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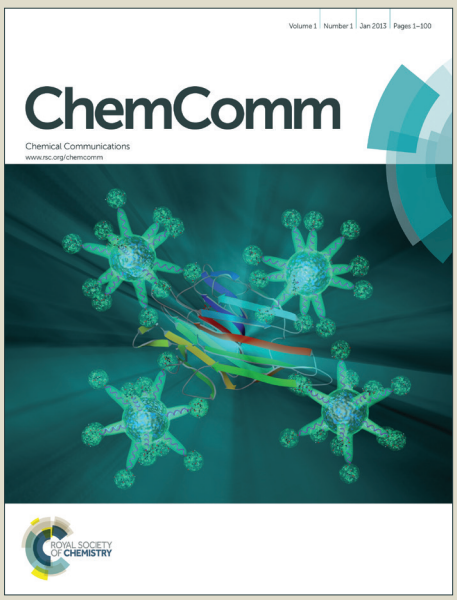

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ARTICLE

Synthetic, Semisynthetic and Natural Analogues of Peloruside A

Cite this: DOI: 10.1039/x0xx00000x

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Received 00th December 2014,
Accepted 00th January 2015

DOI: 10.1039/x0xx00000x

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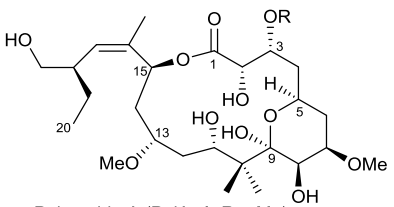
Peloruside A is a macrocyclic natural product from a New Zealand marine sponge *Mycale hentscheli*. It has attracted significant attention in the synthetic chemistry, cellular and structural biology communities due to its complex structure and potent anticancer activity. Several natural congeners have since been isolated and synthetic analogues have been prepared. This review describes in detail the published syntheses of peloruside analogues and discusses the structure-activity relationships available to date.

Introduction

The marine environment is a treasure trove of novel, therapeutically relevant natural products due to the relative lack of exploration of the ocean biota and the potency of the secondary metabolites produced by the mainly sessile inhabitants under high dilution conditions.[1] Cytoskeletal components such as microtubules are found to be targets of many marine natural products, and their necessity in cell division and other essential processes means that compounds that interact with them represent potential cancer leads.[1] One such natural product of interest is peloruside A (PelA, **1**, Figure 1), isolated by Northcote and co-workers from the sponge *Mycale hentscheli* found in the Pelorus Sound on the coast of the South Island of New Zealand.[2] It was found to be potently cytotoxic and cytostatic towards cancer cells.[1,2] PelA is a microtubule-stabilising agent that causes arrest in the G_2/M phase of the cell cycle.[3] It binds to a distinct site on β-tubulin compared to the established microtubule-stabilising agents paclitaxel, docetaxel, epothilone A, ixabepilone and discodermalide, while it shares a binding site with the marine sponge metabolite laulimalide.[4,5,6] The recently published crystal structure of peloruside A bound to β-tubulin unequivocally shows the distinct position of its binding site relative to the taxoid site.[5] The key importance of the pyran substitution pattern present in peloruside A for cross-linking between β-tubulin monomers on adjacent protofilaments of the microtubule is also evident.[5,6] Furthermore, allosteric stabilisation of the M-loop and the taxoid site of β-tubulin by the binding of peloruside A was identified from the crystal structure.[5] These results are consistent with the observed synergistic activity between peloruside A and paclitaxel or epothilone A[7,8] and the microtubule stabilising effect of peloruside A.[3] The physical properties of PelA, together with the distinct binding site, make it attractive as an alternative or combination therapy to circumvent paclitaxel-resistance in tumours.[4]



Peloruside A (PelA, **1**, R = Me)
Peloruside B (**2**, R = H)

Figure 1

The isolation of three further natural congeners of peloruside from *Mycale hentscheli* has been reported.[9,10] Notably, peloruside B (**2**, see Figure 1) has essentially the same structure as PelA, only differing in the lack of the methyl group attached to O3, and has very similar bioactivity.[9] Peloruside C (**3**, Figure 2) differs in the degree of oxygenation at the pyran, containing an enol functionality in place of the hemiacetal and C8 hydroxyl.[10] This change significantly reduces the cytotoxicity but does not wipe it out completely.[10] In peloruside D (**4**), on the other hand, the pyran ring is shifted, with the hemiacetal located

at C7 (resulting from a ketone at C7 in the ring-open form).[10] This has a large negative impact on the inhibitory activity towards cancer cells.[10]

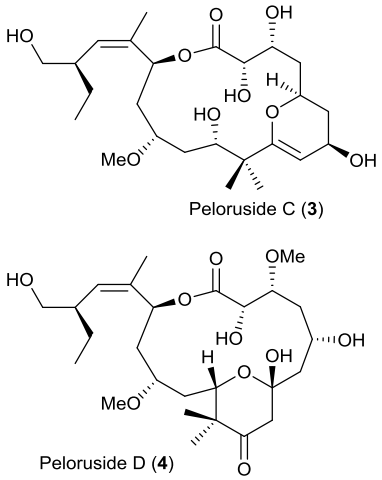


Figure 2

To date, six total syntheses of peloruside A have been reported[11–16] and partially reviewed.[17–19] The polyketide-derived structure of PelA lends itself to aldol methodology, and this is reflected in the synthetic strategies. Furthermore, the macrocyclisations are invariably performed through lactonisation. The first total synthesis, by De Brabander,[11] delivered *ent*-PelA, which served to elucidate the absolute configuration of the natural product. The synthetic strategy involved early formation of the embedded pyranoside in protected form and, ultimately, a Mitsunobu macrolactonisation.[11] The first total synthesis of the natural epitope of PelA was achieved by Taylor and Jin.[12] This, like De Brabander's route, relied upon epoxidation of a γ-pyrone in order to install the C8-C9 oxygenation and continued with a Yamaguchi macrolactonisation.[12] Ghosh's synthesis introduced the use of a reductive aldol coupling between an *iso*-propenyl ketone and an aldehyde to assemble the full carbon skeleton.[13] This, and subsequent syntheses, allowed the pyranose to form spontaneously after final deprotection. Evans' method made significant use of aldol methodology throughout.[14] Jacobsen's total synthesis relied on transition metal catalysis for several key steps, including epoxidations.[15] Hoye's route began with a Sharpless AD-controlled desymmetrisation that led to a selective lactonisation, delivering the C1–C9 fragment.[16] The side-chain was generated by relay ring-closing metathesis of either a silyl acetal, in a manner related to the method developed by Hoberg[20] and later used by us,[21] or an ester, similar to the developments of Ermolenko[22] and De Brabander.[11] A synthesis of peloruside B[9] and fragments pertaining to the peloruside skeleton have also been reported.[20–34]

The preparation of analogues of peloruside A has attracted interest for several reasons. Firstly, structurally simplified variants could facilitate the development of this important preclinical anticancer lead. Secondly, enhanced binding of analogues to the isoforms of β-tubulin[6,35] that are over-expressed in cancer cells could allow selective activity, minimise off-target interactions and avoid the typical undesirable effects of chemotherapy on normal cells. Thirdly, knowledge of the structure-activity relationships provides further understanding about the binding characteristics and mechanism of action of peloruside A. However, the design of active analogues of peloruside A presents a major challenge because the chemical structure of PelA appears to be close to optimal for activity, as demonstrated by the lower cell growth inhibition measured for all known analogues (*vide infra*), including its natural congeners.[9,10] Nonetheless, several analogues of PelA have been prepared, some intentionally, others as side-products or deviations from various synthetic strategies. This review aims to provide the reader with detailed information about the synthetic work that has gone into the preparation of analogues and an overview of the structure-activity relationships being elucidated as a result of these endeavours.

Syntheses of Peloruside A Analogues

The synthetic strategies employed for peloruside analogues are highly varied by virtue of the significantly different target structures. Nonetheless, aldol methodology remains a common theme in these strategies, although less consistently used than in the total syntheses. Dithiane coupling also emerges as a trend in the syntheses of analogue fragments for generation of 1,2- and 1,3-oxygenated species.

As with the total syntheses, lactonisation with Yamaguchi's method remains a popular macrocyclisation strategy. However, ring-closing metathesis is a close second, allowing closure of the carbon skeleton at diverse positions.

The side-chain olefin of synthesised analogues has been generated almost invariably by Wittig type processes including Still-Gennari and Ando olefinations, although Corey-Fuchs and ring-closing metathesis approaches have also been employed.

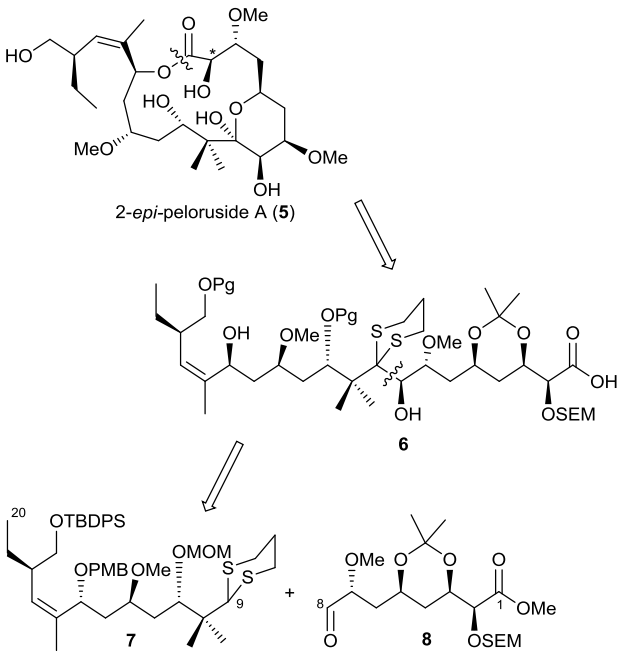
The pyran rings of the analogues have been generated by diverse methods ranging from Prins cyclisation to ring-closing methathesis. Intramolecular alkyne additions, acid-induced condensative cyclisation and oxidative cyclisation have also been applied. As for some total syntheses, allowing the pyranose to form from the fully functionalised macrolactone remains a viable option.

The following sections provide detailed summaries of the peloruside analogue syntheses reported to date.

Stereoisomeric Analogues.

