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A common and versatile synthetic route to (−) and (+) pentenomycin I, (+) halopentenomycin I and dehydropentenomycin

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ABSTRACT

A versatile and stereoselective total synthesis of (+) and (−) pentenomycin I, (+) halopentenomycins I and dehydropentenomycin from a common chiral polyhydroxylated cyclopentene through oxidation and protection/deprotection has been described. Stereoselective hydroxymethylation, stereoselective Grignard reaction and ring closing metathesis are the key features of our approach.

1. Introduction

Cyclopentenones and their congeners[1] are widely used as chiral building blocks in organic synthesis and have been used for the synthesis of a large number of natural and unnatural products such as punaglandins **1**,[2] xanthocidin **2**,[3] untenone A **3**,[4] and (−) pentenomycin I **4**,[5] prostaglandins,[6] cyclopentanoid monoterpenoids,[7] carbocyclic nucleosides,[8] etc. (Fig. 1). In addition, a diverse range of natural products for example didemnenone **6**, parthenin **7**, tricycloclavulone **8**, etc.[9–11] contain cyclopentenone structural entities as important segments in their basic core structures (Fig. 1). Generally such molecules bearing cyclopentenone framework exert their biological effects through highly reactive α, β unsaturated carbonyl center which behaves as an excellent Michael acceptor toward various cellular nucleophiles.[12] Moreover, the highly oxygenated cyclopentanoid analogues are of increasing interest among the synthetic chemists because of their promising biological activity profiles[13] such as glycosidase inhibitor,[13a–g] aminoglycosidase antibiotic,[13h] anticancers,[13i–l] etc. In particular, pentenomycin, a cyclopentanoid class of antibiotics, exhibits moderate to strong activity against both Gram-positive and Gram-negative bacteria.[5a] It was isolated by Umino and co-workers in 1973 from culture strains of *Streptomyces eurythermus*.[5b,c] The assemblage of a variety of reactive functional groups along with the quaternary chiral center makes the molecule interesting for its synthesis. In addition, pentenomycin congeners with interesting biological properties have generated renewed interest in the chemistry of cyclopentanoid within past few years.[14–19] Various synthetic methods such as ring closing metathesis,[14] 1,3-dipolar nitrone alkene cycloaddition,[15] Pauson–Khand reaction,[16] Diels–Alder cycloaddition followed by decarbonylation[17] etc. have been reported regarding the total synthesis of pentenomycin including both racemic as well as enantiopure forms. Recently, Rao's group[18] have reported the synthesis of both natural (−) and unnatural (+) pentenomycin I using Tebbe olefination and intramolecular aldol condensation as their key steps.

Although many successful synthetic methods have been reported for the total synthesis of pentenomycin,[19] however, there is a still demand to synthesize both the isomers of pentenomycin I from a single precursor. On this line, dehydropentenomycin **5** (Fig. 1) is a closely related member of the pentenomycin family and has reasonable antibiotic potency.[20a,b] However a limited literature is available for the total synthesis of dehydropentenomycin.[20c] Therefore, we wish to report herein the total synthesis of both natural (−) and unnatural (+) pentenomycin I, dehydropentenomycin and halo derivatives of unnatural (+) pentenomycin I from a polyoxygenated cyclopentene as the common chiral building block, which has been synthesized from easily available starting material D-ribose *via* stereoselective hydroxymethylation, stereoselective Grignard reaction and ring closing metathesis as key steps.

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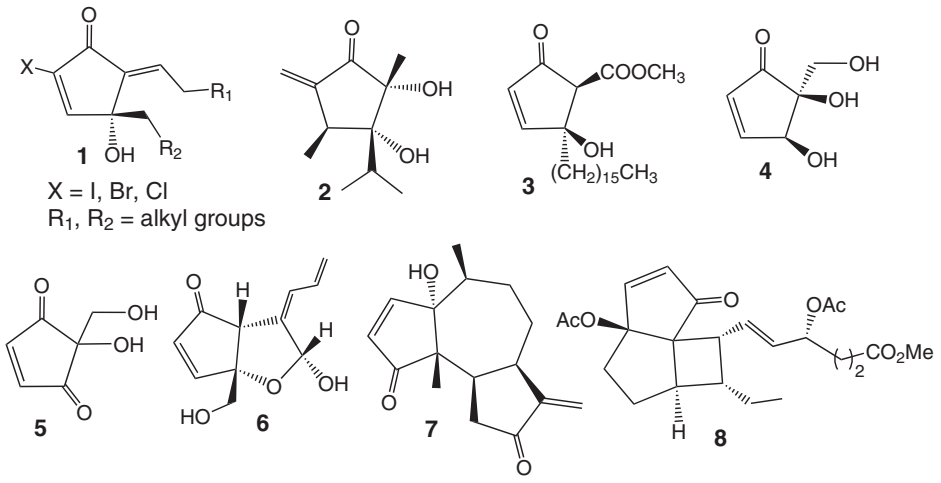


Fig. 1. Naturally occurring biomolecules: punaglandins **1**, xanthocidin **2**, untenone-A **3**, (−) pentenomycin I **4**, dehydropentenomycin **5**, didemnenone **6**, parthenin **7**, tricycloclavulone **8**.

