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Communication

Total Synthesis of Leiodermatolide A via Transfer Hydrogenative Allylation, Crotylation, and Propargylation: Polyketide Construction beyond Discrete Allyl- or Allenylmetal Reagents

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ABSTRACT: The total synthesis of leiodermatolide A was accomplished in 13 steps (LLS). Transfer hydrogenative variants of three carbonyl additions that traditionally rely on premetalated reagents (allylation, crotylation, and propargylation) are deployed together in one total synthesis.

Natural products that disrupt microtubule dynamics have found broad use as anticancer agents.[1] Leiodermatolide A is an antimitotic marine macrolide that was isolated in 2008 from crude extracts of a deep sea lithistid sponge of the genus *Leiodermatium* found off the Florida coast (Figure 1).[2] In a panel of human cancer cell lines, leiodermatolide A exhibited potent antiproliferative effects, selectively perturbing tubulin dynamics at nM concentrations through a novel mechanism: while incurring abnormal spindle formation at nM concentrations in two different cancer cell lines, purified tubulin remained undisturbed in vitro even at much higher concentrations.[2,3] The scarce supply and compelling biology of leiodermatolide A has driven efforts toward its de novo chemical synthesis, resulting in truly impressive total syntheses by Paterson[4] and Fürstner[5] and substructure syntheses by Maier.[6] The synthesis of leiodermatolide analogues[5b,c,6d] have led to additional biological data that reveal mitotic arrest, micronucleus induction, centrosome amplification, and tubulin disruption in human U2OS cells without evidence for direct binding of tubulin in cell-free analyses.[5b] On the basis of these data, centrosome declustering was suggested as a possible mechanism of action.[7] Further investigations into leiodermatolide's unique biology have been prohibited due to lack of material.

The issues surrounding leiodermatolide A are emblematic of the persistent challenges associated with the construction of structurally complex secondary metabolites that continue to evoke innovation across the field of chemical synthesis. In the specific context of type I polyketides, which are ubiquitous in human medicine,[8] commercial manufacturing routes rarely exploit de novo chemical synthesis, highlighting the need for more efficient and process-relevant synthetic methods. Inspired by the broad use of hydrogenation and transfer hydrogenation in the production of clinical candidates, we have advanced a suite of catalytic enantioselective carbonyl reductive couplings based on alcohol mediated hydrogen transfer.[9,10] Using these methods, an initial (but unsuccessful) campaign toward leiodermatolide A was undertaken.[11] Here, we disclose a more fruitful approach employing catalytic enantioselective

Leiodermatolide A Total Syntheses	LLS (TS)	Skeletal Assembly	Redox Reactions	Protection-Deprotection	Other Reactions
Paterson (ref. 4)	25 (50)	7 (28%)	5 (20%)	9 (36%)	4 (16%)
Fürstner (ref. 5)	19 (47)	9 (47%)	3 (16%)	5 (26%)	2 (11%)
Krische (*This Work*)	13 (38)	8 (62%)	2 (15%)	1 (8%)	2 (15%)

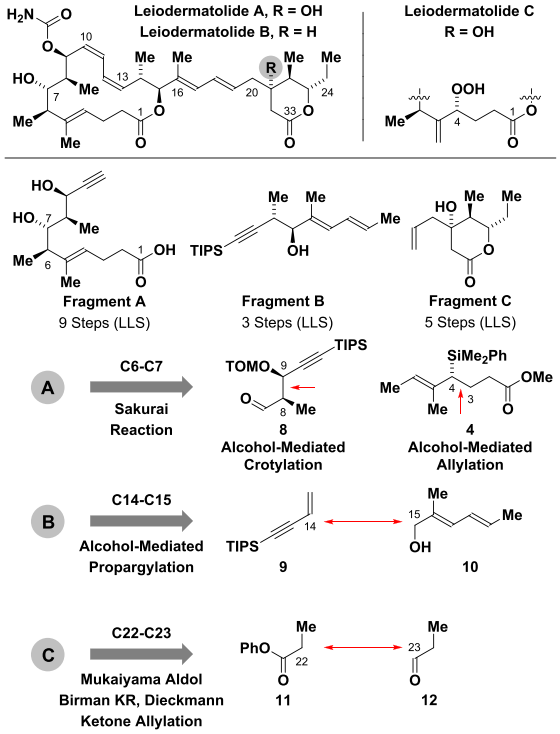

Figure 1. Structures of leiodermatolides A−C, prior total syntheses, and retrosynthetic analysis. Longest linear sequence (LLS); total steps (TS).

