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Synthesis of the C(1)−C(13) Fragment of Leiodermatolide via Hydrogen-Mediated C−C Bond Formation

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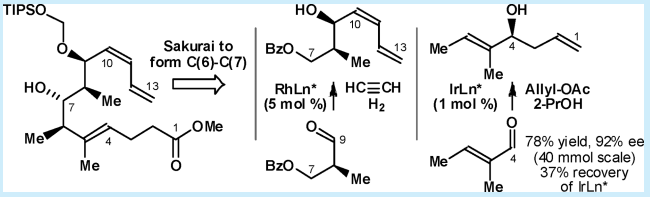
Supporting Information

ABSTRACT: The C(1)−C(13) fragment of the antimitotic marine macrolide leiodermatolide is prepared in seven steps via hydrogenative and transfer-hydrogenative reductive C−C couplings. A hydrogen-mediated reductive coupling of acetylene with a Roche-type aldehyde is used to construct C(7)−C(13). A 2-propanol-mediated reductive coupling of allyl acetate with (*E*)-2-methylbut-2-enal at a low loading of iridium (1 mol %) is used to construct C(1)−C(6), which is converted to an allylsilane using Oestereich's copper-catalyzed allylic substitution of Si−Zn reagents. The union of the C(1)−C(6) and C(7)−C(13) fragments is achieved via stereoselective Sakurai allylation.



As exemplified by vincristine, paclitaxel, docetaxel, ixabepilone, eribulin, and the antibody−maytansinoid conjugate Kadcyla, anticancer agents based on natural products that perturb microtubule dynamics have found broad use in human medicine.[1] Leiodermatolide, a marine macrolide isolated in 2008 from crude extracts of a deep water lithistid sponge of the genus *Leiodermatium*, was identified in connection with efforts aimed at the discovery of antimitotic agents.[2] Leiodermatolide displays potent and selective antiproliferative activity against a panel of human cancer cell lines by virtue of what appears to be a unique mechanism for disruption of tubulin dynamics: while causing irregular spindle formation in two different cancer cell lines at nanomolar concentrations, purified tubulin was unaffected even at significantly higher concentrations.[2,3]

The intriguing biological properties and scarcity of leiodermatolide have motivated efforts toward its preparation through de novo chemical synthesis. To date, total syntheses of leiodermatolide have been reported by Fürstner[4] and Paterson.[5] Additionally, several leiodermatolide substructures were prepared by Maier.[6] Despite this progress, existing routes to leiodermatolide are on the order of roughly 20 steps (LLS) or more,[4,5] warranting further work toward strategies that might streamline its synthesis and broaden access to structural analogues.

We have developed a suite of reductive C−C bond formations mediated by elemental hydrogen[7a] or hydrogen transfer from alcohols.[7] Application of these methods to the synthesis of type I polyketides has enabled routes significantly more concise than previously possible.[8] Given the challenges posed by leiodermatolide, a campaign toward its preparation via hydrogenative coupling was undertaken. Here, we describe our initial approach to the C(1)−C(13) fragment, which exploits a hydrogen-mediated reductive coupling of acetylene to assemble the C(7)−C(13) fragment and a 2-propanol-mediated reductive coupling of allyl acetate with (*E*)-2-methylbut-2-enal to construct the C(1)−C(6) fragment. A stereoselective Sakurai allylation enables union of the C(1)−C(6) and C(7)−C(13) fragments.

Retrosynthetically, we envisioned a convergent route to leiodermatolides A and B from Fragments A and B via esterification and (*Z*)-selective ring-closing metathesis (RCM) (Figure 1).[9] The synthesis of Fragment A, the topic of this report, would be realized through Sakurai reaction of allylsilane **6** and *α,β*-stereogenic chiral aldehyde **12**.[10] The requisite allylsilane **6** appeared accessible from allyl alcohol **2** through *anti*-Markovnikov Wacker oxidation[11] and copper-catalyzed allylic substitution.[12] The allyl alcohol **2** could, in turn, be prepared through 2-propanol-mediated reductive coupling of allyl acetate with tiglic aldehyde **1**.[13] The *α,β*-stereogenic chiral aldehyde **12** is prepared through hydrogen-mediated reductive coupling of acetylene[14] with "Roche-type" aldehyde **9**. On the basis of this plan, Fragment A, which incorporates six stereogenic structural features, is accessible in seven steps (LLS).

