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COMMUNICATION

Facile carbohydrate-based stereocontrolled divergent synthesis of (+)-pericosines A and B†

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An isomer-divergent synthesis of naturally occurring pericosines A and B is described starting from a known D-ribose derived ene-diol in 35% and 41% overall yields respectively of which the latter is the best synthetic method reported for pericosine B. The key features of this synthesis include the stereoselective NHK vinylation of the terminal aldehyde to the versatile diolefinic chiral intermediate and elegant conversions of the same to the corresponding final products *via* RCM (Ring Closing Metathesis).

Introduction

Pericosines A–E (Fig. 1) have gained considerable interest in the repertoire of synthetic organic chemistry since their isolation from the cytotoxic shikimate related metabolites of the fungus *Periconia byssoides*[1] found in the gastrointestinal track of the sea hare *Aplysia kurodai*. In the family of pericosines, the main focus of the cytotoxicity remained with pericosine A, due its significant growth inhibitory activity against protein kinase EGFR, human topoisomerase II and selective inhibition against human cancer cell lines HBC-5 and SNB-75 along with anticancer activity against P388 lymphocytic leukemia cells both *in vitro* and *in vivo*.[2] Understandably, several efficient synthetic efforts[3–5] have been initiated towards these compounds and their epimers in order to find a robust synthetic route and to allow their correct structural reassignments of which contributions from the Usami[4] group are worth mentioning. A more recent report of a chemoenzymatic synthesis of pericosines A–C by Stevenson[5] and coworkers is also a valid addition in this direction. The noticeable common feature of these approaches is that different chiral starting materials have been chosen for each different target in a scattered manner. Thus, we felt the urgent need for devising a divergent synthetic route for these highly potent targets which definitely fall under the category of multifuntionalized cyclohexenoid carbasugars.[6]

Carbohydrates are considered as important chiral starting materials for stereocontrolled synthesis of many natural products[7] due to their two distinct advantages; one is undeniably their easy availability with the other being their inherent chirality that can be well-manoeuvred for establishment of important chiral centers in the target compounds. With this backdrop of using a chirality-rich carbohydrate based starting materials; we envisaged our retrosynthetic plan based on a Ring-Closing Metathesis (RCM) mediated strategy[8] which is still not reported for pericosines to the best of our knowledge. Accordingly, a suitably substituted di-olefinic intermediate as a precursor for the cyclohexene core of the majority of the pericosine related targets looked evident. A close inspection revealed the resemblance of related stereocenters of this intermediate to those of D-ribose and these are in the desired orientation for the final products. We understood that the success of our synthetic effort essentially lay upon two important tasks ahead; how well we could retain all the three hydroxyl containing chiral centers of ribose and secondly, the introduction of the fourth one in a stereocontrolled manner. Thus, the known D-ribose derived ene-diol **6**[9] was identified as the ideal starting point for our approach. According to our plan selective oxidation of the diol to the terminal aldehyde followed by introduction of vinyl carbomethoxy group would lead to the versatile intermediate **8**, in which the fourth chiral hydroxyl substituent is embedded automatically. Now direct RCM cyclization or cyclization after methylation of **8** with the residual synthetic manipulations *en route* to both the pericosine A and B would be a be routine synthetic exercise (Fig. 2).

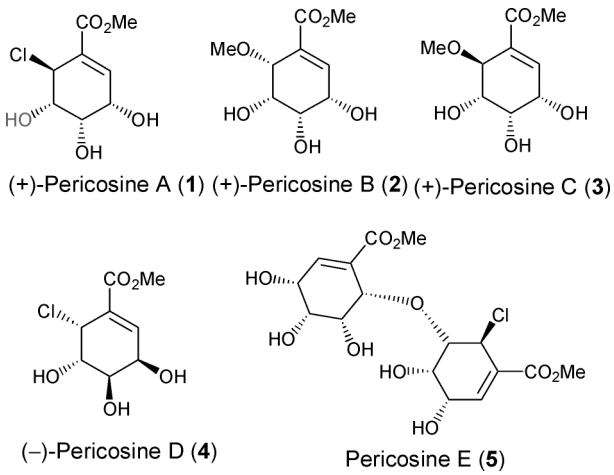

Fig. 1 Structures of naturally occurring pericosines.

