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Stereoselective Synthesis of Premisakinolide A, the Monomeric Counterpart of the Marine 40-Membered Dimeric Macrolide Misakinolide A

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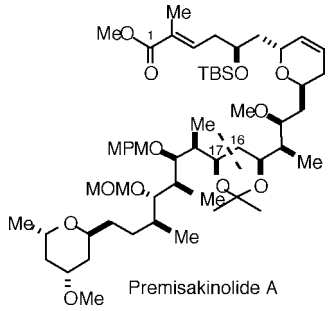
ABSTRACT



The first synthesis of premisakinolide A, the monomeric counterpart of misakinolide A, the marine 40-membered macrolide displaying potent activity against a variety of human carcinoma cell lines, has been reported. The strategy was highlighted by a crucial coupling of a tetrahydropyran fragment and an alkynylaluminum reagent having a polypropionate chain, the highly stereoselective cross aldol reaction of segment A and segment B, and the stereospecific construction of the polypropionate structure based on original acyclic stereocontrol.

The marine natural products swinholides,[1] 44-membered dimeric macrolides, isolated from the Okinawan marine sponge *Theonella swinhoei*, and misakinolide A[2a−c] (**1**) (bistheonellide A),[2b,d] a 40-membered dimeric macrolide, isolated from another Okinawan marine sponge *Theonella*, have been revealed to exhibit potent cytotoxicity against a variety of human carcinoma cell lines, as well as a broad spectrum of antifungal activity.[1−3] The stereostructures of the monomeric units of swinholide A and misakinolide A (termed preswinholide A and premisakinolide A (**2**), respectively), are remarkably similar, and only the number of double bonds connected to a carboxyl group is different. Also, the polypropionate structures of these monomeric counterparts are similar to that of scytophycin C, the 22-membered macrolide isolated from the terrestrial blue-green alga, *Scytonema pseudohofmanni*,[4] which also exhibits significant activity against a variety of human carcinoma cell lines, including solid tumors.[5] The structures of the swinholide and misakinolide families are characterized by the C_2-symmetrical dimeric macrolides in which two polypropionate-derived chains, including a gigantic lactone ring, are axially oriented on a tetrahydropyran ring. Their unique structures as well as potent anticancer activities have elicited much attention from synthetic chemists.[6] However, total synthesis of misakinolide A (**1**) has not been achieved yet,

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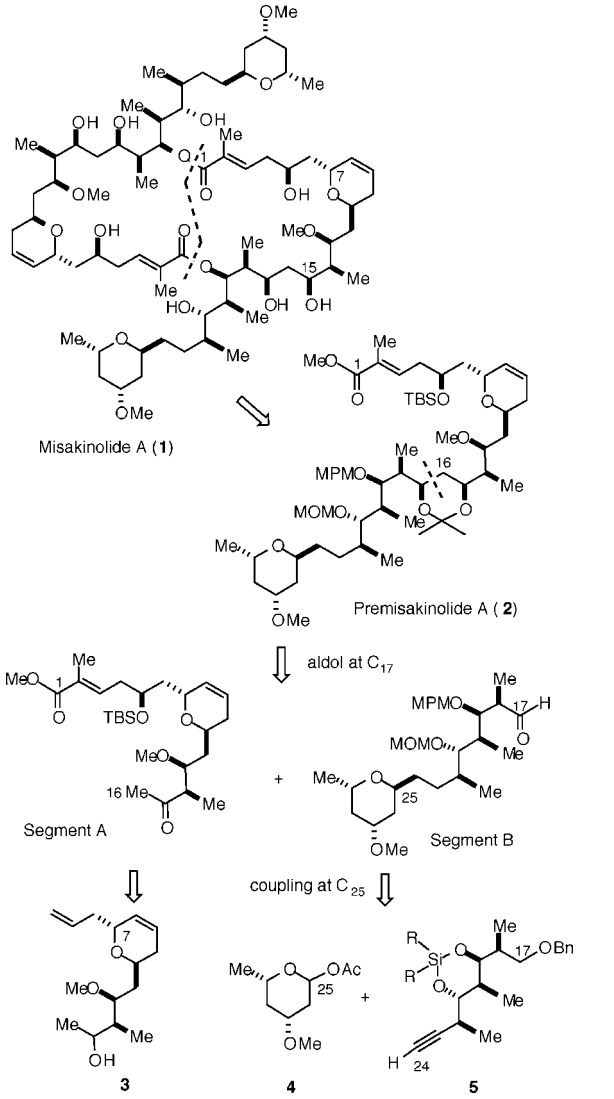
although total syntheses of swinholide A have been reported by two groups, those of Paterson[7a−e] and Nicolaou.[7f]