The synthesis of allylsilane **6** begins with the 2-propanol-mediated reductive coupling of allyl acetate with tiglic aldehyde **1** (Scheme 1).[13] This reaction was conducted on 40 mmol scale using the iridium catalyst modified by (*S*)-BINAP at roughly 1 mol % loadings. The secondary homoallylic alcohol **2** was obtained in 78% yield in highly enantiomerically enriched form (92% ee). The cyclometalated *π*-allyliridium *C,O*-benzoate catalyst, which was generated in situ from its components, was recovered from the reaction mixture in 39% yield. Using 1 mol % of the recovered catalyst, tiglic aldehyde **1** was converted to allyl alcohol **2** on 10 mmol scale in 73% yield with comparable levels of enantioselectivity (93% ee). Benzoylation of **2** followed by *anti*-Markovnikov Wacker oxidation of the terminal olefin in the presence of the allylic benzoate provided the

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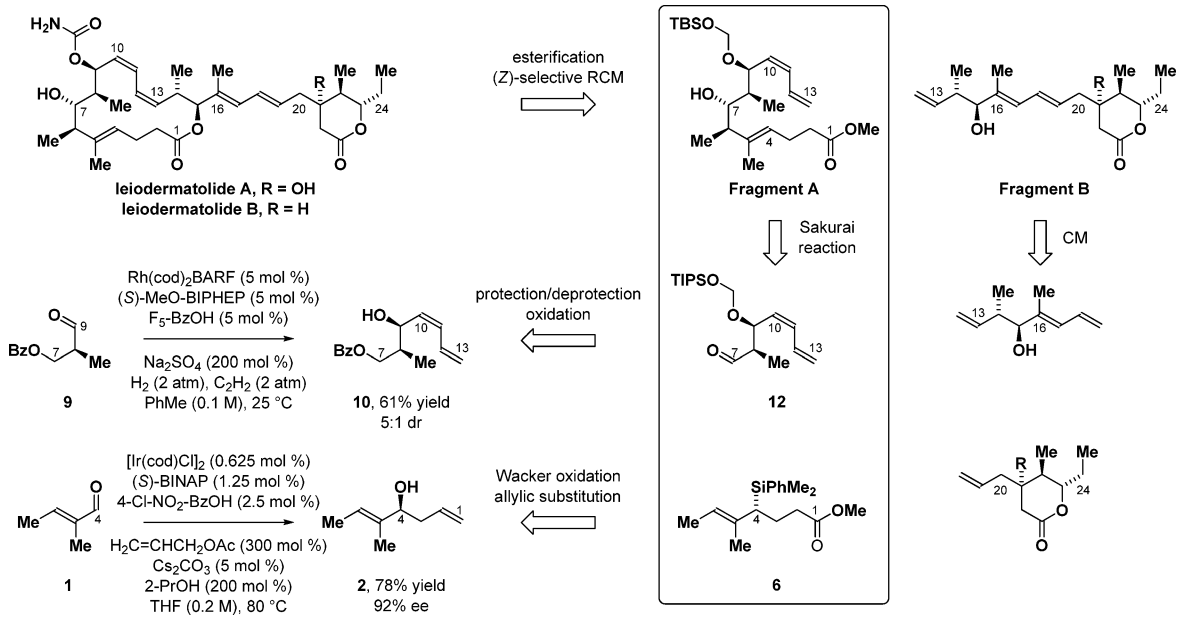
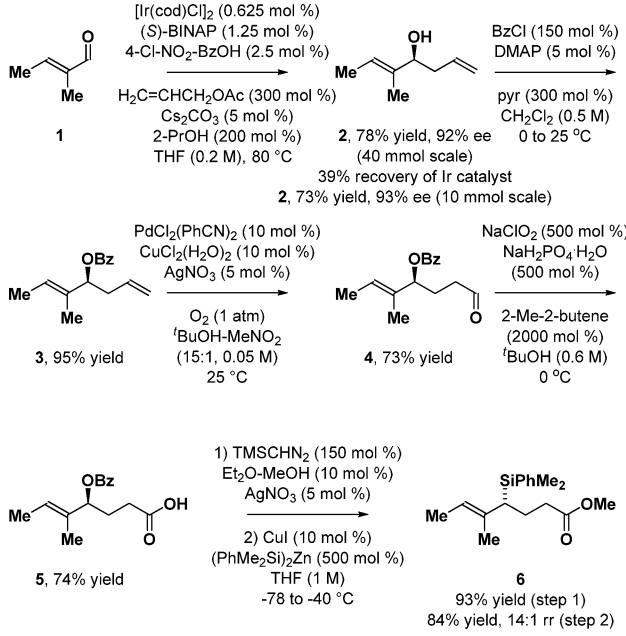


