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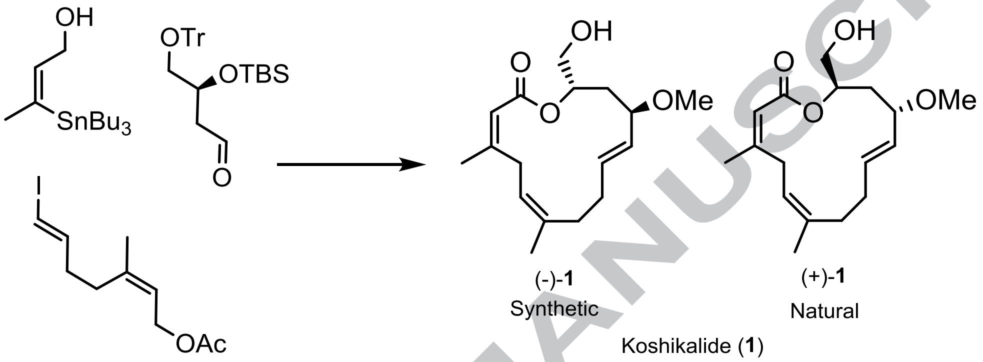

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Total Synthesis and Absolute Configuration of Koshikalide

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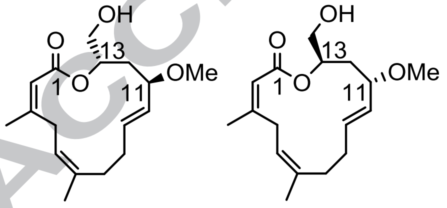
ABSTRACT

The first total synthesis of koshikalide, a 14-membered macrolide that contains three olefins, was achieved. The skipped diene in the cyclic system was efficiently constructed by very mild Stille coupling at low temperature. The absolute stereochemistry was established by comparison of the specific optical rotations of natural and synthesized koshikalide.

In 2010, koshikalide (**1**), a 14-membered macrolide that exhibits moderate cytotoxicity, was isolated from a marine cyanobacterium *Lyngbya* sp., and its relative stereochemistry was established on the basis of spectroscopic analyses.[1] However, its absolute stereochemistry could not be elucidated due to the scarcity (0.3 mg) of the sample. To clarify the complete stereochemistry of **1**, we carried out the first total synthesis of koshikalide (**1**).



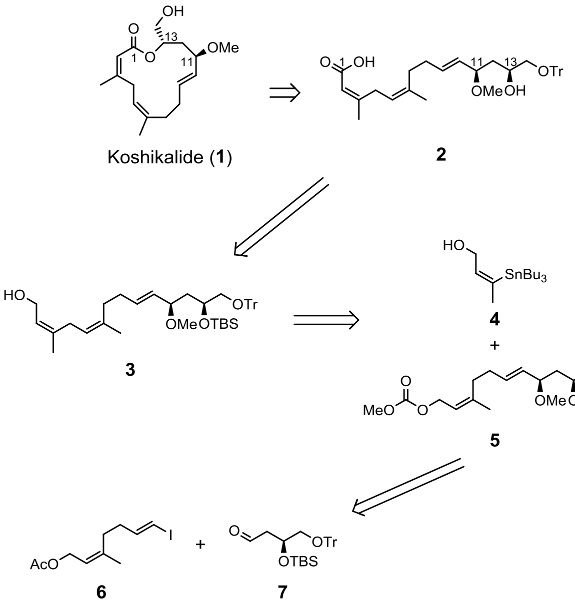
(-)-**1**
Synthetic

(+)-**1**
Natural

Koshikalide (**1**)

The structure of **1** includes a 14-membered macrolide containing two (*Z*)-trisubstituted olefins and one (*E*)-disubstituted olefin. In addition, the two trisubstituted olefins are sequenced as a skipped-form. Thus, koshikalide (**1**) is highly functionalized despite the size of the macrolactone ring. So far, there has been only one published synthetic study of **1**.[2] In that report, the authors encountered isomerization of the skipped diene throughout the synthesis, and finally achieved the construction of the 14-membered core structure by a nonbasic lactonization method using a Mitsunobu reaction. Based on this previous knowledge, we envisioned the retrosynthesis of koshikalide (**1**) as follows (Scheme 1).

