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Marine natural products: synthetic aspects

Cite this: *Nat. Prod. Rep.*, 2013, **30**, 783

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Covering: January to December 2010. Previous review: *Nat. Prod. Rep.*, 2011, **28**, 269.

Received 27th November 2012

DOI: 10.1039/c3np20116c

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An overview of marine natural products synthesis during 2010 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.

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1 Introduction

This review is designed to provide an overview of key features of the 2010 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: "Silicon-based cross-coupling reactions in the total synthesis of natural products",[2] "Convergence leads to success: total synthesis of the complex nonribosomal peptide polytheonamide B",[3] "Treasures from the sea: discovery and total synthesis of ammosamides",[4] "Marine toxins with spiroimine rings: total synthesis of pinnatoxin A",[5] "Salinosporamide natural products: potent 20S proteasome inhibitors as promising cancer chemotherapeutics",[6] "Total synthesis of structurally complex marine oxacyclic natural products",[7] "SmI_2-induced cyclizations and their applications in natural product synthesis",[8] "Calyculins and related marine natural products as serine-threonine protein phosphatase PP1 and PP2A inhibitors and total syntheses of calyculin A, B, and C",[9] "Synthesis of marine polycyclic polyethers *via endo*-selective epoxide-opening cascades",[10] "Marine natural products: Totally tubular peptide synthesis",[11] "Studies on marine natural products containing unusual amino acids",[12] "Approaches to the total synthesis of biologically active natural products: studies directed towards bryostatins",[13] "Recent advances in the total synthesis of agelastatins",[14] "Synthesis of oximinotyrosine-derived marine natural products",[15] "Total syntheses of trikentrins and of herbindoles",[16] "Total synthesis of antimicrobial and antitumor cyclic depsipeptides".[17] Other reviews of relevance are cited in the text.

3 Polyketides: peloruside A and B, proposed structure of iriomoteolide-1a, phorbaside A

Peloruside A (**1**) has biological activity similar to paclitaxel and has proved to be a popular synthetic target. In 2010, two new total syntheses, from the groups of Jacobsen and Hoye, respectively, were reported.[18,19] Furthermore, the groups of Northcote and Ghosh have reported the isolation and total synthesis of peloruside B (**2**), which is a natural congener of peloruside A.[20] The retrosynthetic analysis of the syntheses are summarized in Fig. 1. All syntheses use a macrolactonisation step and then form the hemiketal in the last step when removing the protecting groups.

Ghosh's synthesis of peloruside B (**2**) was based on his previous total synthesis of peloruside A[21] and utilizes a reductive aldol coupling to join fragments **3** and **4** together (Scheme 1). Fragment **3** was prepared in 17 steps from commercially available diethyl D-tartrate (**5**). The aldehyde **4** had been previously

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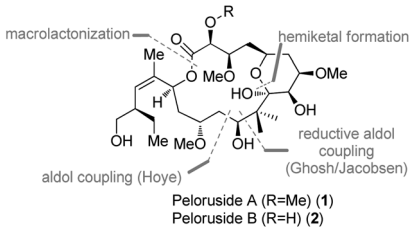
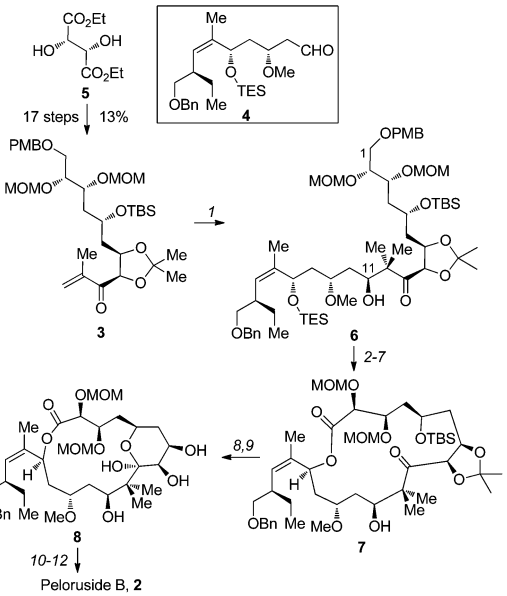


Fig. 1 Retrosynthetic analyses of pelorusides A (**1**) and B (**2**).

prepared for Ghosh's peloruside A total synthesis. The enone **3** was reacted with L-selectride to generate the enolate, which reacted with **4** to form the aldol product **6** in 66% yield, in a diastereomeric ratio of 6.5 : 1.

The aldol product **6** was transformed into macrolactone **7** in 6 steps. The C11 alcohol was protected as a TES-ether (TESOTf, pyridine) and the PMB ether at C1 was removed using DDQ to afford a primary alcohol in 65% yield for the two steps. Conversion to the carboxylic acid was achieved in 2 steps (DMP; Pinnick oxidation) and this material was reacted with HF·pyridine to generate the *seco*-acid in 70% yield for the three step process. Macrolactonization was achieved using the Yamaguchi protocol (2,4,6-trichlorobenzoyl chloride, iPr$_2$NEt, DMAP, CH_2Cl_2), generating macrolactone **7** in 77% yield. Reaction of **7** with HF·pyridine removed the silyl protecting group and subsequent treatment with 80% aqueous acetic acid at 50 °C cleaved the isopropylidene group and allowed the formation of the hemiketal **8** in 52% yield. The total synthesis was completed by selective methylation ($Me_3O^+BF_4^-$, 2,6-di-*t*-butylpyridine) of the diol, removal of the MOM protecting groups with 4N HCl solution, and a catalytic transfer hydrogenation (Pd/C, HCO_2H, MeOH) that removed the benzyl ether to generate peloruside B (**2**) in 24% yield for the three steps.

Jacobsen's synthesis of peloruside A (**1**) also utilizes a reductive aldol coupling to assemble the framework of the natural product (Scheme 2).[18] Jacobsen prepared the fragments **9** and **10** using methodology developed in his laboratory. For example, enone **9** is prepared in 11 steps, with key features being the asymmetric Payne rearrangement of *meso*-diol **11**,



Scheme 1 The Ghosh synthesis of peloruside B, **2**. *Reagents and conditions*: (1) L-selectride, Et_2O, −78 °C, then **4**, 66%, d.r. 6.5 : 1; (2) TESOTf, pyridine, CH_2Cl_2, 0 °C, 88%; (3) DDQ, pH 7 buffer, CH_2Cl_2, 74%; (4) DMP, CH_2Cl_2, $NaHCO_3$; (5) $NaClO_2$, $NaHPO_4·H_2O$, 2-methyl-2-butene, *tert*-BuOH, H_2O, 88% (over 2 steps); (6) 2% HF·pyridine in THF, 80%; (7) 2,4,6-$Cl_3C_6H_2COCl$, iPr$_2$NEt, THF/PhMe; then DMAP, toluene, 77%; (8) HF·pyridine, THF (9) 80% aq. HOAc, 50 °C, 52%; (10) Me_3OBF_4, 2,6-*tert*-butylpyridine, CH_2Cl_2; (11) 4N HCl, THF; (12) 10% Pd/C, HCO_2H, EtOAc/MeOH, 24% (over 3 steps).

using the oligomeric cobalt salen catalyst **12**, to generate epoxide **13** and the hetero-Diels–Alder reaction of **14** and **15**, using the chiral chromium Schiff base complex **16**, to form dihydropyran **17**. The Diels–Alder adduct was transformed into enone **9** in 6 steps. Access to aldehyde **10** was achieved in 10 steps starting from enyne **18**. Enyne **18** was transformed into a epoxide in 98% ee using a (salen)manganese-catalyzed epoxidation/hydrolytic kinetic resolution sequence. Ring-opening of the epoxide was achieved with ethyl magnesium chloride and the resulting primary alcohol was protected as a TIPS ether (TIPSCl, imidazole). This afforded chiral alkyne **19** in 30% overall yield. Transformation to bromide **20** was achieved by using a one-pot hydroboration/bromination /elimination/silyl deprotection sequence (catecholborane; Br_2; TBAF) and a protection of the primary alcohol (2-benzyloxy-1-methylpyridinium triflate, MgO, $C_6H_5CF_3$). This sequence proceeded in 69% overall yield. Synthesis of aldehyde **10** was achieved by halogen-lithium exchange (*sec*-BuLi, THF −78 °C) and reaction with the readily available aldehyde **21** to form an alcohol (64% yield after chromatography). After protection (PMBBr, NaH, DMF) as a PMB ether, the primary TBS ether was selectively removed and the resulting primary alcohol oxidized with Dess–Martin periodinane to generate the key aldehyde **10** in 58% yield for the three step sequence. Completion of the total synthesis required 7 steps. The reductive aldol coupling of **9** and **10** yielded the aldol product as a 1.7 : 1 mixture, but chromatography allowed the isolation of the desired stereoisomer **22** in 52% yield. Conversion of this material to macrolactone **23** was achieved in 5 steps and 38% overall yield. Deprotection of the

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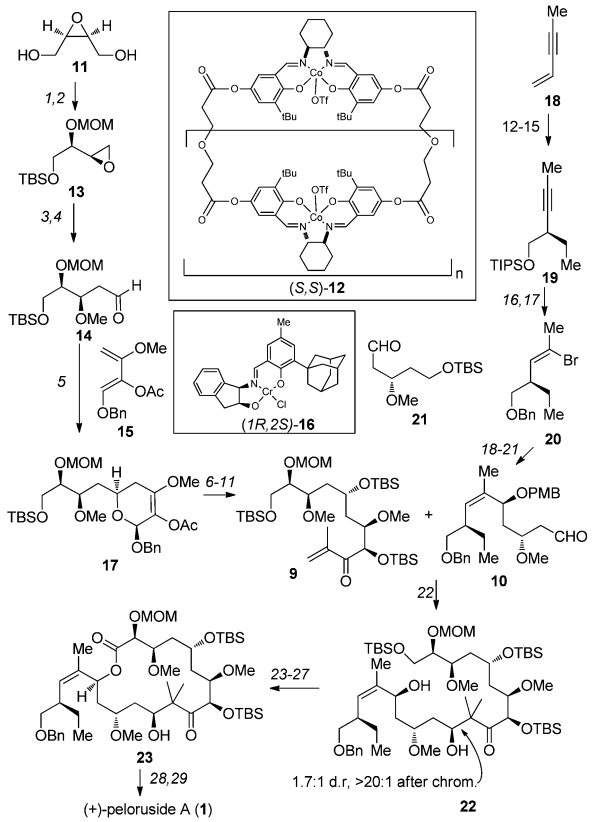
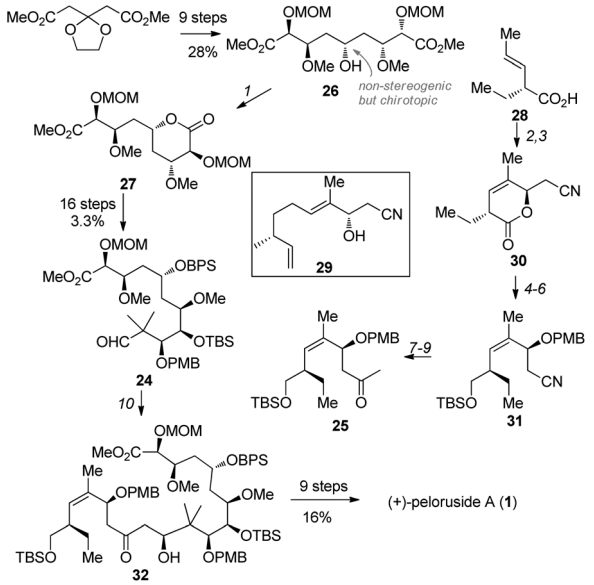


Scheme 2 The Jacobsen synthesis of peloruside A, **1**. *Reagents and conditions*: (1) (*S,S*)-**12** (0.02 mol% Co), MeCN, then TBSCl, DMAP, NEt_3, CH_2Cl_2, −20 °C; (2) MOMCl, *i*-Pr_2NEt, PhMe, 56% (over 2 steps); (3) CuBr (10 mol %), CH_2=CHMgBr, −40 °C, 2 h; then HMPA, Me_2SO_4; (4) O_3, CH_2Cl_2, −78 °C; then PPh_3, 66% (over 2 steps); (5) (1*R*,2*S*)-**16** (6.2 mol %), 4 Å MS, TBME, 76%, d.r. 7 : 1; (6) Pd/C, *i*PrOH, pH 7 buffer, H_2 (200 psi), 69%, d.r. 10 : 1 at C7, C8; (7) KBr, TEMPO, NaOCl, pH 7 buffer, CH_2Cl_2, 0 °C; (8) (MeO)(Me)NH_2Cl, $AlMe_3$, PhMe, −10 °C, 85% (over 2 steps); (9) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C; (10) isopropenylmagnesium bromide, THF, 45% (over 2 steps); (11) TBSOTf, 2,6-lutidine, CH_2Cl_2, −10 °C, 86%; (12) (*R,R*)-salen(Mn)Cl (5.0 mol %), NaOCl, CH_2Cl_2, 0 °C; (13) (*R,R*)-salen(Co)OAc (0.50 mol %), H_2O, Et_2O, 0 °C to rt, 41%, e.r. 99 : 1; (14) EtMgCl, THF, −78 °C to rt; (15) TIPSCl, imidazole, DMF, 72% (over 2 steps); (16) catecholborane, 40 °C → 50 °C; then Br_2, CH_2Cl_2, −78 °C; then TBAF, THF, 40 °C; (17) 2-benzyloxy-1-methylpyridinium triflate, MgO, $C_6H_5CF_3$, 83 °C, 69% (over 2 steps); (18) *sec*-BuLi, THF, Et_2O, −78 °C; then **21**, THF, −78 °C to rt, 64%, d.r. >20 : 1 after chromatography; (19) PMBBr, NaH, DMF; (20) HOAc, H_2O, THF; (21) Dess–Martin periodinane, CH_2Cl_2, 58% (over 3 steps); (22) L-Selectride, THF, −78 °C; then **10**, −40 °C, 52%, d.r. >20 : 1 after chromatography; (23) HF·pyridine, pyridine, THF, 0 °C to rt; (24) $PhI(OAc)_2$, TEMPO, CH_2Cl_2, 74% (over 2 steps); (25) $NaClO_2$, NaH_2PO_4, isoamylene, H_2O, *t*BuOH; (26) DDQ, pH 7 buffer, CH_2Cl_2; (27) 2,4,6-$Cl_3C_6H_2COCl$, DIPEA, THF, 16 h; then DMAP, PhMe, 60 °C, 52% (over 3 steps); (28) Pd/C, HCO_2H, EtOAc, MeOH; (29) 1 N HCl, THF; then 4 N HCl, THF, 57% (over 2 steps).



Scheme 3 The Hoye synthesis of peloruside A, **1**. *Reagents and conditions*: (1) $HNC(NMe_2)_2$, C_6H_6; then TFA, 98%, d.r. 12 : 1; (2) **29**, DCC, DMAP, CH_2Cl_2, 0 °C to rt, 82%; (3) [Ru=CHPh(Cl)$_2$(PCy_3)–(H_2IMes)], CH_2Cl_2, 45 °C, 70%; (4) $NaBH_4$, AcOH, EtOH, 0 °C to rt, 82 %; (5) TBSCl, Et_3N, DMAP, CH_2Cl_2, 99%; (6) Cl_3CC(=NH)OPMB, CSA, CH_2Cl_2, 77%; (7) Zn^0, Cp_2TiCl_2, allyl 2-bromoacetate, THF, 60 °C; (8) pH 3 buffer, *i*PrOH/H_2O/THF (4 : 1 : 2); (9) $Pd(PPh_3)_4$, HCO_2H, Et_3N, THF, 61% (over 3 steps); (10) *c*Hex_2BCl, Et_3N, **25**, Et_2O, −78 °C to −40 °C; then **24**, Et_2O, −78 °C to −20 °C, 64%.

primary TBS ether (HF·pyridine) and sequential oxidations ($PhI(OAc)_2$, TEMPO; then Pinnick oxidation) yielded a carboxylic acid. After deprotection of the C15 PMB ether (DDQ, pH 7 buffer), the material was cyclized under Yamaguchi conditions to form macrolactone **23**. Removal of the benzyl protecting group (Pd/C, HCO_2H, MeOH) and a global removal of the remaining protecting groups under acidic conditions afforded peloruside A (**1**) in 57% yield. The longest linear sequence was 20 steps from commercially available materials.

