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Total Synthesis of Iejimalide B. An Application of the Shiina Macrolactonization

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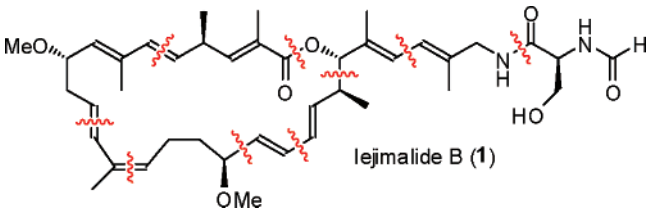
ABSTRACT



Iejimalide B (**1**)

The potent anticancer compound iejimalide B (1) was prepared by a total synthesis through a strategy that features Julia olefinations, Wittig olefinations, a Carreira enantioselective alkynylation, a Heck reaction, a Marshall propargylation reaction, a Stille coupling, and a Shiina macrolactonization.

The iejimalides[1,2] are a class of marine microbial secondary metabolites that were originally isolated from tunicate species native to the coral reefs in the vicinity of Ie Island (Iejima) near Okinawa, Japan. Work by Kobayashi[1] and us[3] has shown that the iejimalides possess potent growth inhibitory activity against a wide range of human tumor cell lines. Especially potent is iejimalide B (**1**). For example, it is cytostatic (GI_{50}) at <5 nM against 40 of the 56 cell lines tested in the NCI screen.[4] Recently, novel modes of anticancer activity were shown to be exhibited by the iejimalides.[5,6]

Their structures consist of a 24-membered lactone ring, containing five chiral centers and four dienes, one of which is a skipped triene, to which an *N*-formyl (*S*)-serine terminated diene side chain is attached (Figure 1). In the initially assigned structure, the absolute configurations of the chiral carbons within the macrolactone remained unspecified. It was at this point that we commenced the total synthesis of one of its diastereomers.[7−10] However, a follow-up study, by the

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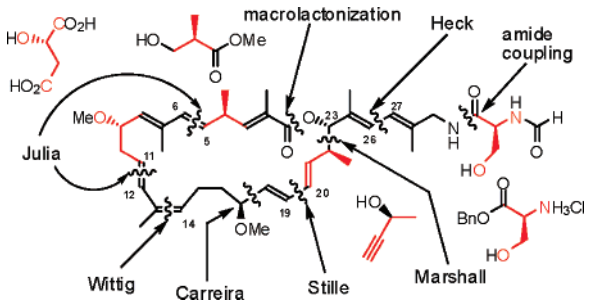


Figure 1. Key bond formations and key starting materials in the construction of iejimalide B (**1**).

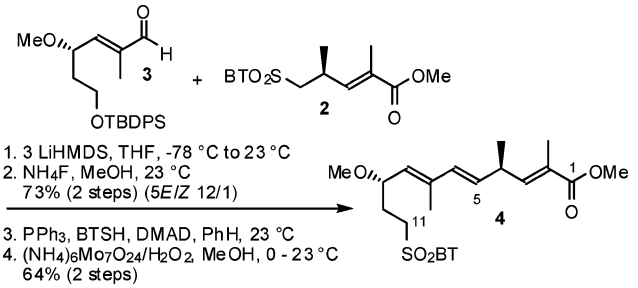
same group that had originally isolated the iejimalides, assigned the absolute configuration of all of the stereocenters (4*R*,9*S*,17*S*,22*S*,23*S*,32*S*) and revised the configuration of the C(13)−C(14) double bond from *E* to *Z*.[2] These changes led us to modify our synthesis.

We have previously reported a basic strategy and the synthesis and assembly of several of the subunits of the iejimalides.[5,7−10] Recently, a total synthesis was published by Fürstner,[11] employing much of the same strategy and many of the same subunits, but differing most importantly in the macrocyclic ring formation method. Fürstner used an elegant ring-closing alkene metathesis when macrolactonization failed. However, we now wish to report that the synthesis of iejimalide B can be completed successfully utilizing an appropriate macrolactonization procedure despite Fürstner's report of difficulty with this transformation.