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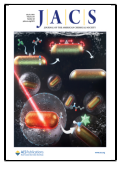

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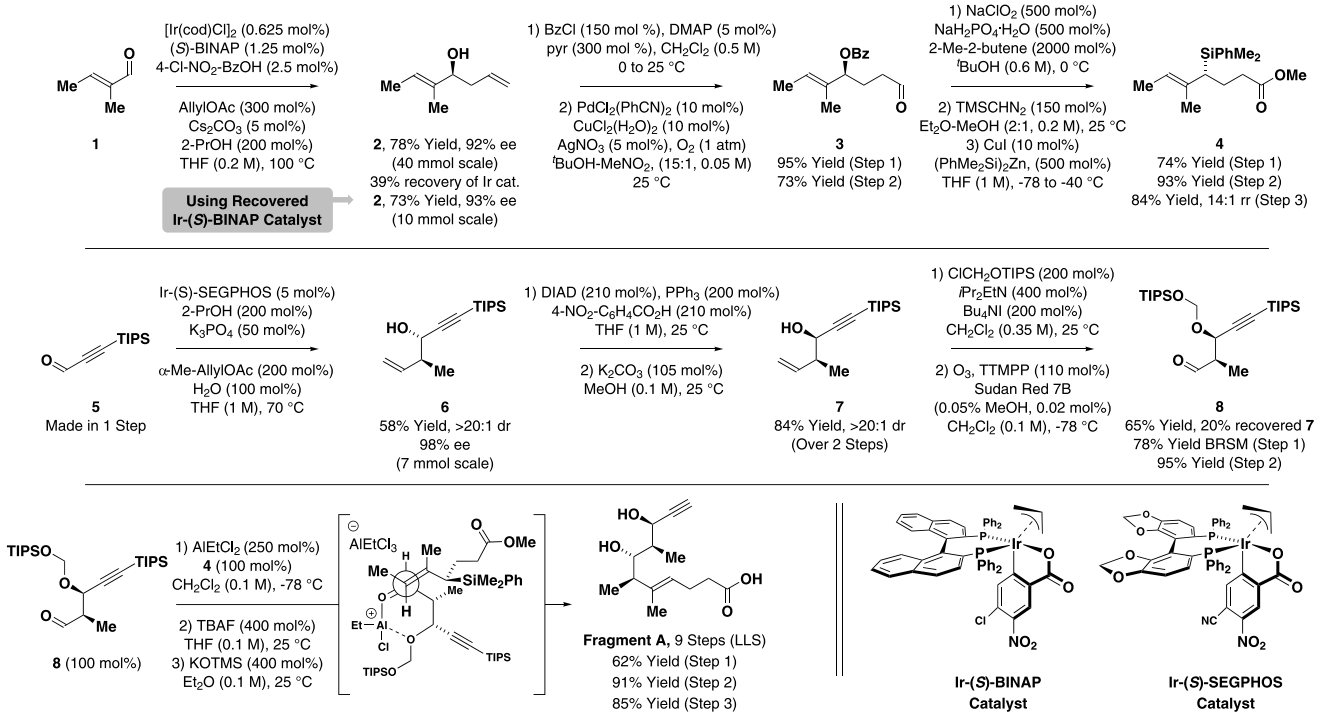
Scheme 1. Preparation of Fragment A via Catalytic Enantioselective Transfer Hydrogenative Carbonyl Allylation and Crotylation[a]