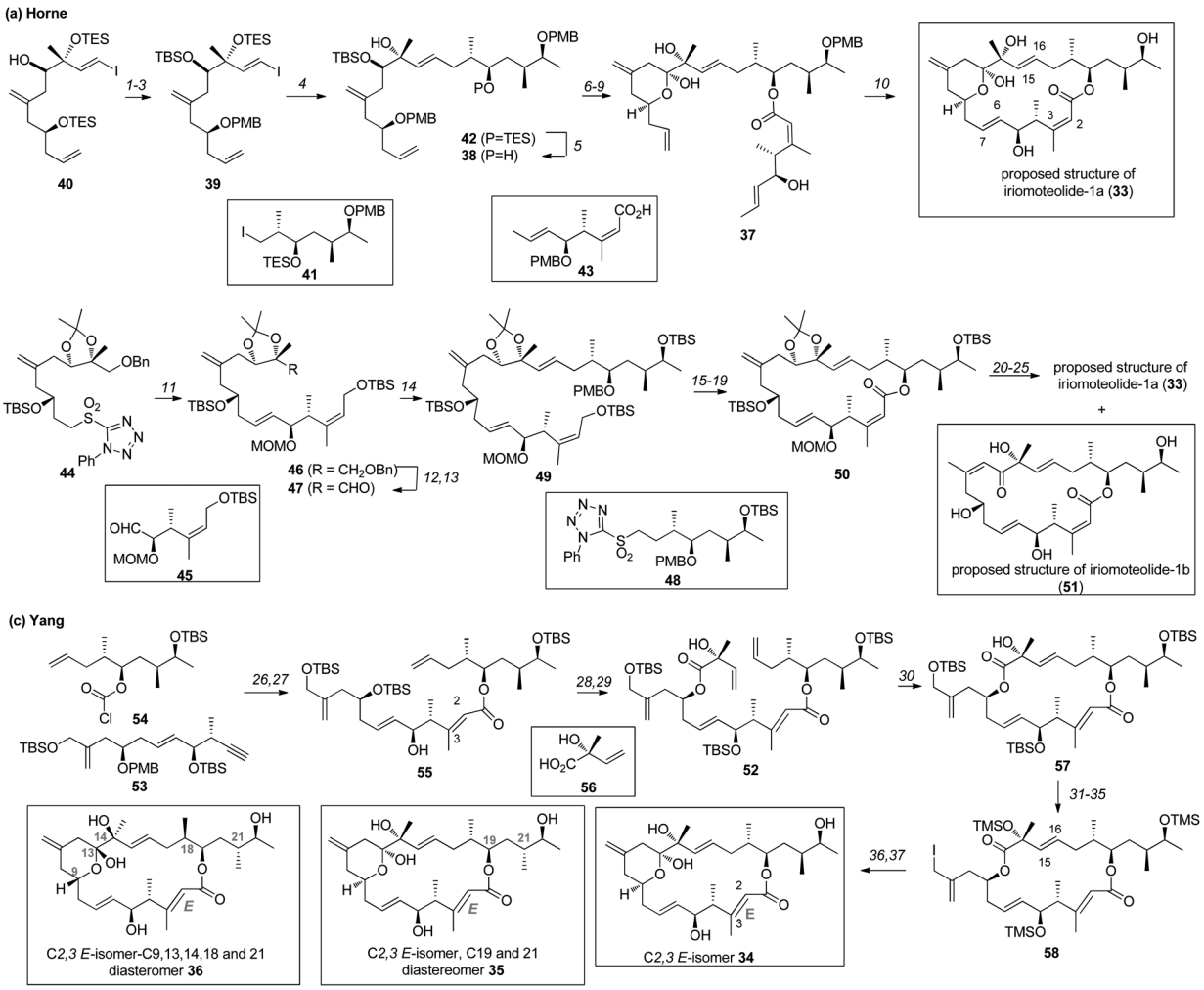
Hoye and coworkers used an alternate disconnection for their fragment coupling, which leads to an aldol reaction between aldehyde **24** and methyl ketone **25** (Scheme 3).[19] The aldehyde **24** was prepared using a kinetic lactonization of C1-symmetric alcohol **26**, using tetramethylguanidine (TMG) followed by anhydrous TFA. This impressive reaction proceeded in 98% yield and with a diastereomeric ratio of 12 : 1. The resulting lactone **27** was converted into aldehyde **24** in a 16 step sequence. Access to methyl ketone **25** was pursued *via* a relay ring-closing metathesis protocol, starting from the readily available acid **28**. Coupling of acid **28** with chiral alcohol **29** gave the ester, which was treated with Grubbs second generation metathesis catalyst to initiate the relay ring-closing metathesis. The resulting lactone **30** was reduced with $NaBH_4$ in acetic acid and the TBS and Bn ethers were introduced sequentially to generate the nitrile **31** in 62% overall yield.

Transformation of nitrile **31** to methyl ketone **25** proved to be challenging due to the instability of the substrate to base, but application of a modified Blaise reaction allowed this sequence to proceed. The reagent was formed *in situ* by reacting allyl bromoacetate, zinc metal and titanocene dichloride together and subsequent reaction with nitrile **31**, followed by careful hydrolysis (pH 3, 2 days), generated a β-ketoester, which was decarbalkoxylated with $Pd(PPh_3)_4$, formic acid and triethylamine. The methyl ketone **25** was obtained in 61% yield over the three steps. A Paterson boron aldol coupling using methyl ketone **25** and aldehyde **24** was used to produce ketoalcohol **32** in 64% yield and as a single stereoisomer. Transformation of this material to peloruside A (**1**) was achieved in 9 steps.

The amphidinolide family of polyketides continues to attract attention, as structure determination of this class of compound,

and in particular assignment of the relative and absolute stereochemistry, is fraught with difficulty.[22] An excellent example of this is iriomoteolide-1a (**33**), which was isolated from a benthic HYA024 strain of *Amphidinium* sp. and was reported to have exceptional cytotoxicity, rivalling compounds that are in current clinical use. In 2010, the groups of Horne,[23] Ghosh[24] and Yang[25] reported their efforts to synthesize iriomoteolide-1a (**33**) (Scheme 4). Horne reported the first total synthesis and found that the reported structure did not match that of the natural product. Shortly after the Horne paper appeared, the groups of Ghosh and Yang published within days of each other and confirmed Horne's work. Yang's group prepared diastereomers **34**, **35** and **36** to see if one of these were the true structure of iriomoteolide-1a, but none matched the data from the natural product.

Horne's strategy for synthesising iriomoteolide-1a (**33**) relied on the assembly of the macrocycle in the final step, using a ring-closing metathesis of alkene **37** (Scheme 4a). To generate the metathesis substrate **37**, access to alcohol **38** was required. The vinyl iodide **39** was prepared from a previously synthesized fragment **40** and coupled to the previously synthesized alkyl iodide **41** *via* a Suzuki–Miyaura coupling and afforded alkene **42** in an efficient 84% yield and with complete control of the alkene geometry. After deprotection of the secondary TES ether (HF·pyridine, pyridine, 90%) of alkene **42**, a Yamaguchi esterification with acid **43** was carried out. A three step sequence



Scheme 4 Syntheses of the proposed structure of iriomoteolide-1a and alternate structures: (a) Horne (b) Ghosh (c) Yang. *Reagents and conditions*: (1) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C to rt, 90%; (2) HF·pyridine, pyridine, THF, 88%; PMBC(=NH)CCl_3, $Sc(OTf)_3$, PhMe, 70%; (4) **39**, *t*-BuLi, 9-MeO-BBN, Et_2O, THF, −78 °C to rt; then **41**, $Pd(dppf)Cl_2$, $AsPh_3$, Cs_2CO_3, H_2O, DMF, 84%; (5) HF·pyridine, pyridine, THF, 90%; (6) 2,4,6-$Cl_3C_6H_2COCl$, NEt_3, THF; then **43**, DMAP, PhMe, 93%; (7) TBAF, THF, 91%; (8) SO_3·pyridine, *i*Pr_2NEt, DMSO, CH_2Cl_2, 70%; (9) DDQ, CH_2Cl_2, pH 7 buffer, 67%; (10) [Ru=CHPh$(Cl)_2(PCy_3)$–(H_2IMes)], CH_2Cl_2, 73%, C6,7 *E* : *Z* = 2.5 : 1; (11) KHMDS, DME; then **45**, 83%; (12) Li, $NH_{3(l)}$, $EtOCH_2CH{=}CH_2$; (13) DMP, $NaHCO_3$, CH_2Cl_2, 82% (over 2 steps); (14) KHMDS, DME; then **47**, 70%; (15) DDQ, pH 7 buffer; (16) NH_4F, MeOH, 72% (over 2 steps); (17) MnO_2, CH_2Cl_2; (18) $NaClO_2$, NaH_2PO_4; (19) 2,4,6-$Cl_3C_6H_2COCl$, *i*Pr_2NEt, THF, DMAP, 61% (over 3 steps); (20) HF·pyridine, THF; (21) HOAc, H_2O, 72% (over 2 steps); (22) bromocatecholborane; (23) TESCl, DMAP, CH_2Cl_2, 66% (over 2 steps); (24) DMP, CH_2Cl_2, 65% (90% b.r.s.m.); (25) HF·pyridine, THF, 56% **33** and 17% **51**; (26) **53**, *n*BuLi, THF, −78 °C; then add **54**, THF, −78 °C to 0 °C, 94%; (27) Me_2CuLi, TMSCl, THF, −78 °C to 0 °C, 98%, *E* : *Z* = 10 : 1; (28) DDQ, CH_2Cl_2, $-H_2O$; (29) **56**, DEAD, PPh_3, THF, 70% (over 2 steps); (30) [Ru=CHPh$(Cl)_2(PCy_3)$–(H_2IMes)], CH_2Cl_2, reflux, 62%, *E* : *Z* = 100 : 0; (31) PPTS, EtOH, reflux; (32) MsCl, NEt_3, CH_2Cl_2, 0 °C; then LiCl, HMPA, 79% (over 3 steps); (33) HF·pyridine, THF; (34) TMSOTf, pyridine, CH_2Cl_2, 0 °C; (35) NaI, Me_2CO, 87% (over 3 steps); (36) SmI_2, THF, 0 °C, 71%; (37) TBAF, HF·pyridine, THF, 74%.

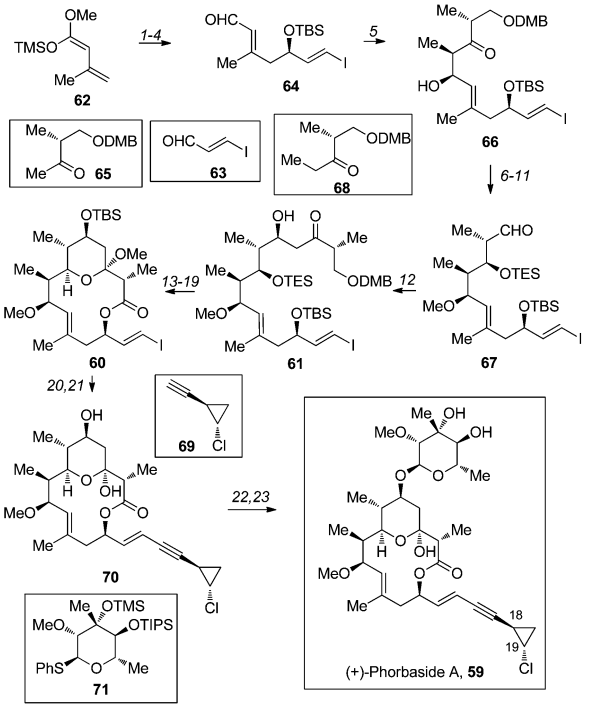
involving deprotection of the silyl groups (TBAF, THF), oxidation ($SO_3 \cdot$pyridine, iPr$_2$NEt, DMSO, CH_2Cl_2) and PMB deprotection (DDQ, CH_2Cl_2, pH 7 buffer) afforded the metathesis precursor **10** in 40% overall yield for the four steps. Treatment with Grubbs 2nd generation catalyst gave the *E*- and *Z*-geometric isomers of iriomoteolide-1a (**33**) in a 2.5 : 1 ratio. None of the spectroscopic data matched that reported for the natural product.

Ghosh and Yuan also developed an enantioselective synthesis of the proposed structure, utilizing a Julia–Kocienski olefination and a macrolactonization using Yamaguchi conditions (Scheme 4b).[24] The readily available sulfone **44** was deprotonated with KHMDS and reacted with aldehyde **45** to afford *E*-olefin **46** (R = CH_2OBn) as a single isomer in 83% yield. A two step sequence involving deprotection of the benzyl group (Li, $NH_{3(l)}$, allyl ethyl ether) and oxidation (DMP, $NaHCO_3$) generated the aldehyde **47** in 82% yield. A second Julia–Kocienski olefination was carried out, coupling aldehyde **47** with sulfone **48**, to prepare the *E*-alkene **49** in 70% yield. This material was transformed into macrolactone **50** in 5 steps, proceeding in 44% overall yield. The total synthesis was completed by sequential removal of the silyl ether and acetonide protecting groups, followed by deprotection of the MOM group with bromocatecholborane. Selective triethylsilylation of the free alcohols allowed oxidation (DMP, $NaHCO_3$) of the diol and after treatment with HF$\cdot$pyridine complex, a 3 : 1 mixture of the proposed structure of iriomoeolide-1a (**33**) and iriomoteolide-1b (**51**) was obtained. After chromatography, **33** was obtained in 56% yield and **51** in 17% yield. Neither compound matched the reported data.

As it had become clear that the proposed structure was not correct, Yang and coworkers actually reported their efforts to prepare alternate structures that could be the natural product (Scheme 4c).[25] During their studies they had already established that the C2–C3 alkene was more likely to be the *E*-geometry rather than the reported *Z*-geometry. Accordingly, their initial focus was on the synthesis of **34**. They also utilized a ring-closing metathesis for their macrocyclization, but in contrast to Horne they used the strategy to form the C15–C16 alkene. Access to the metathesis precursor **52** was achieved by firstly coupling alkyne **53** to chloroformate **54** and carrying out a conjugate addition with Me_2CuLi to generate alkene **55** in a 10 : 1 ratio of *E* : *Z* geometric isomers and in an impressive 92% yield for the two steps. After oxidative removal of the PMB group (DDQ), a Mitsunobu reaction with acid **56** generated the metathesis precursor **52** in 70% yield. The ring closing metathesis of **52**, using Grubbs 2nd generation catalyst, generated *E*-alkene **57** in 62% yield. To assemble the six-membered hemiketal, Yang decided to utilise a intramolecular reductive cyclization of iodoester **58**. Accordingly, alkene **57** was transformed into **58** in an efficient 5 step sequence. Treatment with SmI_2 in THF, followed by a global desilylation (TBAF, HF.pyridine) generated the C2,C3 *E*-isomer of the proposed structure of iriomoetolide-1a (**34**) in 52% yield. Again, the spectroscopic data for this material did not match that reported for the natural product. Consequently, Yang and coworkers also prepared diastereomers **35** and **36**, in which the stereochemistry at C9, C13, C14, C18, C19, and C21 was varied, but neither compound matched the reported data. At the time of publication of this review, the true structure of iriomoteolide-1a is yet to be established.