First, the labile skipped diene should be introduced at a point close to the final step in the scheme, and all subsequent reaction conditions should be as mild as possible. Therefore, a Shiina macrolactonization was used to construct the lactone skeleton of **1** from **2**. For introduction of the conjugated carbonyl group at C-1, mild oxidation of allyl alcohol **3** could be achieved by TEMPO oxidation. The skipped diene of **3** could be prepared by a very mild Stille coupling reaction between stannane **4** and carbonate **5** at 0 °C. Carbonate **5** could be prepared from vinyl iodide **6** and aldehyde **7** by NHK coupling.[3]



Scheme 1. Retrosynthesis of koshikalide(**1**)

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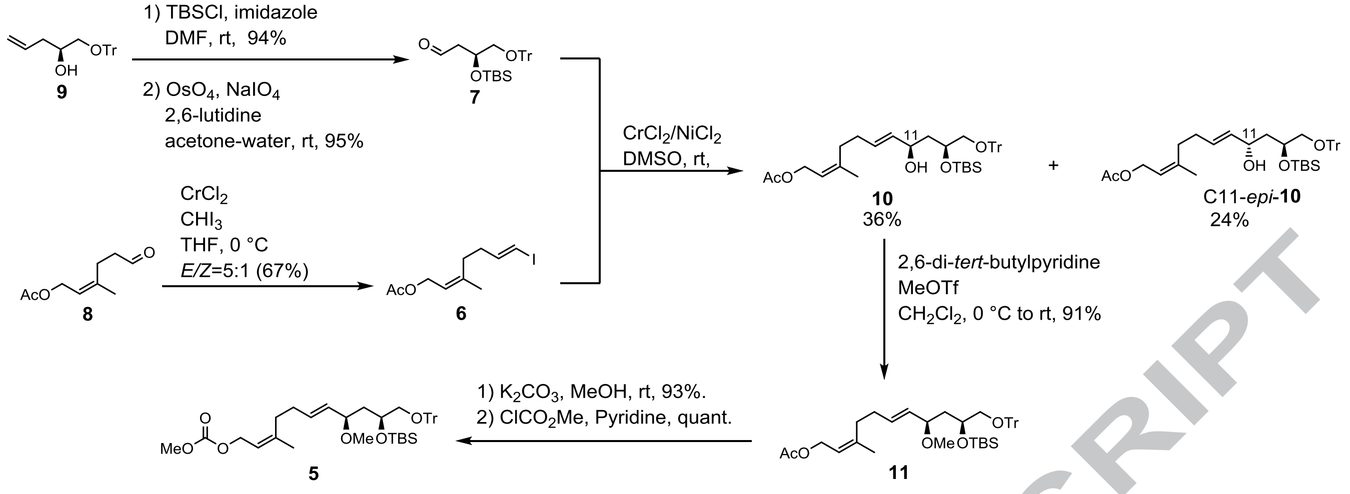
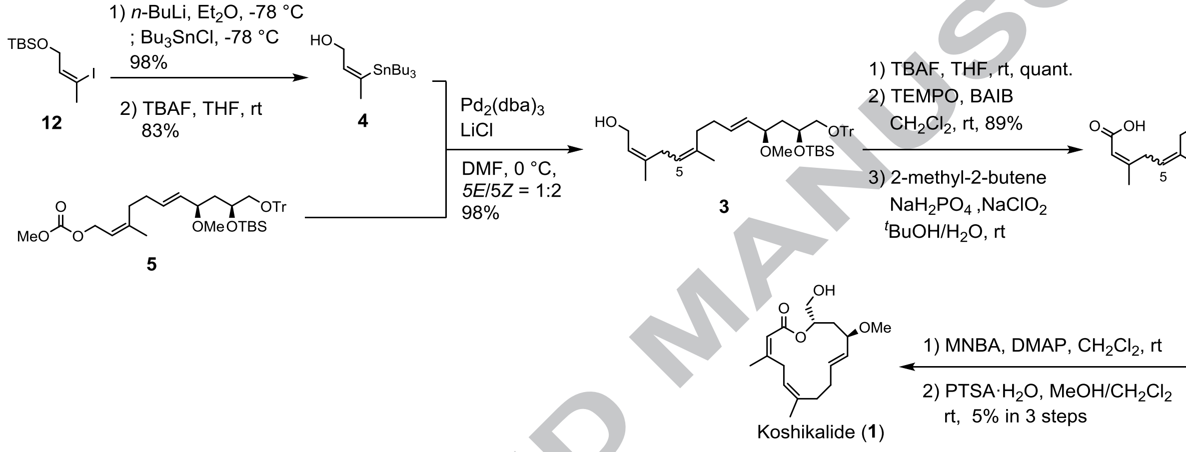


