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Studies on the synthesis of reidispongiolide A: stereoselective synthesis of the C(22)–C(36) fragment

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ABSTRACT

A highly stereoselective synthesis of the C(22)–C(36) fragment **2** of reidispongiolide A is described. This synthesis features the highly stereoselective mismatched double asymmetric crotylboration reaction of the aldehyde derived from **5** and the new chiral reagent (*S*)-(*E*)-**7** that provides **12** with >15:1 dr. Subsequent coupling of the derived vinyl iodide **3** with aldehyde **16** provided allylic alcohol **17**, that was elaborated by three steps into the targeted reidispongiolide fragment **2**.

1. Introduction

The reidispongiolides and sphinxolides are structurally related, biologically active families of marine natural products isolated from the New Caledonian sponges *Reidispongia coerulea* and *Neosiphonia superstes*.[1–4] According to previous research, these compounds inhibit actin filament assembly assembling and induce F-actin depolymerization.[5] These compounds also have the ability to circumvent multi-drug resistance mediated by P-glycoprotein in cell-based assays.[5] Reidispongiolide A, the most active member of reidispongiolide family, exhibits potent cytotoxicity against various human cancer cell lines (IC_{50} 0.01–0.16 μg/mL).[3]

The relative configuration of the C(7), C(10–15), C(24–28), and C(32–33) subunits of sphinxolide B were first assigned by J-based NMR methods.[6] The relative and absolute stereochemistry of the C(17–22)[7], C(22–35),[8] and C(5–16)[9] subunits of reidispongiolide A were assigned via asymmetric synthesis. The absolute configuration of this family of natural products was determined from the actin-bound X-ray crystal structure of reidispongiolide A (Fig. 1).[10]

The structure complexity and biological properties of reidispongiolide A have stimulated interest in its synthesis. The total synthesis of reidispongiolide A was reported by Paterson and co-workers in 2007.[11,9,12] More recently, Suenaga and co-workers reported the synthesis of the C(11–22) and C(23–35) fragments of **1**.[13] Because recent research suggests that the C(24)–C(36) side chain plays a very important role in the binding of the reisipongiolides to the actin target,[14,15] we have focused our current efforts on this segment of the natural product.

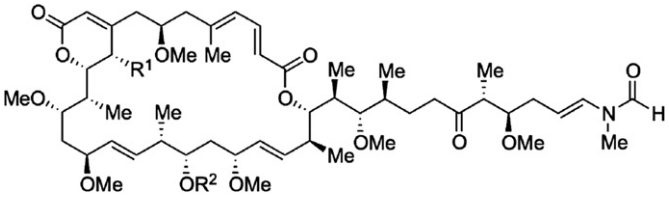

Fig. 1. Structures of selected members of the reidispongiolide–sphinxolide natural products.

We report here a highly stereoselective synthesis of the reidispongiolide A C(22)–C(36) subunit **2** that proceeds along the general outline of the retrosynthetic analysis that is presented in Scheme 1. The synthetic target **2** possesses seven stereocenters, including the C(26)–C(28) anti–anti stereotriad that represents a historically difficult challenge for synthesis via asymmetric aldol or crotylmetalation reactions,[16] as this bond construction is stereochemically

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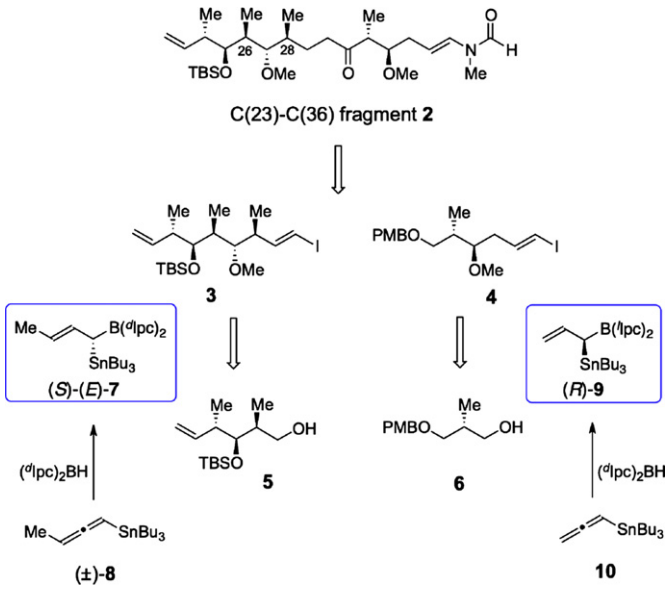
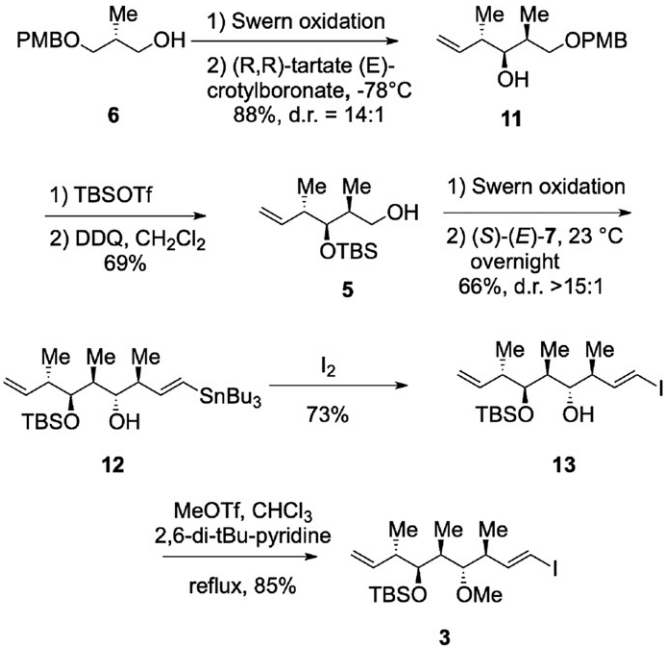
mismatched. However, synthesis of the anti, anti stereotriad with exceptional stereochemical control is now possible by virtue of the remarkable enantioselectivity of the new α-stannyl crotylborane **7**, that is, accessible via enantioselective hydroboration of racemic allene **8** with diisopinocampheylborane [$(Ipc)_2BH$].[17,18] Thus, by application of this new crotylboration technology we anticipated that vinyl iodide intermediate **3** could be assembled via α-stannylcrotylboration of the aldehyde deriving from **5** with the chiral reagent (*S*)-(*E*)-**7**. Similarly, we anticipated that vinyl iodide fragment **4** would be accessible via α-stannylallylboration of the aldehyde deriving from **6** with the α-stannylallylborane (*R*)-**9**, that is, readily accessible via the hydroboration of allenylstannane **10** with [$(^{l}Ipc)_2BH$].[19]