Paterson and Paquet have reported the total synthesis of phorbaside A (**59**) in 23 steps (for the longest linear sequence) and 8.2% overall yield (Scheme 5).[26] Phorbaside A belongs to a class of glycosylated macrolides that have significant levels of cytotoxicity against the HCT116 cell line. The synthesis confirmed the configurational assignment. To allow late-stage diversification so that structure–activity relationships could be established, the macrolactone **60** was prepared first, then the *trans*-chlorocyclopropyl enyne side chain and the glycoside were appended. To access the macrolactone **60**, the linear precursor **61** was prepared starting from silyl ester enolate **62**.

Treatment of **62** with (*R*)-BINOL-Ti(OiPr)$_4$ and reaction with aldehyde **63** gave an aldol adduct (87%, >95% ee), which was transformed into aldehyde **64** in 97% yield over 3 steps. Aldehyde **64** was reacted with the E-boron-enolate of ketone **65** to



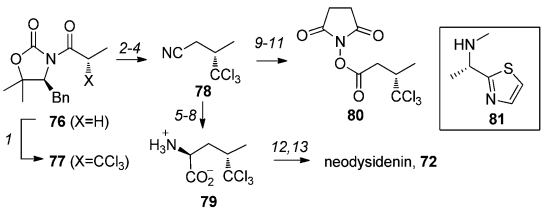
Scheme 5 The Paterson synthesis of (+)-phorbaside A, **59**. *Reagents and conditions*: (1) (*R*)-BINOL, Ti(O*i*Pr)$_4$, THF, −78 °C, then **63**, 87%, >95% ee; (2) TBSCl, imidazole, CH_2Cl_2; (3) DIBAL, CH_2Cl_2, −78 °C; (4) MnO_2, Et_2O, 97% (over 3 steps); (5) *c*-Hex$_2$BCl, NEt_3, Et_2O, 0 °C, then **65**, −78 °C, 98%, d.r. >95 : 5; (6) SmI_2, EtCHO, THF, −10 °C, d.r. >95 : 5; (7) TESOTf, 2,6-lutidine, CH_2Cl_2, −78 °C; (8) DIBAL, CH_2Cl_2, −78 °C, 87% (over 3 steps); (9) Me_3OBF_4, Proton Sponge, CH_2Cl_2; (10) DDQ, pH 7 buffer, CH_2Cl_2, 60 °C; (11) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 95% (over 3 steps); (12) *c*-Hex$_2$BCl, NEt_3, Et_2O, 0 °C, then **68**, −78 °C, 97%, d.r. >95 : 5; (13) PPTS, CH(OMe)$_3$, MeOH; (14) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C; (15) DDQ, MeOH, CH_2Cl_2, 77% (over 3 steps); (16) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2; (17) $NaClO_2$, NaH_2PO_4, H_2O, *t*-BuOH, 2-methyl-2-butene; (18) TBAF, THF, 93% (over 3 steps); (19) 2,4,6-Cl$_3$C$_6$H$_2$COCl, NEt_3, then DMAP, PhMe, 42%; (20) **69**, PdCl$_2$(PPh$_3$)$_2$, CuI, *i*-Pr$_2$NH, EtOAc; (21) TFA, THF, H_2O, 64% (over 2 steps); (22) **71**, NIS, DTBMP, TfOH, CH_2Cl_2, 4 Å MS; (23) TBAF, THF, 64% (over 2 steps).

give the 1,2-*anti*-1,4-*syn* adduct **66** in 98% yield and in a diastereomeric ratio of >95 : 5. This material was elaborated in 6 steps to aldehyde **67** in 83% overall yield. A second boron-mediated aldol coupling, in this case using the dicyclohexylboron enolate of methyl ketone **68** with aldehyde **67**, afforded the linear precursor **61** in 97% yield (d.r. >95 : 5). Elaboration to the macrolactone **60** was achieved in 7 steps and 30% overall yield, with the challenging macrolactonisation proceeding in 42% yield using modified Yamaguchi conditions (2,4,6-$Cl_3C_6H_2COCl$, NEt_3, then DMAP, PhMe, 60 °C). A Sonogashira coupling ($[PPh_3P]_4PdCl_2$, CuI, iPr_2NH, EtOAc) of iodide **60** with alkyne **69** was carried out and after treatment with TFA in wet THF the aglycone **70** was obtained in 64% yield for the 2 steps. To complete the synthesis, the glycosylation was achieved by reacting **70** and thioglycoside **71** with *N*-iodosuccinimide, catalytic TfOH and 2,6-di-*t*-butyl-4-methylpyridine in CH_2Cl_2. TBAF in THF removed the silyl protecting groups and afforded phorbaside A (**59**) in 64% yield for the 2 steps. The 18(*S*), 19(*R*) diastereomer was also prepared so as to allow verification of the absolute configuration.

4 Chloro-containing compounds: neodysidenin and the sintokamides

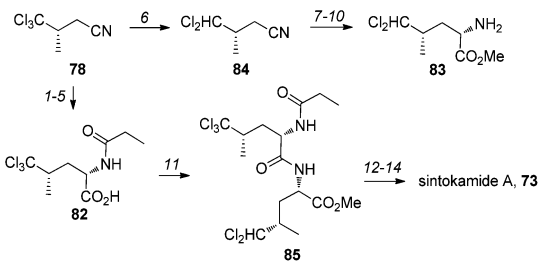
Neodysidenin (**72**) and the sintokamides (**73–75**) are examples of a unique sub-class of halogenated natural products, which are biosynthesised by direct chlorination (Fig. 2).[27] Synthetic access to such molecules has been limited by the lack of suitable methods for preparing the polychlorinated materials in a stereoselective fashion. However, recent work by the Zakarian group has seen the development of an efficient and highly stereoselective chloroalkylation process which has allowed the efficient synthesis of neodysidenin and the sintokamides.[28,29]

It was found that reaction of titanium enolates with haloalkanes could be achieved by using a ruthenium-catalysed radical process (Scheme 6). For example, using the titanium enolate of chiral 5,5-dimethyl oxazolidinone **76** and three equivalents of $BrCCl_3$ in the presence of 7 mol% of $[Ph_3P]_3RuCl_2$, trichloride **77** was obtained in 96% yield and in greater than 98 : 2 diastereomeric ratio.[28] The oxazolidinone **77** was transformed into nitrile **78** in three steps. Nitrile **78** is the key material for the synthesis of neodysidenin and the sintokamides. To prepare neodysidenin (**72**), **78** was transformed into (2*S*,4*S*)-5,5,5-trichloroleucine (**79**) in 4 steps, with the key step being a diastereoselective scandium-catalysed Strecker reaction. *N*-Hydroxysuccinimide ester **80** was prepared from the same nitrile **78** and coupled with the leucine derivative **79**. Conversion to the target molecule **72** was achieved in 85% yield (over the two steps) by amidation with amine **81** using EDC and HOAt.



Scheme 6 The Zakarian synthesis of neodysidenin, **72**. *Reagents and conditions*: (1) $TiCl_4$, iPr_2NEt, CH_2Cl_2, 0 °C, then $BrCCl_3$, $[Ph_3P]_3RuCl_2$ (0.07 eq.), 45 °C, 96%, d.r. >98 : 2; (2) $NaBH_4$, THF, H_2O, 61%; (3) Tf_2O, pyridine, CH_2Cl_2; (4) Et_4NCN, CH_2Cl_2, 71% (over 2 steps); (5) DIBAL, CH_2Cl_2; (6) (*S*)-(−)-*tert*-$BuSONH_2$, $MgSO_4$, CH_2Cl_2, 67%; (7) Me_3SiCN, $Sc(OTf)_3$, CH_2Cl_2; (8) 6 M HCl, H_2O, 82% (over 2 steps), d.r. 94 : 6; (9) DIBAL, CH_2Cl_2, −78 °C; (10) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*BuOH, H_2O; (11) *N*-hydroxysuccinimide, DCC, CH_2Cl_2 76% (over 3 steps); (12) **80**, $NaHCO_3$, THF, 99%; (13) **81**, EDC, HOAt, THF, 86%.

In his total synthesis of the sintokamides (**73–75**), Zakarian decided to assemble the central tetramic acid subunit in the final stage of the synthesis as this eliminated the need for protecting groups (Scheme 7).[29] Thus, from his retrosynthetic analysis, sintokamide A (**73**) should be readily prepared from a (2*R*,4*S*)-5,5,5-trichloroleucine derivative **82** and (2*S*,4*S*)-5,5-dichloroleucine methyl ester (**83**). By careful planning, it proved possible to prepare both materials from nitrile **78**, which had been used in the synthesis of neodysidenin. Leucine derivative **82** was readily prepared using the same synthetic strategy that yielded leucine **79**, however the synthesis began with the *R*-enantiomer of *tert*-$BuSONH_2$. While the ruthenium-catalysed haloalkylation methodology could readily deliver the dichloronitrile **84**, it was found that trichloronitrile **78** could be monodechlorinated when reacted with triethylsilane and 1 mol% of the catalyst $[(Ph_3P)_2RuCl_2]$ to afford the nitrile **84** in 76% yield. Conversion to the methyl ester **83** was achieved in 4 steps using



Scheme 7 The Zakarian synthesis of sintokamide A, **73**. *Reagents and conditions*: (1) DIBAL, CH_2Cl_2, −78 °C; (2) (*R*)-(+)-*tert*-$BuSONH_2$, $CuSO_4$, CH_2Cl_2, 88% (over 2 steps); (3) Me_3SiCN, $Sc(OTf)_3$, CH_2Cl_2, 0 °C, 83%, d.r. >95 : 5; (4) 6 M HCl, H_2O, reflux; (5) *N*-hydroxysuccinimide propionic ester, $NaHCO_3$, H_2O, THF, 83% (over 2 steps); (6) Et_3SiH, $[(Ph_3P)_3RuCl_2]$ (1 mol%), neat, 100 °C, 76%; (7) DIBAL, CH_2Cl_2, −78 °C; (8) (*S*)-(−)-*tert*-$BuSONH_2$, $CuSO_4$, CH_2Cl_2, 98% (over 2 steps); (9) Me_3SiCN, $Sc(OTf)_3$, THF, 0 °C, 86%, d.r. = 87 : 13; (10) HCl, MeOH, 88%; (11) **70**, EDCI, HOAt, THF, 91%; (12) LiOH, THF/H_2O; (13) Meldrum's acid, DMAP, isopropenyl chloroformate, CH_2Cl_2, −10 °C, 72% (over 2 steps), d.r. = 67 : 33; (14) CH_3CN, 81 °C, then MeOH, PPh_3, $(EtO_2C)_2CN_2$, THF, 48%.

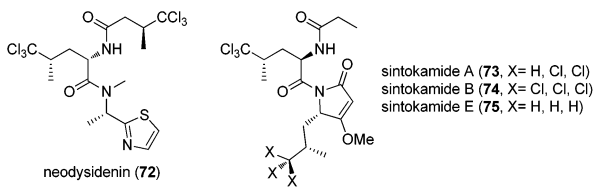


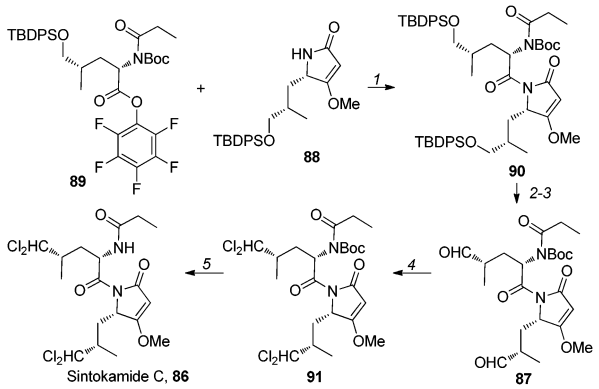
Fig. 2 Neodysidenin (**72**) and sintokamides A, B and E (**73–75**).

the same diastereoselective Strecker methodology used previously.

To complete the synthesis, **82** and **83** needed to be coupled together and after extensive experimentation, it was found that this could be achieved using EDC and HOAt to form the peptide **85** in 91% yield, and as a single diastereomer. It was found that the formation of the tetramic acid fragment was best achieved using a minor modification of a sequence described by Jouin and Castro.[30] Thus, peptide **85** was hydrolyzed (LiOH, THF/H_2O, 0 °C) and the resulting acid reacted with Meldrum's acid, 5 equivalents of DMAP and isopropenyl chloroformate at −10 °C to form the adduct in 72% yield (from **85**) and in a diastereomeric ratio of 67 : 33. Thermolysis of the adduct, followed by reaction with methanol, triphenylphosphine and diethyl azodicarboxylate, resulted in the formation of sintokamide A (**73**) in 48% yield after chromatography. The total synthesis required 14 steps and proceeded in 14% overall yield. This synthetic strategy was also applied to the synthesis of sintokamides B (**74**) and E (**75**).

The group of Ye reported the total synthesis of sintokamide C (**86**), which is the only member of the family not to contain a 5,5,5-trichloroleucine fragment (Scheme 8).[31] Ye took a different approach to Zakarian and decided to install the *gem*-dichloride moieties in the final stage of the synthesis. This analysis meant that access to dialdehyde **87** was required. The latter could be prepared in a three step sequence starting with the readily available tetramic acid **88** and pentafluorophenol ester **89**.

Treatment of tetramic acid **88** with LiHMDS in THF at −55 °C generated the anion, which was reacted with ester **89** to form amide **90** in 71% yield. Removal of the silicon protecting groups (HF·pyridine; 69%) and oxidation using the Parikh–Doering protocol (SO_3·py, NEt_3, DMSO; 80%) gave the desired dialdehyde **87**. After some experimentation, it was found bisaldehyde **87** could be chlorinated by reaction with triphenyl phosphate and chlorine in the presence of triethylamine to generate the tetrachloride **91** in 70% yield. Removal of the Boc protecting group (TFA, CH_2Cl_2) afforded sintokamide C (**86**) in 73% yield.

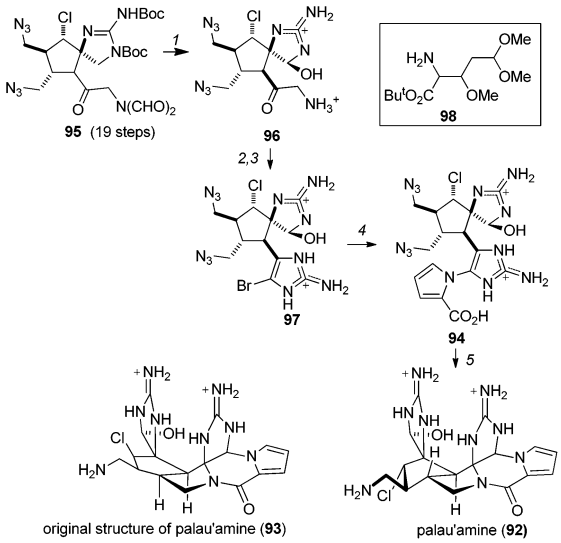


Scheme 8 The Ye synthesis of sintokamide C, **86**. *Reagents and conditions*: (1) **88**, LiHMDS, THF, −55 °C, then **89**, −55 °C to −45 °C, 71%; (2) HF·py, THF, 69%; (3) SO_3·py. NEt_3, DMSO, CH_2Cl_2, 80%; (4) $(PhO)_3P$, Cl_2, NEt_3, 70%; (5) TFA, CH_2Cl_2, 73%.

