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REVIEW

Marine natural products: Synthetic aspects†

Jonathan C. Morris*[a] and Andrew J. Phillips[b]

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An overview of marine natural products synthesis during 2009 is provided. As with earlier installments in this series, the emphasis is on total syntheses of molecules of contemporary interest, new total syntheses, and syntheses that have resulted in structure confirmation or stereochemical assignments.

1 Introduction

This review is designed to provide an overview of key features of the 2009 literature covering the synthesis of marine natural products and should act as a companion to the Marine Natural Products review published in this journal.[1] The emphasis is on total syntheses of molecules of contemporary interest. Tabulated data for other syntheses are also provided. While every effort has been made to be comprehensive within these boundary conditions, we apologize in advance for any oversights.

2 Reviews

A number of reviews that cover various aspects of marine natural products synthesis have appeared: "From nature to the laboratory and into the clinic",[2] "Recent synthetic studies leading to structural revisions of marine natural products",[3] "The chemical synthesis of discodermolide",[4] "Chasing the treasures of the sea – bacterial marine natural products",[5] "Recent synthesis of marine natural products with antihypertensive activity: An overview",[6] "Aplysinopsins – marine indole alkaloids: chemistry, bioactivity and ecological significance",[7] "Preparation of hymenialdisine, analogs and their evaluation as kinase inhibitors",[8] "Chemistry and biology of Okinawan marine natural products",[9] "New tricks from ancient algae: natural products biosynthesis in marine cyanobacteria",[10] "Syntheses and biological activity of the HDAC class I inhibitor largazole",[11] "Discovery and development of the anticancer agent salinosporamide A (NPI-0052)",[12] "Studies for the synthesis of marine natural products",[13] "Development of Yondelis (trabectedin, ET-743). A semisynthetic process solves the supply problem",[14] "Chemistry of trisdecacyclicpyrazineantineoplastics: the cephalostatins and ritterazines",[15] "Total synthesis of the marine alkaloid palau'amine",[16] "The halichondrins and E7389",[17] and "Synthesis and stereochemical determination of the spirastrellolides".[18] Other reviews of relevance are cited in the text.

3 Spirastrellolide F

The Fürstner group has completed the second total synthesis of a spirastrellolide-class macrolide, in this case spirastrellolide F, **1**.[19] The overall execution of the synthesis occurred along the outline in Scheme 1. The C43–C47 domain would be introduced at a late stage, and the key macrocycle **2** could be dissected to give C1–C23 domain **3** and C24–C40 trioxadispiroketal, **4** as the significant subunit targets. Although their earlier reports[20] had detailed routes to closely related fragments, the total synthesis employed a new route to the C1–C23 domain that commenced with the coupling of silylenol ether **5** and aldehyde **6** to give **7** in 77% yield (over 2 steps). Evans–Tischenko reduction gave **8** with excellent diastereoselectivity (dr >95 : 5). A three-step sequence of standard reactions (DIBAL-H reduction of the ester to the alcohol, removal of TIPS group from the alkyne, and silylation of the alcohols) gave **9**. The aldehyde required for coupling with

[a]*School of Chemistry, University of New South Wales, Sydney, Australia 2052. E-mail: jonathan.morris@unsw.edu.au; Fax: +61 2 93856141; Tel: +61 2 93854733*
[b]*Department of Chemistry, Yale University, New Haven, Connecticut, 06520, USA*
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this alkyne, **10**, was prepared from known epoxide **11** by opening with lithiated TMS-propyne to yield **12**. Methylation with methyl triflate, diastereoselective dihydroxylation under Sharpless conditions, and $Pb(OAc)_4$-mediated cleavage gave aldehyde **13**. Mukaiyama aldol with silylketene acetal **14** in the presence of $MgBr_2 \cdot Et_2O$ gave **15** in an excellent 81% yield over the two steps and with high diastereoselectivity (dr = 10 : 1). Removal of the TBS group, protection of the 1,2-diol as an acetonide, and a subsequent three-step process gave aldehyde **10**. Deprotonation of **9** with *n*-BuLi and reaction with **10** gave **16** in 81% yield, and Dess–Martin oxidation led to alkynone **17**. Reduction of the alkyne and removal of the PMB groups over $Pd(OH)_2$ led directly to spiroketal **18** in 80% yield. The ethyl ester was converted to methyl ketone **19** by reaction with lithiated phenylmethylsulfone to yield a β-ketosulfone that was desulfonylated with Bu_3SnH and AIBN. A further 4 steps advanced **19** to **3**.

The synthesis of the C24–C40 trioxadispiroketal domain followed an earlier reported route[21] that involved an alkoxy-directed diastereoselective [3 + 2]-cycloaddition between allylic alcohol **20** and nitrile oxide (formed *in situ*) **21** to yield isoxazoline **22** in 76% yield after removal of the TIPS group with TBAF (Scheme 2). Conversion to the iodide **23**, followed by a Stork cyanohydrin alkylation between the anion of TES-protected cyanohydrin **24**, produced **25** in 90–99% yield. Reductive cleavage of the N–O bond and imine hydrolysis provided β-hydroxy ketone **26**, which, when subjected to acidic conditions (PPTS, CH_2Cl_2), was converted to the trioxadispiroketal **27** in 61% yield.

Subunit assembly and completion of the synthesis of spirastrellolide F is outlined in Scheme 3. Treatment of **4** with an excess of 9-BBN resulted in hydroboration to produce an intermediate alkylborane that was readily coupled with vinyl triflate **3** in the presence of aqueous base and $PdCl_2$(dppf) to give seco-acid **28** in an excellent 75% yield. Macrocyclization using the Yamaguchi protocol provided the macrolactone **29** in 80% yield and set the stage for the closing steps. The remaining stereocenter to be installed was introduced by hydrogenation under macrocyclic stereocontrol. In this case, the *Si* face of the olefin is occluded by the macrocycle (see model **30**) and reduction occurs in the presence of a modified Crabtree catalyst from the exposed *Re* face to give **31**. Removal of the benzyl ether under standard hydrogenation conditions, oxidation of the primary alcohol to the aldehyde and Wittig olefination with methylene triphenylphosphorane gave **32** in 89% yield over the three steps. Following the precedent of Paterson, **32** was subjected to cross-metathesis to give allyl acetate **33**. A Stille–Tsuji–Trost reaction introduced the remaining carbon atoms, and global deprotection under mild acid conditions completed the total synthesis of spirastrellolide F.

4 Norhalichondrin B

Almost 20 years after the Kishi synthesis[22] of halichondrin B and norhalichondrin B, the Phillips group has described the second total synthesis of norhalichondin B, **35**.[23] In contrast to the Kishi synthesis, which relied on sugars as the basic template for building blocks, the Phillips synthesis employs *de novo* strategies for the synthesis of building blocks from furan. The overall strategy (outlined in Scheme 4) involves the assembly of four building blocks, **36** → **39** by a combination of cross-metathesis, Horner–Wadsworth–Emmons reaction and a Nozaki–Hiyama–Kishi coupling.

The synthesis of the C1–C13 subunit commenced with known bicyclic ring system **40**, which was converted by a four-step sequence to mixed acetal **41** (Scheme 5). Exposure of **41** to the second-generation Grubbs catalyst in the presence of ethylene, followed by quenching with ethyl vinyl ether gave fused bicycle **42** in 71% yield. A seven-step sequence of protecting group and redox manipulations led to **43**, which was converted to **44** by Petasis–Tebbe olefination and then hydroboration–oxidation of the olefin. Completion of the C1–C13 subunit was achieved by oxidation of the primary alcohol **44** with Dess–Martin periodinane and reaction of the aldehyde with vinyl iodide under Nozaki–Hiyama–Kishi conditions to give **37**.

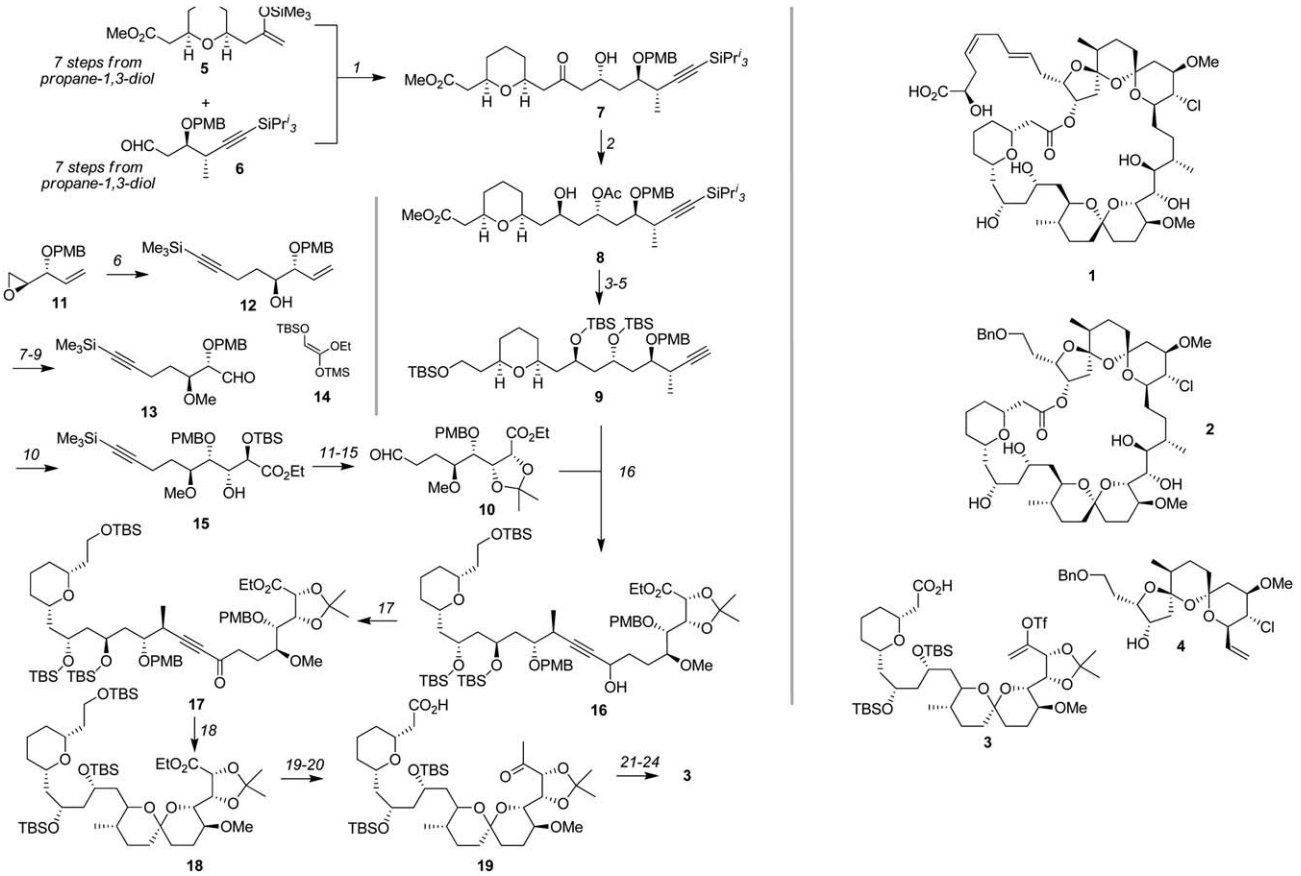
The syntheses of both the C40–C53 subunit **36** and C27–C38 domain **38** featured the straightforward conversion of furan derivatives to 2,6-*syn* pyranones by the signature Achmatowicz

Jonathan C. Morris

Jonathan C. Morris obtained his B.Sc. (Hons) degree from the University of Western Australia and his Ph.D. degree from The Australian National University in Canberra, Australia. After a postdoctoral appointment with Professor Phil Magnus at the University of Texas at Austin, he joined the faculty at the University of Canterbury, New Zealand. In 2004, he moved to the University of Adelaide. In late 2009, he was appointed at the University of New South Wales. His research interests focus around the synthesis of biologically active natural products.

Andrew J. Phillips

Andrew J. Phillips obtained his B.Sc. (Hons) and Ph.D. degrees from the University of Canterbury in Christchurch, New Zealand. After a postdoctoral appointment with Professor Peter Wipf at the University of Pittsburgh, he joined the faculty at the University of Colorado. In August 2010 he joined the faculty at Yale University. His research interests are broadly defined by the chemistry and biology of small molecules, including natural products.

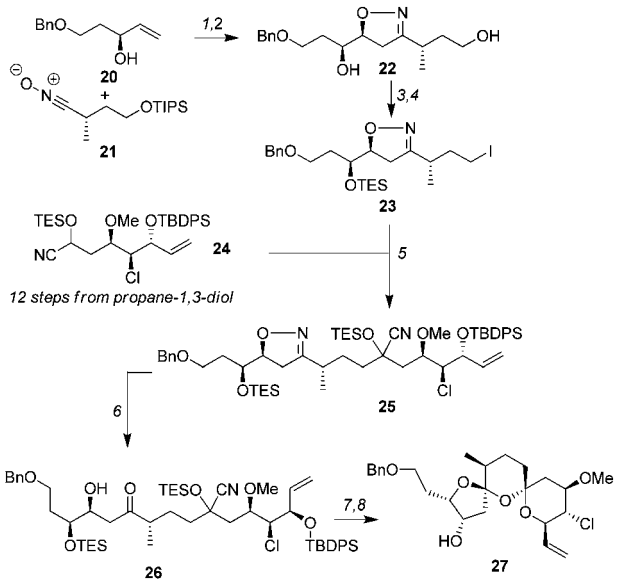


Scheme 1 An overview of Fürstner's plan for the synthesis of spirastrellolide F, and the construction of the C1–C23 domain. *Reagents and conditions*: (1) $BF_3 \cdot Et_2O$, CH_2Cl_2, −78 °C, 77% (2 steps from the ketone precursor to **5**); (2) 15 mol% SmI_2, MeCHO, THF, −10 °C, 98%; (3) DIBAL-H, PhMe, 99%; (4) TASF, THF, 0 °C→ rt; (5) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, quant.; (6) TMSCCMe, *n*BuLi, TMEDA, Et_2O, −25 → −5 °C, 81%; (7) MeOTf, LiHMDS, THF, 84%; (8) cat. OsO_4, $(DHQ)_2PYR$, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH, 0 °C → rt, 64%; (9) $Pb(OAc)_4$, CH_2Cl_2; (10) **14**, $MgBr_2 \cdot Et_2O$, toluene, −78 °C→ rt, 81% (2 steps, dr 10 : 1); (11) TBAF, THF, 0 °C, quant.; (12) $Me_2C(OMe)_2$, cat. CSA, 0 °C → rt, 90%; (13) Lindlar catalyst, H_2 (1 atm), quinoline, EtOAc, 1-hexene; (14) cat. OsO_4, NMO, 89% (over 2 steps); (15) $Pb(OAc)_4$, CH_2Cl_2, 86%; (16) **9**, *n*-BuLi, THF, then **10**, −78 °C, 81%; (17) Dess–Martin periodinane, CH_2Cl_2, 0 °C→ rt, 99%; (18) $Pd(OH)_2$, H_2 (1 atm), EtOAc, 80%; (19) $PhSO_2Me$, *n*-BuLi, THF, −78 °C, 90%; (20) AIBN, Bu_3SnH, PhMe, reflux, 80%; (21) KHMDS, THF, then *N*-(4-*tert*-butylphenyl)bis(trifluoromethanesulfonimide), −78 °C; (22) HF·py, THF, py, 60% (2 steps); (23) Dess–Martin periodinane, CH_2Cl_2, 0 °C→ rt; (24) $NaClO_2$, NaH_2PO_4, *t*-BuOH, H_2O, 2-methyl-2-butene, 95% (2 steps). TASF = tris[dimethylamino]sulfonium difluorotrimethyl silicate.

oxidation and oxacarbenium ion reduction sequence (Scheme 5). In the case of **36**, the synthesis commenced with furfural **45**. Brown crotylation produced **46**, and when this was exposed to $VO(acac)_2$ and TBHP, pyranone hemi-acetal **47** was obtained. Treatment of **47** with Et_3SiH in the presence of TFA gave the desired 2,6-*syn* pyranone **48** as a single diastereomer. Removal of the primary TBS ether under carefully controlled conditions (TFA, H_2O–CH_2Cl_2, −37 °C) was followed by oxidation of the alcohol to the acid with Jones reagent, and under these conditions hetero-conjugate addition of the acid occurred to produce lactone **49**. The remaining pyran stereocenter was introduced by reduction of the ketone with $NaBH_4$ to give **50**, which was advanced to **51** in four steps. The C40–C53 subunit **36** was generated in 62% yield by addition of the lithio species **53**, prepared from **52**, to the aldehyde **51**, followed by a Dess–Martin periodinane oxidation.

The synthesis of the C27–C38 domain **38** commenced with the conversion of **54** to bicyclic lactone **57**in a sequence of Achmatowicz–ionic reduction and subsequent lactonization and reduction; an overall process analogous to that used for the conversion of **46** → **50**. A four-step sequence produced **58**, and catalytic asymmetric Nozaki–Hiyama–Kishi reaction with methyl-β-iodoacrylate in the presence of ligand **61** gave **59**. Protection of the secondary alcohol as the PMB ether and TBAF cleavage of the TES group, with concomitant hetero-conjugate addition, yielded **60**. Protecting group and redox manipulations led to **38** in four further steps.