Figure 1. Retrosynthetic analysis of leiodermatolides A and B highlighting construction of the C(1)−C(13) fragment via hydrogenative and transfer-hydrogenative reductive coupling.

Scheme 1. Enantioselective Synthesis of Allylsilane 6 via 2-Propanol-Mediated Reductive Coupling of Allyl Acetate with Tiglic Aldehyde 1.[a]

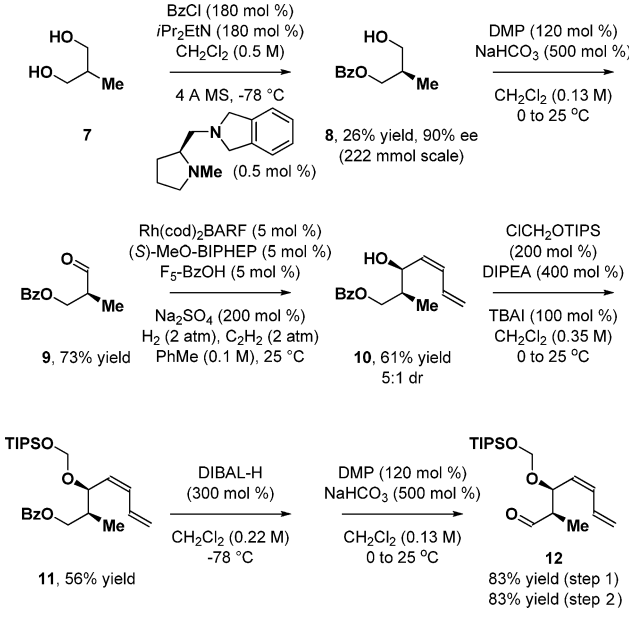


[a]Yields are of material isolated by silica gel chromatography. Enantioselectivity was determined by chiral stationary phase HPLC analysis. See the Supporting Information for further experimental details.

aldehyde **4**. Pinnick oxidation[15] delivered carboxylic acid **5**, which upon treatment with TMS-diazomethane[16] provided the corresponding methyl ester. Initial attempts to convert the allylic benzoate (**5**-methyl ester) to the allylsilane **6** under Fleming's conditions, which utilize the cuprate generated from stoichiometric quantities of silyl lithium reagent, cuprous cyanide, and triphenylphosphine,[12a] provided allylsilane **6** in modest yields and regioselectivities. Fortunately, Oestereich's related copper-catalyzed allylic substitution using silylzinc reagents provided superior yields and regioselectivities, enabling formation of allylsilane **6** in 84% yield as a 14:1 mixture of regioisomers.[12b]

Construction of α,β-stereogenic chiral aldehyde **12** begins with enantioselective benzoylation of diol **7** (Scheme 2).[17] Although the yield in this reaction was modest, exceptionally low loadings of the easily prepared diamine catalyst[18] were

Scheme 2. Enantioselective Synthesis of α,β-Stereogenic Chiral Aldehyde 12 via Hydrogen-Mediated Reductive Coupling of Acetylene with "Roche-Type" Aldehyde 9[a]



[a]Yields are of material isolated by silica gel chromatography. Enantioselectivity was determined by chiral stationary-phase HPLC analysis. See the Supporting Information for further experimental details.