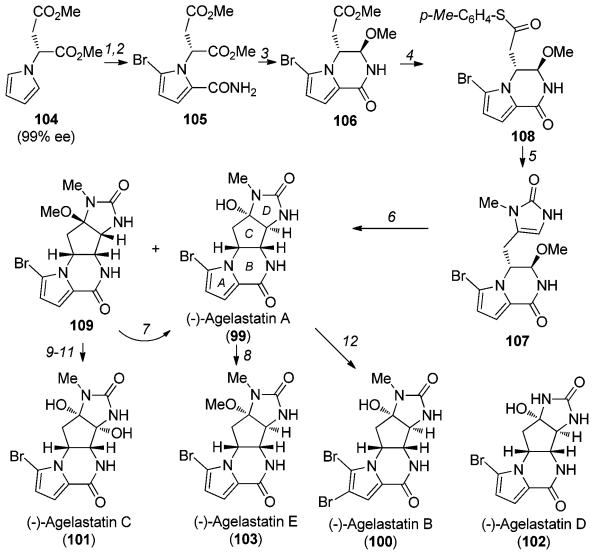
5 Alkaloids: palau'amine, agelastatins, diazonamide A, (±)-haliclonacyclamine C, communesin F amd (+)-perophoramidine, (−)-crambidine

One of the major challenges of total synthesis has been the complex hexacyclic architecture of palau'amine (**92**) (Scheme 9).[32] The groups of Quinn, Fustetani and Kock, in 2007, established that the geometry of the azabicyclo[3.3.0]octane core was *trans*, rather than the proposed *cis* **93**.[33] With this new insight, Baran and coworkers were able to complete a total synthesis of palau'amine (**92**).[34] The key part of their synthetic strategy was that a 'macro palau'amine' could be generated from **94** and an irreversible transannular cyclization would yield the desired target. Using a selective silver(II)-oxidation protocol, Baran was able to convert the cyclopentane core **95** (available in 19 steps)[35] to the hemiaminal **96** in 64% yield. Conversion to the 2-aminoimidazole moiety was achieved by reaction of **96** with cyanamide and this compound was brominated (Br_2, TFA, TFAA) to generate the bromide **97** in 35% yield for the two steps. After initial efforts to introduce an intact pyrrole failed, bromide **97** was reacted with amino ester **98** (AcOH, THF), then heated in TFA to afford the key pyrrole **94** in 44% yield. Reduction of the azide groups was achieved by reaction with hydrogen gas and palladium acetate, and this was then followed by reaction with EDC to form the macrocycle. Without isolating the material, TFA was added and the solution heated at 70 °C to trigger the critical transannular cyclization and generate palau'amine (**92**) in 17% yield (from **94**).

Movassaghi and coworkers have developed a concise, enantioselective synthesis that allows the generation of all the known agelastatins (**99–102**), a class of pyrrole-imidazole marine alkaloids (Scheme 10).[36] The synthetic strategy was based on a biosynthetic hypothesis in which the C-ring was formed at a late



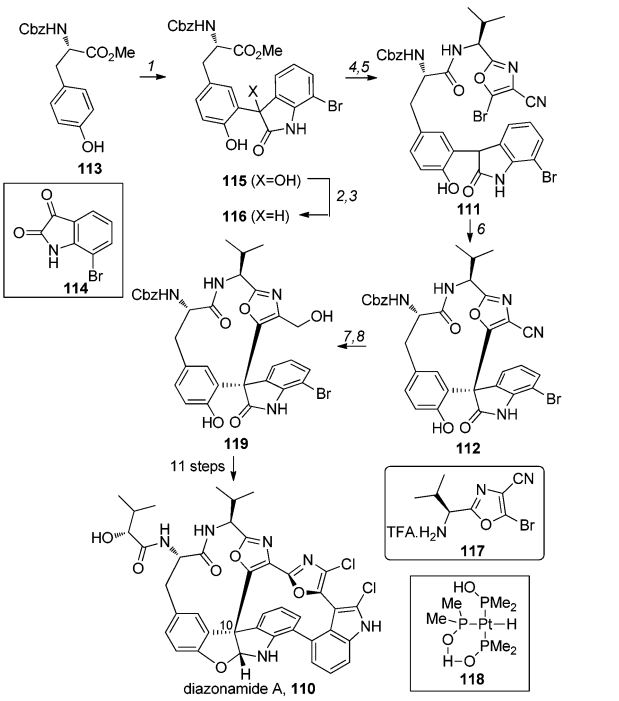
Scheme 9 The Baran synthesis of palau'amine, **92**. *Reagents and conditions*: (1) 50% TFA/H_2O; 10% TFA, silver(II)-picolinate, H_2O, 64%; (2) H_2NCN, brine; (3) TFAA/TFA; Br_2, 35% (over 2 steps); (4) AcOH, THF; TFA/CH_2Cl_2, 44%; (5) $Pd(OAc)_2$, H_2, TFA/H_2O; EDC, HOBt, DMF; TFA, 17%.



Scheme 10 The Movassaghi synthesis of the agelastatins, **99–102**. *Reagents and conditions*: (1) NBS, 2,6-di-*tert*-butyl-4-methylpyridine, THF, 92%, 99% ee; (2) $ClSO_2NCO$, MeCN, 0 °C, then Na(Hg), NaH_2PO_4, 82%; (3) $NaBH_4$, MeOH, 0 °C, then $TsOH{\cdot}H_2O$, rt, 90%; (4) HSC_6H_4-*p*-Me, $AlMe_3$, CH_2Cl_2, 0 °C, 92%; (5) CuTC, $cHx_3SnCH_2NH(CO)NHMe$, THF, 50 °C, then HCl (0.5 N), MeOH, rt, 58%; (6) $MeSO_3H$, H_2O, 100 °C, then MeOH, 71%, d.r. 2 : 1; (7) $MeSO_3H$, H_2O, 100 °C, then MeOH, 66% of **99**, 30% of **109** recovered;(8) Amberlyst 15, MeOH, 65 °C, 96%; (9) pyridine, 115 °C, 99%; (10) DMDO, acetone, H_2O, 98%; (11) Amberlyst 15, MeOH, 100 °C, 41%; (12) NBS, DTBMP, THF, H_2O, 0 °C, 84%.

stage. Pyrrole **104**, which is readily available from D-aspartic acid, was treated with NBS in the presence of 2,6-di-*tert*-butyl-4-methylpyridine to generate a bromopyrrole (92% yield), which was reacted with chlorosulfonyl isocyanate and then Na/Hg amalgam to generate the amide **105** in 82% yield. The B-ring was formed by reacting **105** with $NaBH_4$ in MeOH at 0 °C, then stirring with *p*-TSA. This generates the bicyclic lactam **106** in 90% yield and as a single diastereomer. After some experimentation, the substituted imidazolone **107** was generated in 58% overall yield by firstly converting ester **106** into thioester **108**, using 4-methylbenzenethiol and $AlMe_3$, followed by reaction with $cHx_3SnCH_2NH(CO)NHMe$ and copper(I)-thiophene-2-carboxylate (CuTC) and an acidic workup. Exposure of **107** to methanesulfonic acid in water at 100 °C resulted in the formation of (−)-agelastatin A (**99**) and an *O*-methylated diastereomer **109** in a 2 : 1 ratio and 71% combined yield. Diastereomer **109** could be resubjected to the above reaction conditions to furnish **99** in 66% yield (96% brsm). Thus, (−)-agelastatin A (**99**) was prepared in 7 steps from commercially available materials and 22% overall yield. Access to (−)-agelastatin E (**100**) was achieved by treating agelastatin A (**99**) with Amberlyst 15 and methanol (96% yield). Furthermore, the generation of the *O*-Methyl derivative **109** proved to be useful as it could be used to prepare (−)-agelastatin C (**101**). Heating this material in pyridine at 115 °C eliminated methanol and the resulting compound was oxidized with dimethyldioxirane in acetone and after exposure to Amberlyst 15 in methanol, (−)-agelastatin C (**101**) was obtained in 40% overall yield. Bromination of **99** using *N*-bromosuccinimide gave (−)-agelastatin B (**100**) in 84% yield. Access to (−)-agelastatin D (**102**) were also possible using this versatile synthetic strategy (not shown).

Sammakia and coworkers have completed a formal total synthesis of diazonamide A (**110**) that employs an elegant approach for forming the C10 quaternary center (Scheme 11).[37] A intramolecular nucleophilic aromatic substitution reaction was used to form the quaternary center at the same time as closing one of the macrocycles (**111** → **112**). A key feature of the synthesis was that the cyclisation was mild enough that no protecting groups were required. Indeed, the use of protecting groups on either the phenol of the indole nitrogen lead to no cyclization or *O*-alkylation. The cyclization precursor **111** was assembled in 5 steps, starting from commercially available tyrosine derivative **113** and 7-bromoisatin (**114**). Treatment of **113** with MeMgBr in THF, followed by addition of **114** formed tertiary alcohol **115** in 74% yield. Deoxygenation of **15** to form **116** was achieved in two steps ($SOCl_2$, followed by $NaCNBH_3$), proceeding in an efficient 82% yield for the 2 steps. Hydrolysis of ester **116** with LiOH in aqueous THF generated a carboxylic acid, which was coupled with aminooxazole **117** using EDC and HOBt to form the cyclization precursor **111** (72% yield). The cyclization of **111** was achieved by adding sodium carbonate in DMF at 65 °C and generated the macrocycle **112** in 56% yield. The structure and stereochemistry was confirmed by X-ray crystallography. Hydrolysis of the cyano group to the carboxamide group was achieved by reaction with Parkin's catalyst **118** in ethanol at 120 °C (92%) and this material was reduced with



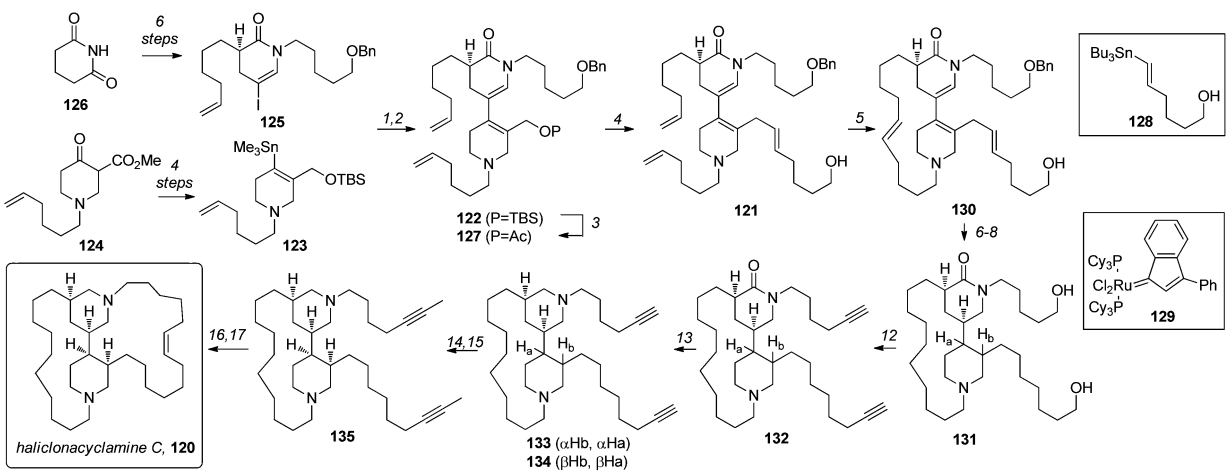
Scheme 11 The Sammakia formal synthesis of diazonamide A, **110**. *Reagents and conditions*: (1) MeMgBr, THF; then **114**, CH_2Cl_2, 74%; (2) $SOCl_2$, neat; (3) $NaBH_3CN$, MeCN, 82% (over 2 steps); (4) LiOH, THF/H_2O; (5) **117**, EDC, HOBt, NEt_3, 72% (over 2 steps); (6) Na_2CO_3, DMF, 65 °C, 56%; (7) **118**, 95% EtOH, 120 °C, 92%; (8) SmI_2, H_2O, 52%.

samarium diiodide and water to generate primary alcohol **119** in 52% yield. As alcohol **119** had previously been used in Nicolaou's total synthesis,[38] this meant that Sammakia and coworkers had achieved a formal total synthesis of diazonamide A (**110**).

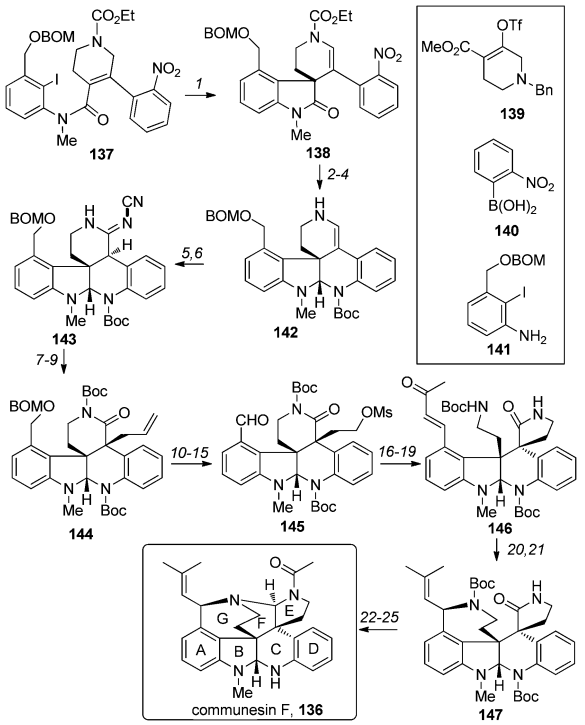
Smith and Sulikowski have reported a total synthesis of (±)-haliclonacyclamine C (**120**), which is a member of the alkylpiperidine alkaloid family (Scheme 12).[39] It was envisaged that the two macrocyclic rings (17 and 18-membered rings respectively) could be generated from ring-closing metathesis reactions and accordingly, the initial target was the diene **121**, which contains the appropriate functionality to allow the addition of the required side-chains for the metathesis chemistry. Diene **122** was prepared by Stille cross-coupling of stannane **123** (synthesized in 4 steps from **124**) and iodide **125** (prepared in 6 steps from glutarimide (**126**)). It was found that the Stille coupling could be achieved in 75% yield when $Pd(PPh_3)_4$ and CuCl were used. Exchange of the TBS ether for an acetate was achieved in 2 steps and generated allylic acetate **127**, which upon exposure to $[Pd(dba)_2]$ and LiCl, could be coupled to stannane **128** to generate diene **121** in 80% yield. After conversion to the hydrochloride salt (HCl, Et_2O) a ring-closing metathesis, using Fürstner's ruthenium indenylidine catalyst **129**, converted diene **121** into tricycle **130** in 64% yield. Hydrogenation of all the alkenes was achieved by carrying out the reaction at 500 psi H_2 in ethanol using Pearlman's catalyst at 70 °C for 8 days. This afforded **131** as an inseparable 1.3 : 1 mixture of isomers in 79% yield. To complete the synthesis, a ring closing alkyne metathesis/partial hydrogenation strategy was utilized. The isomeric mixture **131** was oxidized with Dess–Martin periodinane to afford the dialdehyde and this material was immediately reacted with an excess of the Bestmann–Ohira reagent to afford the bis(alkyne) **132** in 54% yield for the 2 steps. Treatment with Red-Al removed the carbonyl group of the lactam and allowed the isolation of isomers **133** (51%) and **134** (39%). Attempts to methylate the alkynes resulted in *N*-methylation as well, but it was found that exhaustive methylation (8 eq. *n*BuLi, excess MeI) followed by treatment with an excess of sodium thiophenoxide in DMF allowed the isolation of diyne **135** in 41% yield for the two steps. After extensive experimentation, it was found the ring-closing alkyne metathesis could be achieved by using the catalyst system derived from the *in situ* combination of Ph_3SiOH and $[(Me_3SiO)_2\{Me_3Si)_2N\}MoN]$ and afforded the tetracycle in 63% yield. Racemic haliclonacyclamine C (**120**) was obtained in 88% yield by semi-hydrogenation using hydrogen and Lindlar's catalyst.