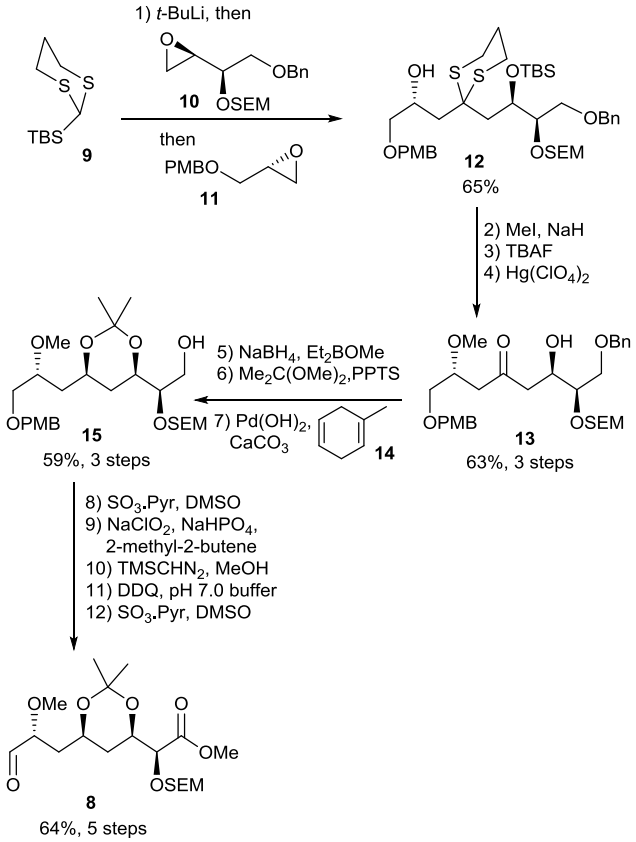
C2-*epi*-PelA. In 2008, Smith III *et al.* reported the synthesis of the 2-*epi* analogue, **5**, of peloruside A (Scheme 1).[36,†] The synthesis was intended to produce PelA (**1**), and employed a dithiane linchpin strategy to connect the C1–C8 (**8**) and C9–C20 (**7**) fragments, thus producing the complete carbon backbone of

peloruside A (**6**). The retrosynthetic strategy originally envisioned a Mitsunobu macrolactonisation, which proved to be unsuccessful. The alternative, Yamaguchi macrolactonisation of the peloruside A carbon backbone resulted in an unexpected epimerisation at C2 and delivered the C2-epimeric analogue **5**.



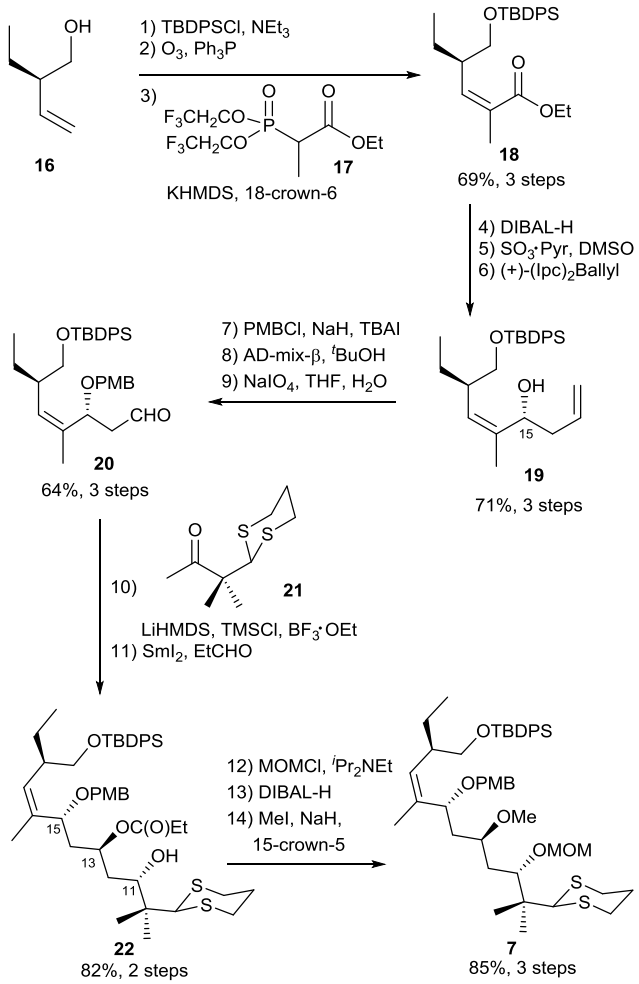
Scheme 1

The synthesis of the C1–C8 fragment **8** employed type I anion relay chemistry (ARC) where a trialkylsilyl dithiane **9** was sequentially treated with base and epoxides **10** and **11** (Scheme 2). Addition of the lithium anion of TBS-1,3-dithiane (**9**) to epoxide **10** and subsequent Brook rearrangement was followed by addition of the second epoxide **11**, providing fragment **12**. The alcohol **12** was converted into the corresponding methyl ether, and the TBS protecting group and dithiane were then removed to afford C5-ketone **13**. The ketone **13** was reduced via a 1,3-*syn* hydroxyl-directed sodium borohydride reduction, which was followed by protection of the C3 and C5 hydroxyl groups as an acetonide. Benzyl deprotection was achieved by transfer hydrogenation using 1-methylcyclohexane-1,4-diene (**14**) and the resulting primary alcohol **15** was converted into the corresponding methyl ester in a three-step reaction sequence. Lastly, removal of the PMB protecting group afforded an alcohol which was oxidised to aldehyde **8** via Parikh-Doering oxidation, thus completing the synthesis of the C1–C8 fragment.



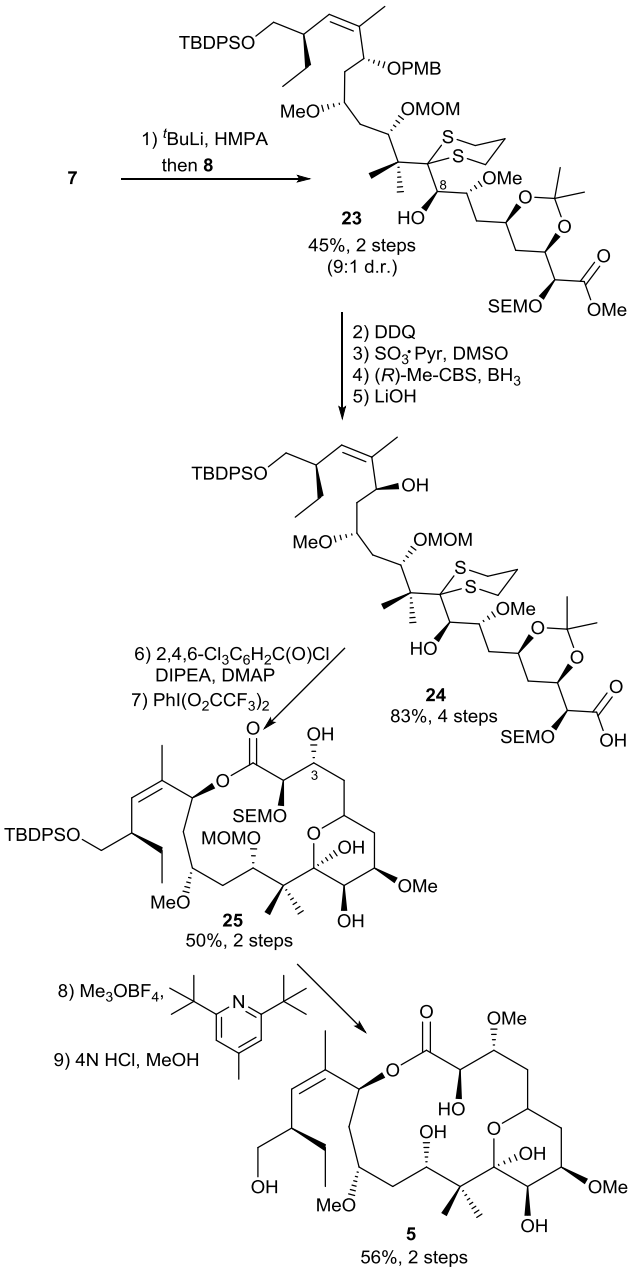
Scheme 2

The synthesis of the C9–C20 fragment **7** started from optically pure homoallylic alcohol **16** (Scheme 3). The hydroxyl group was protected and then the olefin underwent ozonolysis to give a C17 aldehyde. The aldehyde was treated under Still-Gennari conditions with reagent **17** to afford trisubstituted *Z*-olefinic ester **18**, which was subjected to a redox sequence to produce a C15 aldehyde. Next, Brown allylation was employed, producing the alcohol **19** with the desired configuration at C15 in a ratio greater than 20:1. The hydroxyl group at C15 was protected as a PMB ether. Then, selective terminal olefin dihydroxylation with Sharpless methodology afforded a diol which was cleaved to provide aldehyde **20**. This aldehyde then underwent a highly diastereoselective Mukaiyama aldol reaction with the silyl enol ether derived from the dithianyl ketone **21**, which produced the desired β-hydroxy ketone in greater than a 20:1 ratio with its C13 epimer. The SmI_2-promoted Evans-Tishchenko disproportionative reduction of the ketone gave the alcohol **22** with the desired configuration at C11. Finally, MOM protection of the C11 hydroxyl group in **22** was followed by reductive deprotection of the ester group at C13 and installation of the required methyl ether functionality to afford the major fragment **7**.



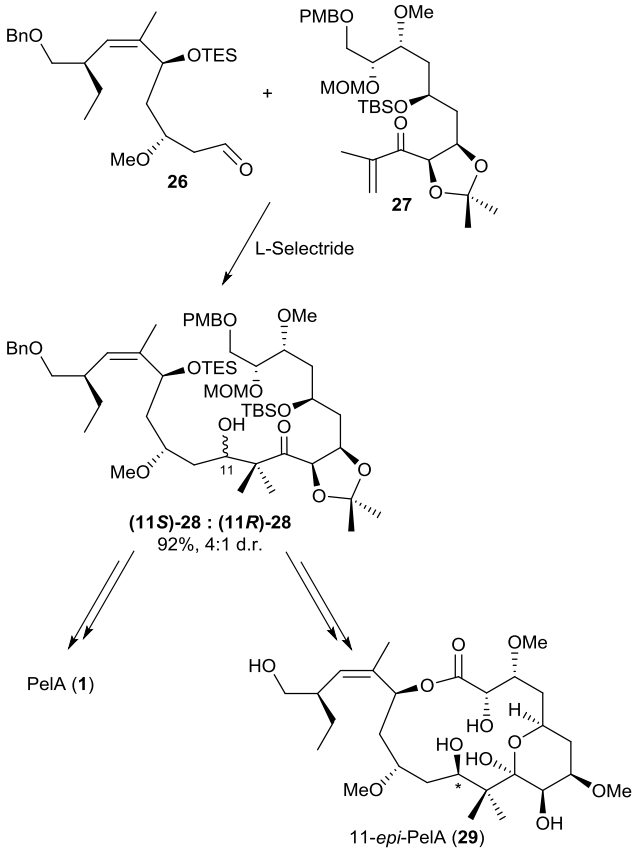
Scheme 3

Coupling of the C1–C8 aldehyde fragment **8** with the lithium anion derived from C9–C20 dithiane **7** gave the desired stereoisomer **23** in a 9:1 ratio with its C8 epimer (Scheme 4). The selectivity of the reaction was attributed to Felkin-Anh control. Because of difficulties that arose when Mitsunobu macrolactonisation was attempted, an alternative route was found that involved PMB deprotection of **23**, a two-step inversion of stereochemistry at C15, followed by saponification of the methyl ester to produce seco-acid **24**. Yamaguchi macrolactonisation resulted in an unexpected, and initially undetected, epimerisation at C2 that was attributed to additional torsional strain in the natural isomer. The 2-*epi*-macrolide then underwent concomitant dithiane and acetonide hydrolysis and hemiketal formation when treated with Stork's reagent to afford pyranose-containing **25**. Meerwein's reagent was then used to selectively methylate **25** at C3. The last step, global deprotection with 4 N HCl in MeOH, afforded 2-*epi*-peloruside A (**5**) in 0.56% overall yield with a longest linear sequence of 25 steps.



