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Towards a simplified peloruside A: synthesis of C1–C11 of a dihydropyran analogue

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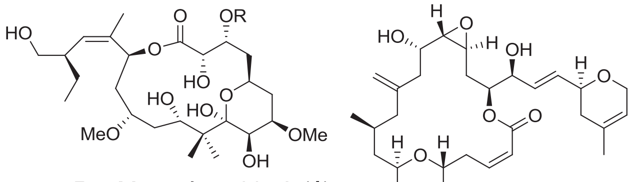
ABSTRACT

A simplified analogue of the C1–C11 fragment of peloruside A has been synthesised starting from a monoprotected 2,2-dimethylpropane-1,3-diol. Oxidation, asymmetric allylation and acryloylation provided a substrate for ring-closing metathesis to a δ-lactone. Reduction, acylation and homologation with trimethyl(vinyloxy)silane provided a protected C3–C11 analogue in a stereoisomer manner. Introduction of the C1–C2 fragment and incorporation of the 2,3-*syn* stereochemistry was achieved by a boron-mediated Evans aldol reaction.

1. Introduction

Microtubule stabilisers such as the taxanes and epothilones are among the most successful anti-cancer drugs in current use.[1] With one in four deaths in the United States during 2010 attributed to cancer,[2] there is an ongoing need for improved clinical agents. Peloruside A (**1**, Fig. 1) is a microtubule stabilising agent[3] that was first reported by Northcote et al. in 2000[4] and has sparked a flurry of biological and chemical endeavour. It has high potency against cancer cells, low susceptibility towards resistance through P-glycoprotein-mediated efflux,[5] synergistic activity with taxoid site binders,[6] interactions with a previously uncharacterised binding site on tubulin,[5] and a unique mode of microtubule stabilisation.[7] In vivo animal study data show that peloruside A has good pharmacokinetic and pharmacodynamic profiles,[8] indicating that compounds based on its structure will be especially useful agents in cases where resistance to existing drugs forces the termination of treatment.



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

laulimalide (**3**)

Fig. 1. Structures of peloruside A (**1**), peloruside B (**2**) and laulimalide (**3**).

To date there have been six total syntheses of peloruside A,[9–15] along with a number of syntheses of fragments and analogues, including the C1–C11[16,17] and C12–C24 fragments,[18] the unexpected synthesis of (−)-2-*epi*-peloruside A,[19] a monocyclic analogue,[20] and the naturally occurring congener peloruside B (**2**, Fig. 1).[21]

There is experimental evidence pointing to a peloruside A binding site on β-tubulin that coincides with that of laulimalide (**3**, Fig. 1),[5] a highly potent macrolide isolated from the sponge *Cacospongia mycofijiensis* that also stabilises microtubules.[22] However, uncertainty remains about the exact binding mode of peloruside A within this site.[7]

There are a number of structural changes that might be explored in seeking an analogue that is as potent as, and synthetically more tractable than, peloruside A. It is noticeable that with existing analogues or congeners of peloruside A, removal or modification of the pyran impacts severely on cytotoxicity, suggesting that the presence and position of the pyran ring are crucial to the binding/activity.[20,23] In order to probe this further, we have chosen to

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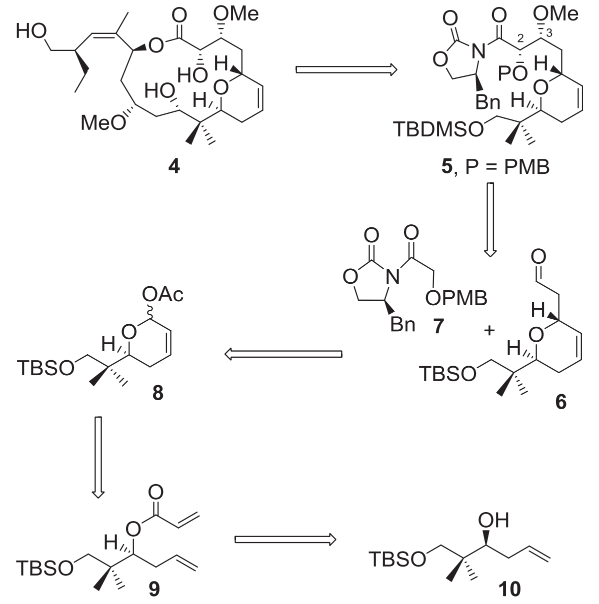
replace the pyranose ring of peloruside A with the dihydropyran of laulimalide, leading conceptually to analogue **4** (Scheme 1). The laulimalide-like dihydropyran presents the advantages over the peloruside A tetrahydropyran of having two fewer chiral centres and no hemiacetal functionality, thereby allowing greater ease of synthesis and higher metabolic stability. Several syntheses of laulimalide have been undertaken, with the most relevant to our work being that of Ghosh and Wang who prepared the dihydropyran using ring-closing methathesis.[24]