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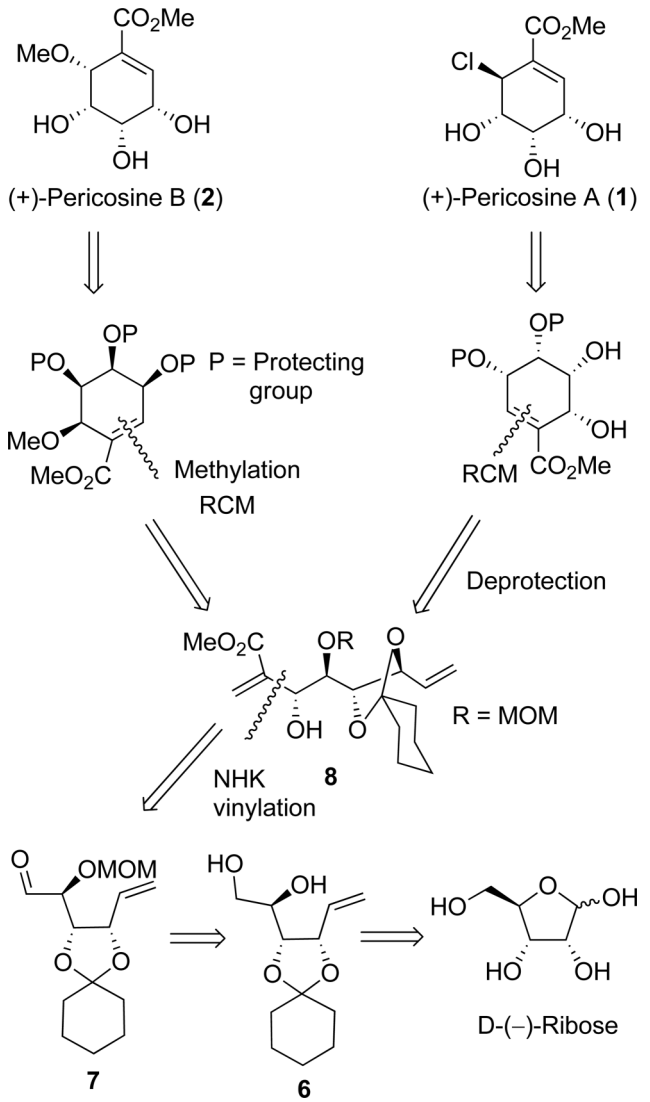
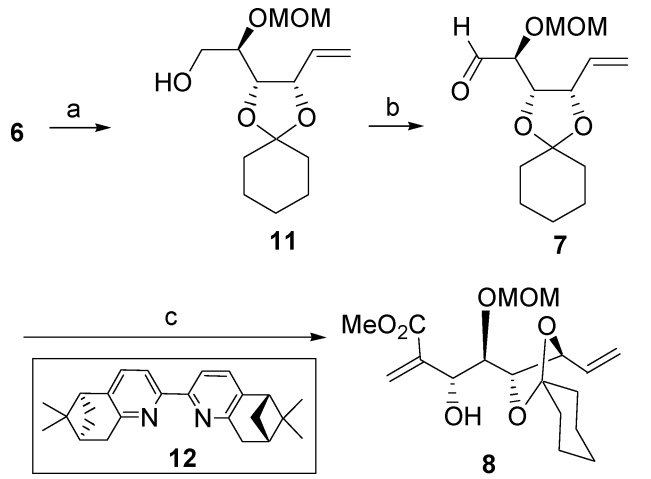


Fig. 2 Retrosynthetic analysis of pericosine A and B.



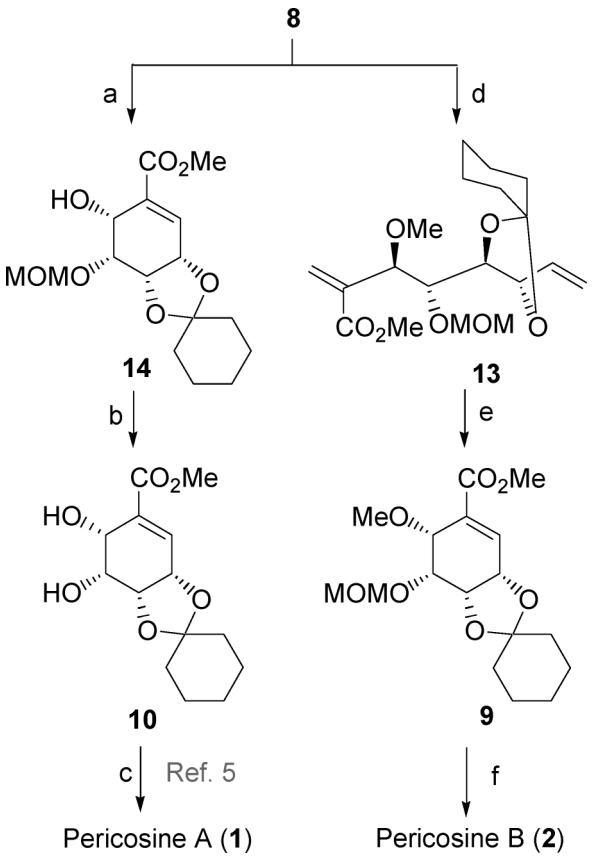
Scheme 1 *Reagents and conditions*: (a) (i) Me_3SiCl, imidazole, CH_2Cl_2, 0 °C to rt, (ii) MOMBr, DIPEA, DMAP, CH_2Cl_2, reflux, (iii) TBAF, THF, 86% (over three steps); (b) $(COCl)_2$, DMSO, TEA, CH_2Cl_2, −78 °C, 91%; (c) methyl 2-iodoacrylate, $CrCl_2/NiCl_2$ (2 : 1), **12**, THF, rt, 84%.