Scheme 4

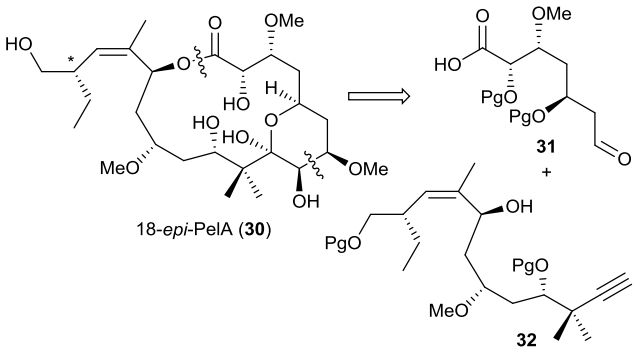
C11-*epi*-PelA. Ghosh and co-workers have disclosed spectroscopic data for C11-*epi*-peloruside A (**29**)[37] and stated that the synthesis is similar to that published by the group for the natural product.[13] Presumably, the synthesis diverges from their route to peloruside A[13] after the fragment coupling of aldehyde **26** with enone **27** (Scheme 5). This reductive aldol reaction produces a 4:1 mixture of the natural diastereomer and its C11 epimer. Subjecting the minor isomer [**(11*R*)-28**] to the same endgame as that described for peloruside A (**1**), from [**(11*S*)-28**], would afford the C11-epimer **29**.



Scheme 5

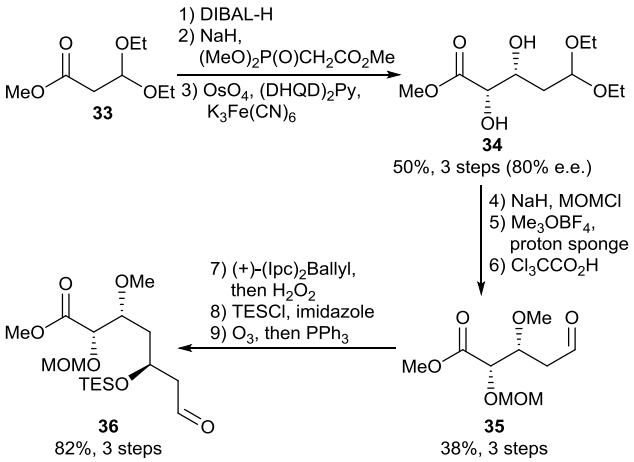
C18-*epi*-PelA. While attempting to prepare peloruside A itself, Trost and co-workers instead generated the C18-epimer, **30**, due to the incorrect choice of catalyst configuration in a desymmetrisation reaction.[38] This provides a unique analogue whose activity against cancer cells would provide further understanding of the binding requirements of the side-chain.

The retrosynthesis of **30** hinges around a Yamaguchi macrolactonisation and alkynylation of aldehyde **31** with the anion derived from **32** as the primary disconnections (Scheme 6).



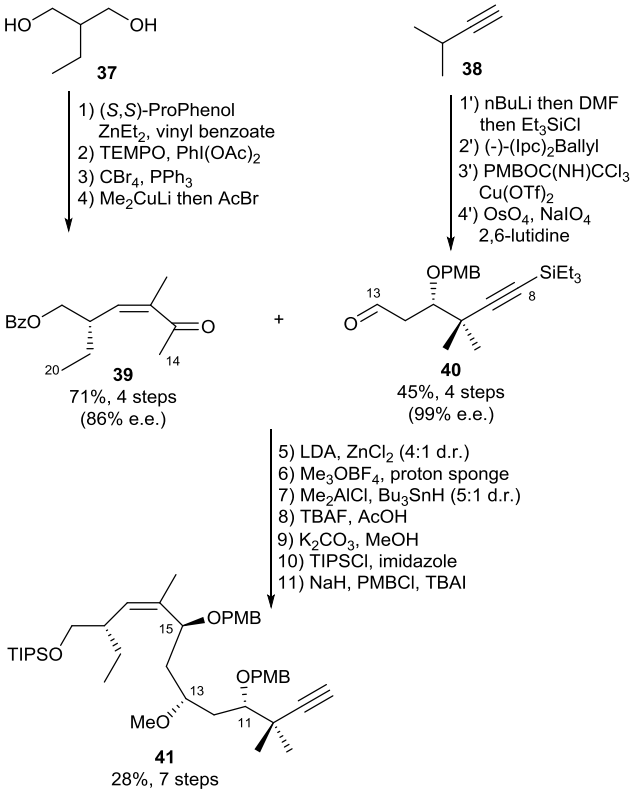
Scheme 6

The C1–C7 portion **36** was prepared by Horner-Wadsworth-Emmons homologation of the aldehyde derived from methyl 3,3-diethoxypropionate (**33**) by ester reduction (Scheme 7). Sharpless-type asymmetric dihydroxylation of the resulting enoate provided the diol **34**, which was differentially protected as α-MOM and β-methyl ethers. Acetal hydrolysis provided aldehyde **35**. After this, asymmetric Brown allylation of **35**, followed by protection and ozonolytic alkene cleavage produced the aldehyde **36**.



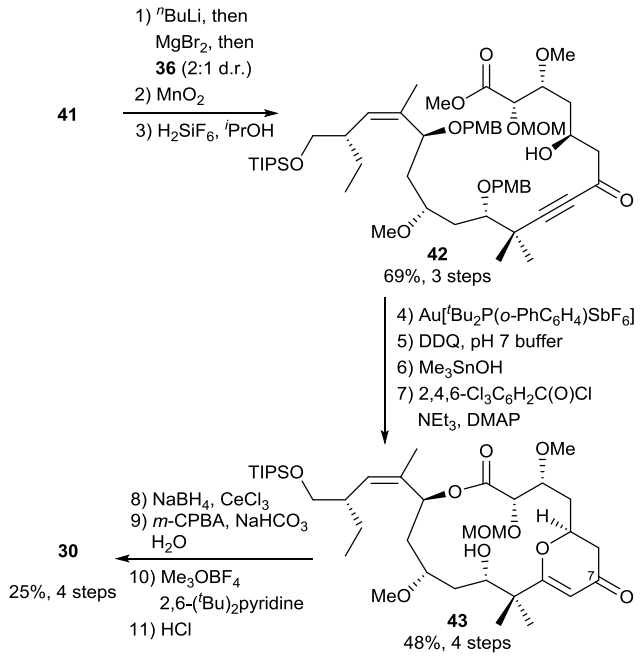
Scheme 7

The major C8–C20 fragment **41** was constructed from the diol **37** and alkyne **38** (Scheme 8). Desymmetrisation of the diol **37** was performed with catalytic (*S*,*S*)-ProPhenol/diethylzinc and vinyl benzoate to provide a monobenzoate (86% e.e.). This was the point of stereochemical deviation from the planned synthesis of peloruside A; use of the enantiomeric ligand would be expected to deliver the natural product. The other hydroxyl group was oxidised to the corresponding aldehyde, which underwent the Wittig-type step of the Corey-Fuchs reaction to afford a dibromoalkene. This was methylated at the less hindered bromine and the intermediate (*Z*)-alkenyl cuprate reacted with acetyl bromide to afford the methyl ketone **39**. Meanwhile, 3-methylbut-1-yne (**38**) was subjected to double lithiation and sequential treatment with *N*,*N*-dimethylformamide (DMF) and chlorotriethylsilane. The resulting aldehyde underwent asymmetric Brown allylation, PMB protection and osmium tetroxide-sodium periodate mediated oxidative alkene cleavage to afford aldehyde **40**. The C14–C20 ketone **39** was coupled with the C8–C13 aldehyde **40** by an aldol reaction that proceeded with 1,3-*anti* selectivity (4:1 d.r.). The resulting C13 alcohol was methylated with Meerwein's salt, the ketone at C15 was reduced with 1,3-*syn* selectivity (5:1 d.r.) and the silyl group removed from the alkyne with tetra-*n*-butylammonium fluoride (TBAF). The primary alcohol protecting group was swapped for a silyl ether to avoid interference by the benzoate in the aldehyde alkynylation. Finally, PMB protection of the C15 hydroxyl provided the terminal alkyne **41**.



Scheme 8

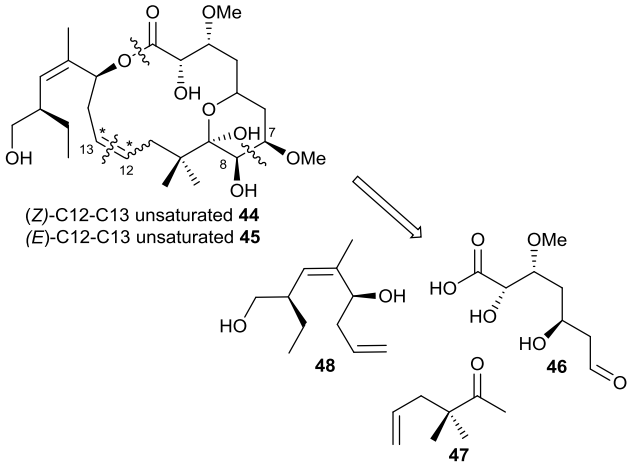
The two hemispheres were connected through alkynylation of the aldehyde **36** with the magnesium salt of alkyne **41** (Scheme 9). The 2:1 mixture of allylic alcohol diastereomers was oxidised to the conjugated ketone and the TES protecting group selectively removed to afford ynone **42**. Intramolecular alcohol addition to the alkyne was facilitated with a gold(I) catalyst to generate the pyranone ring. Removal of the PMB protecting groups and careful hydrolysis of the methyl ester provided a seco-acid that was macrolactonised using the Yamaguchi procedure to give compound **43**. Finally, Luche reduction of the enone, an epoxidation-hydrolytic ring opening sequence, methylation and global deprotection produced the 18-*epi* analogue **30**.



Scheme 9

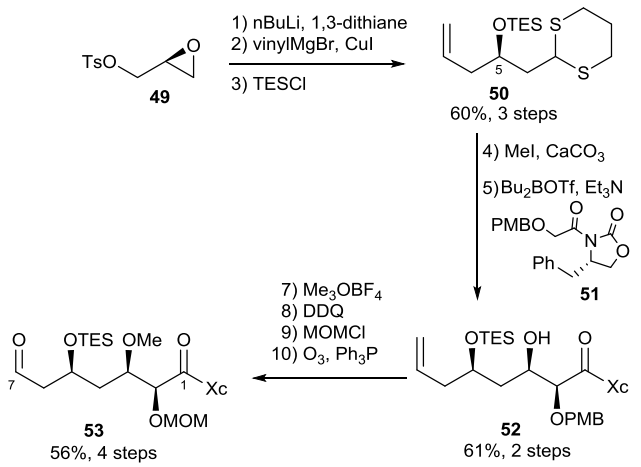
Deoxygenated Analogues.

