Total Synthesis

DOI: 10.1002/anie.200601860

Total Synthesis of Iejimalide B**

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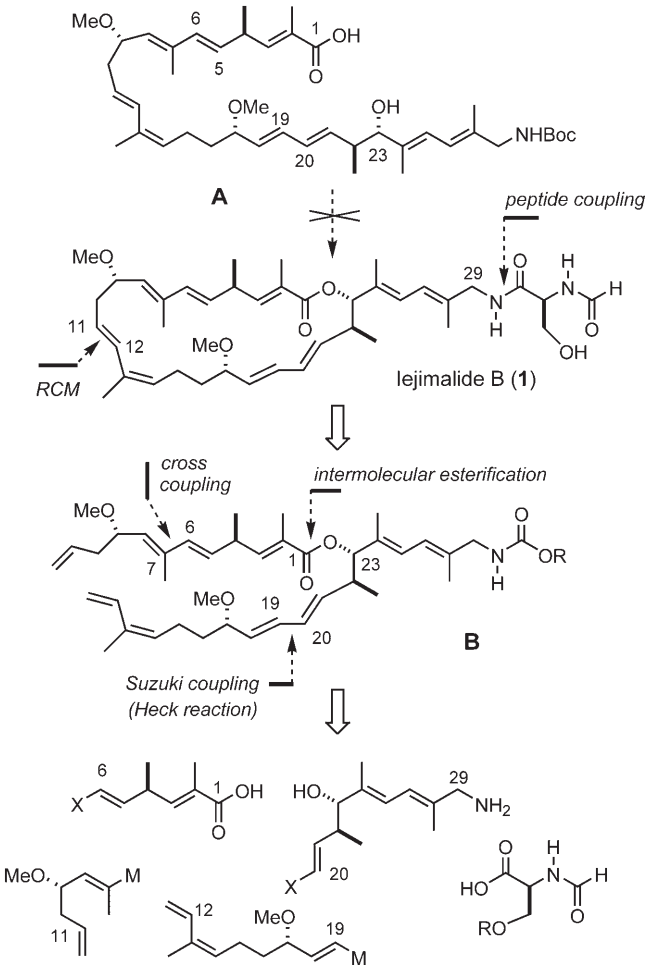
Recent disclosures of the potent cytotoxicity and in vivo anticancer activity of the iejimalides are expected to revitalize the interest in these polyene macrolides, which were reported by Kobayashi and co-workers as early as 1988.[1–3] Extracted in minute amounts from tunicates harvested off the south Japanese coast, the limited availability of these natural products constitutes the prime obstacle for more detailed preclinical investigations. Intrigued by the prospect of contributing to an in-depth evaluation and challenged by the notably fragile structures of these polyunsaturated compounds, we embarked on a synthesis-driven investigation at the chemistry/biology interface. As the initial step of this endeavor, we now present the first total synthesis of iejimalide B (**1**), the most active member of this family.

This project would not have been successful without the intelligence gathered in a parallel approach in which a macrolactonization was envisaged for the formation of the 24-membered ring.[4] This key step, however, failed to afford the desired lactone but engaged the seco acid (**A**, Scheme 1) in a previously unknown aromatization process. Therefore, we concluded that the ester bond in **1** should be formed intermolecularly and hence the macrocyclization must occur at a C–C bond. Although counterintuitive at first sight, we opted for metathesis,[5] not least because of our excellent experiences with this catalytic transformation in a variety of complex settings.[6]

Nonetheless, this strategic decision bore considerable risk because application of RCM to the present case demands for no less than the selective activation of two out of ten double bonds in the cyclization precursor **B** (Scheme 1).[7] Moreover,



Scheme 1. Refined retrosynthetic analysis of iejimalide B. RCM = ring-closing metathesis, Boc = *tert*-butyloxycarbonyl.

conjugated dienes in general are known to be problematic substrates for metathesis. It is well precedented that Grubbs-type catalysts may attack either double bond; in a cyclization process, this lack of regioselectivity engenders problems with ring contraction, not to mention the still missing control over the stereochemical outcome of the reaction.[7,8] With this analysis and the known influence of chelating groups on the effectiveness of RCM in mind,[9] the C11–C12 double bond in **1** seemed to be the only promising site for an RCM-based macrocyclization approach.