Scheme 1. Retrosynthetic analysis of **2**.

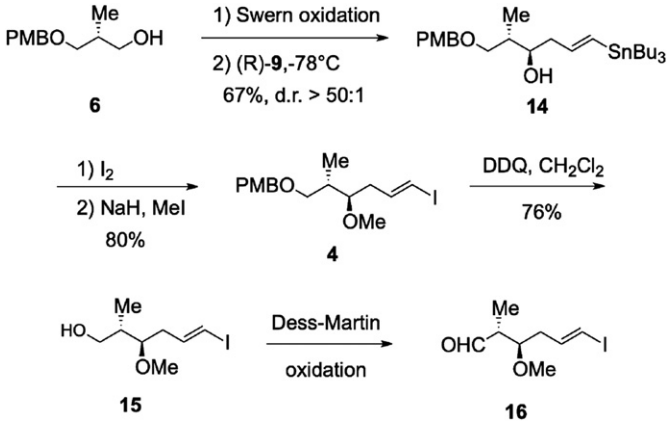
2. Results and discussion

The synthesis of fragment **3** (Scheme 2) starts from the primary alcohol **6**, which is prepared in two steps from commercially available precursors.[20] Alcohol **6** was oxidized to the corresponding aldehyde using a Swern procedure[21] and then the aldehyde was treated with the diisopropyl (*R*,*R*)-tartrate (*E*)-crotylboronate reagent[22] to give the known homoallylic alcohol **11** in 88% yield with 14:1 diastereoselectivity.[23] Protection of the hydroxyl group of **11** as a TBS ether followed by PMB ether deprotection with DDQ[24] provided primary alcohol **5** in 69% yield over the two steps. Alcohol **5** was then oxidized to the corresponding aldehyde and then added to a solution of α-stannylcrotylborane (*S*)-(*E*)-**7** that was generated, as previously described, via the hydroboration of racemic allene **8** with $(^{d}Ipc)_2BH$.[17] This reaction proceeded overnight at ambient temperature and provided the vinylstannane product **12**, with the requisite anti–anti stereochemistry at C(26–28), in 66% yield with >15:1 dr. The stereochemistry of **12** was assigned by analogy to related mismatched double asymmetric reactions described elsewhere.[18] Treatment of **12** with I_2 in Et_2O effected tin–iodine exchange and afforded vinyl iodide **13** in 73% yield. O-Methylation of the hindered hydroxyl group of **13** proved challenging. Attempted use of NaH and MeI for this step caused partial migration of the TBS unit between two hydroxyl groups, while use of Me_3OBF_4 and Proton Sponge® led to partial deprotection of TBS ether. Fortunately, use of MeOTf and 2,6-di-*tert*-butylpyridine resulted in a very clean reaction that provided **3** in 85% yield.[25]



Scheme 2. Synthesis of vinyl iodide **3**.

Alcohol **6** also served as the starting material for synthesis of vinyl iodide fragment **4** (Scheme 4). The aldehyde generated by Swern oxidation of **6** was added to a −78 °C solution the α-stannylallylborane reagent (*R*)-**9**, generated by the hydroboration of allenylstannane **10** with $(^{l}Ipc)_2BH$ as previously described,[19] to give **14** in 67% yield and with >50:1 dr. The (*R*)-stereochemistry of the hydroxyl group of **14** was assigned by using the Mosher ester method. Treatment of **14** with I_2 followed by alcohol O-methylation gave vinyl iodide **4** in 80% yield. Deprotection of PMB ether of **4** gave the primary alcohol **15** in 76% yield, which was then oxidized under Dess–Martin oxidation[26] conditions to give aldehyde **16**. Aldehyde **16** is not stable for long-term storage and was usually freshly prepared before immediately before use in subsequent chemistry (Scheme 3).



Scheme 3. Synthesis of vinyl iodide **4** and elaboration to aldehyde **16**.

Treatment of vinyl iodide **3** with *t*-BuLi at −78 °C generated the corresponding the vinyllithium intermediate which was then treated with aldehyde **16**, also at −78 °C. This reaction gave alcohol **17** in 50% yield as a ca. 2:1 mixture of diastereomers (Scheme 4). This mixture was of no consequence, as both alcohols smoothly were oxidized in the next step upon treatment with the Dess–Martin periodinane reagent. The resulting enone was then