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Glucosinolate Chemistry. First Synthesis of Glucosinolates Bearing an External Thio-Function

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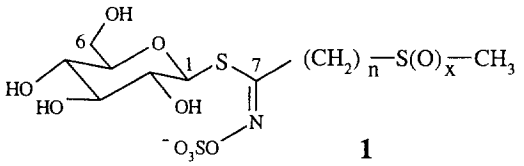
Abstract : A general strategy was developed to synthesize ω-methylthioalkyl glucosinolates through a coupling reaction between 1-thio-β-D-glucopyranose and a hydroximoyl halide obtained from the corresponding nitroalkyl methylsulfide precursor. Copyright © 1996 Elsevier Science Ltd

Glucosinolates constitute a family of biologically-significant natural compounds, found in all cruciferous plants, whose physiological activity has been widely documented.[1] More than one third of the *ca.* 100 actually registered glucosinolate structures bear an external thio-function - namely sulfide, sulfoxide or sulfone - in their aglycon part, as represented in **1** :



1

n = 2, 3, ... 10
x = 0, 1, 2

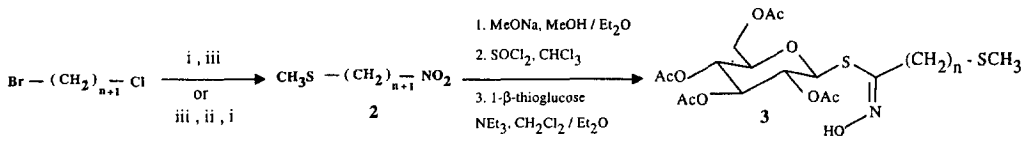
Notwithstanding the wide distribution of compounds **1** in cruciferous vegetables and their marked biological activity,[2] they have been so far the less studied among glucosinolates : no specific analytical protocols, nor synthetic pathways are available to date, which hampers further exploration of this odd family of molecules - particularly with regard to the physiology of taste.[3]

We report here a synthesis of the three simplest representatives in the series of ω-methylthioalkyl glucosinolates **1** (x = 0), namely glucoviorylin **1a** (n = 2), glucoibervirin **1b** (n = 3) and glucoerucin **1c** (n = 4), which are in great part responsible for the specific flavour of horseradish, cauliflower and garden rocket, respectively.[4]

The key-step in glucosinolate synthesis generally consists of the stereospecific coupling of protected 1-thio-β-D-glucopyranose with the appropriate hydroximoyl chloride.[5] In this particular case however, the presence of a reactive methylsulfide function precludes the usual chlorine or NCS chlorination of the corresponding aldoxime precursor.[6] We had therefore to turn to the alternative nitronate methodology[7], which required prior elaboration of nitroalkyl methylsulfides **2**.

We expected such compounds to be *a priori* readily obtainable from the corresponding ω-bromochloroalkanes : actually, in addition to the known chemo-isomerism problem associated with the ambident character of the nitrite ion in the Kornblum reaction[8], we had to face the unwanted formation of 3-nitro-2-isoxazoline[9] in the particular case of n = 2. Moreover, the reaction sequence in the case of n = 3 or 4 could be disrupted through the formation of cyclic sulfonium salts.[10]

Careful selection of n-dependent individualized reaction conditions allowed the preparation of substrates **2** with overall yields ranging from 40 to 65% from the starting bromochloroalkanes.



i) $NaNO_2$, DMSO , R.T. ii) NaI , acetone , reflux iii) CH_3SNa , MeOH , reflux

According to a well-tried protocol[7], the nitronate salts readily prepared from **2** were transformed into hydroximoyl chlorides, which were immediately reacted with 2,3,4,6-tetra-O-acetyl-1-thio-β-D-glucopyranose to afford (in 32 to 40% yield from **2**) the anomeric thiohydroximates **3**.[11]

Final O-sulfation ($ClSO_3H$, pyridine, dichloromethane, 0°C, 61 to 86% yield), then quantitative deprotection of the sugar moiety (MeOK, MeOH, R.T.) gave after Sep-Pak chromatography and freeze-drying the expected glucosinolates **1**, whose spectra and physical constants[12] were very close to those reported for authentic samples.[13] Further synthetic work is currently under way in our laboratory with a view to elaborate sulfinyl- and sulfonyl-functionalized glucosinolates meant for diverse biological studies.

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11. All new compounds gave satisfactory spectroscopic and microanalytical data. Selected data for **3c** (n = 4) :
$[\alpha]_D$ - 17 (c 1.0, $CHCl_3$); ^{1}H-RMN ($CDCl_3$, 300 MHz), δ ppm (J Hz): 1.60-1.85 (m, 4H, CH_2), 2.02, 2.05, 2.07, 2.09 (4s, 12H, Ac), 2.11 (s, 3 H, SMe), 2.45-2.55 (m, 4H, CH_2), 3.79 (ddd, 1H, $J_{4,5}$ 7.9, H-5),4.14 (dd, 1H, $J_{5,6b}$ 2.5, $J_{6a,6b}$ 12.6, H-6b), 4.22 (dd, 1H, $J_{5,6a}$ 5.4, H-6a), 5.05-5.15 (m, 3H, H-1,), 5.25 (dd, 1H, $J_{3,4}$ 10.0, H_3), 7.37 (bs, 1H, NOH).

12. Selected data for **1c** (n = 4): $[\alpha]_D$ - 20 (*c* 1, H_2O); ^{1}H-NMR (D_2O, 500 MHz) δ (ppm), J (Hz): 1.75 (m, 2H, (CH_2)-10), 1.85 (m, 2H, (CH_2)-9), 2.13 (s, 3H, SCH_3), 2.62 (t, 2H, J_{vic} 7.4, (CH_2)-11), 2.77 (t, 2H, (CH_2)-8), 3.48 (t, 1H, $J_{2,3}$ 8.9, H-2), 3.49 (t, 1H, $J_{4,5}$ 9.3, H-4), 3.59 (t, 1H, $J_{3,4}$ 9.0, H-3), 3.60 (m, 1H, H-5), 3.74 (dd, 1H, $J_{5,6b}$ 6.0, $J_{6a,6b}$ 12.5, H-6b), 3.93 (dd, 1H, $J_{5,6a}$ 2.0, H-6a), 5.09 (d, 1H, $J_{1,2}$ 9.8, H-1)

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