Carbohydrate Research 388 (2014) 130–137

Contents lists available at ScienceDirect

Carbohydrate Research

journal homepage: www.elsevier.com/locate/carres

Toward synthesis of carbasugars (+)-gabosine C, (+)-COTC, (+)-pericosine B, and (+)-pericosine C

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ARTICLE INFO

Article history:
Received 24 June 2013
Received in revised form 3 August 2013
Accepted 9 August 2013
Available online 20 August 2013

Keywords:
Carbasugars
Streptomyces
Periconia byssoides
Morita–Baylis–Hillman (MBH) reaction
Luche reduction D-(−)-isoascorbic acid and D-ribose

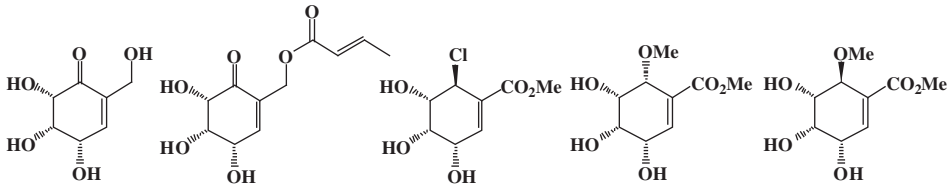
ABSTRACT

Asymmetric total synthesis of (+)-gabosine C, (+)-pericosine B, and (+)-pericosine C has been reported from readily available D-(−)-isoascorbic acid and D-ribose involving *Grubbs* ring closing metathesis, *Morita–Baylis–Hillman* (MBH) reaction, and *Luche* reduction.

1. Introduction

Carbasugars demonstrate glyoxylase inhibitory, antitumor, antibacterial, antifungal, antimalarial, and antiviral activities.[1] Among them gabosines and pericosines exhibit a pivotal role, which are cyclohexene carbasugars. An account of isolation of gabosines and pericosines, their synthetic studies and biological activities has been found in the literature.[2–4] In 1974 (−)-gabosine C, was isolated from culture broth of *Streptomyces filipensis*,[2a] that has been identical to a known antibiotic KD16-U1. Later its crotonic ester was isolated from the culture broth of *Streptomyces griseosporeus*, known as (−)-COTC and shown to be a potent glyoxylase I inhibitor.[2b,c] Pericosines (A–E) were isolated from a micro organism *Perconia byssoides* (OUPS-N133) separated from the gastrointestinal tract of the sea hare *Aplyasia kurodai*.[4a,h] (+)-Pericosine A (**3**), (+)-pericosine B (**4**), and (+)-pericosine C (**5**) demonstrated remarkable activity (ED_{50} = 0.1, 4 and 10.5 μg/mL, respectively) against P388 lymphocytic human cancer (leukemia) cells.[4a,h,i]

Common structural building of (+)-gabosine C (**1**), (+)-COTC (**2**), (+)-pericosine A (**3**), (+)-pericosine B (**4**), and (+)-pericosine C (**5**), and their biological activity inspired us in their synthesis. For the past several years we have been engaged in the synthesis of biologically active compounds by using natural and commercially available sources.[5,6]



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† Condolences: We expressing our deepest grief and sorrow for sudden death of Dr. Y. Vekateswarlu on 17th July, 2013. He is an excellent teacher and human being; he supported and encourages us at stages of our research career.

