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Protecting-Group-Free Total Synthesis of (−)-Jiadifenolide: Development of a [4 + 1] Annulation toward Multisubstituted Tetrahydrofurans

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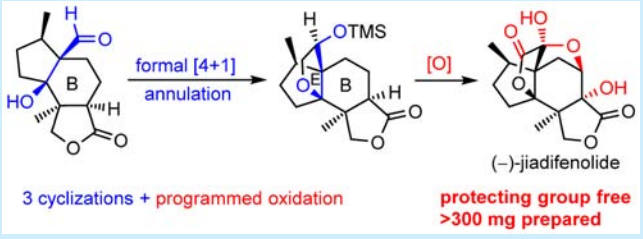
Supporting Information

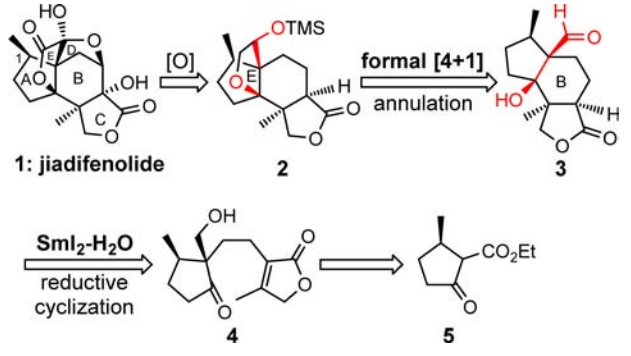
ABSTRACT: A concise, protecting-group-free total synthesis of (−)-jiadifenolide, a synthetically challenging *seco*-prezizaane sesquiterpene with potent neurotrophic activity, is reported. The convergent route features a SmI_2/H_2O-mediated stereoselective reductive cyclization, an unprecedented formal [4 + 1] annulative tetrahydrofuran-forming reaction and programmed redox manipulations. The newly developed annulation of β-hydroxy aldehydes or ketones with lithium trimethylsilyldiazomethane provides access to a diverse array of multisubstituted tetrahydrofurans. The synthetic jiadifenolide exhibited weak cytotoxicity against five human cancer cell lines.



Terpenes exhibit a broad range of biological activities and have been widely used in medicine and other industries.[1] Chemically, they often provide opportunities for the discovery and invention of new ring-forming reactions in organic synthesis.[2] The genus *Illicium* is a rich source for chemically and biologically intriguing secondary metabolites, especially sesquiterpenes.[3] Many of them have attracted considerable attention from chemists and biologists.[4]

(−)-Jiadifenolide (**1**, Scheme 1) is a complex sesquiterpene isolated in 0.0009% yield from the dried pericarps of *Illicium jiadifengpi* by Fukuyama and co-workers in 2009.[5] It displayed prominent neurotrophic activity at low concentration (10 nM), which renders it a promising lead compound for developing therapeutics for neurodegenerative diseases.[6] Structurally, jiadifenolide features a highly oxygenated cagelike architecture with seven contiguous stereocenters, in particular, a highly congested cyclohexane (B ring) containing four quaternary stereocenters. Notably, the diverse oxygenation patterns of **1**, such as α-hydroxy lactone and α-hemiketal lactone, posed considerable challenges for the differentiation of functional groups in chemical synthesis, and thus, protecting-group manipulations seemed inevitable. Its fascinating structure and potential therapeutic value have attracted extensive synthetic interest, thus resulting in four elegant total syntheses of jiadifenolide by Theodorakis (25 steps),[7] Sorensen (18 steps),[8] and Paterson (23 steps)[9] and very recently by Shenvi (eight steps).[10] Although preliminary evaluations of neurotrophic activity have been carried out by the groups of Fukuyama[5] and Theodorakis,[11] full biological profiling of jiadifenolide, which is indispensable for its development toward a therapeutic agent, is still pending. Herein, we describe a concise, protecting-group-free total synthesis[12] of (−)-jiadifenolide. Furthermore, we also present a case study in which the total synthesis of complex natural products directly drives the discovery and development of a new formal [4 + 1] annulation toward tetrahydrofurans.

