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Enantioselective Total Synthesis of (+)-Jasplakinolide

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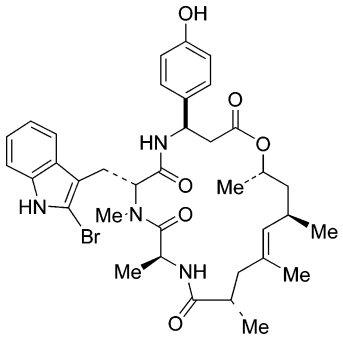
ABSTRACT



(+)-Jasplakinolide (1)

An enantioselective total synthesis of (+)-jasplakinolide is described. The synthesis of the polyketide template utilized a diastereoselective *syn*-aldol, ortho-ester Claisen rearrangement followed by efficient conversion to a cyanide. The *β*-amino acid unit was constructed in a highly diastereoselective manner utilizing nucleophilic addition to a chiral sulfinimine. Yamaguchi macrocyclization and removal of the protecting group provided a convenient access to (+)-jasplakinolide.

Jasplakinolide (**1**), a 19-membered cyclic depsipeptide, initially was isolated from the marine sponge *Jaspis splendens* in 1986.[1] It was later found in other marine sponges, including *Auletta* sp., *H. minor*, and *Cymbastela* sp.[2] Jasplakinolide exhibited a number of very interesting biological properties. It is active against 36 human solid tumor types in cell culture assays.[3] It has also exhibited other important biological properties, including insecticidal, antifungal, and antihelminthic activities.[4] The mechanism of action is known to involve stabilization of actin filaments by binding to F-actin similar to phalloidin.[5] Preclinical trials of jasplakinolide were carried out by the National Cancer Institute as an anti-actin agent. However, the study was terminated as it showed significant toxicity.[6] Jasplakinolide is often used as a molecular probe for actin polymerization studies. Its biological properties and structural features attracted attention for total synthesis[7] and structural modification.[8] We recently reported an enantioselective total synthesis of (−)-doliculide,

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another cyclic depsipeptide isolated from *Dolabella auricularia* by Ishiwata and co-workers.[9] Using synthetic doliculide, we established that it too arrests cell growth at the G_2/M phase of the cell cycle by interfering with normal actin assembly similar to jasplakinolide.[10] Doliculide exhibited no toxicity. Structural similarities of doliculide and jasplakinolide suggest that both compounds bind to the same site on F-actin. To investigate structure−activity studies of jasplakinolide, we sought an efficient synthesis of jasplakinolide for further structural modification. Herein we report an enantioselective total synthesis of (+)-jasplakinolide. The synthesis features asymmetric synthesis of 8-hydroxynonenoic acid **3** and (*R*)-*β*-tyrosine unit **4**.

Our convergent approach to jasplakinolide synthesis is shown in Figure 1. As shown, **1** is derived from hydroxyl

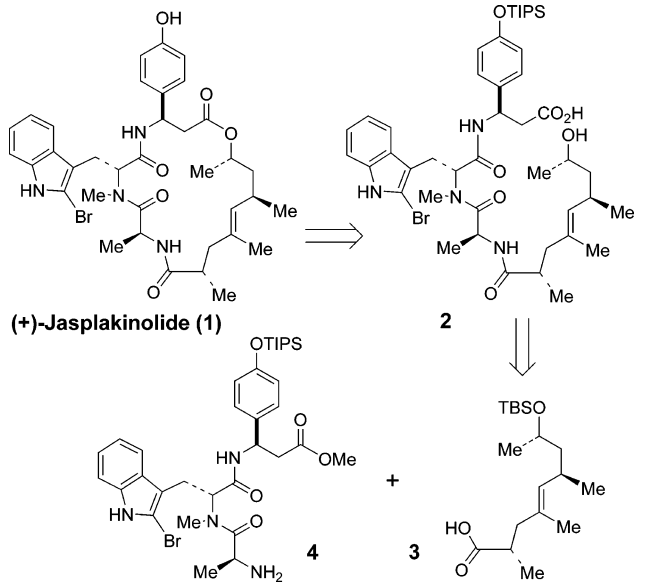
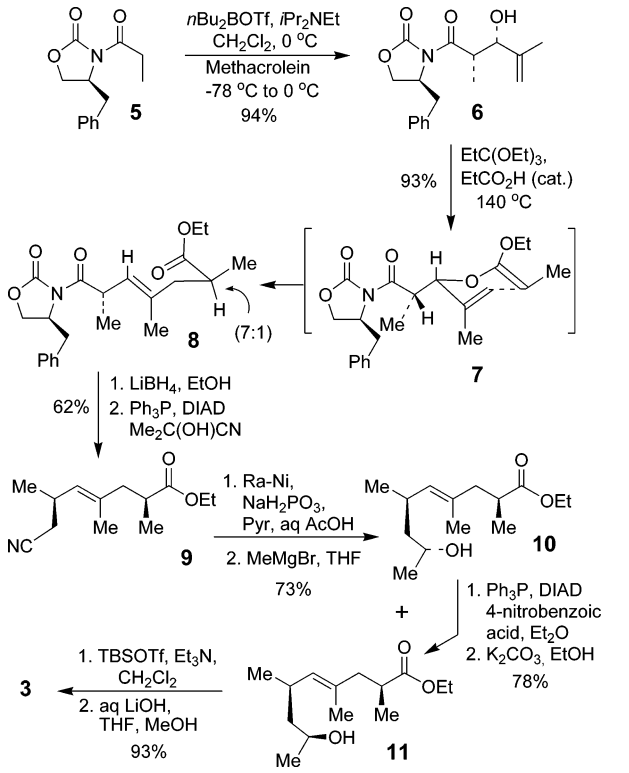


