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A SHORT SYNTHESIS OF cis-2-FORMYL-5-HYDROXY-2-CYCLOPENTENE-1-ACETIC ACID γ-LACTONE. THE KEY INTERMEDIATE OF PROSTAGLANDIN SYNTHESIS

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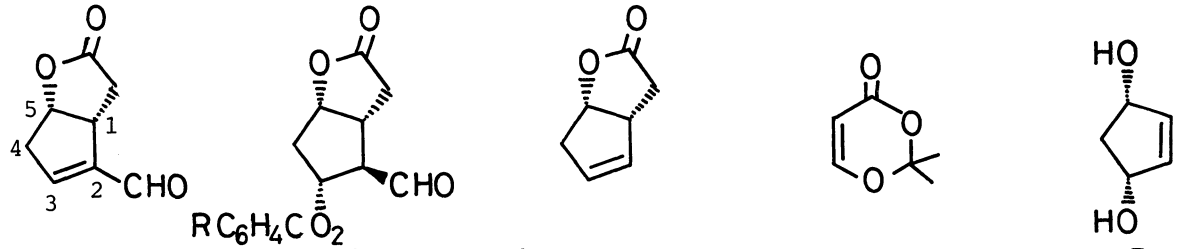
A practically one-pot synthesis of the title compound from 2,2-dimethyl-1,3-dioxin-4-one and cis-2-cyclopentene-1,4-diol by an application of de Mayo method is described.

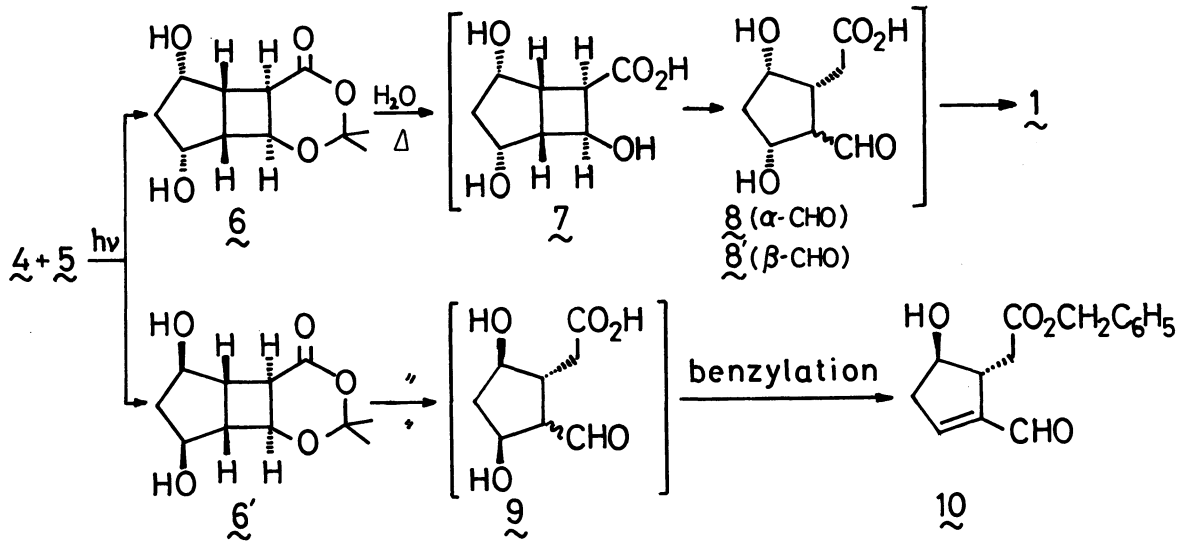
cis-2-Formyl-5-hydroxy-2-cyclopentene-1-acetic acid γ-lactone 1 has been found to have considerable utility in the preparation of prostaglandin derivatives, namely, 11,12-difluoromethanoprostaglandin,[1] prostaglandin C_2,[2] and thromboxane B_2.[3] This lactone was originally prepared from the Corey lactone 2 by the base-promoted elimination of the C_3-substituent.[1-3] Recently, the same lactone 1 was synthesized either from commercially available ene lactone 3[4] or from cis-1,5-cyclooctadiene.[5] However, these syntheses require multi steps and the overall yields are poor. A search for an alternative and more straight approach to 1 was therefore undertaken. In this context, we have recently developed an efficient method for the introduction of carboxaldehyde and acetic acid appendages at the vicinal position of alkenes by an application of de Mayo method[6] by using 5,6-unsubstituted 1,3-dioxin-4-one (e. g., 4) as a photochemical equivalent of formyl acetic ester.[7] We have also established efficient synthetic methods of 4 and its analogues[8] and cis-2-cyclopentene-1,4-diol 5[9] from readily available materials, both of which can be carried out in a multi-gram scale.



1 2 (R=H or C_6H_5) 3 4 5

Based on these facts, we have accomplished a synthesis of 1 as shown in the Scheme. The scheme enjoys the economical advantage of being based on the inexpensive materials (4 and 5), its short step, and a satisfactory overall yield (30%).

The dioxinone 4 (5 mM) was irradiated in ethyl acetate (180 ml) containing an excess (25 mM) of the diol 5 by a high-pressure mercury lamp (Ushio UM-452, 450W) with a Vycor filter until the consumption of 4 (30 min). The residue[10] obtained after evaporation of the solvent was refluxed in water (50 ml) for 2 h. The portion extracted with dichloromethane (each 25 ml, three times) was purified by a short



column of silica (ether as an eluent) to give 1[4] in 30% yield. Analytically pure sample[11] [mp 52-53 °C, ν_{max} ($CHCl_3$): 1780, 1680 cm^{-1}, δ ($CDCl_3$): 2.82 (m, 2H), 3.00 (m, 2H), 3.72 (m, 1H), 5.20 (dt, J=6 and 4 Hz, 1H), 6.88 (q, J=2 Hz, 1H), 9.77 (s, 1H)] was obtained by sublimation [90-98 °C (bath temp)/0.04 Torr]. Obviously, the other hydroxy acid 9 derived from the other adduct 6' was left in the aqueous layer, because benzylation ($PhCH_2Br/NaHCO_3/DMF$) of its residue afforded the ester 10[11] [oil, ν_{max} ($CHCl_3$): 3375, 1720, 1680 cm^{-1}, δ ($CDCl_3$): 1.90-3.46 (m, 5H), 4.34 (m, 1H), 5.14 (s, 2H), 6.79 (m, 1H), 7.34 (br s, 5H), 9.67 (s, 1H)].

Thus, we now have established a practically one-pot synthesis of 1 from readily available materials 4 and 5. Considering our earlier experimental results,[7] the intermediate in the above transformation (6→1) is (at least partly) an equivalent (cf., 8') of the Corey lactone. Efforts are now paid in order to get 8' or its equivalents, either by using the appropriately protected diol or by modifying the hydrolysis condition to a milder one.

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10) Acetylation (Ac_2O/pyridine) of the residue afforded two diacetates in nearly equal amounts. Both of them were obtained by photoaddition of 4 to the diacetate of 5. The NMR spectra showed that both of them had the cis-anti-cis configuration (e. g., 6 and 6') as judged from the coupling patterns of CH-O-C (δ 4.60 dd, J=6.2 and 2.2 Hz, and δ 4.30 dd, J=6.8 and 2.6 Hz).
11) The structures of 1 and 10 were supported by elemental analyses.

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