The tetrahydrofuran-containing C14–C26 domain was prepared by a route that is detailed in Scheme 6. β-Ketoester **62** was reduced under Noyori conditions to give a β-hydroxy ester that was allylated with allyl ethyl carbonate in the presence of $Pd_2(dba)_3$ and dppb to give **63**. Hydrolysis to the acid and conversion to the diazoketone **64** was followed by a Cu-catalyzed [2,3]-Wittig rearrangement to fashion the tetrahydrofuran ring with the desired 2,5-*anti* relationship of the side-chains (**64** → **65**, 91%). Wittig olefination (**65** → **66**), selective hydroboration of the terminal olefin with disiamylborane and oxidation of the resulting alcohol gave the aldehyde **67**. Recent advances in catalytic asymmetric Co-mediated chemistry were leveraged to introduce the 5-carbon iodoalkene group by reaction of **67** with



Scheme 2 Construction of the C24–C40 domain of spirastrellolide F. *Reagents and conditions*: (1) **21** (generated by treatment of the oxime wth *t*-BuOCl, −78 °C, CH_2Cl_2) then alkene **14**, EtMgBr, *i*-PrOH; (2) TBAF, THF, 76 % (2 steps); (3) I_2, imid., PPh_3, THF, 83%; (4) TESOTf, 2,6-lutidine, THF; (5) LDA, THF, −78 °C, 90–99%; (6) $Mo(CO)_6$, MeCN–H_2O (10 : 1), 90 °C, 93%; (7) TASF (aq.), DMF, 94%; (8) PPTS (cat.), CH_2Cl_2, 61%.

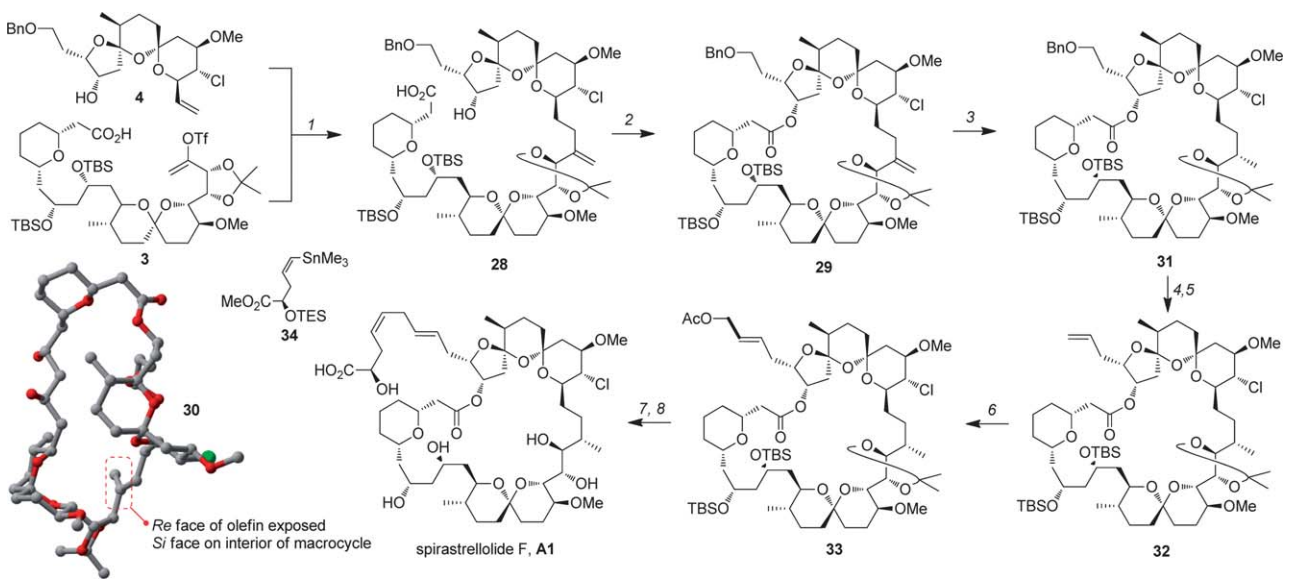
68 in the presence of Co phthalocyanine and ligand **69**, yielding the desired alcohol **70** in 52% yield after removal of the TIPS group with TBAF and with a d.r. of 6 : 1. The subunit was completed by pivalate protection of the primary alcohol and mesylation of the secondary alcohol to give **39**.

The initial phase of subunit couplings occurred by Nozaki–Hiyama–Kishi union of aldehyde **38** and iodide **39** to produce **71** (Scheme 7). Cyclization of the crude intermediate material in an S_N2 process gave pyran **72** as an ~3.7 : 1 mixture of non-separable diastereomers in 59% yield over the two steps. Straightforward manipulations advanced this material to enone **73**, which could be engaged in a cross-metathesis with the C1–C13 subunit **37** in the presence of the Stewart–Grubbs catalyst **74** to give complex enone **75** in 62% yield. The polycyclic acetal domain was installed by removal of the TBS ethers with a non-aqueous workup, giving **76** in 64% yield. Three steps of protecting group manipulations produced the seco-acid **77**, which was cyclized to **78** in an excellent 92% yield using Yamaguchi's conditions.

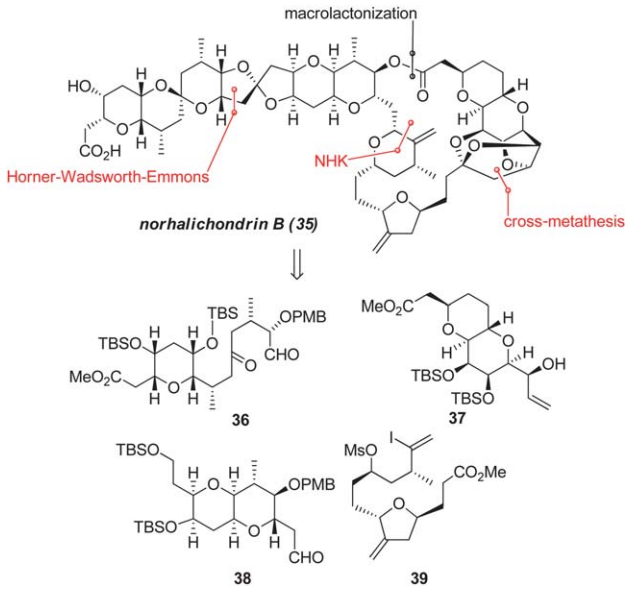
Conversion of **78** to phosphonate **79** in three steps (TBS removal, oxidation to the aldehyde and Roskamp reaction) and Horner–Wadsworth–Emmons reaction with aldehyde **36** gave **80** in an excellent 83% yield (Scheme 8). Removal of the TBS and PMB groups with TBAF and then DDQ (in the interesting solvent mixture CH_2Cl_2–MeOH) gave **81**. Saponification of the methyl ester then completed the synthesis of norhalichondrin B. The Kishi group has also published a number of methodological improvements in the realm of the halichondrins.[24]

5 (+)-11,11′-Dideoxyverticillin A

The dimeric epidithiodiketopiperazine alkaloids, represented by (+)-11,11′-dideoxyverticillin A (**82**), are challenging synthetic targets. Using biosynthetic principles, Movassaghi proposed the retrosynthetic analysis that is outlined in Scheme 9.[25] It was envisaged that dimerization of diketopiperazine **83** would afford **84** (R = H), which could be oxidized to the tetraol **85** (R = OH).



Scheme 3 Completion of Fürstner's synthesis of spriastrellolide F. *Reagents and conditions*: (1) **4**, 9-BBN dimer, THF then **3**, 20 mol% [$PdCl_2$(dppf)], Ph_3As, aq. NaOH, THF, 75%; (2) 2,4,6-trichlorobenzoyl chloride, Et_3N, PhMe then DMAP, PhMe reflux, 80% (3) 20 mol% [Ir(cod)(PCy_3)(py)][BARF], H_2 (200 atm), 1,2-dichloroethane, 59%; (4) $Pd(OH)_2$, H_2 (1atm), EtOAc; (5) Dess–Martin periodinane, CH_2Cl_2, 0 °C → rt; (6) $Ph_3P{=}CH_2$, THF, 89% (over 3 steps); (7) (*Z*)-1,4-diacetoxy-2-butene (15 equiv.), 20 mol% Grubbs cat., PhMe, 47%, (*E*/*Z* ≥ 8 : 1);(8) **34**, 20 mol% [$Pd_2(dba)_3$], LiCl, NMP; (9) cat. PPTS, MeOH/Et_2O/H_2O (7 : 2 : 1), 50 °C, 50% (2 steps). BARF = tetrakis(3,5-bis(trifluoromethylphenyl))borate, 9-BBN = 9-borabicyclo[3.3.1]nonane. Structure **30** is derived from the X-ray coordinates of a closely related compound in which the Bn group is not present.



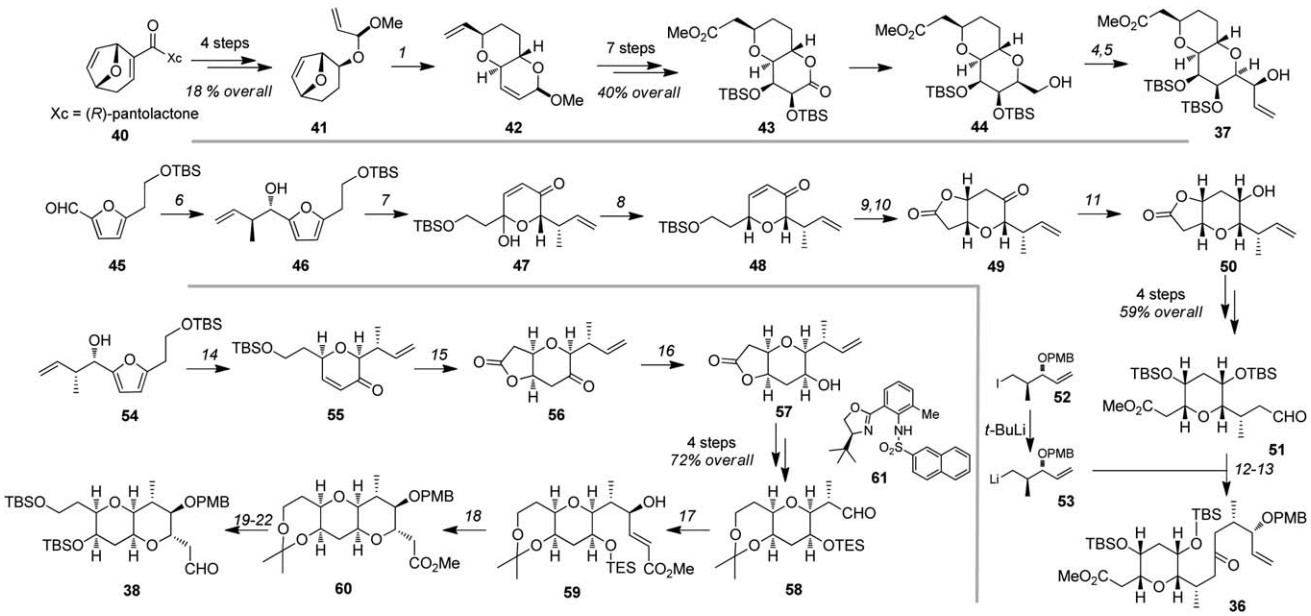
Scheme 4 A strategy-level overview of Phillips' synthesis of norhalichondrin B, **35**.

From this key intermediate the thiols can be introduced and oxidized to afford the epidithiodiketopiperazine system.

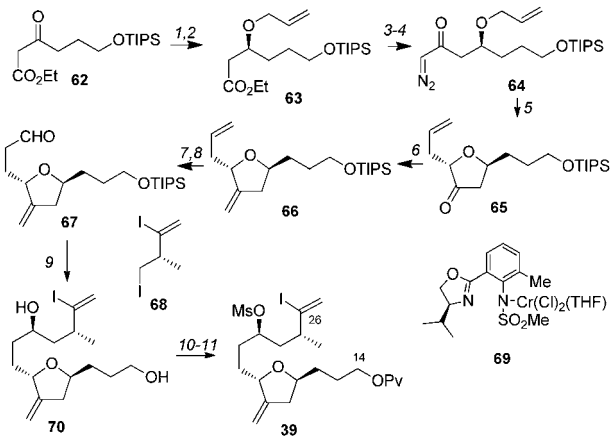
The dimerization precursor **86** was readily prepared in 58% yield by first reacting diketopiperazine **87** with bromine (MeCN, 0 °C), then methylation with methyl iodide and potassium carbonate. Reductive dimerization of **86** with tris(triphenylphosphine)cobalt(I) chloride in acetone gave the dimer **88** in 46% yield. After much experimentation, it was determined that the desired tetraol **89** could be prepared by oxidation with 4.8 equivalents of bis(pyridine)silver(I) permanganate in dichloromethane. This provided the tetraol **89** as a single diastereomer in an impressive 63% yield. However, it was found that **89** was highly acid- and base-sensitive, and while it could be transformed into the target molecule, it was a low-yielding process. It was discovered that these difficulties could be overcome by conversion to the diol **90**. This was prepared in 55% yield by selective protection using *tert*-butyldimethylsilyl chloride and 5 mol% of Fu's PPY catalyst **91**. Removal of the benzenesulfonyl groups was achieved by reaction of **90** with sodium amalgam to provide the stable diaminodiol **92** in 87% yield. Again, after much experimentation it was found that this compound could be converted into 11,11′-dideoxyverticillin (**82**) in just two steps. Reaction with potassium trithiocarbonate and trifluoroacetic acid, followed by addition of ethanolamine, gave a tetrathiol, which could be readily converted to the target molecule by reaction with potassium triiodide. This impressive sequence proceeded in 35% overall yield. Clearly, the success of this strategy suggests that the proposed biosynthetic sequence is plausible.

6 Sporolide B

Nicolaou and coworkers have reported a total synthesis of the unusual natural product sporolide B (**93**) (Scheme 10), which confirms the proposed structure and absolute configuration.[26]



Scheme 5 Pyran-containing subunit syntheses for Phillips' synthesis of norhalichondrin B. *Reagents and conditions*: (1) 3 mol% Grubbs II, $H_2C{=}CH_2$, PhMe, rt, then ethyl vinyl ether, 71%; (2) Cp_2TiMe_2, PhMe, 71%; (3) $BH_3{\cdot}THF$, THF, H_2O_2–NaOH, 48%; (4) Dess–Martin periodinane, CH_2Cl_2; (5) vinyl iodide, 1% $NiCl_2/CrCl_2$, 84% (2 steps); (6) 1. (−)-Ipc_2-(*E*)-crotylborane, then H_2O_2, NaOH, 71%; (7) *t*-BuOOH, $VO(acac)_2$, CH_2Cl_2; (8) Et_3SiH, TFA, CH_2Cl_2, −40 °C, 86% (2 steps); (9) TFA, H_2O, CH_2Cl_2, −37 °C; (10) Jones reagent, acetone, 0 °C → rt, 63% (2 steps); (11) $NaBH_4$, MeOH, −10 °C, 83%; (12) **53**, Et_2O, −78 °C; (13) Dess–Martin periodinane, CH_2Cl_2, rt, 62% (2 steps); (14) *t*-BuOOH, $VO(acac)_2$, CH_2Cl_2 then Et_3SiH, TFA, CH_2Cl_2, −40 °C, 90%; (15) (a) TFA, H_2O, CH_2Cl_2, −37 °C; (b) Jones reagent, acetone, 0 °C to rt, 63%; (16) $NaBH_4$, MeOH, −10 °C, 80%; (17) methyl-β-iodoacrylate, 0.22 mol% **61**, Cr_2Cl_2, proton sponge, LiCl, Mn, $NiCl_2$(dppp), 2,6-lutidine, Cp_2ZrCl_2, MeCN, rt, 75%; (18) (a) PMBOC(=NH)CCl_3, $BF_3{\cdot}OEt_2$; (b) TBAF, MeOAc, THF, 50% (2 steps); (19) PPTS, MeOH; (20) TBSOTf, NEt_3, CH_2Cl_2, 87% (2 steps); (21) LAH, Et_2O, 0 °C; (22) Dess–Martin periodinane, CH_2Cl_2, 90% (2 steps).



Scheme 6 Synthesis of the C14–C26 domain. *Reagents and conditions*: (1) (*S*)-BINAP-$RuBr_2$, EtOH, 50 °C, H_2, 62%; (2) 2.5 mol% allyl ethyl carbonate, $Pd_2(dba)_3$, dppb, THF, 60 °C, 80%; (3) LiOH, MeOH–THF, 99%; (4) (i) $(COCl)_2$, DMF, THF; (ii) CH_2N_2, Et_3N, Et_2O, 60%; (5) $Cu(acac)_2$, THF, reflux, 91%; (6) $MePPh_3Br$, *t*-BuOK, THF, rt, 99%; (7) Sia_2BH, THF then NaOH, H_2O_2, 84%; (8) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 99%; (9) **68** (2 equiv.), **69** (0.5 equiv.), Co phthalocyanine, Mn, $Et_3N{\cdot}HCl$, LiCl, TMSCl, DME, rt then TBAF, 52% (d.r. = 6 : 1); (10) PvCl, DMAP, py, CH_2Cl_2, 87%; (11) Ms_2O, Et_3N, DMAP, CH_2Cl_2, 99%.

The retrosynthetic analysis is detailed in Scheme 10, and involves two key bond-forming events – an intramolecular [4 + 2]-cycloaddition of **94**, which would be generated by an intermolecular [2 + 2 + 2]-cycloaddition of **95** and **96**.