Figure 1. Retrosynthetic analysis of (+)-jasplakinolide.

acid **2** by a macrocyclization reaction. Macrocyclic precursor **2** would be obtained by coupling of the polypropionic acid segment **3** and tripeptide **4**. The tripeptide fragment is composed of amino acids, (*R*)-2-bromoabrine, (*R*)-*β*-tyrosine, and (*S*)-alanine.

The synthesis of protected 8-hydroxynonenoic acid **3** is shown in Scheme 1. Asymmetric aldol addition of the boron enolate derived from oxazolidinone **5** with methacrolein gave the aldol adduct **6** in 94% yield.[11] Allylic alcohol **6** was subjected to acid-catalyzed ortho ester Claisen rearrangement with triethyl orthopropionate at 140 °C for 1 h to afford *γ*,*δ*-unsaturated ester **8** in 93% yield as a mixture (7:1 by ^{1}H NMR) of diastereomers. This Claisen rearrangement protocol di-

Scheme 1. Synthesis of Carboxylic Acid **3**



astereoselectively introduced the α-methyl carbonyl functionality through 1,4-chirality transfer.[12] The Claisen rearrangement presumably proceeded through a chair-like transition state as shown in **7** that accounts for the observed diastereoselectivity as well as the *E*-olefin geometry in **8**. Ethyl ester **8** was converted to cyanide **9** by reduction with $LiBH_4$ and EtOH[13] followed by Mitsunobu reaction of the resulting alcohol using acetone cyanohydrin in the presence of diisopropyl azodicarboxylate and triphenylphosphine.[14] Nitrile **9** was obtained in 62% yield in a two-step sequence. Reduction of nitrile with Raney nickel in the presence of NaH_2PO_3, pyridine, and aqueous acetic acid provided the corresponding aldehyde.[15] Reaction of aldehyde with methylmagnesium bromide afforded diastereomeric alcohols **10** and **11** as a 1:1 mixture in 73% yield in two steps. The alcohols were separated by flash column chromatography over silica gel. Mitsunobu inversion[16] of (*R*)-alcohol **10** with Ph_3P and *p*-NO_2-benzoic acid in the presence of diisopropyl azodicarboxylate followed by ester hydrolysis of the resulting benzoate derivative with potassium carbonate in ethanol furnished the desired (*S*)-alcohol **11**. Protection of alcohol **11** with TBSOTf, Et_3N at 23 °C, and saponification with aqueous lithium hydroxide furnished 8-hydroxynonenoic acid **3** in 93% yield.

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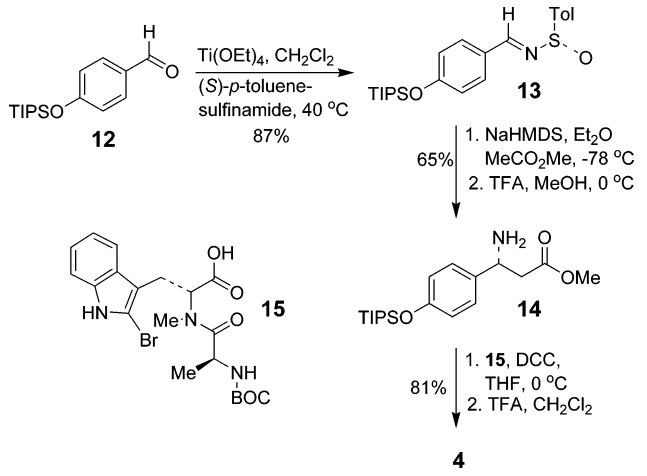
Diastereoselective synthesis of desired (*R*)-*β*-tyrosine derivative was achieved using an asymmetric protocol developed by Davis and co-workers,[17] as shown in Scheme 2. Aldehyde **12** was readily prepared by protection of