C12–C13 unsaturated PelA. Zhao and Taylor reported a synthesis of simplified C12–C13 analogues of (+)-peloruside A in 2012.[39] Computational and NMR studies had suggested that the PelA structure comprised a flexible C9–C15 region and rigid features at the C2,C3-diol and C5–C9 dihydropyran. Replacement of the C11 and C13 stereogenic centres with (*Z*)- and (*E*)-olefins would give access to analogues **44** and **45** (Scheme 10), in two different conformational families, whose activity would in turn aid elucidation of the conformation of the tubulin-bound peloruside A. The synthesis of these conformational analogues involved preparation of three fragments: C1–C7 (**46**), C8–C12 (**47**) and C13–C20 (**48**). The retrosynthetic strategy centred on the ring-closing metathesis between C12 and C13, which produced the desired modification for the synthesis of olefinic analogues of peloruside A. Yamaguchi esterification and aldol coupling (for the C7–C8 connection) were other key steps. The syntheses of the C1–C7 and C13–C20 fragments, **46** and **48**, respectively, were previously reported by the Taylor group as they were required for the total synthesis of peloruside A.[40,41]



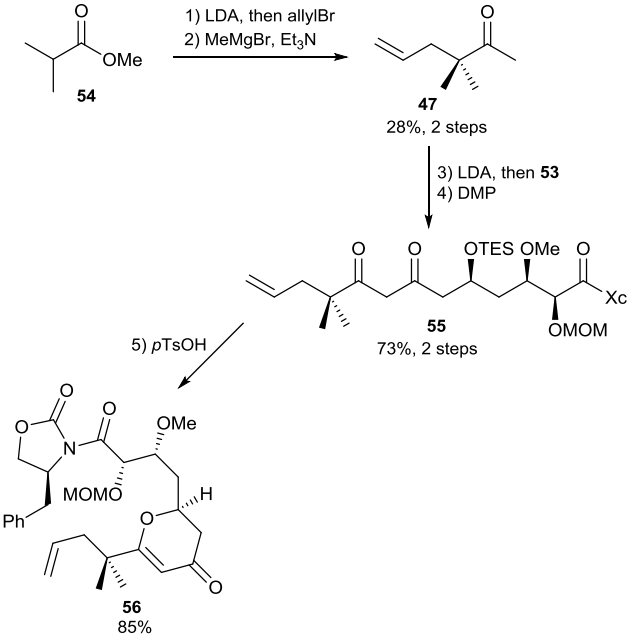
Scheme 10

In the synthesis of the C1–C7 fragment **53**,[41] (*S*)-glycidyl tosylate (**49**) was converted to a C5 secondary alcohol upon sequential treatment with lithiated 1,3-dithiane and copper-catalysed Grignard addition (Scheme 11). TES protection of the alcohol afforded C3–C7 compound **50**. The dithiane group was cleaved and the resulting aldehyde coupled with oxazolidinone **51** to create two new stereocentres in the desired diastereomer **52**. Formation of a methyl ether at C3 was followed by removal of the PMB protecting group and installation of a MOM ether at C2. The last step in the synthesis of the C1–C7 fragment was the ozonolysis of the terminal olefin to afford the desired aldehyde **53**.



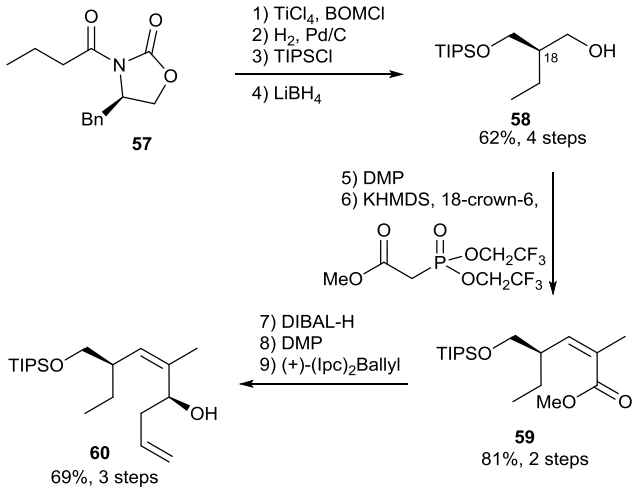
Scheme 11

The C8–C12 fragment **47** was prepared in two steps from methyl isobutyrate (**54**) through allylation of the derived lithium enolate, followed by transformation of the ester into the methyl ketone **47** by treatment with methylmagnesium bromide (Scheme 12).[39] To connect the C1–C7 aldehyde **53** to the C8–C12 fragment **47**, an aldol reaction was employed. As the aldol condensation produced a mixture of diastereomeric β-hydroxyketones, Dess-Martin oxidation was used to obtain 1,3-diketone **55**. This diketone was then converted to pyranone **56** upon treatment with acid to cleave the TES ether and effect dehydrative cyclisation.



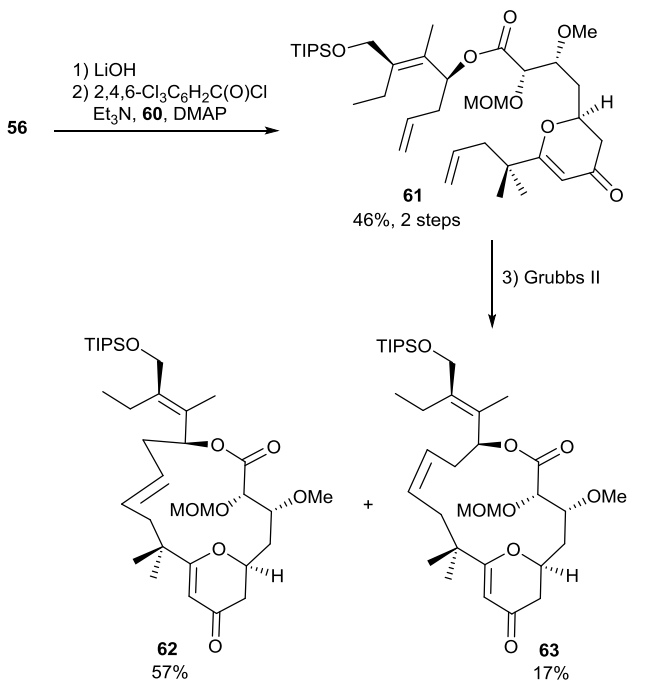
Scheme 12

The synthesis of the C13–C20 fragment **60** started from acyl oxazolidinone **57** (Scheme 13).[40] Chiral oxazolidinone auxiliary-directed alkylation with $PhCH_2OCH_2Cl$ (BOMCl) afforded the desired stereochemistry at C18. After hydrogenolysis of the benzyl ether and TIPS protection of the resulting primary alcohol, treatment with $LiBH_4$ removed the auxiliary and delivered the alcohol **58**, which was oxidised to the corresponding aldehyde. The desired (*Z*)-trisubstituted olefin **59** was formed exclusively by reacting the aldehyde with methyl bis(trifluoroethyl)phosphonoacetate under Still-Gennari olefination conditions. In the next two steps, the methyl ester of **59** was reduced to a primary alcohol then oxidised to an aldehyde. Lastly, Brown asymmetric allylation of the aldehyde gave fragment **60** with the correct configuration at C15.



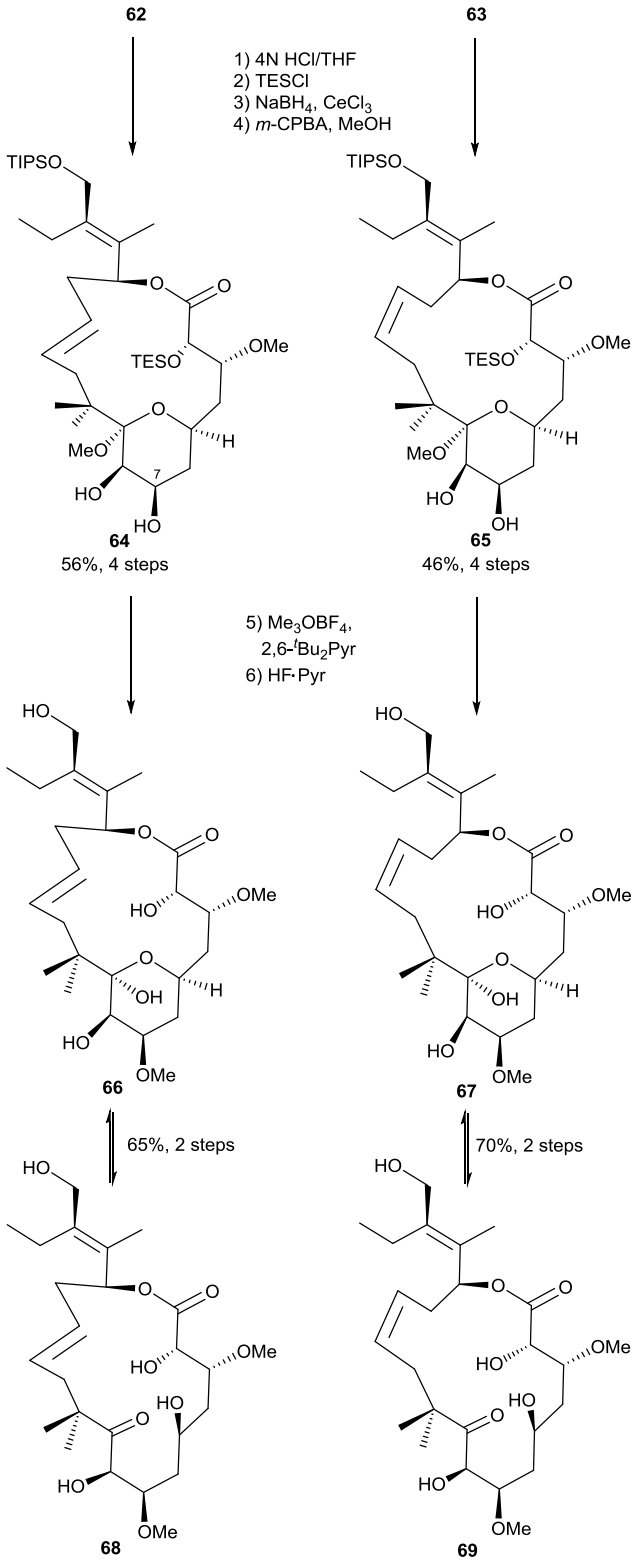
Scheme 13

The carboxylic acid derived from acyl oxazolidinone **56** was revealed by saponification and subjected to Yamaguchi esterification to connect the acid to alcohol **60**, affording **61** and completing the carbon backbone of the analogues (Scheme 14). The resulting diene underwent ring-closing metathesis with Grubbs' second generation catalyst, giving (*E*)- and (*Z*)-alkenes **62** and **63**, respectively, in a 3.5:1 ratio.



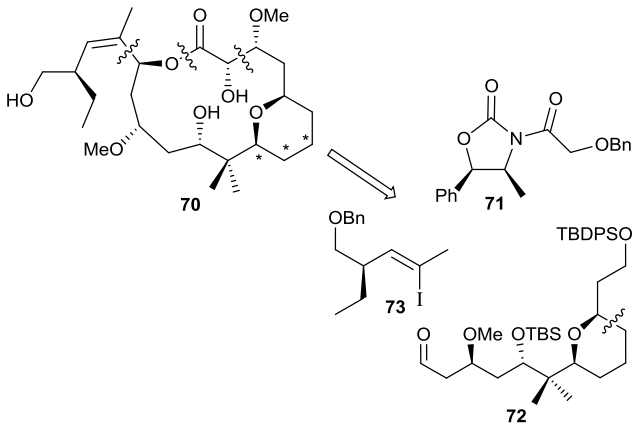
Scheme 14

Separation of the alkene isomers **62** and **63** was followed by replacement of the MOM protecting group at C2 with a TES ether, and selective reduction of the ketone under Luche conditions (Scheme 15). Next, epoxidation with *m*-CPBA in the presence of methanol was used to selectively obtain methyl pyranoside diols **64** and **65**. Selective methylation of the C7 hydroxyls, followed by global deprotection afforded the desired (*Z*)- and (*E*)-alkene analogues **66** and **67**, as well as their monocyclic counterparts **68** and **69**. These C12–C13 unsaturated analogues proved to be less stable than peloruside A and degraded before SAR studies could be undertaken.