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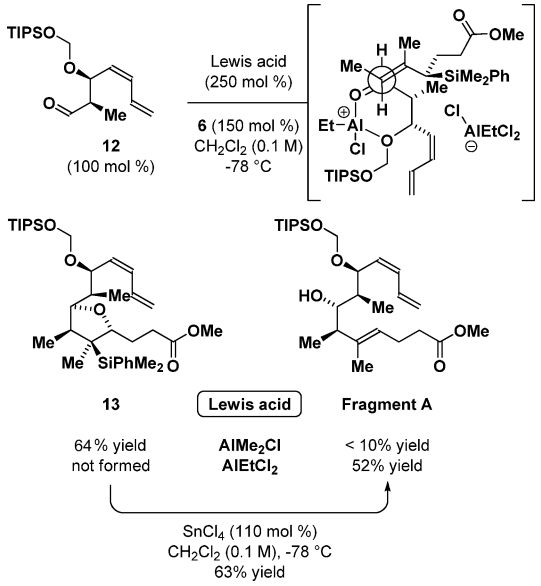
required (0.5 mol %). Dess–Martin oxidation of the resulting alcohol provided the "Roche-type" aldehyde **9**.[19] The hydrogen mediated reductive coupling of acetylene[14] to aldehyde **9** was quite challenging due to branching at the α-position and the relatively remote location of the σ-inductive benzoyloxy moiety. Eventually, using a cationic rhodium catalyst modified by the Roche ligand,[20] conditions were identified that enabled formation of the (*Z*)-butadienylated adduct **10** in 61% yield as a 5:1 mixture of diastereomers. Protection of the allylic hydroxyl as the TOM ether ($^{i}Pr_3SiOCH_2$)[21] followed by reductive removal of the benzoate and Dess–Martin oxidation provided the α,β-stereogenic chiral aldehyde **12**.

The diastereoselective Sakurai reaction of allylsilane **6** and α,β-stereogenic chiral aldehyde **12** was initially explored under conditions reported by Panek (Scheme 3).[10] Standard

Scheme 3. Sakurai Reaction of Allylsilane 6 and Aldehyde 12 To Assemble Fragment A, Which Incorporates C(1)–C(13) of Leiodermatolides A and B[a]



[a]Yields are of material isolated by silica gel chromatography. See the Supporting Information for further experimental details.

conditions using $TiCl_4$ resulted in decomposition, as did certain other Lewis acids (e.g., $SnCl_4$, $MgBr_2{\cdot}OEt_2$). More promising results were obtained using $AlMe_2Cl$ (250 mol %), which led to the formation of the silyl-substituted furan **13** as a single diastereomer as determined by ^{1}H NMR. Although furan **13** could be converted to Fragment A in 63% yield upon treatment with $SnCl_4$, direct access was preferred. It was reasoned that a more "chloride rich" reaction medium might enable elimination rather than migration of the silicon-stabilized cation that forms transiently upon addition. Indeed, using $AlEtCl_2$ (250 mol %), the desired Sakurai addition product Fragment A was obtained in 52% yield. Judicious selection of the TOM protecting group provided Cram-chelate control while enabling mild deprotection in subsequent steps.[21]

In summary, we report the preparation of the C(1)–C(13) fragment of the antimitotic marine macrolide leiodermatolide in seven steps (LLS) using hydrogenative and transfer hydrogenative reductive C–C couplings. Beyond defining more concise routes to the leiodermatolides and their structural analogues, the present study has several broader impacts. The merger of our asymmetric allylation method with Oestereich's protocol[12b] for regio- and stereospecific formation of allylsilanes should broaden access to chiral reagents of this type. Additionally, the generality of the hydrogen-mediated reductive coupling of acetylene with carbonyl compounds to form enantiomerically enriched (*Z*)-butadienyl alcohols is demonstrated. Future work will be devoted to the discovery and development of related hydrogen-mediated reductive couplings and their application to target oriented synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03351.

Spectral data for all new compounds (^{1}H NMR, ^{13}C NMR, IR, HRMS) (PDF)

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Notes

The authors declare no competing financial interest.

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