Selenium as Antioxidant: New Glycoconjugates to Prevent Oxidative Stress

Luigia Serpico,[a] Mauro De Nisco,[b] Flavio Cermola,[a] Michele Manfra,[b] Claus Jacob,[c] Silvana Pedatella[a]

[a]Department of Chemical Sciences, University of Napoli Federico II, Via Cintia 4, I-80126 Napoli, Italy
[b]Department of Sciences, University of Basilicata, Viale dell'Ateneo Lucano 10, I-85100 Potenza, Italy
[c]Department of Pharmacy, Saarland State University, D-66123 Saarbruecken, Germany

luigia.serpico@unina.it

Introduction

Oxidative stress (OS) is an altered intracellular condition in which an increased production of reactive oxygen species (ROS) occurs. ROS are small biological molecules that contain oxygen and one or more unpaired electrons; they are very reactive and are involved in cell death and hence neurodegeneration through an array of different pathways.[1] In the last decades, antioxidant therapies have been proposed to prevent ROS-induced injury which is a hallmark of several diseases, such as cardiovascular diseases, Alzheimer's disease, and cancer.[2]

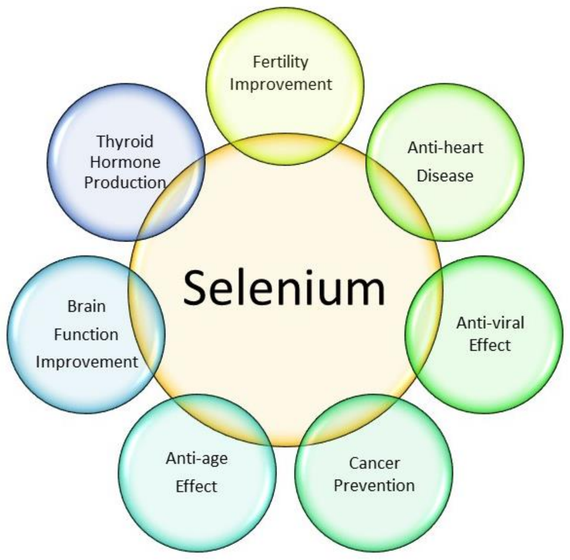


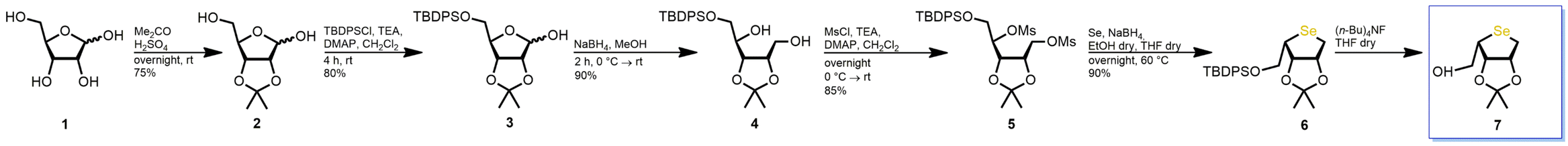
Figure 1. Selenium functions.

New potential antioxidant molecules

Selenium is an essential trace element for human health owing many biological functions (**Fig. 1**). Indeed, Reactive Selenium Species (RSeS),[3] like redox and biologically active selenium molecules of natural origin, have been gaining interest over the past decade and have led to the development of various reaction strategies for accessing new Se-compounds that turned out to be potent antioxidant agents with modest effect on normal tissues and clinically well tolerated.[4]
Among the other molecules with good antioxidant properties are polyphenolic compounds,[5] as caffeic acid, curcumin and dopamine.
As part of our current interest in novel and more efficient supplements to be used in oxidative stress prevention, we designed and synthetized new molecules having both a phenolic moiety and selenium in a sugar-type structure which in turn should provide a carrier function.

