*Total Synthesis*

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# Studies on Iejimalide B: Preparation of the Seco Acid and Identification of the Molecule's "Achilles Heel"**

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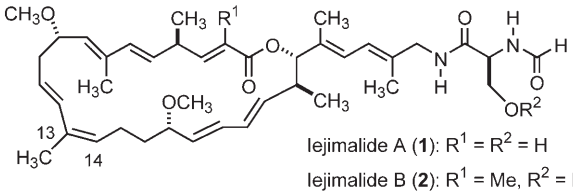
Extraction of the tunicate *Eudistoma* cf. *rigida* collected off Ie island, Okinawa province, Japan, led to the isolation of a family of novel 24-membered polyene macrolides designated iejimalides A–D (**1**–**4**).[1] Although the structure of these



Iejimalide A (**1**): $R^1 = R^2 = H$
Iejimalide B (**2**): $R^1 = Me$, $R^2 = H$
Iejimalide C (**3**): $R^1 = H$, $R^2 = SO_3Na$
Iejimalide D (**4**): $R^1 = Me$, $R^2 = SO_3Na$

extremely scarce cytotoxic metabolites (0.0003–0.0006 % of the tunicates wet weight) could be established, it was only after a reextraction from a *Cystodytes* sp. that enough

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material was accumulated to allow for the establishment of their relative and absolute stereochemistry; at the same time, the configuration of the C13–C14 double bond was corrected to *Z* (rather than *E* as originally assigned).[2]

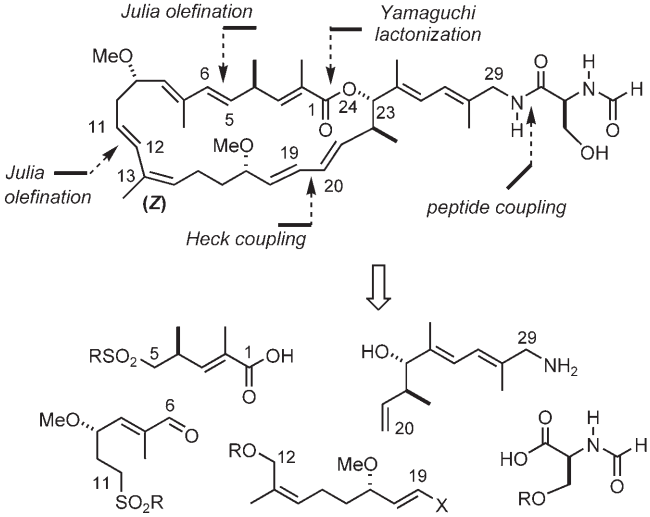
The scarcity of the iejimalides also delayed in-depth studies of their physiological properties; details reported recently, however, are very encouraging. Specifically, the data for iejimalide A, disclosed in 2005 by the National Cancer Institute (NCI), illustrates the truly remarkable potency of **1** against the panel of 60 standard human cancer cell lines, with the concentrations required to inhibit growth by 50% ($GI_{50}$) and tumor gene index (TGI) values in the low nanomolar range.[3,4] Equally remarkable is the report by Kobayashi and co-workers that the activity profile of **1**–**4** does not correlate with those of other anticancer drugs, which might indicate an unprecedented mode of action.[2] The same authors also demonstrated the potent in vivo activity of **3** and **4** against P388 leukemia.[2a]

Collectively, these data suggest that the iejimalides may be candidates for further development in a (pre)clinical setting. Spurred on by this prospect, we ventured into a synthesis-driven investigation of these enticing targets.[5] Therefore, it was necessary to prepare sufficient amounts for further testing. Presented in this and the following Communication is a preliminary report on our endeavors in the field, which not only led to the first total synthesis of iejimalide B (**2**) as the most active member of the series, but also unraveled many of the peculiar chemical characteristics of these delicate lead compounds.[6,7]

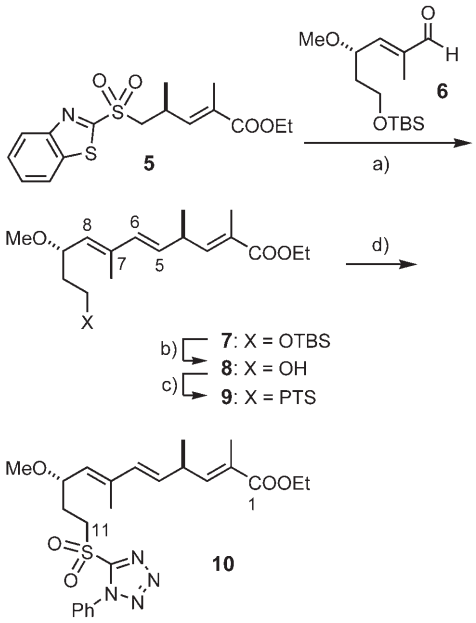
A cursory inspection of **1**–**4** shows that five of the six chiral centers reside at allylic or even doubly allylic sites. Apprehensive that this feature likely potentiates the lability of their polyunsaturated backbones, our first approach to **2** gravitated toward methodology that is believed to cope with such potentially fragile structural elements.