Communesin F (**136**) is an indole alkaloid isolated form a marine fungal strain of *Penicillium* species. In 2010, Weinreb and coworkers reported[40] on their development of a synthesis of racemic communesin F (Scheme 13), while Ma and coworkers have completed[41] a total synthesis of the naturally occurring enantiomer, confirming its absolute configuration (Scheme 14).

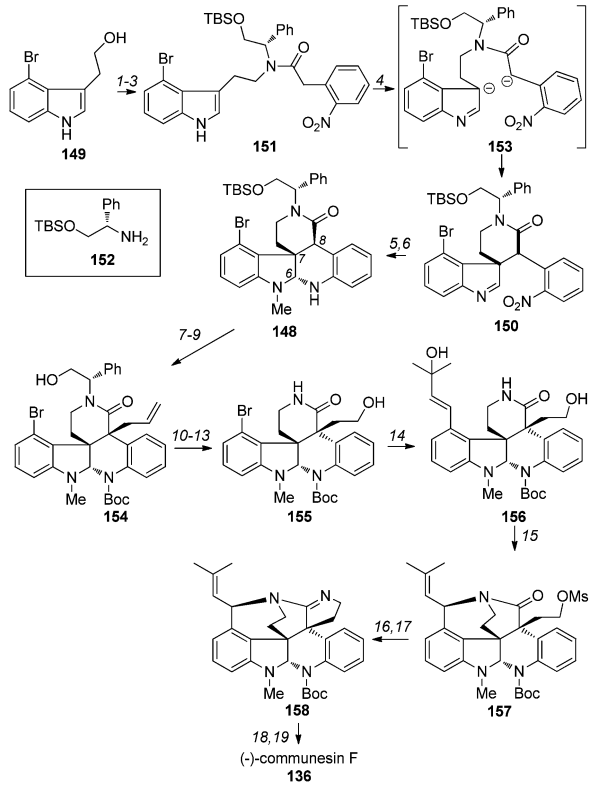
Weinreb's synthesis began with an impressive intramolecular Heck reaction onto a tetrasubstituted alkene **137** to form enamide **138** (Scheme 13). The tetrasubstituted alkene **137** was generated in a 5 step sequence and 65% overall yield, using triflate **139**, boronic acid **140** and iodoaniline **141** as the key starting materials. The Heck reaction on **137** was carried out using $Pd(OAc)_2$, PPh_3, K_2CO_3 and nBu_4NBr in *N*,*N*-dimethylacetamide at 150 °C and formed enamide **138** in 90% yield. This material was elaborated to the pentacyclic aminal **142** in 3 steps (64% yield), which involved reduction (H_2, Pt/C) of the nitro group, amine protection (Boc_2O, K_2CO_3, THF/H_2O) and partial reduction with $AlH_3.NMe_2Et$ complex. To install the quaternary centre at C8, the enamide **142** was hydrolyzed with 1 M KOH solution and the resulting enamine was reacted with cyanogen azide in a [3 + 2] dipolar cycloaddition and subsequent rearrangement to afford the cyanoamidine **143** in 93% yield for the



Scheme 12 The Smith and Sulikowski synthesis of haliclonacyclamine C, **120**. *Reagents and conditions*: (1) **123**, **125**, CuCl, LiCl, $[Pd(PPh_3)_4]$, DMSO, 60 °C, 67%; (2) TBAF, THF, 0 °C; (3) Ac_2O, NEt_3, DMAP, CH_2Cl_2, 96% (over 2 steps); (4) **128**, LiCl, $[Pd(dba)_2]$, DMF, 65 °C, 80%; (5) HCl/Et_2O, then **129** (10 mol %), CH_2Cl_2, 40 °C, 64%; (6) TFA, H_2 (500 psi), $Pd(OH)_2$, EtOH, 70 °C, 79%, d.r. = 1.3 : 1; (7) Dess–Martin periodinane, CH_2Cl_2, 0 °C → rt; (8) KHMDS, methyltriphenylphosphonium bromide, THF, 0 °C, 51% (over 2 steps); (12) $(MeO)_2P(O)C(N_2)C(O)Me$, K_2CO_3, MeOH, 54%; (13) Red-Al, toluene, reflux, 51% **134** and 39% **135**; (14) *n*-BuLi (8 equiv), THF, −78 °C → rt then MeI (excess), −78 °C → rt; (15) NaSPh (10 equiv), DMF, 130 °C. 41% (over 2 steps); (16) Ph_3SiOH (3 equiv), $[(Me_3SiO)_2\{(Me_3Si)_2N\}MoN]$, PhMe, 80 °C then **135**, rt → 130 °C, 63%; (17) H_2, Lindlar's catalyst, EtOAc, 88%.



Scheme 13 The Weinreb synthesis of (±)-communesin F, **136**. *Reagents and conditions*: (1) $Pd(OAc)_2$, PPh_3, DMA, K_2CO_3, nBu_4NBr, 150 °C, 90%; (2) 5% Pt/C, H_2 (40 atm), PhMe, rt; (3) Boc_2O, K_2CO_3, THF, H_2O, 60 °C, 87% (over 2 steps); (4) $AlH_3 \cdot Me_2NEt$, THF, 0 °C → rt, 74%; (5) 1 M KOH, EtOH, 94 °C; (6) NCN_3, MeCN, 93% (over 2 steps); (7) 1M KOH, EtOH, 94 °C, 60%; (8) Boc_2O, LiHMDS, THF, 95%; (9) KO*t*Bu, THF, allyl iodide, −78 °C → rt, 87%; (10) 1 M KOH, EtOH, 80 °C, 94%; (11) OsO_4, NMO, THF, H_2O; then $NaIO_4$; (12) $NaBH_4$, EtOH, 0 °C; (13) MsCl, NEt_3, CH_2Cl_2, 0 °C, 83% (over 3 steps); (14) Pearlman's catalyst, H_2, THF; (15) DMP, CH_2Cl_2, 75% (over 2 steps); (16) NaN_3, DMF, 90 °C, 61%; (17) Me_2CO, 10% NaOH/H_2O, 60 °C, 93%; (18) Boc_2O, LiHMDS, THF, 81%; (19) PMe_3, THF, H_2O, 70 °C, 88%; (20) MeLi, THF, −78 °C, 73%; (21) PPTS, $CHCl_3$, RT, 62%; (22) $Me_3O^+BF_4^-$, *i*Pr_2NEt, CH_2Cl_2, 86%; (23) 5% TFA in CH_2Cl_2, 88%; (24) $NaBH_4$, Ac_2O, HOAc; (25) 40% TFA in CH_2Cl_2, 66% (over 2 steps).



Scheme 14 The Ma synthesis of (−)- communesin F, **136**. *Reagents and conditions*: (1) IBX, DMSO; (2) **152**, $NaBH(OAc)_3$; (3) 2-(2-$NO_2C_6H_4$)–CH_2CO_2H, BOPCl, Et_3N, CH_2Cl_2, 0 °C to rt, 65% (over 3 steps); (4) LiHMDS, THF, −78 °C followed by I_2, −78 °C to rt; (5) Fe, NH_4Cl, *t*BuOH, H_2O, reflux; (6) KO*t*Bu, MeI, THF, 0 °C, 66% (over 3 steps); (7) KHMDS, $(Boc)_2O$, THF, 0 °C, 89%; (8) KO*t*Bu, $CH_2{=}CHCH_2I$, Et_2O; (9) TBAF, THF, 92% (over 2 steps); (10) LiOH·H_2O, DMSO, 100 °C; (11) HCl, THF, 60 °C, 93% (over 2 steps); (12) $NaIO_4$, $K_2OsO_4 \cdot 2H_2O$, NMO, THF, H_2O; (13) $NaBH_4$, MeOH, 95% (over 2 steps); (14) $Pd(OAc)_2$, P(*o*-tol)$_3$, PMP, nBu_4NBr, 2-methyl-3-buten-2-ol/DMF (3 : 2), μW, 140 °C, 80% (b.r.s.m.); (15) MsCl, Et_3N, CH_2Cl_2, 0 °C, 63%; (16) NaN_3, nBu_4NBr, DMF, 90 °C, 78%; (17) P(*n*Bu)$_3$, PhMe, 80 °C, 83%; (18) $NaBH_4$, HOAc, Ac_2O; (19) CF_3CO_2H, CH_2Cl_2, 73% (over 2 steps).

2 steps. Base hydrolysis (1 M KOH, EtOH, 60%) and acylation with Boc_2O (95%) generated a lactam, that was deprotonated with potassium *t*-butoxide to form an enolate which was reacted with allyl iodide to form **144** as a single stereoisomer (87% yield).

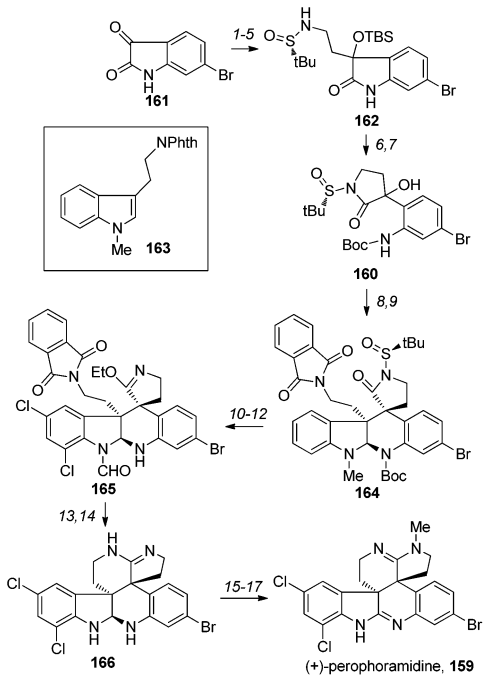
The stereocontrol in this reaction was the result of attack of the iodide on the enolate from the less hindered convex face. With this material in hand, the lactam **144** was transformed into the mesylate aldehyde **145** in an efficient 6 step sequence. After displacement of the mesylate group in **144** with azide ion, the aldehyde functionality was involved in a cross-aldol reaction with acetone to produce a *E*-enone (93%), and the lactam N-atom was protected (using Boc_2O; 81%) and treated with PMe_3 in aqueous THF which reduced the azide moiety and triggered an *in situ* rearrangement to generate the spiro-γ-lactam **146** in 88% yield. To complete the total synthesis, the B and G rings had to be constructed. The G-ring was assembled first, by reaction of **146** with methyllithium to afford a allylic alcohol, which upon treatment with PPTS underwent a stereoselective allylic substitution with the adjacent amino group to form **147** in 45% yield for the 2 steps. This material was transformed into communesin F (**136**) by generating an imidate ($Me_3O^+BF_4^-$, *i*Pr_2NEt, CH_2Cl_2, 86%), selective removal of the upper Boc protecting group (5% TFA in CH_2Cl_2, 88%) which formed a heptacyclic amidine. This material was reduced with sodium borohydride in acetic acid and after removal of the Boc protecting group with 40% TFA in CH_2Cl_2, communesin F (**136**) was obtained in 66% yield for the 2 steps.

In contrast to Weinreb, Ma and coworkers decided to install the A ring in the final stages of the synthesis and thus, their initial focus was on the preparation of the BCDEF pentacycle **148** (Scheme 14). This was achieved in 6 steps, starting from 4-bromotryptophol (**149**). Inspired by Baran's direct intermolecular coupling of indoles with carbonyl compounds,[42] Ma decided to prepare spiro-fused indoline **150** using an intramolecular oxidative coupling of indole **151**. To allow for the preparation of chiral material, the chiral auxillary TBS-protected (*S*)-phenylglycinol (**152**) was used. Thus, 4-bromotryptophol (**149**) was converted to a chiral amine by a oxidation (IBX, DMSO) / reductive amination ($NaBH(OAc)_3$) protocol and the resulting amine was coupled with 2-(2-nitrophenyl)acetic acid

with BOPCl to form oxidative coupling precursor **151** in 66% yield for the 3 steps.

Double deprotonation of **151** with 2 equivalents of LiHMDS gave the dianion **153**, which was oxidized with iodine to generate the spiro-fused indoline **150**. The nitro group was reduced (Fe, NH_4Cl, *t*BuOH, H_2O) and after the resulting amine had reacted with the imine part of the molecule, a selective methylation generated the desired pentacycle **148** in 50% yield for the 3 steps. The 6(*S*),7(*R*),8(*R*) diastereomer (not shown) was also isolated in 16% yield. The allyl group was introduced in a similar fashion to that described by Weinreb. Protection of the remaining amino group in **148** with Boc_2O provided material that was readily allylated (KO*t*Bu, allyl iodide) and after removal of the silyl group afforded alcohol **154** as a single stereoisomer and in 82% overall yield for the 3 step sequence. Removal of the chiral auxiliary was achieved by reaction with $LiOH \cdot H_2O$ in DMSO at 100 °C, followed by hydrolysis using HCl in THF (93% yield over the two steps). Lemieux–Johnson oxidative cleavage ($NaIO_4$, $K_2OsO_4 \cdot 2H_2O$, NMO), followed by $NaBH_4$ reduction afforded the primary alcohol **155** in 95% yield. A modified Heck reaction between **155** and 2-methyl-3-buten-2-ol produced the diol **156** in 80% yield (based on recovered starting material). Mesylation (MsCl, NEt_3) of the diol **156** resulted in the formation of hexacyclic mesylate **157** in 63% yield, with the G-ring being formed by an allylic substitution reaction. Addition of sodium azide to mesylate **157** gave the azide, which upon treatment with tributylphosphine in toluene at 80 °C underwent a Staudinger reaction and the resulting amine spontaneously cyclized to generate the amidine **158** in 82% yield. It is speculated that the lactam is in fact a twisted amide and thus, the carbonyl group would be more reactive. To complete the synthesis, the amidine **158** was reduced with $NaBH_4$, followed by treatment with TFA to afford (−)-communesin F (**136**) in 73% yield for the 2 steps.