Scheme 1. Retrosynthetic Strategy toward Jiadifenolide (1)



Cyclization and oxidation are extensively studied topics in terpenoid synthesis,[13] and the deliberate arrangement of these two kinds of manipulations could dramatically enhance the efficiency of synthesis. As outlined in Scheme 1, we envisaged that the pentacyclic skeleton of **1** could be assembled via three diastereoselctive cyclizations from the known β-keto ester **5**:[14] a sequence of oxidations followed by hemiketalization to form

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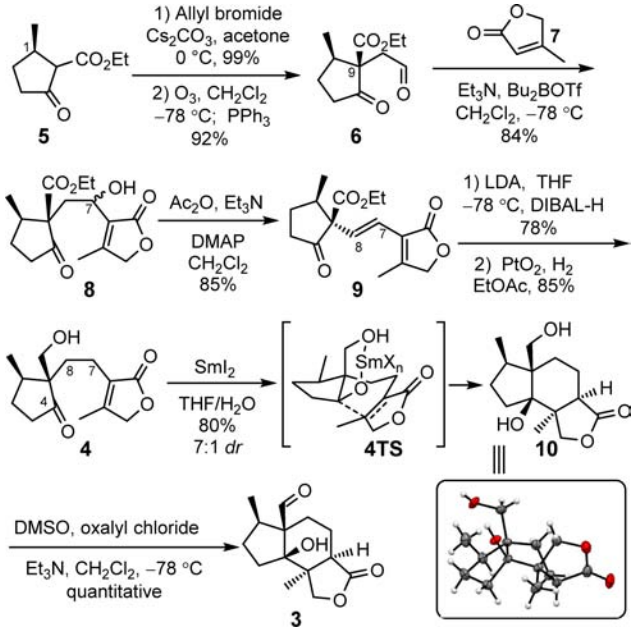
the D ring (**2** → **1**), formal [4 + 1] annulation to generate the tetrahydrofuran E ring (**3** → **2**), and reductive cyclization mediated by samarium diiodide and water to create the central B ring (**4** → **3**). We also anticipated that programmed redox manipulations would install the requisite oxygen-containing functional groups and enable an "economic"[15] and protecting-group-free total synthesis of sesquiterpene **1**.

As depicted in Scheme 2, our synthesis commenced with diastereoselective allylation of the known β-keto ester **5**, which

Scheme 2. Synthesis of Intermediate 3



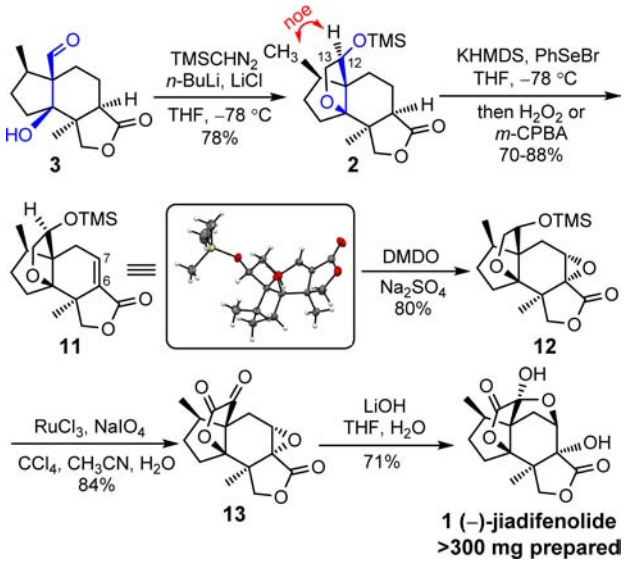
could be prepared in large scale from (*R*)-(+)-pulegone in a modified two-step procedure (see the Supporting Information). Subsequent ozonolytic cleavage of the resulting terminal double bond afforded aldehyde **6** in 91% yield. Selective aldol addition between the aldehyde group of **6** and a boron furanolate[16] generated in situ from butenolide **7** provided Baylis–Hillman-type adducts **8** as a mixture of inseparable diastereomers, which underwent dehydration via an acetylation–elimination cascade to deliver diene **9** with an overall yield of 71%. To circumvent the utilization of protecting groups and achieve chemoselectivities between the oxygenated functional groups, we designed a group of programmed reduction manipulations. First, a selective reduction of the hindered ester group of **9** in the presence of a ketone and an unsaturated lactone functions was achieved by in situ conversions of the ketone and lactone to enolates[17] by treatment with LDA prior to the introduction of DIBAL-H. Subsequently, a hydroxy-directed selective hydrogenation[18] of disubstituted double bond (C7–C8) in the resulted dienol was achieved by Adam's catalyst under a H_2 atmosphere (1 atm),[19] providing **4** in 85% yield.