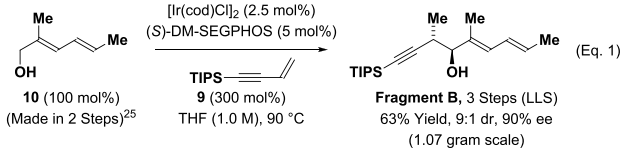
[a]Yields are of material isolated by silica gel chromatography. Diastereoselectivities were determined by ^{1}H NMR of crude reaction mixtures. Enantioselectivities were determined by chiral stationary phase HPLC analysis. TTMPP = Tris(2,4,6-trimethoxyphenyl)phosphine. See Supporting Information for experimental details.

transfer hydrogenative allylation,[12a,b] crotylation,[12c−e] and propargylation[12f,13] that has resulted in a 13 step longest linear sequence (LLS) total synthesis of leiodermatolide A, constituting the most concise route to this compound reported, to date.

Retrosynthetically, leiodermatolide A was envisioned to arise through a polyconvergent assembly of Fragments **A**, **B**, and **C** (Figure 1). Fragment **A** is accessible through the Hosomi−Sakurai reaction[14] of aldehyde **8** (prepared by catalytic enantioselective transfer hydrogenative crotylation of acetylentic aldehyde **5**),[12e] with allylsilane **4** (prepared by enantioselective transfer hydrogenative allylation of tiglic aldehyde **1**).[11,12a−c] Fragment **B** is generated via transfer hydrogenative carbonyl propargylation employing an enyne pronucleophile.[12f,13] Finally, Fragment **C** is prepared by Mukaiyama aldol reaction of phenyl acrylate **11** with propanal **12** to give the *anti*-aldol[15,16] followed by kinetic resolution via asymmetric acetylation using Birman's catalyst,[17] and then Dieckmann condensation-ketone allylboration.[5b,18]

The synthesis of Fragment **A** begins with the conversion of tiglic aldehyde **1** to allyl silane **4** (Scheme 1).[11] Using 1.25 mol % loadings of the π-allyliridium-*C*,*O*-benzoate modified by (*S*)-BINAP, 2-propanol-mediated reductive coupling of tiglic aldehyde **1** with allyl acetate delivers the homoallylic alcohol **2** in 78% yield and 92% ee.[12a,b] As shown, the chromatographically stable iridium catalyst could be recovered in 39% yield and recycled without erosion in performance. Conversion of alcohol **2** to aldehyde **3** is achieved via benzoylation of secondary alcohol followed by chemoselective *anti*-Markovnikov Wacker oxidation[19] of the less substituted olefin. Aldehyde **3** is transformed to allyl silane **4** via Pinnick oxidation,[20] treatment of the resulting carboxylic acid with TMS-diazomethane,[21] and silylzinc-mediated regio- and stereospecific copper-catalyzed allylic substitution, as described by Oestereich.[22] Aldehyde **8** is prepared through transfer hydrogenative crotylation of acetylenic aldehyde **5**[12c−e] followed by Mitsunobu inversion-saponification[23] to furnish 1,5-enyne **7**. Conversion of **7** to the TOM ether (^{i}Pr$_3$SiOCH$_2$)[24] followed by ozonolysis delivers aldehyde **8**. With allyl silane **4** and aldehyde **8** in hand, Hosomi−Sakurai reaction[14] was attempted. Upon evaluation of different Lewis acids,[11] it was found that chelation-controlled addition could be achieved in 62% yield using AlEtCl$_2$ (250 mol%). Exhaustive deprotection of the Hosomi−Sakurai product delivers Fragment **A**.

Fragment **B** is prepared via iridium-catalyzed enyne-mediated propargylation of dienol **10** (eq 1),[12f,13] which is a known compound accessible in 2 steps from crotonaldehyde.[25]



The reported method for propargylation utilized an enyne substituted by (TIPSO)Me$_2$C. However, it was anticipated that the δ-lactone of leiodermatolide A would not tolerate conditions required for deprotection of this group (which involves base-mediated elimination of acetone). Hence, the indicated triisopropylsilyl terminated enyne **9** was used and, to our delight, good levels of diastereo- and enantioselectivity were observed.