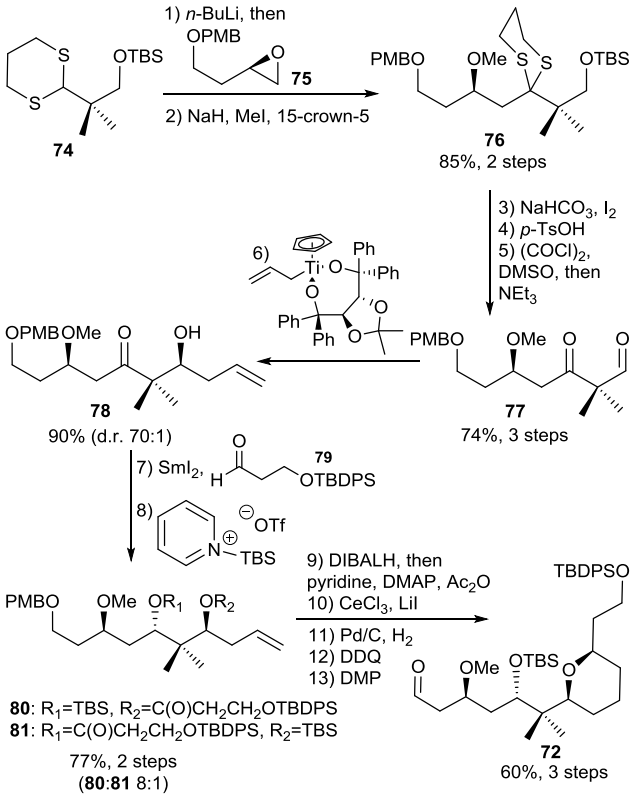
Scheme 15

7-Desmethoxy-8,9-dideoxy-peloruside A. In 2013, Altmann *et al*. published the synthesis of 7,8,9-trideoxygenated peloruside A **70** (Scheme 16).[42] Vinyl lithium addition was employed to attach the side-chain **73** to aldehyde **72**. Aldol methodology connected the C2–C3 bond. A Yamaguchi esterification was employed for the macrolactonisation. A Prins cyclisation was used to form the tetrahydropyran portion of the major C3–C15 fragment **72**.



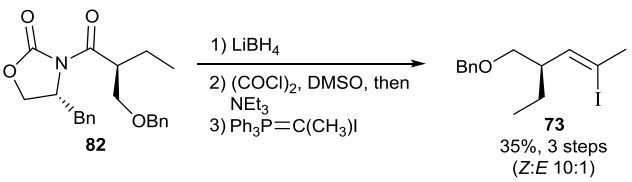
Scheme 16

The synthesis of fragment **72** commenced with lithiation of dithiane **74**, followed by addition of epoxide **75** (Scheme 17).[43] The resulting alcohol was methylated to afford dithiane **76**. Removal of the dithiane moiety and TBS protecting group gave, after Swern oxidation of the intermediate primary alcohol, β-ketoaldehyde **77**. Asymmetric allylation under Duthaler-Hafner conditions provided the homoallylic alcohol **78** in high yield and diastereoselectivity. 1,3-Reduction of β-hydroxyketone **78** under Evans–Tishchenko conditions with aldehyde **79** and subsequent TBS protection using *N-tert*-butyldimethylsilylpyridinium triflate produced an inseparable 8:1 mixture of **80** and **81**, the minor regioisomer resulting from acyl migration.[42] Reduction of the ester mixture **80** and **81** to hemiacetal intermediates and acetylation afforded the Prins precursor contaminated with unchanged **81**. Best results (quantitative yield) for the tetrahydropyran formation were observed when Lewis acidic $CeCl_3$ and LiI were used for the Prins reaction. Reductive removal of the iodide was performed prior to the removal of the PMB protecting group and oxidation of the deprotected alcohol to the aldehyde fragment **72**.



Scheme 17

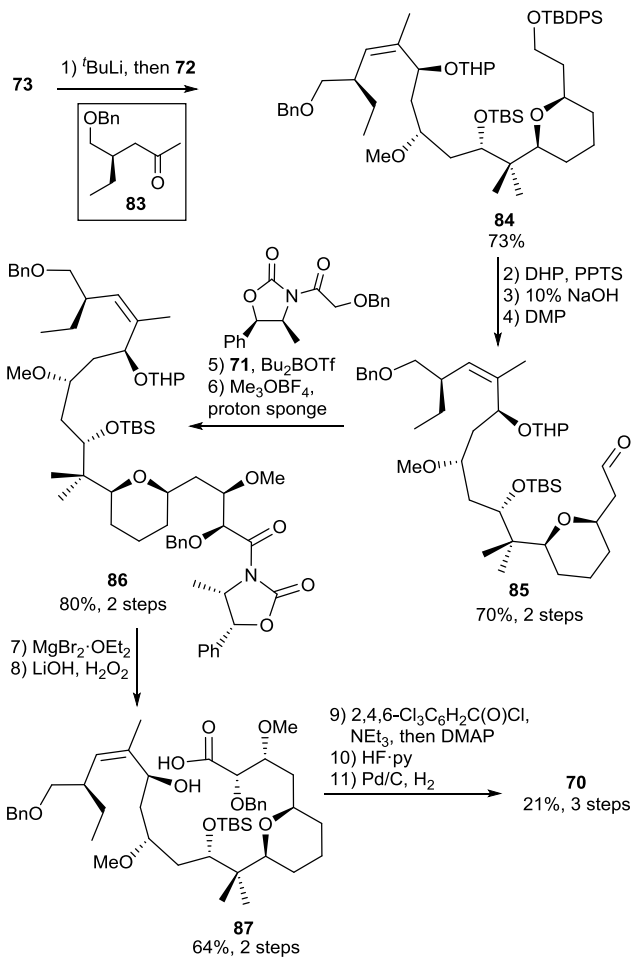
The synthesis of the C16–C20 fragment **73** proceeded from oxazolidinone **82**, which was reductively cleaved using $LiBH_4$ to give a primary alcohol (Scheme 18). The alcohol was oxidised to an aldehyde, and reaction with iodoethylphosphonium iodide in a Wittig reaction afforded the desired *Z*-iodoalkene **73**.



Scheme 18

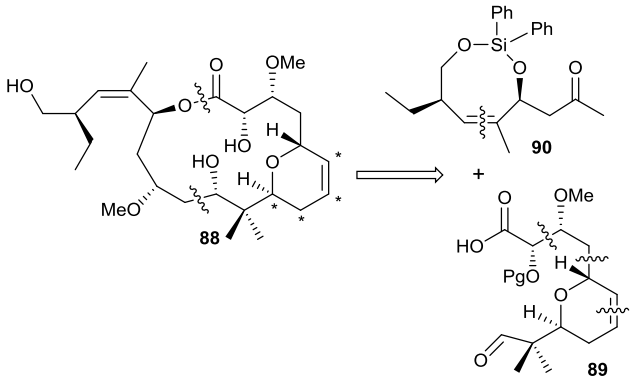
Addition of the side-chain to the C3–C15 aldehyde was achieved by reaction of the iodoalkene **73** with *tert*-butyl lithium, followed by addition of aldehyde **72** (Scheme 19).[42] The product **84** was contaminated with methyl ketone **83**, a by-product of the reaction of iodoalkene **73** with ^{t}BuLi. The resulting mixture was reacted with 3,4-dihydro-2*H*-pyran (DHP) and an acid catalyst in order to protect the C15 alcohol as separable THP acetal diastereomers. The following steps involved deprotection and oxidation of the C3 alcohol. The resulting aldehyde **85** then underwent Evans aldol reaction with the enolate derived from acyl oxazolidinone **71**, the product of which was methylated to afford **86**. Removal of the THP protecting group and the chiral auxiliary left the *seco*-acid **87** ready for the macrolactonisation. Yamaguchi esterification was followed by cleavage of the TBS

and benzyl ethers to give the 7,8,9-trideoxy-peloruside A analogue **70**.



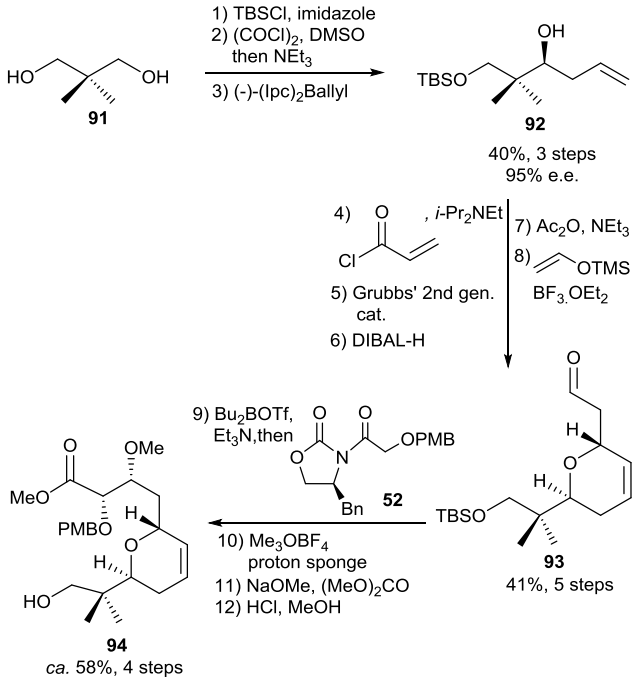
Scheme 19

Dihydropyran analogue. Our group embarked on the synthesis of a dihydropyran analogue of peloruside A several years ago.[44] Based on the evidence for a common binding site for peloruside A and laulimalide on β-tubulin,[4] it was surmised that they might bind in an orientation where the pyranose ring of peloruside A would coincide with the endocyclic dihydropyran of laulimalide.‡ Therefore, the 2,6-*trans*-dihydropyran analogue **88** was targeted (Scheme 20). The analogue would be generated in a convergent manner from major fragments **89**[21] and **90** by a aldol reaction with 1,5-*anti*-selectivity.[20] The ketone **90** was prepared through a silyl-tethered diastereomer-discrimiating ring-closing metathesis,[21] based on a strategy devised by Hoberg *et al.*[20]