At this stage, we turned our attention to the construction of the central, highly substituted B ring via a SmI_2-mediated reductive cyclization.[20] In Paterson's pioneering work,[9] a similar strategy was also conceived to close the B ring. However, due to low diastereoselectivity in the aldol reaction and moderate yield of the SmI_2-mediated reductive cyclization, the overall efficiency of this key transformation was not satisfactory. After extensive studies of this key transformation over a series of substrates (for details, see Supporting Information), we finally chose compound **5** as the cyclization precursor. Our initial attempts with traditional conditions (such as SmI_2 in THF, SmI_2/LiCl/*t*-BuOH in THF) only resulted in ketone-reduction products. Enlightened by Flowers'[21] and Procter's findings,[22] we decided to use H_2O to modulate the redox potential of SmI_2 and stabilize the possible radical intermediate. To our delight, with a large amount of H_2O (7000 equiv) as cosolvent, treatment of **4** with 2.2 equiv of SmI_2 provided the desired tricycle **10** in 70% yield. The relative stereochemistry of diol **10** was confirmed by X-ray crystallography. The stereochemical outcome of this transformation can be rationalized as the result of ketyl radical addition to unsaturated lactone via a chelated chair/twist boat conformation shown as **4TS** (Scheme 2). Subsequent Swern oxidation smoothly delivered β-hydroxy aldehyde **3** in quantitative yield.

Serendipitous discoveries have led to many new reactions and thus inspired new approaches to natural products.[23] Initially, we planned to access the E ring via a terminal alkyne, which was supposed to be obtained from aldehyde **3** by treatment with lithium trimethylsilyldiazomethane (TMSC(Li)N_2).[24] However, a novel formal [4 + 1] annulative tetrahydrofuran-forming reaction[25] was discovered that dramatically expedited the synthetic journey (see the Supporting Information for the condition optimization and see below for further investigation of this novel reaction). Specifically, with LiCl as an additive, reaction of β-hydroxy aldehyde **3** with TMSC(Li)N_2 at −78 °C afforded 3-trimethylsiloxy furanoid **2** via a cascade process in 78% yield as a single diastereomer. It should be noted that the reaction temperature was critical. When the reaction mixture was warmed to 0 °C before being quenched with saturated $NaHCO_3$ solution, the only identified product was dihydrofuran species (see the Supporting Information). The configuration of the newly built stereocenter (C12) in **2** was assigned by NOE NMR spectroscopic studies and further confirmed by the X-ray crystal structure of a later intermediate **11** (Scheme 3).

With tetracycle **2** in hand, our efforts were then focused on the incorporation of oxygen-containing functions. A program of oxidation manipulations finalized the actual oxidation state of jiadifenolide (Scheme 3). Dehydrogenation at C6–C7 via a

Scheme 3. Completion of Total Synthesis



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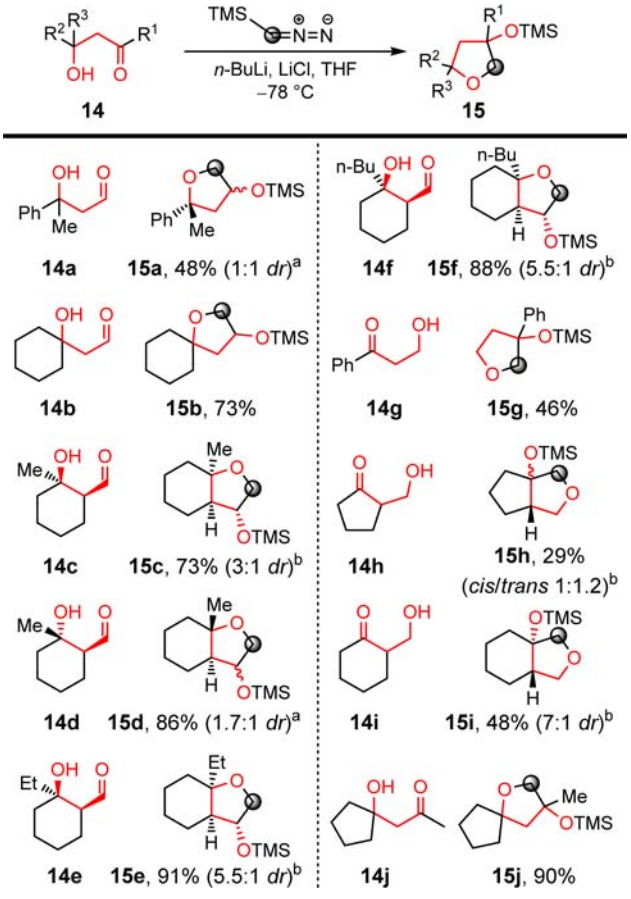
one-pot phenylselenation and oxidative elimination furnished unsaturated lactone **11**, which was further converted to epoxide **12** with DMDO. 3-Trimethylsiloxy furanoid **12** was oxidized under Sharpless conditions,[26] probably via a 3-furanone intermediate to the α-keto lactone **13**, which possesses the same oxidation level as that of the natural product.

Finally, a cascade reaction triggered by LiOH[8,27] afforded (−)-jiadifenolide (**1**) in 71% yield, and more than 300 mg of the final product was obtained. The synthetic sample exhibited spectroscopic properties identical with those reported for the natural product.[5,28] The absolute stereochemistry of **1** was confirmed by an X-ray crystal structure in conjunction with the absolute stereochemistry of C1 inherited from (*R*)-(+)-pulegone.