In order to have the greatest flexibility in controlling the absolute configurations of the chiral centers, our strategy was based upon the use of fragments carrying individual stereochemical elements (Figure 1). Since the Julia olefination has been well precedented in challenging structures,[12] we decided to employ it for two of the diene constructions along with organometallic couplings for the formation of the other two dienes.

As we have reported earlier, both the C(1)−C(5) and the C(6)−C(11) subunits were prepared from the chiral pool. Roche ester contributed chiral carbon C(4), while malic acid provided C(9).[8] Initially, we formed the C(5)−C(6) double bond[8] between C(1)−C(5) sulfone **2** and C(6)−C(11) aldehyde **3** employing the traditional, three-step M. Julia olefination protocol.[13] However, we subsequently found that the modified, one-step S. Julia−Kocieński olefination protocol[12,14] using an excess of base under Barbier conditions proceeded in excellent yield and selectivity (Scheme 1).

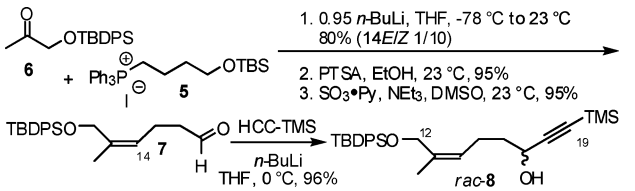
Scheme 1. Synthesis of the C(1)−C(11) Subunit



Hydroxyl deprotection, Mitsunobu reaction, and oxidation yielded the completed C(1)−C(11) subunit (**4**) ready for the second Julia olefination. The mild conditions of NH_4F/MeOH allowed clean deprotection of the TBDPS group[15,16] without epimerization of the C(4) stereocenter, which was caused by TBAF/THF or HF/Py.

The *Z* olefin, within the C(12)−C(19) subunit, was formed by a Wittig reaction between the phosphonium salt (**5**)[17] of THF-derived 4-iodo-1-silyloxybutane[18] and TBDPS-protected acetol (**6**)[19] using a substoichiometric amount of *n*-BuLi as the base (Scheme 2).[20] An excess of this base or the use

Scheme 2. Preparation of the C(12)−C(19) Intermediate *rac*-**8**



of other bases resulted in lower selectivity and decomposition. Selective deprotection[21] followed by oxidation yielded aldehyde **7**. Addition of TMS-acetylene produced racemic propargylic alcohol *rac*-**8**.[22]

Three methods to access enantiomerically enriched propargylic alcohol (*S*)-**8** were successfully employed (Scheme 3). First, a kinetic resolution of racemic propargylic alcohol **8** by Amano AK Lipase, which catalyzes only the formation of the (*R*)-acetate,[23] was achieved. Second, the enantioselective reduction of the corresponding alkynyl ketone **10**

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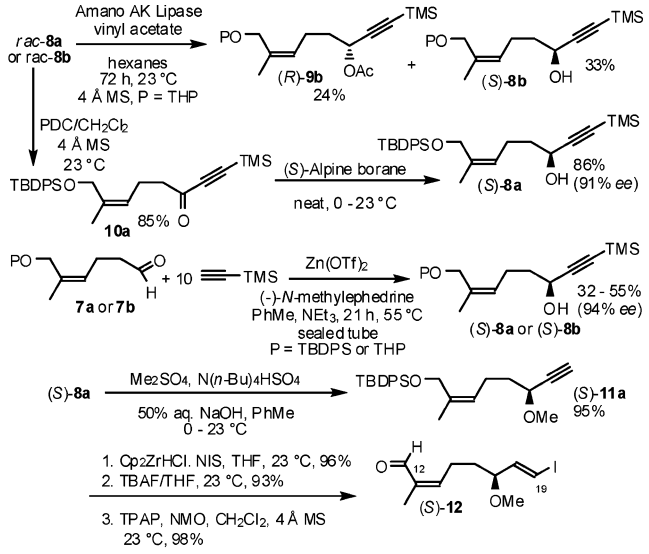
Scheme 3. Completion of C(12)−C(19) Subunit[a]



[a] **a**: R = TBDPS, **b**: R = THP.