Specifically, it was planned to incorporate the peptide residue at the very end of the synthesis, because of the proclivity of *N*-formylserine derivatives toward racemization, formyl cleavage, and oxazoline formation. The success of the venerable Yamaguchi macrolactonization in complex settings[8,9] and our excellent experiences with the Julia olefination for the elaboration of sensitive, and even enolizable compounds, suggested the use of these transformations in the present context.[10,11] Complemented by Pd-catalyzed C–C bond formations,[12] this ensemble of reliable and mild chemical reactions promised a flexible access route to **2** starting from five synthons of similar size and moderate complexity (Scheme 1).

The required building block **10** (Scheme 2) was prepared by a Julia olefination of sulfone **5** (derived from the commercial Roche ester)[13] and aldehyde **6** (derived from commercial (*S*)-2-hydroxybutyrolactone)[13] to give alkene **7** in almost quantitative yield in a diastereomeric ratio of *E*/*Z* = 4:1. Since attempted isomerization with PhSSPh/azobisisobutyronitrile (AIBN) led to a complex mixture, (*E*)-**7** and (*Z*)-**7** were separated by preparative HPLC prior to removal of the terminal *tert*-butyldimethylsilyl (TBS) ether and installation of a phenyltetrazolyl sulfone terminus in **10** by the standard two-step protocol. It is notable that the cleavage of the silyl




***Scheme 1.*** "First generation" retrosynthetic analysis and Kobayashi's numbering scheme of iejimalide B (**2**).



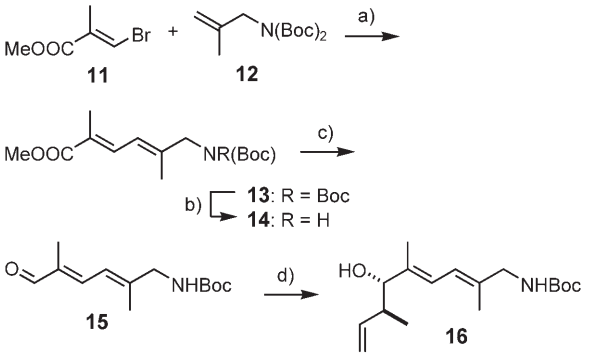

***Scheme 2.*** a) NaHMDS, THF, −78 °C→RT ("Barbier conditions"), 89% (*E*/*Z* = 4:1); b) HCl (5% in EtOH), EtOH, 0 °C, 60%; c) 1-phenyl-1*H*-tetrazol-5-thiol, DEAD, $PPh_3$, THF, 82%; d) cat. $[Mo_7O_{24}(NH_4)_6]\cdot 4H_2O$, aq $H_2O_2$, EtOH, 75%. HMDS = 1,1,1,3,3,3-hexamethyldisilazane, DEAD = diethylazodicarboxylate, PTS = 1-phenyl-1*H*-tetrazol-5-thiyl.

ether in **7** worked only with dilute HCl in EtOH; the use of tetra-*n*-butylammonium fluoride (TBAF)/HOAc affected the integrity of the conjugated diene. Although this finding forecasted there would be subtle stability issues, it was not until the late stages of the synthesis that this aspect was fully appreciated.

