A NEW PROSTAGLANDIN INTERMEDIATE FROM AUCUBIGENIN[1]

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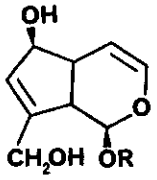
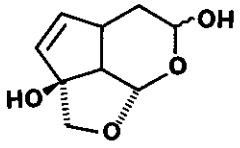
Abstract - The synthesis of the new prostanoid intermediate 9 (Corey lactone analogue) from iridoid aglycone aucubigenin 2 is described.

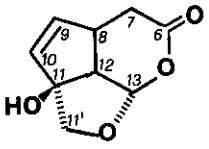
Aucubigenin 2, an hemiacetalic compound with heterocyclic (cyclopenta[c]pyran) skeleton, was first obtained[3] in moderate yield (ca. 52%) by enzymatic hydrolysis (β-glucosidase) of its parent glucoside aucubin 1 , the most common and abundant representative[4] of naturally occurring iridoid glucosides.[5]
Although iridoid aglycones have always been considered as unstable compounds,[3,5] we have recently developed a new procedure for the quantitative extraction of 2[6] from the enzymatic hydrolisate of 1.
This improved availability of 2 made it easier to utilize as starting material in the ambit of our program of syntheses[7-11] of bioactive cyclopentanoid compounds from iridoid glucosides. In particular, we have examined the possible utilization for PG syntheses of the tricyclic hemiacetal 3 , obtained[12] by acid-catalyzed rearrangement (2N HCl, 15 min, 5°C) of 2 (yield$_{2\rightarrow3}$ = 33%). In this report we describe the conversion of 3 into the prostanoid intermediate 9 (Corey lactone analogue) with an overall yield of about 16% for the whole transformation 2 → 9 (7 steps).
The low yield (33%) of the initial step 2 → 3 prompted us to do a preliminary investigation for alternative and more profitable catalytic conditions. Good results were obtained by treating 2 with $FeCl_3$ in MeCN-H_2O (20:1) for 12 h at room temp. ($y_{2\rightarrow3}$ = 65%).
By successive short exposure of 3 to Jones reagent, the hemiacetalic function was oxidized to give the more stable and crystalline tricyclic lactone 4[13] which was quantitatively transformed by acidic methanolysis (anh. MeOH, gas. HCl) into methyl ester methylacetal 5 (yield $_{3\rightarrow5}$ = 51%), an excellent starting material for synthesis of PG intermediates.
Basic hydrolysis of 5 with saturated $Ba(OH)_2$ solution gave acid 6 which was subjected to lactone ring closure with the classical iodolactonization procedure (I_2/KI)[14]. The iodolactone 7 was successively deiodinated (tri-n-butyltin hydride)[15] to tricyclic methylacetal 8 (yield $_{5\rightarrow8}$ = 49%).[13]



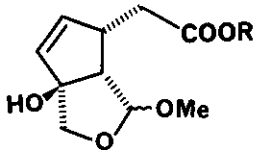
(1) R=β-Glu
(2) R=H



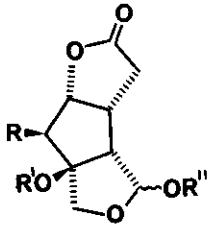
(3)



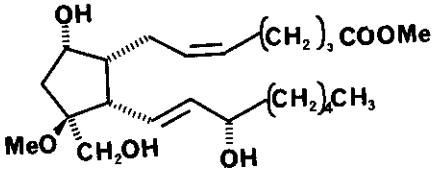
(4)



(5) R=Me
(6) R=H



(7) R=I, R'=H, R''=Me
(8) R=R'=H, R''=Me
(9) R=R'=R''=H
(11) R=R''=H, R'=Me



(10)

Selective cleavage of methylacetal protecting group (0.5 N HCl in H_2O-MeCN 2:1, 12 h, room temperature) gave almost quantitatively the free hemiacetal 9 , a Corey lactone analogue which contains in masked form either the formyl group at C-12 or the vic-diol system at C-11 (potential oxo group), both significant features of prostanoid precursors.

Recently, we have described[8] the synthesis from 1 of a new 11-deoxy-11β-methoxy-11α-(hydroxymethyl)-12-epi $PGF_{2\alpha}$ methyl ester 10 whose key-intermediate was precisely the lactone 11, i.e. the O-methylether derivative of 9 at the tertiary OH function. Therefore, the structural features of 9 appoint this compound as a versatile precursor of prostaglandins and, firstly, of the 11β-demethoxy-11β-hydroxy derivative of 10. Further research, actually in progress and in part under publication,[10,11] is confirming the established importance[16-20] of easily accessible aucubin 1 as chiral starting material for the synthesis of PG's and other bioactive cyclopentanoid compounds.

REFERENCES AND NOTES

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13. Selected spectral data of the products (PG numbering): 4 : ^{1}H-nmr (300 MHz, D_2O) δ 6.1-5.6 (cm, 3H, H-9, H-10, H-13), 4.08 (dd, 2H, 2H-11', J_{AB}= 10.0 Hz), 3.47 bs, 1H, H-8), 3.14 (dd, 1H, H-12), 2.60 (pd, 2H, 2H-7); ^{13}C-nmr (75 MHz, D_2O): δ 194.98 (s, C-6), 137.24 (d, C-9), 134.48 (d, C-10), 105.78 (d, C-13), 92.30 (s, C-11), 80.15 (t, C-11'), 55.42 (d, C-12), 38.70 (d, C-8), 30.34 (t, C-7).

8 : ^{1}H-nmr (300 MHz, $CDCl_3$) : δ 5.05 (dd, 1H, H-9), 4.92 (s, 1H, H-13), 3.97 (dd, 2H, 2H-11'), 3.37 (s, 3H, OMe), 2.67-2.24 (cm, 2H, 2H-7).

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