Although the assembly of the required precursor **B** could certainly be achieved merely by adapting the route leading to the seco acid **A**,[4] we took the relaunch of the project as an

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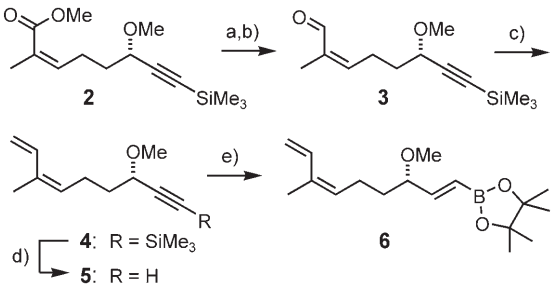
[**] Generous financial support from the MPG, the Fonds der Chemischen Industrie, the Alexander-von-Humboldt Foundation (fellowship to C.N.), the NSERC Canada (fellowship to M.T.), and the Austrian Fonds zur Förderung der Wissenschaftlichen Forschung (fellowship to M.W.) is gratefully acknowledged. We thank Dr. R. Mynott, B. Gabor, and C. Wirtz for their invaluable help with the structure assignment of several key compounds, and R. Leichtweiß for HPLC assistance.

opportunity to address some of the encountered shortcomings. Highest priority on our agenda was given to the fragment coupling at C19-C20 by a Heck reaction, which afforded only 46% yield of the product and required a tedious chromatographic purification. Therefore we opted for a Suzuki coupling as an alternative, which is known to be highly effective even in demanding cases.[10] Likewise, the entire assembly process might be streamlined if the stereo-unselective Julia olefination forging the C5–C6 alkene in **A** could be replaced by a stereochemically unambiguous step; again, a palladium-catalyzed cross coupling at the adjacent C6–C7 bond might qualify for this purpose.

The implementation of this refined analysis started with the readily available ester **2**,[4] which was converted by a sequence of routine operations into diene **4** (Scheme 2).

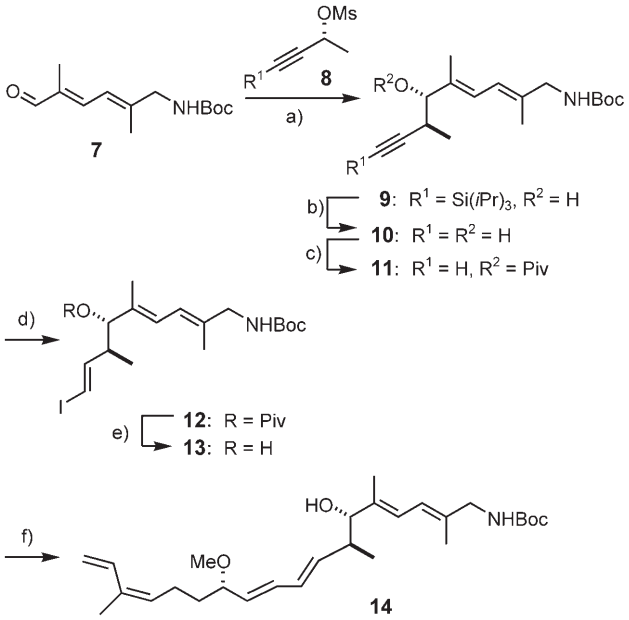


Scheme 2. a) DIBAL-H, CH_2Cl_2, −78 °C; b) MnO_2, CH_2Cl_2, 96% (over two steps); c) Ph_3PCH_3Br, *n*BuLi, THF, −78 °C→RT, quant.; d) K_2CO_3, MeOH, 83%; e) pinacolborane, 9-BBN (10 mol%), THF, 45 °C, 56%. DIBAL-H = diisobutylaluminum hydride, 9-BBN = 9-borabicyclo-[3.3.1]nonane.

