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Glucosinolates: The synthetic approach[☆]

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ABSTRACT

Acting generally as bio-precursors of isothiocyanates, glucosinolates (GLs) are important thiosaccharidic metabolites which occur in all plant families of the order Brassicales – namely in our daily vegetables. All known GLs (*ca* 120 characterized molecules) display a remarkable structural homogeneity invariably based on a β-D-glucopyrano unit and an O-sulfated anomeric *(Z)*-thiohydroximate function connected to a side chain which constitution, depending on plant species, is the sole structural variant. Dedicated extractive methods allow one to isolate a number of GLs from adequate plant material, but in many cases, organic synthesis brings crucial help for the production of natural GLs. In other respects, synthesis is the only way to elaborate a diversified range of artificial GL analogues. This account summarizes the varied synthetic approaches developed by us and by others since the early 1960s.

RÉSUMÉ

Les familles de l'ordre végétal des Brassicales – qui rassemblent une partie notable de nos légumes quotidiens – sont chimio-caractérisées par la présence de métabolites secondaires de nature thiosaccharidique appelés glucosinolates (GLs), qui opèrent en général comme des bio-précurseurs d'isothiocyanates. La structure de ces métabolites comporte invariablement trois parties: une unité β-D-glucopyranosyle, une fonction thiohydroximate anomérique O-sulfatée et une chaîne latérale dont la constitution est la seule variable naturelle, selon les espèces (environ 120 molécules caractérisées). Des méthodes extractives dédiées permettent d'isoler à partir du matériel végétal approprié un certain nombre de ces GLs mais dans bien des cas, la synthèse apporte un renfort décisif pour la production de GLs naturels. Elle est par ailleurs incontournable pour élaborer les analogues artificiels les plus variés. Cette revue recense les différentes approches synthétiques qui ont été développées depuis les premiers travaux de M.G. Ettlinger et de M. Benn au début des années 1960.

1. Introduction

From the writings of Hippocrates (460–356 BC) about the consumption of cress and poems by Horatius (65–68 BC) on the flavour of cabbage to the "*Natural History*" by Pliny the Elder (23–79 AD) and the "*De Materia Medica*" pharmacopoeia drawn up by Dioscorides (40–90 AD), the beneficial effects of vegetables of the crucifer family have long been observed. Nowadays, this positive health impact is recognized to be due to sulfur-containing secondary metabolites known as glucosinolates (GLs).

These chemical tags are the most strikingly bio-relevant thiosaccharidic molecules in the order Brassicales, which includes 16 plant families (Table 1) of dicotyledonous

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[☆] In memory of the late Pr Wolfgang Walter (Universität Hamburg), a reputed organosulfur chemist, who first suggested to draw up such an account.

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Table 1
The botanical order Brassicales.

Bataceae	*Moringaceae*
Brassicaceae (cabbages)	*Pentadiplandraceae*
Bretschneideraceae	*Phytolaccaceae*
Capparaceae (capers)	*Pittosporaceae*
Caricaceae (papaya)	*Resedaceae* (reseda)
Euphorbiaceae	*Salvadoraceae*
Gyrostemonaceae	*Tovariaceae*
Limnanthaceae	*Tropaeolaceae* (Indian cress)

angiosperms among which the Brassicaceae (synonymous of Cruciferae) are by far the most important, because they encompass 350 plant genera and *ca.* 3200 species [1].

Associated in plants with an atypical glycohydrolase, myrosinase (E.C.3.2.1.147), GLs behave and, in fact, operate like bio-precursors – in accordance with Robiquet's prediction [2] – to produce electrophilic isothiocyanates, compounds displaying a diversified and generally marked biological activity including, in certain concentrations, high cytotoxicity [3]. Indeed, myrosinase-assisted hydrolytic cleavage of those S-glucopyranosyl thioesters – erroneously called "thioglucosides" – releases a labile aglycon which is converted into isothiocyanate through a Lossen-type rearrangement (Scheme 1).