The complementary hemisphere of **2** was accessible by adaptation of a literature route,[7a] involving an effective Heck reaction of **11** and **12** as the key step,[14] delivering multigram

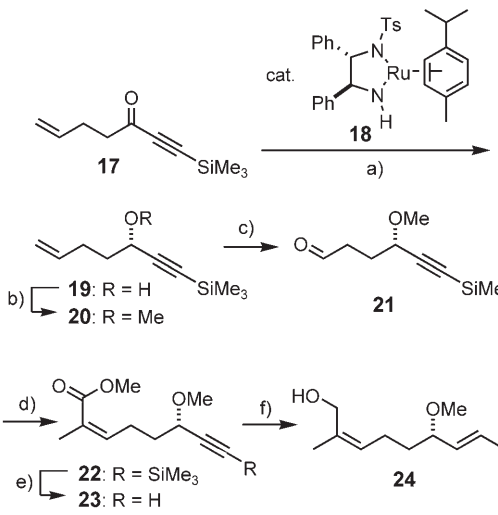
amounts of aldehyde **15** (Scheme 3). This compound was then subjected to Brown crotylation[15] to install the *anti*-configured homoallylic motif of **16** in excellent chemical yield and remarkable optical purity (*anti*/*syn* 98:2, 95 % *ee*).



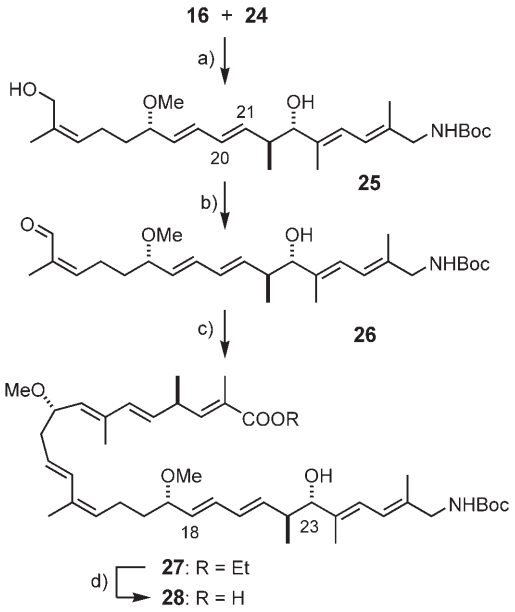

***Scheme 3.*** a) $Pd(OAc)_2$ (3 mol%), P(*o*-tol)$_3$ (6 mol%), $Et_3N$, 100°C, 84%; b) trifluoroacetic acid, $CH_2Cl_2$, 87%; c) 1. DIBAL-H, $CH_2Cl_2$, −78°C, 97%; 2. DMSO, $(COCl)_2$, $Et_3N$, $CH_2Cl_2$, −78°C→RT, 79%; d) (+)-((*E*)-crotyl)-B(Ipc)$_2$, THF, −78°C, 82% (95% *ee*). Boc = *tert*-butyloxycarbonyl, tol = tolyl, DIBAL-H = diisobutylaluminum hydride, Ipc = isopinocampheyl.

The coupling partner **24** was prepared by asymmetric transfer hydrogenation of ketone **17**[13] following conditions developed by Noyori and co-workers and furnished propargyl alcohol **19** in 98% yield and 98.8% *ee*, without affecting the olefinic and the acetylenic sites in the vicinity (Scheme 4).[16] In contrast, however, the seemingly trivial conversion of **19** into methyl ether **20** was surprisingly troublesome. After considerable experimentation, it was found that the use of DMSO as a dipolar cosolvent gave satisfactory and reproducible results on fairly large scale reactions.[17] Oxidative cleavage of the double bond followed by a modified Still–Gennari olefination of the resulting aldehyde **21** afforded the required *Z*-configured enoate **22** as a single isomer.[18,19] Cleavage of the silyl group with $K_2CO_3$ in MeOH,[20] exhaustive reduction/carbometalation of the resulting product **23** with an excess of $[Cp_2Zr(H)Cl]$,[21] and an iodolytic workup completed the synthesis of alkenyl iodide **24**, which was obtained in 34% yield over seven readily scalable operations.

Since the homoallylic terminus renders **16** directly amenable to cross-coupling under Heck conditions, this particular C–C bond formation was preferred over other conceivable reactions. Despite its impressive track record,[14] attempted fusion of iodide **24** with alkene **16** under various experimental conditions led to a morass of isomers. A successful coupling of these components was only possible after switching to the "cationic manifold", which is operative upon addition of AgOAc (1.2 equiv)[22] (Scheme 5). The desired *E*,*E*-configured diene **25** could be separated from the *E*,*Z* isomer by careful chromatography.




***Scheme 4.*** a) **18** (0.6 mol%), *i*PrOH, 98% (98.8% *ee*); b) 1. *n*BuLi, MeI, THF, −78°C; 2. DMSO, −25°C→RT; c) cat. $OsO_4$, $NaIO_4$, 2,6-lutidine, aq 1,4-dioxane, 74% (over two steps); d) $(CF_3CH_2O)_2P(O)CH(Me)COOMe$, KHMDS, [18]crown-6 (0.7 equiv), toluene, −20°C, 87%; e) $K_2CO_3$, MeOH, 80%; f) $[Cp_2Zr(H)Cl]$ (3.1 equiv), THF, then $I_2$, 80%. Cp = cyclopentadienyl, Ts = toluene-4-sulfonyl.