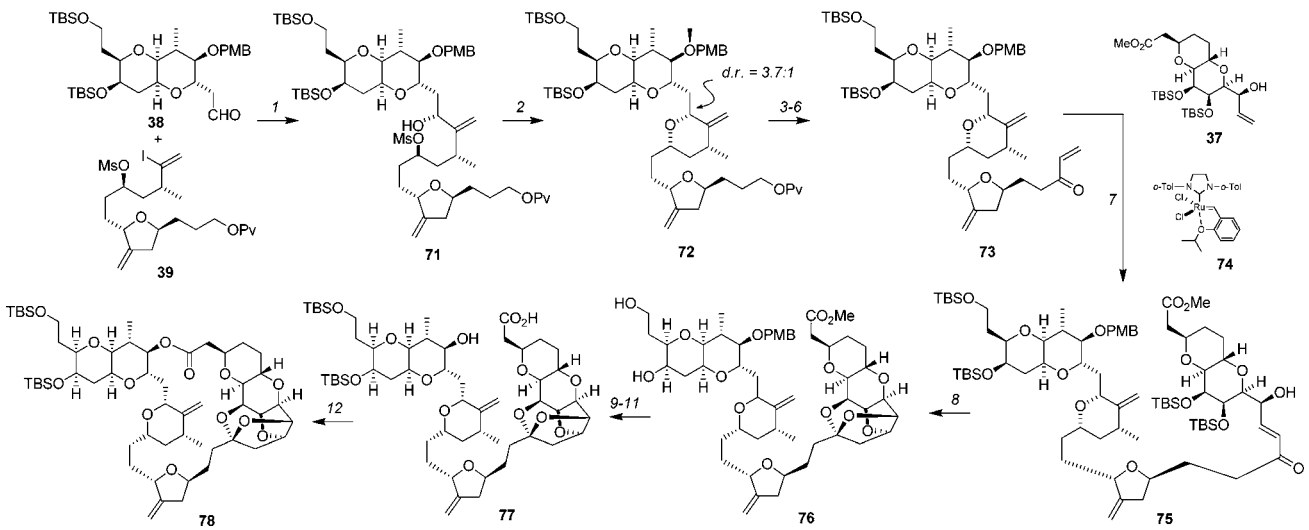
To prepare chloroacetylene **96**, the chiral iodide **97** was first transformed to the aldehyde **98** in 10 steps and 41% overall yield (Scheme 11). Addition of lithiochloroacetylene to the aldehyde **98**, followed by oxidation (Dess–Martin periodane) gave ketone **99** in 93% yield for the two steps. Transformation of ketone **99** to chloroacetylene **96** was achieved by a stereoselective reduction (DIBAL, 81%), removal of the TMS group (K_2CO_3, MeOH, 99%) and acetylation of the alcohol (Ac_2O, NEt_3, DMAP, 98%). The other acetylene **95** required for the [2 + 2 + 2]-cycloaddition was prepared in a nine-step sequence and 43% overall yield, starting from benzaldehyde **100**.

Coupling of **95** and **96** was readily achieved by treatment with 7 mol% of Cp*RuCl(cod) in 1,2-dichloroethane, generating the desired *meta*-chloro aromatic **101** in 87% yield and as a single regioisomer. Alcohol **101** was transformed into the Diels–Alder precursor **94** *via* a sequence of three reactions. After protection of the secondary alcohol of **101** (Ac_2O, NEt_3, DMAP, 92%), treatment with HF and methanol generated a catechol, which was converted to the *o*-quinone **94** by reaction with silver oxide (94% yield). The intramolecular Diels–Alder reaction was initiated by heating **94** in toluene at 110 °C and afforded the Diels–Alder adduct **102** in 40% yield (based on recovered starting materials) and as a single diastereomer. This material was converted into the required *para*-ketal quinone **103** in a three-step sequence. After oxidation of the secondary alcohol (Dess–Martin periodane), the silyl ether was removed, and a stereoselective reduction using $Me_4NBH(OAc)_3$ led to the *anti*-1,3-diol **104** as a single stereoisomer. Removal of the *p*-methoxybenzyl ether and the acetate protecting groups was achieved by sequential treatment with DDQ, then DBU. Finally, reaction with *tert*-butylhydroperoxide in the presence of DBU in CH_2Cl_2 afforded sporolide B (**93**) in 63% yield.

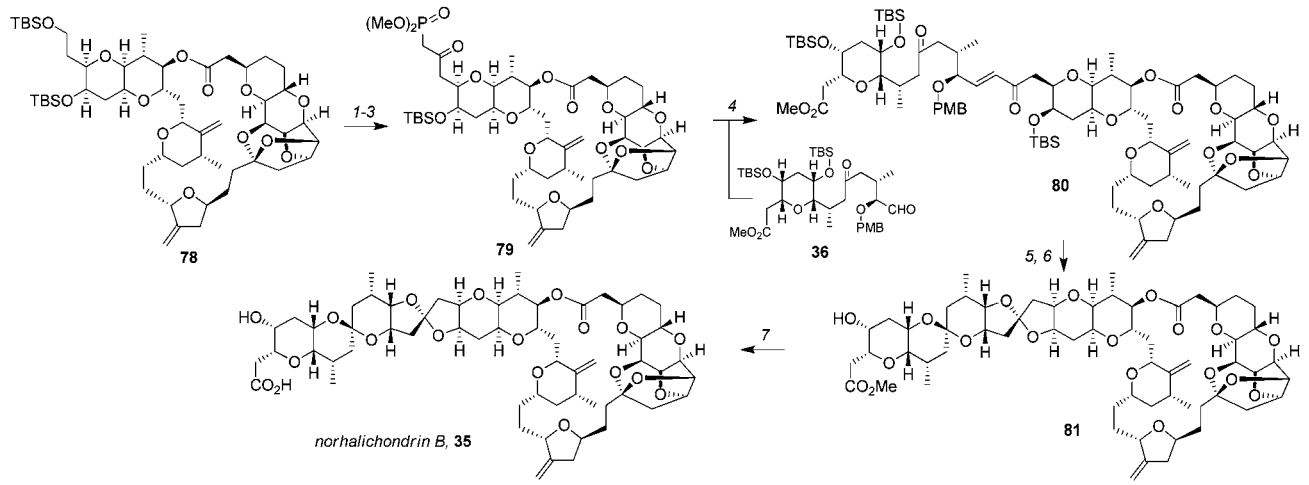
7 Brevisamide

In 2008 Wright and coworkers reported[27] the isolation of brevisamide (**105**), which is believed to be a biosynthetic precursor to brevenal. This report has triggered a great deal of interest in the synthesis of this compound, with four total syntheses being reported in 2009 (Scheme 12).

The first of the syntheses was by the Satake group, who were involved in the isolation of brevisamide (**105**).[28] This total synthesis confirmed the structure proposed. The key step in this



Scheme 7 Norhalichondrin B – intial subunit couplings and macrolactonization. *Reagents and conditions*: (1) 1% $NiCl_2/CrCl_2$, 4 : 1 THF–DMF, rt; (2) KHMDS, THF, 0 °C, 59% (dr = 3.7 : 1); (3) LAH, Et_2O, 0 °C; (4) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, rt; (5) $H_2C{=}CHMgBr$, THF, 0 °C; (6) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, rt, 70% (4 steps); (7) **37** (2 equiv.), 20 mol% **74**, PhMe, 80 °C, 62%; (8) TBAF, AcOH, THF, rt with $CaCO_3$, DOWEX 50WX8-400, MeOH as workup, 64%; (9) TBSOTf, Et_3N, CH_2Cl_2, 0 °C, 78%; (10) DDQ, CH_2Cl_2, pH 7 phosphate buffer, 65% (+16% of C27 epimer); (11) 1 M LiOH, THF, rt, quantitative; (12) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, rt, then DMAP, PhMe, 80 °C, 92%.

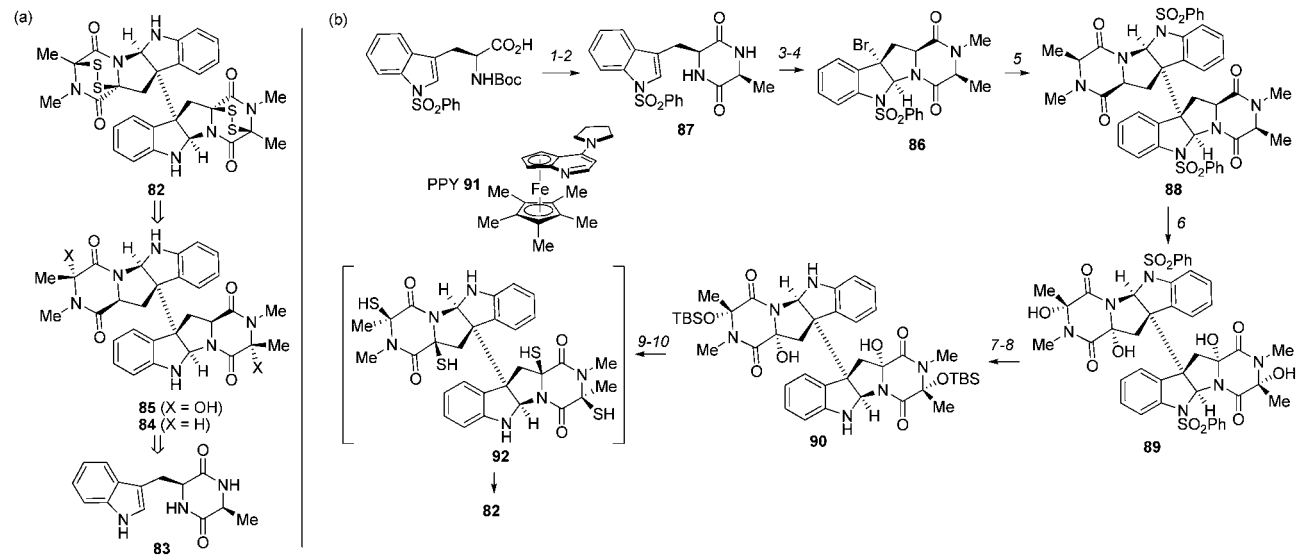


Scheme 8 Norhalichondrin B – initial subunit couplings and macrolactonization. *Reagents and conditions*: (1) PPTS, MeOH, 97% (brsm); (2) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, rt, 89%; (3) dimethyl(diazomethyl)phosphonate (20 equiv.), $SnCl_2$ (3 equiv.), CH_2Cl_2, rt, 74%; (4) **36** (1 equiv.), K_2CO_3, 18-crown-6, PhMe, 60 °C, 83%; (5) TBAF, AcOH, MeOAc–THF, rt; (6) DDQ, CH_2Cl_2–MeOH, 65% (2 steps); (7) LiOH, THF–H_2O, 60%.

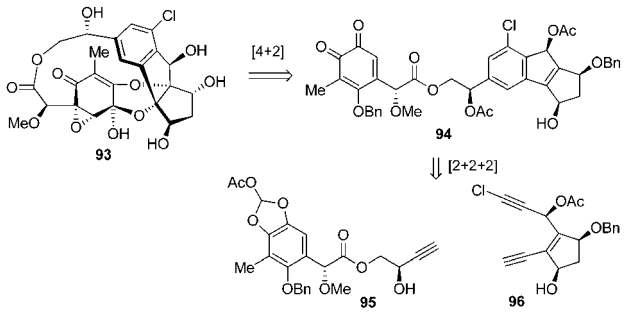
synthesis was the Suzuki–Miyaura coupling of iodide **106** and ether **107** (Scheme 13). Both of these subunits were prepared from (*Z*)-but-2-ene-1,4-diol (**108**) in 7 and 18 steps respectively. Alkene **107** was hydroborated using 9-BBN, and the resulting alkylborane was coupled with iodide **106** ($PdCl_2$(ddpf) (cat.), Cs_2CO_3, DMF, 45 °C). This material was deprotected by treatment with TBAF and afforded a diol **108** in 40% yield for the two steps. Selective oxidation of the allylic alcohol was achieved by stirring with MnO_2, and provided brevisamide (**105**) in 55% yield.

Fadeyi and Lindsley chose to assemble the diene side-chain using a Horner–Wadsworth–Emmons reaction between aldehyde **109** and phosphonate **110** (Scheme 14).[29] The aldehyde **109** was prepared in 14 steps, starting from 4-benzyloxybutan-1-ol (**111**). The key step in the sequence was a samarium iodide-mediated reductive cyclization of **113**. α,β-Unsaturated ester **113** was prepared in 93% yield by slow addition of ethyl propiolate to alcohol **112** in the presence of *N*-methylmorpholine. Conversion to the reductive cyclization precursor **113** was achieved by deprotection of the silyl group (HCl, MeOH) and Swern oxidation. Reaction of the resulting aldehyde with SmI_2 gave pyran **114** in 69% yield for the three steps. A series of functional group manipulations generated the desired aldehyde **109** in 6 steps. Coupling of **109** with the lithium salt of the readily available phosphonate **110** (*n*-BuLi, THF, −78 °C to rt) afforded a diene (78% yield), that was elaborated to the natural product in three steps.

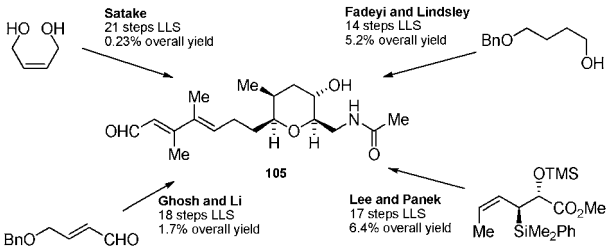
Ghosh and Li utilized the same coupling strategy reported by Satake and coworkers (Scheme 15).[30] They accessed the pyran



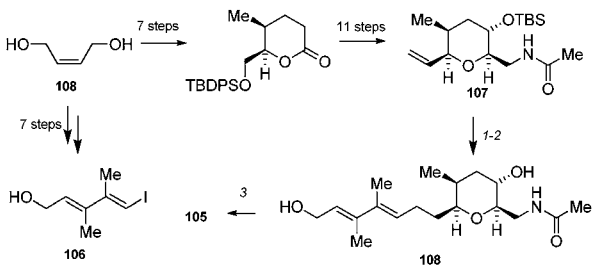
Scheme 9 (a) Movassaghi's retrosynthesis of (+)-11,11′-dideoxyverticillin A. (b) Movassaghi's synthesis. *Reagents and conditions*: (1) L-alanine methyl ester hydrochloride, EDC·HCl, HOBt, Et_3N, CH_2Cl_2, rt, 95%; (2) TFA, CH_2Cl_2, rt, then *t*-BuOH, morpholine, 48 h, 84%; (3) Br_2, MeCN, 0 °C, 76%; (4) MeI, K_2CO_3, acetone, rt, 77%; (5) $CoCl(PPh_3)_3$, acetone, rt, 46%; (6) Py_2AgMnO_4, CH_2Cl_2, rt, 63%; (7) TBSCl, 5 mol% PPY (**91**), NEt_3, DMF, rt, 55%; (8) 5% Na(Hg), NaH_2PO_4, MeOH, rt, 87%; (9) K_2CS_3, TFA, CH_2Cl_2, rt, 56%; (10) $HOCH_2CH_2NH_2$, acetone, rt, then KI_3, py, CH_2Cl_2, rt, 62%.



Scheme 10 Nicolaou's strategy for sporolide B.



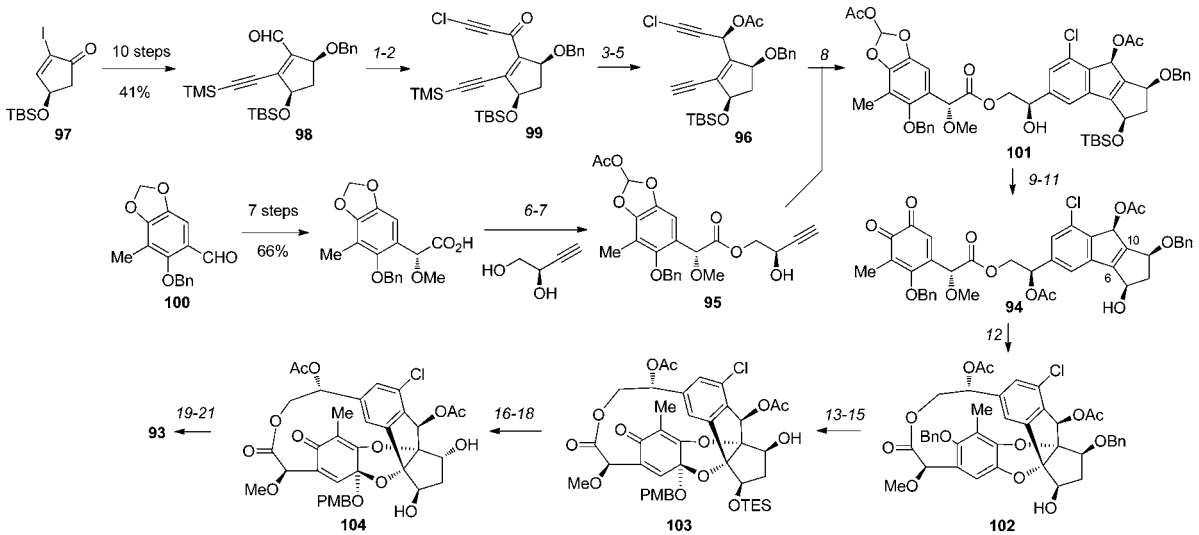
Scheme 12 Summary of the syntheses of brevisamide.



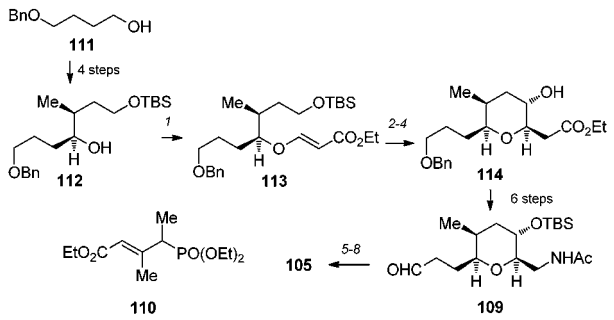
Scheme 13 Satake & Tachibana's synthesis of brevisamide. *Reagents and conditions*: (1) 9-BBN, THF, rt; then **106**, 3 M Cs_2CO_3, $PdCl_2$(dppf), DMF, 45 °C; (2) TBAF, THF, 0 °C, 40% (2 steps); (3) MnO_2, CH_2Cl_2, rt, 55%.