Encouraged by the success of the new formal [4 + 1] annulation in the total synthesis, we next investigated the generality of this reaction (Scheme 4). By treatment with

Scheme 4. Examination of Substrate Scope of the Formal [4 + 1] Annulation

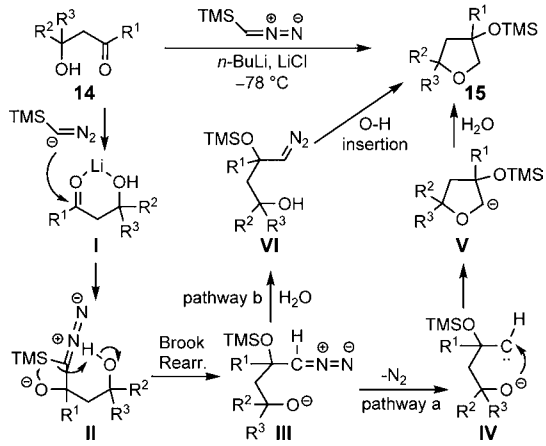


[a]The relative stereochemistry of the products was not determined. [b]The relative stereochemistry of the products was determined by NOE NMR spectroscopic studies and the analogy.

$TMSC(Li)N_2$ at −78 °C, a collection of β-hydroxy aldehydes (**14a−f**) were smoothly converted to the corresponding tetrahydrofuran derivatives (**15a−f**) in moderate to high yield, featuring monocyclic, spirocyclic, and fused ring systems. To our delight, this method was also viable to more challenging β-hydroxy ketone substrates, and a set of β-hydroxy ketones (**14g−j**) was transformed to complex furanoids (**15g−j**) in moderate to good yield. To our surprise, when β-hydroxy ketone **14h** was treated by $TMSC(Li)N_2$, not only the cis-fused tetrahydrofuran (*cis*-**15h**) but also the unusual trans-fused[29] diastereomer with high ring string (*trans*-**15h**) was obtained (29% yield, *cis*/*trans* = 1:1.2). Thus, we provided a highly effective approach for the construction of multisubstituted tetrahydrofurans from readily available β-hydroxy aldehyde or ketone. Furthermore, current transformation could also serve as a stepstone for the preparation of α-keto lactones (e.g., **12** → **13**).

As outlined in Scheme 5, a possible mechanism for the novel formal [4 + 1] annulation toward tetrahydrofurans is proposed.

Scheme 5. Proposed Mechanism for the Formal [4 + 1] Annulation



The nucleophilic addition of $TMSC(Li)N_2$ to the aldehyde/ketone **14** with the help of lithium ion complexation afforded adduct **II**, which usually decomposed to a terminal alkyne when elevating the reaction temperature.[24] However, a tandem Brook rearrangement[30] and 1,5-proton transfer occurred to give intermediate **III**. Decomposition of diazo compound **III** to carbene **IV** followed by addition of the alkoxide anion to carbene[31] afforded anion **V**, which was converted to trimethylsiloxy furanoid **15** by protonation (pathway a). We also cannot completely exclude that **15** could be partially obtained via a protonation and intramolecular carbene O−H insertion[32] sequence (pathway b). As a whole, the tetrahydrofuran was formed through a formal [4 + 1] annulation between an amphiphilic β-hydroxy aldehyde or ketone and a carbene precursor.

As a part of our project of biological evaluation of jiadifenolide and its analogues, the cytotoxicity of the synthetic jiadifenolide against five human cancer cell lines was evaluated. It was found that **1** only showed weak antitumor activities (IC^{50} > 100 μM) (see the Supporting Information).

In summary, a concise, protecting-group-free total synthesis of the complex neurotrophic sesquiterpene (−)-jiadifenolide has been accomplished in 13 steps with an overall yield of 7.9% from known compound **5** (15 steps from (*R*)-(+)-pulegone). A newly developed formal [4 + 1] annulative tetrahydrofuran-forming reaction guaranteed the synthetic efficiency. Furthermore, this novel method exhibited good feasibility for accessing a diverse array of multisubstituted tetrahydrofurans. We expect the reaction will find more use in the synthesis of natural products and pharmaceuticals. Further exploration of the novel annulation and biological evaluation of (−)-jiadifenolide are under way in our laboratory.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02845.

Experimental details and spectral data for all new compounds (^{1}H NMR, ^{13}C NMR, IR, and HRMS) (PDF)

X-ray data for compounds **10**, **11** and **1** (CIF)

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

This work is dedicated to Prof. Zhen Yang (Peking University).

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