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Application of lithium *n*-butylselenolate in the total syntheses of (+)-Pericosine B, (+)-Pericosine C, (+)-COTC and 7-chloro-analogue of (+)-Gabosine C

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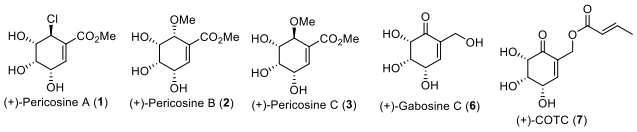
1 Introduction

Carbasugars are important carbohydrate analogs in which the ring oxygen is replaced with a methylene group. This change has no significant impact on structure (bonds length, torsion angles, conformation) but strongly affects biological activity (pharmacokinetics, molecule-enzyme interactions).[1] The therapeutic potential of some carbasugars has led to a growing interest in their development and identification.



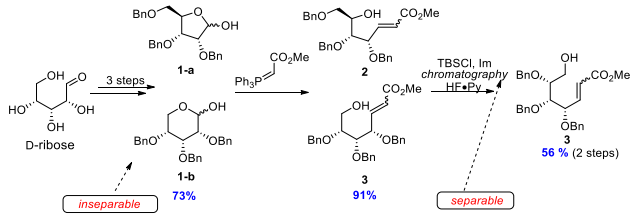
Pericosines (A-E) are a subclass of carbasugars and they have been shown to display a wide range of interesting biological activities such as significant cytotoxicity against P388 lymphocytic human cancer cells, growth inhibition of tumor cell lines HBC-5 and SNB-75, and inhibition of some enzymes including human topoisomerase II or protein kinase EGFR.[2]

In 1974 **(-)-Gabosine C** was isolated from a culture broth of *Streptomyces filipensis* and is identical to a known antibiotic KD16-U1.[3] The crotonic ester of (-)-Gabosine C is known as a **(-)-COTC** and was reported to possess cytotoxic and cancerostatic activity.[4,5]

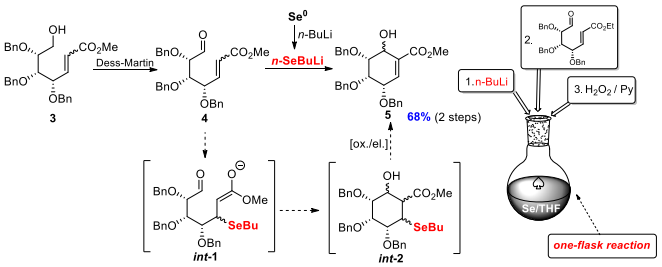
In this work, we present our recent studies of the application of the **lithium *n*-butylselenolate** as an initiator in tandem seleno-Michael/aldol process in carbasugar synthesis involving D-ribose as a readily available and cheap starting material.[6]

2 Methods

The first 6 steps focused on the preparation of linear precursor **3** from D-ribose. The inability to separate pyranoses from furanoses after 3 steps forced us to turn our attention to reagents selective towards primary hydroxyl groups. We chose medium hindered and reactive *tert*-butyldimethylsilyl chloride. The removal of the TBS-ether with an excess of Olah's reagent was quantitative and allowed obtain the desired **3** in **37% yield over 6 steps** from D-ribose.



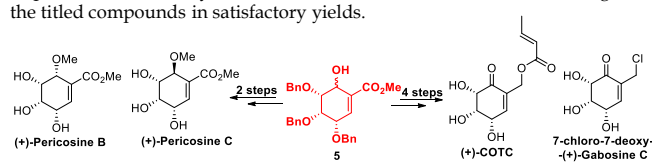
Oxidation of the primary hydroxyl group with Dess-Martin periodinane gave carbasugar precursor **4** as a mixture of diastereoisomers (*E*/*Z* 0.51:1) in a very good yield. The received precursor undergoes a cyclization process induced by ***n*-butylselenolate generated *in situ* from elemental selenium and *n*-butyllithium.** Then consecutive oxidation-elimination steps allowed us to obtain the carbocyclic core **5** in **68% yield** as a nearly equimolar mixture of *syn* and *anti* diastereoisomers.



The obtained carbocyclic core was transformed to obtain derivatives of compounds with documented biological activity (*results*).

3 Results

Further transformation of the carbocyclic core involving a regioselective Steglich esterification or methylation of the secondary hydroxyl group gave rise to protected (+)-COTC, (+)-Pericosine B and (+)-Pericosine C. Deprotection of benzyl ethers with boron trichloride at -78°C gave the titled compounds in satisfactory yields.



Product	Number of steps	Yield [%]
(+)-Pericosine C	2	43
(+)-Pericosine B	2	10
(+)-COTC	4	11
7-chloro-7-deoxy-(+)-Gabosine C	4	17

4 Conclusions

We have synthesized three known carbasugars: **(+)-Pericosine B, (+)-Pericosine C, (+)-COTC (unnatural) and novel derivative 7-chloro-7-deoxy-(+)-Gabosine C** using ***n*-butylselenolate** in intramolecular seleno-Michael/aldol reaction as a key. The developed procedure seems to be a good method for synthesis of the carbasugarcore in general. The newly obtained 7-chloro-analogue of (+)-Gabosine C could be an interesting building block for the preparation of more complex carbasugar structures.

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