115 using Jacobsen's asymmetric hetero-Diels–Alder reaction. Accordingly, aldehyde **116** was transformed into a silyloxydiene in three steps, and this was reacted with 3-*tert*-butyldimethylsilyloxypropanal in the presence of 10 mol% of Jacobsen's chromium catalyst **117**. The highly substituted pyran **115** was formed in high diastereoselectivity (dr = 95%, ee = 96%) and in 37% overall yield. A series of functional group manipulations generated the desired alkene **118** in 11 steps. Transformation to the natural product was achieved in a similar fashion to that of Satake, with the final chemoselective oxidation being achieved using TEMPO in the presence of benzene diacetate in CH_2Cl_2 at rt (87%).

The final synthesis of brevisamide (**105**) was reported by Lee and Panek (Scheme 16).[31] They opted to use a modified Negishi cross-coupling of **120** and **121**to introduce the side-chain. The assembly of the pyran **120** was achieved using Panek's silicon-directed [4 + 2]-annulation strategy. Reaction of the known *Z*-crotylsilane **122** with 3-benzyloxypropanal afforded the 5,6-*cis*-dihydroyran **123** in 70% yield, with a dr of 10 : 1. The original plan was to carry out a diastereoselective hydroboration



Scheme 11 Nicolaou's synthesis of sporolide B. *Reagents and conditions*: (1) (*Z*)-1,2-dichloroethene (4.5 equiv.), MeLi (1.6 M in Et_2O, 3 equiv.), Et_2O, 0 °C, then **11**, Et_2O, 0 °C; (2) DMP (1.5 equiv.), $NaHCO_3$ (5 equiv.), CH_2Cl_2, rt, 93% over 2 steps; (3) DIBAL-H (1.0 M in PhMe, 1.5 equiv.), PhMe, −78 °C, 81%; (4) K_2CO_3 (1.5 equiv.), MeOH, rt, 99%; (5) Ac_2O (1.5 equiv.), Et_3N (1.5 equiv.), DMAP (0.1 equiv.), CH_2Cl_2, 0 °C, 98%; (6) (2*R*)-3-butyn-1,2-diol (1.3 equiv.), EDCI (1.2 equiv.), DMAP (0.2 equiv.), CH_2Cl_2, rt, 73%; (7) $Pb(OAc)_4$ (1.5 equiv.), PhH, 75 °C, 89%. (8) **95** (1.0 equiv.), **96** (1.1 equiv.), [Cp*RuCl(cod)] (0.07 equiv.), 1,2-DCE, rt, 87%; (9) Ac_2O (2 equiv.), Et_3N (2 equiv.), DMAP (0.1 equiv.), CH_2Cl_2, 0 °C, 92%; (10) HF (48% aqueous solution, excess), MeCN, rt, 30 min; then MeOH (excess), rt, 74%; (11) Ag_2O (2.5 equiv.), CH_2Cl_2, rt, 94%. (12) PhMe, 110 °C, 40% (based on 50% recovered starting material); (13) TESOTf (1.5 equiv.), Et_3N (2.0 equiv.), CH_2Cl_2, 0 °C, 95%; (14) H_2 (balloon pressure), $Pd(OH)_2$ (10% on carbon, 2 equiv.), EtOAc, rt, 92%; (15) PIFA (1.5 equiv.), PMBOH (10 equiv.), K_2CO_3 (5 equiv.), MeCN, 0 °C, 75%; (16) DMP (2 equiv.), CH_2Cl_2, rt, 90%; (17) HF (48% aqueous solution, excess), MeCN, rt, 85%; (18) $Me_4NBH(OAc)_3$ (10 equiv.), MeCN–AcOH (10 : 1), rt, 85%; (19) DDQ (5 equiv.), CH_2Cl_2–H_2O (10 : 1), rt, 70%; (20) DBU (10 equiv.), CH_2Cl_2–MeOH (3 : 1), 40 °C, 78%; (21) *t*-BuOOH (10 equiv.), DBU (5 equiv.), CH_2Cl_2, 40 °C, 63%.

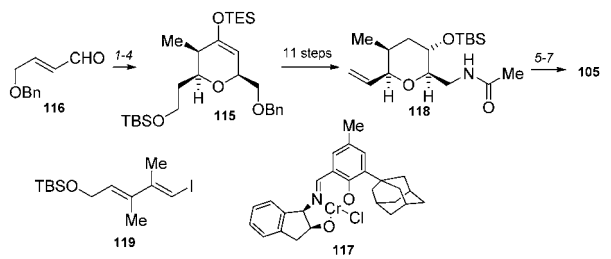


Scheme 14 Fadeyi & Lindsley's synthesis of brevisamide. *Reagents and conditions*: (1) $HCCCO_2Et$, NMM, MeCN, 24 h, 93%; (2) HCl, MeOH, 0 °C; (3) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C, NEt_3; (4) SmI_2, MeOH, THF, 0 °C, 69% (3 steps); (5) **110**, *n*-BuLi, THF, −78 °C to rt, then **109**, 78%; (6) DIBAL, CH_2Cl_2, −78 °C; (7) TBAF, THF, 0 °C to rt, 71% (2 steps); (8) MnO_2, CH_2Cl_2, rt, 74%.

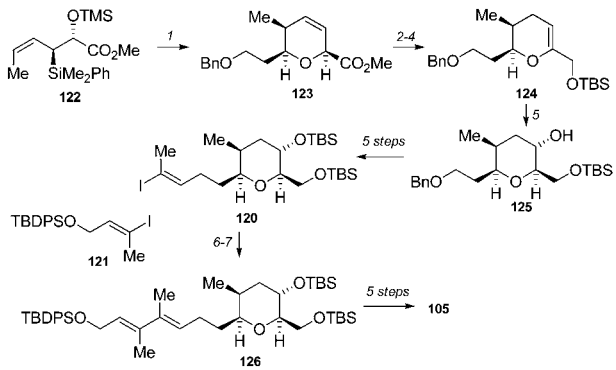
of the alkene, but this strategy gave poor stereocontrol. To overcome this deficiency, a new hydroboration precursor was prepared. Isomerization with DBU (86%), reduction of the ester with $LiAlH_4$ and protection of the alcohol (TBSCl, imid., DMF) gave the allylic TBS ether **124** (84% for 2 steps). Hydroboration with $BH_3{\cdot}SMe_2$ at 0 °C gave the tetrahydropyranol **125** in 90% yield and excellent diastereoselectivity (>11 : 1). This material was transformed into the coupling partner **120** in 5 steps. Coupling of **120** with a vinylzinc species (prepared by reaction of **121** with *t*-BuLi, then $ZnCl_2$) in the presence of 10 mol% of $Pd(PPh_3)_4$ generated a diene, which was selectively deprotected (CSA, MeOH, CH_2Cl_2) to afford the primary alcohol **126** in 58% yield for the two steps. Completion of the synthesis was achieved in five steps.

8 Vannusal B

In the previous installment of this review,[32] the Nicolaou synthesis of the proposed structure of vannusal B (see compound **127** below, Scheme 17) was described. The spectroscopic data of the synthetic material did not match the reported data, and in an epic effort, reminiscent of their efforts in the arena of azaspiracid, the Nicolaou group have performed extensive synthetic and



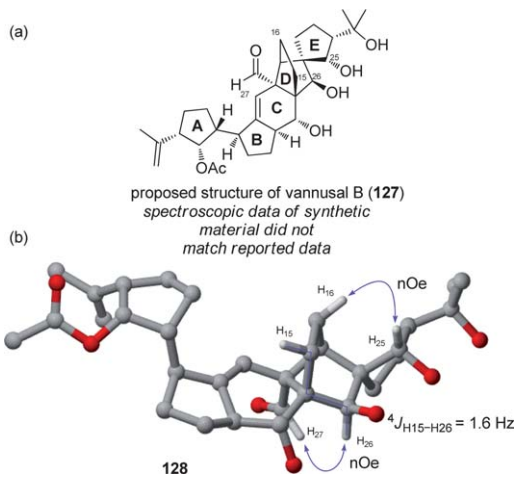
Scheme 15 Ghosh & Li's synthesis of brevisamide. *Reagents and conditions*: (1) EtMgBr, THF; (2) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C, NEt_3, 84% (2 steps); (3) TESOTf, NEt_3, CH_2Cl_2, −78 C, 84%; (4) 3-TBSOCH_2CH_2CHO, **117** (10 mol%), 52% (dr = 95%, ee = 96%); (5) 9-BBN, THF, rt; then aq. Cs_2CO_3,**119**, $PdCl_2(dppf){\cdot}CH_2Cl_2$, DMF, 45 °C; (2) TBAF, THF, 0 °C, 40% (2 steps); (3) TEMPO, $PhI(OAc)_2$, CH_2Cl_2, rt, 1 h, 87%.



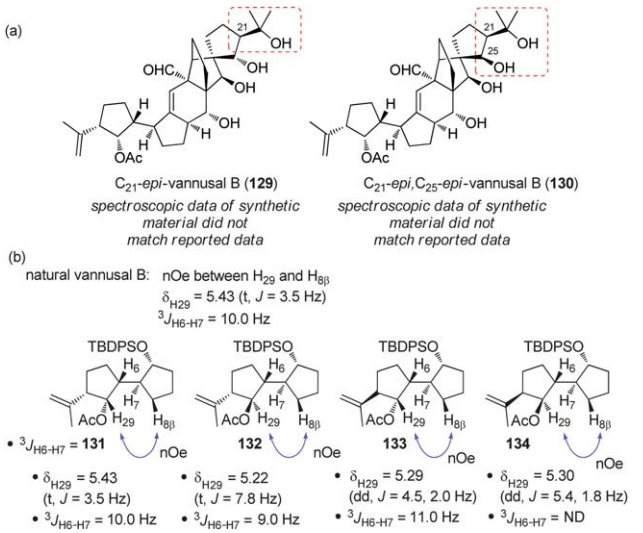
Scheme 16 Lee & Panek's synthesis of brevisamide. *Reagents and conditions*: (1) TMSOTf, 3-benzyloxypropanal, CH_2Cl_2, PhH, −50 °C, 70%, dr = 10 : 1; (2) DBU, THF, rt, 86%; (3) $LiAlH_4$, Et_2O, 0 °C; (4) TBSCl, imid., DMF, rt, 84% (2 steps); (5) $BH_3{\cdot}SMe_2$, THF, 0 °C to rt, H_2O_2, 1 N NaOH, 90%, dr >11 : 1; (6) **121**, *t*-BuLi, $ZnCl_2$, THF, −78 °C to 0 °C, then **120**, 10 mol% $Pd(PPh_3)_4$; (7) CSA, MeOH, CH_2Cl_2, 58% (2 steps).

structural studies that have resulted in a structure correction.[33] The departure point for their studies was the observation that the natural product and the material they synthesized – structure **127** – shared a number of key spectroscopic characteristics. Key features are shown in model **128** and include (i) nOe interaction between H16 and H25 and H26 and H27 and (ii) a W-type coupling between H15 and H26 of 1.6 Hz. On the basis of these observations it was proposed that stereocenters C26 and C18 were likely correct and that attention would initially be focused on targets with changes in the stereochemistry at C21 and C25.

The synthesis of compounds **129** (C21-*epi*-vannusal B) and **130** (C21-*epi*,C25-*epi*-vannusal B) were accomplished by strategies that paralleled the initial route used to access **127** (Scheme 18). Disappointingly, neither compound had spectroscopic data matching the natural product. Having excluded these structures, attention moved to examining the stereochemical relationships in the AB-ring domain of the vannusals. In this case, model studies



Scheme 17 (a) The initially proposed structure of vannusal B that was synthesized by Nicolaou. (b) Key features shared by **128** and the natural product in the DE ring domain.

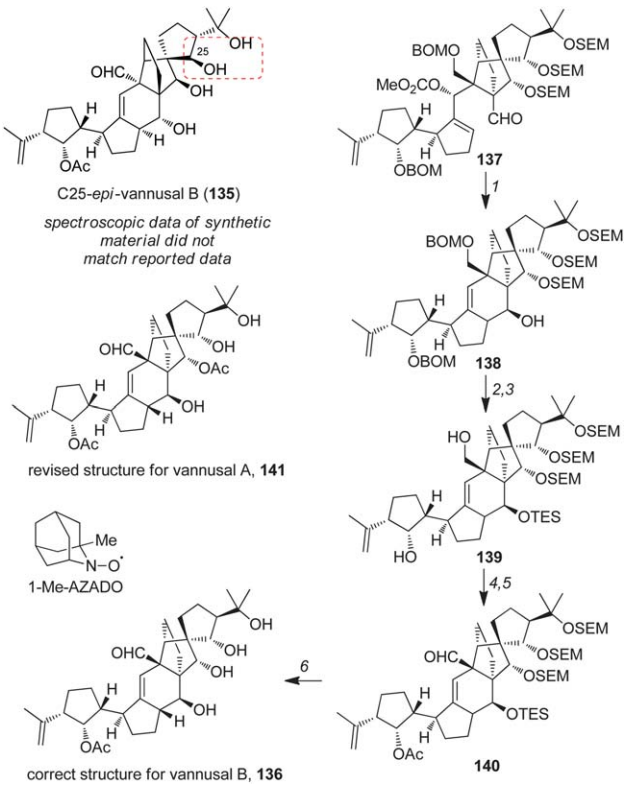


Scheme 18 (a) C21-*epi*-vannusal B **129** and C21-*epi*,C25-*epi*-vannusal B **130**; (b) Model studies exploring the AB ring domain.

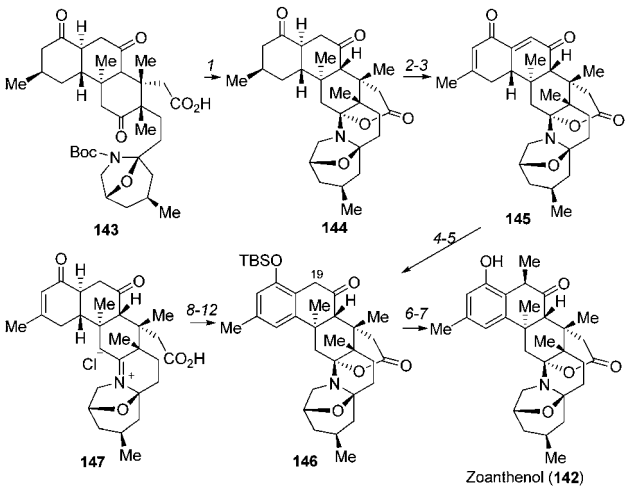
were employed to examine the relationship between structure and the observed nOes and coupling constants. Key observations from the natural product were an nOe between H29 and H8b, $\delta_{H29} = 5.43$ (t, $J = 3.5$ Hz), and $^3J_{H6–H7} = 10.0$ Hz. Of the model systems prepared (**131–134**), only **131** had data that matched (and thus confirmed the originally proposed structure).

With the AB-ring stereochemistry now unquestionable, and the obvious changes in the DE-ring domain having been examined, Nicolaou and coworkers were pressed to question again the stereochemistry in the DE domain, and in particular two questions: (a) could a C25-*epi* structure accommodate the observed coupling constants, or (b) was the relative configuration of the entire E ring incorrect?

Synthesis of C25-*epi*-vannusal B (**135**) ruled out this structure, but contemporaneously with those studies, the synthesis of **136** was completed, and the structure of **136** matched the spectroscopic data for vannusal B (Scheme 19). From a synthesis point of view, the completion of the synthesis of **136** was straightforward, and commenced with key intermediate **137**. SmI_2-mediated ring closure gave **138** in 82% yield, and with the polycyclic ring structure secured, a sequence of protecting group manipulations and redox chemistry ensued to give vannusal B (**136**) in five further steps.



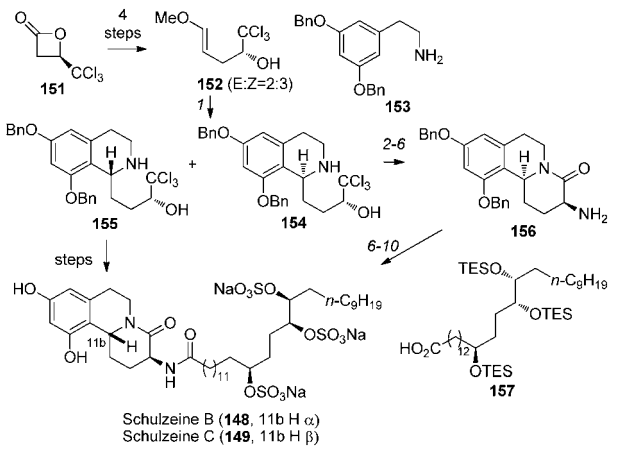
Scheme 19 Synthesis of the correct structure of vannusal B. *Reagents and conditions*: (1) SmI_2 (10 equiv.), HMPA (30 equiv.), THF, −20 → 25 °C, 82%; (3) KHMDS, TESCl, Et_3N, THF, −78 → 25 °C, 94%; (3) LiDBB, THF, −78 → −50 °C, 83%; (4) $PhI(OAc)_2$, 1-Me-AZADO, CH_2Cl_2, 25 °C, (5) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 25 °C, 87% (2 steps); (6) aq. HF, THF, 85%.



Scheme 20 Tanino & Miyashita's synthesis of zoanthenol. *Reagents and conditions*: (1) AcOH (aq.), 100 °C, 76%; (2) TMSCl, LDA, THF, −50 °C; (3) $Pd(OAc)_2$, $CaCO_3$, MeCN, 55 °C; (4) TFA, 50 °C; (5) TBSCl, $AgNO_3$, py, THF, rt, 57% (4 steps); (6) LDA, THF, −78 °C, then MeI; (7) TASF, acetone, rt, 53% (2 steps); (8) Pd/C, H_2 (1 atm), MeOH, rt, then NEt_3, 95%; (9) TMSCl, LDA, THF, −50 °C; (10) $Pd(OAc)_2$, $CaCO_3$, MeCN, 55 °C; (11) TFA, 50 °C; (12) TBSCl, $AgNO_3$, py, THF, rt, 54% (4 steps). TASF = tris[dimethylamino]sulfonium difluorotrimethyl silicate.

