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PROSTAGLANDINS AND CONGENERS II.[1] THE CONJUGATE ADDITION OF 3-t-BUTOXYOCTYL MAGNESIUM BROMIDE TO CYCLOPENTENONES. A SYNTHESIS OF RAC. 11-DEOXY-13-DIHYDROPROSTAGLANDIN-E_1.

Robert E. Schaub and Martin J. Weiss

Lederle Laboratories, Pearl River, New York 10965

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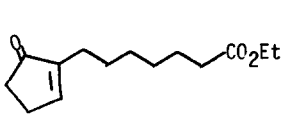
In a program aimed at the preparation of an extensive variety of prostaglandin congeners we have taken the approach that the basis for a convenient and versatile synthetic procedure would be the conjugate 1,4-addition of an elaborated β-chain to a cyclopentenone appropriately substituted in the α-position, and accordingly we have sought various techniques to effect this critical step. A previous communication[1] from this laboratory describes the use of 1-trans-alkenyl-trialkyl alanates for the introduction of the Δ^{13}-trans-15-deoxy β-chain.[2] We now report the use of 3-t-butoxy-1-octyl magnesium bromide (II)[3] for the introduction of the 13-dihydro-15-hydroxy chain leading to a useful synthesis of racemic 11-deoxy-13-dihydroprostaglandin E_1 (IV), a compound reported[4] to have gastric acid secretion inhibitory activity approaching that of 1-prostaglandin E_1 and, as the ethyl ester, marked prostaglandin-like hypotensive activity (rat assays), but little effect on smooth muscle.[5] These observations point to IV as an interesting base for structure-activity studies in the prostaglandin field.

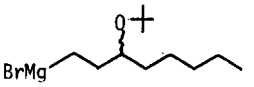
Treatment of cyclopentenone I[6,7] with Grignard II in the presence of tributylphosphine-Cu(I)I[8] gave conjugate addition product III (m/e 424; ir 5.7μ), isolated by distillation and chromatography, in 35% yield (79% when based on non-recovered I).[9] Deblocking was accomplished in 94% overall yield by submission to neat trifluoroacetic acid[7] (1 hr., 0°), followed by brief treatment with aqueous ammonia (partial 15-O-trifluoroacetylation) and finally saponification to IV, which was chromatographed on silica gel (IV: m/e 340; ir 2.80-3.70, 5.75, 5.87μ).[10] The relationship of the two side-chains in III to each other is open to question. Since this substance was obtained after ammonium chloride quenching of the Grignard reaction product a cis relationship might have been expected. On the other hand, treatment of III with ethanolic ethoxide (ambient temp., 18 hr.) produced no change in the ir, nmr or tlc behavior. In any event,

deblocking procedures can reasonably be assumed to have produced a trans relationship in IV.[11]

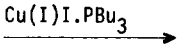
Treatment of ketone IV with lithium perhydro-9b-boraphenalyl hydride[12] in THF at 0° for 30 min. provided the corresponding alcohol (70%) consisting of about 80% 9α-ol, racemic 11-deoxy-13-dihydroprostaglandin $F_{1\alpha}$, and about 20% of the 9β-ol as determined by the relative intensities of the C_9 carbinolic proton signals[13] at 4.22δ (9α-ol) and 3.88δ (9β-ol). Sodium borohydride reduction of the ethyl ester of IV followed by saponification gave a mixture, which by the same method of analysis was 30% 9α-ol and 70% 9β-ol.[14]

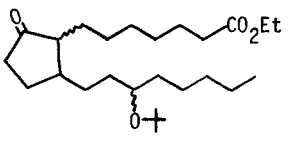


I



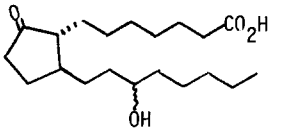
II





III

1. CF_3CO_2H
2. NH_4OH
3. KOH



IV

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9. No attempt was made to maximize yields. All compounds gave satisfactory elemental analyses (±0.4%), consistent spectral data, and were homogeneous by tlc or glc criteria.
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