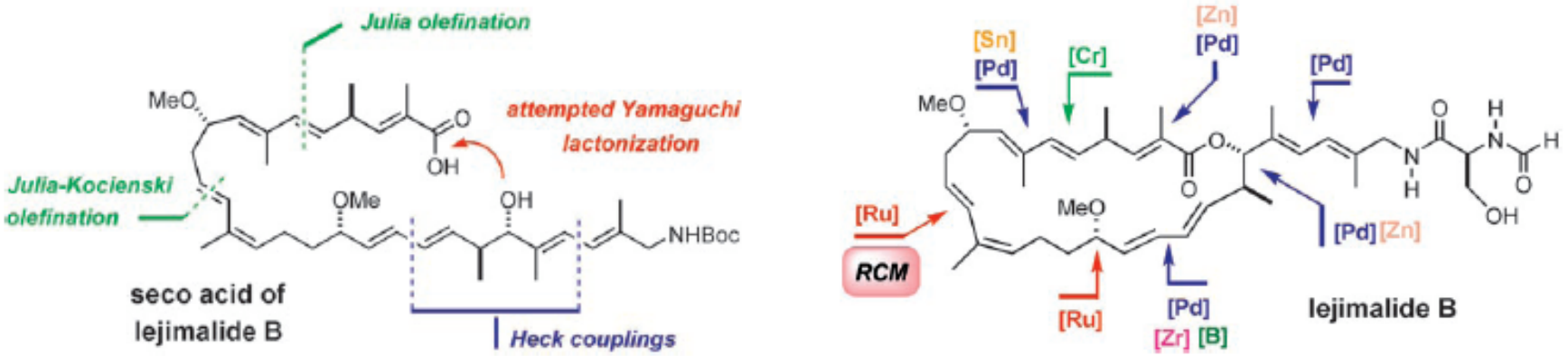
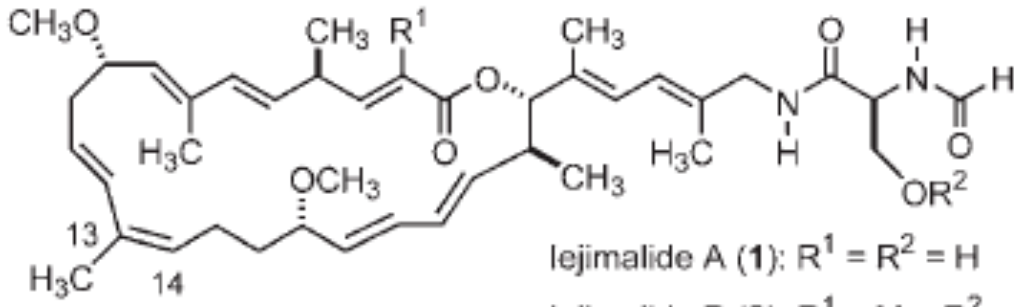
Total Synthesis of Iejimalide B

Furstner, A.; Aissa, C.; Chevrier, C.; Teply, F.; Nevado, C.; Tremblay, M. M. *Angew. Chem. Int. Ed.* ASAP.
Furstner, A.; Nevado, C.; Tremblay, M.; Chevrier, C.; Teply, F.; Aissa, C.; Waser, M. *Angew. Chem. Int. Ed.* ASAP.



Zhiyong Wang
Wipf Group
Current Literature Presentation
August 12th, 2006

Iejimalides - Cytotoxic Polyene Macrolides from *Eudistoma* cf.*Rigida*



Iejimalide A (**1**): $R^1 = R^2 = H$

Iejimalide B (**2**): $R^1 = Me$, $R^2 = H$

Iejimalide C (**3**): $R^1 = H$, $R^2 = SO_3Na$

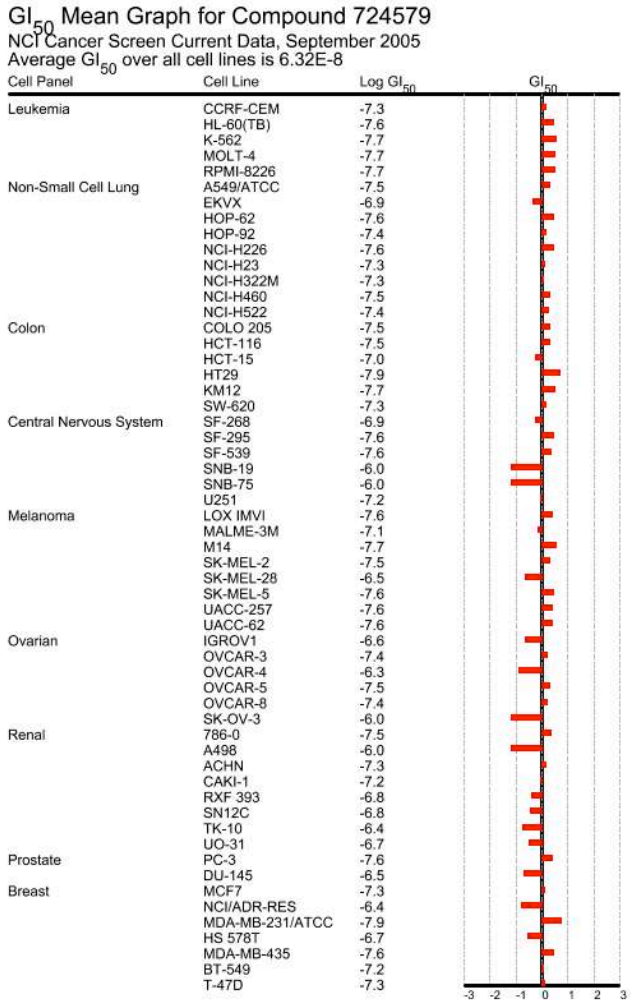
Iejimalide D (**4**): $R^1 = Me$, $R^2 = SO_3Na$

- Extracted from the tunicate Eudistoma cf. rigida
- Extremely scarce (0.0003-0.0006% yield from wet tunicates)

Kobayashi, J. et al. *J. Org. Chem.* **1988**, *53*, 6147-6150.
Kikuchi, Y. et al. *Tetrahedron Lett.* **1991**, *32*, 797-798.