Subsequent cleavage of the silyl group afforded the terminal alkyne **5** (>97% *ee*), which underwent a chemoselective hydroboration with pinacolborane without damaging the tethered 1,3-diene entity, provided that catalytic amounts of 9-BBN were added to the reaction mixture.[11]

A suitable coupling partner for this Suzuki donor was prepared by a palladium-catalyzed, Et_2Zn-mediated addition of the enantiopure propargyl mesylate **8**[12] to aldehyde **7** (Scheme 3).[4] The best *anti* selectivity was obtained with **8a**, which bears a triisopropylsilyl (TIPS) group at the acetylene moiety (7.5:1 d.r.), whereas the use of the terminal alkyne **8b** ($R^1 = H$) was less satisfactory (3.5:1 d.r.). After chromatographic purification, the major isomer **9** was obtained in 72% yield. Subsequent cleavage of the silyl group gave **10** which was temporarily protected as the corresponding pivalate **11**. Hydrozirconation/iodination[13] followed by the chemoselective cleavage of the pivalate with DIBAL-H readily afforded the required alkenyl iodide **13**.

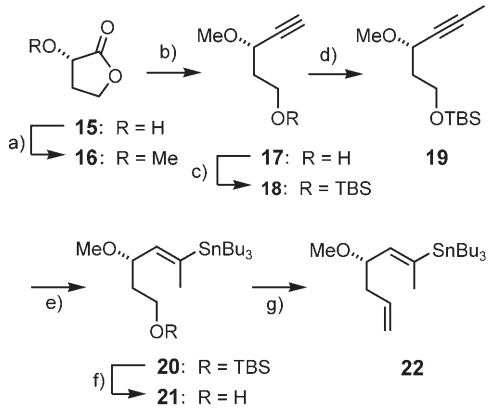
At this juncture, we were facing the challenge to join fragments **6** and **13** by a Suzuki coupling.[10] Having previously experienced the sensitivity of advanced iejimalide subunits towards basic conditions,[4] much care was taken to optimize the reaction conditions. Following a lead from the recent literature in which $Ba(OH)_2{\cdot}8H_2O$ was shown to be a particularly suitable promoter for the formation of products embodying fragile diene units,[14] these conditions were



Scheme 3. a) $[Pd(OAc)_2]$ (5 mol%), PPh_3 (5 mol%), Et_2Zn (3 equiv), THF, −78 °C→−20 °C, 72%; b) TBAF, THF, 94%; c) pivaloyl chloride, pyridine, 0 °C→RT, 76%; d) $[Cp_2Zr(H)Cl]$, THF, then I_2, 0 °C→RT, 85%; e) DIBAL-H, CH_2Cl_2, −78 °C, 87%; f) boronate **6**, $[PdCl_2(dppf)]$ (15 mol%), $Ba(OH)_2{\cdot}8H_2O$ (1.2 equiv), DMF, 40 °C, 70%. Ms = methanesulfonyl, TBAF = tetra-*n*-butylammonium fluoride, Piv = pivaloyl, dppf = 1,1′-bis(diphenylphosphanyl)ferrocene.

adapted to the present case and found to be highly suitable. In fact, the amount of base could be reduced to 1.2 equivalents and the reaction was found to proceed at, or slightly above, room temperature at acceptable rates. Product **14**, as a suitably functionalized surrogate of the entire south-eastern domain of **1**, was thus obtained in 70% yield.