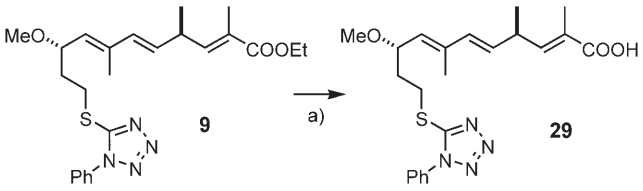



***Scheme 5.*** a) $Pd(OAc)_2$ (10 mol%), AgOAc, DMF, RT, 46% (**25**) + 13% ($\Delta^{[20,21]}$ isomer); b) cat. *t*BuOK, cat. $CuBr_2$, cat. 2,2′-bipyridine, cat. TEMPO, $O_2$ (1 atm), $MeCN/H_2O$ (2:1), 94%; c) **10**, NaHMDS, THF, −78°C→RT, 57% (*E*/*Z* > 10:1); d) $Me_3SnOH$ (40 equiv), 1,2-dichloroethane, 80°C, 94%. TEMPO = 2,2,6,6-tetramethyl-1-piperidinoxyl (free radical), TES = triethylsilyl, PMB = *para*-methoxybenzyl.

Although both alcohol groups in **25** are allylic, the selective oxidation of the primary one was accomplished with the aid of a procedure co-catalyzed by copper and TEMPO, using $O_2$ as the ultimate oxidant.[23] The resulting aldehyde **26** was amenable to Julia–Kocienski olefination[10,24] with tetrazolylsulfone **10**, provided that this reagent was deprotonated with an excess of NaHMDS in the presence of the aldehyde ("Barbier conditions").

The success of this transformation attests to the maturity of the Kocienski methodology, especially if one considers that an unprotected OH group,[25] a carbamate, and potentially acidic C–H sites are present in the reaction partners. The desired alkene **27**, which represents the C1–C28 carbon backbone of **2** in a fully functional form, was obtained in a reproducible yield of 57% with excellent selectivity for the required *E* isomer ($E/Z > 10{:}1$, NMR).

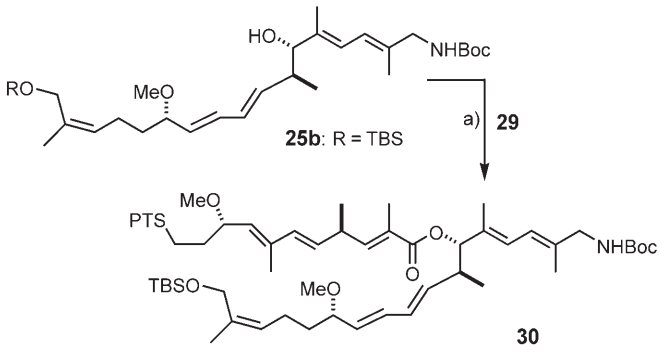
At this stage, iejimalide B seemed to be just a few standard manipulations away; the most important lessons, however, had yet to be learned. First, attempted conversion of ester **27** into the required seco acid **28** turned out to be very difficult. While saponification of the north segment **9**, naively considered as a valid model, worked as expected (Scheme 6),




***Scheme 6.*** a) aq LiOH (1 M), THF/MeOH (1:1), RT, 91%.

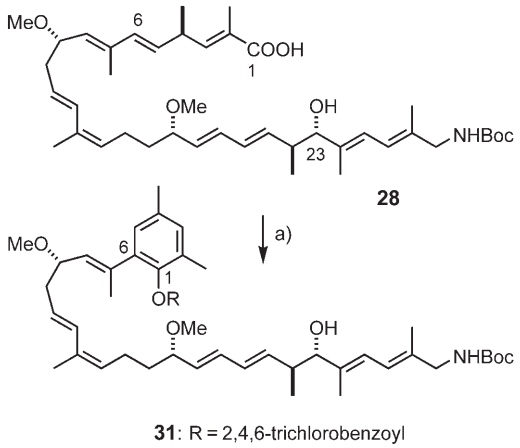
attempted saponification of **27** compromised the seemingly remote C18–C23 region of the molecule without touching the ester function at all; other standard conditions were equally unsuitable. Only the procedure recently outlined by Nicolaou et al. afforded the desired product **28**,[26,27] although a large excess of $Me_3SnOH$ and prolonged ($\geq 5$ days) heating were necessary to obtain satisfactory results.