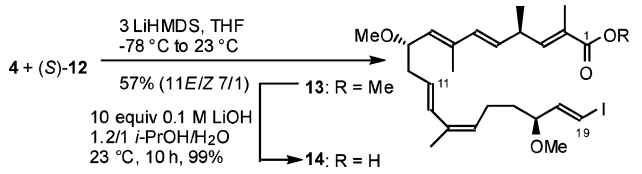
was performed. Most important, however, is the result of extensive investigation of the Carreira-style enantioselective addition of TMS-acetylene to aldehyde **7**. It was found that TMS-acetylene adds enantioselectively to aldehyde **7** if the reaction is performed employing an excess of TMS-acetylene at elevated temperature at a high concentration. Albeit moderate yielding,[24] this protocol represents a significant achievement considering that the attempted Carreira enantioselective addition of a terminal alkyne to an α-unsubstituted aldehyde has failed previously.[25]

Employing very efficient phase-transfer catalysis, alcohol **8** was methylated and the alkenyl TMS group was removed in a one-pot reaction.[26] Hydrozirconation−iodination,[27] hydroxyl deprotection, and allylic alcohol oxidation[28] using TPAP/NMO provided the fully functionalized C(12)−C(19) subunit (**12**). Other oxidizing agents such as MnO_2, SO_3·Py, or even DMP/Py caused partial double-bond isomerization.

Formation of the C(11)−C(12) double bond between sulfone **4** and volatile aldehyde **12** proceeded smoothly again using the Julia−Kocieński olefination (Scheme 4). Methyl ester saponification provided the completed, fully functionalized iejimalide C(1)−C(19) subunit **14**.

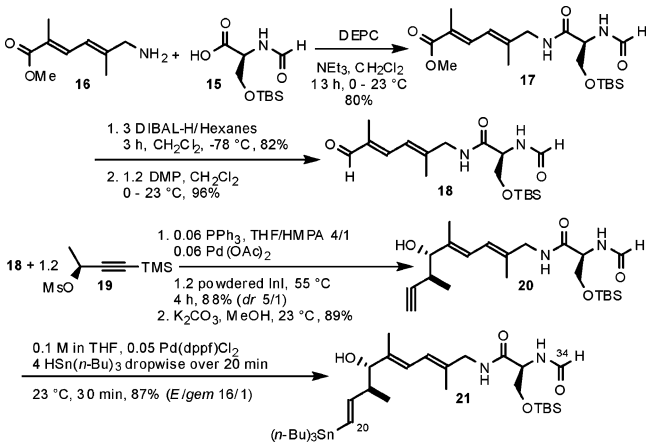
The iejimalide side chain (Scheme 5) was completed by amide formation between *O*-TBS-protected *N*-formylserine (**15**)[29] and diene−amine **16** promoted by diethyl phosphorocyanidate (DEPC).[30] The diene in **16** was formed by our

Scheme 4. Completion of the C(1)−C(19) Fragment



previously reported use of a Heck reaction.[7] We have alternatively synthesized this subunit through use of an alkenyl−alkenyl Suzuki−Miyaura coupling reaction.[10] Following conversion of the methyl ester in **17** to the aldehyde

Scheme 5. Preparation of the C(20)−C(34) Vinylstannane



18, Marshall's diastereoselective addition of an enantioenriched allenylindium reagent derived from (*R*)-4-trimethylsilylbut-3-yn-2-yl mesylate was performed.[23,31] Thus, two chiral centers were produced in good selectivity as compared to 2-*E*-heptenal which gives only 2.4/1 selectivity.[32] K_2CO_3 in MeOH selectively cleaved the alkynyl-TMS group to provide free alkyne **20**, whose hydrostannylation provided the C(20)−C(34) vinylstannane **21**, ready for the ensuing Stille coupling. It was found that $Pd(dppf)Cl_2$ is a far superior catalyst to $Pd(PPh_3)_4$ in the hydrostannylation. Attempted hydroboration or hydrozirconation−iodination of **20** resulted in decomposition.

Since the Stille coupling is compatible with a carboxylic acid functionality, as was reported by Stille himself,[33] we proceeded to the reaction between C(1)−C(19) vinyl iodide carboxylic acid **14** and C(20)−C(34) vinylstannane **21** (Scheme 6). By screening a number of catalytic systems,[34] we found the conditions of Tadano [$Pd(PPh_3)_4$ and CuCl in

(24) An inspection of the NMR spectrum of the reaction mixture taken prior to workup indicates the presence of about 65% desired product and no remaining aldehyde starting material.

