

Enantioselective Total Synthesis of  
(+)-Jasplakinolide

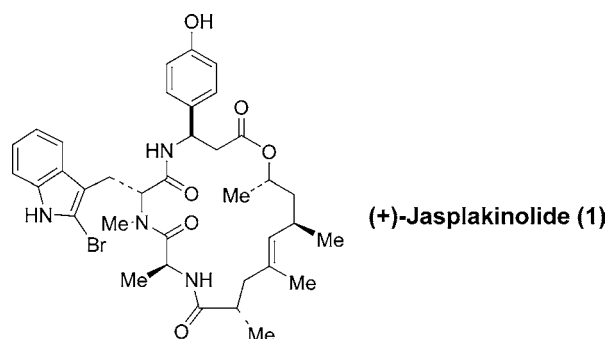
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## ABSTRACT



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  $\beta$ -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.<sup>1</sup> It was later found in other marine sponges, including *Auletta* sp., *H. minor*, and *Cymbastela* sp.<sup>2</sup> Jasplakinolide exhibited a number of very interesting biological properties. It is active against 36 human solid tumor types in cell culture assays.<sup>3</sup> It has also exhibited other important biological properties, including insecticidal, antifungal, and antihelminthic activities.<sup>4</sup> The mechanism of action is known

to involve stabilization of actin filaments by binding to F-actin similar to phalloidin.<sup>5</sup> 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.<sup>6</sup> Jasplakinolide is often used as a molecular probe for actin polymerization studies. Its biological properties and structural features attracted attention for total synthesis<sup>7</sup> and structural modification.<sup>8</sup> We recently reported an enantioselective total synthesis of (–)-doliculide,

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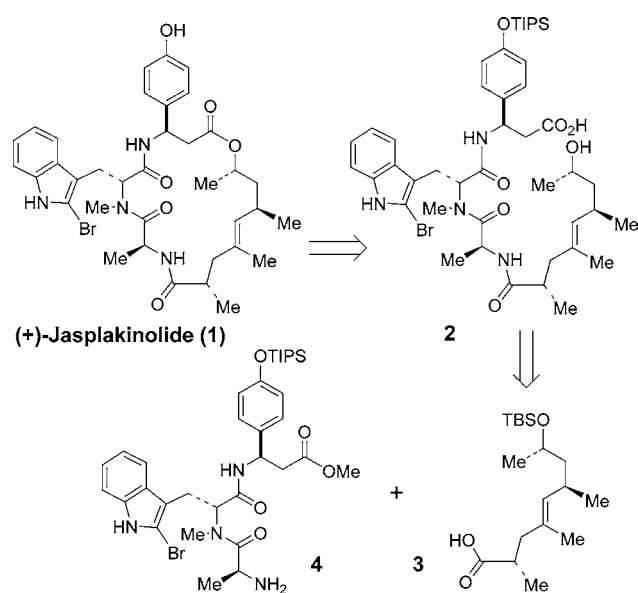
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another cyclic depsipeptide isolated from *Dolabella auricularia* by Ishiwata and co-workers.<sup>9</sup> Using synthetic dolicolide, we established that it too arrests cell growth at the G<sub>2</sub>/M phase of the cell cycle by interfering with normal actin assembly similar to jasplakinolide.<sup>10</sup> Dolicolide exhibited no toxicity. Structural similarities of dolicolide 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*)- $\beta$ -tyrosine unit **4**.

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

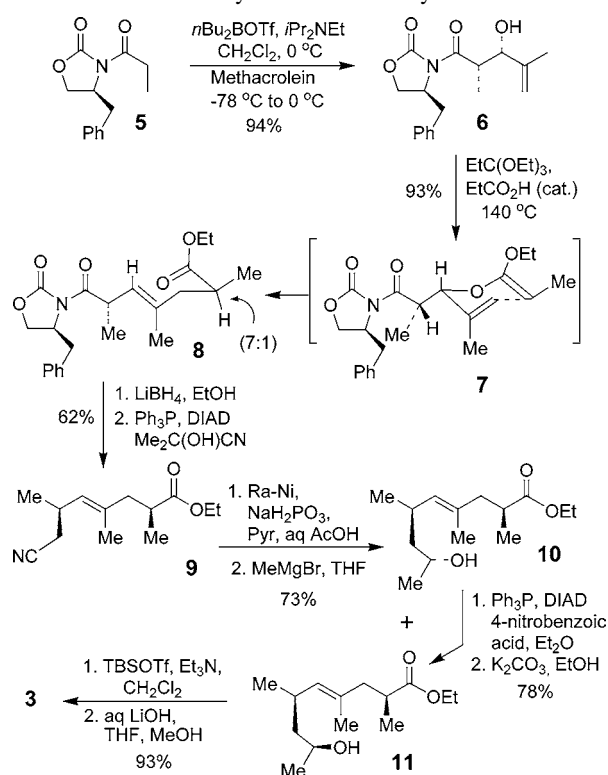


**Figure 1.** Retrosynthetic analysis of (+)-jasplakinolide.

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-bromoalanine, (*R*)- $\beta$ -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.<sup>11</sup> Allylic alcohol **6** was subjected to acid-catalyzed ortho ester Claisen rearrangement with triethyl orthopropionate at 140 °C for 1 h to afford  $\gamma,\delta$ -unsaturated ester **8** in 93% yield as a mixture (7:1 by <sup>1</sup>H NMR) of diastereomers. This Claisen rearrangement protocol di-