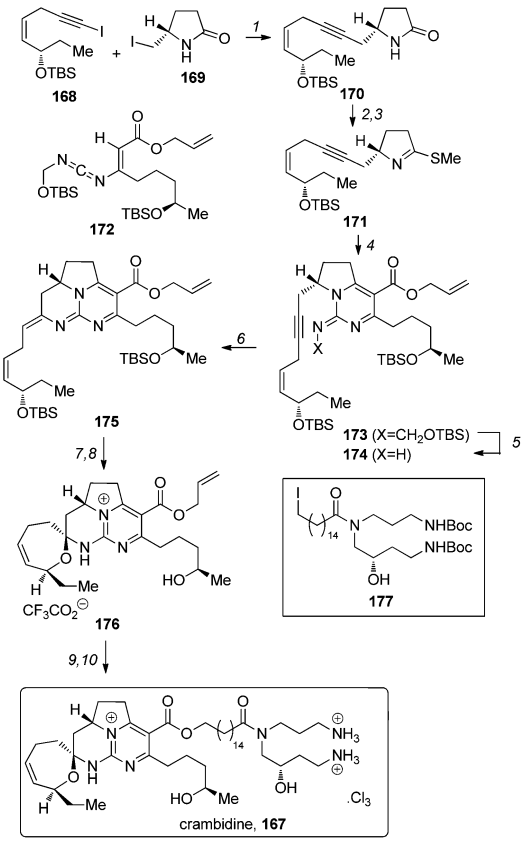
Qin and coworkers have reported a 17 step total synthesis of (+)-perophoramidine (**159**), which allowed the absolute configuration to be confirmed (Scheme 15).[43] The key reaction in the synthesis was an intermolecular hetero-Diels–Alder reaction which was used to assemble the heterocyclic core. The chiral diene precursor **160** was prepared in 7 steps, starting from 6-bromoisatin (**161**). Isatin **161** was allylated with allylmagnesium bromide and the resulting alcohol was silylated (TBSOTf, 2,6-lutidine, 97%). Ozonolysis of the alkene, followed by a two step reductive amination using (*S*)-*t*BuSONH$_2$ and $NaBH_4$ afforded the chiral amine **162** in 64% overall yield. The oxindole nitrogen in **162** was protected (Boc_2O, NaOH, 87%) and upon treatment with TBAF, the lactam ring was opened to afford alcohol **160** in 84% overall yield. The hetero-Diels–Alder reaction was initiated by firstly reacting **160** with $SOCl_2$ in pyridine to form the unstable chloride, which was treated with 3 equivalents of indole **163** and 4.5 equivalents of $AgClO_4$ at −78 °C in toluene to afford the Diels–Alder adduct **164** as a 92 : 8 mixture of diastereomers (88% yield). These adducts were readily separable. The observed stereochemistry of the major adduct **164** would indicate that the Diels–Alder proceeds *via* an *exo* addition with the *in situ* generated *trans*/*trans* diene. Chlorination (NaClO, HOAc, MeOH, −40 °C, 91%) of **164** introduced the two chloro atoms



Scheme 15 The Qin synthesis of (+)-perophoramidine, **159**. *Reagents and conditions*: (1) $CH_2{=}CHCH_2MgBr$, Et_2O, rt, 88%; (2) TBSOTf, 2,6-lutidine, CH_2Cl_2, rt, 97%; (3) O_3, Me_2S, CH_2Cl_2, −78 °C → 0 °C, 84%; (4) (*S*)-*t*BuSONH$_2$, $KHSO_4$, PhMe, 50 °C, 85%; (5) $NaBH_4$, MeOH, 0 °C, 85%; (6) Boc_2O, NaOH, CH_2Cl_2, rt, 87%; (7) TBAF, THF, rt, 90%; (8) $SOCl_2$, pyridine, CH_2Cl_2, 0 °C; (9) $AgClO_4$ (4.5 equiv.), **163** (1 equiv.), **162** (3 equiv.), PhMe, −78 °C, 88% (over 2 steps), d.r. 11 : 1; (10) NaClO, HOAc, MeOH, −40 °C, 91%; (11) PCC, CH_2Cl_2, rt, 89%; (12) Et_3OBF_4, *i*Pr_2NEt, CH_2Cl_2, rt, 85%; (13) $MeNH_2$, MeOH, rt; (14) $CHCl_3$, reflux, 77% (over 2 steps); (15) MnO_2, CH_2Cl_2, rt, 76%; (16) PPTS (0.5 equiv.), $CHCl_3$, reflux, quant.; (17) MeOTf, NaHMDS, THF, −78 °C, 73%.

and simultaneously caused the cleavage of the *t*-butylsulfinyl group. Oxidation with PCC, followed by treatment with Et_3OBF_4 and *i*Pr_2NEt afforded imidate **165** in 76% yield for the 2 steps. Removal of the phthalimide and formyl groups was achieved with methylamine in methanol and the resulting material was heated in chloroform to afford amidine **166** in 77% yield over 2 steps. Conversion of **166** to (+)-perophoramidine (**159**) was achieved in 3 steps and 56% overall yield. Oxidation of the aminal group in **166** with manganese dioxide, followed by heating with 0.5 equivalents of PPTS in $CHCl_3$ generated the thermodynamically favoured amidine and this was selectively methylated by reaction with methyl triflate and NaHMDS in THF at −78 °C to generate (+)-perophoramidine (**159**).

(−)-Crambidine (**167**) is a member of a class of alkaloids which are characterised by a polycyclic guanidine core linked to a hydroxyspermidine by a linear ω-hydroxy fatty acid. Gin and coworkers have completed a convergent synthesis of this molecule, utilising a [4 + 2] thioimidate-vinyl carbodiimide annulation and an intramolecular alkyne-guanidine hydroamination to assemble the target (Scheme 16).[44] Alkynyl iodide **168** was coupled to alkyl iodide **169** *via* a copper-mediated process to generate alkyne **170** in 85% yield. Conversion to the thioimidate **171** was achieved in 89% yield by carbonyl thionation with Lawesson's reagent and *S*-alkylation (MeI, K_2CO_3, THF). The key [4 + 2] annulation of **171** with vinyl carbodiimide



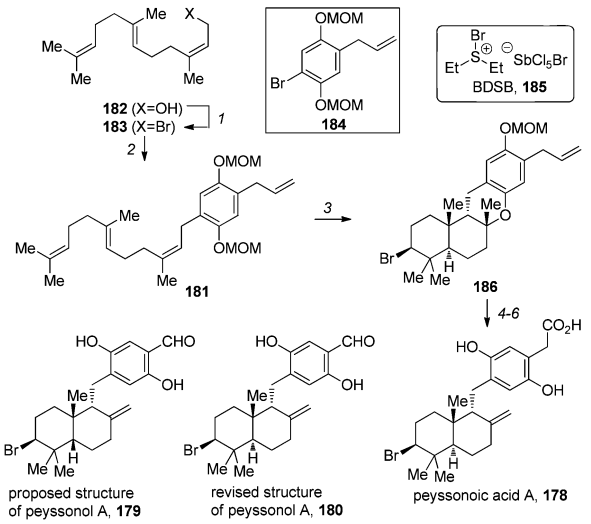
Scheme 16 Gin's synthesis of (−)-crambidine, **167**. *Reagents and conditions*: (1) **169**, Zn, DMF, 0 °C; CuCN, LiCl, THF, DMF, −40 °C → rt; add **168**, −40 °C → rt, 54%; (2) Lawesson's reagent, THF, 0 °C, 94%; (3) MeI, K_2CO_3, THF, 95%; (4) **172** (2 equiv), $ClCH_2CH_2Cl$, 65%; (5) NH_4F, MeOH, 79%; (6) $AuCl_3$, MeCN, 40 °C, 78%; (7) *p*-TsOH·H_2O, MeCN, 77%; (8) $Pd(PPh_3)_4$, pyrrolidine, MeCN, 81%; (9) **177**, Cs_2CO_3, DMF, 88%; (10) HCl, Et_2O, 0 °C, 77%.

172 was carried out by stirring 2 equivalents of **172** with **171** at room temperature and afforded the bicyclic pyrimidine **173** in 65% yield. Removal of the CH_2OTBS group was achieved by treatment of **173** with ammonium fluoride and the resulting aminopyrimidine **174** was exposed to 10 mol% $AuCl_3$ at 40 °C to trigger the intramolecular alkyne hydroamination. The tricyclic pyrimidine **175** was formed in 78% yield and as a single stereoisomer.

Formation of the spiroaminal **176** was achieved by exposure of **175** to *p*-TsOH in acetonitrile and this also removed the secondary TBS ether. To complete the synthesis the attachment of the sidechain was required and this was achieved by deprotection of the allyl ester **176** by reaction with $Pd(PPh_3)_4$, formation of the cesium carboxylate (Cs_2CO_3, DMF, 88%) and selective reaction with iodide **177** to generate the Boc protected crambidine in 55% yield. Removal of the Boc protecting groups with HCl in ether generated (−)-crambidine (**167**) in 77% yield.

6 Total syntheses of other compounds

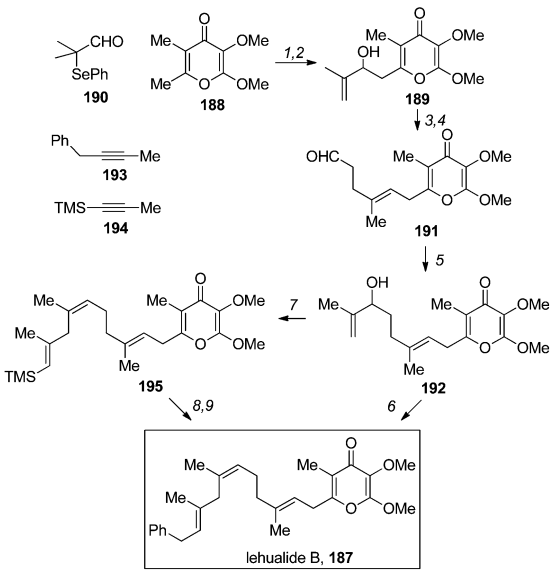
Snyder and coworkers have reported a total synthesis of peyssonoic acid A (**178**), which was originally isolated from a marine alga (Scheme 17).[45] The synthesis resulted from an investigation



Scheme 17 The Snyder synthesis of peyssonoic acid A, **178**. *Reagents and conditions*: (1) PBr_3 (0.5 equiv.), Et_2O, −20 → 0 °C; (2) **184** (1.7 equiv.), *n*BuLi (2.5 M in hexanes, 1.7 equiv.), THF, −78 °C, then **183**, −40 → 5 °C, 74% (over 2 steps); (3) BDSB (**185**), (1.1 equiv.), $MeNO_2$, 31%; (4) OsO_4 (0.2 equiv), $NaIO_4$ (5 equiv), pyridine (3 equiv), THF/*t*BuOH/H_2O (4/1/3), 0 → rt, 89%; (5) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, THF/*t*BuOH/H_2O (5/2/3), 0 °C, 81%; (6) BCl_3 (1 M in CH_2Cl_2, 6 equiv), CH_2Cl_2, −78 °C, 72%.

into direct halonium-induced polyene cyclizations using reagents developed in the Snyder laboratory. This work has also lead to the revision of the structure of peyssonol A (**179** to **180**). The key polyene cyclization substrate **181** was prepared in two steps from (2*Z*,6*E*)-farnesol (**182**). Reaction of **182** with PBr_3 generated bromide **183**, which was treated with the lithio reagent generated by reaction of bromide **184** with *n*BuLi at −78 °C to afford the cyclization precursor **181** in 74% yield over the two steps. Exposure of **181** to bromodiethylsulfonium bromopentachloroantimonate (BDSB) (**185**) in nitromethane for 5 min. at −25 °C generated tetracycle **186** in 31% yield. This represents a cyclization efficiency of 68% per ring. To complete the synthesis, three steps were required. The alkene functionality was converted to a carboxylic acid *via* a Lemieux–Johnson oxidation/Pinnick oxidation (72% yield for the two steps) and then the compound was treated with an excess of BCl_3 in CH_2Cl_2 at −78 °C, which removed the protecting group and cleaved the C–O bond at C8 to afford peyssonoic acid A (**178**) in 72% yield.

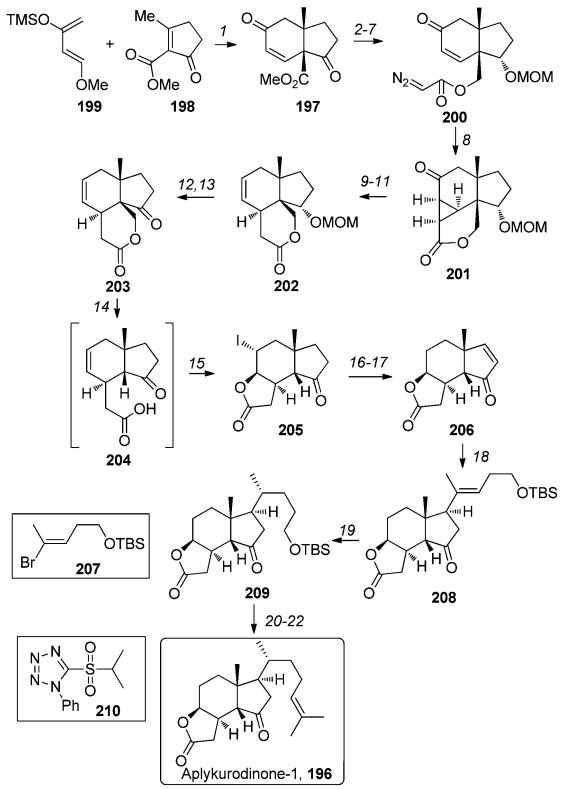
Jeso and Micalizio[46] have reported an 8 step protecting group free synthesis of the potent anti-cancer natural product lehualide B (**187**) (Scheme 18). The bis-trisubstituted diene moiety was introduced late in the synthesis and a titanium-mediated reductive cross-coupling of an alkyne with an allylic alcohol was used in its construction. Pyrone **188** was assembled in three steps from readily available materials and in 16% overall yield. Conversion of pyrone **188** to allylic alcohol **189** was achieved by metallation of pyrone **188** with LiHMDS and reaction with aldehyde **190** (78%), followed by oxidation and *syn*-elimination (*m*CPBA, then NEt_3, 94%). The trisubstituted alkene **191** was generated in 90% yield by a Claisen rearrangement (PhMe, 150 °C) on the enol ether formed when alcohol **189** was reacted



Scheme 18 Jeso and Micalizio's synthesis of lehualide B, **187**. *Reagents and conditions*: (1) LiHMDS (2 equiv), THF, −78 °C, then **190**, THF, 0 °C, 78%; (2) *m*-CPBA (1 equiv), CH_2Cl_2, −10 °C, then NEt_3, 0 °C → rt, 94%; (3) $Hg(OTFA)_2$ (1.2 equiv), $EtOCH{=}CH_2$ (excess), 97%; (4) PhMe, 150 °C, 93%, 10 : 1 *E* : *Z*; (5) 2-propenylmagnesium bromide (1.05 equiv), THF, −78 → −25 °C, 59%; (6) LiHMDS (1 M in THF, 2 equiv), THF, −78 °C, then **193** (6 equiv), PhMe, −78 °C, followed by $ClTi(OiPr)_4$ (1 M in hexanes, 6 equiv), *c*-C_5H_9MgCl (1.97 M in Et_2O, 12 equiv), −78 → 0 °C, 50%, d.r. = 1.3 : 1; (7) **194** (4 equiv), $ClTi(OiPr)_4$ (4 equiv., 1 M in hexanes), *c*-C_5H_9MgCl (1.97 M in Et_2O, 8 equiv), PhMe, −78 → −40 °C, then added to dianion of **192** [LiHMDS (1 M in THF, 2.5 equiv), THF, −78 °C], 61%, 7 : 1 *E* : *Z*; (8) NIS (2 equiv), $ClCH_2CN$: EtOAc (2 : 1), 93%; (9) BnZnBr (0.5 M in THF, 2 equiv), $Pd(PPh_3)_4$ (15 mol%), THF, 68%.

with ethyl vinyl ether and mercury trifluoroacetate. Addition of 2-propenylmagnesium bromide to aldehyde **191** afforded the allylic alcohol **192** in 59% yield. The lithium dianion of **192** was generated by using two equivalents of LiHMDS and reacted with the Ti-alkyne complex (formed by reaction of alkyne **193** with $ClTi(OiPr)_3$ and *c*-C_5H_9MgCl) to afford lehualide B (**187**) in 50% yield. However, the regiocontrol was poor and a 1.3 : 1 mixture of isomers was produced. To overcome this, the reductive cross-coupling of TMS-propyne (**194**) with allylic alcohol **192** was carried out and it was found that this reaction was much more successful, affording the vinyl silane **195** in 61% yield and with excellent control of the alkene geometry. Lehualide B (**187**) was synthesised in 63% yield by converting the vinylsilane **195** to the iodide using NIS and carrying out a palladium-cross coupling with benzylzinc bromide.