Biological Activities of Iejimalides

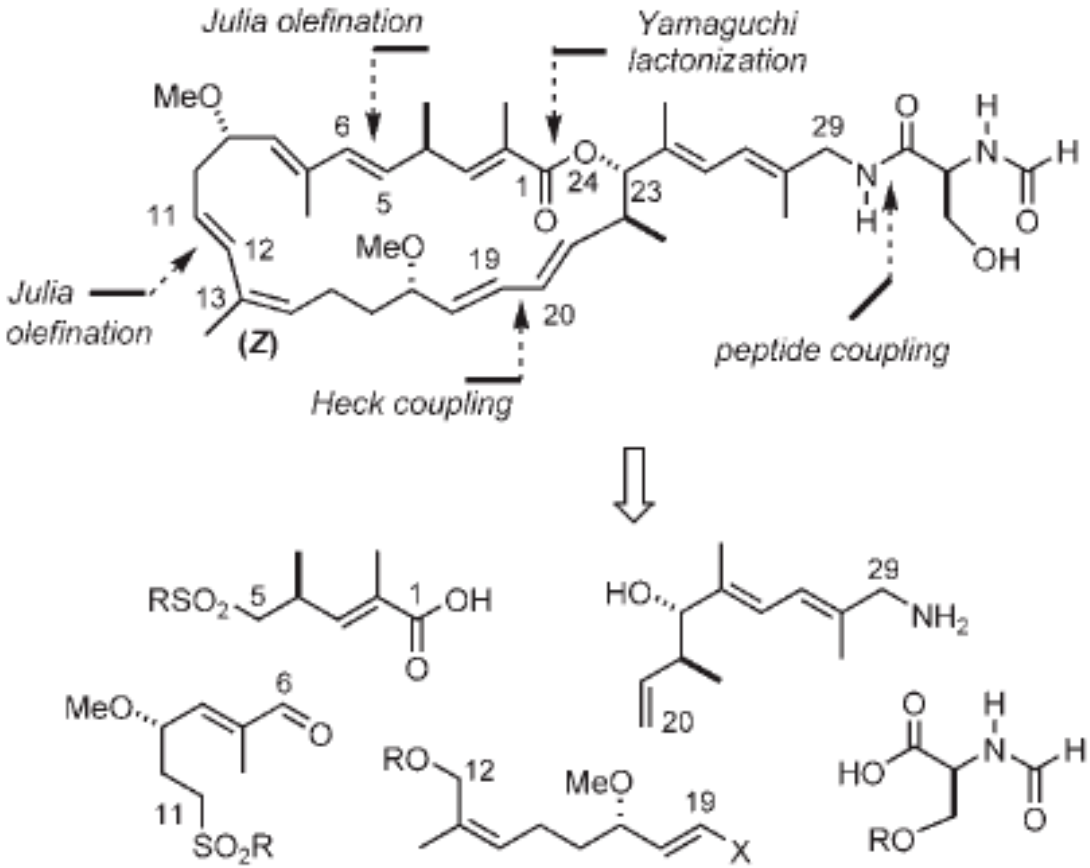
- GI_{50} (50% growth inhibition) and TGI (tumor gene index) in the low nanomolar range against NCI cancer cell lines.
- The activity profile of iejimalides does not correlate with those of other anticancer drugs, which might indicate an unprecedented mode of action.



http://www.dtp.nci.nih.gov/docs/dtp_search.html

Nozawa, K. et al. *Bioorg. Med. Chem.* **2006**, *14*, 1063-1067.

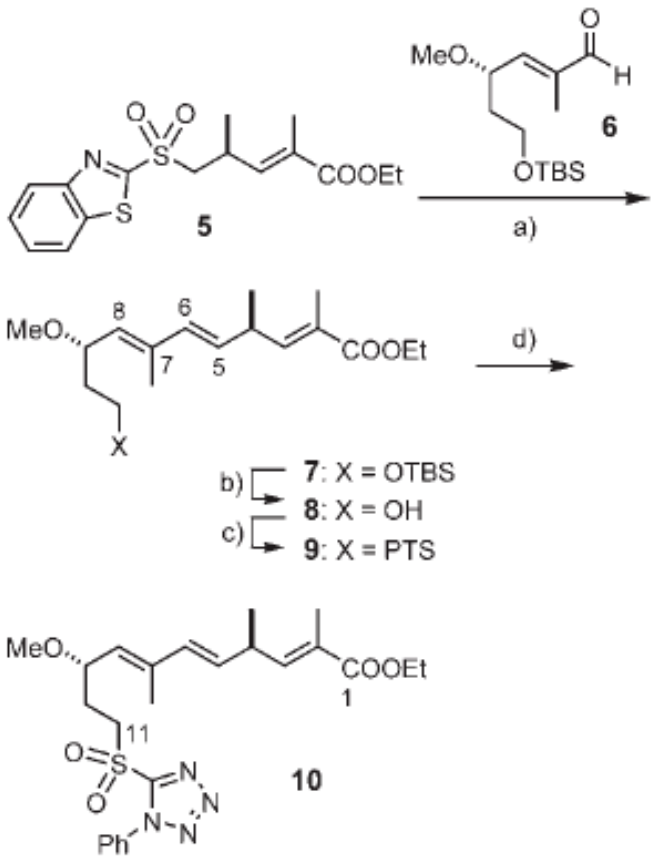
Part I. Identification of the Molecule's "Achilles Heel'

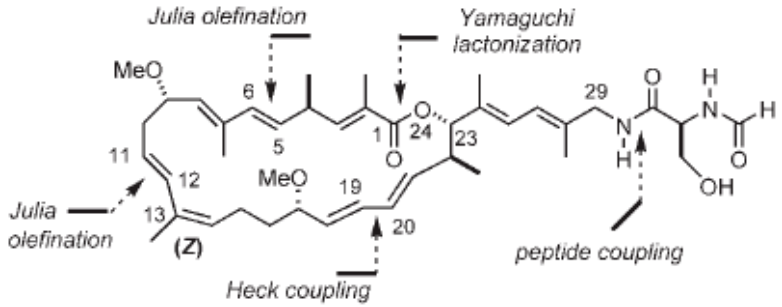


Scheme 1. "First generation" retrosynthetic analysis and Kobayashi's numbering scheme of iejimalide B (**2**).

Furstner, A. et al. *Angew. Chem. Int. Ed.* ASAP.

