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FIRST SYNTHESIS OF AN INDOLE GLUCOSINOLATE[1]

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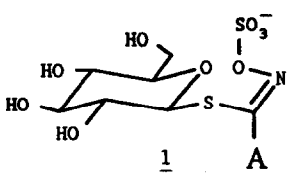
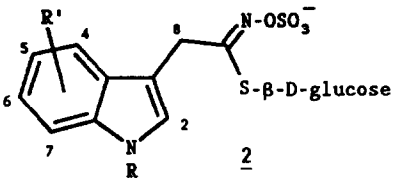
Summary: The synthesis of glucobrassicin, the parent structure of the indole glucosinolate family, and its desulfo-analogue is described.

Optimal utilization of the high nutritive value of rapeseed meal requires maximum lowering and complete control of its glucosinolate content. Glucosinolates 1 constitute a structurally homogeneous group[2] of anomeric thiohydroximoyl derivatives of 1-thio-β-D-glucopyranose which differ only in the aglycon A.



1 A

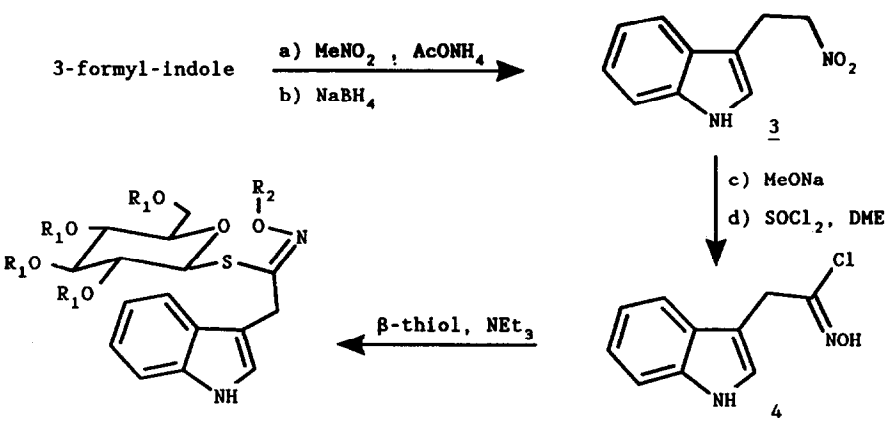


2

R= H, OMe, OSO_3^-

R'= H, 4-OH, 4-OMe

Among the ten major glucosinolates of oil-seed rape, tryptophan-derived indole structures 2 seem to induce a strong physiological activity (goitrogenicity, nitrite-trapping, alteration of chemically-induced carcinogenesis...) in animals bred on rapeseed meal diets[3].A better knowledge of their behaviour requires efficient synthetic routes to the glucobrassicins 2.
Thus, 3-formyl-indole was converted in a 56% yield to 3-(2'-nitroethyl)-indole 3[4] through a Knoevenagel-type condensation ($MeNO_2$, $AcONH_4$, 100°C)[5] followed by chemoselective hydrogenation ($NaBH_4$, SiO_2 230-400 mesh, $CHCl_3$, iPrOH)[6] of the intermediate 3-(2'-nitrovinyl)-indole.



5 R_1= Ac R_2= H 7 R_1= Ac R_2= SO_3K

6 R_1= R_2= H 8 R_1= H R_2= SO_3K

The sodium nitronate derived from 3 (MeONa, MeOH, Et_2O) was transformed ($SOCl_2$, DME, -78°C) into (indol-3'-yl)acethydroxamoyl chloride 4, which was used directly in the next step : *in situ* generation (Et_2O, Et_3N) of the corresponding (indol-3'-yl)acetonitrile oxide in the presence of 2,3,4,6-tetra-O-acetyl-1-thio-β-D-glucopyranose led stereospecifically to the (Z)-thiohydroximate 5 (50% overall yield from 3)[7,8].

Deacetylation of 5 (MeOH, H_2O, Et_3N) yielded (92%) desulfoglucobrassicin 6[9]. On the other hand, selective O-sulfation of 5 (Pyr.SO_3, CH_2Cl_2, RT, then aq.$KHCO_3$) furnished proglucobrassicin 7 in 85% yield[10] and final deacetylation (MeOH, H_2O, Et_3N) gave a 96% yield of glucobrassicin 8[11]. Synthetic accesses to other biologically significant substituted glucobrassicins 2 are now being studied in our laboratory.

Acknowledgments
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References and notes

1) Taken from the forthcoming doctorate thesis of M.C.Viaud, Université d'Orléans, this work was presented at EUROCARB V, 21-25/08/1989, Prague.

2) More than 100 molecules have now been characterized mainly in plants of the family Cruciferae; for a recent review, see G.R.Fenwick, R.K.Heaney & W.J.Mullen, CRC Crit.Rev.Fd.Sci.Nutr.,18, 123 (1983).

3) R.McDanell, A.E.M.McLean, A.B.Hanley, R.K.Heaney & G.R.Fenwick, Fd.Chem.Toxic., 26, 59 (1988).

4) D.Ranganathan, C.Bhushan Rao, S.Ranganathan, A.K.Mehrotra & R.Iyengar, J.Org.Chem., 45, 1185 (1980).