9 Zoanthenol

The group of Tanino and Miyashita have developed a total synthesis of zoanthenol (**142**),[34] with their prior work on the syntheses of norzoanthamine and zoanthamine providing a starting point.[35] Zoanthenol (**142**) differs from these targets as it has an aromatic A ring. Accordingly, initial approaches were based on an oxidative aromatization of zoanthamine, but these were unsuccessful. To achieve the aromatization, a four-step sequence had to be employed (Scheme 20). Intermediate **143**, which had been utilized in the total synthesis of norzoanthamine



Scheme 21 Liu & Romo's syntheses of schulzeines B and C. *Reagents and conditions*: (1) **153**, HOAc, 100 °C, 24 h, **154** (33%), **155** (41%); (2) $(Boc)_2O$, CH_2Cl_2, 92%; (3) NaOH, NaN_3, DME–H_2O (1 : 1), $c = 0.008$ M; (4) TFA, CH_2Cl_2, 0 °C; (6) NEt_3, DPPA, DMF, 47% (3 steps); (7) PPh_3, THF–H_2O, 93%; (8) **157**, EDCI, HOBt, NEt_3, DMF, 65%; (9) HOAc, THF–H_2O, 99%; (10) SO_3·py, DMF, 0 °C to rt; (11) Pd/C, H_2, MeOH, 82% (2 steps).

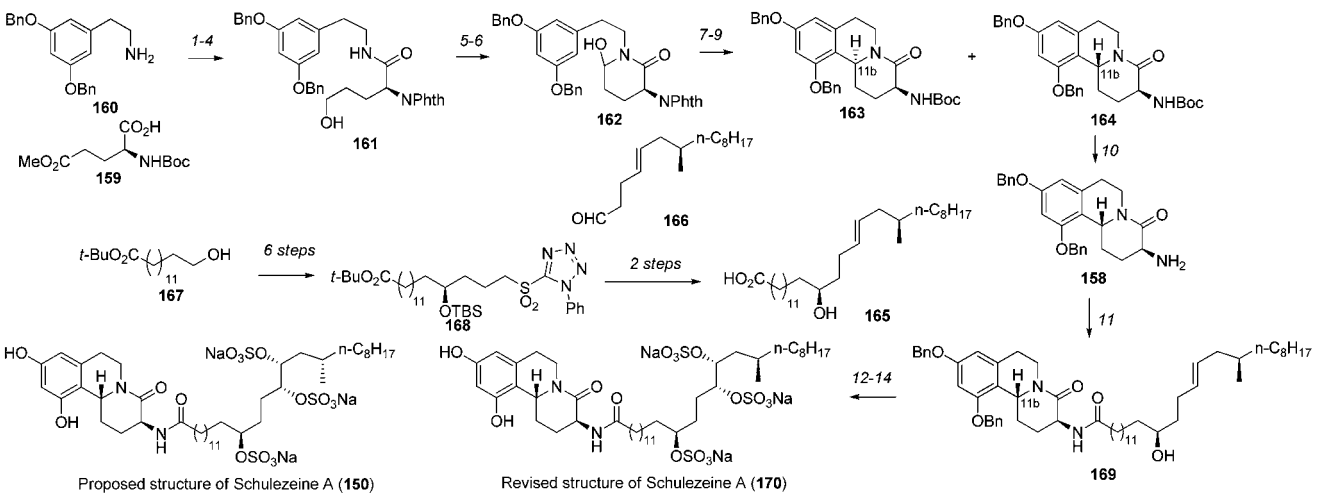
and zoanthamine, was converted into dihydronorzoanthamine **144** in 76% yield by reaction with aqueous acetic acid at 100 °C. Transformation to the bis-enone **145** was achieved using the Ito–Saegusa methodology (LDA, TMSCl; then $Pd(OAc)_2$, $CaCO_3$). The calcium carbonate was crucial in removing the acetic acid formed in the process.

The desired aromatic A-ring compound **146** was then generated by reacting **145** with TFA at 50 °C to isomerize the alkene to afford the phenol, which was protected (TBSCl, $AgNO_3$, pyridine) as its silyl ether. This four-step sequence proceeded in an efficient 57% yield. To complete the synthesis, the C19 methyl group was stereoselectively introduced by deprotonation of **146** with LDA, then reaction with methyl iodide. Deprotection with TASF (tris[dimethylamino]sulfonium difluorotrimethyl silicate) afforded the sensitive zoanthenol (**142**) in 53% yield for the two steps. Further investigation led to an alternate five-step synthesis of **146** that proceeded in 51% overall yield, starting from commercially available norzoanthamine hydrochloride (**147**).

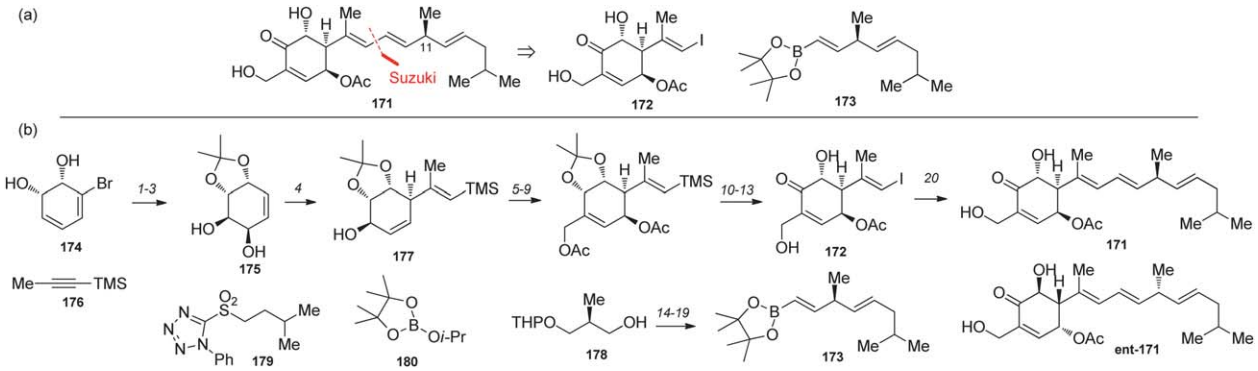
10 Schulzeines

The schulzeines are potent α-glucosidase inhibitors ($IC_{50} = 48$–170 nM), and as such, have great potential as antidiabetic agents. Both the groups of Romo and Wardrop have reported total syntheses of schulzeines B (**148**) and C (**149**), which are epimers at C11b. Furthermore, Bowen and Wardrop have completed a total synthesis of schulzeine A (**150**), which has resulted in a structural revision of the proposed structure.

Liu and Romo's synthesis of schulzeines B (**148**) and C (**149**) focuses on the preparation of the ε-lactam-fused tetrahydroisoquinoline moiety using the β-lactone **151** (Scheme 21).[36] The commercially available lactone **151** is transformed into the vinyl ether **152** in four steps. Pictet–Spengler condensation of **152** (*E*:*Z* = 2 : 3) with the readily available amine **153** gave the tetrahydroisoquinolines as a ~1 : 1 ratio of diastereomers **154** and **155**. These could be readily separated, and each diastereomer can be utilized to prepare schulzeines B (**148**) and C (**149**) respectively. To illustrate the endgame, diastereomer **154** was transformed into the amine **156** in 5 steps. Conversion to schulzeine B (**148**) was achieved in 4 steps. After coupling of amine **156** with the readily available acid **157** (EDCI, HOBt, 65%) the silyl protecting groups were removed (HOAc, 99%), the resulting alcohols were sulfated (SO_3·py) and the benzyl groups removed by hydrogenolysis (Pd/C, H_2, 82% for 2 steps). The diastereomer **155** could be carried through the same sequence to yield schulzeine C (**149**).



Scheme 22 Bowen & Wardrop's synthesis of the revised structure of schulzeine A (**170**). *Reagents and conditions*: (1) *i*-BuOCOCl, NMM, CH_2Cl_2, −35 °C, then **160**, DMF, CH_2Cl_2, rt; (2) $NaBH_4$, LiCl, THF, MeOH, 0 °C, 79% (2 steps); (3) HCl–Et_2O, CH_2Cl_2, rt; (4) *N*-(ethoxycarbonyl)phthalimide, Na_2CO_3, THF, rt, 49% (2 steps); (5) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C, NEt_3, 79%; (6) AcOH, CH_2Cl_2, rt, 76%; (7) TFA, CH_2Cl_2, −78 °C, 93%, *cis*/*trans* = 2 : 1; (8) H_2NNH_2, EtOH, rt; (9) $Boc_2(O)$, CH_2Cl_2, rt, **163** (57%), **164** (26%); (10) **164**, TFA, CH_2Cl_2, 0 °C, 85%); (11) **166**, EDC, CH_2Cl_2, rt, 80%; (12) AD-mix-α, $MeSO_2NH_2$, *t*-BuOH–*t*-BuOMe–H_2O (1 : 1 : 1), 0 °C, 77%, dr >91 : 9; (13) SO_3·py, DMF, rt; (14) H_2, Pd/C, EtOH, rt, 75% (2 steps).



Scheme 23 (a) Macklin & Micalizo's retrosynthesis of (+)-phorbasin C. (b) Macklin & Micalizio's synthesis of (+)-phorbasin C. *Reagents and conditions*: (1) 2,2-dimethoxypropane, *p*-TsOH; (2) OsO_4, NMO; (3) Bu_3SnH, AIBN, dr ≥20 : 1, 65% (3 steps); (4) **3**, Ti(O*i*-Pr)$_4$, *c*-C_5H_9MgCl, Et_2O then add bis-lithium alkoxide of **2**, −78 °C to rt, H^+ quench, dr ≥20 : 1, 47%; (5) $VO(acac)_2$, TBHP, PhH, 50 °C, 63%; (6) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2; (7) $Ph_3P{=}CH_2$, THF, 0 to 5 °C, 79% (2 steps); (8) $Pd(PPh_3)_4$, AcOH, THF; (9) Ac_2O, py, DMAP, CH_2Cl_2, 90% (2 steps); (10) NIS, MeCN, 77%; (11) TFA, H_2O, THF; (12) IBX, DMSO, 75% (2 steps); (13) $Sc(OTf)_3$, MeOH, H_2O, 80%; (14) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2; (15) KHMDS, **179**, DME, 51% (2 steps); (16) *p*-TsOH, MeOH, CH_2Cl_2; (17) DMP, CH_2Cl_2, H_2O; (18) $CrCl_2$, CHI_3, THF, 44% (3 steps); (19) *t*-BuLi, then **180**, 76%; (20) **173**, $Pd(PPh_3)_4$, Tl_2CO_3, THF, H_2O, 67%.

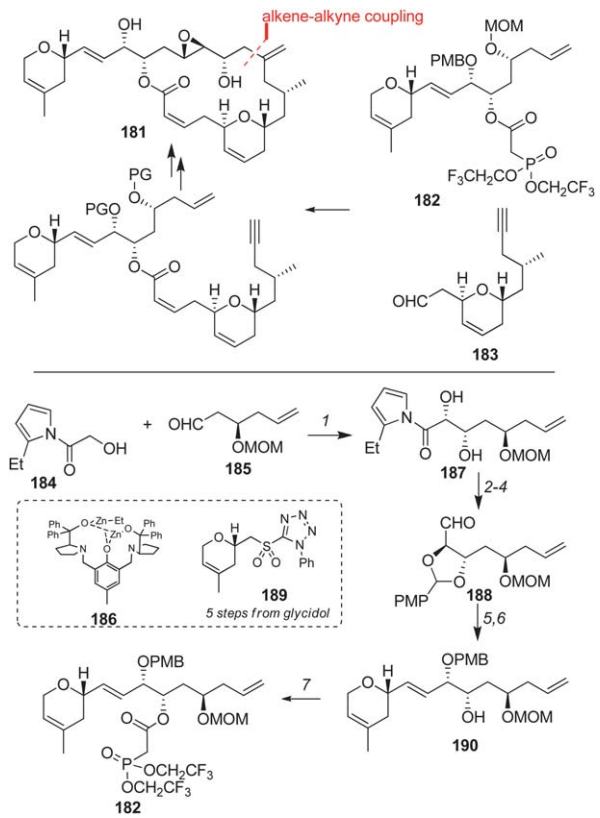
Bowen and Wardrop have also developed syntheses of schulzeines B (**148**) and C (**149**).[37] Moreover, they also synthesized the proposed structure for schulzeine A (**150**) (Scheme 22). To access this compound they utilized the same disconnection as Romo. Schulzeine A (**150**) contains an extra methyl group, which had been proposed to be the *S*-configuration at C20. They prepared the amine **158** in 9 steps starting from methyl ester **159**, as illustrated in Scheme 22. The appropriate acid (*S*)-**165** was prepared (not shown), coupled to the amine and the diol generated using a Sharpless asymmetric dihydroxylation (not shown). However, conversion to the proposed structure **150** *via* persulfation and debenzylation provided material that did not match the natural product. As the key discrepancies were centered around the C20 stereocentre, it was decided to prepare the C20 diastereomer.

Starting from (*R*)-3-methylundecanal (**166**), acid (*R*)-**165** was prepared in 8 steps, with a Julia–Kocienski olefination generating the key alkene. After coupling with amine **158**, the alkene **169** was dihydroxylated using the Sharpless asymmetric dihydroxylation conditions (AD-mix-α) to generate a triol as a >91 : 9 mixture of diastereomers. Persulfation ($SO_3{\cdot}py$) and debenzylation (Pd/C, H_2) provided material **170** that was identical to the natural product.

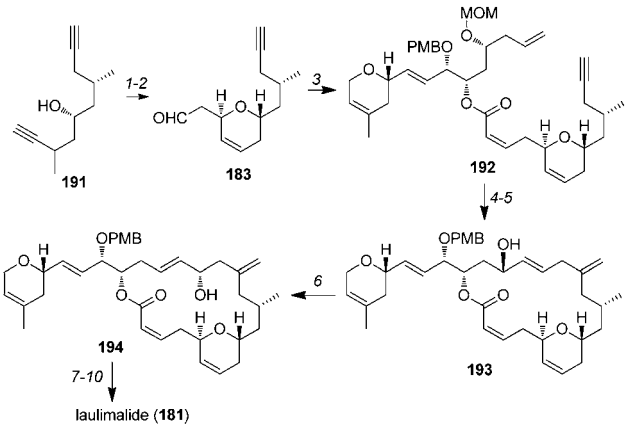
11 Other compounds

Completion of a total synthesis of phorbasin C (**171**) has allowed Macklin and Micalizo to determine the relative stereochemistry at C11 and assign the absolute stereochemistry.[38] As summarized in Scheme 23, it was decided to assemble the target using a Suzuki cross-coupling of iodide **172** and boronate **173**, particularly as this allowed the stereochemistry at C11 to be readily varied.

Iodide **172** was prepared in a 13-step sequence, starting from the readily available chiral diol **174**. The key step in this sequence was the allylic alcohol–alkyne reductive cross-coupling of allylic alcohol **175** with acetylene **176**. The bis-lithium alkoxide of diol was reacted with the titanium reagent prepared from reaction of acetylene **176** with titanium isopropoxide and cyclopentyl magnesium chloride to afford the allylic alcohol **177** in 47% yield and an impressive diastereomeric ratio of ≥20 : 1. This material



Scheme 24 Trost's synthetic plan for laulimalide and assembly of the phosphonate. *Reagents and conditions*: (1) 15 mol% (*R*,*R*)-**186**, THF, 53%, 10 : 1 dr; (2) *p*-MeOPhCH(OMe)$_2$, 10-CSA, CH_2Cl_2, 81%; (3) $NaBH_4$, THF, 86%; (4) Dess–Martin periodinane, CH_2Cl_2; (5) **189**, LiHMDS, 3 : 1 DMF–HMPA, then **188**, 64% over 2 steps; (6) DIBAL-H, CH_2Cl_2, 61%; (7) $(CF_3CH_2O)_2P(O)CH_2CO_2H$, 2,4,6-trichlorobenzoylchloride, *i*-Pr_2EtN, THF, then DMAP, PhH, 99%.