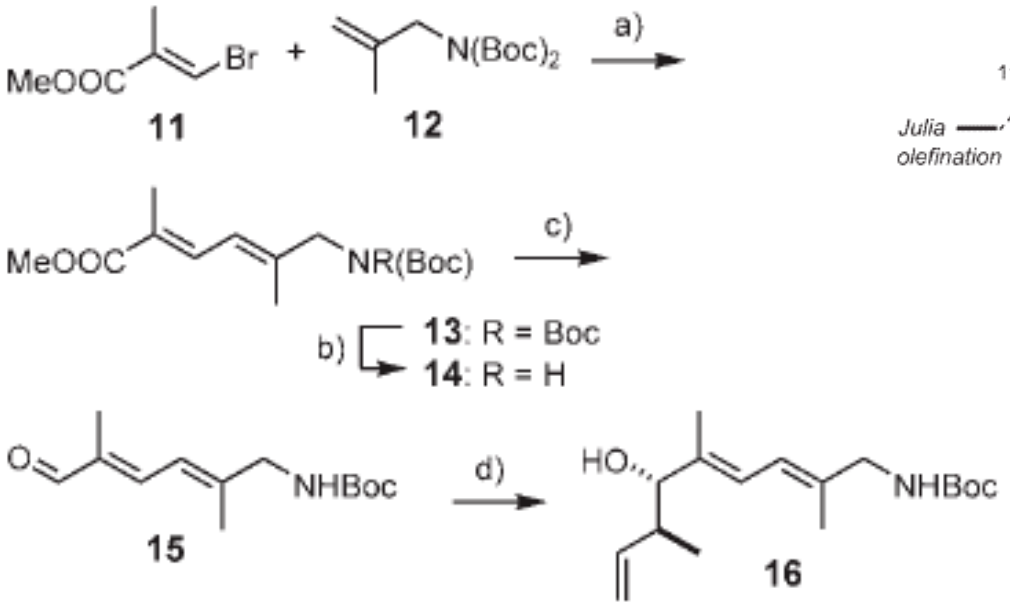
Synthesis of *C*1-*C*11

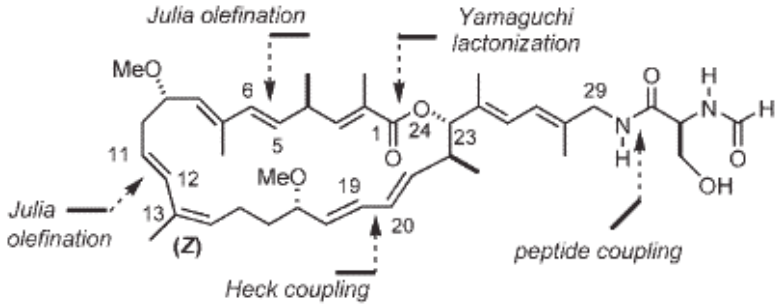




Scheme 2. a) NaHMDS, THF, −78 °C → RT ("Barbier conditions"), 89% (*E*/*Z* = 4:1); b) HCl (5% in EtOH), EtOH, 0 °C, 60%; c) 1-phenyl-1*H*-tetrazol-5-thiol, DEAD, PPh_3, THF, 82%; d) cat. $[Mo_7O_{24}(NH_4)_6]\cdot 4H_2O$, aq H_2O_2, EtOH, 75%. HMDS = 1,1,1,3,3,3-hexamethyldisilazane, DEAD = diethylazodicarboxylate,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

Synthesis of *C*20-*C*29

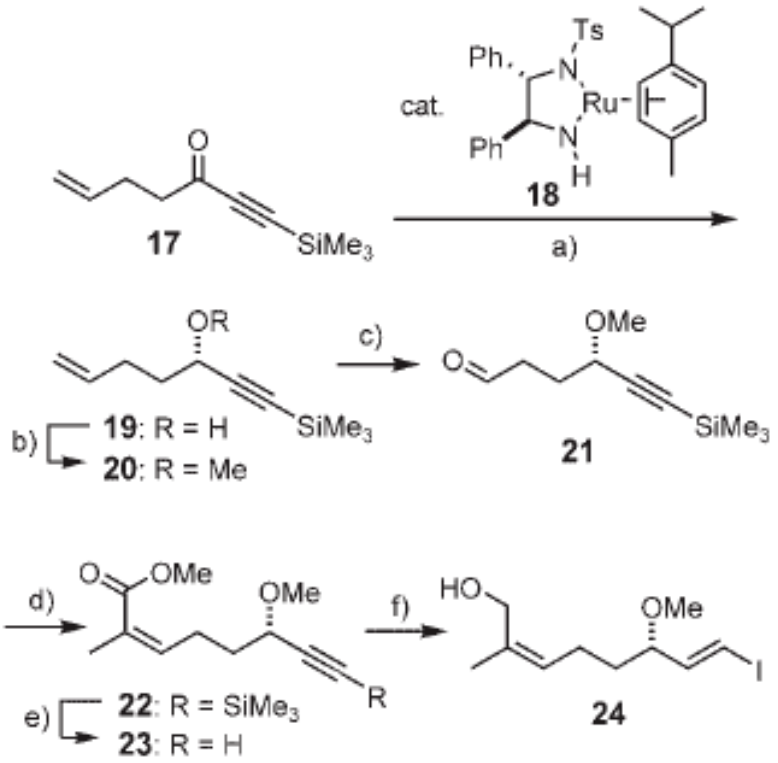


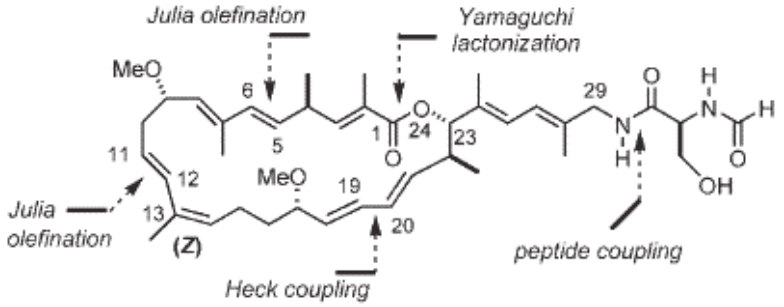


Scheme 3. a) $Pd(OAc)_2$ (3 mol%), P(*o*-tol)$_3$ (6 mol%), Et_3N, 100 °C, 84%; b) trifluoroacetic acid, CH_2Cl_2, 87%; c) 1. DIBAL-H, CH_2Cl_2, −78 °C, 97%; 2. DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78 °C → RT, 79%; d) (+)-((*E*)-crotyl)-B(Ipc)$_2$, THF, −78 °C, 82% (95% *ee*). Boc = *tert*-butyloxycarbonyl,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

Cottard, M. et al. *Tetrahedron Lett.* **1995**, *36*, 3115-3118.

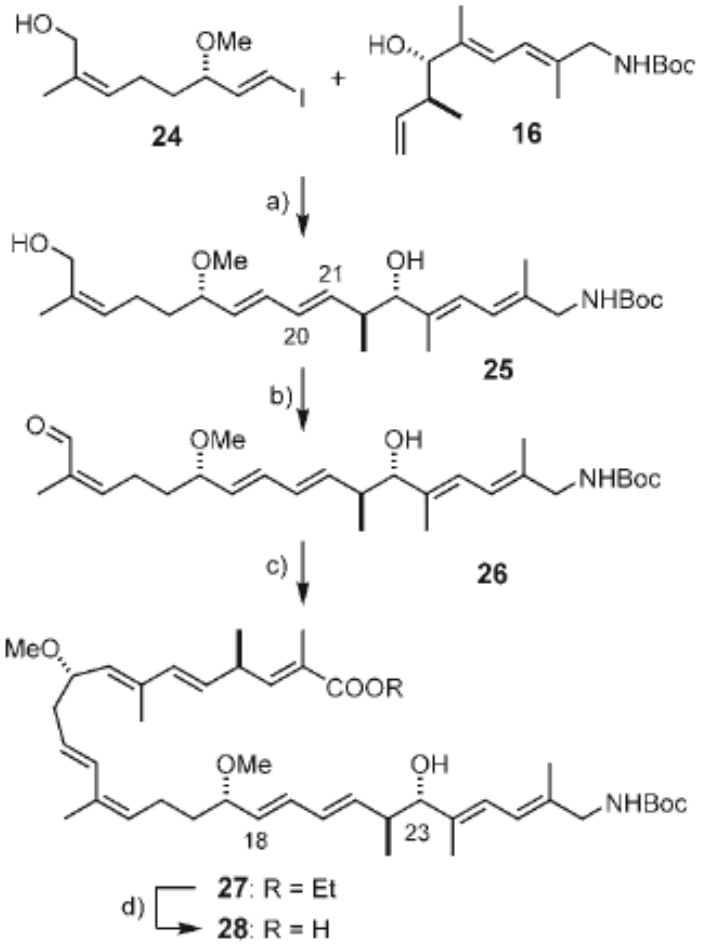
Synthesis of *C*12-*C*19: 34% over Seven Steps