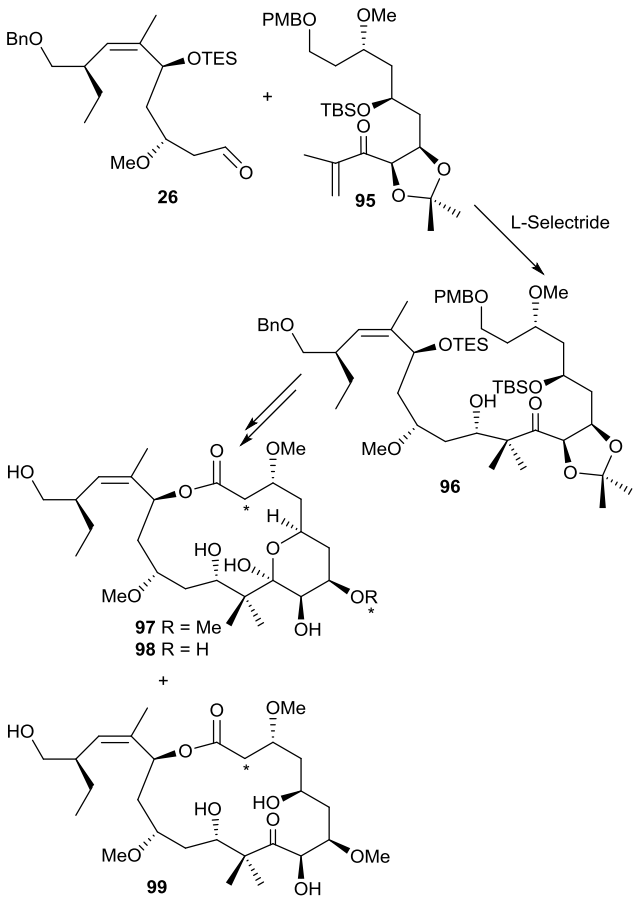
Scheme 20

The synthesis of the C1–C11 fragment **94** began with monoprotection of 2,2-dimethylpropane-1,3-diol (**91**), followed by Swern oxidation and Brown allylation to afford the secondary alcohol **92** (>95% e.e.) (Scheme 21). Esterification with acryloyl chloride and ring closing metathesis formed a dihydropyranone ring, which was reduced to the corresponding lactol and acetylated. Lewis acid-assisted substitution of the anomeric acetate by TMS vinyl ether produced only the desired 2,6-*trans*-diastereomer of dihydropyranylacetate **93**, representing the C3–C11 fragment of the analogue **88**. A reaction between **93** and the oxazolidinone-linked glycolate **52** afforded the corresponding aldol product with good diastereoselectivity (10:1 d.r.). Methylation followed by removal of the auxiliary using the Kanomata method and deprotection of the silyl ether provided the methyl ester **94**. This product underwent oxidation to the corresponding aldehyde in variable yields depending on the method used (70–85%). Preliminary studies of the aldol reaction between this aldehyde and the ketone **90** appeared promising but, unfortunately, subsequent attempts were unsuccessful and therefore characterisation of the full carbon skeleton of the analogue was not possible.



Scheme 21

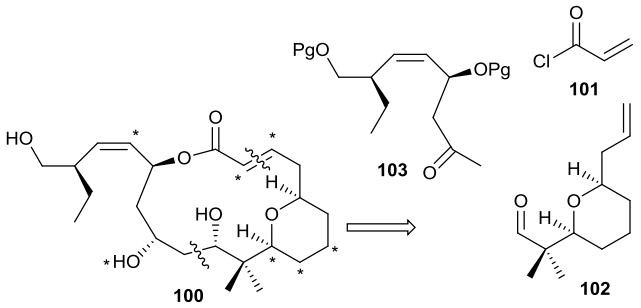
2-Deoxy- and 2-Deoxy-7-*O*-desmethyl PelA. Ghosh has provided spectroscopic and SAR data for 2-deoxy- and 2-deoxy-7-*O*-desmethyl peloruside A (**97** and **98**, respectively, Scheme 22).[37] Although no synthetic details are given, their formation via similar methodology to that used in the same group's total syntheses of peloruside A[13] and C11-*epi*-PelA (see Scheme 5) is stated. Thus, a reductive aldol coupling of enone **95** with aldehyde **26** to afford the full skeleton **96** was presumably employed (Scheme 22). Methylation of O7 was performed at a late stage in the total synthesis, immediately prior to the final deprotection steps.[13] Application of this method to the 2-deoxy series would ultimately provide analogue **97**. Omitting the methylation step would lead to the 7-*O*-desmethyl variant **98**. The ring-open isomer **99** was also formed alongside **97**. The position of the equilibrium between ketone and hemiacetal forms of peloruside A lies far towards the ring-closed hemiacetal form. In contrast, alterations to the structure appear to drastically affect the equilibrium.[39] Presumably, removal of the 2-hydroxyl group causes relative favouring of the ring-open form **99** compared to natural PelA.



Scheme 22

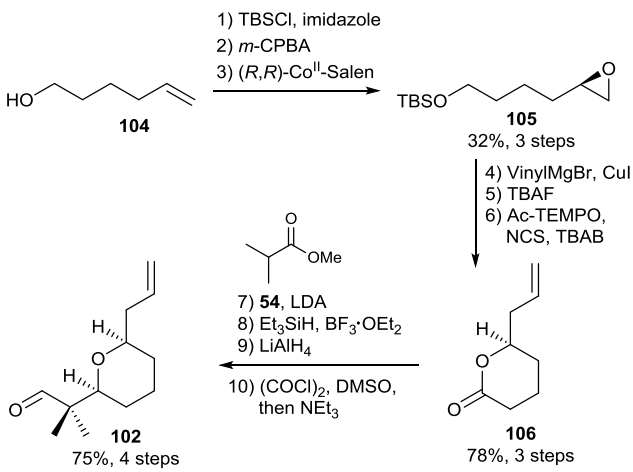
C2–C3 unsaturated analogue with simplified pyran and side-chain. The group of Lebreton and Mathé-Allainmat has published the synthesis of **100**, a simplified tetrahydropyran analogue of peloruside A bearing unsaturation at the C2 and C3 and a disubstituted desmethyl alkene in the side-chain.[45]

The retrosynthesis involved an RCM macrocyclisation strategy to form the C2–C3 unsaturation (Scheme 23). A 1,5-*anti*-aldol reaction between aldehyde **102** and ketone **103** would put in place the C11–C12 bond in a stereoselective manner.



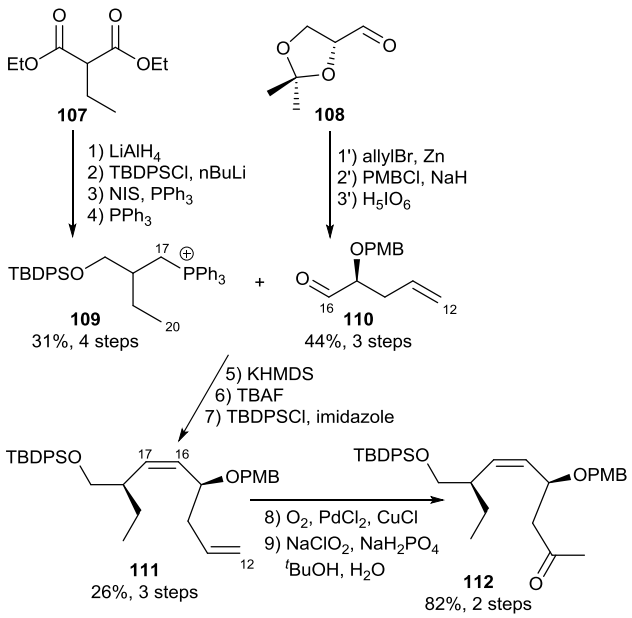
Scheme 23

The C3–C11 fragment **102** was prepared from hex-5-en-1-ol (**104**) by protection, epoxidation and hydrolytic kinetic resolution by Jacobsen's method to afford epoxide **105** (Scheme 24). Vinylation at the terminal position followed by deprotection and oxidative cyclisation provided the lactone **106**. This was treated with the lithium enolate derived from methyl isobutyrate (**54**) followed by reduction of the resulting hemiacetal with triethylsilane. A redox sequence was then employed to give aldehyde **102**.



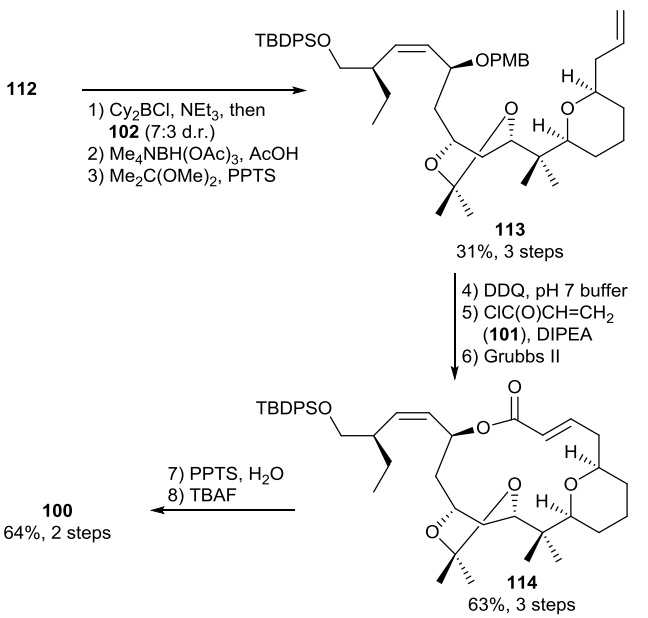
Scheme 24

The side-chain alkene was constructed by a Wittig reaction. Racemic phosphonium salt **109** was prepared from 2-ethylmalonate **107** (Scheme 25). The process involved reduction of both esters, monoprotection of the resulting diol and conversion of the remaining hydroxyl group, via the iodide, into the salt **109**. Meanwhile, the C12–C16 fragment **110** was generated from the glyceraldehyde derivative **108** (Scheme 25). From **108**, diastereoselective allylation (78:22 d.r.), protection followed by *in situ* diol deprotection and cleavage provided aldehyde **110**. Wittig coupling of these two entities **109** and **110** was followed by a deprotection-reprotection sequence to allow separation of compound **111** from its diastereomer at the primary alcohol stage. A Tsuji-Wacker oxidation provided the methyl ketone **112**, which was purified after oxidative removal of the aldehyde regioisomer by Pinnick oxidation.



Scheme 25

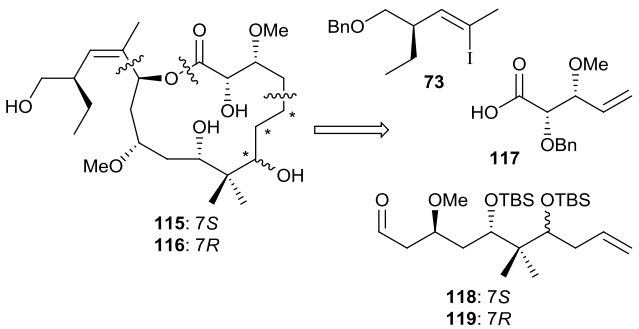
The methyl ketone **112** was married to the aldehyde **102** through an aldol coupling (Scheme 26). This reaction was modestly 1,5-*anti*-diastereoselective (7:3 d.r.) Hydroxyl-directed 1,3-*anti*-reduction of the ketone was then carried out using $NMe_4BH(OAc)_3$ and the resulting diol protected as the acetonide derivative **113**. The PMB protecting group was then removed and the alcohol transformed into the corresponding acrylate to put in place the C1–C2 building block. The key RCM proceeded stereoselectively to afford the *E*-alkene **114**. Acid- and fluoride-assisted deprotections of compound **114** delivered the desired analogue **100**.