Recently, we reported a stereoselective total synthesis of scytophycin C based on new acyclic stereocontrol.[8,9] As part of our synthetic program toward the polypropionate-derived natural products,[6e,8,10] we report herein the first synthesis of premisakinolide A (**2**), the monomeric counterpart of misakinolide A (**1**),[2] which involves a crucial coupling of a tetrahydropyran fragment and an alkynylaluminum reagent having a polypropionate chain bearing five consecutive stereogenic centers, the highly stereoselective cross aldol reaction of segment A and segment B, and the stereospecific construction of the polypropionate structures in these segments as the key steps.

Our retrosynthesis of premisakinolide A (**2**) is shown in Scheme 1. Namely, **2** was divided into the C(1)−C(16) segment (segment A) and the C(17)−C(30) segment (segment B), and both segments were designed to connect by an aldol reaction at the C16 and C17 positions under Felkin−Anh control similarly to the synthesis of scytophycin C.[8,9] Segment A, including a dihydropyran ring bearing trans-substituted side chains, could be straightforwardly synthesized from the intermediate **3** used in our total synthesis of scytophycin C.[8] On the other hand, to construct segment B containing a tetrahydropyran ring and eight asymmetric carbon atoms, we envisaged the coupling reaction of the tetrahydropyran derivative **4** and the alkynyl segment **5** having five consecutive stereogenic centers.

Segment A was straightforwardly synthesized starting from the intermediate **3** in the synthesis of scytophycin C[8] according to Scheme 2, which involves the Grubbs olefin metathesis and chemoselective reduction of epoxy aldehyde as the key steps.

Scheme 1. Synthetic Strategy of Misakinolide A (**1**)



Thus, treatment of **3** with the second-generation Grubbs' catalyst[11] (2 mol %) and crotonaldehyde in CH_2Cl_2 at reflux gave unsaturated aldehyde **6** in 78% yield. The product was then converted to β-epoxy alcohol **7** in two steps in 90% yield: (1) reduction with DIBAH in THF (92%) and (2) the Katsuki−Sharpless asymmetric epoxidation[12] (98%). Oxidation of the epoxy diol **7** with Dess−Martin periodinane[13] followed by treatment of the resulting epoxy aldehyde with $Na[PhSeB(OEt)_3]$[14] and AcOH in EtOH furnished hydroxy aldehyde **8**, which was then subjected to a Wittig reaction with $Ph_3P{=}C(CH_3)CO_2Me$ in toluene to give rise to the (*E*)-unsaturated ester in 69% yield for three steps. Notably, chemoselective reduction of the epoxide functionality in the epoxy aldehyde cleanly occurred with the use of benzene-

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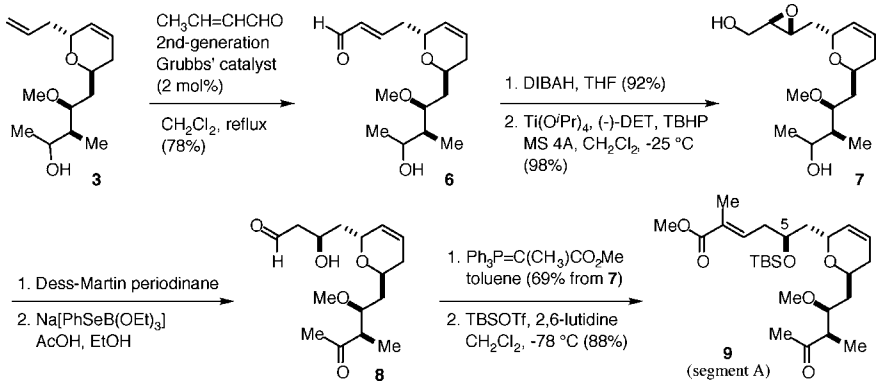
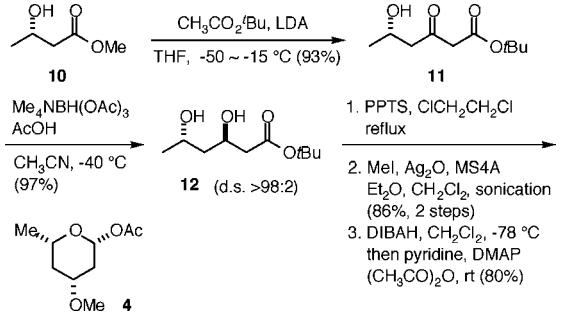
Scheme 2. Stereoselective Synthesis of Segment A