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(31) A similar reaction was employed by Fürstner in ref 11.

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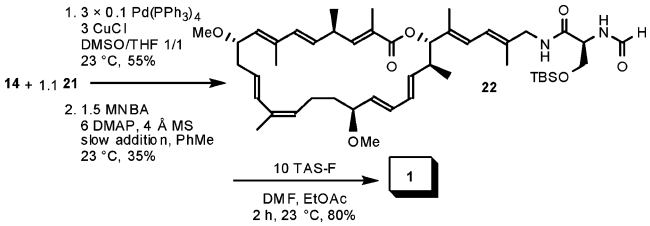
(33) Stille, J. K.; Sweet, M. P. *Tetrahedron Lett.* **1989**, *30*, 3645.

(34) Conditions screened: $PdCl_2(MeCN)_2$, $PdCl_2(BnCN)_2$, $PdCl_2(PPh_3)_2$, $PdCl_2(AsPh_3)_2$, $Pd(PPh_3)_4$, $Pd_2(dba)_3$, CuTC, CuCl, CuI, $AsPh_3$, P(*o*-Tol)$_3$, ([(*n*-Bu)$_4$N][Ph_2PO_2]), LiCl, CsF, O=PPh_3, BHT, and/or *i*-Pr_2NEt in various solvents.

Scheme 6. Completion of the Total Synthesis



DMSO/THF][15] to give the most reproducible results and the highest yield for this Stille coupling at room temperature. A maximum yield of 58% was achieved in simpler model systems, with loss of material caused by protodestannylation. Since the resulting *O*-TBS-protected iejimalide open-chain carboxylic acid proved difficult to purify, we employed the crude product in the subsequent macrocyclization step.

We realized that the formation of the macrolide ring would be challenging in this system due to a combination of the hindered nature of the secondary C(23) hydroxyl group, the complex functionalization pattern of the substrate, and the usual problems associated with large ring formation. We, therefore, explored the use of selected methods of macrolactonization, including those of Yamaguchi,[35] Mukaiyama,[36] and Shiina.[37] For our substrate, we found the Shiina macrolactonization protocol to be the most effective;[38] a solution of the intermediate *seco*-acid was slowly added to a solution of DMAP and 2-methyl-6-nitrobenzoic anhydride containing powdered molecular sieves. Although occurring in modest yield, this is the first case of its application to form such a richly functionalized large-ring system compared to other recent applications.[39] Desilylation completed the total synthesis of iejimalide B (**1**).

Synthetic iejimalide B is identical by HPLC, ^{1}H NMR, HRMS, and biological activity (within normal assay limits) to natural iejimalide B, which was isolated in our laboratory from the tunicate[3] [LC_{50} (prostate cancer cell line LNCaP, 72 h) = 5−8 nM (synthetic **1**) and 20−30 nM (natural **1**)], and therefore, Kobayashi's assignment[2] of its structure and absolute configuration is confirmed. In comparison, the biological activity of *O*-TBS protected iejimalide B (**22**), LC_{50} (LNCaP, 72 h) = 160−225 nM, is reduced but falls within the range of one of the iejimalide *O*-carbamate derivatives previously studied by us.[3]

In conclusion, this total synthesis of iejimalide B provides access to the final product and potentially many possible analogues. The overall yield is 3% for the longest linear sequence of 13 steps starting from **5** or **6**. Notable features of this total synthesis include Julia couplings of elaborated substrates, an application of Carreira's enantioselective alkyne addition to an α-unsubstituted aldehyde, a Marshall propargylation with good selectivity, the use of Pd(dppf)Cl_2 as a superior catalyst for hydrostannylation, a Stille coupling of highly complex substrates, and a complex application of the Shiina macrolactonization.

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Supporting Information Available: Experimental procedures and characterization data of all key reaction products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(38) In our hands, application of Mukaiyama conditions did not result in macrolactonization. However, the Yamaguchi macrolactonization also provided the desired product, but only in about half the yield of the Shiina method. We did not observe aromatization to a phenol during the Yamaguchi macrolactonization as was reported by Fürstner in ref 11a.

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