Scheme 26

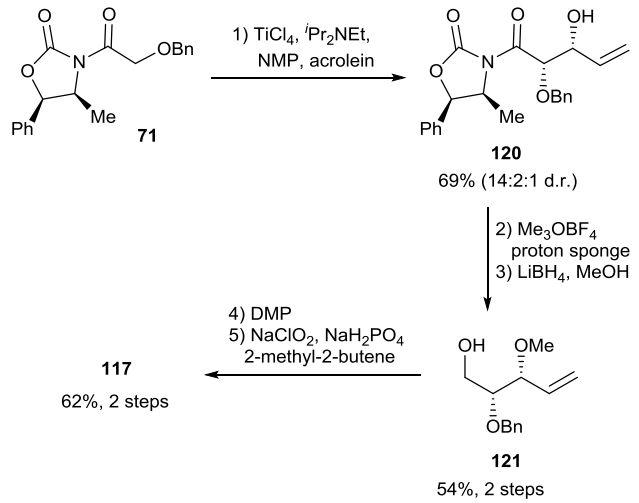
Monocyclic Analogues.

7*S* and 7*R*-desTHP-PelA. The role of the pyran can be probed by generating analogues devoid of the embedded ring. Altmann *et al.* published syntheses of the epimeric monocyclic analogues **115** and **116** (Scheme 27).[42,43] The carbon skeleton of these analogues lacks the tetrahydropyran moiety of peloruside A (**1**) and the perimeter of the macrocycle is shrunk. The retrosynthetic strategy involves Yamaguchi esterification, ring-closing metathesis and a vinyl lithium addition to attach the side-chain.



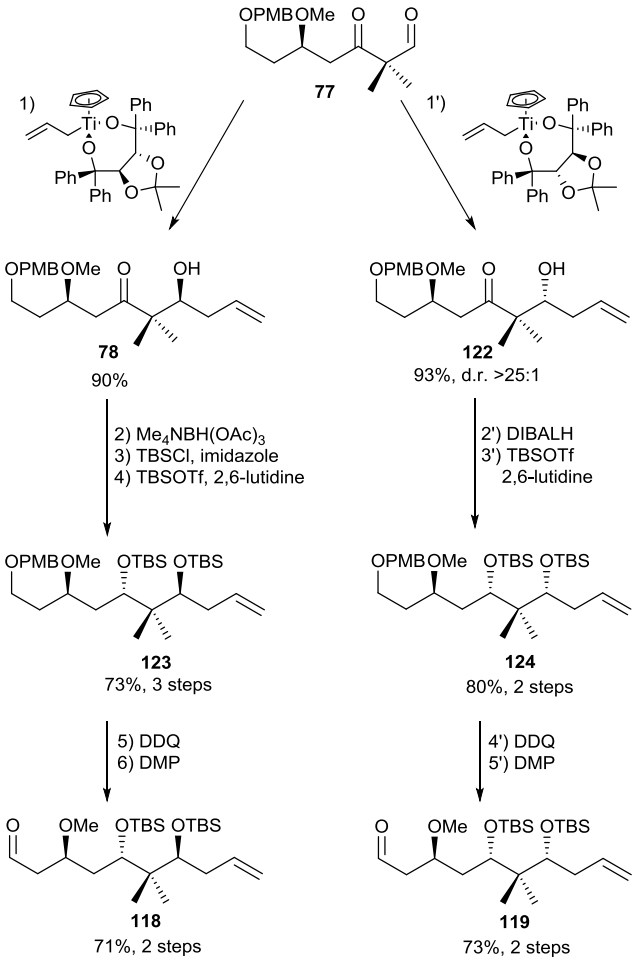
Scheme 27

Evans oxazolidinone **71** was used as a starting point for the synthesis of the C1–C4 fragment **117** (Scheme 28). Its aldol reaction with acrolein gave the optimal yield of the desired diastereomer **120** when employing $TiCl_4$ as a Lewis acid. The aldol product **120** was then methylated and the resulting methyl ether subjected to $LiBH_4$-mediated chiral auxiliary removal to afford alcohol **121**. Two sequential oxidations produced acid **117**.



Scheme 28

The epimeric C5–C13 fragments **118** and **119** were prepared by allylation of the ketoaldehyde **77** under Duthaler-Hafner conditions (see Scheme 17). Homoallylic alcohol **78** and its diastereomer **122** were prepared from aldehyde **77** using enantiomeric allyl titanium reagents (Scheme 29). The epimeric ketones **78** and **122** were individually reduced: for **78**, hydroxyl-directed reduction afforded an *anti*-diol, while for **122**, non-chelating reduction from the less hindered face provided a *syn*-diol. Both diols were doubly silyl protected to give compounds **123** and **124**. Removal of the PMB protecting groups and oxidation with Dess-Martin periodinane (DMP) produced

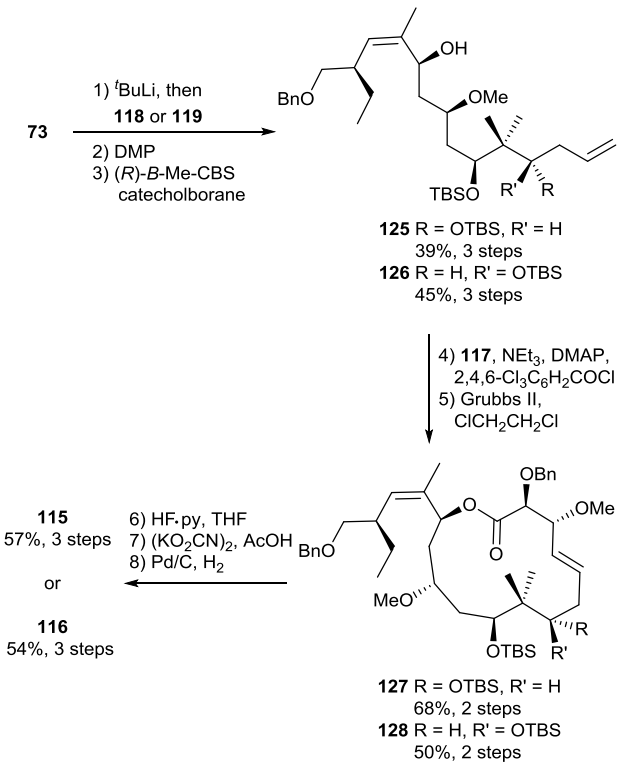


aldehydes **118** and **119**.

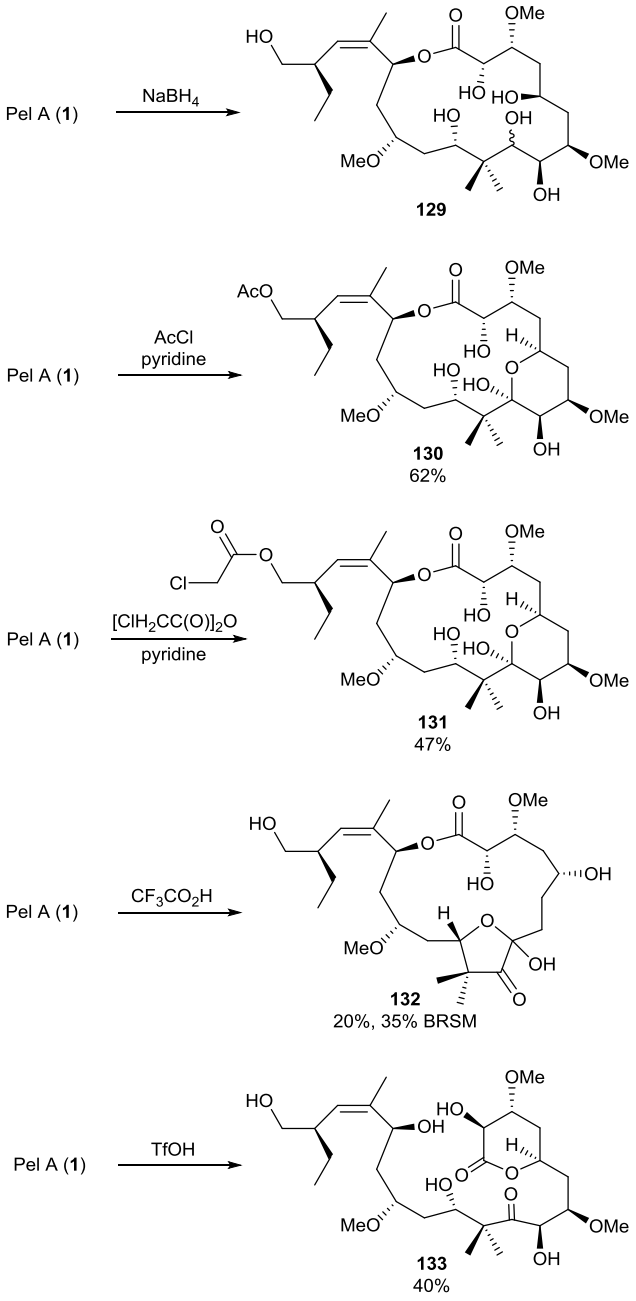
Scheme 29

The connection of the three fragments started with lithiation of the side-chain alkene fragment **73** and addition to the epimeric aldehydes **118** and **119** (Scheme 30). The products were oxidised with Dess-Martin periodinane in order to remove the byproduct ketone **83** (see Scheme 19), then reduced with the Corey-Bakshi-Shibata (CBS) method to provide purified **125** and **126**. The C1–C4 fragment **117** was appended to the C15 hydroxyl by Yamaguchi esterification. Macrocyclisation was achieved by ring-closing metathesis to afford epimeric *E*-alkenes **127** and

128. Final deprotection and selective hydrogenation of the macrolides **127** and **128** was best carried out by a three-step process involving desilylation, then sequential diimide-promoted reduction of the alkene and hydrogenolytic debenzylation. In this way, the epimeric monocyclic analogues **115** and **116** were prepared.



Scheme 30



Scheme 31

Semisynthetic transformations of PelA.

Northcote and co-workers have performed semisynthetic studies on peloruside A.[3,10,46] Sodium borohydride reduction of the masked ketone at C9 afforded the hexaol **129** (Scheme 31).[3] Selective acylation of the primary hydroxyl was possible by treatment of peloruside A with either acetyl chloride or chloroacetic anhydride at -100 °C to provide acetate **130** and chloroacetate **131**, respectively.[46] Treatment of peloruside A with acid led to ring opening of the pyranose and alternative cyclisation pathways.[10] When catalytic trifluoroacetic acid was used, the furanose **132** was observed to form, which arises by elimination of methanol from C7–C8 and attack on the resulting C8 ketone by the C11 hydroxyl group. In contrast, with trifluoromethane sulfonic acid, the pyranone **133** was obtained, which can be attributed to attack of the C5 hydroxyl on the lactone carbonyl.

Structure-Activity Relationship Studies of Natural and Synthetic Pelorusides

Peloruside A (**1**) is potently active in a number of cancer cell lines, with half-maximal inhibitory concentration (IC_{50}) values in the low nanomolar range (5–19 nM, see Table 1).[1,2,3] Its effect on cell growth is to halt replication in the G_2/M phase of the cell cycle, with 67% of cells arrested at G_2/M when treated with 200 nM PelA; in comparison, only 23% of untreated cells were arrested in G_2/M.[3] The observed lack of activity of *ent*-peloruside A[11] towards cancer cells indicates the importance of

the three-dimensional structure and served to confirm that the enantiomer of the potently activity natural product had indeed been prepared. Peloruside B displays similar activity to the natural product towards cancer cell lines and comparable accumulation of cells in the G_2/M phase of the cell cycle (56% arrested at G_2/M phase in the presence of 200 nM peloruside B). Interestingly, synthetic and natural peloruside B had slightly different inhibitory patterns (synthetic **2** IC_{50} = 48 nM, natural **2** IC_{50} = 71 nM in 1A9 cells),[9] which probably reflects the nature of trace contaminants present in the samples. Peloruside C (**3**) has a lower, but still significant, potency (IC_{50} = 221 nM in human leukaemia cells). It did not block growth at G_2/M but seemed to cause accumulation of cells at G_1 (71% of cells at G_1, compared with 54% in the control and 13% with PelA).[10] Hence, it has been proposed that microtubule stabilisation might not be the primary cause of the observed cytotoxicity for **3**.[10] Peloruside D (**4**), with a repositioned pyranose ring, had a significantly decreased activity towards cancer cells (IC_{50} = 2 μM in human leukaemia cells),[10] indicating the crucial importance of the nature and position of the embedded ring.