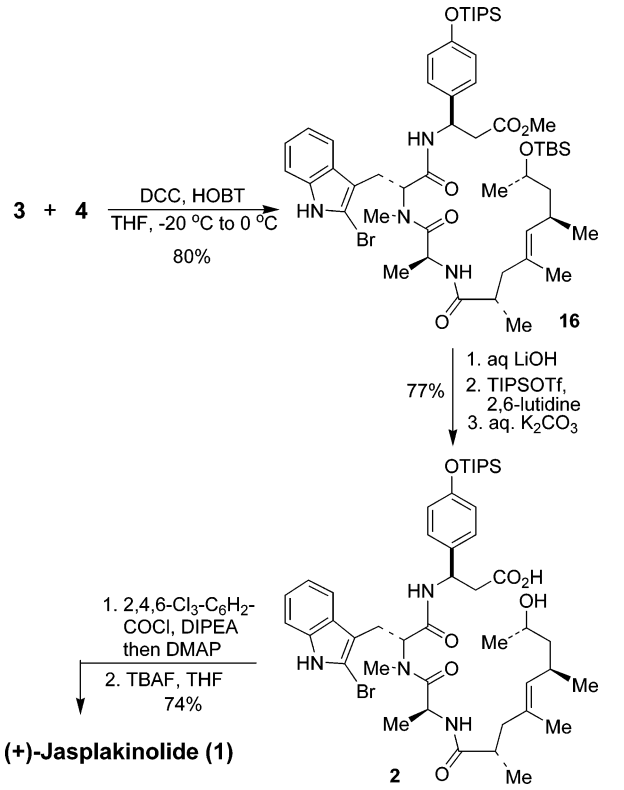
Scheme 2. Synthesis of *β*-Amino Acid Units **14** and **4**



4-hydroxybenzaldehyde with TIPSOTf and triethylamine in CH_2Cl_2 at 0 °C for 3 h. Reaction of **12** with enantiopure *p*-toluenesulfinamide in CH_2Cl_2 in the presence of $Ti(OEt)_4$ at 40 °C afforded sulfinimine **13** in 87% yield. Reaction of **13** with enolate derived from methyl acetate in diethyl ether at −78 °C afforded the corresponding addition product as a single diastereomer (by ^1H NMR). Treatment of this resulting sulfinamide with trifluoroacetic acid in CH_2Cl_2 removed the *N*-sulfinyl auxiliary and afforded (*R*)-*β*-tyrosine derivative **14** in 65% yield in two steps. Construction of the tripeptide fragment **4** was then achieved by coupling reaction of known dipeptide **15**[7b] with **14** in the presence of DCC in THF at 0 °C for 12 h. Removal of the BOC group by exposure to trifluoroacetic acid in CH_2Cl_2 provided amino ester **4** in 81% yield.

The final assembly of jasplakinolide fragments is illustrated in Scheme 3. The coupling of the above amino ester **4** with 8-hydroxynonenoic acid **3** in the presence of DCC and HOBT in THF at −20 to 0 °C for 24 h furnished coupling product **16** in 80% yield. Saponification of **16** with aqueous LiOH at 23 °C affected removal of the TIPS group and afforded the corresponding phenolic acid. Treatment of the resulting phenolic acid with TIPSOTf in the presence of 2,6-lutidine at 23 °C for 2 h followed by exposure of the resulting TIPS derivative with aqueous potassium carbonate afforded seco acid **2** in 77% yield in three steps. Acid **2** was subjected to Yamaguchi macrolactonization protocol[18] with 2,4,6-trichlorobenzoyl chloride in the presence of DMAP to

Scheme 3. Synthesis of (+)-Jasplakinolide



provide the corresponding macrolactone in 82% yield. Removal of the TIPS group by treatment of the macrolactone with TBAF in THF at 0 °C for 10 min furnished synthetic (+)-jasplakinolide (**1**, $[\alpha]^{23}_D$ +67.7, *c* 0.2, CH_2Cl_2). The spectral data (^1H and ^{13}C NMR) of synthetic (+)-jasplakinolide are identical with those reported for the natural (+)-jasplakinolide.[6]

In summary, we have achieved an enantioselective synthesis of (+)-jasplakinolide (**1**). The convergent synthesis features diastereoselective *syn*-aldol, ortho-ester Claisen rearrangement and asymmetric synthesis of the (*R*)-*β*-tyrosine derivative. The synthesis will provide a convenient access to a variety of jasplakinolide derivatives. Structural modifications of jasplakinolide are currently in progress.

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Supporting Information Available: Experimental procedures, spectral data for compounds **1**−**4**, **6**, **8**−**11**, **13**, **14**, and **16**, and ^1H NMR and ^{13}C NMR spectra for compounds **1**, **2**, **4**, **8**−**11**, **13**, **14**, and **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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