http://dx.doi.org/10.1016/j.carres.2013.08.008
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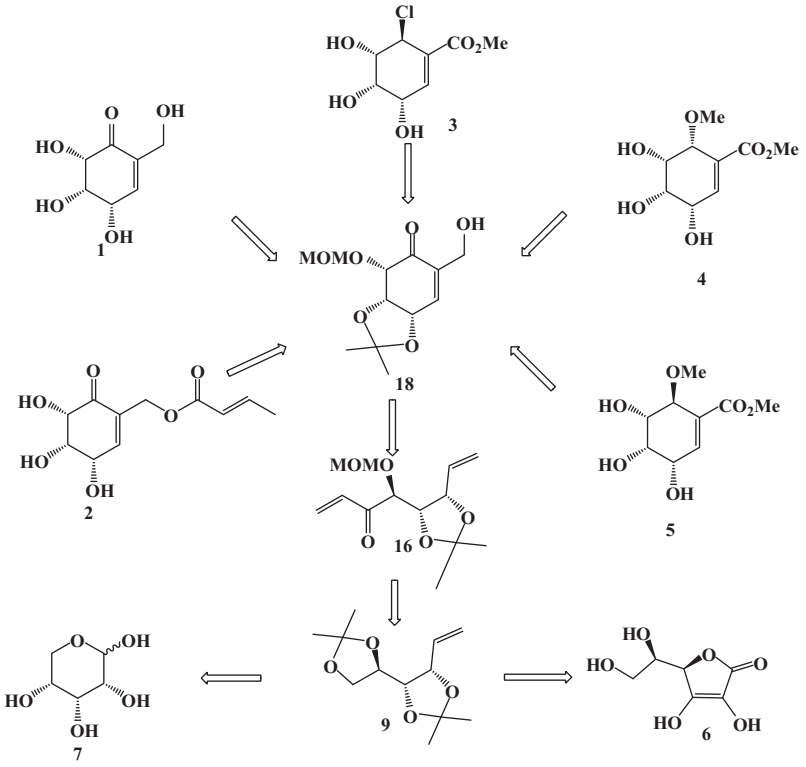
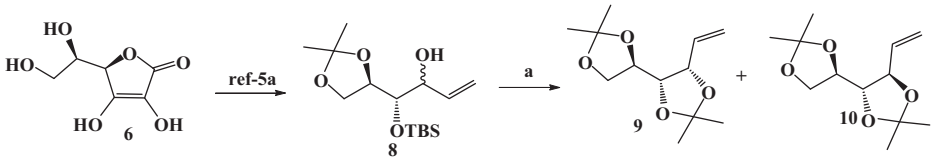
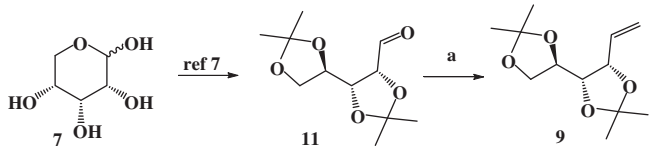


Scheme 1. The retro synthetic analysis of the (+)-gabosine C (**1**), (+)-COTC (**2**), (+)-pericosine A (**3**), (+)-pericosine B (**4**), and (+)-pericosine C (**5**).



Scheme 2. Reagents and conditions: (a) (i) TBAF, THF, rt, 8 h, (ii) 2,2 DMP, TsOH, DCM, 12 h, two steps 85%.



Scheme 3. Reagents and conditions: (a) ^{t}BuOK, $PPh_3PCH_3^+Br^-$, THF, −10°, 4 h, 75%.

2. Results and discussion

We envisaged (Scheme 1) that a common intermediate **18**, that would give (+)-gabosine C (**1**), (+)-COTC (**2**), (+)-pericosine A (**3**), (+)-pericosine B (**4**), and (+)-pericosine C (**5**) which in turn could be obtained from *Grubbs* cross metathesis reaction of allyl ketone **16** followed by employing and *Morita–Baylis–Hillman* reactions as key steps. Ketone **16** can be derived from diacetonide **9** using sequential reactions, which could be furnished from either D-(−)-isoascorbic acid **6** or D-ribose **7**.

Accordingly, alcohol **8** was obtained from D-isoascorbic acid[5a] (Scheme 2). The TBS protecting group in **8** was removed using TBAF to give diol, which was protected with 2, 2 DMP in DCM to give separable diastereomers compound **9** and compound **10**. In a different route compound **9** was prepared from compound **11** which in turn prepared from D-ribose (Scheme 3).[7] Accordingly, aldehyde **11** was converted into compound **9** using *Wittig* reaction with methyltriphenylphosphonium bromide salt in the presence of ^{t}BuOK.

Hydrolysis of primary acetonide in compound **9** in PPTS/methanol at 0 °C yielded diol **12** (Scheme 4) in 70% yield. The primary alcohol in compound **12** was selectively protected with benzoyl chloride in the presence of pyridine to afford benzoyl ester **13** in 92% yield. Further, the secondary alcohol was masked as MOM ether using MOM-Cl and DIPEA (*Hunig's* base), followed by deprotection of benzoyl group in compound **13** with K_2CO_3 leading to the desired primary alcohol **14**. Now, alcohol **14** was oxidized to corresponding aldehyde using *Swern* oxidation, which on treatment with vinyl magnesium bromide afforded a diastereomeric mixture of alcohol **15**, which was oxidized to enone **16** by treating with IBX in DMSO. Compound **16** was subjected to ring closing metathesis reaction (RCM) using *Hoyeda Grubbs* catalyst to afford cyclohexenone **17** in 60% yield for 8 h. The *Morita–Baylis–Hillman* reaction for α-hydroxymethylation on cyclohexenone **17** was attempted with aqueous formaldehyde (37%) in the presence of imidazole and 1 M $NaHCO_3$ in THF to obtain a mixture of products.[8] However, when compound **17** was reacted with aqueous formaldehyde (37%) in the presence of DMAP at −10 °C furnished intermediate **18** in 38% yield for 3 days.[9] The protecting groups MOM and acetonide in compound **18** were removed using trifluoroacetic acid in methanol to afford (+)-gabosine C (1), [mp 113–115 °C and optical