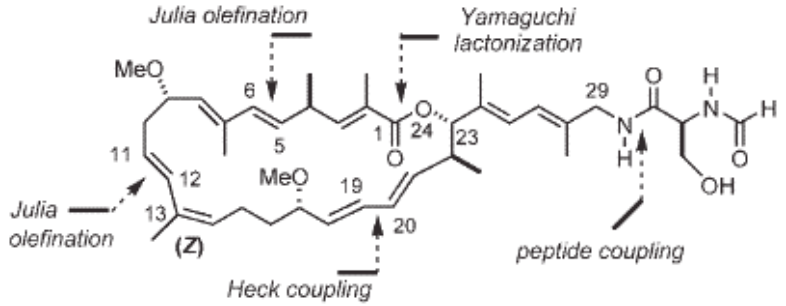


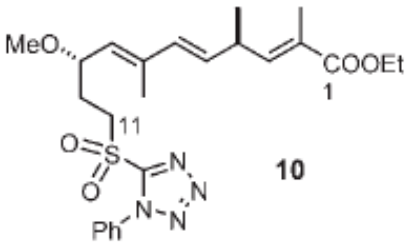


Scheme 4. a) **18** (0.6 mol%), *i*PrOH, 98% (98.8% *ee*); b) 1. *n*BuLi, MeI, THF, −78 °C; 2. DMSO, −25 °C→RT; c) cat. OsO_4, $NaIO_4$, 2,6-lutidine, aq 1,4-dioxane, 74% (over two steps); d) $(CF_3CH_2O)_2P(O)CH(Me)COOMe$, KHMDS, [18]crown-6 (0.7 equiv), toluene, −20 °C, 87%; e) K_2CO_3, MeOH, 80%;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

Coupling of the Three Fragments

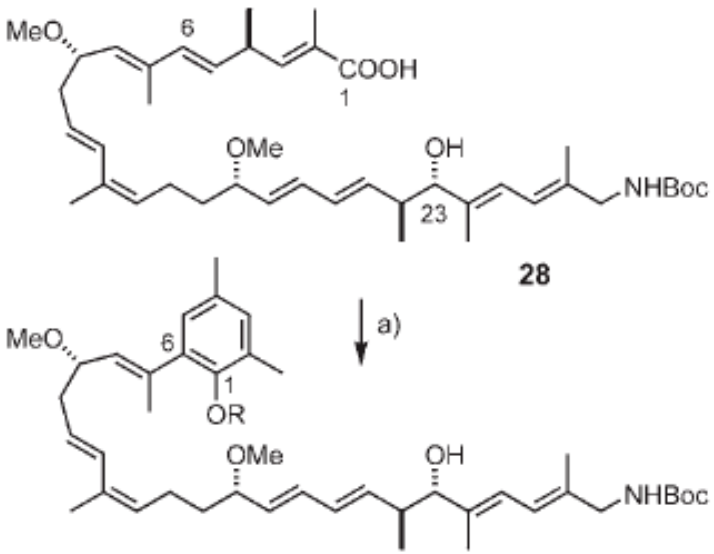






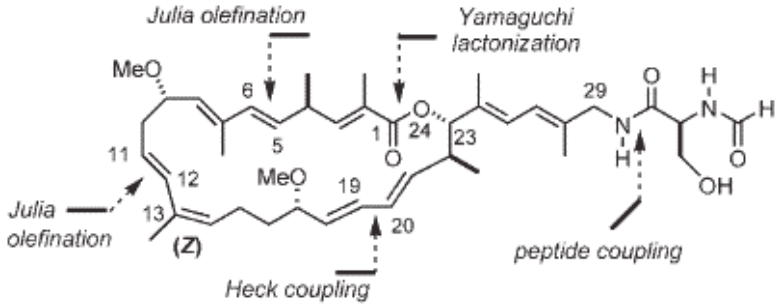
Scheme 5. a) $Pd(OAc)_2$ (10 mol%), AgOAc, DMF, RT, 46% (**25**) + 13% ($\Delta^{[20,21]}$ isomer); b) cat. *t*BuOK, cat. $CuBr_2$, cat. 2,2′-bipyridine, cat. TEMPO, O_2 (1 atm), $MeCN/H_2O$ (2:1), 94%; c) **10**, NaHMDS, THF, −78 °C → RT, 57% ($E/Z > 10:1$); d) Me_3SnOH (40 equiv), 1,2-dichloroethane,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

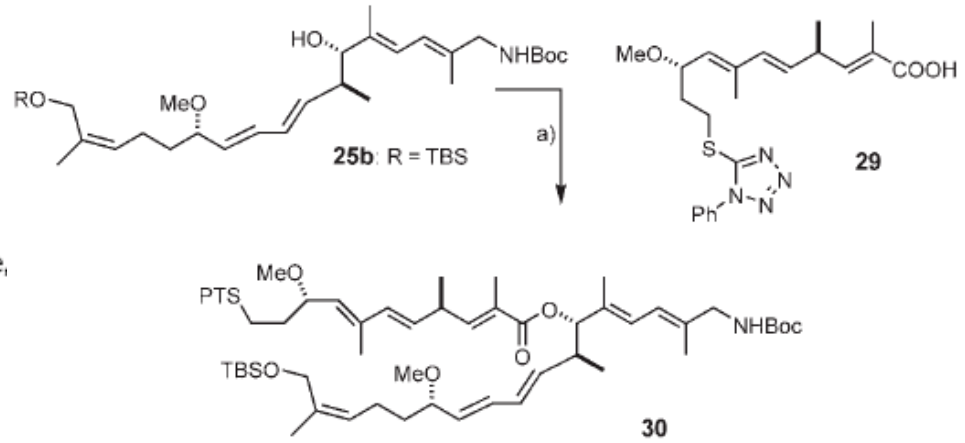
Lactonization-the Molecule's "Achilles Heel"



