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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 (2), respec-

10.1021/ol050864v CCC: \$30.25 © 2005 American Chemical Society Published on Web 06/10/2005 tively), 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 C₂-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 transsubstituted 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.

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2930



Thus, treatment of **3** with the second-generation Grubbs' catalyst¹¹ (2 mol %) and crotonaldehyde in CH₂Cl₂ 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 epoxidation¹² (98%). Oxidation of the epoxy diol **7** with Dess–Martin periodinane¹³ 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 Ph₃P=C(CH₃)CO₂Me 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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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.

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 acetate¹⁵ in THF afforded keto ester **11** in 93% yield, which was reduced with tetramethylammonium triacetoxyborohydride¹⁶ and AcOH in CH₃CN 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 PPTS¹⁷ and subsequent O-methylation of the secondary hydroxyl group with MeI and Ag₂O¹⁸ 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 5. Stereoselective Synthesis of Premisakinolide (2)



Initially, the intermediate **13**, which was used in our total synthesis of scytophycin C⁸, 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 'Bu₂Si(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)triphenylphosphorane¹⁹ (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 CH₂Cl₂ 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 Me₂AlOTf was of critical importance in this particular reaction and that the use of 3.2 equiv of Me₂AlOTf 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-MeOC₆H₄CH-(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 CH₂Cl₂ furnished the primary alcohol in 88% yield, which was then subjected to oxidation with Dess–Martin periodinane¹³ 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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