

A NEW PROSTAGLANDIN INTERMEDIATE FROM AUCUBIGENIN¹Enrico Davini,² Carlo Iavarone, and Corrado Trogolo

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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 obtained³ in moderate yield (ca. 52%) by enzymatic hydrolysis (β -glucosidase) of its parent glucoside aucubin 1, the most common and abundant representative⁴ of naturally occurring iridoid glucosides.⁵

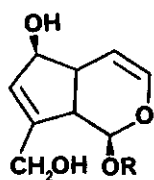
Although iridoid aglycones have always been considered as unstable compounds,^{3,5} we have recently developed a new procedure for the quantitative extraction of 2⁶ from the enzymatic hydrolysis of 1.

This improved availability of 2 made it easier to utilize as starting material in the ambit of our program of syntheses⁷⁻¹¹ of bioactive cyclopentanoid compounds from iridoid glucosides. In particular, we have examined the possible utilization for PG syntheses of the tricyclic hemiacetal 3, obtained¹² by acid-catalyzed rearrangement (2N HCl, 15 min, 5°C) of 2 (yield 2 \rightarrow 3 = 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 \rightarrow 9 (7 steps).

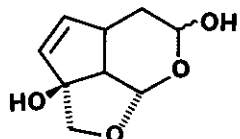
The low yield (33%) of the initial step 2 \rightarrow 3 prompted us to do a preliminary investigation for alternative and more profitable catalytic conditions. Good results were obtained by treating 2 with FeCl₃ in MeCN-H₂O (20:1) for 12 h at room temp. (yield 2 \rightarrow 3 = 65%).

By successive short exposure of 3 to Jones reagent, the hemiacetalic function was oxidized to give the more stable and crystalline tricyclic lactone 4¹³ which was quantitatively transformed by acidic methanolysis (anh. MeOH, gas. HCl) into methyl ester methylacetal 5 (yield 3 \rightarrow 5 = 51%), an excellent starting material for synthesis of PG intermediates.

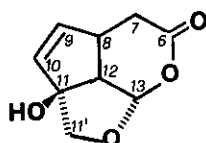
Basic hydrolysis of 5 with saturated Ba(OH)₂ solution gave acid 6 which was subjected to lactone ring closure with the classical iodolactonization procedure (I₂/KI)¹⁴. The iodolactone 7 was successively deiodinated (tri-n-butyltin hydride)¹⁵ to tricyclic methylacetal 8 (yield 5 \rightarrow 8 = 49%).¹³



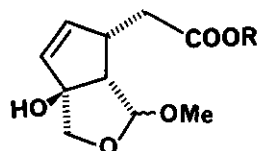
- (1) $R = \beta\text{-Glu}$
 (2) $R = \text{H}$



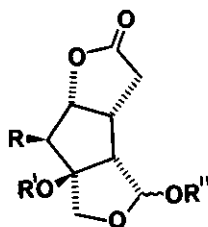
(3)



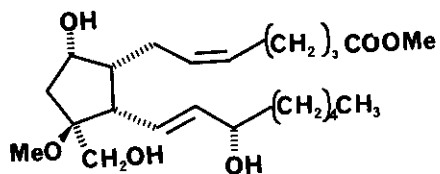
(4)



- (5) $R = \text{Me}$
 (6) $R = \text{H}$



- (7) $R = \text{I}, R' = \text{H}, R'' = \text{Me}$
 (8) $R = R' = \text{H}, R'' = \text{Me}$
 (9) $R = R' = R'' = \text{H}$
 (11) $R = R'' = \text{H}, R' = \text{Me}$



(10)

Selective cleavage of methylacetal protecting group (0.5 N HCl in H₂O-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 prostanoïd precursors.

Recently, we have described⁸ the synthesis from 1 of a new 11-deoxy-11 β -methoxy-11 α -(hydroxymethyl)-12-*epi* PGF_{2 α} 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 11 β -demethoxy-11 β -hydroxy derivative of 10. Further research, actually in progress and in part under publication,^{10,11} is confirming the established importance¹⁶⁻²⁰ of easily accessible aucubin 1 as chiral starting material for the synthesis of PG's and other bioactive cyclopentanoid compounds.

REFERENCES AND NOTES

1. Abstracted in part from the "Dottorato di Ricerca" Thesis of E.D., Rome University, 1984-86.
2. Present address: Eni Ricerche Spa., Via Ercole Ramarini 32, 00015 Monterotondo, Italy.
3. A.Bianco, M.Guiso, C.Iavarone, P.Passacantilli, and C.Trogolo, Tetrahedron, 1977, 33, 847.
4. Compound 1 (49 g) was obtained from 2.5 kg of fresh leaves of the common shrub Aucuba japonica.¹⁰
5. J.M.Bobbitt and K.P.Segebarth, in "Cyclopentanoid Terpene Derivatives", ed. by A.R.Battersby and W.I.Taylor, Dekker, New York, 1969, p.3.
6. E.Davini, C.Iavarone, C.Trogolo, P.Aureli, and B.Pasolini, Phytochemistry, 1986, 25, 2420.
7. C.Bonini, C.Iavarone, C.Trogolo, and R. Di Fabio, J.Org.Chem., 1985, 50, 958.
8. R.Bernini, E.Davini, C.Iavarone, and C.Trogolo, J. Org. Chem., 1986, 51, 4600.
9. E. Davini, C.Iavarone, and C.Trogolo, Phytochemistry, 1987, 26, 1449.
10. E.Davini, C.Iavarone, F.Mataloni, and C.Trogolo, J. Org. Chem., in the press.
11. E.Davini, C.Iavarone, and C.Trogolo, Heterocycles, 1988, 27, 57.
12. A.Bianco, M.Guiso, C.Iavarone, P.Passacantilli, and C.Trogolo, Tetrahedron, 1984, 40, 1191.
13. Selected spectral data of the products (PG numbering): 4 : ¹H-nmr (300 MHz, D₂O) 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); ¹³C-nmr (75 MHz, D₂O): 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).

δ : ^1H -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).

14. H.L.Slates, Z.S.Zelawski, D.Taub, and N.L. Wendler, Tetrahedron, 1974, 30, 819.
15. H.G. Kuivila, and O.F. Beumel jr. J. Am. Chem. Soc., 1961, 83, 1246.
16. M.Naruto, K.Ohno, and N.Naruse, Chem.Lett., 1978, 1419.
17. M.Naruto, K.Ohno, N.Naruse, and H.Takeuchi, Chem.Lett., 1978, 1423.
18. M.Naruto, K.Ohno, N.Naruse, and T.Takeuchi, Tetrahedron Lett., 1979, 251.
19. W.F.Berkowitz, I.Sasson, P.S. Sampathkumar, J.Hrabie, S.Choudhry, and D.Pierce, Tetrahedron Lett., 1979, 1641.
20. K.Ohno, and M.Naruto, Chem.Lett., 1979, 1015.

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