31: R = 2,4,6-trichlorobenzoyl

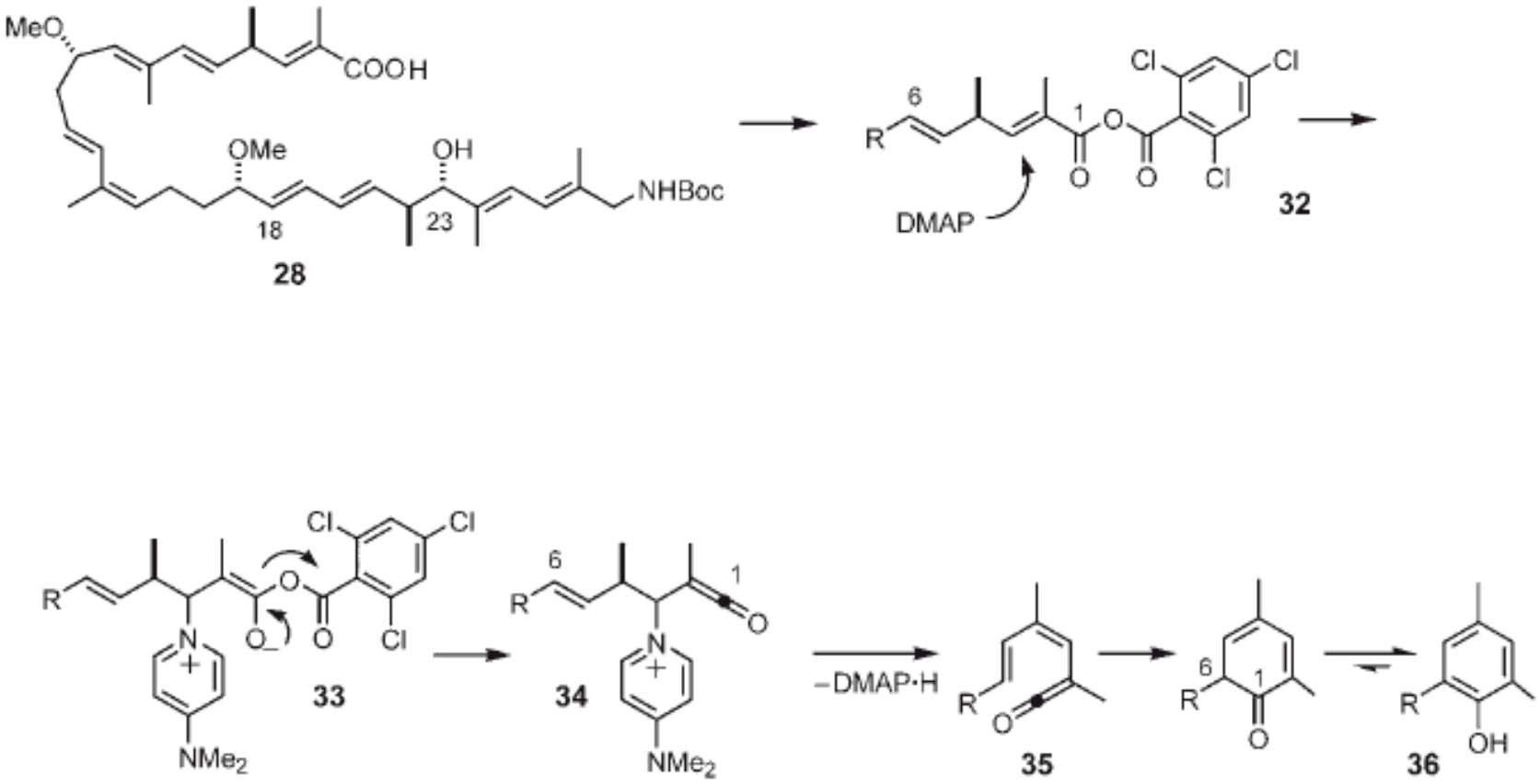
Scheme 8. Attempted macrocyclization under Yamaguchi conditions: a) 1. 2,4,6-trichlorobenzoyl chloride, Et_3N, THF; 2. cat. DMAP, toluene, see text.





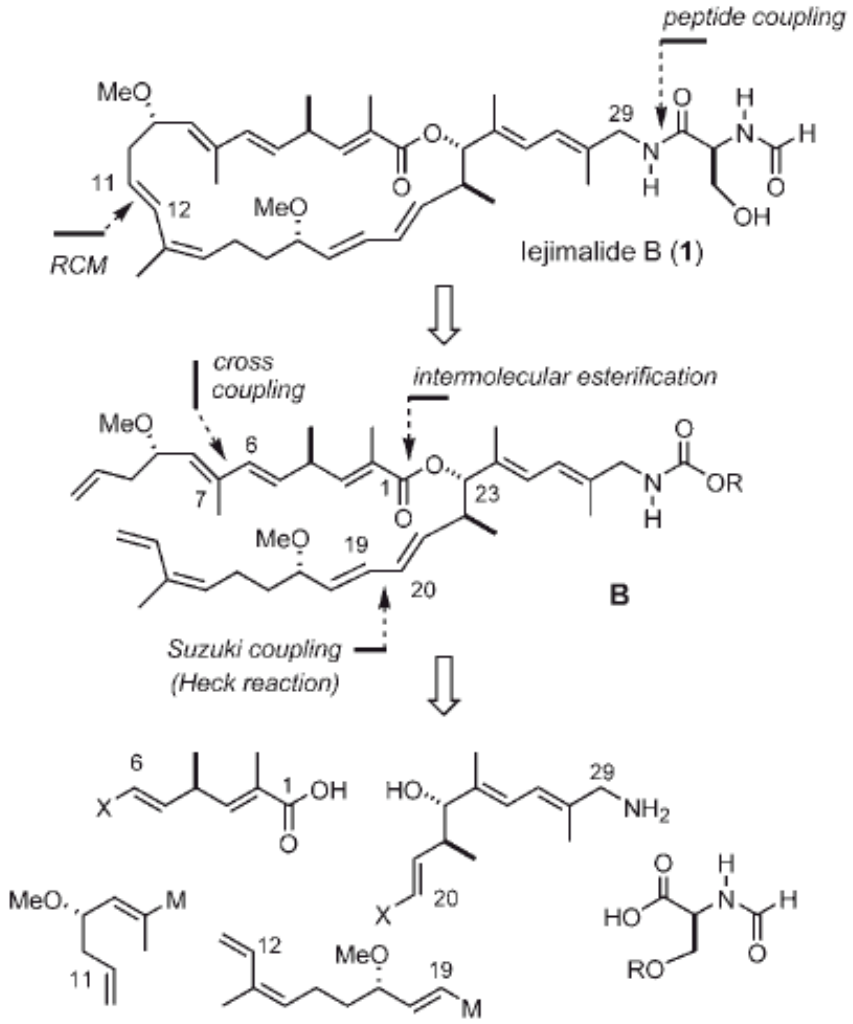
Scheme 7. An intermolecular esterification serving as a model for the projected macrocyclization: a) 2,4,6-trichlorobenzoyl chloride, Et_3N, cat. DMAP, toluene, 72%. DMAP = 4-dimethylaminopyridine.

Potential Aromatization Mechanism



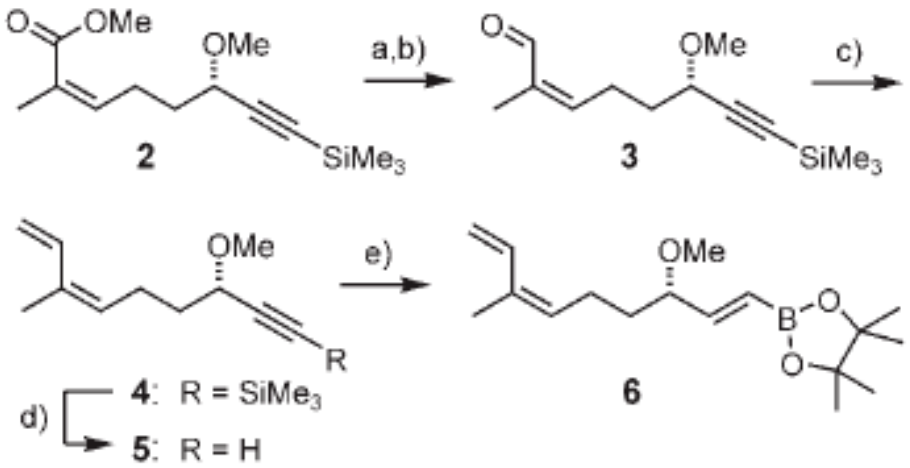
Scheme 9. Proposed mechanism for the observed phenol formation under Yamaguchi conditions.