Scheme 2. Synthesis of carbonate **5**



Scheme 3. Total synthesis of koshikalide (**1**)

First, we synthesized carbonate **5** as follows (Scheme 2). The known aldehyde **8**[4] was converted to vinyl iodide **6** by a Takai reaction,[5] and aldehyde **7** was prepared from allyl alcohol **9**[6] in two steps. These two fragments (**6** and **7**) were connected by NHK coupling to afford allyl alcohol **10** in 36% yield along with its epimer at C-11.[7] The stereochemistry of the hydroxyl group in **10** was established by a modified Mosher's method.[8] Methylation of **10** gave methyl ether **11**,[9] and methanolysis of the acetyl group in **11** followed by carbonation using methyl chloroformate afforded carbonate **5** in good yield (91% in three steps).

Halogen-lithium exchange of the known vinyl iodide **12**[10] followed by tin-lithium exchange and deprotection of a hydroxyl group afforded allyl alcohol **4**, quantitatively. The very mild Stille coupling reaction between **4** and **5** at 0 °C proceeded quantitatively to give skipped diene **3** as a 1:2 mixture of *E*:*Z* isomers without migration of olefins. The TBS group of **3** was removed with TBAF in good yield (88%), and the resulting allyl alcohol was oxidized in two steps to afford carboxylic acid **2**. To avoid the undesired isomerization of olefins, macrolactonization of **2** was carried out under mild conditions using Shiina macrolactonization.[11] Finally, deprotection of the trityl group by PTSA afforded koshikalide (**1**) (Scheme 3). We did not obtain any products derived from the 5*E* isomer of **3**; they might decompose during macrolactonization.

The spectral data of synthesized koshikalide (**1**) matched those of natural koshikalide, except for the sign of the specific rotation (Table 1). Therefore, the absolute stereochemistry of natural koshikalide was established as an enantiomer of the synthesized compound, (+)-**1**.

Table 1. Optical rotation of koshikalide (**1**)

Type	Specific rotation
Synthetic	$[\alpha]_D^{25}$ -165 (*c* 0.02, MeOH)
Natural	$[\alpha]_D^{22}$ +156 (*c* 0.03, MeOH)

In conclusion, the first total synthesis of koshikalide (**1**) was achieved in 14 steps (longest linear sequence from nerol, a precursor of **8**.). Based on a comparison of the signs of the specific rotations, the absolute stereochemistry of natural koshikalide was determined to be (+)-**1**. Formation of the skipped diene moiety was achieved using very mild Stille coupling at 0 °C without the migration of olefins.

Acknowledgments

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References and notes

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7. At this stage, an undesired coupling product derived from *Z*-isomer of **6** was also obtained (12%). This by-product was removed by column chromatography.
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11. The yield of the macrolactonization step was poor, probably due to the polymerization of **2**.

Supplementary Material

Supplementary material (Experimental procedures and spectroscopic data of new compounds) associated with this article can be found, in the online version, at XXX.

Highlights

The first total synthesis of koshikalide was achieved.
The absolute configuration of koshikalide was established.
Formation of a skipped diene moiety was achieved using very mild Stille coupling.