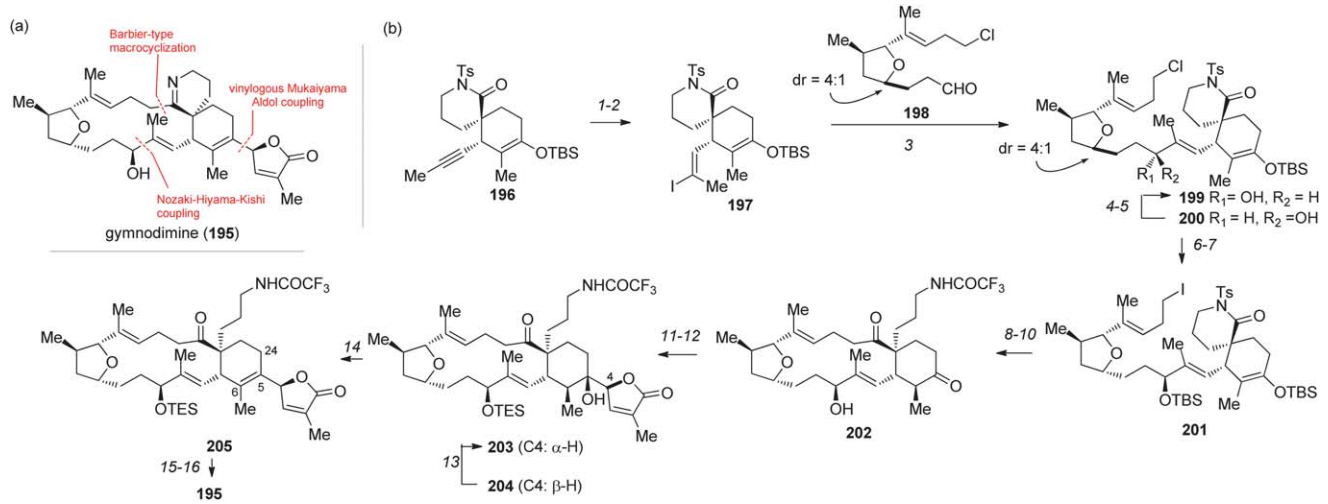
Scheme 25 Trost's synthesis of laulimalide. *Reagents and conditions*: (1) 5 mol% $[Rh(COD)Cl]_2$, 10 mol% $[m\text{-}F(C_6H_4)]_2PCH_2CH_2P[m\text{-}F(C_6H_4)]_2$, DMF, 55%; (2) $CH_2{=}CHOTBS$, Montmorillomite K-10, CH_2Cl_2, 82%; (3) **182**, KHMDS, 18-crown-6, THF, then **183**, *E*/*Z* = 1 : 5, 62% (50% isolated *Z* isomer); (4) 5 mol% $[CpRu(CH_3CN)_3]PF_6$, acetone (*c* 0.001 M), 50 °C, 15 min, 99%; (5) PPTS, *t*-BuOH, 66%; (6) $O_3ReOSiPh_3$, Et_2O, 5 min, 78% (97% brsm); (7) Dess–Martin periodinane, CH_2Cl_2; (8) (*R*)-Me-CBS, $BH_3{\cdot}THF$, THF, 93% over 2 steps; (9) (+)-DET, $Ti(Oi\text{-}Pr)_4$, TBHP, 4 Å MS, CH_2Cl_2, 88%; (10) DDQ, CH_2Cl_2–pH 7 buffer–*t*-BuOH, 89%.

was elaborated to the iodide **172** in 9 steps. Synthesis of the boronate coupling partner **173** was achieved in 6 steps starting from known chiral alcohol **178**. As the stereochemistry of C11 was unknown at the time, both enantiomers of **173** were prepared (only the *R* series is shown). Suzuki coupling of **172** and **173**, using the standard conditions of $Pd(PPh_3)_4$ and Tl_2CO_3, yielded phorbasin C (**171**) in 67% yield. The stereochemical relationship was determined by comparison of the ^{13}C NMR spectrum of the natural product with that of the synthetic material. Furthermore, from the optical rotation it was determined that the absolute stereochemistry of the natural product is *ent*-**171**.

Trost and Dong have reported a concise synthesis of laulimalide (**181**) that provides a further example of the utility of their Ru-catalyzed alkene–alkyne couplings for macrocyclization reactions.[39] A broad overview of the synthesis plan is provided in Scheme 24, and the synthesis of subunit **182** commenced with a Zn-catalyzed direct aldol reaction between glycolic acid derivative **184** and aldehyde **185** to give **187**. Protection of the 1,2-diol as the PMP acetal, and conversion of the pyrrole amide to an aldehyde yielded **188**, which could be engaged in a Julia olefination with *N*-phenyltetrazolyl sulfone **189** to give **190**. Reductive conversion of the PMP acetal to the PMB ether followed by acylation with a phosphonoacetic acid derivative completed the route to subunit D **182**.

The other coupling partner **183** was prepared in two steps and 45% overall yield by carrying out a Rh-catalyzed cycloisomerization on diyne **191**, then reacting the resulting vinylogous acetal with *tert*-butyldimethylsilyl vinyl ether under acidic conditions (Scheme 25). Coupling of **183** with the phosphonate **182** under Still–Gennari conditions gave the alkenoate **192** as a 1 : 5 mixture of *E* and *Z* isomers, with the *Z* isomer being isolated in 50% yield after chromatography.

Upon treatment of the enyne **192** with 5 mol% $[CpRu(CH_3CN)_3]PF_6$ in acetone the required 1,4-diene was formed, and subsequent removal of the MOM group gave the allylic alcohol **193** in 65% overall yield. After attempts to utilize a Payne rearrangement failed, it was found that the allylic alcohol **193** could be rearranged to alcohol **194** with complete retention of configuration when reacted with one equivalent of $O_3ReOSiPh_3$ (Et_2O, −50 °C, 78% yield, 97% based on recovered



Scheme 26 Romo's synthesis of (−)-gymnodimine. *Reagents and conditions*: (1) $PdCl_2(PPh_3)_2$, *n*-Bu_3SnH, THF–hexanes (1 : 7), 85%; (2) I_2, CH_2Cl_2, −78 °C, 76%; (3) **198**, $CrCl_2$, 0.5 mol% $NiCl_2$, DMF–THF (1 : 1), dr 1.3 : 1**199**:**200**, 97%; (4) Dess–Martin periodane, $NaHCO_3$, CH_2Cl_2, 88%; (5) (*R*)-Me-CBS, catecholborane, CH_2Cl_2, 0 °C, dr = 6 : 1, 80%; (6) TBSOTf, NEt_3, CH_2Cl_2, −78 °C, 86%; (7) NaI, acetone, 65 °C, 99%; (8) *t*-BuLi, Et_2O, rt, 56–61%; (9) $(CF_3CO)_2O$, NEt_3, CH_2Cl_2, 0 °C, then SmI_2, rt, 73%; (10) *p*-TSA, CH_2Cl_2–THF–MeOH, 84%; (11) $TiCl_4$, 2-triisopropylsilyloxy-3-methylfuran, CH_2Cl_2, dr = 1 : 1, 61%; (12) TESCl, imid., DMAP, CH_2Cl_2, rt, dr = 1 : 1**203**:**204**, 76%; (13) DBU, CH_2Cl_2, dr = 2 : 1**203**:**204**, 60%; (14) $SOCl_2$, NEt_3, CH_2Cl_2, −78 °C, $\Delta^{5,6}/\Delta^{5,24}$ = 3 : 1, 82%; (15) Boc_2O, NEt_3, DMAP, CH_2Cl_2, then H_2NNH_2, 99%; (16) TFA, CH_2Cl_2, then 10 h under vacuum, 68%.

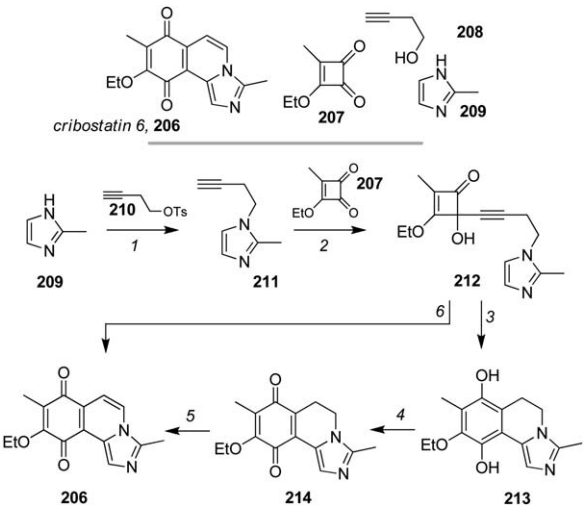
starting material). A four-step sequence, involving an oxidation–CBS-reduction sequence, an asymmetric Sharpless epoxidation and DDQ deprotection, delivered laulimalide (**181**) in 73% overall yield.

Romo and coworkers have reported the first total synthesis of (−)-gymnodimine (**195**), which is a member of the spirocyclicimine family of marine toxins.[40] Their retrosynthetic plan is summarized in Scheme 26, and hinges on a Barbier-type macrocyclization and a vinylogous Mukaiyama aldol coupling.

The optically active spirolactam alkyne **196** was converted to the vinyl iodide **197** in 65% overall yield by first converting the alkyne to the vinyl stannane using a palladium-catalyzed hydrostannylation using a non-polar solvent, then reaction with iodine at low temperature. A standard Nozaki–Hiyama–Kishi coupling of **197** and the readily available **198** (used as a 4 : 1 mixture of diastereomers at C13) gave a diastereoisomeric mixture **199** and **200** (1.3 : 1 epimers at C10). After separation, the α epimer **200** can be converted to the desired β epimer **199** *via* an oxidation–reduction protocol (diastereomeric ratio = 6 : 1). Protection of the hydroxy group and conversion of the chloro group to the iodo group provided the macrocyclization precursor **201** in 85% yield. Importantly, it was now possible to remove the undesired C13 epimer.

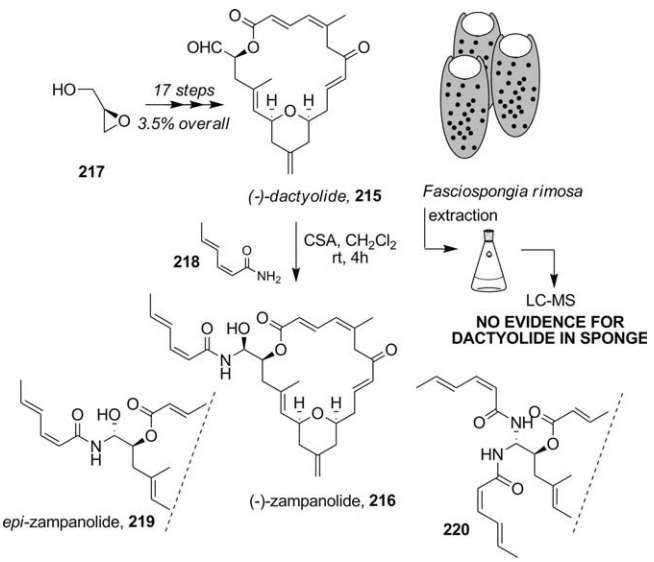
Surprisingly, the Barbier-type macrocyclization of **201** using *t*-BuLi was found to proceed at room temperature, rather than the more normal −78 °C. This reaction provided the macrocycle in 56–61% yields on scales up to 100 mg. This material was converted into the substrate **202** required for the vinylogous Mukiayama aldol reaction by swapping the *N*-Ts for *N*-$COCF_3$ and then removal of the silyl protecting groups. Reaction of the ketone and 2-(triisopropylsilyloxy)-3-methylfuran with $TiCl_4$ for 5 min yielded the butenolide in 76% yield as a 1 : 1 mixture of diastereomers (epimeric at C4). After protection of the secondary alcohol, the epimeric alcohols **203** and **204** were separated by chromatography. Reaction of the undesired diastereomer **204** with DBU provided a 2 : 1 mixture of the epimers, which allowed access to more of the desired epimer. Treatment of the tertiary alcohol **203** with thionyl chloride and triethylamine generated the alkene **205** as a 3 : 1 mixture of regioisomers. The protecting groups were removed by firstly converting the trifluoroacetamide group (Boc_2O, Et_3N, then NH_2NH_2) to the *N*-Boc group, then reaction with trifluoroacetic acid to remove all the acid-labile protecting groups. After standing the reaction mixture under high vacuum for 10 h, gymnodimine **195** was obtained in 68% yield.

The Martin group has chronicled a very concise total synthesis of cribostatin 6 **206** that employs a Moore–Myers-type cyclization[41] as the key step (Scheme 27).[42] By this strategy, cribostatin 6 could be dissected to give **207**, **208**, and **209**. Alkylation of 2-methylimidazole **209** with butynyl tosylate **210** gave **211**, which was readily deprotonated and reacted with squarate derivative **207** to yield **212**. When a dilute solution of **212** was heated at reflux in acetonitrile, Moore–Myers cyclization occurred to give hydroquinone **213**. Exposure to air at room temperature for 18 h produced **214** in 24% yield, and **214** could be dehydrogenated over Pd/C in anisole to give cribostatin 6, **206** in 69% yield. Alternatively, the sequence of **212** → **206** could be performed without isolation of the intermediates to give a 26% overall yield.

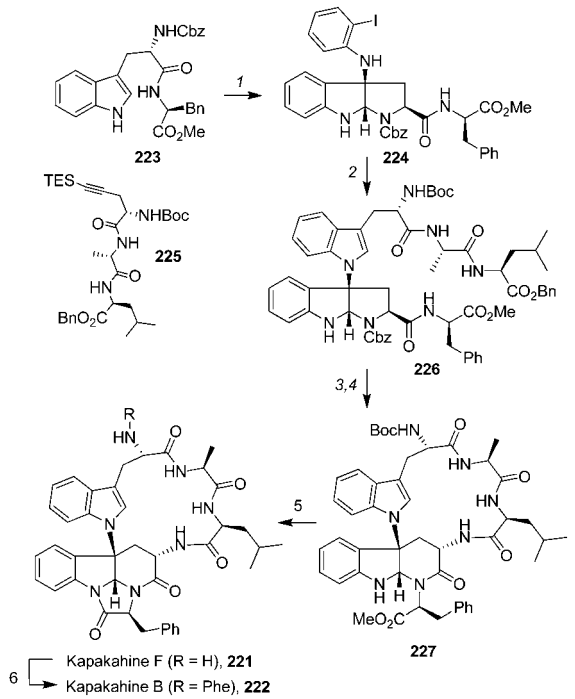


Scheme 27 Martin's synthesis of cribostatin 6. *Reagents and conditions*: (1) CH_3CN, 70 °C, 92%; (2) *n*-BuLi, THF, −78 °C then **207** −78 → 0 °C, 62%; (3) 0.001 M in CH_3CN, reflux, 35 min; (4) air, rt, 18 h, 24%; (5) Pd/C, PhOMe, 90 °C, 69%; (6) 0.001 M in CH_3CN, reflux, 35 min then remove majority of solvent, add Pd/C, 80 °C, 4 h, 26% overall.

Tanaka and Higa's 1996 report[43] of the structure of (−)-zampanolide from *Fasciospongia rimosa* (collected at Cape Zampa, Okinawa) and the subsequent description of (+)-dactylolide from a *Dactylospongia* sp. (collected off the coast of Vanuatu) by Riccio and co-workers[44] has produced a significant amount of synthesis activity in the period since.[45] One of the important observations made during the course of the Smith syntheses was that the two natural products are enantiomeric. The obvious biosynthetic connection between the two would suggest that (−)-dactylolide should be present in *F. rimosa*, and in



Scheme 28 Uenishi's synthesis of (−)-zampanolide and associated investigations of *F. rimosa*.



Scheme 29 Baran's synthesis of kapakahine B and F. *Reagents and conditions*: (1) *o*-iodoaniline (1.2 equiv.), *N*-iodosuccinimide (1.6 equiv.), MeCN, −45 to −35 °C, 65%; (2) $Pd(OAc)_2$ (0.20 equiv.),NaOAc (7.0 equiv.), LiCl (1.0 equiv.), **225** (2.2 equiv.), DMF, 100 °C, 24 h, 49%; (3) 10% Pd/C (0.20 equiv.), H_2, MeOH, 1 h; (4) EDC (3.0 equiv.), HOAt (6.0 equiv.), CH_2Cl_2–DMF (20 : 1), 12 h, 70% (11 : 1); (5) LiOH, THF–H_2O–MeOH, 1 h; then $(COCl)_2$ (4.0 equiv.), Et_3N (1.0 equiv.), CH_2Cl_2, 1 h; TFA–DCM, 1 : 10, 1 h, 64% (3 steps); (6) Boc-Phe-OH (1.2 equiv.), EDC (2.0 equiv.), HOBt (1.8 equiv.), Et_3N (3.0 equiv.), CH_2Cl_2 1 h; TFA–CH_2Cl_2, 1 : 10, 1 h, 81% (2 steps).

an effort to investigate this prospect, Uenishi has synthesized (−)-dactyolide and studied its conversion to (−)-zampanolide (Scheme 28).[46] Treatment of (−)-dactylolide **215** (prepared in 17 steps from glycidol, **217**) and dienyl amide **216** with CSA in CH_2Cl_2 gave three compounds: (−)-zampanolide **216**, *epi*-zampanolide **219**, and **220**, establishing the feasibility of the preparation of (−)-zampanolide from (−)-dactylolide with simple organic acid catalysis. As a counter to the conclusion that might be drawn from this experiment, extraction of *F. rimosa* and detailed analysis by LC–MS of the extract failed to show any evidence of dactyolide.

Baran has completed concise total syntheses of kapakahine F **221** and kapakahine B **222** (Scheme 29). As with many of Baran's recent syntheses, brevity is maximized by careful synthesis planning, and the 3-indolyl-pyrrolo[2,3-*b*]hexahydroindole core of the kapakahines is an exemplary case: this motif is fashioned by (i) treatment of readily accessible **223** with *N*-iodosuccinimide in the presence of *o*-iodoaniline to give **224** (65%) and (ii) subsequent Pd-catalyzed indole synthesis with alkyne **225** produced **226** in 49% yield. Removal of the Cbz group under hydrogenolysis conditions, rearrangement to produce the 6-membered ring and EDCI/HOAt-mediated macrocycle formation gave **227**. Three further steps produced kapakahine F **221**, and introduction of the phenylalanine at the appropriate position then provided kapakahine B **222** after removal of the final Boc carbamate.

A large number of other total syntheses of marine natural products were reported in the review period, and papers describing first total syntheses are presented in Table 1. New total syntheses of compounds previously prepared are summarized in Table 2.

