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CUPRIC BROMIDE UTILIZATION IN THE SYNTHESIS OF PROSTANOID INTERMEDIATES

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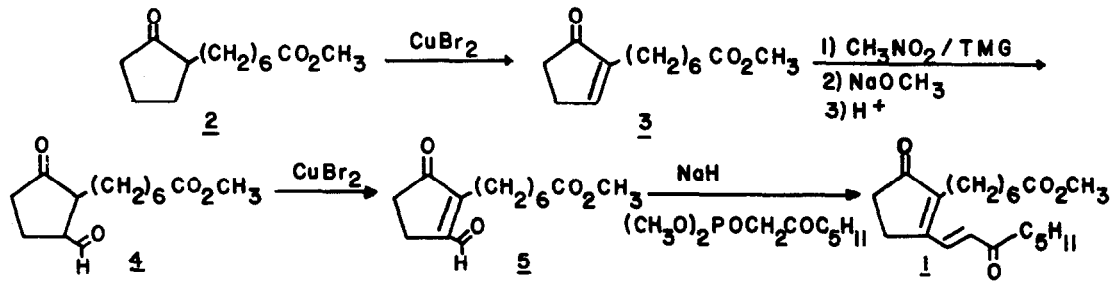
Abstract: An effective, one-step procedure using $CuBr_2$ is reported for the introduction of a double bond into the prostanoid nucleus.

Prostaglandin B_x (PGB_x) is a new oligomeric derivative of prostaglandin B_1 (PGB_1) which is prepared from the methyl ester of 15-keto-PGB_1.[1,2] PGB_x has been reported to restore oxidative phosphorylation of isolated degraded rat liver mitochondria. Considerable effort has been directed towards the isolation and characterization of components of PGB_x.[1,2,3] We have been investigating new shortened synthetic sequences to the methyl ester of 15-keto-PGB_1[2,4] (1) that would provide large quantities of this material for the eventual preparation of PGB_x. In this work we found an unusual reaction of cupric bromide that allows for a one-step introduction of a double bond in the prostanoid cyclopentane ring system.

In a number of approaches to prostanoids, methyl or ethyl 2-oxocyclopentane heptanoate (2) has been reported as an important intermediate.[5] Dropwise addition of 5.7g (25.2 mmol) of 2 in 30 ml of $CHCl_3$ was carried out over a 10 min. period to a refluxing suspension of 12g cupric bromide (53.7 mmol, anhydrous, 99%, Aldrich Chemical Co.) in anhydrous ethyl acetate (30 ml) with vigorous stirring. The stirred solution was allowed to reflux for an additional 30 min. until the color of the reaction mixture changed from green to amber. After cooling to room temperature and filtration, the solvent was removed to give a residue which was dissolved in ether (50 ml) and washed with brine (50 ml). The organic layer was dried ($MgSO_4$), treated with charcoal and evaporated to give an oil that was purified by chromatography on silica gel using CH_2Cl_2 as the eluent to afford 3.6g (66% yield) of the cyclopentenone (3). We found this one-step procedure to be superior to the multiple-step procedure recently reported by Bernady and co-workers[6] for the preparation of 3. The conversion of 3 to 4 was carried out according to the procedure of Bagli and Bogri.[7] The same cupric bromide procedure was applied to keto aldehyde 4 and it afforded a 38% yield of the

desired product 5. The reaction of 5 with dimethyl 2-oxoheptyl phosphate in the presence of sodium hydride gave the desired methyl ester of 15-keto-PGB_1 (1).[8]



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8. This material was identical to methyl 15-keto-PGB_1 prepared in Reference 2 via oxidation of PGB_1. A sample of the latter material was kindly provided by Dr. Shmukler.

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