Natural Products Synthesis

Total Synthesis and Stereochemical Assignment of Myriaporones 1, 3, and 4**

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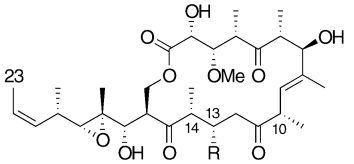
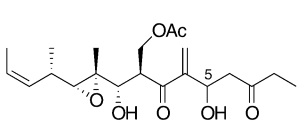
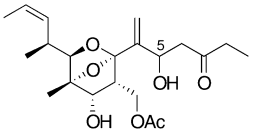
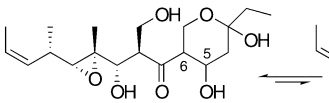
The natural products tedanolide (**1a**) and 13-deoxytedanolide (**1b**), which were isolated by Schmitz et al.[1] and Fusetani et al.,[2] respectively, exhibit picomolar activity against a range of cancer cell lines. Their biological activity coupled with their scarcity has prompted considerable synthetic attention.[3] Our interest in these compounds stems from the isolation of a related class of natural products, the myriaporones (**2a**–**d**), reported by Rinehart et al. in 1995.[4,5] The myriaporones are nearly identical structurally to the C10–C23 portion of tedanolide (**1a**); it is therefore possible that these two classes of compounds share the same biological receptor and have similar modes of action. As a result of their limited availability, the biology of both classes remains a mystery. Therefore, our goal is to provide material to facilitate such studies and, herein, we report the total synthesis of myriaporones 1, 3, and 4 (**2a**,**c**,**d**) and the unambiguous assignment of their previously undetermined stereogenic configurations at C5 and C6.

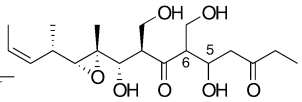
Recently, we reported the completion of the carbon skeleton of myriaporone 1 (**2a**) through a stereoselective homoallenylboration and a nitrile oxide cycloaddition.[5a] Construction of myriaporone 4 (**2d**) began with known alcohol **3**[3c] (Scheme 1). Oxidation with IBX[6] was followed by an Evans aldol[7] reaction to set the C8 and C9 stereocenters in high yield and excellent diastereoselectivity. During the course of that work, incorporation of the epoxide at an early stage limited the scope of reaction conditions that subsequent intermediates could withstand and ultimately prevented completion of the total synthesis. Since then, Loh and Feng[3g] and Smith III et al.[3k] reported highly selective late-stage epoxidations in their efforts toward tedanolide. With these results as precedence, our focus switched to the incorporation of this particularly sensitive functional group in the penultimate step of the synthesis.