Table 1 First total syntheses of marine natural products reported in 2009

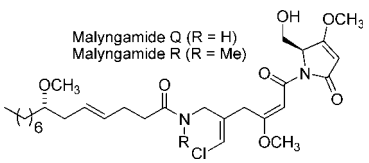
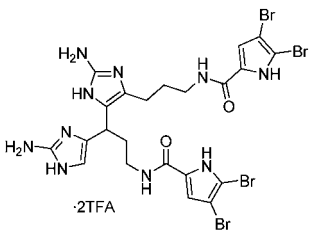
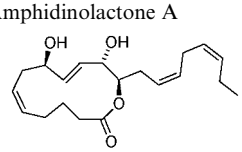
Compound	Reference	Notes
Malyngamides O, P, Q and R 	Chen *et al.*[47]	• Malyngamide R – 14 steps (longest linear sequence) from known compound • Malyngamide Q – 16 steps (longest linear sequence) from known compound • Malyngamide O and P – 13 and 14 steps (longest linear sequence) from known compound • Cytotoxic activity
Putative structure of nagelamide D 	Bhandari *et al.*[48]	• 14 steps (longest linear sequence) from known compound • Discrepancy with published NMRs
Amphidinolactone A 	Hangyou *et al.*[49]	• 17 steps (longest linear sequence) from known compound • Absolute configuration determined • Cytotoxicity

Table 1 (*Contd.*)

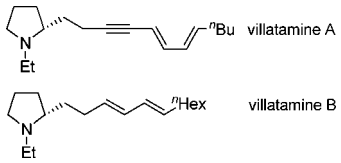
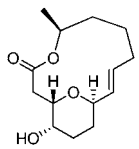
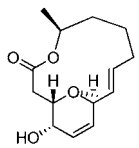
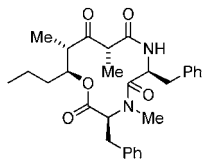
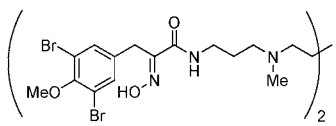
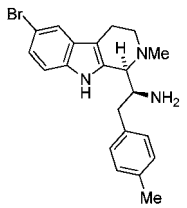
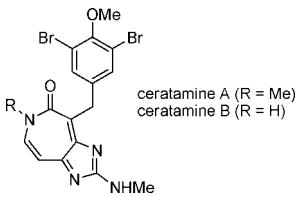
Compound	Reference	Notes
(+)-Villatamines A and B 	Hu *et al.*[50]	• Villatamine A – 6 steps from known compound • Villatamine B – 5 steps from known compound • Non-racemic synthesis • Absolute configuration determined • Cytotoxicity
Aspergillide B 	Hande and Uenishi[51]	• Aspergillide B – revised structure • 16 steps (longest linear sequence) from known compound • Enantioselective synthesis • Structure of aspergillide A is unclear • Biological activity: cytotoxic
Aspergillide C 	Nagasawa and Kuwahara[52]	• Confirmed structural elucidation • 15 steps (longest linear sequence) from known compound • Enantioselective synthesis • Biological activity: cytotoxic
Proposed structure of stereocalpin A 	Ghosh and Xu[53]	• Data of proposed structure does not match natural product • 14 steps (longest linear sequence) from known compound • Non-racemic synthesis • Cytotoxicity
Spermatinamine 	Garcia *et al.*[54]	• 5 steps from known compound • Non-racemic synthesis • Inhibitor of isoprenylcysteine carboxyl methyltransferase
Putative structure for eudistomidin B 	Ito *et al.*[55]	• Data does not match that reported for the natural product • 19 steps (longest linear sequence) from known compound • Non-racemic synthesis • Biological activity: potent cytotoxicity and actomysin ATPase activator
Ceratamines A and B 	Coleman *et al.*[56]	• Ceratamine A – 11 steps (longest linear sequence) from known compound (28% overall yield) • Ceratamine B – 12 steps (longest linear sequence) from known compound (12% overall yield) • Biological activity: anti-mitotic

Table 1 (*Contd.*)

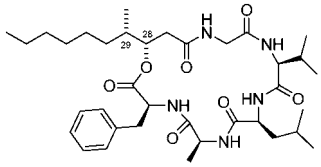
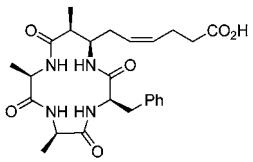
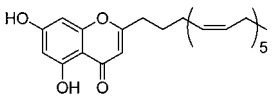
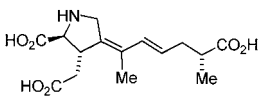
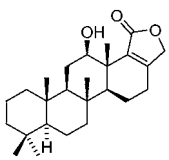
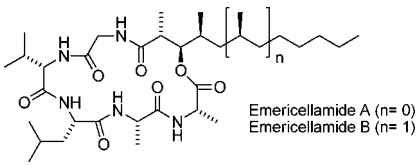
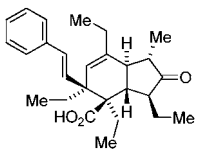
Compound	Reference	Notes
Arenamide A 	Chandrasekhar *et al.*[57]	• 14 steps (longest linear sequence) from known compound • Determined that the natural product has the 28*S*,29*S* configuration • Biological activity: NF-κB inhibitor
Azumamide E 	Chandrasekhar *et al.*[58]	• 17 steps (longest linear sequence) from pent-4-yn-1-ol • Biological activity: histone deacetylase inhibitor
5,7-Dihydroxy-2-(4*Z*,7*Z*,10*Z*,13*Z*,16*Z*-nonadecapentaenyl)chromone 	Anwar and Hansen[59]	• 6 steps from ethyl eicosapentaenoate (14% overall yield) • Biological activity: not known
Isodomoic acid H 	Denmark *et al.*[60]	• 11 steps (longest linear sequence) from known compound • Also completed synthesis of isodomoic acid G • Biological activity: neuroexcitatory agent
(+)-Scalarolide 	Meng *et al.*[61]	• 19 steps (longest linear sequence) from known compound (4.4% overall yield) • Absolute configuration confirmed • Biological activity: unknown
Emericellamides A and B 	Li *et al.*[62]	• Emericellamide A – 10 steps (longest linear sequence) from known compound (22% overall yield) • Emericellamide B – 12 steps (longest linear sequence) from known compound (14% overall yield) • Absolute configuration confirmed • Biological activity: anti-bacterial
(+)-Spiculoic acid A 	Matsumura *et al.*[63]	• Synthesis of natural enantiomer • 24 steps (longest linear sequence) from known compound • Biological activity: cytotoxicity against MCF-7 cells

Table 1 (*Contd.*)

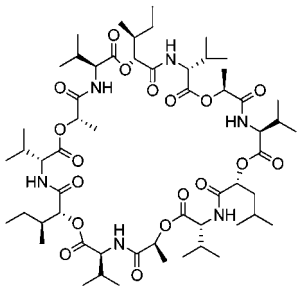
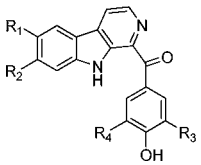
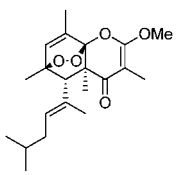
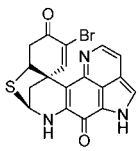
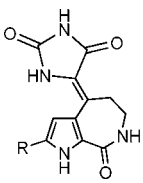
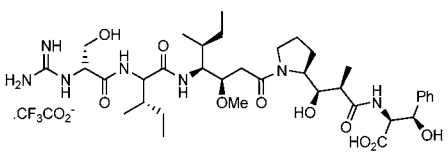
Compound	Reference	Notes
Bacillistatin 2 	Pettit *et al.*[64]	• 11 steps (longest linear sequence) from D-*allo*-Ile • Biological activity: cytotoxic
Eudistomins Y_1–Y_6  Eudistomin Y_1 $R_1=R_2=R_3=R_4=H$ Eudistomin Y_2 $R_1=Br$, $R_2=R_3=R_4=H$ Eudistomin Y_3 $R_3=Br$, $R_1=R_2=R_4=H$ Eudistomin Y_4 $R_1=R_3=Br$, $R_2=R_4=H$ Eudistomin Y_5 $R_3=R_4=Br$, $R_1=R_2=H$ Eudistomin Y_6 $R_1=R_3=R_4=Br$, $R_2=H$	Lindsley *et al.*[65]	• 3 steps (longest linear sequence) from tryptamine derivatives • Biological activity: cytotoxic, antiviral, antimicrobial *etc.*
Tridachiahydropyrones 	Moses *et al.*[66]	• Tridachiahydropyrone B and C shown to be the same compound. Renamed as (+)-oxytridachiahydropyrone (structure shown) • 3 steps from known building blocks
Prianosin B 	Fujioka and Kita *et al.*[67]	• 10 steps from TyrOMe·HCl • Biological activity: cytotoxic, antiviral, antimicrobial *etc.*
(*Z*)-Axino- and (*Z*)-debromoaxinohydantoin  R = H, (*Z*)-debromoaxinohydantoin R = Br, (*Z*)-axinohydantoin	Papeo *et al.*[68]	• 7 and 6 steps respectively from 2-trichloroacetylpyrrole • Biological activity: kinase inhibitors
Gymnangiamide 	Tone *et al.*[69]	• 13 steps from BocProOH • Structure reassigned to that shown • Biological activity: cytotoxic

Table 1 (*Contd.*)

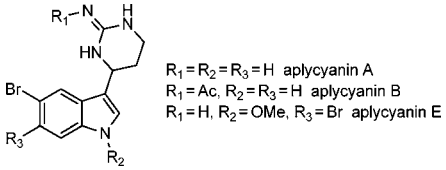
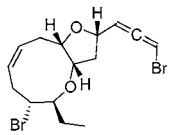
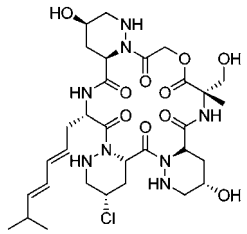
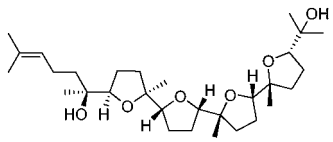
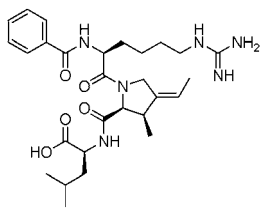
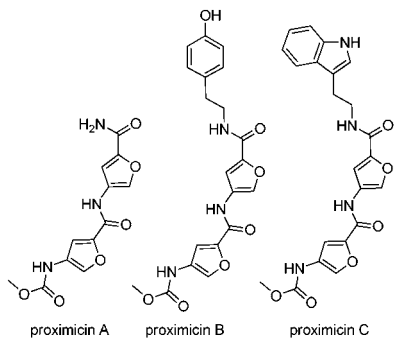
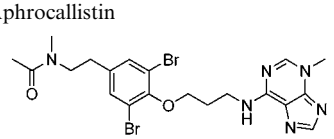
Compound	Reference	Notes
Aplicyanins A, B, and E 	Alvarez *et al.*[70]	• 6 steps from known compounds • Biological activity: cytotoxic
(+)-Itomanallene A 	Kim *et al.*[71]	• 18 steps from PMB-protected glycidol • Structure revised to that shown
Piperazimycin A 	Li, Gan and Ma[72]	• 26 steps (longest linear sequence) from known compound • Biological activity: cytotoxic
(+)-Omaezakianol 	Morimoto *et al.*[73]	• 20 steps (longest linear sequence) from geranyl acetate
Lucentamycin A 	Del Valle *et al.*[74]	• Doesn't match reported data for natural product • Biological activity: cytotoxic
Proximicins A–C 	Sussmuth *et al.*[75]	• 9 steps each from 3-furaldehyde • Biological activity: anti-tumor
Aphrocallistin 	Wright *et al.*[76]	• 7 steps • Biological activity: anti-tumor

Table 2 New total syntheses of marine natural products previously prepared that were reported in 2009

Compound	Reference
Lamellarin G trimethyl ether and ningalin B	Gupton *et al.*[77]
(−)-Agelastatin A	Hama *et al.*[78] Dickson and Wardrop[79] Wehn and Du Bois[80]
(+)-Neopeltolide	Guinchard and Roulland[81]
Cyclotheonamide C	Faure *et al.*[82]
Pachastrissamine (jaspine B)	Inuki *et al.*[83] Canals *et al.*[85]
Aigialomycin D	Calo *et al.*[84]
Amphidinolide T1	Yadav and Suresh Reddy[86]
(±)-Liphagal	Mehta *et al.*[87]
Saliniketal B	Liu and Brabander[88]
Preclathridine A and clathridine A	Koswatta and Lovely[89]
ent-Convolutamydine E and CPC-1	Itoh *et al.*[90]
Theopederin B	Nakata *et al.*[91]
(+)-Didemniserinolipid B	Ramana and Induvadana[92]
(−)-Didemniserinolipid B	Prasad[93]
ent-Agelasine F	Proszenyák *et al.*[94]
Salinosporamide A	Struble and Bode[95]
(−)-Napyradiomycin A1	Snyder *et al.*[96]
(+)-Spongistatins 1 and 2	Smith *et al.*[97]
Dictyostatin	Shimp and Micalizio[98]
Siphonarienal, siphonarienone, and pectinatone	Sabitha, Yadav *et al.*[99]
Pericosines A and C	Usami *et al.*[100]
Kulokekahilide-2	Kimura *et al.*[101]
(+)-Dibromophakellin	Nagasawa *et al.*[102]
Brevanal	Yamamoto *et al.*[103]
(−)-Amphidinolide X	Jung and Lee[104]
(−)-Dysibetaine	Isaacson and Kobayashi[105]
(−)-Amphidinolide K	Lee *et al.*[106]
Palmerolide	Hall *et al.*[107]
Isodomic acids G and H	Montgomery *et al.*[108]
Frondosin B	Ovaska *et al.*[109]
Cicutoxin	Gung and Omollo[110]
Coelenterazine	Knochel *et al.*[111]
Polyandrocarpamines A and B	Davis *et al.*[112]
Haouamine A	Baran *et al.*[113]
Cortistatin A	Tamashita *et al.*[114]
(−)-Renieramycins M and G	Wu and Zhu[115]
Pyranones	Sabitha *et al.*[116]
Neohelmanticins A–D	Sreedhar *et al.*[117]
Marinostatin	Taichi *et al.*[118]