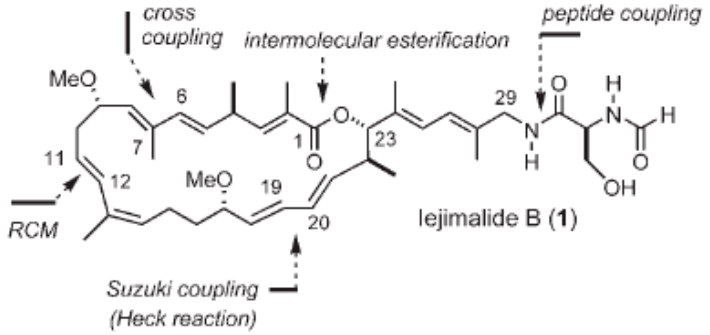
Part II. Total Synthesis of Iejimalide B



Furstner, A. et al. *Angew. Chem. Int. Ed.* ASAP.

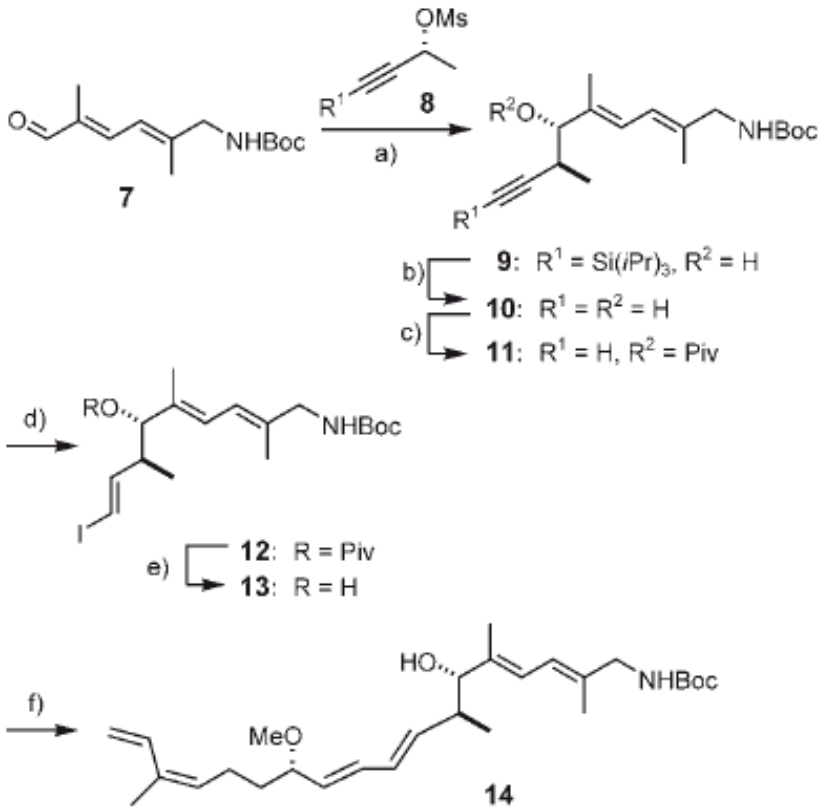
Synthesis of *C*12-*C*19



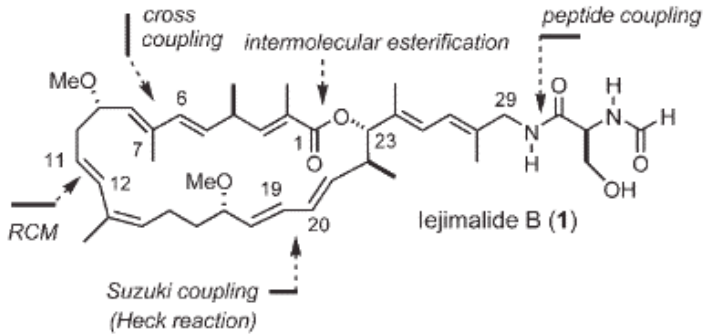


Scheme 2. a) DIBAL-H, CH_2Cl_2, −78 °C; b) MnO_2, CH_2Cl_2, 96 % (over two steps); c) Ph_3PCH_3Br, *n*BuLi, THF, −78 °C → RT, quant.; d) K_2CO_3, MeOH, 83 %; e) pinacolborane, 9-BBN (10 mol %), THF, 45 °C, 56 %. DIBAL-H = diisobutylaluminum hydride, 9-BBN = 9-borabicyclo-[3.3.1]nonane.

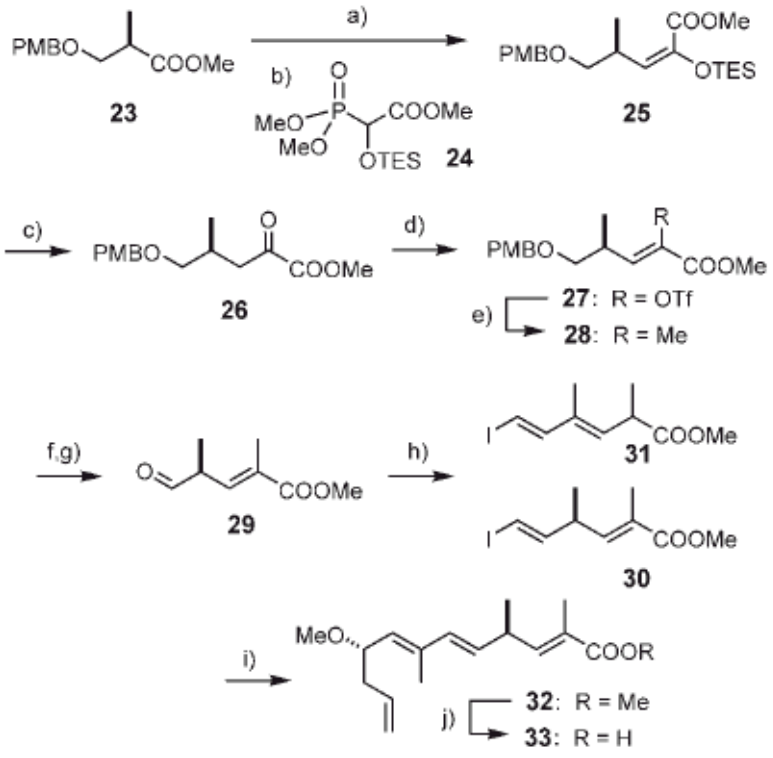
Suzuki Coupling to Join *C*19 and *C*20

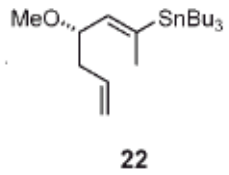


Scheme 3. a) $[Pd(OAc)_2]$ (5 mol%), PPh_3 (5 mol%), Et_2Zn (3 equiv), THF, −78°C→−20°C, 72%; b) TBAF, THF, 94%; c) pivaloyl chloride, pyridine, 0°C→RT, 76%; d) $[Cp_2Zr(H)Cl]$, THF, then I_2, 0°C→RT, 85%; e) DIBAL-H, CH_2Cl_2, −78°C, 87%; f) boronate **6**, $[PdCl_2(dppf)]$ (15 mol%), $Ba(OH)_2 \cdot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

