ester **24** was directly reduced with DIBAL-H at −78 °C to the corresponding alcohol which subsequently was protected as

Scheme 4. Formation of Vinyl Stannane 31



Scheme 5. Formation of Core Structure 35



TBDPS ether **25** in 53% yield over three steps (including the HWE reaction to form **24**). The acetal function was then cleaved using PPTS in wet acetone under reflux to provide aldehyde[21] **26**, required for the Marshall−Tamaru reaction, in 98% yield. The *E*/*Z* ratio for **26** was at least 9:1. With the (*R*)-mesylate[22] **27**, ZnEt$_2$, and the catalyst system Pd(OAc)$_2$/PPh$_3$, the secondary alcohol **28** could be obtained. It was protected as TES-ether **29** by treating it with TESOTf and 2,6-lutidine at −65 °C. The TMS group at C7 was replaced by iodine using NIS and AgNO$_3$ (0.2 equiv) in DMF at room temperature.[23,24] The triple bond was reduced with dipotassium diazodicarboxylate in MeOH at room temperature.[4a] The resulting *Z*-vinyl iodide was converted to vinyl stannane **31** with *t*BuLi and Bu$_3$SnCl.

With the key fragments **23** and **31** in hand, a Stille coupling was used to combine them. Thus, best result were obtained using Pd(PPh$_3$)$_4$ as the catalyst and CuTC and [NMe$_4$]-[Ph$_2$PO$_2$] as additives providing diene **32** in an acceptable yield of 60% (Scheme 5). To complete core structure **35**, the pivaloate was cleaved using DIBAL-H at −90 °C, followed by oxidation of alcohol **33** under Stark conditions[25] using TPAP and NMO·H$_2$O. Thereafter, the protecting groups were cleaved under acidic conditions (AcOH, 1 N HCl) to provide seco acid **34**. A final macrolactonization under Yamaguchi conditions led to core structure **35** in good yield (71%). A comparison of the ^{13}C NMR data of **35** with leiodermatolide (**1**) showed good agreement for peaks that we could assign unambigously. Chemical shift differences were seen for carbon atoms around C9 which carries a carbamate function. The expected large coupling constants seen for 15-H [^3J(14H,15H) of 10.4 Hz] and 7-H [^3J(6H,7H) of 10.1 Hz] of **35** match well with the stereochemistry and local conformation of the natural product. The olefinic protons of the diene part show similar chemical shifts and coupling constants as the reference compound 10-H (δ = 5.59, dd, J = 10.4, 10.4 Hz), 11-H (δ = 6.44, dd, J = 11.2, 11.2 Hz), 12-H (δ = 6.28, dd, J = 11.2, 11.2 Hz), 13-H (δ = 5.32, dd, J = 10.6, 10.6 Hz) (see also SI).

In summary, we achieved the synthesis of core structure **35** of the natural product (−)-leiodermatolide in 20 steps based on the known aldehyde **11** and ketone **12** in an overall yield of 1.3%. Further studies to complete the natural product are ongoing in our group.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01355.

Experimental procedures, spectroscopic data, and images of ^{1}H and ^{13}C NMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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