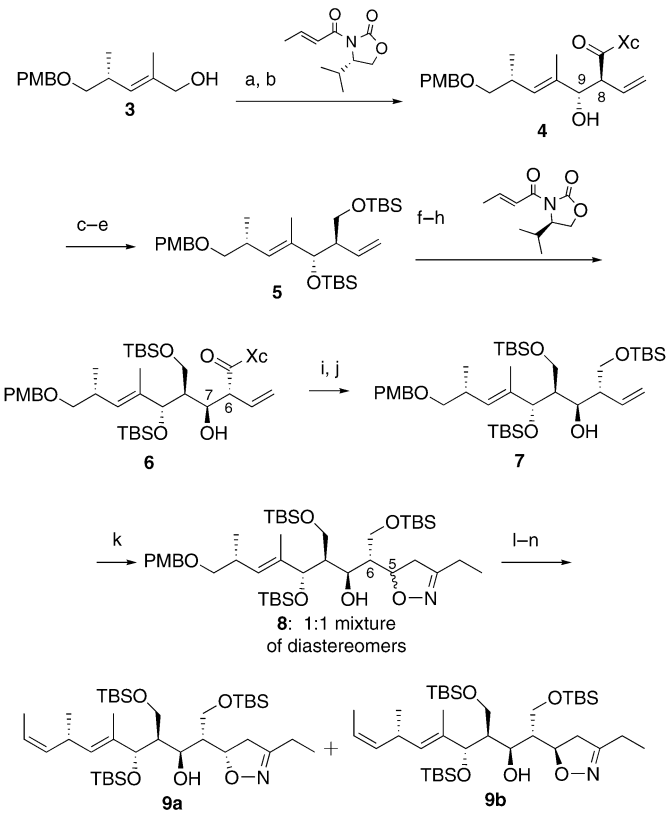












Scheme 1. Synthesis of C5-epimeric isoxazolines **9a** and **9b**. Reagents and conditions: a) IBX, 95%; b) Bu_2BOTf, Et_3N, 93%; c) TBSOTf, 85%; d) $LiBH_4$; e) TBSCl, 89% (two steps); f) OsO_4, NMO, 95%; g) $NaIO_4$, 84%; h) Bu_2BOTf, Et_3N, 99%; i) $LiBH_4$; j) TBSCl, 92% (two steps); k) $PrNO_2$, PhNCO, 64%; l) DDQ, 88%; m) IBX; n) $Ph_3P{=}CHCH_3$, 63% (two steps). IBX = *o*-iodoxybenzoic acid; Tf = trifluoromethanesulfonyl; TBS = *tert*-butyldimethylsilyl; NMO = *N*-methylmorpholine-*N*-oxide; DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

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Supporting information for this article (experimental and characterization data for synthetic and authentic samples of **2a**,**c**,**d**) is available on the WWW under http://www.angewandte.org or from the author.

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The aldol product **4** was converted efficiently into bis(TBS ether) **5** by protection, reductive cleavage of the chiral auxiliary, and a second protection step. Oxidative cleavage of the terminal olefin was followed by a second Evans aldol reaction to form the C6–C7 bond and to provide **6** in nearly quantitative yield. The appropriate oxazolidinone was chosen to generate the *R* configuration at C6, an assumption based on the corresponding stereogenic center C14 in tedanolide (**1a**). Once again, the chiral auxiliary was removed reductively and the primary hydroxy was protected with TBSCl to provide compound **7** in excellent yield for the 10-step conversion from **3**. Regioselective nitrile oxide cycloaddition led to the formation of isoxazoline **8** as an inseparable mixture of diastereomers at C5.[8] The lack of selectivity of this reaction was desired because of the uncertain relative stereochemical configuration of the target molecule. Removal of the PMB protecting group was followed by oxidation to the aldehyde and olefination to give **9a** and **9b**. Upon installation of the C13–C14 *cis* double bond, the two diastereomers were easily separated by column chromatography and each taken on independently. The configuration of the C5 stereogenic center of each diastereomer was assigned upon completion of the synthesis (see below).

The less-polar diastereomer **9a** was converted into myriaporones 3 and 4 (**2c**,**d**) by the sequence outlined in Scheme 2. Dess–Martin periodinane[9] was used to oxidize the secondary hydroxy group to the corresponding ketone. Subsequent global silyl deprotection and reprotection provided **10a**. Reduction of the isoxazoline group with $Mo(CO)_6$ successfully unmasked the β-hydroxyketone[10] and set the stage for the key epoxidation reaction. It was necessary to use slightly less than one equivalent of MCPBA and to maintain the reaction temperature at $-50\,^{\circ}C$ to prevent overoxidation. Under the optimized conditions, only the desired epoxide (as a single diastereomer) and unreacted starting material were obtained. The final step, deprotection of the primary hydroxy groups with TAS-F,[11] resulted in the formation of the desired product, myriaporone 4 (**2d**) as an equilibrium mixture with myriaporone 3 (**2c**). The ^1H NMR spectrum of the final deprotected product from diastereomer **9a** was identical to that of an authentic sample of the natural product (see Supporting Information) and showed the presence of an equilibrating mixture of myriaporones 3 and 4. Diastereomer **9b** was converted into 5-*epi*-myriaporone 4 (**2d**) by an identical sequence (full details included in the Supporting Information).