The synthesis of Fragment **C**, which incorporates the δ-lactone of leiodermatolide A, is accomplished in 5 steps (Scheme 2). The δ-lactone of leiodermatolide A was previously

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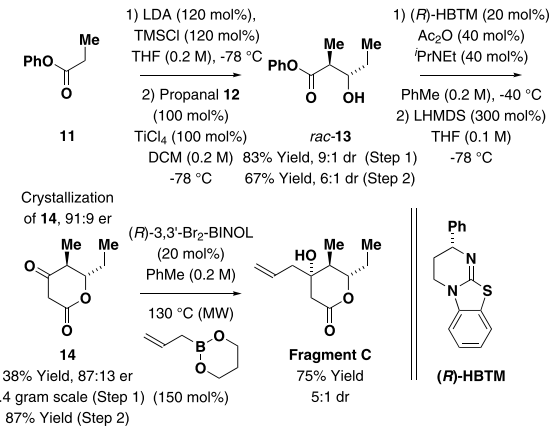
Scheme 2. Preparation of Fragment C via Kinetic Resolution of *anti*-Aldol 13 Using Birman's Catalyst[a]

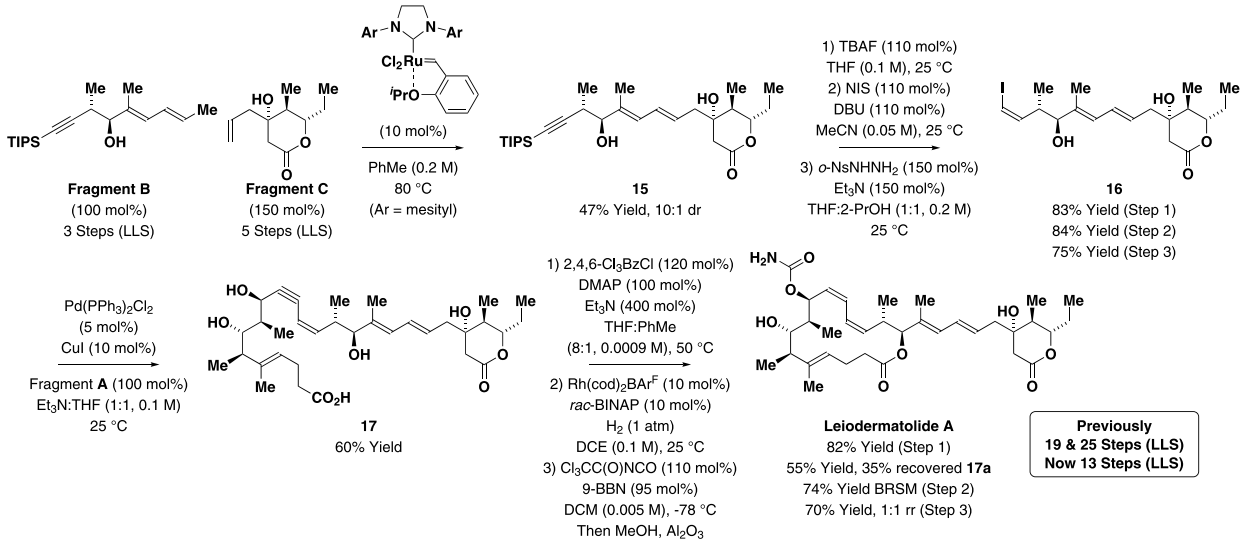


[a]Diastereoselectivities were determined by ^{1}H NMR of crude reaction mixtures. Enantioselectivities were determined by chiral stationary phase HPLC analysis.

prepared by Fürstner using a chiral enolate modified by Evan's auxiliary.[5] Direct catalytic enantioselective aldol addition of a propionate ester such as **11** with propanal **12** would avoid manipulations associated with the preparation, installation, and removal of an auxiliary, yet aldol additions of this type remain an unmet challenge. Kinetic resolution of the racemic aldol *rac*-**13**, which is accessible via *anti*-diastereoselective Mukaiyama aldol addition,[15,16] was deemed an attractive alternative, as the resulting acetate could be directly subjected to Dieckmann condensation to deliver the cyclic *β*-ketoester **14**. Using Birman's catalyst,[17] (*R*)-HBTM, formation of the acetate was realized with useful levels of selectivity and, therefrom, enantiomerically enriched *β*-ketoester **14** was made. BINOL-catalyzed allylboration of *β*-ketoester **14**[5b,18] completes the synthesis of Fragment **C**. Upon use of racemic BINOL as catalyst, a 1:3 diastereomeric ratio was observed in favor of the opposite stereoisomer, indicating that the asymmetric allylation used to form Fragment **C** represents the mismatched case.

