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The first synthesis of *C*-glucotropaeolin †

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Abstract

Starting from tetra-*O*-benzyl-D-glucose (**2**), the first synthesis of a *C*-analogue **7** of glucotropaeolin, the major glucosinolate of the genus *Nasturtium* was performed. Compound **7** constitutes a potential non-hydrolyzable inhibitor of the enzyme myrosinase. © 1999 Published by Elsevier Science Ltd. All rights reserved.

Keywords: glucosinolates; *C*-glycosides; myrosinase inhibition.

Glucosinolates constitute a large family of naturally occurring thiosugars found particularly in Brassicales which can be hydrolyzed by myrosinase (thioglucoside glucohydrolase EC 3.2.3.1) into D-glucose, hydrogen sulphate ion and various products depending on the aglycon.[1] Glucotropaeolin **1** is the major glucosinolate isolated from plants of the genus *Nasturtium*. Different types of analogues have been synthesized to shed light on the mechanism of glucosinolate enzymatic hydrolysis. Using synthetic deoxyglucotropaeolins[2] and 2-fluoro-2-deoxyglucotropaeolin[3,4] and studying the myrosinase activity in comparison with native glucotropaeolin, the importance of the hydroxyl group at C-2 for glucosinolate binding was established, and the molecular mechanism for its hydrolysis by myrosinase could thus be clarified. The design and synthesis of a non-hydrolyzable substrate analogue would be of great interest in order to get additional information about the substrate positioning, conformation and binding into the active site of myrosinase by X-ray analysis.

We herein describe the first synthesis of a *C*-analogue of glucotropaeolin which is a potential non-hydrolyzable inhibitor of myrosinase. Following Kishi's procedure,[5,6] 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**2**) led to the known epoxide **3** via *m*CPBA oxidation[7] of the transient 3-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)prop-1-ene. Phenyllithium cleavage[8] of **3** afforded the mixed diastereomeric alcohols **4** which were converted into ketone **5** by Jones oxidation (Scheme 1).

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† P. Rollin wishes to dedicate this paper to Professor Pierre Sinaÿ (Ecole Normale Supérieure, Paris) who taught him modern organic chemistry.

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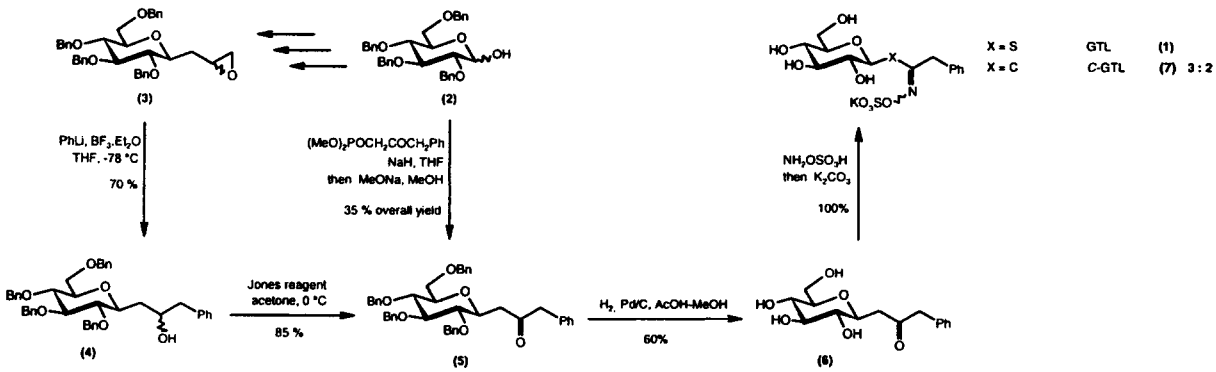

Scheme 1.

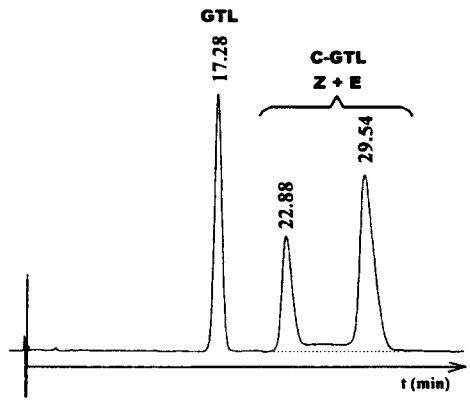

Figure 1. Hypercarb S column (100×4.6 mm I.D.). Mobile phase: 14% acetonitrile in water and trifluoroacetic acid (40 mM). GTL for glucotropaeolin **1** and *C*-GTL for the *C*-glycosidic analogue **7**

An alternative approach to the key-compound **5** is based on an original Horner–Emmons reaction[9] applied to **2** and followed by basic treatment to obtain the thermodynamically favoured β-anomer.[10] Nevertheless, this route offered poorer yields (ca. 25–30%) and in addition, the synthesis of the required phosphonate by reaction of the anion of dimethyl methylphosphonate with ethyl phenylacetate[11] is rather inefficient (average yield 30%).

After deprotection by hydrogenolysis, the ketone **6** was directly transformed into the oxime-*O*-sulfonic acid potassium salt using hydroxylamine-*O*-sulfonic acid[12] to furnish the *C*-analogue **7** of glucotropaeolin in the form of a mixture of stereomers. The diastereomeric ratio (3:2) was determined by ^{1}H NMR.[13] The HPLC chromatogram (Fig. 1) confirmed this ratio and showed a plateau indicating an equilibrium occurring between the two diastereoisomers.[14]

Preliminary investigations on the inhibition properties of these analogues have been undertaken.

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13. ^{1}H NMR (500 MHz) D_2O: Major isomer: 2.39 (dd, 1H, $J_{1'a-1'b}$=14.7 Hz, $J_{1'a-1}$=9.9 Hz, H-1'a), 2.81 (dd, 1H, $J_{1'a-1}$=2.9 Hz, H-1'b), 2.87–2.94 (m, 1H, H-5), 3.06–3.16 (m, 3H, H-2), 3.25–3.35 (m, 4H, H-3 and H-4), 3.39 (ddd, 1H, J_{1-2}=9.9 Hz, H-1), 3.54 (dd, 1H, J_{5-6a}=4.8 Hz, J_{6a-6b}=12.9 Hz, H-6a), 3.63 (dd, 1H, J_{5-6b}=2.1 Hz, H-6b), 3.77 (d, 1H, $J_{3'a-3'b}$=14.2 Hz, H-3'a), 3.93 (d, 1H, H-3'b), 7.25–7.40 (m, 10H, HAr); Minor isomer: 2.55 (dd, 1H, $J_{1'a-1'b}$=14.2 Hz, $J_{1'a-1}$=10.1 Hz, H-1'a), 2.74 (dd, 1H, $J_{1'a-1}$=2.9 Hz, H-1'b), 3.06–3.16 (m, 3H, H-2 and H-5), 3.25–3.35 (m, 4H, H-3 and H-4), 3.44 (ddd, 1H, J_{1-2}=10.1 Hz, H-1), 3.60 (dd, 1H, J_{5-6a}=5.3 Hz, J_{6a-6b}=12.3 Hz), 3.68 (d, 1H, $J_{3'a-3'b}$=14.9 Hz, H-3'a), 3.72 (dd, 1H, J_{5-6b}=2.1 Hz, H-6b), 3.74 (d, 1H, H-3'b), 7.25–7.40 (m, 10H, HAr). MS (FAB, glycerin): M+K$^+$=468.
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