## IRIDOIDS : AN EFFICIENT CONVERSION OF (-)-CATALPOL INTO (-)-SPECIONIN

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ABSTRACT : A partial synthesis of the antifeedant (-)-specionin (8) starting from the readily available (-)-catalpol (1) is described. It also allows the formation of analogs of 8 via specific transformations on intermediates 3 or 5 for screening of antifeedant properties.

Based on chemical evidence (total synthesis) and <sup>1</sup>H NMR analysis, we have recently proven the revised structure  $\underline{8}^{2-4}$  for specionin<sup>5</sup>. This iridoid is an effective antifeedant against the Eastern spruce budworm; it has a rather simple structure compared to other antifeedants. It therefore seemed worthwhile to establish an approach which could provide large quantities of  $\underline{8}$  and of analogues for adequate testing. We presently want to describe an efficient partial synthesis of (-)-specionin starting from the abundant iridoid (-)-catalpol  $(1)^{6,7}$ .



(a)  $\beta$ -D-glucosidase, H<sub>2</sub>O, 37°C, 4 h; (b) EtOH, PTSA, r.t., 120 h; (c) 4,4'-DMTC1, Et<sub>3</sub>N, DMAP, CH<sub>2</sub>Cl<sub>2</sub>, r.t., 5 h; (d) p.Bn OC<sub>6</sub>H<sub>4</sub>COC1, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, r.t., 6 days; (e) Pd-C, H<sub>2</sub>, EtOH, r.t., 1 atm; (f) EtOH, BF<sub>3</sub>.Et<sub>2</sub>O, r.t., 11 days.

Enzymatic hydrolysis (EC 3.2.1.21, type II, Sigma) of  $\underline{1}$  and subsequent lyophilization of the aqueous solution afforded the aglucone  $\underline{3}$  (clean on TLC; quant. yield). The structure was determined after transformation of a sample to the triacetate  $\underline{4}$ . The crude  $\underline{3}$  was taken

up in EtOH, the denaturated enzyme filtered off and a trace of PTSA was added. After stirring the solution for 5 days, column chromatography (silica gel; hexane-EtOAc, 2:8) gave a 53 % yield (from <u>1</u>) of a mixture of <u>5</u> and of the anomer  $1\beta$ ,  $3\alpha$  (ratio 83:17). Pure  $5^8$  (ca 45 % yield;  $|\alpha|_{D}^{25}$  = + 50.1°, c = 0.73; CHCl<sub>3</sub>) was obtained upon HPLC (reversed phase RSiL- $C_{18}$ -HL-D, 10 µm; MeOH-H<sub>2</sub>O, 3:7) separation. The anomers of <u>5</u> were obtained in a combined yield of 35 %. With respect to the acid catalyzed isomerization (vide infra) of the final products 8 and 8' this somewhat tedious separation is not necessary at this point. Indeed the mixture of all anomers 5 (88 % yield from 1) can be used subsequently, as a facile separation<sup>4</sup> is possible at the stage of <u>8</u>. However for the present purpose we decided to take pure 5 and a mixture of the three undesired anomers separately through the subsequent steps.

Protection of the primary alcohol function in 5 as the 4,4'-dimethoxytrityl ether (6; 93 % yield) subsequent esterification to  $\overline{7}$  and hydrogenolysis of both protective groups (81 % combined yield) gave (-)-specionin (8)<sup>8</sup>;  $|\alpha|_{D}^{21} = -27.2^{\circ}$  (c = 0.52; CHCl<sub>3</sub>)<sup>9</sup>.

The overall yield of (-)-specionin (8) from (-)-catalpol is 30 %, not taking into account the possible isomerization of the other anomers. The mixture of anomers  $\underline{8'}$  were separated by HPLC and the two major isomers 8'a and 8'b were subjected to BF3.Et20 mediated isomerization until the equilibrium was obtained (HPLC monitoring). The ratio is 8'a (14 %), <u>8'b</u> + <u>8'c</u> (20 %) and <u>8</u> (66 %)<sup>10</sup>.

The predominant formation of  $\underline{8}$  could be related to the suggestion of Chang and Nakanishi<sup>5</sup> that specionin is an artefact derived from catalposide ( $\underline{2}$ ) during ethanol extraction of the plant material. The isolation of other anomers was not reported by these authors.

This partial synthesis constitutes an additional proof for the substitution pattern on the cyclopentane nucleus in 8 and establishes the absolute configuration.

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- 7. Recently K. Weinges et al. (ref. 6) described the isolation of the iridoid catapol (1) in a 100 g size from Picrorhiza kurroa (Scrophulariaceae); 1.6 % of dry weight.
- 8. The spectroscopic data are identical to those previously described for racemic material
- (ref. 4). 9. No  $|\alpha|_{D}$  value is given in ref. 5; on a natural sample (6 mg) we measured  $|\alpha|_{D}^{21} = -23.5^{\circ}$ (c = 0.31, CHCl<sub>3</sub>).
- 10. The isomer <u>8'c</u> is found as a small shoulder (ca 5 % of the peak representing <u>8'b</u>). HPLC conditions are identical to those given in ref. 4; 25 x 2.2 cm column RSiL-C<sub>18</sub>-HL-D 10  $\mu$ m (MeOH-H<sub>2</sub>O 55:45; 10 m1/min).

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