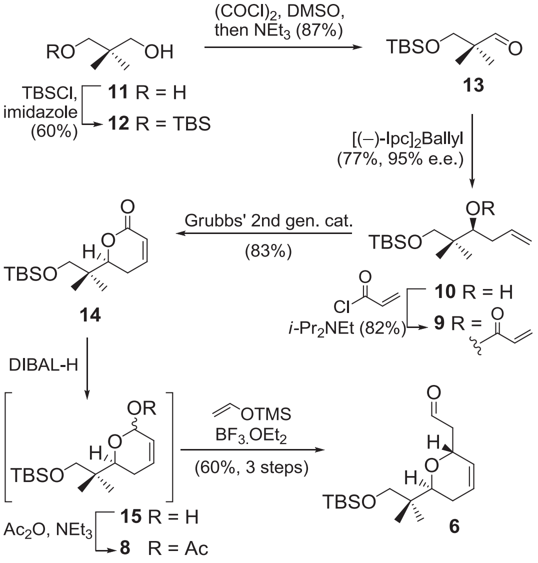
Scheme 1. Retrosynthetic strategy for the synthesis of simplified peloruside A analogue, **4**.

For optimal convergence in a synthetic strategy, precedent has shown it to be ideal to disconnect the macrocycle of peloruside A at both the lactone and a bond in the C9–C13 region. Two of the prior total syntheses have selected the C11–C12 bond for this latter purpose,[12,14] and the same strategy was implicit in the reported synthesis of the C12–C24 fragment by Stocker, Hoberg and ourselves.[18,25] We have thus targeted the synthesis of a C1–C11 analogue in the work presented here.

Our retrosynthetic analysis of the C1–C11 fragment of analogue **4** (viz. compound **5**) is shown in Scheme 1. A 1,2-*syn*-aldol reaction between aldehyde **6** and an Evans oxazolidinone **7** was envisaged to set the C2–C3 stereochemistry. Aldehyde **6** would be obtained by substitution of lactol acetate **8** with a vinyl enol ether nucleophile. Lactol acetate **8** would be synthesised by ring-closing metathesis of diene **9**, followed by reduction and acetylation. Diene **9** would ultimately be derived from acryloyl chloride and alcohol **10**, the product of an asymmetric Brown allylation of an unsymmetrically oxidised 1,3-propanediol.

2. Results and discussion

The synthesis of the C5–C11 fragment of analogue **4** proceeded as described in Scheme 2. Synthesis of allylic alcohol **10** began with monoprotection of 1,3-propanediol (**11**) to provide **12** in reasonable yield. Formation of the accompanying bis-protected product was minimised by using a slight excess of **11** over the protecting group. While several possible protecting groups were considered, ultimately the TBS group was chosen to provide stability through the synthesis of the C1–C11 fragment, whilst allowing orthogonal deprotection prior to oxidation and subsequent aldol coupling to a C12–C24 fragment. Alcohol **12** was subsequently oxidised in a reliably high yield under Swern conditions to provide aldehyde **13**. Allylation using Brown's boron-mediated asymmetric methodology provided secondary alcohol **10**. Although removal of magnesium salts created during the standard preparation of the allyldiisopinocampheylborane has been reported to improve enantioselectivity,[26] we found this to be unnecessary and we were able to obtain an ee of at least 95% according to Mosher ester analysis. Alcohol **10** was esterified with acryloyl chloride; subsequent ring-closing metathesis of the resulting diene **9** using Grubbs' second generation catalyst provided lactone **14**. Although a single step conversion equivalent to transformation of aldehyde **13** to lactone **14** via a vinylogous aldol reaction has been achieved,[27] our three-step approach allowed us to obtain good stereochemical control and a higher overall yield than reported for the single step transformation.



Scheme 2. Synthesis of C3–C11 fragment **6** via lactone **14**.

Synthesis of the C3–C11 fragment was completed in three further steps without purification of the intermediates in order to minimise degradation. Thus, careful reduction of **14** with DIBAL-H provided the hemiacetal **15** as a ca. 5:1 mixture of diastereomers, accompanied by about 10% of the ring-open aldehyde congener. This material was immediately acetylated under mild conditions to provide lactol acetate **8**, again as a mixture of diastereomers. Treatment with trimethyl(vinyloxy)silane under Lewis acidic conditions provided the C3–C11 aldehyde **6** in good overall yield, now as a single diastereomer. The laulimalide-like trans substitution across the dihydropyran of aldehyde **6** was confirmed by the observation of NOE correlations between H9 and H4a (Fig. 2). This stereochemical control presumably arises from steric shielding of one face of the conjugated oxonium intermediate by the bulky C9 substituent.

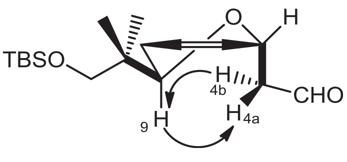


Fig. 2. NOE correlations within **6** confirming the trans-orientation of the ring substituents.

The required *syn*-relationship between the C2 and C3 substituents was set using an Evans' oxazolidinone-directed 1,2-*syn*-aldol reaction.[28] Oxazolidinone glycolate **7** is well known.[29]