Zhang and Danishefsky have reported a 22 step synthesis of aplykurodinone-1 (**196**), which is an example of a highly degraded marine steroid (Scheme 19).[47] The *cis*-fused hydrindane **197** was readily prepared in 73% yield *via* an anionically mediated cycloaddition of the enolate derived from **198** with diene **199**. Attempts to utilise dienophile **198** in the cycloaddition were not successful. After a series of functional group manipulations, **197** was transformed into diazoacetate **200** in 47% overall yield. Intramolecular cyclopropanation of **200**, using a copper catalyst, provided the cyclopropane **201** in a modest 40% yield. Transformation to the required lactone **202** was achieved by firstly reducing the ketone under Luche



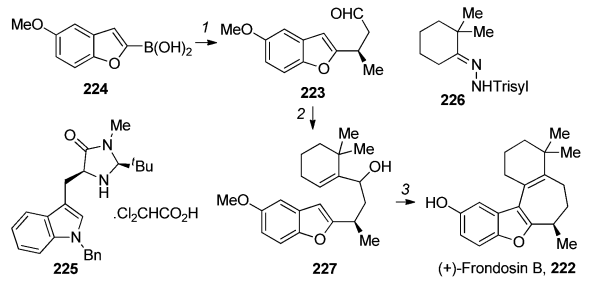
Scheme 19 The Danishefsky synthesis of aplykurodinine, **196**. *Reagents and conditions*: (1) (a) MeLi, DME/THF, −50 °C; TFA, $CHCl_3$, reflux, 73%; (2) $HSCH_2CH_2SH$, AcOH, *p*-TSA, 74%; (3) $NaBH_4$, CH_2Cl_2/MeOH, −78° → −40 °C; (4) MOMCl, iPr_2NEt, CH_2Cl_2, 84% (over two steps); (5) DIBAL-H, CH_2Cl_2, −78 °C; (6) $Tl(NO_3)_3$, MeOH/THF/H_2O, 95% (over 2 steps); (7) $TsNHN{=}CHCOCl$, $PhNMe_2$, Et_3N, CH_2Cl_2, 0 °C, 88%; (8) bis-(*N*-*tert*-butylsalicylaldiminato) copper(II), PhMe, reflux, 40%; (9) $NaBH_4$, $CeCl_3 \cdot 7H_2O$; (10) I_2, PPh_3, imidazole, PhMe, reflux, 78% (over two steps); (11) SmI_2, THF/MeOH, 85%; (12) HCl, THF/H_2O; (13) DMP, CH_2Cl_2, 80% (over two steps); (14) K_2CO_3, H_2O, 100 °C; (15) NIS, CH_2Cl_2, 75%; (16) Ra–Ni, CH_2Cl_2/EtOH, 90%; (17) TMSOTf, Et_3N, CH_2Cl_2, 0 °C; $Pd(OAc)_2$, CH_3CN, 76% (90% brsm). (18) **207**, *t*-BuLi, CuCN, $BF_3 \cdot OEt_2$, −78 → −98 °C, 73%, d.r. = 10 : 1; (19) Crabtree catalyst, H_2, CH_2Cl_2, 50%; (20) HF, CH_3CN/THF; (21) DMP, CH_2Cl_2, 87% (over two steps); (22) THF, LiHMDS, −78 °C, 68%. (23) **210**, *t*-BuLi, CuCN, Et_2O, −78 °C, 51%; (24) Wilkinson catalyst, H_2, benzene, 67%.

conditions ($NaBH_4$, $CeCl_3$), then converting the resulting alcohols to the iodides by reaction with I_2, PPh_3 and imidazole. Ring opening of the cycloproprane moiety was achieved in 85% yield by reaction with SmI_2. Conversion to the lactone **203** was achieved in 80% yield by removal of the MOM group (HCl, THF/H_2O) and oxidation with Dess–Martin periodinane. This sequence effectively delivers the correct stereochemical relationship between C7 and C3. The redundant oxymethylene group was removed by a hydrolysis/retroaldol process which was triggered by exposure of **203** to potassium carbonate in water at 100 °C to afford **204**. The resulting intermediate **204** was not isolated but treated with NIS to effect an iodolactonisation and provide **205** in 75% overall yield from **203**. Reaction with RANEY® nickel in CH_2Cl_2 and ethanol removed the iodo group and a Saegusa oxidation (TMSOTf, NEt_3, then $Pd(OAc)_2$, MeCN) generated the enone **206** in 68% yield for the two steps.

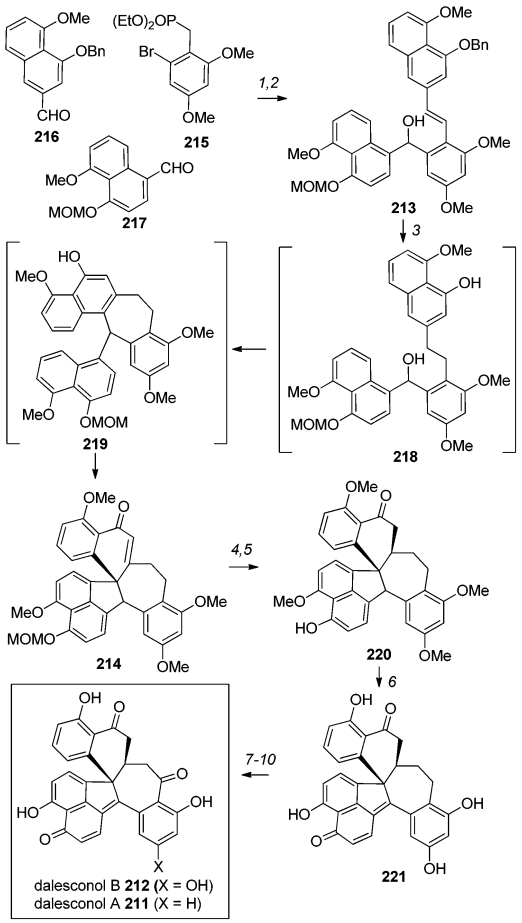
The side-chain at C11 was added by using a BF_3-mediated conjugate addition of the cuprate derived from vinyl bromide

207 and this provided ketone **208** in 73% yield (d.r. 10 : 1). Homogenous hydrogenation of **208** with Crabtree's catalyst and H_2 reduced the trisubstituted alkene and provided **209** in 50% yield (d.r. > 5 : 1). To complete the synthesis, the following sequence was employed: the TBS group was removed (HF), the resulting primary alcohol was oxidised with Dess–Martin periodinane, and the final carbons added by carrying out a modified Julia olefination with sulfone **210**. This three step sequence generated aplykurodinone-1 (**196**) in 59% yield.

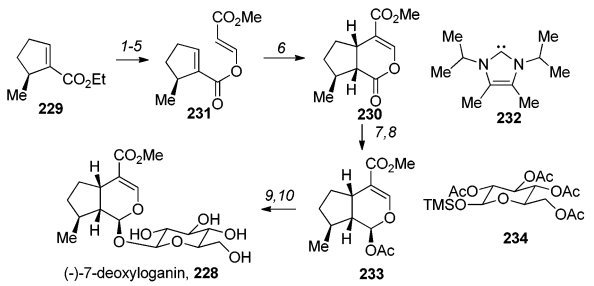
Dalesconol A (**211**) and B (**212**) are unique natural products that have been found to have immunosuppressive properties comparable to cyclosporine A, which is used in the clinic. Snyder and coworkers have developed a strategy which allows the synthesis of these molecules, as well as access to analogs (Scheme 20).[48] To prepare dalesconol B (**212**), Snyder decided to prepare secondary alcohol **213** and convert it into the core of dalesconol B **214** in a single, cascade process. Access to **213** was readily achieved in 2 steps and 58% yield using a Horner–Wadsworth–Emmons olefination between phosphonate **215** and aldehyde **216**, followed by generation of a lithio species (*via* halogen-Li exchange with *n*-BuLi) and addition to aldehyde **217**. The cascade sequence involves 4 distinct operations and was initiated by hydrogenation of **213** with 1 equivalent of 10% Pd/C in an atmosphere of H_2, and after the benzyl protecting group has been removed and the double bond hydrogenated, the reaction was filtered and the solvent removed. Addition of one equivalent of TFA in 2,2,2-trifluoroethanol to **218** caused the ionization of the secondary alcohol and initiated a Friedel–Crafts reaction to form the seven-membered ring **219**. To complete the cascade, 1.1 equivalents of iodobenzene diacetate was added at −45 °C and this lead to the formation of the final ring and the formation of the dalesconol core **214** in 32% overall yield. Selective hydrogenation of the alkene **214** was achieved with careful selection of solvents (EtOAc/EtOH 3 : 1) and the resulting ketone was treated with concentrated HCl in THF to remove the MOM group and produce naphthol **220** in 83% yield for the 2 steps. The use of DDQ oxidised **200** into the *para*-quinone methide and this was immediately reacted with BBr_3 to produce the tetrol **221** in 73% yield for the 2 steps. It



Scheme 21 The MacMillan synthesis of (+)-frondosin B, **222**. *Reagents and conditions*: (1) crotonaldehyde, 20 mol % (S,S)-**225**.DCA, HF (1 equiv.), EtOAc, rt, 84%, 93% ee; (2) **226**, *n*BuLi, THF, −78 °C; then **223**, 86%; (3) BBr_3 (3.5 equiv.), CH_2Cl_2, −78 °C → 0 °C, 66%.



Scheme 20 The Snyder syntheses of dalesconol B, **212**. *Reagents and conditions*: (1) KO*t*Bu (1.0 M in THF, 1.1 equiv), THF, −78 °C, then **216** (1.0 equiv), −78 °C → rt, 87%; (2) *n*BuLi (1.6 M in hexanes, 1.5 equiv), THF, −78 °C; then **217** (2.0 equiv), −78 °C → rt, 67%; (3) H_2 (1 atm), Pd/C (10%, 1 equiv), EtOAc/EtOH (2 : 3); filter, solvent removal, then TFA (1.0 equiv), CF_3CH_2OH, −45 °C, 15 min.; then $PhI(OAc)_2$ (1.1 equiv), −45 °C, 32%; (4) H_2 (1 atm), Pd/C (10%, 1.0 equiv), EtOH/EtOAc (3 : 1) 84%; (5) conc. HCl (40 equiv), THF, 0 °C → rt 99%; (6) DDQ (0.97 equiv), CH_2Cl_2, −78 °C, BBr_3 (1.0 M in CH_2Cl_2, 25 equiv), −78 °C → 0 °C, 73%; (7) KHMDS (0.5 M in THF, 5.0 equiv), MOMCl (20 equiv), THF, 0 °C, 91%; (8) $Pd(OAc)_2$ (1.0 equiv), *t*BuOOH (25 equiv), K_2CO_3 (10 equiv), CH_2Cl_2, 42%; (9) Dess–Martin periodinane (5.0 equiv), $NaHCO_3$ (10 equiv), CH_2Cl_2, 99%; (10) BBr_3 (1.0 M in CH_2Cl_2, 25 equiv), CH_2Cl_2, −78 °C, 73%.



Scheme 22 The Candish and Lupton synthesis of (−)-7-deoxyloganin, **228**. *Reagents and conditions*: (1) aq. KOH, DMSO, rt; (2) cat. DMF, $(COCl)_2$, CH_2Cl_2, rt, 68% (over 2 steps); (3) *t*-butyl formyl acetate, *i*Pr_2NEt, 0 °C, 89%; (4) TFA, CH_2Cl_2, rt; (5) $TMSCHN_2$, $CHCl_3$, 0 °C, 78% (over 2 steps); (6) 20 mol % **232**, THF, −78 C rt, 63%, 97% ee; (7) $NaBH_4$, MeOH, 0 C; (8) Ac_2O, pyridine, DMAP, CH_2Cl_2, 0 °C, 41% (over 2 steps); (9) **234**, cat. TMSOTf, MeCN, −30 °C; (10) MeOH, NEt_3, H_2O, rt, 43% (over 2 steps).

Table 1 First total syntheses of marine natural products reported in 2010

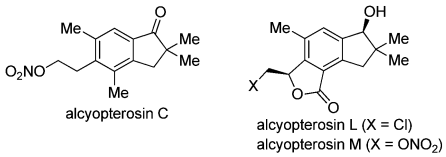
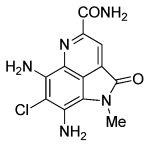
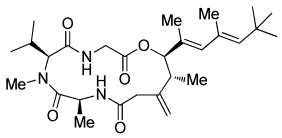
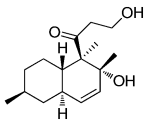
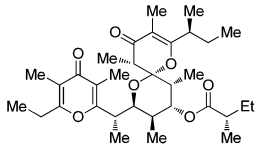
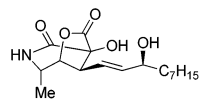
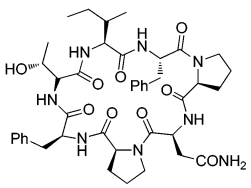
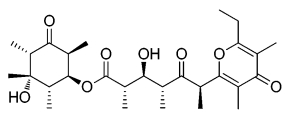
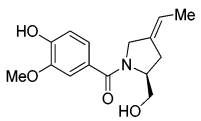
Compound	Reference	Notes
Alcyopterosin C, L and M  alcyopterosin C alcyopterosin L (X = Cl) alcyopterosin M (X = ONO_2)	Welsch *et al.*[51]	• alcyopterosin L and M –12 steps from ethyl 2-methylpropionate • alcyopterosin L and M –10 and 6% overall yields • alcyopterosin C: cytotoxicity against HT29 cell line
Ammosamide B  Ammosamide B	Hughes and Fenical,[52] Reddy *et al.*[53]	• Hughes and Fenical – first synthesis, prepared all the ammosamides; 17–19 steps from 4-chloroisatin • Reddy *et al.* – 9 steps and 6.9% overall yield
Antillatoxin 	Okura *et al.*[54]	• 16 steps from *E*-2-methyl-3-iodoprop-2-enal • 10% overall yield • VGSC activator
(+)-Aspermytin A 	Inuoe *et al.*[55]	• 24 steps from (−)-citronellal • 9.7% overall yield • neurotrophic effect on rat PC2 cells
Auripyrone B 	Hayakawa *et al.*[56]	• 20 steps from known epoxide • 8% overall yield • potent cytotoxicity against HeLa S_3 cell line • absolute configuration
(+)-Awajanomycin 	Fu *et al.*[57]	• 13 steps from known compound • 3.8% overall yield • cytotoxicity against A549 cell line
Axinellin A 	Fairweather *et al.*[58]	• 2 steps from linear peptide precursors • original isolation reported *in vitro* anti-tumor activity but synthetic material is inactive in same assays
Baconipyrone A 	Beye and Ward[59]	• 9 steps from readily available starting material
Barmumycin 	Lorente *et al.*[60]	• revised structure • 5 steps from commercially available starting material • 18% overall yield • cytotoxic against human tumor cell lines

Table 1 (*Contd.*)

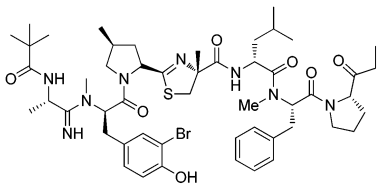
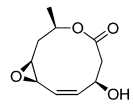
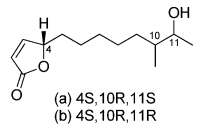
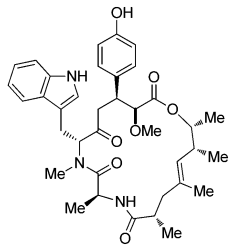
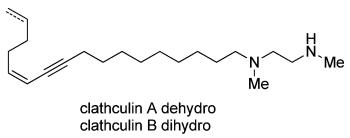
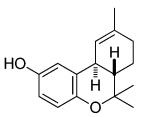
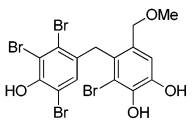
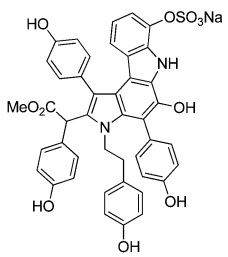
Compound	Reference	Notes
Bisebromoamide 	Gao *et al.*[61]	• 14 steps (longest linear sequence), starting from chiral propionate • assigned absolute configurations • cytotoxic against K562 and P388 cell lines
Botryolide B 	Reddy and Meshram[62]	• 10 steps (longest linear sequence), starting from homoallyl alcohol • 11% overall yield
Butenolides  (a) 4S,10R,11S (b) 4S,10R,11R	Wang and Dai[63]	• 14 steps (longest linear sequence), starting from chiral propionate • assigned absolute configurations • cytotoxic against K562 and P388 cell lines
Chondramide A 	Schmauder *et al.*[64]	• 11 steps from known compound • 3.9% overall yield • cytotoxic against various cancer cell lines
Clathculins A and B  clathculin A dehydro clathculin B dihydro	Hoye *et al.*[65]	• clathculin A – 9 steps (longest linear sequence) from known compound • clathculin B – 5 steps (longest linear sequence) from known compound • dependence of NMR spectroscopic data as a function of protonation state
(+)-Conicol 	Hong *et al.*[66]	• 9 steps (longest linear sequence) from known compound • anti-proliferative activity against human ALL cells • established absolute configuration
3,4-Dibromo-5-[2-bromo-3,4-dihydroxy-6-(methoxymethyl)-benzyl]benzene-1,2-diol 	Akbaba *et al.*[67]	• 5 steps from known compound • 34% overall yield • various biological activities
Dictyodendrin A 	Okano *et al.*[68]	• 21 steps (longest linear sequence), starting from *p*-nitrophenol • 8.2% overall yield • telomerase inhibitor