Three epimeric analogues of peloruside A have been synthesised,[36,37,38] but bioactivity data were only been disclosed for one of them.[37] C11-*epi*-pelA (**29**) was generated by Ghosh and co-workers and was found to be similarly potent to pelA (IC_{50} = 10 nM in P388 murine leukaemia cells).[37]

Several analogues with carbon skeletons similar to that of the natural product **1** but with different substitution patterns have been described and their bioactivity assessed.[37,39,42,45,46] The 7,8,9-trideoxygenated analogue **70** retained some inhibitory activity towards proliferation of three human cancer cell lines (IC_{50} = 124, 163 and 247 nM in A549, HCT116 and MCF-7, respectively), with only about a 10-fold decrease in activity despite the loss of three oxygen groups and the associated binding affinity that they impart.[42] The related simplified analogue **100**, with additional deoxygenation and loss of methyl groups, was found to be only mildly cytotoxic in colon carcinoma cell lines (IC_{50} = 12 and 15 μM in CaCo2 and HCT116 cells, respectively) and a prostate carcinoma cell line (IC_{50} = 15 μM in PC3 cells).[45] Evidently, the removal of additional groups, beyond the tetrapyran modifications, has a significant negative effect on the activity. The silyl-protected variant **134** lost all growth inhibitory activity in cancer cells. In contrast, retaining the pyran oxygen substituents while removing the C2-hydroxyl afforded compounds that were inhibitory, with about a 10-fold decrease compared to the natural product **1**. Thus, 2-deoxyPelA (**97**) was still active in cell-based assays (IC_{50} = 120 nM in P388 murine leukaemia cells), while the 7-*O*-des-methyl variant **98** was slightly less active (IC_{50} = 320 nM in the same assay).[37] Together, these results demonstrate modest flexibility in the substitution pattern of the peloruside skeleton while retaining bioactivity.

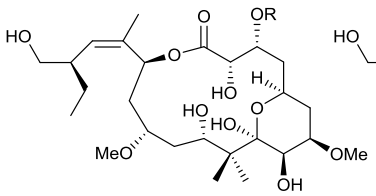
Protected derivatives of peloruside A, namely 24-*O*-acetyl- and 24-*O*-chloroacetyl-PelA demonstrate the requirement of the primary hydroxyl group for potency.[46] The acetate **130** had reduced activity (IC_{50} = 256.6 nM) in ovarian cancer cells, while that of the chloroacetate **131** (IC_{50} = 26.6 nM) was similar to the natural product. This apparent discrepancy was attributed to the enhanced susceptibility of the more electrophilic chloroacetate to hydrolysis in the *in vitro* assay conditions, producing PelA *in situ*. The slightly lowered potency of analogue **131** relative to the natural product is probably due to incomplete hydrolysis under the reaction conditions.

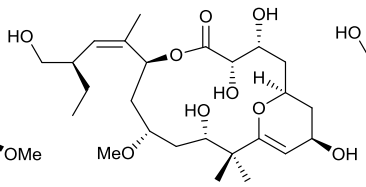
Investigation of the importance of the pyranose ring for antiproliferative activity has been studied by generating analogues lacking the embedded ring. The pyran ring-open form of **97**, *viz.* **99**, was inactive up to 5 μM.[37] Removal of the pyranose ring by reduction of PelA reduced the activity but, interestingly, did not wipe it out (IC_{50} = 221 nM in HL-60 cells).[3] Indeed, the resulting analogue **129** had inhibition comparable to the trideoxygenated pyran-containing species **70**. When the analogues **115** and **116**, with fewer hydroxyl groups and a smaller macrocycle, were analysed, sensitivity to the configuration at C7 was evident. The 7*R*-desTHP analogue **116** had antiproliferative activity in the low micromolar concentration range for three cancer cell lines, whereas the 7*S*-epimer **115** was inactive.[42,43] This demonstrates an intriguing stereochemical tolerance, because the equivalent position in PelA has the hemiacetal OH group apparently oriented more similarly to the 7*S*-isomer. The acid-rearrangement products **132** and **133** were only mildly cytotoxic (IC_{50} = 15 and 7 μM, respectively, in HL-60 cells),[10] in keeping with the results from other analogues with alterations to the pyranose ring.

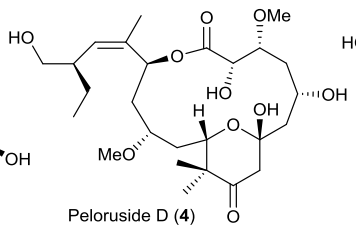
Overall, the SAR studies to date highlight the integral nature of both the position and decoration of the tetrahydropyran moiety embedded within the peloruside framework. While the PelA reduction product indicates that the pyran is not essential for activity, the results from the groups of compounds with and without the C5–C9 pyran motif generally show that it is beneficial for antiproliferative activity.

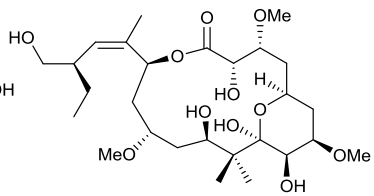
Table 1

Peloruside A, Natural Congeners and Epimers

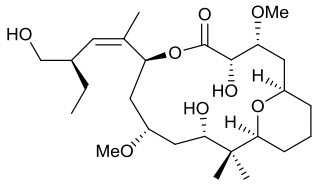

Peloruside A (PelA, **1**, R = Me)
Peloruside B (**2**, R = H)

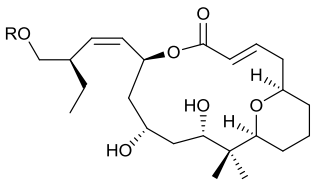

Peloruside C (**3**)

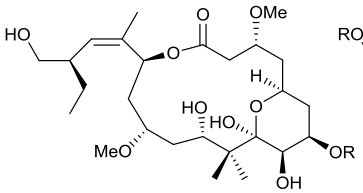

Peloruside D (**4**)

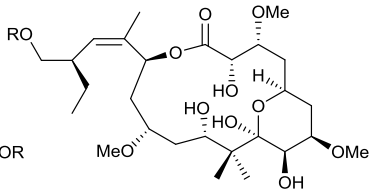

C11-*epi*-PelA (**29**)

Substituent Variations

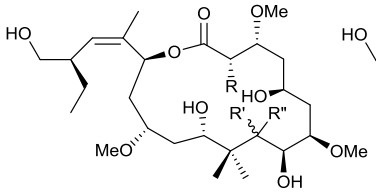

7-Desmethoxy-8,9-dideoxy-PelA (**70**)

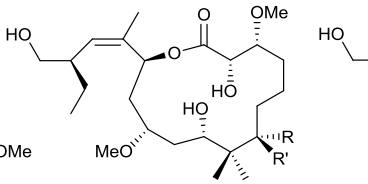

7-Desmethoxy-13-*O*-desmethyl-16-desmethyl-2,3,8,9-tetradeoxy-didehydroPelA (**100**, R = H)
Silyl-protected **134** (R = $SiMe_2{}^tBu$)

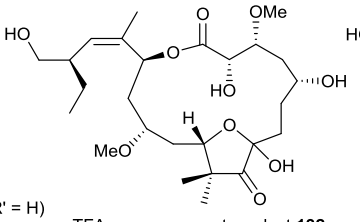

2-DeoxyPelA (**97**, R = Me)
2-Deoxy-7-*O*-desmethylPelA (**98**, R = H)

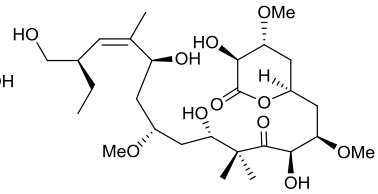

24-*O*-AcetylPelA (**130**, R = Ac)
24-*O*-ChloroacetylPelA (**131**, R = $ClCH_2C(O)$-)

Pyran Ring-Open Analogues


PelA reduction product **129**
(R = OH, R' = OH, R" = H)
Ring-open 2-deoxyPelA **99**
(R = H, R',R" = =O)


7*S*-des-THP-PelA (**115**, R = OH, R' = H)
7*R*-des-THP-PelA (**116**, R = H, R' = OH)


TFA-rearrangement product **132**


TfOH-rearrangement product **133**

Compound	IC$_{50}$ values in specified cell lines (nM)										
	HL-60	**P388**	**A2780**	**1A9**	**CaCo2**	**HCT116**	**PC3**	**MCF-7**	**A549**	**SK-MEL-5/ HeLa**	**Ref**
Pel A (**1**)	7–35	18	19.2					4.9			1,3,10,46
ent-**1**										>10,000	11
2	33			48–71							9
3	221										10
4	2,000										10
29		10									37
70						163		247	124		42
100					12,000	15,000	15,000				45
134					>25,000	>25,000	>25,000				45
97		120									37
98		320									37
130			256.6								46
131			26.6								46
99		>5,000									37
129	221										3
115						>20,000		>20,000	16,400		42,43
116						1,170		2,050	1,390		42
132	15,000										10
133	7,000										10

HL-60 = human leukaemia cells, P388 = murine leukaemia cells, A2780 = ovarian carcinoma cells, 1A9 = human ovarian carcinoma cells, CaCo2 = colon carcinoma cells, HCT116 = colon carcinoma cells, PC3 = prostate carcinoma cells, MCF-7 = breast carcinoma cells, A549 = lung cancer cells.

Conclusions

A number of syntheses of analogues of peloruside A have been achieved to date and they, together with the natural congeners, begin to provide a sense of the structure-activity relationships of this complex natural product. Through these studies, significant alteration of the structure is seen to be detrimental to the stability of the compounds and/or their potent effect on cancer cells operating through interaction with microtubules. The presence and position of the pyranose ring is of crucial importance while modest functional group variations are tolerated. Yet, there are many sites and variations still to be explored. The recently published crystal structure of peloruside A bound to β-tubulin[5] is expected to instil new vigour into the design and synthesis of new analogues.

Acknowledgements

The authors are grateful to Peter Northcote, Paul Teesdale-Spittle, Peter Tyler, Richard Furneaux and John Miller (VUW), and Karl-Heinz Altmann (ETH) for valuable discussions. The Stewart Charitable Trust is gratefully acknowledged for financial support towards a PhD scholarship (A.B). Funding from the Foundation for Research Science and Technology, New Zealand, is also acknowledged.

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† Asterisks are shown on analogue structures to highlight the points of difference from the natural product **1**.

‡ The recent crystal structure has demonstrated that this in incorrect: the relative orientation is different, such that these two rings are not overlapping.[5]

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