Prior to subjecting this valuable material to macrocyclization, the arsenal of feasible methods[8b] was validated in various model reactions. By far the best results over the entire series were obtained with the Yonemitsu variant of the Yamaguchi method.[8,28] The most advanced and instructive case is the successful esterification of the northern domain **29** with the elaborate south-eastern hemisphere **25b** (R = TBS), which afforded product **30** in a respectable 72% yield (Scheme 7).



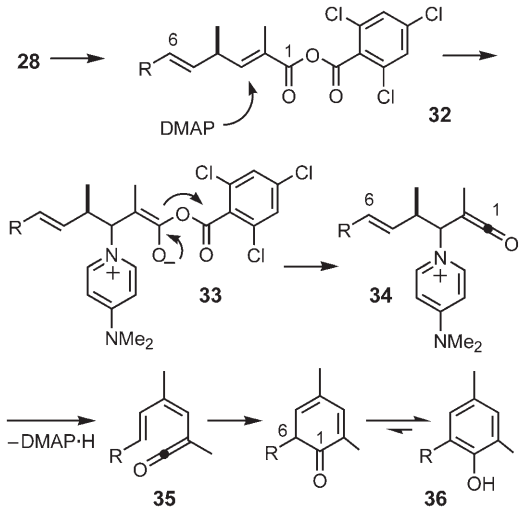

***Scheme 7.*** An intermolecular esterification serving as a model for the projected macrocyclization: a) 2,4,6-trichlorobenzoyl chloride, $Et_3N$, cat. DMAP, toluene, 72%. DMAP = 4-dimethylaminopyridine.

Despite this encouraging precedent, attempted lactonization of seco acid **28** failed to afford the desired macrocycle (Scheme 8). Rather, the C1–C6 unit of the substrate was




***Scheme 8.*** Attempted macrocyclization under Yamaguchi conditions: a) 1. 2,4,6-trichlorobenzoyl chloride, $Et_3N$, THF; 2. cat. DMAP, toluene, see text.

aromatized to a phenol ring, as shown by extensive 2D NMR spectroscopic investigations. The contrast between this outcome and the intermolecular esterification depicted in Scheme 7 is striking. Although phenol **31** was isolated in rather low yields (25–40%), it was the only distinct product that was reproducibly formed under the standard Yamaguchi, as well as the "one-pot" Yonemitsu conditions. Unaware of any precedent, we propose the mechanism depicted in Scheme 9 to explain this unusual result. Attack of the base (most likely DMAP)[29] on the α,β-unsaturated mixed anhydride **32** initially formed may outperform the attack by the hindered alcohol at C23. Collapse of the resulting intermediate **33** is thought to release ketene **34**, which eliminates the dimethylpyridinium moiety to give the polyunsaturated




***Scheme 9.*** Proposed mechanism for the observed phenol formation under Yamaguchi conditions.

ketene **35**, which is set-up for a subsequent 6π-electrocyclization with formation of phenol **36**.[30] This compound is finally acylated to give the observed product **31**.

Despite considerable experimentation, this unfavorable reaction channel could not be avoided.[29] Gentle warming of the mixture with the hope of rendering the attack by the tethered alcohol competitive, only led to the rapid destruction of the starting material. Similarly, applications of other standard macrolactonization strategies[8b] failed.

At this point, we had to conclude that the lactone entity of **2** constitutes a highly vulnerable "Achilles heel" of this unusually sensitive marine natural product in a synthetic context. Even though the required seco acid **28** could be secured by a convergent approach involving one of the most advanced applications of the Julia–Kocienski olefination known to date,[10] our inability to lactonize the seco acid enforced a relaunch of the entire project. Since the crucial ester clearly must be installed intermolecularly, only a macrocyclization by C–C-bond formation can forge the 24-membered ring of **2**. Among the various conceivable options, ring-closing metathesis (RCM) ultimately proved viable,[31] even though application of this method may seem counter-intuitive in view of the necessity to activate a polyunsaturated and likely very fragile cyclization precursor by the catalyst in a strictly regio- and chemoselective fashion. The following Communication reports how this ambitious plan was achieved in practice, although success came only after experiencing yet another "Achilles heel" of the iejimalides that went undetected in the studies summarized above.[6]

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