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SYNTHESIS OF A COREY'S LACTONE ANALOGUE FROM THE IRIDOID AUCUBIN[1]

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Abstract Synthesis of a Corey's lactone analogue and a synthon for 11-deoxy-11-methyl prostaglandin and prostacyclin from the iridoid glucoside Aucubin is described

Natural iridoid glucosides such as Aucubin and Asperuloside have recently been reported to be starting materials for prostaglandins [2] These glucosides are commercially attractive because they are readily available, in excellent yield, from several common plants In a recent publication we also reported obtaining two new prostaglandin synthons (9,11-deoxy-11-methyl) starting from Aucubin 1 [3] Now we wish to report our approach to a modified Corey's lactone 10, which constitutes a formal total synthesis of the analogous prostaglandin and prostacyclin[4] (scheme 1)

Aucubin 1 was transformed in good yield (80%) to the known monodeoxyaucubin 2[5] by Birch reduction (Li/NH_3), performed at low temperature (-70°C) for 10 min to avoid, as much as possible, the formation of the dideoxyaucubin 3 (in this way, 3 was obtained as only 10% of the overall yield from Aucubin 1) After purification (silica gel chromatography) 2 was acetylated (Ac_2O in Py, 1h, r t) to give 4 which was treated with NBS in anhydrous DMSO for 20 min to yield the bromolactone 5 Without purification 5 was reduced by Zn/CH_3COOH in ether (10 min) to the crude lactone 6 (95% overall yield from 3), which crystallized from EtOH as a white powdered product (m p 79-80°C) ^{1}H-NMR H-7, 5 61 bs, H-1, 5 63 bd, H-4, 2 72 bd, CH_3-10, 1 83 bs, $OCOCH_3$, 2 06, 2 01 and 1 97 s (15 H) [6]

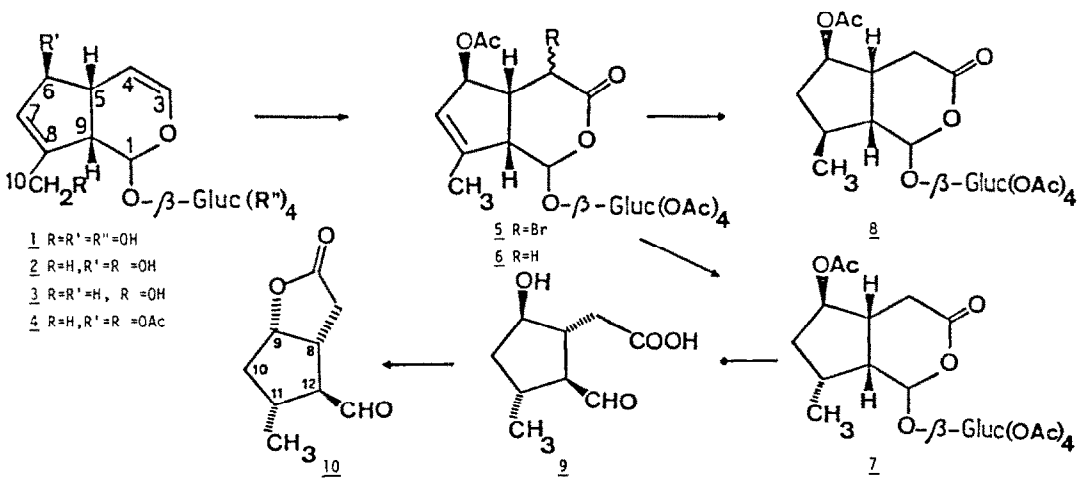
The subsequent hydrogenation of 6 was carefully examined with different catalysts (Pd/C, PtO_2, Rh/C), in different solvents The best results were with Rh on alumina at 1 atm in distilled EtOAc with the temperature ranging from 0°C to r t over 24 hrs We were able, with the latter conditions, to obtain 7 and 8 in the ratio of 2 1 (95% yield), without traces of hydrogenolysis products The crude mixture was chromatographed (silica gel) to give almost pure products subsequently crystallized from EtOH 7 (m p 81-83°C) and 8 (m p 89-90°C)

The exact configuration of the methyl group in both 7 and 8 was assigned by ^{13}C-NMR analysis, on the basis of several analogous examples [7]

Subsequently, the lactone 7 was hydrolyzed with aqueous K_2CO_3 in MeOH affording the hydroxy acid 9 as colorless oil IR ($CHCl_3$) 3500, 2730, 1730 and 1710 cm^{-1}, ^{1}H-NMR COOH, 10 5 s, CHO, 9 10 d, J=4 Hz, CH_3, 1 10 d, J=6 5 Hz Alkaline hydrolysis effected, as expected, the inversion

of configuration at C-12, with the isomerization of the CHO group to the more stable trans position

SCHEME 1



Finally the treatment of 9 with MsCl in anhydrous Py (0°C for 1 hr) afforded the desired Corey's lactone analogue 10 (65% overall yield from 7) as colorless oil, after purification by silica gel chromatography IR ($CHCl_3$) 2730, 1765 and 1720 cm^{-1} ^{1}H-NMR CHO, 9 61 d, J=3 3 Hz, H-9, 4 93 m, CH_3, 1 10 d, J=6 6 Hz

NOTES AND REFERENCES

1 This work has been part of a paper presented at the 184th meeting of the A C S. in Kansas City, Sept 13-17, 1982, Division of Organic Chemistry, paper no 169

2 a) M Naruto, K Ohno, N Naruse and H. Takeuchi, Tetrahedron Lett. 251 (1979) and references therein, b) W F Berkowitz, S C Choudhry and J A Hrabie, J Org Chem 47, 824 (1982) and references therein, c) A Tixidre, Y. Rolland, J Garnier and J Poisson, Heterocycles 19, 253 (1982)

3. C Bonini and R Di Fabio, J Org Chem. 47, 1343 (1982).

4. The synthesis of methyl prostaglandins has been realized by several groups (see K Inoue, J Ide and K Sakai, Bull Chem Soc Japan 51, 2361 (1978) and references therein, also, recently there has appeared another approach to these biologically important prostaglandin analogues (A E Greene, M A Teixejria, E Barreiro, A Cruz and P Crabbé, J Org Chem 47, 2553 (1982))

5 A Bianco, M Guiso, C Iavarone, P Passacantilli and C Trogolo, Gazz. Chim Ital 107, 83 (1977)

6 ^{1}H-NMR spectra were recorded at 90 MHz (compounds 6, 7, 8, 9, in $CDCl_3$ with TMS as internal standard) and at 300 MHz (compound 10 in $CDCl_3$)

7 The significant chemical shift values which allowed the assignment of structures to compounds 7 and 8 are ($CDCl_3$ with TMS as internal standard) 15 41 ppm (CH_3) and 42 09 ppm (C-9) for 7, 18 93 ppm (CH_3) and 46 46 ppm (C-9) for 8 See ref 3 and references therein)

8 All the new compounds gave satisfactory elemental analysis

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