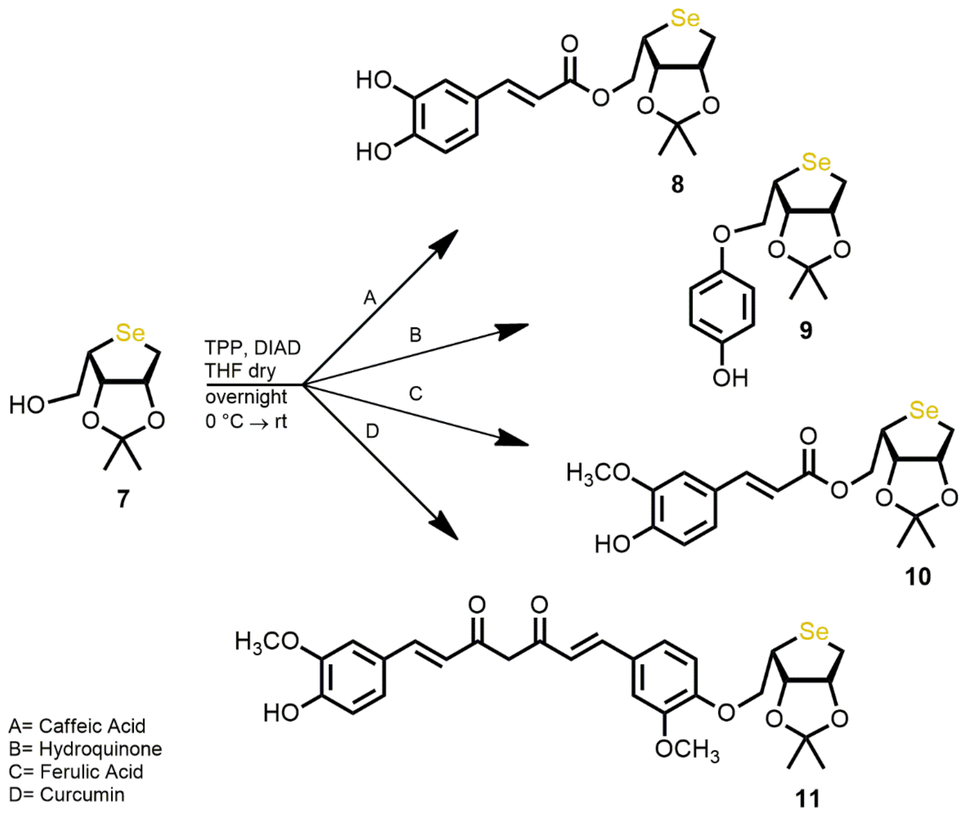
Synthesis

First of all, we prepared the seleno-sugar **7** with 39% overall yield starting from the commercially available D-ribose exploiting a reported procedure[6] as described in the **Scheme 1**. Compound **7** was then used as building block in the preparation of the new glycoconjugates.

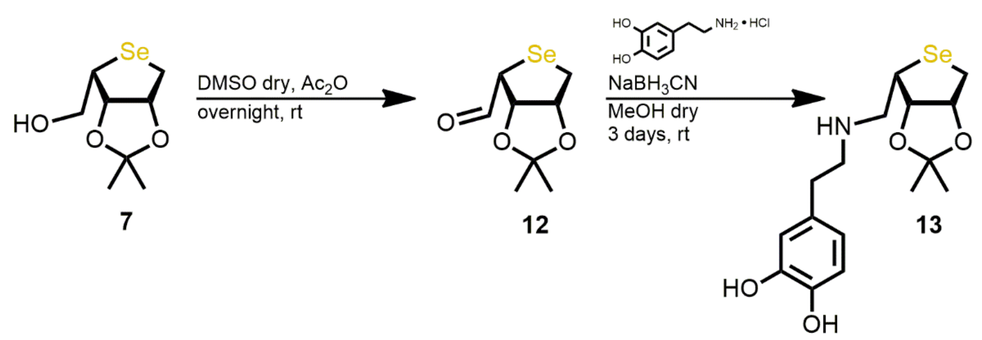


Scheme 1. Synthesis of seleno-sugar **7**.

Therefore, we elaborated two different synthetic pathways to introduce the selected phenolic units. Namely, the latter were linked to derivative **7** by a Mitsunobu reaction, leading to derivative **8**, **9**, **10** and **11** (**Scheme 2**). Whereas a Swern oxidation of seleno-sugar **7** followed by a reductive-amination provided the glycoconjugate **13** containing a dopamine residue (**Scheme 3**).
All compounds have been obtained with good yields (40-60%); then they have been fully characterized by 1D- and 2D-NMR spectroscopy.

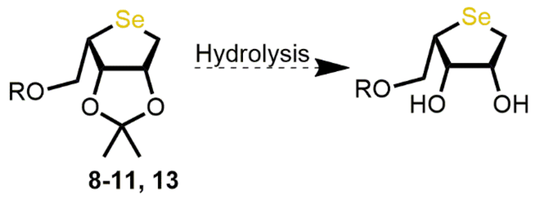


Scheme 2. Synthesis of glycoconjugates **8**, **9**, **10** and **11**.



Scheme 3. Synthesis of glycoconjugate **13**.

Due to the labile nature of the products, presently we are investigating conditions to remove the isopropylidene protecting group. Indeed, in a pilot study, the use of a solution of AcOH/H_2O (8:2) for two hours, at 80 °C furnished promising results (**Scheme 4**).



Scheme 4. Removal of protecting group.

Future Perspectives

All compounds (**8-11**, **13** and their deprotected derivatives as well), will be tested to evaluate their antioxidant activity:
- preliminary **DPPH** (2,2-diphenyl-1-picrylhydrazyl) and **FRAP** (Ferric Reducing Antioxidant Power) assays.
- Bioassays to test both their potential toxicity than their beneficial effects in model biological systems.

1. Reynolds, A.; Laurie, C.; Mosley, R.L.; Gendelman H.E. *Int. Rev. Neurobiol.* **2007**, *82*, 297-325.
2. a) Lin, M.T.; Beal. M.F. *Nature* **2006**, *443*, 787-795. b) Barnham, K.J.; Masters, C.L.; Bush, A. I. *Nat. Rev. Drug Discov.* **2004**, *3*, 205-214.
3. Nasim, M.J.; Ali, W.; Domínguez-Álvarez, E.; da Silva Júnior, E.N.; Saleem, R.S.Z.; Jacob, C. In *Organoselenium Compounds in Biology and Medicine: Synthesis, Biological and Therapeutic Treatments*, Vimal Kumar Jain and K. Indira Priyadarsini (Eds.), RSC Publishing, Cambridge, Chapter 10, **2017**, 277-302.
4. Schiesser, C.H.; Storkey, C.; Davies M.J. *U.S. Patent* No. US 2015/0191446A1.
5. Shahidi, F.; Priyatharini A. *J. Func. Foods* **2015**, *18*, 820-897.
6. Jeong, L.S.; Tosh, D.K.; Kim, H.O.; Wang, T.; Hou, X.; Yun, H.S.; Kwon, Y.; Lee, S.K.; Choi, J.; Zhao, L.X. *Org. Lett.* **2008**, *10*, 209-212.

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