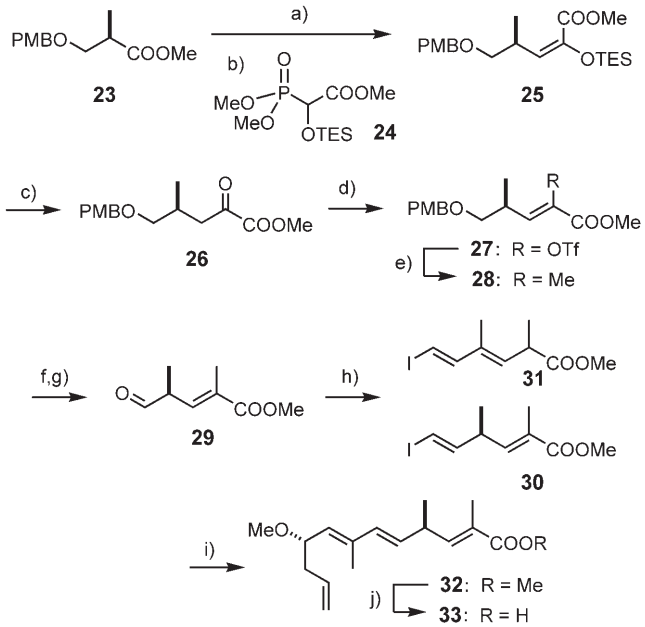
The revised approach to the northern segment of iejimalide B (Scheme 4) commenced with commercial lactone **15**, which was converted on a large scale into alkyne **17** by three



Scheme 4. a) MeI, Ag_2O, MeCN, 92%; b) 1. DIBAL-H, CH_2Cl_2, −78 °C; 2. $MeOC(=N_2)P(O)(OMe)_2$, K_2CO_3, MeOH, 70% (over two steps); c) TBSCl, Et_3N, cat. DMAP, CH_2Cl_2, 90%; d) *n*BuLi, MeI, THF, 98%; e) Bu_3SnH, $[PdCl_2(PPh_3)_2]$ (5 mol%), THF, 65%; f) TBAF, THF, 93%; g) 1. Dess–Martin periodinane, CH_2Cl_2, 84%; 2. $[Ph_3P{=}CH_2]$, THF, −78 °C→RT, 93%. DMAP = 4-dimethylaminopyridine.

routine operations. Subsequent O-silylation and end-capping of the alkyne unit with a methyl group set the stage for a palladium-catalyzed hydrostannation which afforded product **20** in 65% yield.[15] Conventional management of protecting groups and oxidation states, followed by a Wittig reaction, finally delivered compound **22** in pure form.

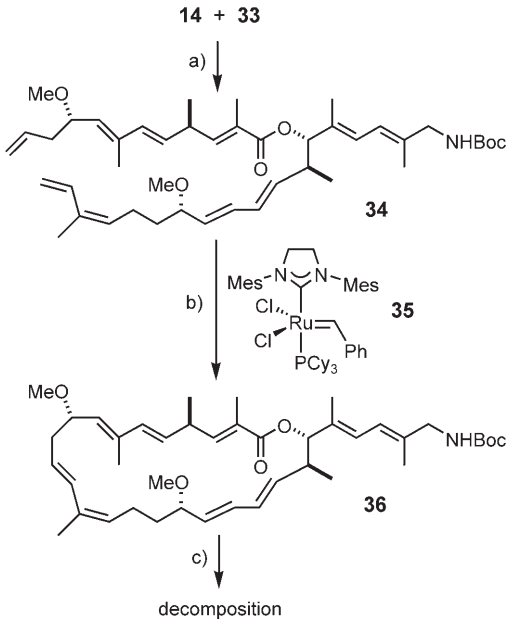
Reduction of the Roche ester derivative **23** with DIBAL-H and chain extension with the functionalized phosphonate **24**[16] gave enol silane **25** as a single isomer (Scheme 5). This



Scheme 5. a) DIBAL-H, CH_2Cl_2, −78 °C; b) **24**, LiHMDS, THF, −78 °C→−40 °C, 75% (over both steps); c) aq HCl, THF, 91%; d) *N*-(5-chloro-2-pyridyl)-bis(trifluoromethansulfonimide), KHMDS, THF, −78 °C→−40 °C, 65%; e) MeZnCl, $[Pd(PPh_3)_4]$ (5 mol%), THF, 50 °C, 91%; f) DDQ, CH_2Cl_2/H_2O, 91%; g) Dess–Martin periodinane, CH_2Cl_2; h) CHI_3, $CrCl_2$, THF/1,4-dioxane (1:6), 62% (over two steps); i) stannane **22**, $[Pd(PPh_3)_4]$ (5 mol%), CuTC, $Ph_2PO_2NBu_4$, DMF, RT, 82%; j) aq LiOH, THF/MeOH, 87%. HMDS = 1,1,1,3,3,3-hexamethyldisilazane, TES = triethylsilyl, PMB = *p*-methoxybenzyl, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, Tf = triflate.