selenol (PhSeH) generated from $Na[PhSeB(OEt)_3]$ in situ,[14] as we expected. Protection of the secondary alcohol with TBSOTf and 2,6-lutidine in CH_2Cl_2 provided **9** (segment A) in 88% yield. The present synthetic route enabled the stereoselective introduction of the hydroxyl group at the C5 position without formation of any stereoisomers.

Scheme 3. Chiral Synthesis of the Tetrahydropyran Moiety **4**

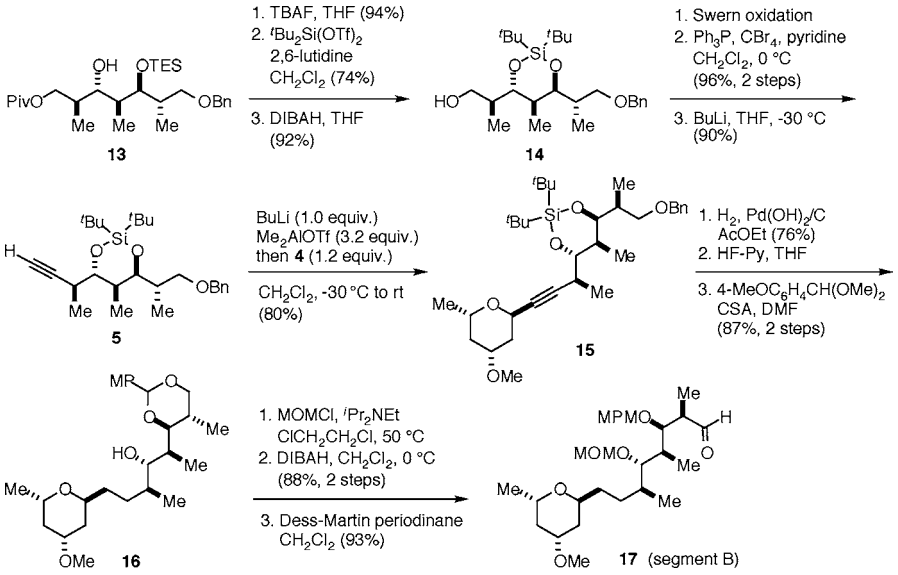


On the other hand, the tetrahydropyran fragment **4** was also efficiently synthesized by using the new synthetic route (Scheme 3). Namely, the Claisen condensation of the commercially available methyl (*S*)-3-hydroxybutanoate (**10**) with a lithium ester enolate of *tert*-butyl acetate[15] in THF afforded keto ester **11** in 93% yield, which was reduced with tetramethylammonium triacetoxyborohydride[16] and AcOH in CH_3CN to produce *anti*-diol **12** in a highly stereoselective manner (ds > 98:2) in 97% yield.

