AUCUBIN, A SOURCE OF PROSTANOID SYNTHONS - NEW HEMISYNTHETIC PATHWAYS

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Abstract - New preparation from aucubin of synthons with a monoterpenic iridoid framework, bearing an available lactol group. These synthons are useful for access to analogs of prostaglandins.

Recently, reports from two different laboratories have shown the great interest of iridoid glycosides, specially aucubin 1 [1, 2] and asperuloside 2 [3], as source of synthons suitable for chiral synthesis of prostaglandins. The removal of the glucose moiety is an important step during these synthesis. Most of the previous works use drastic conditions, in an acidic medium, on unprotected substrate with a free alcohol on carbon 10. This procedure leads to compounds containing the structure 3 in their skeleton. The acetalic function of 3 is quite stable and its cleavage is very hard to obtain in the regiospecific way needed to continue the synthesis. This situation prompts us to report here two different pathways avoiding the formation of structure 3 and leading directly to synthons containing a free or protected lactol group on Carbon 1. This function as shown previously [1,3] can be used directly to introduce one of the side chains of prostaglandins.

The first pathway uses an enzymatic cleavage of the glycosidic bond by β-glycosidase : aucubin 1 is quantitatively hydrogenated (H_2 1 atm, Pd/C 5 %, ethanol) to compound 4 [4]. Treatment of 4 by β-glycosidase (37° C ; H_2O/pH 4.8 citrate buffer) leads, after repeated extractions with ethyl acetate, to compound 5 which is directly acetylated (Ac_2O/Py) to give the triacetyl derivative 6 (50 %) [ir (CCl_4) ν: 1735 cm^{-1} ; ms : m/z 314 (M^+) ; nmr ($CDCl_3$) δ : 1.8 - 2.0 (9 H, 3s, acetyl groups)]. In acidic conditions (AcOH/THF/H_2O) compound 6 gives directly the desired lactol 7 (90 %) [ir (CCl_4) ν: cm^{-1} 3600, 3400 - 3500 (OH), 1735 (CH_3-C(=O)-O-); ms : m/z 272 ($M^{+\cdot}$) ; nmr ($CDCl_3$) δ : 2.2 (6H, s, acetyl groups]. The interest of the enzymatic pathway being confirmed (yield 45 % from aucubin 1 to 7), we are now studying the

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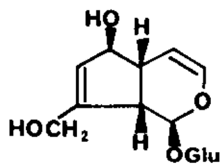

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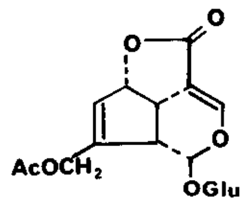

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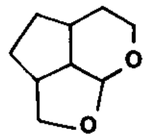

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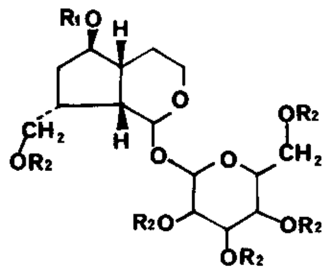
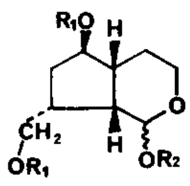


4 R1 = R2 = H

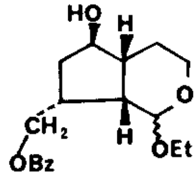
8 R1= H R2 = Bz



5 R1 = R2 = H

6 R1 = R2 = Ac

7 R1 = Ac R2 = H



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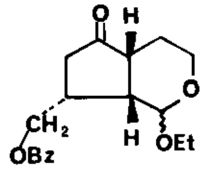

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possibility of a Wittig reaction with this lactol and with analogues possessing different protecting groups on the oxygen atoms located on carbon 6 and 10.

The second pathway uses acidic hydrolysis of the glycosidic linkage, but contrary to previous works [1,2,3] alcohol functions were protected before hydrolysis in order to avoid the formation of the quite stable acetal. Tetrahydro-aucubin 4 is benzylated (NaH/DMF; benzyl bromide) and this reaction leads to compound 8 (70 %) which is directly treated with HCl-EtOH and readily yields the aglycone 9 (80 %) [ir (CCl_4) ν : 3500 cm^{-1} (OH); ms : m/z 306 ($M^{+\cdot}$); nmr ($CDCl_3$) δ : 1.2 (3 H, t, CH_2-$C\underline{H}_3$), 2.0 (2 H, q, $C\underline{H}_2$-CH_3), 4.5 (2 H,s, $C\underline{H}_2$-Ph)]. The structure of 9 shows an interesting feature of the benzylation reaction which protects only five of the six hydroxyl groups of 4. This unexplained peculiarity allows the isolation, after acidid ethanolysis, of compound 9 where each of the oxygenated functions can be individually transformed either directly or after specific deprotection. The position of the free alcohol function in 8 and 9 is definitively proved by oxidation of 9 (pyridinium chlorochromate) to the five membered ketone 10 (65 %) [ir (CCl_4) ν : 1740 cm^{-1} ; ms : m/z 304 ($M^{+\cdot}$) ; nmr ($CDCl_3$) δ : 1.2 (3 H, t, CH_2-$C\underline{H}_3$), 3.2 (2 H, q, $C\underline{H}_2$-CH_3), 4.6 (2 H, s, $C\underline{H}_2$-Ph)]. Compounds 9 and 10, possessing selective protecting groups on the alcoholic functions, are valuable intermediates for further investigation in the prostaglandin field.

Experiments are in progress to assess the interest of synthons 7, 9 and 10, readily available from the common glycoside aucubin 1, in view of the synthesis of prostanoid structures.

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