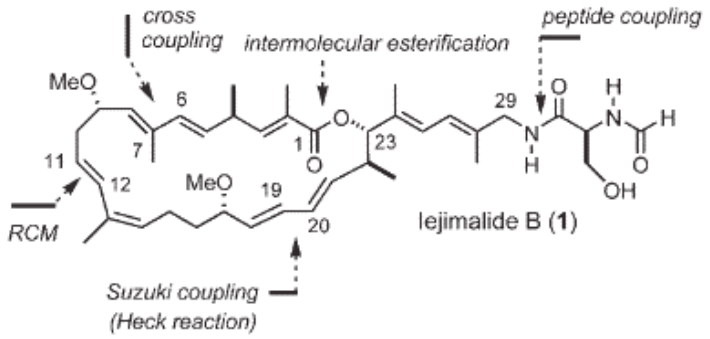


Synthesis of *C*1-*C*11



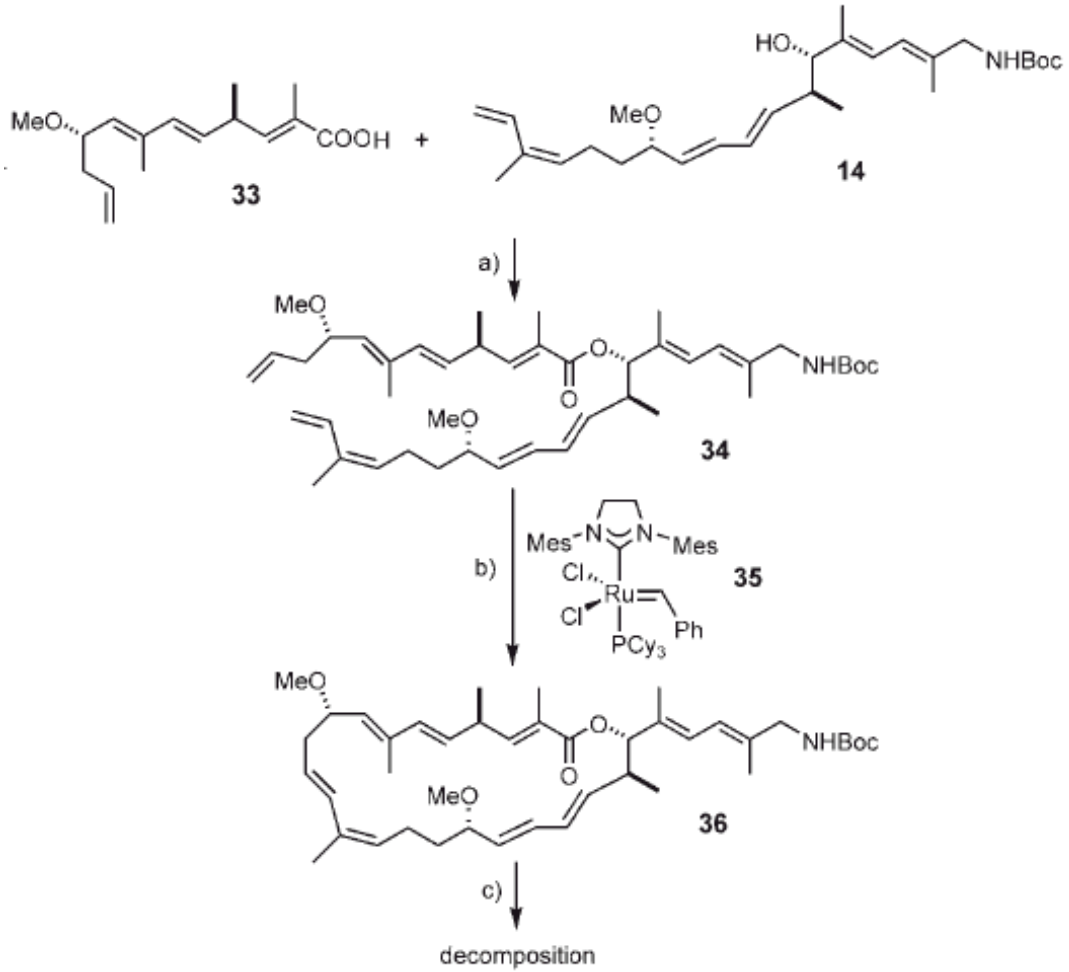


22

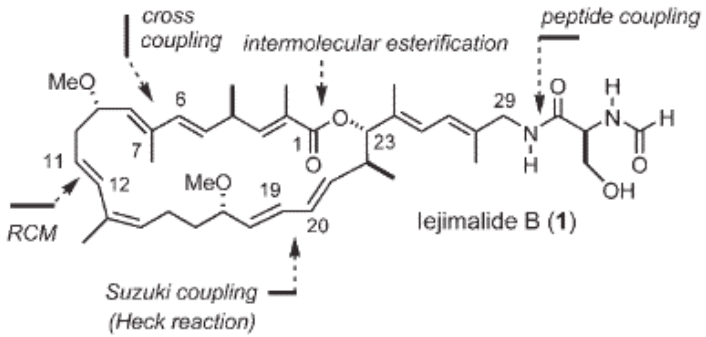


Scheme 5. a) DIBAL-H, CH_2Cl_2, −78 °C; b) **24**, LiHMDS, THF, −78 °C → −40 °C, 75% (over both steps); c) aq HCl, THF, 91%; d) *N*-(5-chloro-2-pyridyl)-bis(trifluoromethansulfonimide), KHMDS, THF, −78 °C → −40 °C, 65%; e) MeZnCl, $[Pd(PPh_3)_4]$ (5 mol%), THF, 50 °C, 91%; f) DDQ, CH_2Cl_2/H_2O, 91%; 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.