The stereochemical configuration at C5 was determined by ^1H NMR spectroscopic analysis of myriaporone 3 (**2c**). Vicinal coupling constants account for the fact that C5-OH and 6-H are both axial (Figure 1). Thus we have unambiguously determined the stereochemistry of the myriaporone class of polyketides to correspond identically to the stereochemical pattern of the macrolide tedanolide (**1a**).

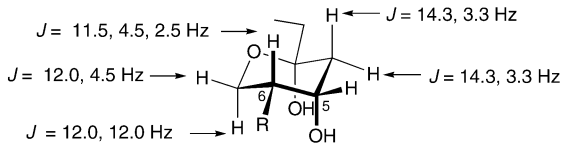
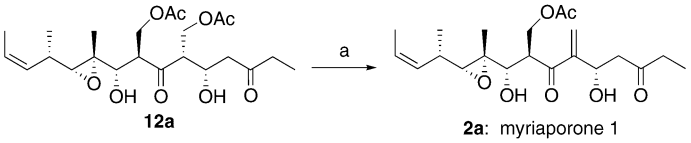
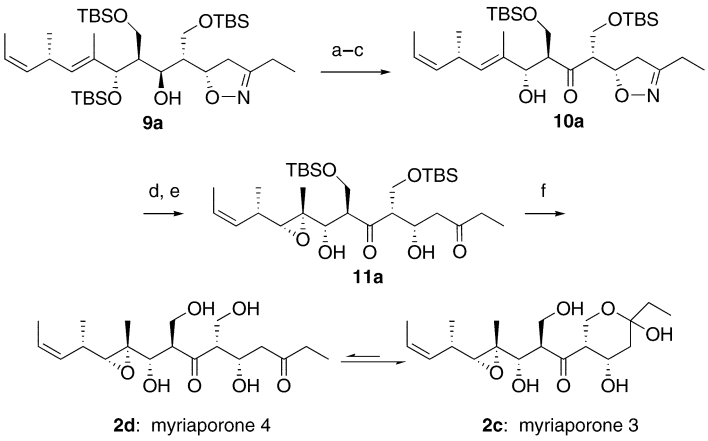


Figure 1. ^1H NMR spectroscopic analysis of myriaporone 3 (C1–C7) for the assignment of the relative stereochemistry of C5 and C6.

The use of acetate protecting groups instead of TBS ethers led to an unexpected reaction (Scheme 3). An attempted *mild* deprotection of **12a**, prepared from diasteromer **9a**, induced selective elimination to form myriaporone 1 (**2a**). In fact, this elimination is quite facile and **12a** proved difficult to handle upon preparation. The propensity for this group to eliminate suggests that the compound designated myriaporone 1 (**2a**) may actually be a product of isolation rather than a direct product of polyketide biosynthesis. Not surprisingly, the C5 stereogenic center of **2a** was determined to have the identical configuration to that of the corresponding center in myriaporones 3 and 4 (**2c**,**d**).



Scheme 3. Selective elimination for the synthesis of myriaporone 1. Reagents and conditions: a) KCN, 66%.



Scheme 2. Completion of the synthesis of myriaporones 3 and 4. Reagents and conditions: a) DMP, 98%; b) $HF{\cdot}Et_3N$, 83%; c) TBSCl, 81%; d) $Mo(CO)_6$, 65%; e) MCPBA, 62%; f) TAS-F, 70%. DMP = Dess–Martin periodinane; MCPBA = *m*-chloroperoxybenzoic acid; TAS-F = tris(dimethylamino)sulfur (trimethylsilyl)difluoride.

An important phase of this research has been completed. The efficiency of the synthetic route presented herein has enabled the preparation of significant quantities of these interesting marine natural products as well as analogues.[12] Studies currently underway will seek to identify the biological receptor and mode of action of the myriaporones. Furthermore, modified routes may provide access to compounds more closely related to tedanolide.

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Keywords: aldol reaction · diastereoselectivity · epoxidation · natural products · total synthesis

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