With Fragments **A**, **B** and **C** in hand, the total synthesis of leiodermatolide A was undertaken (Scheme 3). The union of Fragment **B** and **C** is achieved via cross-metathesis using the second generation Hoveyda–Grubbs catalyst. The alkyne moiety present in Fragment **B** made this transformation challenging, yet dienyne **15** could be formed in 47% yield along with a dimer derived from Fragment **C** (that could be subjected to cross-metathesis with Fragment **B** to provide **15** in comparable yield). Conversion of **15** to the *cis*-vinyl iodide **16** was accomplished in a three step sequence involving silyl-deprotection of the TIPS alkyne, NIS-mediated iodination of the resulting terminal alkyne,[26] and diimide reduction of the acetylenic iodide to the *cis*-vinyl iodide **16** using NBSH.[27] Sonogashira coupling of equimolar quantities of *cis*-vinyl iodide **16** and Fragment **A** occurred in the presence of the free carboxylic acid[28] to deliver the conjugated enyne **17** in 60% yield. Yamaguchi lactonization[29] of compound **17** occurred in remarkably high yield despite the presence of multiple unprotected hydroxyl groups. Several methods for semi-hydrogenation of the macrocyclic enyne were explored, including Zn(Cu/Ag) amalgam as described by Fürstner.[4] In our hands, these methods were problematic due to over-reduction accompanied by isomerization of the initially formed *cis*,*cis*-diene. We eventually found that semihydrogenation using a cationic rhodium catalyst provided the most reliable results.[30,31] It should be noted that our *cis*,*cis*-diene is identical with material prepared by Paterson, who found that treatment of the C7,C9-diol with $Cl_3CC(O)NCO$ resulted in a 4:1 ratio of the C7 and C9 carbamates (favoring the undesired isomer).[5] In a model system, we found the regioselectivity of carbamoylation could be inverted upon pretreatment with 9-BBN (eq 2).[32] This effect was less pronounced in the carbamoylation en route to leiodermatolide A, but still availed an improvement relative to the intrinsic bias of the system, enabling access to leiodermatolide A in 13 steps (LLS)—the most concise synthesis of leiodermatolide A reported, to date.

Scheme 3. Union of Fragments A, B, and C and Total Synthesis of Leiodermatolide A[a]



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

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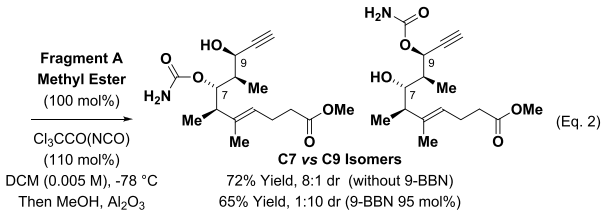

To conclude, the synthetic challenges posed by the structural complexity of polyketide natural products have evoked numerous advances in acyclic stereocontrol, especially in the context of carbonyl addition. Whereas the initial lexicon of asymmetric methods that emerged focused on the use of premetalated *C*-nucleophiles and chiral auxiliaries, we aim to advance a suite of catalytic enantioselective C−C couplings that bypass discrete organometallic reagents and stoichiometric chiral inducing elements. The present total synthesis of leiodermatolide A, which exploits asymmetric alcohol-mediated allylation, crotylation, and propargylation, exemplifies how time-honored transformations that have traditionally relied on premetalated reagents can now be conducted catalytically from tractable π-unsaturated pronucleophiles.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c06062.

Graphical summaries of prior total syntheses, experimental procedures, and spectral data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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