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



astereoselectively introduced the  $\alpha$ -methyl carbonyl functionality through 1,4-chirality transfer.<sup>12</sup> 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<sub>4</sub> and EtOH<sup>13</sup> followed by Mitsunobu reaction of the resulting alcohol using acetone cyanohydrin in the presence of diisopropyl azodicarboxylate and triphenylphosphine.<sup>14</sup> Nitrile **9** was obtained in 62% yield in a two-step sequence. Reduction of nitrile with Raney nickel in the presence of NaH<sub>2</sub>PO<sub>3</sub>, pyridine, and aqueous acetic acid provided the corresponding aldehyde.<sup>15</sup> 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<sup>16</sup> of (*R*)-alcohol **10** with Ph<sub>3</sub>P and *p*-NO<sub>2</sub>-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<sub>3</sub>N at 23 °C, and saponification with aqueous lithium hydroxide furnished 8-hydroxynonenoic acid **3** in 93% yield.

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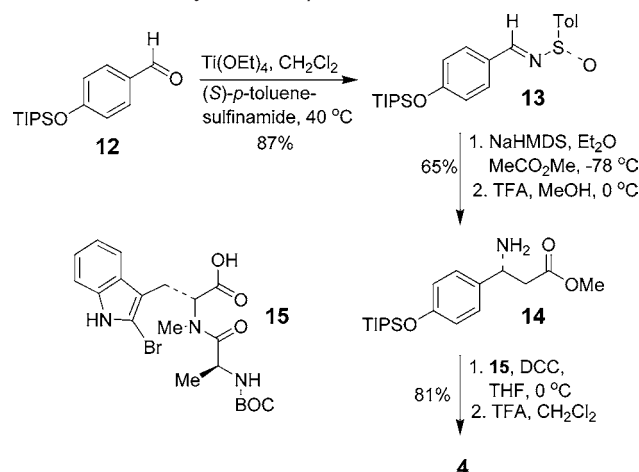
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Diastereoselective synthesis of desired (*R*)- $\beta$ -tyrosine derivative was achieved using an asymmetric protocol developed by Davis and co-workers,<sup>17</sup> as shown in Scheme 2. Aldehyde **12** was readily prepared by protection of

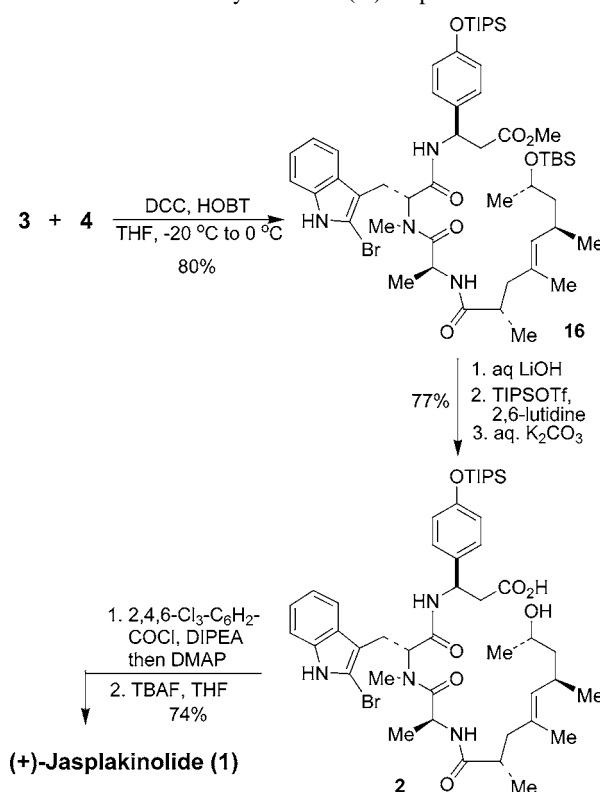
**Scheme 2.** Synthesis of  $\beta$ -Amino Acid Units **14** and **4**



4-hydroxybenzaldehyde with TIPSOTf and triethylamine in  $\text{CH}_2\text{Cl}_2$  at 0 °C for 3 h. Reaction of **12** with enantiopure *p*-toluenesulfinamide in  $\text{CH}_2\text{Cl}_2$  in the presence of  $\text{Ti}(\text{OEt})_4$  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  $^1\text{H}$  NMR). Treatment of this resulting sulfinamide with trifluoroacetic acid in  $\text{CH}_2\text{Cl}_2$  removed the *N*-sulfinyl auxiliary and afforded (*R*)- $\beta$ -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**<sup>7b</sup> 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  $\text{CH}_2\text{Cl}_2$  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<sup>18</sup> 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**,  $[\alpha]_{\text{D}}^{23} +67.7$ , *c* 0.2,  $\text{CH}_2\text{Cl}_2$ ). The spectral data ( $^1\text{H}$  and  $^{13}\text{C}$  NMR) of synthetic (+)-jasplakinolide are identical with those reported for the natural (+)-jasplakinolide.<sup>6</sup>

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*)- $\beta$ -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  $^1\text{H}$  NMR and  $^{13}\text{C}$  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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