compound afforded the corresponding enol triflate **27** of opposite double-bond configuration by acid-catalyzed hydrolysis, followed by treatment of **26** with Comins reagent[17] in the presence of KHMDS as the optimal base. Triflate **27** could be cross-coupled with MeZnCl in the presence of catalytic amounts of $[Pd(PPh_3)_4]$.[18,19] The PMB ether in the resulting enoate **28** was cleaved with DDQ and the liberated alcohol was oxidized to the corresponding aldehyde **29**, which underwent a Takai olefination[20] to give the desired alkenyl iodide **30** and its double bond isomer **31**.[21] Since these compounds could not be separated, the mixture was subjected to Stille cross-coupling[22] with stannane **22**. This transformation required careful optimization but proceeded nicely under notably mild conditions in the presence of $[Pd(PPh_3)_4]$, copper-2-thiophenecarboxylate (CuTC), and $Ph_2PO_2NBu_4$ in DMF.[23] Since the by-product derived from the cross-coupling of the isomeric iodide **31** could be easily removed after saponification of the ester group, a productive entry into the required acid **33** was secured.

With all the necessary components in hand, the stage was set to probe the envisaged end game of the synthesis. In line with our previous experiences,[4] the intermolecular esterification of **14** and **33** could be effected under Yonemitsu conditions (Scheme 6).[24] We were delighted to see that the

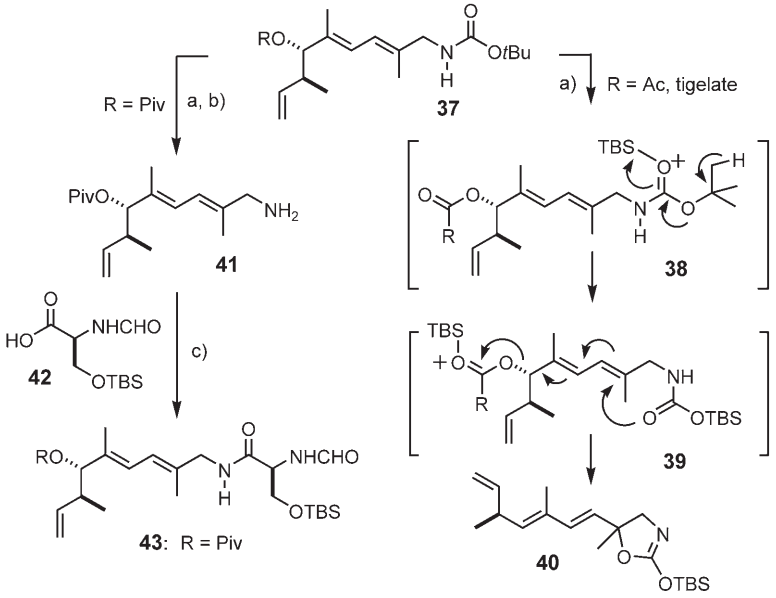


Scheme 6. a) 2,4,6-trichlorobenzoyl chloride, Et_3N, cat. DMAP, toluene, 73%; b) complex **35**, (2×10 mol%), CH_2Cl_2, RT, 2 d, 96%; c) TMSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, see text for further details. TMS = trimethylsilyl, Cy = cyclohexyl, Mes = mesityl.