Table 1 (*Contd.*)

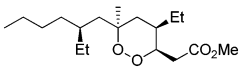
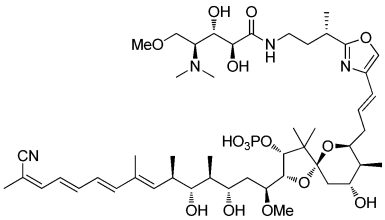
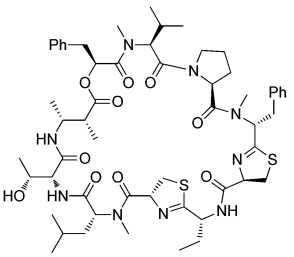
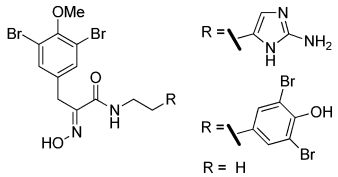
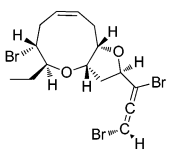
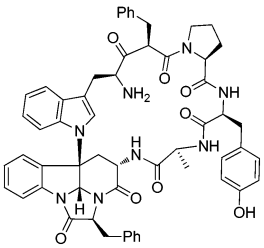
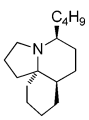
Compound	Reference	Notes
9,10-Dihydroplakortin 	Gemma *et al.*[69]	• 17 steps from known compound • activity against malaria and cancers
Enigmazole A 	Skepper *et al.*[70]	• 22 steps (longest linear sequence), starting from known compound • 0.41% overall yield • selectively target aberrant C-Kit signal • cytotoxic against IC-2 mast cells
Grassypeptolide 	Liu *et al.*[71]	• 12 steps (longest linear sequence), starting from known compound • 11% overall yield • inhibits HeLa and HT29 cell growth
Ianthelline, 5-bromoverongamine and JBIR-44 	Shearman *et al.*[72]	• 5 steps from commercially available benzaldehyde • activity against HeLa cell line; antibacterial and antifungal activity
Revised structure of (+)-Itomanallene A 	Jeong *et al.*[73]	• first asymmetric total synthesis • structure revision
Kapakahine E 	Espejo and Rainier[74]	• 17 steps from known compound • 4% overall yield • cytotoxic against P388 murine leukemia cell line
Lepadiformine C 	Meyer *et al.*[75]	• 9 steps from known compound • 10% overall yield • potassium ion channel blockers

Table 1 (*Contd.*)

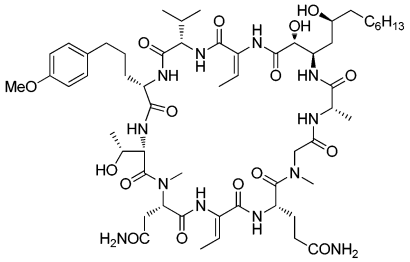
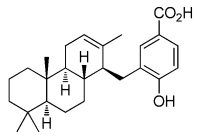
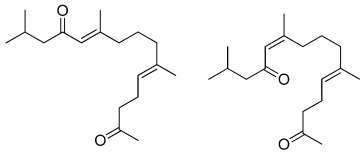
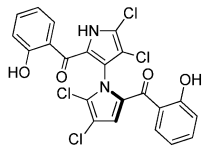
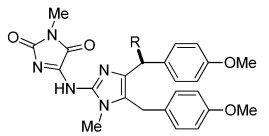
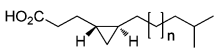
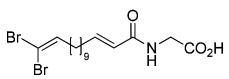
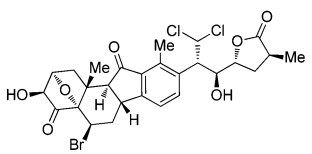
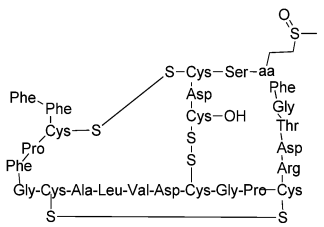
Compound	Reference	Notes
Largamide H 	Liang *et al.*[76]	• 10 steps (longest linear sequence), starting from known compound • 5% overall yield • cytotoxic against HCT116 cell lines
(+)-Makassaric acid 	Basabe *et al.*[77]	• 9 steps (longest linear sequence) from known compound • inhibitor of protein kinase MK2 • controls antiflammatory processes
Marine farnesylacetones 	Oh *et al.*[78]	• 9 steps from known compound • vasodilation
(±)-marinopyrrole 	Cheng *et al.*[79]	• 9 steps from known compound • 30% overall yield • cytotoxic against HCT116 cell line and antibiotic activity
14-Methoxynaamidine G and naamidine G  Naamidine G (R=H) 14-Methoxy naamidine G (R=OMe)	Koswatta and Lovely[80]	• 8 steps from 4,5-diiodo-1-methylimidazole • 14-methoxynaamidine G: 4.8% overall yield • naamidine G: 41% overall yield
(±)-17-methyl-*trans*-4,5-methyleneoctadecanoic acid 	Carballeira *et al.*[81]	• 8 steps from 1-bromo-12-methyltridecane • 9% overall yield • *cis*-isomer has moderate antileishmanial activity
Motualevic acid 	Cheruku *et al.*[82]	• 12 steps from known compound • 31% overall yield • antimicrobial activity
Nakiterpiosinone 	Gao *et al.*[83]	• 21 steps from known compound • 5% overall yield • blocks Hedgehog pathway responses
Neopetrosiamindes 	Liu *et al.*[84]	• 4 steps from linear peptide • revised structure • inhibitor of human tumor cell invasion in cancer metastasis

Table 1 (*Contd.*)

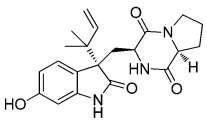
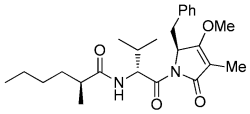
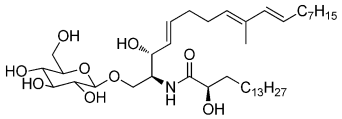
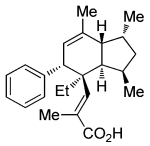
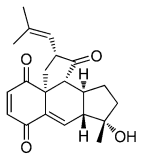
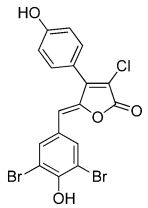
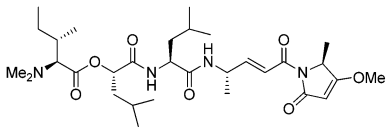
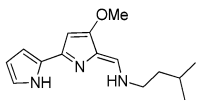
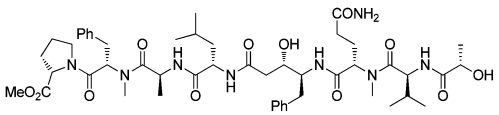
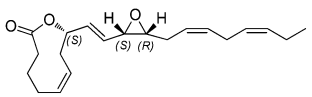
Compound	Reference	Notes
Notoamide J 	Finefield and Williams[85]	• 15 steps from commercially available starting material • 0.78% overall yield • wide range of biological activity
Palau'imide 	Lan *et al.*[86]	• 9 steps from readily available material • 15% overall yield • activity against KB and LoVo cell lines
Phalluside-1 	Black and Kocienski[87]	• 18 steps from (*E*)-1-iodononene
Plakotenin 	Arzt *et al.*[88]	• 13 steps from chiral propionate • moderate cytotoxicity • reduces proliferation of rheumatoid synovial fibroblasts
(±)-Rossinone B 	Zhang *et al.*[89]	• 13 steps from readily available material • biomimetic strategy • anti-proliferative against P388 cell line
Rubrolide L 	Boukouvalas and McCann[90]	• 4–5 steps from 3-chlorotetronic acid • 37–42% overall yield • inhibits human ALR2 at submicromolar levels
Symplostatin 4 	Conroy *et al.*[91]	• 7 steps from Boc-L-Ala-OH • confirmed absolute configuration • significant anti-malarial activity (ED_{50} 74 nM)
Tambjamine K 	Aldrich *et al.*[92]	• 3 steps from readily available material • 18% overall yield • activity against HCT116 breast carcinoma cell line
Tasiamide B 	Sun *et al.*[93]	• 10 steps (longest linear sequence) from readily available material • 9.9% overall yield • cancer cell line data does not match original isolation report
ent-Topsentolide A_1 	Kobayashi *et al.*[94]	• 15 steps from known aldehyde • determined absolute configuration

Table 2 New total syntheses of marine natural products previously prepared that were reported in 2010

Compound	Reference	Compound	Reference
Aspergillides A and B	Fuwa *et al.*[95]	Lycogarubin C	Fu and Gribble[96]
Aciphyllene	Srikrishna and Pardeshi[97]	(±)-Marinopyrrole	Kanakis and Sarli[98]
Auripyrone B	Jung *et al.*[99]	Meridianins	Tibiletti *et al.*[100]
Bengazole A	Chandrasekhar and Sudhakar[101]	(+)-Nakadomarin A	Inagaki *et al.*[102]
(−)-Brevenal	Crimmins *et al.*[103]	Naamines A, C, E–G and leucettamine A	Ermolat'ev *et al.*[104]
(−)-brevisamide	Tsutsumi *et al.*[105]	(+)-Neopeltolide	Fuwa *et al.*,[106] Yadav *et al.*[107]
Callipeltoside A	Hoye *et al.*[108]	(−)-Neopeltolide	Martinez-Solorio and Jennings[109]
(±)-$\Delta^{9,12}$-Capnellene	Hsu *et al.*[110]	Okadaic acid	Fang *et al.*[111]
Cladiellins (Eunicellins)	Clark *et al.*[112]	Palmerolide A	Gowrisanker *et al.*[113]
Cortistatin	Simmons *et al.*[114]	Pestalone	Slavov *et al.*[115]
Ent-Cycloorodin	Mukherjee *et al.*[116]	Purpurone	Li *et al.*[117]
Cylindrocyclophanes A and F	Nicolaou *et al.*[118]	Salinosporamide A	Ling *et al.*,[119] Nguyen *et al.*[120]
(−)-Dactylolide	Zurwerra *et al.*[121]	Solandelactone E	Robinson and Aggarwal[122]
Dictyodendrin B	Hirao *et al.*[123]	Spisulosine	Dinda *et al.*,[124] Amarante *et al.*,[125] Ghosal and Shaw[126]
Emericellamide B	Mohapatra *et al.*[127]	(−)-Spongidepsin	Zhu *et al.*[128]
Eudistomin U	Panarese and Waters[129]	Sporiolide A	Kumar Reddy *et al.*[130]
Fascaplysin and homofascaplysin C	Waldmann *et al.*[131]	(−)-sporochnol A.	Inokoishi *et al.*[132]
(±)-Frondosin B	Masters and Flynn[133]	Undeca-(1,3*E*,5*E*)-triene, nona-(1,3*E*,5*E*)-triene & octa-(1,3*E*,5*E*)-triene	Dabdoub *et al.*[134]
Irciniastatin A	Watanabe *et al.*[135]	Untenone A	Kunitada *et al.*[136]
Jaspine B	Salma *et al.*,[137] Inuki *et al.*,[138] Yoshimitsu *et al.*[139]	Various 2-aminoimidazole alkaloids	Ando and Terashima[140]
Largazole	Zeng *et al.*[141]	Varitrol	Brichacek *et al.*,[142] Palek *et al.*,[143] Srinivas *et al.*[144]
(+)-Laurencin	Lorente *et al.*[145]	(−)-Zearalenone	Miyatake, Ondozabal and Barrett[146]
(+)-Liphagal	Alvarez-Manzaneda *et al.*,[147] George *et al.*[148]		

was originally planned to carry out a benzylic oxidation on this material, but after extensive experimentation, it was found that reprotection of all the phenols as MOM ethers (KHMDS, MOMCl, THF, 91%) was necessary. Treatment of the resulting tetraether with palladium acetate, *tert*-butylhydroperoxide, K_2CO_3 in CH_2Cl_2 in an open flask for 3 days generated the benzylic alcohol, which was oxidised to the ketone with Dess–Martin periodinane. Removal of the protecting groups was achieved with an excess of BBr_3 in CH_2Cl_2 and afforded dalesconol B (**212**) in 73% yield for the 3 step procedure. This strategy has also been applied to the synthesis of dalesconol A (**211**).

MacMillan and coworkers have reported a three step synthesis of (+)-frondosin B (**222**), which proceeds in 50% overall yield (Scheme 21).[49] MacMillan utilized his organocatalyzed Friedel–Crafts alkylation methodology to generate the chiral aldehyde **223**. This was achieved by reacting commercially available boronic acid **224** with crotonaldehyde in the presence of 20 mol% imidazolidinone catalyst **225**. This procedure went in 84% yield and 93% ee.

The key additive in this experiment was the use of one equivalent of HF, which activated the boronic acid and allowed the aryl transfer to take place. Indeed, the trifluoroborate salt (not shown) can also be used in this protocol. The Shapiro reaction of hydrazone **226** with *n*-BuLi generated a vinyl lithium species which was added to aldehyde **223** at −78 °C and afforded the alcohol **227** in 86% yield. Treatment of the alcohol **227** with 3.5 equivalents of BBr_3 afforded (+)-frondosin B (**222**) in 66% yield after chromatography. This one-pot/one reagent reaction involves an allylic Friedel–Crafts alkylation, demethylation of the methoxy group and an olefin isomerization.

Candish and Lupton have reported a 10 step synthesis of (−)-7-deoxyloganin (**228**) from chiral cyclopentane **229** (Scheme 22).[50] The bicyclic core **230** was assembled using a substrate-directed NHC-catalyzed rearrangement. Readily available **229** was converted to the enol ester **231** in 5 steps and 47% overall yield. Addition of **232** triggered a rearrangement to form the cyclopenta[*c*]pyranone core **230** in 63% yield.

Elaboration to the natural product involved reduction of the lactone moiety and acetylation to afford lactol acetate **233** in 41% yield for the 2 steps. The use of catalytic TMSOTf allowed the glycosylation of **233** with tetraacetate **234** and after deprotection of the acetate groups with MeOH/NEt_3 in water, (−)-7-deoxyloganin (**228**) was obtained in 43% yield for the 2 step sequence.

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.

7 Acknowledgements

I would like to thank Professor John Blunt and Professor Murray Munro (University of Canterbury, Christchurch, New Zealand) for a copy of the 2010 version of the MarinLit database[149] which facilitated data collection for this review.

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