12 Acknowledgements

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13 References

1 J. W. Blunt, B. R. Copp, M. H. G. Munro, P. T. Northcote and M. R. Prinsep, *Nat. Prod. Rep.*, 2011, **28**, DOI: 10.1039/c005001f.
2 K. C. Nicolaou, J. S. Chen and S. M. Dalby, *Bioorg. Med. Chem.*, 2009, **17**, 2290–2303.
3 Y. Usami, *Mar. Drugs*, 2009, **7**, 314–30.
4 I. Paterson and G. J. Florence, *Top. Curr. Chem.*, 2009, **286**, 73–119.
5 T. A. Gulder and B. S. Moore, *Curr. Opin. Microbiol.*, 2009, **12**, 252–260.
6 N. S. Dighe, S. R. Pattan, D. S. Musmade, P. A. Chavan, S. K. Tambe, M. S. Sanap and V. M. Gaware, *J. Chem. Pharm. Res.*, 2009, **1**, 54–61.
7 D. Bialonska and J. K. Zjawiony, *Mar. Drugs*, 2009, **7**, 166–183.
8 T. N. T. Nguyen and J. J. Tepe, *Curr. Med. Chem.*, 2009, **16**, 3122–3143.
9 J. Kobayashi, *Pure Appl. Chem.*, 2009, **81**, 1009–1018.
10 A. C. Jones, L. Gu, C. M. Sorrels, D. H. Sherman and W. H. Gerwick, *Curr. Opin. Chem. Biol.*, 2009, **13**, 216–223.
11 T. Seiser and N. Cramer, *Chimia*, 2009, **63**, 19–22.
12 W. Fenical, P. R. Jensen, M. A. Palladino, K. S. Lam, G. K. Lloyd and B. C. Potts, *Bioorg. Med. Chem.*, 2009, **17**, 2175–2180.
13 D. R. Williams, M. J. Walsh, C. D. Claeboe and N. Zorn, *Pure Appl. Chem.*, 2009, **81**, 181–194.
14 C. Cuevas and A. Francesch, *Nat. Prod. Rep.*, 2009, **26**, 322–337.
15 S. Lee, T. G. LaCour and P. L. Fuchs, *Chem. Rev.*, 2009, **109**, 2275–2314.
16 H. J. Jessen and K. Gademann, *Angew. Chem., Int. Ed.*, 2010, **49**, 2972–2974.
17 K. L. Jackson, J. A. Henderson and A. J. Phillips, *Chem. Rev.*, 2009, **109**, 3044–3079.
18 I. Paterson and S. M. Dalby, *Nat. Prod. Rep.*, 2009, **26**, 865–873.
19 (*a*) G. W. O'Neil, J. Ceccon, S. Benson, M. P. Collin, B. Fasching and A. Furstner, *Angew. Chem., Int. Ed.*, 2009, **48**, 9940–9945; (*b*) S. Benson, M.-P. Collin, G. W. O'Neil, J. Ceccon, B. Fasching, M. D. B. Fenster, C. Godbout, K. Radkowski, R. Goddard and A. Fürstner, *Angew. Chem., Int. Ed.*, 2009, **48**, 9946–9950.
20 (*a*) A. Furstner, B. Fasching, G. W. O'Neil, M. D. Fenster, C. Godbout and J. Ceccon, *Chem. Commun.*, 2007, 3045–3047; (*b*) A. Furstner, M. D. Fenster, B. Fasching, C. Godbout and K. Radkowski, *Angew. Chem., Int. Ed.*, 2006, **45**, 5510–5515; (*c*) A. Furstner, M. D. Fenster, B. Fasching, C. Godbout and K. Radkowski, *Angew. Chem., Int. Ed.*, 2006, **45**, 5506–5510.
21 A. Fürstner, M. D. B. Fenster, B. Fasching, C. Godbout and K. Radkowski, *Angew. Chem.*, 2006, **118**, 5636–5641.
22 T. Aicher, K. Buszek, F. Fang, C. Forsyth, S. Jung, Y. Kishi, M. Matelich, P. Scola, D. Spero and S. Yoon, *J. Am. Chem. Soc.*, 1992, **114**, 3162–3164.
23 K. L. Jackson, J. A. Henderson, H. Motoyoshi and A. J. Phillips, *Angew. Chem., Int. Ed.*, 2009, **48**, 2346–2350.
24 (*a*) Y. R. Yang, D. S. Kim and Y. Kishi, *Org. Lett.*, 2009, **11**, 4516–4519; (*b*) X. Liu, J. A. Henderson, T. Sasaki and Y. Kishi, *J. Am. Chem. Soc.*, 2009, **131**, 16678–16680; (*c*) S. Liu, J. T. Kim, C. G. Dong and Y. Kishi, *Org. Lett.*, 2009, **11**, 4520–4523; (*d*) D. S. Kim, C. G. Dong, J. T. Kim, H. Guo, J. Huang, P. S. Tiseni and Y. Kishi, *J. Am. Chem. Soc.*, 2009, **131**, 15636–15641; (*e*) C. G. Dong, J. A. Henderson, Y. Kaburagi, T. Sasaki, D. S. Kim, J. T. Kim, D. Urabe, H. Guo and Y. Kishi, *J. Am. Chem. Soc.*, 2009, **131**, 15642–15646; (*f*) C. L. Chen, K. Namba and Y. Kishi, *Org. Lett.*, 2009, **11**, 409–412.
25 J. Kim, J. Ashenhurst and M. Movassaghi, *Science*, 2009, **324**, 238–241.
26 (*a*) P. Li and D. Menche, *Angew. Chem., Int. Ed.*, 2009, **48**, 5078–5080; (*b*) K. C. Nicolaou, Y. Tang and J. Wang, *Angew. Chem., Int. Ed.*, 2009, **48**, 3449–3453.
27 M. Satake, A. J. Bourdelais, R. M. Van Wagoner, D. G. Baden and J. L. C. Wright, *Org. Lett.*, 2008, **10**, 3465–3468.
28 T. Kuranaga, T. Shirai, D. G. Baden, J. L. C. Wright, M. Satake and K. Tachibana, *Org. Lett.*, 2009, **11**, 217–220.
29 O. O. Fadeyi and C. W. Lindsley, *Org. Lett.*, 2009, **11**, 3950–3952.
30 A. K. Ghosh and J. Li, *Org. Lett.*, 2009, **11**, 4164–4167.
31 J. Lee and J. S. Panek, *Org. Lett.*, 2009, **11**, 4390–4393.
32 J. C. Morris and A. J. Phillips, *Nat. Prod. Rep.*, 2009, **26**, 245.
33 (*a*) K. C. Nicolaou, A. Ortiz and H. Zhang, *Angew. Chem., Int. Ed.*, 2009, **48**, 5648–5652; (*b*) K. C. Nicolaou, H. Zhang and A. Ortiz, *Angew. Chem., Int. Ed.*, 2009, **48**, 5642–5647.
34 Y. Takahashi, F. Yoshimura, K. Tanino and M. Miyashita, *Angew. Chem., Int. Ed.*, 2009, **48**, 8905–8908.
35 (*a*) M. Miyashita, M. Sasaki, I. Hattori, M. Sakai and K. Tanino, *Science*, 2004, **305**, 495–499; (*b*) F. Yoshimura, M. Sasaki, I. Hattori, K.; (*c*) Komatsu, M. Sakai, K. Tanino and M. Miyashita, *Chem. Eur. J.*, 2009, **15**, 6626–6644.
36 G. Liu and D. Romo, *Org. Lett.*, 2009, **11**, 1143–1146.
37 E. G. Bowen and D. J. Wardrop, *J. Am. Chem. Soc.*, 2009, **131**, 6062–6063.
38 T. K. Macklin and G. C. Micalizio, *J. Am. Chem. Soc.*, 2009, **131**, 1392–1393.
39 B. M. Trost, D. Amans, W. M. Seganish and C. K. Chung, *J. Am. Chem. Soc.*, 2009, **131**, 17087–17089.
40 K. Kong, D. Romo and C. Lee, *Angew. Chem., Int. Ed.*, 2009, **48**, 7402–7405.
41 J. O. Karlsson, N. V. Nguyen, L. D. Foland and H. W. Moore, *J. Am. Chem. Soc.*, 1985, **107**, 3392–3393.
42 D. Knueppel and S. F. Martin, *Angew. Chem., Int. Ed.*, 2009, **48**, 2569–2571.
43 J. Tanaka and T. Higa, *Tetrahedron Lett.*, 1996, **37**, 5535–5538.

44 A. Cutignano, I. Bruno, G. Bifulco, A. Casapullo, C. Debitus, L. Gomez-Paloma and R. Riccio, *Eur. J. Org. Chem.*, 2001, 775–778.
45 (*a*) T. R. Hoye and M. Hu, *J. Am. Chem. Soc.*, 2003, **125**, 9576–9577; (*b*) A. B. Smith, III, I. G. Safonov and R. M. Corbett, *J. Am. Chem. Soc.*, 2001, **123**, 12426–12427; (*c*) Smith, III, I. G. Safonov and R. M. Corbett, *J. Am. Chem. Soc.*, 2002, **124**, 11102–11113; (*d*) A. B. Smith, III and I. G. Safonov, *Org. Lett.*, 2002, **4**, 635–637; (*e*) F. Ding and M. P. Jennings, *Org. Lett.*, 2005, **7**, 2321–2324; (*f*) F. Ding and M. P. Jennings, *J. Org. Chem.*, 2008, **73**, 5965–5976; (*g*) I. Louis, N. L. Hungerford, E. J. Humphries and M. D. McLeod, *Org. Lett.*, 2006, **8**, 1117–1120; (*h*) D. L. Aubele, S. Wan and P. E. Floreancig, *Angew. Chem., Int. Ed.*, 2005, **44**, 3485–3488; (*i*) C. C. Sanchez and G. E. Keck, *Org. Lett.*, 2005, **7**, 3053–3056.
46 J. Uenishi, T. Iwamoto and J. Tanaka, *Org. Lett.*, 2009, **11**, 3262–3265.
47 J. Chen, X.-G. Fu, L. Zhou, J.-T. Zhang, X.-L. Qi and X.-P. Cao, *J. Org. Chem.*, 2009, **74**, 4149–4157.
48 M. R. Bhandari, R. Sivappa and C. J. Lovely, *Org. Lett.*, 2009, **11**, 1535–1538.
49 M. Hangyou, H. Ishiyama, Y. Takahashi, T. Kubota and J. i. Kobayashi, *Tetrahedron Lett.*, 2009, **50**, 1475–1477.
50 L. Hu, L. Zhang and H. Zhai, *J. Org. Chem.*, 2009, **74**, 7552–7555.
51 S. M. Hande and J. i. Uenishi, *Tetrahedron Lett.*, 2009, **50**, 189–192.
52 T. Nagasawa and S. Kuwahara, *Org. Lett.*, 2009, **11**, 761–764.
53 A. K. Ghosh and C.-X. Xu, *Org. Lett.*, 2009, **11**, 1963–1966.
54 J. Garcia, R. Pereira and A. R. de Lera, *Tetrahedron Lett.*, 2009, **50**, 5028–5030.
55 T. Ito, M. Kitajima and H. Takayama, *Tetrahedron Lett.*, 2009, **50**, 4506–4508.
56 R. S. Coleman, E. L. Campbell and D. J. Carper, *Org. Lett.*, 2009, **11**, 2133–2136.
57 S. Chandrasekhar, G. Pavankumarreddy and K. Sathish, *Tetrahedron Lett.*, 2009, **50**, 6851–6854.
58 S. Chandrasekhar, C. L. Rao, M. Seenaiah, P. Naresh, B. Jagadeesh, D. Manjeera, A. Sarkar and M. P. Bhadra, *J. Org. Chem.*, 2009, **74**, 401–404.
59 H. F. Anwar and T. V. Hansen, *Org. Lett.*, 2009, **11**, 587–588.
60 S. E. Denmark, J. H.-C. Liu and J. M. Muhuhi, *J. Am. Chem. Soc.*, 2009, **131**, 14188–14189.
61 X. J. Meng, Y. Liu, W. Y. Fan, B. Hu, W. Du and W. P. Deng, *Tetrahedron Lett.*, 2009, **50**, 4983–4985.
62 S. Li, S. Liang, W. Tan, Z. Xu and T. Ye, *Tetrahedron*, 2009, **65**, 2695–2702.
63 D. Matsumura, T. Toda, T. Hayamizu, K. Sawamura, K.-i. Takao and K.-i. Tadano, *Tetrahedron Lett.*, 2009, **50**, 3356–3358.
64 G. R. Pettit, S. Hu, J. C. Knight and J.-C. Chapuis, *J. Nat. Prod.*, 2009, **72**, 372–379.
65 J. P. Kennedy, M. L. Breininger and C. W. Lindsley, *Tetrahedron Lett.*, 2009, **50**, 7067–7069.
66 P. Sharma, B. Lygo, W. Lewis and J. E. Moses, *J. Am. Chem. Soc.*, 2009, **131**, 5966–5972.
67 Y. Wada, K. Otani, N. Endo, Y. Harayama, D. Kamimura, M. Yoshida, H. Fujioka and Y. Kita, *Tetrahedron*, 2009, **65**, 1059–1062.
68 F. Tutino, H. Posteri, D. Borghi, F. Quartieri, N. Mongelli and G. Papeo, *Tetrahedron*, 2009, **65**, 2372–2376.
69 H. Tone, M. Buchotte, C. Mordant, E. Guittet, T. Ayad and V. Ratovelomanana-Vidal, *Org. Lett.*, 2009, **11**, 1995–1997.
70 M. Sísa, D. Pla, M. Altuna, A. Francesch, C. Cuevas, F. Albericio and M. Alvarez, *J. Med. Chem.*, 2009, **52**, 6217–6223.
71 W. Jeong, M. J. Kim, H. Kim, S. Kim, D. Kim and K. J. Shin, *Angew. Chem., Int. Ed.*, 2010, **49**, 752–756.
72 W. Li, J. Gan and D. Ma, *Angew. Chem., Int. Ed.*, 2009, **48**, 8891–8895.
73 Y. Morimoto, T. Okita and H. Kambara, *Angew. Chem., Int. Ed.*, 2009, **48**, 2538–2541.
74 U. Pal, S. Ranatunga, Y. Ariyarathna and J. R. Del Valle, *Org. Lett.*, 2009, **11**, 5298–5301.
75 F. E. Wolter, K. Schneider, B. P. Davies, E. R. Socher, G. Nicholson, O. Seitz and R. D. Süssmuth, *Org. Lett.*, 2009, **11**, 2804–2807.
76 A. E. Wright, G. P. Roth, J. K. Hoffman, D. B. Divlianska, D. Pechter, S. H. Sennett, E. A. Guzmán, P. Linley, P. J. McCarthy, T. P. Pitts, S. A. Pomponi and J. K. Reed, *J. Nat. Prod.*, 2009, **72**, 1178–1183.
77 J. T. Gupton, B. C. Giglio, J. E. Eaton, E. A. Rieck, K. L. Smith, M. J. Keough, P. J. Barelli, L. T. Firich, J. E. Hempel, T. M. Smith and R. P. F. Kanters, *Tetrahedron*, 2009, **65**, 4283–4292.
78 N. Hama, T. Matsuda, T. Sato and N. Chida, *Org. Lett.*, 2009, **11**, 2687–2690.
79 D. P. Dickson and D. J. Wardrop, *Org. Lett.*, 2009, **11**, 1341–1344.
80 P. M. Wehn and J. Du Bois, *Angew. Chem., Int. Ed.*, 2009, **48**, 3802–3805.
81 X. Guinchard and E. Roulland, *Org. Lett.*, 2009, **11**, 4700–4703.
82 S. Faure, T. Hjelmgaard, S. P. Roche and D. J. Aitken, *Org. Lett.*, 2009, **11**, 1167–1170.
83 S. Inuki, Y. Yoshimitsu, S. Oishi, N. Fujii and H. Ohno, *Org. Lett.*, 2009, **11**, 4478–4481.
84 F. Calo, J. Richardson and A. G. M. Barrett, *Org. Lett.*, 2009, **11**, 4910–4913.
85 D. Canals, D. Mormeneo, G. Fabriàs, A. Llebaria, J. Casas and A. Delgado, *Bioorg. Med. Chem.*, 2009, **17**, 235–241.
86 J. S. Yadav and C. S. Reddy, *Org. Lett.*, 2009, **11**, 1705–1708.
87 G. Mehta, N. S. Likhite and C. Ananda Kumar, *Tetrahedron Lett.*, 2009, **50**, 5260–5262.
88 J. Liu and J. K. De Brabander, *J. Am. Chem. Soc.*, 2009, **131**, 12562–12563.
89 P. B. Koswatta and C. J. Lovely, *Tetrahedron Lett.*, 2009, **50**, 4998–5000.
90 T. Itoh, H. Ishikawa and Y. Hayashi, *Org. Lett.*, 2009, **11**, 3854–3857.
91 Y. Nishii, T. Higa, S. Takahashi and T. Nakata, *Tetrahedron Lett.*, 2009, **50**, 3597–3601.
92 C. V. Ramana and B. Induvadana, *Tetrahedron Lett.*, 2009, **50**, 271–273.
93 K. Prasad and V. Gandi, *Synlett*, 2009, 2593–2596.
94 A. Proszenyàk, M. Brændvang, C. Charnock and L.-L. Gundersen, *Tetrahedron*, 2009, **65**, 194–199.
95 J. R. Struble and J. W. Bode, *Tetrahedron*, 2009, **65**, 4957–4967.
96 S. A. Snyder, Z.-Y. Tang and R. Gupta, *J. Am. Chem. Soc.*, 2009, **131**, 5744–5745.
97 (*a*) A. B. Smith III, Q. Lin, V. A. Doughty, L. Zhuang, M. D. McBriar, J. K. Kerns, A. M. Boldi, N. Murase, W. H. Moser, C. S. Brook, C. S. Bennett, K. Nakayama, M. Sobukawa and R. E. Lee Trout, *Tetrahedron*, 2009, **65**, 6470–6488; (*b*) A. B. Smith III, C. Sfouggatakis, C. A. Risatti, J. B. Sperry, W. Zhu, V. A. Doughty, T. Tomioka, D. B. Gotchev, C. S. Bennett, S. Sakamoto, O. Atasoylu, S. Shirakami, D. Bauer, M. Takeuchi, J. Koyanagi and Y. Sakamoto, *Tetrahedron*, 2009, **65**, 6489–6509.
98 H. L. Shimp and G. C. Micalizio, *Tetrahedron*, 2009, **65**, 5908–5915.
99 G. Sabitha, P. Gopal and J. S. Yadav, *Tetrahedron: Asymmetry*, 2009, **20**, 2205–2210.
100 Y. Usami, K. Suzuki, K. Mizuki, H. Ichikawa and M. Arimoto, *Org. Biomol. Chem.*, 2009, **7**, 315–318.
101 M. Umehara, Y. Takada, Y. Nakao and J. Kimura, *Tetrahedron Lett.*, 2009, **50**, 840–843.
102 T. Imaoka, O. Iwamoto, K.-i. Noguchi and K. Nagasawa, *Angew. Chem., Int. Ed.*, 2009, **48**, 3799–3801.
103 H. Takamura, S. Kikuchi, Y. Nakamura, Y. Yamagami, T. Kishi, I. Kadota and Y. Yamamoto, *Org. Lett.*, 2009, **11**, 2531–2534.
104 J. H. Jung and E. Lee, *Angew. Chem., Int. Ed.*, 2009, **48**, 5698–5700.
105 J. Isaacson and Y. Kobayashi, *Angew. Chem., Int. Ed.*, 2009, **48**, 1845–1848.
106 H. M. Ko, C. W. Lee, H. K. Kwon, H. S. Chung, S. Y. Choi, Y. K. Chung and E. Lee, *Angew. Chem., Int. Ed.*, 2009, **48**, 2364–2366.
107 M. Penner, V. Rauniyar, L. T. Kaspar and D. G. Hall, *J. Am. Chem. Soc.*, 2009, **131**, 14216–14217.
108 Y. Ni, R. M. Kassab, M. V. Chevliakov and J. Montgomery, *J. Am. Chem. Soc.*, 2009, **131**, 17714–17718.
109 T. V. Ovaska, J. A. Sullivan, S. I. Ovaska, J. B. Winegrad and J. D. Fair, *Org. Lett.*, 2009, **11**, 2715–2718.
110 B. W. Gung and A. O. Omollo, *Eur. J. Org. Chem.*, 2009, 1136–1138.
111 M. Mosrin, T. Bresser and P. Knochel, *Org. Lett.*, 2009, **11**, 3406–3409.
112 R. A. Davis, P. S. Baron, J. E. Neve and C. Cullinane, *Tetrahedron Lett.*, 2009, **50**, 880–882.
113 N. Z. Burns, I. N. Krylova, R. N. Hannoush and P. S. Baran, *J. Am. Chem. Soc.*, 2009, **131**, 9172–9173.
114 S. Yamashita, K. Kitajima, K. Iso and M. Hirama, *Tetrahedron Lett.*, 2009, **50**, 3277–3279.
115 Y.-C. Wu and J. Zhu, *Org. Lett.*, 2009, **11**, 5558–5561.
116 G. Sabitha, S. Nayak, M. Bhikshapathi and J. S. Yadav, *Tetrahedron Lett.*, 2009, **50**, 5428–5429.
117 E. Sreedhar, R. S. C. Kumar, G. V. Reddy, A. Robinson, K. S. Babu, J. M. Rao and P. V. Srinivas, *Tetrahedron: Asymmetry*, 2009, **20**, 440–448.
118 M. Taichi, T. Yamazaki, T. Kimura and Y. Nishiuchi, *Tetrahedron Lett.*, 2009, **50**, 2377–2380.
119 *MarinLit Database*, Department of Chemistry, University of Canterbury: http://www.chem.canterbury.ac.nz/marinlit/marinlit.shtml.