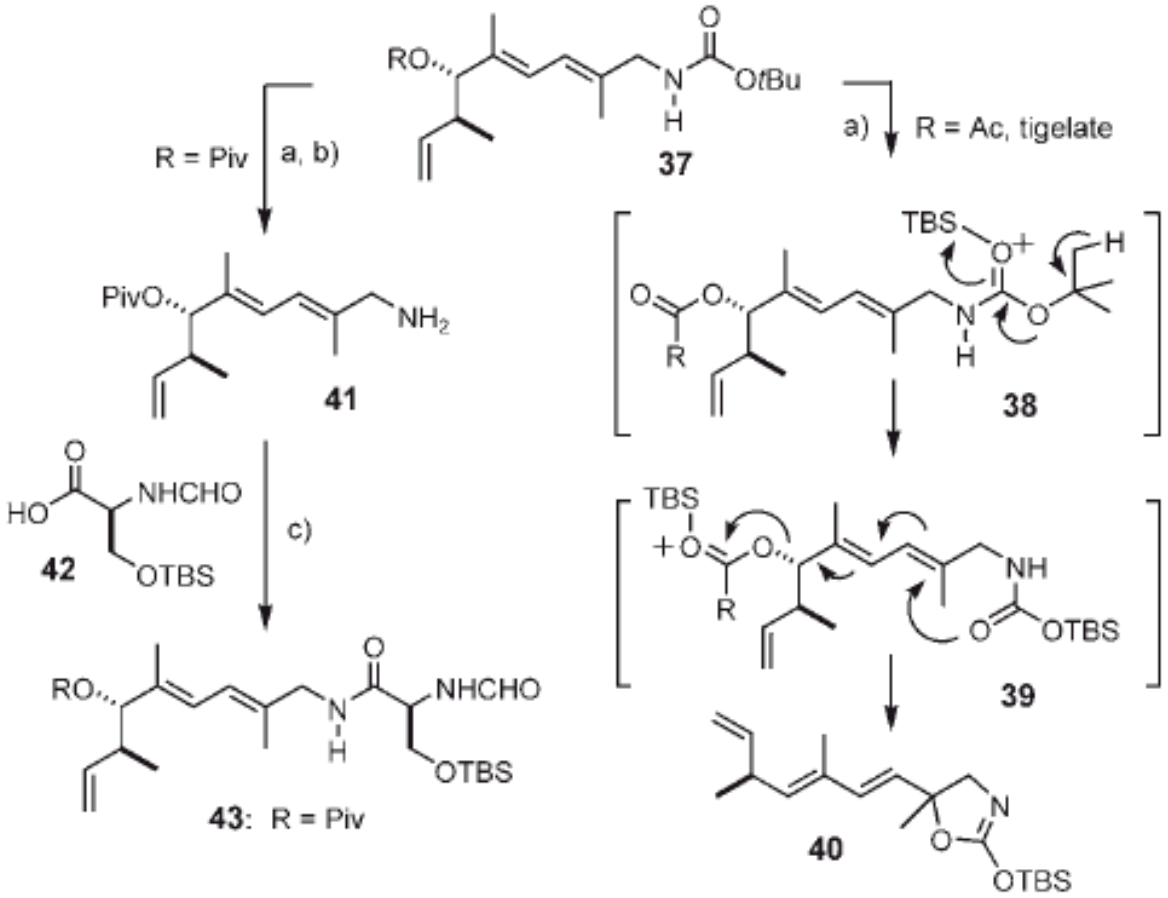
Another "Achilles Heel"



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.

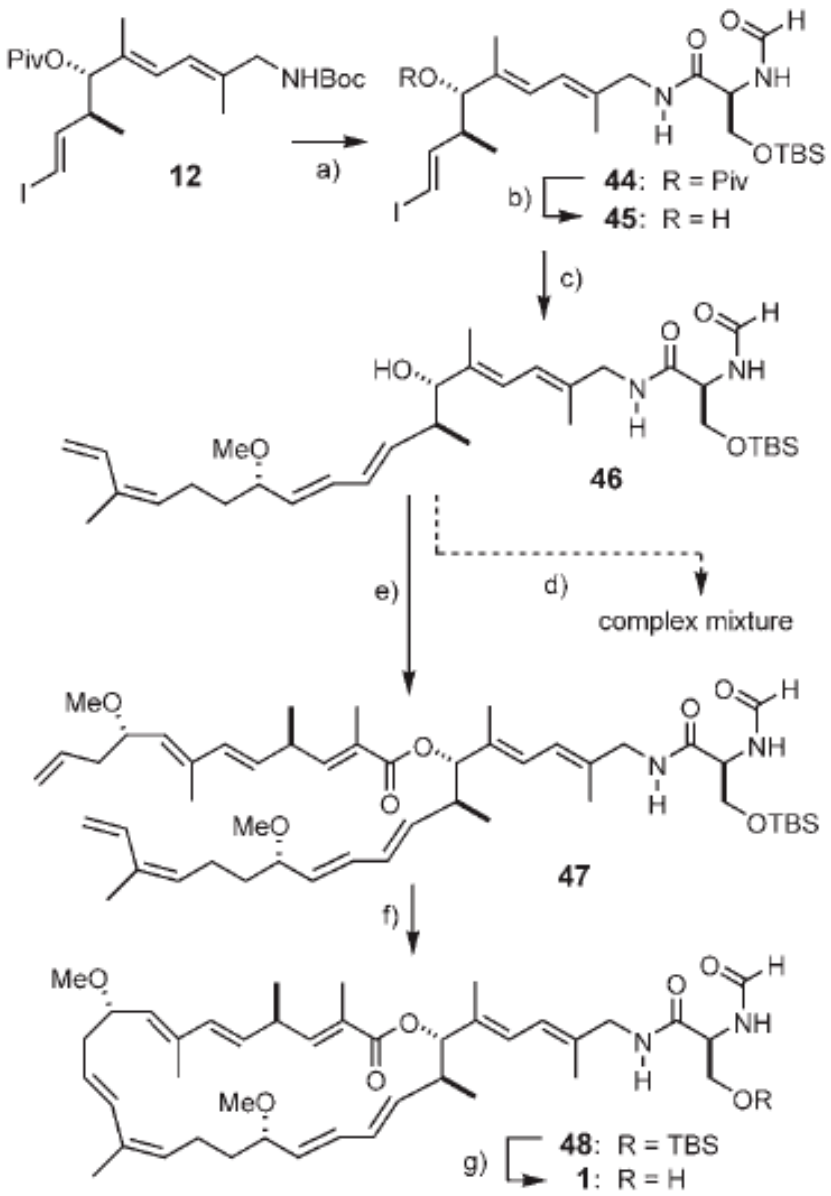


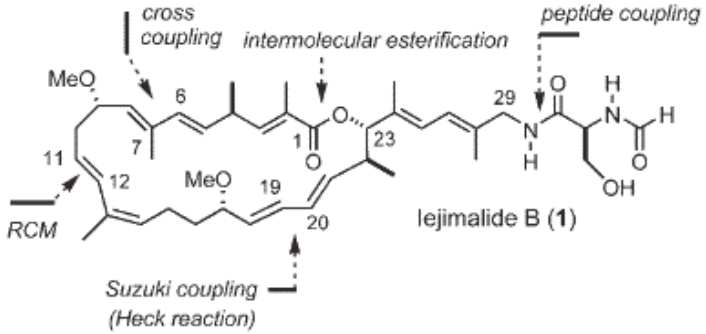
Possible Decomposition Pathway



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-dimethylamino-propyl)-1-ethylcarbodiimide, HOBT = 1-hydroxy-1*H*-benzotriazole, NMM = *N*-methylmorpholine.

Final Revision





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.

Summary

- The first stereoselective synthesis of iejimalide B has been achieved after several rounds of adjustment and fine tuning.
- The strategic advantages of RCM are illustrated.
- Exceptionally low level of homology in the behavior of closely related compounds that differ in remote and ostensibly innocent substituents was encountered, and the information should be helpful for the synthesis of other members of this family.