All known GLs (*ca* 120 molecules) display a remarkable structural homogeneity based on a hydrophilic β-D-glucopyrano unit, a O-sulfated anomeric *(Z)*-thiohydroximate function connected to a rather hydrophobic side chain whose constitution, depending on plant species, is the sole structural variant (Scheme 2) in which diversified aliphatic, arylaliphatic or heterocyclic arrangements can be found.

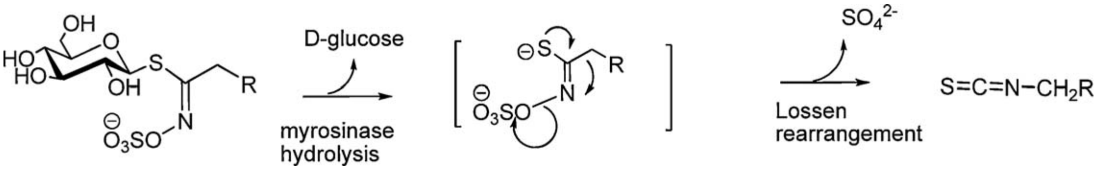
The glucosinolate-myrosinase couple underlies intriguing and complex relationships, not only between plants and animals but also between scientific disciplines such as ecology, agronomy, physiology, biochemistry and, at the molecular level, chemistry. Since several decades, scientists have put many efforts into clarifying this unique enzyme-substrate relationship and the mechanism of action of myrosinase – the only glycohydrolase able to break an anomeric carbon-sulfur bond.

Although they are usually not straightforward operations, extraction of GLs from appropriate vegetable sources and refining by dedicated chromatographic procedures can prove convenient in a number of cases to obtain pure GLs [4]. Nevertheless, the chemical synthesis approach has appeared to be a more general and more efficient way to access GLs – either natural or artificial (mainly targeting the myrosinase inhibition process) – in pure form. An overview of the chemical methods developed to produce tailor-made GLs and diversified analogues is presented.

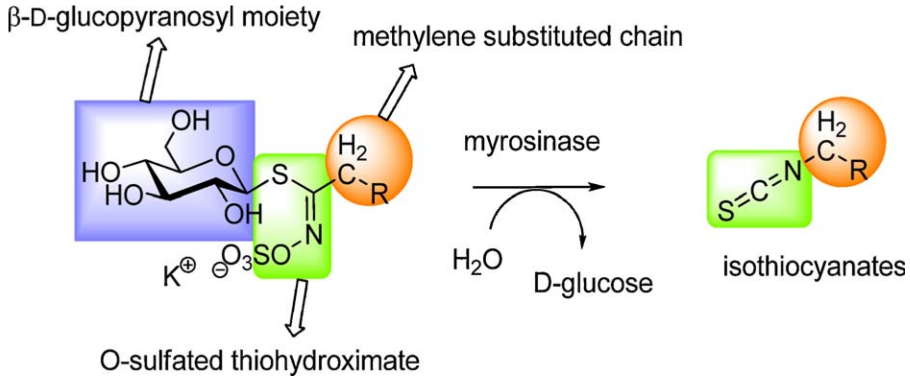
2. Synthesis of glucosinolates – the methods

From a chemical synthetic point of view, two major approaches – depicted in Scheme 3 – for the elaboration of GLs structures have been developed by a limited number of groups over the past 50 years: these are based on a retrosynthetic scheme where a single specific bond formation affords the GL skeleton: two types of disconnection have been considered, either on the anomeric center (A) or onto the hydroximoyl moiety (B).

GLs display an uncommon thiofunction indeed – a (Z) *O*-sulfated thiohydroximate invariably connected through a methylene knuckle to the variable aglycon chain (up to 120 moieties). Several synthetic routes to naturally-occurring different GLs have been developed since the pioneering synthesis of glucotropaeolin (benzyl GL) by Ettlinger and Lundeen [5]. During the 1960–1980 period, syntheses of simple aliphatic and arylaliphatic GLs were mainly performed by three groups: A. Kjaer, the major



Scheme 1.



Scheme 2.