Results and discussion

Our synthetic journey began with the selective protection of the secondary alcohol functionality as its MOM ether of the known D-ribose derived vinyl diol **6** following a smooth protection–deprotection strategy. The primary TBS ether, isolated in high yield from **6** was treated with MOMBr–DIPEA conditions[10] in refluxing CH_2Cl_2 to give fully protected **11**, desilylation thereof and subsequent Swern oxidation furnished the desired terminal aldehyde **7** in 78% isolated overall yield over four steps (Scheme 1). Now the stage is set for the stereoselective C–C bond formation through Nozaki–Hiyama–Kishi (NHK) reaction[11] Based on our vast experience in the field asymmetric NHK reactions by using bis-pinenopyridine ligands[12] on various aromatic as well as aliphatic aldehydes and ketones, we envisaged the application of the same protocol to the task in hand. Gratifyingly, NHK reaction of terminal aldehyde **11** with methyl 2-iodoacrylate[13] using simple bis-pinenopyridine ligand **12**[12] worked well with a very high degree of distereoselectivity.[14] The reaction not only established the very important hydroxyl functionality which could be strategically utilizable for a diversified approach leading to both **1** and **2**, but also appends a non-terminal carbomethoxy substituent and double bond with it. Obviously, at this point the absolute stereochemistry of the generated hydroxyl at C-3 in the major isomer may be doubted and accordingly we realized that a decision could be made only after elaboration of this intermediate to a particular target molecule. Then, confirmation could be made by comparison of data with that of the corresponding reported values. Thus, we felt pericosine B could be the ideal target to serve this purpose as it could be accessible *via* a three step sequence *viz* methylation, RCM and deprotection without affecting the chiral center in question.

Much to our expectation the selection of suitable methylation condition[15] proved to be a tricky one as the substrate contained both acid and base sensitive functional groups within. Almost all methylation protocols, with MeI under strong to moderate basic conditions, indeed proved futile as they ended up in hydrolysis of the important carbomethoxy substituent instead, in most cases. Even, mild neutral methylating reagents,[16] *e.g.* MeI with freshly prepared Ag_2O, were unreactive to this particular substrate. This unusual passivity of the hydroxyl group towards methylating reagents could be explained by possible involvement of intramolecular hydrogen bonding of the hydroxyl proton with the adjacent carbomethoxy carbonyl. Even the failed attempt of methylation of the same hydroxyl after the RCM substantiated our claim. Finally, carrying out the reaction in scrupulously dried ether at reflux in the presence of excess MeI and powdered KOH as base; till the disappearance of starting material followed by a quick non-aqueous work up, afforded 76% of the product, which helped to get over the impasse in the methylation step. Subsequent RCM reaction in the penultimate step was smooth with Hoveyda–Grubbs (II) (HG-II) catalyst in refluxing toluene; produced the cyclohexene core in 86% yield, followed by a TFA induced global deprotection lead to the final product **2**. Thus, we were able to synthesize pericosine B in 41% overall yield from **6** which happens to be the best reported in the literature for this molecule. Furthermore, the spectroscopic data of pericosine B synthesized by us were in excellent agreement with reported values, and settled the absolute stereochemistry of the generated chiral

center of **8** during NHK vinylation step as well as detailed in the Scheme 2.



Scheme 2 *Reagents and conditions*: (a) HG-II cat., toluene, reflux, 86%; (b) Cp_2ZrCl_2, isopropanol, 83%; (c) (i) 1-chlorocarbonyl-1-methylethyl acetate, MeCN, 0 °C, 15 min, rt, 2 h, (ii) MeOH, cat. MeCOCl, rt, 12 h; (d) MeI, KOH, 76%; (e) HG-II cat., toluene, reflux, 86%; (f) TFA(aq), 96%.

Our next target pericosine A, the most potent member of the pericosine family, was synthesized by cyclization of the NHK product under similar RCM conditions as mentioned before to the corresponding cyclohexenoid intermediate **14** in 86% yield. As expected, the selective deprotection of MOM ether in presence of cyclohexylidene moiety to intermediate diol **10** would be crucial as the remaining synthetic elaboration to the target is known. Indeed, several attempts with a variety of conditions for attainment of selectivity in the deprotection step were unsuccessful as they led to either global deprotection or no reaction. Even the use of Lewis acids *e.g.* $ZrCl_4$[17] for MOM deprotections where acetonides are reported to survive, proved fatal to our case. Finally, the method developed in our laboratory was as follows: deprotection under mild condition using Cp_2ZrCl_2, selectively cleaved MOM ether in 83% yield and the product diol was successfully converted to the target pericosine A following Stevenson's protocol[5] recording an overall yield of 35% from **6**. Consequently, we succeeded in synthesizing both the members of pericosine family from easily available acyclic starting material following a well defined divergent methodology in a reasonably good overall yield utilizing RCM reaction as key step.

Conclusion

In essence, we have demonstrated the first RCM driven isomer-divergent stereocontrolled synthesis of both isomers of pericosine family pericosines A and B from an easily available carbohydrate based acyclic precursor with 35% and 41% overall yields respectively. Our method provides a simple means to these chirality-rich targets without unnecessary dragging of synthetic steps. We feel the well-knotted use of NHK vinylation and RCM in our effort should find application in simplifying problems in many related synthesis in future.

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