2. Result and discussion

As a part of our ongoing research for the exploration of novel carbocyclic nucleoside template, and inspiration from the extensive and pioneering work of Jeong and co-workers,[21] we devised a common synthetic strategy for the total synthesis of both (+) and (−) pentenomycin I, (+) halopentenomycin I as well as dehydropentenomycin as shown in Scheme 1.

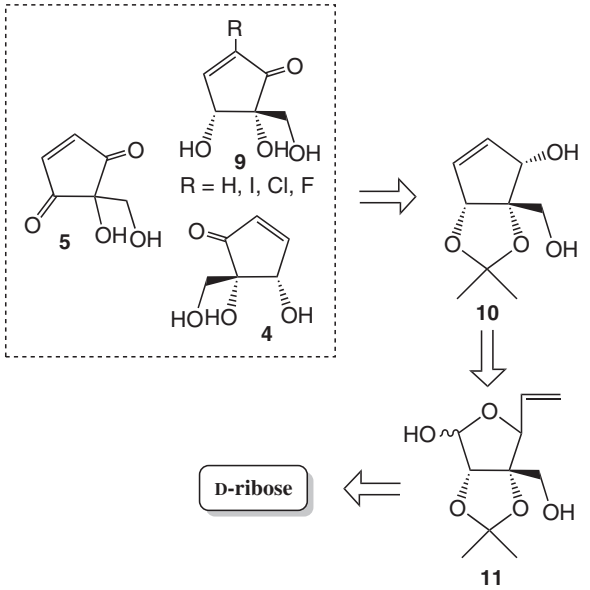
The carbocyclic framework **10** was envisioned as being a versatile synthetic building block towards the synthesis of pentenomycin analogues and dehydropentenomycin *via* oxidation, functional group transformations and deprotection. The carbocyclic framework **10** in turn could be obtained from the lactol **11** using Wittig and RCM reaction. The lactol **11** can be prepared from D-ribose *via* protection, stereoselective hydroxymethylation, stereoselective Grignard followed by oxidative cleavage.

A unified and general approach for chiral cyclopentenol **10** was commenced with the protection of D-ribose to 2,3 acetonide protected D-ribose **12** by treatment with catalytic amount of conc. H_2SO_4 in acetone. It was followed by stereoselective aldol condensation[22] using 37% aqueous formaldehyde in methanol to yield hydroxymethylated compound **13** which established a quarternary chiral center at the desired position with very good yield.

The hydroxymethylated compound **13** was subjected to a stereoselective Grignard reaction with vinyl magnesium bromide in THF under –78 °C to yield the ring opened polyhydroxylated alkene **14**. The stereoselectivity of Grignard reaction may be explained *via* the Felkin–Anh cyclic chelate transition model as shown in Fig. 2. This chelate transition state explains the β-attack of nucleophile from the less hindered face providing a single stereoisomer in a predominant amount. It was observed that Grignard reaction on acetonide protected D-ribose without hydroxymethylated chain[23] and with hydroxymethylated chain conserves the steroselectivity.

It was directly used for next step without purification due to its high polar nature. The ring opened Grignard adduct **14** was subjected to oxidative cleavage with sodium *m*-periodate in order to yield the desired lactol intermediate **11**. Wittig olefination of lactol **11** with methyl triphenylphosphonium ylide gave the diene **15** in a satisfactory yield which set the stage for ring closing metathesis.[24] Cyclization proceeded smoothly on the substrate **15** by employing Grubbs' second generation catalyst providing the cyclopentenol **10** in quantitative yield (Scheme 2). The structure of cyclopentenol **10** has been deduced through ^1H and ^{13}C NMR and HRMS. The stereochemical structure of compound **10** was confirmed with the help of single crystal X-ray structure (Fig. 3).

Selective allylic oxidation of **10** afforded the cyclopentenone **17** in a good yield. Then acetonide deprotection was accomplished by



Scheme 1. Retrosynthetic analysis.

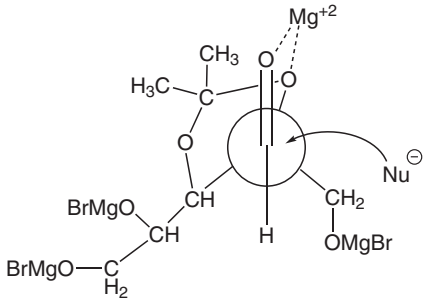


Fig. 2. Felkin–Anh cyclic chelate transition model.