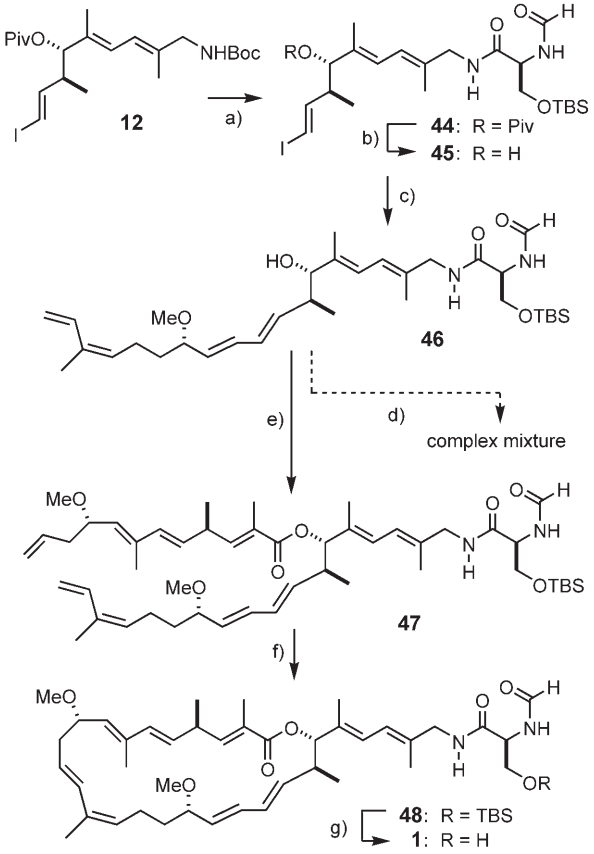
projected ring closure of the polyunsaturated compound **34** with the aid of the "second generation" ruthenium alkenylidene complex **35**[25] gave the desired macrocycle in almost quantitative yield as the required *E* isomer only.

With this gratifying result, the completion of the total synthesis of iejimalide B seemed to be just a matter of two routine operations, that is, cleavage of the Boc group followed by attachment of the serine residue. However, our hopes were dashed by the inability to remove the *N*-Boc group of **36** under a variety of experimental conditions. Even the use of TMSOTf buffered with 2,6-lutidine, reported to be a particularly mild method,[26] failed completely and decomposed the valuable product virtually instantaneously.

Although the degradation pathway of **36** remains unknown, model experiments explain, at least in part, this unexpected behavior (Scheme 7). Thus, treatment of **37a**,**b** (R = Ac and tigelate respectively) with TBSOTf/2,6-lutidine converted these compounds into a common product **40**. It is believed that the conjugated diene efficiently communicates activation of the Boc moiety by the Lewis acid to the remote substituent residing at C23. Rearrangement of the π system extrudes the ester and engenders formation of the heterocyclic motif.



Scheme 7. a) TBSOTf, 2,6-lutidine, CH_2Cl_2, 40 °C, 91 % (R = Ac, 1:1 d.r.); 85 % (R = −C(O)C(Me)=CHMe); b) HOAc, THF, 50 °C; c) compound **42**, EDC, HOBt, NMM, CH_2Cl_2, 0 °C → RT, 95 % (over steps (a)–(c)). EDC = 3-(3-dimethylaminopropyl)-1-ethylcarbodiimide, HOBT = 1-hydroxy-1*H*-benzotriazole, NMM = *N*-methylmorpholine.



Scheme 8. a) 1. TMSOTf, 2,6-lutidine, CH_2Cl_2, then CsF, 0 °C; 2. **42**, EDC, HOBt, NMM, CH_2Cl_2, 85 % (over two steps); b) $LiBEt_3H$, THF, 0 °C, 70 %; c) boronate **6**, [$PdCl_2$(dppf)] (15 mol %), $Ba(OH)_2 \cdot 8H_2O$ (1.2 equiv), DMF, RT, 70 %; d) 2,4,6-trichlorobenzoyl chloride, Et_3N, cat. DMAP, toluene; e) **33**, DCC, 4-pyrrolidinylpyridine (30 mol %), CH_2Cl_2, 0 °C → RT, 84 %; f) complex **35** (15 mol %), CH_2Cl_2 (5×10^{-3} M), RT, 69 %; g) TBAF, THF, 0 °C, 80 %. DCC = *N*,*N*′-dicyclohexylcarbodiimide.