5) L.Canoira, J.Gonzalo.Rodriguez, J.B.Subirats, J.A.Escario, I.Jimenez & A.R.Martinez-Fernandez, Eur.J.Med.Chem., 24, 39 (1989).

6) A.K.Sinhababu & R.T.Borchardt, Tetrahedron Lett., 24,227 (1983).

7) Anterior use of the nitronate-pathway : see A.J.McLeod & J.T.Rossiter, J.Chem.Soc. Perkin Trans. I, 717 (1983) and references cited therein.

8) Fully satisfactory spectroscopic (IR, UV and 300 MHz ^1H NMR) and analytical data were obtained for all new compounds. 5: syrup, $[\alpha]_D$ +4° (c 0.70, $CHCl_3$), NMR ($CDCl_3$), δ(ppm) 7.61 (d, 1H, $J_{4i,5i}$ 7.8 Hz, H-4i), 7.40 (d, 1H, $J_{7i,6i}$ 7.9 Hz, H-7i), 7.24 (ft, 1H, H-6i), 7.15 (ft, 1H, H-5i), 7.10 (d, 1H, $J_{2i,NH}$ 2.0 Hz, H-2i), 4.90-5.05 (m, 4H, H-1, H-2, H-3, H-4), 4.10 & 4.02 (2d, 2H, J_{gem} 16.4 Hz, H-8 & H-8'), 4.07 (dd, 1H, $J_{6,5}$ 5.5 Hz, J_{gem} 12.5 Hz, H-6), 3.94 (dd, 1H, $J_{6',5}$ 2.2 Hz, H-6'), 3.27 (m, 1H, H-5). Hi refers throughout to the indole moiety.

9) 6 : syrup, $[\alpha]_D$ +2° (c 0.70, MeOH), NMR (D_2O), δ(ppm) 7.72 (d, 1H, $J_{4i,5i}$ 7.8 Hz, H-4i), 7.57 (d, 1H, $J_{7i,6i}$ 8.1 Hz, H-7i), 7.32 (s, 1H, H-2i), 7.30(ft, 1H, H-6i), 7.22 (ft, 1H, H-5i), 4.85 (d, 1H, $J_{1,2}$ 9.5 Hz, H-1), 4.21 & 4.11 (2d, 2H, J_{gem} 16.2 Hz, H-8 & H-8'), 3.62 (d, 2H, $J_{6,5}$ 3.0 Hz, H-6 & H-6'), 3.38 (dd, 1H, $J_{4,5}$ 9.7 Hz, H-4), 3.33 (dd, 1H, $J_{2,3}$ 9.5 Hz, H-2), 3.25 (dd, 1H, $J_{3,4}$ 9.5 Hz, H-3), 3.01 (ddd, 1H, H-5).

10) 7 : amorphous solid, $[\alpha]_D$ -4° (c 2.40, MeOH), NMR (DMSO-d_6), δ(ppm) 7.67 (d, 1H, $J_{4i,5i}$ 7.8 Hz, H-4i), 7.37 (d, 1H, $J_{2i,NH}$ 2.5 Hz, H-2i), 7.35 (d, 1H, $J_{7i,6i}$ 8.0 Hz, H-7i), 7.07 (ft, 1H, H-6i), 6.96 (ft, 1H, H-5i), 5.41 (d, 1H, $J_{1,2}$ 10.0 Hz, H-1), 5.24 (dd, 1H, $J_{3,4}$ 9.0 Hz, H-3), 4.89 (dd, 1H, $J_{4,5}$ 9.0 Hz, H-4), 4.80 (dd, 1H, $J_{2,3}$ 8.8 Hz, H-2), 4.06 (dd, 1H, $J_{6,5}$ 5.2 Hz, J_{gem} 12.3 Hz, H-6), 4.05 (s, 2H, H-8 & H-8'), 3.95 (m, 1H, H-5), 3.82 (dd, 1H, $J_{6',5}$ 1.5 Hz, H-6').

11) 8 : amorphous solid, $[\alpha]_D$ -9.5° (c 2.0, H_2O)[12], NMR (D_2O), δ(ppm) 7.79 (d, 1H, J4i,5i 7.8 Hz, H-4i), 7.56 (d, 1H, J7i,6i 8.1 Hz, H-7i), 7.37 (s, 1H, H-2i), 7.31 (ft, 1H, H-6i), 7.23 (ft, 1H, H-5i), 4.83 (d, 1H, $J_{1,2}$ 9.6 Hz, H-1), 4.31 & 4.21 (2d, 2H, J_{gem} 16.3 Hz, H-8 & H-8'), 3.59 (d, 2H, $J_{6,5}$ 3.3 Hz, H-6 & H-6'), 3.38 (dd, 1H, $J_{4,5}$ 9.8 Hz, H-4), 3.31 (dd, 1H, $J_{2,3}$ 9.6 Hz, H-2), 3.21 (dd, 1H, $J_{3,4}$ 9.6 Hz, H-3), 2.96 (ddd, 1H, H-5).

12) R.Gmelin & A.I.Virtanen, Ann.Acad.Sci.Fenn.(A), 107, 1 (1961); $[\alpha]_D$ -13.3° (c 3.0, H_2O) reported for the tetramethylammonium salt.

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