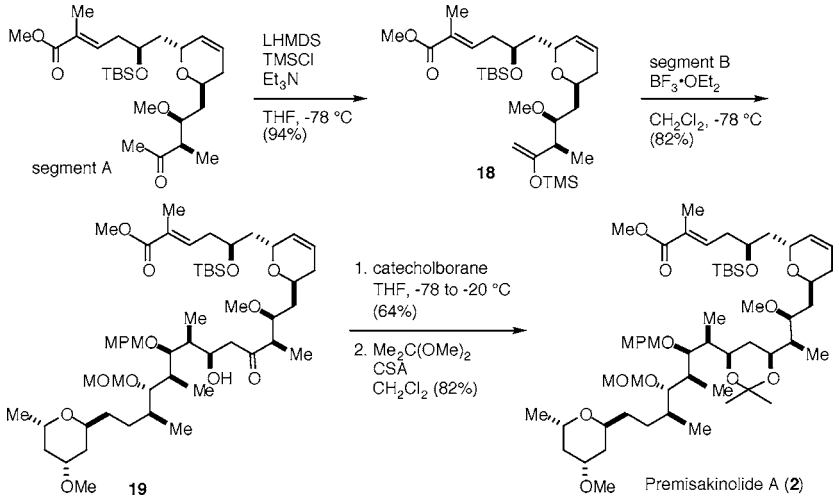
Conversion of **12** to the hydroxy lactone by treatment with PPTS[17] and subsequent O-methylation of the secondary hydroxyl group with MeI and Ag_2O[18] afforded the β-methoxy lactone (86% yield for two steps), which was then converted to the tetrahydropyran fragment **4** by reduction with DIBAH, followed by acetylation in a one-pot operation in 80% yield.

Segment B containing a tetrahydropyran ring was efficiently and highly stereoselectively synthesized according to Scheme 4, which involves a novel coupling reaction of acetoxy tetrahydropyran **4** with an alkynylaluminum reagent, including the polypropionate chain bearing five consecutive stereogenic centers, as the key step.

Scheme 4. Stereoselective Syntheses of Alkynyl Segment **5** and Segment B



Scheme 5. Stereoselective Synthesis of Premisakinolide (**2**)



Initially, the intermediate **13**, which was used in our total synthesis of scytophycin C[8], was routinely converted to alcohol **14** in three steps: (1) removal of the TES group with TBAF, 94% yield; (2) protection of the secondary hydroxyl groups with $^{t}Bu_2Si(OTf)_2$, 74% yield; and (3) reduction of the pivaloate with DIBAH, 92% yield. The resulting alcohol **14** was readily transformed into the crucial alkyne segment **5** by a Swern oxidation followed by a Wittig reaction with (dibromomethylene)triphenylphosphorane[19] (96% yield for two steps) and subsequent treatment with BuLi in THF (90% yield).

With the requisite segments **4** and **5** in hand, we focused on the coupling reaction of both segments leading to segment B, the key step in the present synthesis. After a number of experiments, we found that the coupling reaction of **4** and **5** successfully occurred with the use of the alkynylaluminum reagent prepared from **5** in situ. Namely, initial treatment of **5** with BuLi in CH_2Cl_2 followed by treatment of the resulting lithium acetylide with dimethylaluminum triflate produced the requisite alkynyldimethylaluminum reagent, which was reacted with **4** to give rise to the desired product **15** in 80% yield. It should be noted that the quantity of Me_2AlOTf was of critical importance in this particular reaction and that the use of 3.2 equiv of Me_2AlOTf gave the best result. The coupling reaction exclusively occurred from the opposite side of two substituents on the tetrahydropyran ring, giving rise to **15** as a single product.

In turn, the adduct **15** was transformed into acetal **16** by a three-step reaction sequence: (1) hydrogenation of the triple bond and concomitant deprotection of the benzyl group (76% yield), (2) removal of the silylene group with HF−Py, and (3) acetalization of the resulting triol with 4-$MeOC_6H_4CH(OMe)_2$ (87% yield for two steps). Protection of the secondary hydroxyl group in **16** with MOMCl followed by reductive cleavage of the acetal with DIBAH in CH_2Cl_2 furnished the primary alcohol in 88% yield, which was then subjected to oxidation with Dess−Martin periodinane[13] to produce **17** (segment B) in 93% yield.

The key coupling reaction of segments A and B was performed by the aldol reaction of silyl enol ether **18** derived from segment A and the aldehyde segment B by using conditions similar to those employed in the synthesis of scytophycin C[8,9] resulting in the formation of an almost single aldol **19** in 82% yield (Scheme 5). Then, the aldol was treated with catecholborane[8,9] to give the *syn*-diol exclusively in 64% yield, which was eventually converted to the fully protected premisakinolide A (**2**) by treatment with 2,2-dimethoxypropane and a catalytic amount of CSA in 82% yield.

Thus, we have established a highly stereoselective synthesis of the fully protected premisakinolide A (**2**) required for the total synthesis of misakinolide A on the basis of the original synthetic methodology.

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Supporting Information Available: Experimental details and characterization data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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