The subtleties in the behavior of iejimalide and the limited analogy between seemingly closely related cases previously encountered on several occasions,[4] re-appeared in this series. Thus, in striking contrast to acetate **37a**, the corresponding pivalate **37c** (R = Piv) allowed for the clean removal of the Boc substituent under otherwise identical conditions; the bulky ester most likely forces **37c** to adopt a conformation in which orbital overlap between the C–O bond and the π system of the diene is minimized, thus blocking the decomposition pathway. The resulting amine **41** was coupled to the L-serine derivative **42**[27] to give product **43** in excellent overall yield.

This dichotomy in the reactivity pattern enforced a final adjustment of our synthetic plan. The crucial role of the protecting group on the lateral amine invalidated the original idea to introduce the peptide moiety last. Since the preparation of **43** provided a way to attach this entity to a readily accessible and validated segment, it was decided to repeat the assembly process with the L-serine already in place, even though the presence of yet another labile structural motif was daunting.

In fact, the method for the introduction of the serine moiety could be translated from the model compound **37c** to alkenyl iodide **12**; the pivalate in the resulting compound **44** was removed with the aid of $LiBEt_3H$ without affecting the formamide entity (Scheme 8). The previous careful optimization of the Suzuki reaction also paid off, since the use of $Ba(OH)_2 \cdot 8H_2O$ allowed for the coupling of **45** and boronate **6** at ambient temperature, which was absolutely crucial for the success of this particular transformation.[28] Although the Yonemitsu method had worked well in several advanced models,[4] most notably in the closely related case depicted in Scheme 6, the seemingly remote serine terminus clearly interfered and did not allow for proper esterification of acid **33** and alcohol **46**; only small amounts (≤ 20 %) of product **47** were formed at 20 °C,[29] while even a moderate increase of the temperature to 35–45 °C destroyed the compound. Gratifyingly, however, the use of DCC/4-pyrrolidinylpyridine worked exceptionally well in this case, and gave ester **47** in 84 % yield.

Cyclization of this polyene with the aid of the ruthenium catalyst **35**[25] delivered the 24-membered macrocycle **48** in 69 % yield as a single *E* isomer. In view of the exceptional thermal lability of the iejimalide precursors in the Suzuki and the esterification steps, it was instrumental that this key operation proceeded at ambient temperature. The outcome of the reaction is truly remarkable if interpreted in light of the implicit selectivity and stability issues. Although the strategic advantages of RCM have been illustrated many times and need no further confirmation,[5,6] we believe that this specific case is particularly instructive, and highlights the superb application profile of Grubbs-type catalysts in general. The first total synthesis of iejimalide B was then completed by cleavage of the remaining TBS ether from the serine residue in **48**. The analytical and spectroscopic data of the synthetic

samples of **1** matched those of the natural product in every detail.[1,2]

In summary, a synthetic route to the potent cytotoxic macrolide iejimalide B (**1**) has been established which provides this valuable marine natural product in sufficient quantity for further testing. As evident from this and the preceding Communication,[4] the development of the successful route required several rounds of adjustment and fine tuning. This struggle largely originated from the exceptionally low level of homology in the behavior of seemingly closely related compounds that differed only in remote and ostensibly innocent substituents. The gathered intelligence, however, should provide a sound basis for the next round of exploration of this promising lead structure. We are currently extending our studies to the other members of this family and translating the acquired knowledge to the design of potential analogues with optimized application profiles.

Received: May 11, 2006
Published online: July 28, 2006

Keywords: anticancer agents · cross-coupling · macrolides · metathesis · natural products

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[19] This route to **27** was chosen for two reasons: first, problems with partial racemization were encountered when the aldehyde derived from **23** was treated with Wittig reagents in an attempt to form **28** directly; secondly, it is known that iejimalide B bearing a methyl group at C2 is more active than iejimalide A which features a proton at this position, see Ref. [2]; the chosen route via triflate **27** allows for systematic variations at this position.

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