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PROSTAGLANDINS AND CONGENERS I. THE SYNTHESIS OF 11,15-BISDEOXYPROSTAGLANDINS E_1, E_2, and $F_{1\alpha}$. THE STEREOSPECIFIC CONJUGATE ADDITION OF A LITHIUM TRANS-1-ALKENYLALANATE.

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As a convenient approach to the synthesis of the prostaglandins and their congeners, we have envisioned the stereospecific introduction of the trans-1-octenyl β-chain into an α-alkylated cyclopentenone nucleus. In this communication we report the synthesis of 11,15-bisdeoxyprostaglandins E_1, E_2, and $F_{1\alpha}$ according to this design, which incorporates a novel and efficient conjugate addition reaction of an aluminum "ate complex".[1]

Diisobutylaluminum hydride reduction of 1-octyne in heptane yields the trans-1-octenylalane I, which upon treatment with an ethereal solution of methyllithium affords the lithium trans-1-octenylalanate II.[2] Reaction of the "ate complex" II with 2-(6-carbethoxyhexyl)-2-cyclopentenone (IIIa)[3,4] at room temperature gives after acid work-up and isolation ethyl 9-oxo-13-trans-prostenoate (IVa) in 76% yield: ir 1745 and 967 cm^{-1}; nmr ($CDCl_3$) δ 5.55 (m, 2H, $J_{13,14}$ = 15 Hz); m/e 350.[5] Likewise, treatment of 2-(4-carbethoxybutyl)-2-cyclopentenone (IIIb) and 2-(carbethoxymethyl)-2-cyclopentenone (IIIc) with reagent II produces prostenoates IVb (66%) and IVc (57%) respectively.[5]

The reactivity of the alanate reagent deserves comment. Only the vinyl ligand of alanate II is transferred in a 1,4-manner and its trans-stereochemistry is preserved. No 1,2-addition of the vinyl group to the unsaturated carbonyl is observed nor is there any reaction at the ester function. The alkyl ligands also do not appear to participate in addition reactions to either carbonyl function of cyclopentenones III. In contrast, reaction of cyclopentenone IIIa with either vinylalane I itself or with vinylalane I complexed with triethylamine fails to yield any 1,4-addition product IVa. Vinylalane I gives products derived from 1,2-addition to the ketone carbonyl of cyclopentenone IIIa. Finally, alanate

II does not undergo any appreciable 1,2-vinyl transfer to the ketone of cyclopentanone V[4] under the same conditions that it reacts with cyclopentenone IIIa.

Compounds IV are readily converted to 11,15-bisdeoxyprostaglandins. Saponification of IV gives the corresponding prostenoic acids.[5a] Reduction of IVa with lithium perhydro-9b-boraphenalylhydride stereoselectively yields the $PGF_{1\alpha}$ derivative VI.[5a,6] The PGE_2 analogue VIII is obtained from IVc by the sequence of ketalization to VIIa (ethylene glycol, pTSA, benzene, 80% yield),[5a] diisobutylaluminum hydride reduction of the ester at -78° to aldehyde VIIb, (83% yield), Wittig condensation (4-carboxybutyltriphenylphosphonium bromide, NaH, DMSO), to cis-olefinic acid VIIc and deketalization to ketone VIII (aqueous THF, 0.1N HCl, 85% yield from VIIb).[5a,7]

Further application of the "alanate" process to the synthesis of prostaglandins and the reaction of "alanate" reagents with other conjugate addition receptor molecules will be reported by us at a future date.

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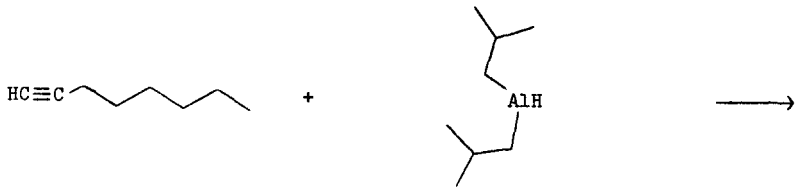
REFERENCES

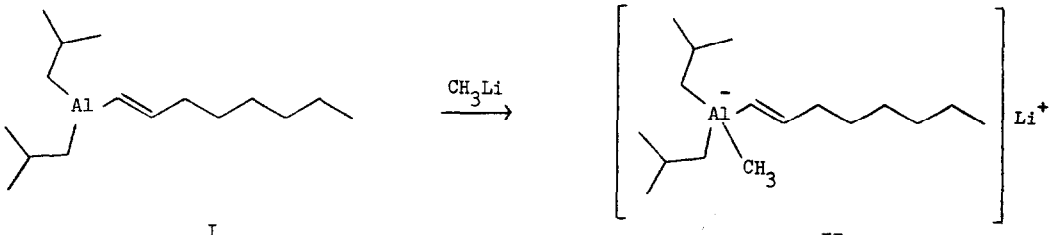
1. A recent publication [C. J. Sih, R. G. Salomon, P. Price, G. Peruzzoti, and R. Sood, Chem. Commun., 240 (1972)] appearing after the completion of our studies reports the conjugate addition of lithium di-trans-1-octenylcuprate to a 4-hydroxy-cyclopentenone derivative.

2. G. Zweifel and R. B. Steele, J. Amer. Chem. Soc., 89, 2754 (1967). These authors have demonstrated that alkenylalanates will undergo selective transfer of the alkenyl ligand, with retention of configuration, to carbon dioxide, formaldehyde, and acetaldehyde.

3. J. F. Bagli, T. Bogri, R. Deghenghi and K. Wiesner, Tetrahedron Letters, 465 (1966).

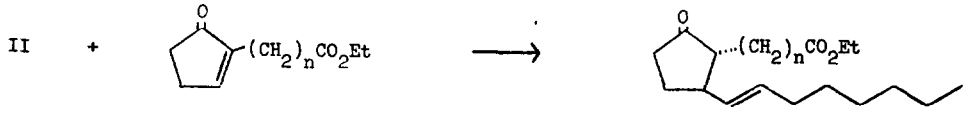
4. Cyclopentenones III were prepared from 2-carbethoxycyclopentanone and the ethyl ω-haloalkanoates by the sequence of alkylation, acid decarboxylation, reesterification, enolacetylation, bromination, and dehydrobromination and will be the subject of a forthcoming publication from our laboratories.





I

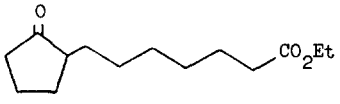
II



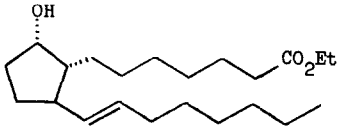
III

IV

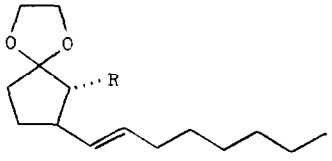
n : a = 6, b = 4, c = 1



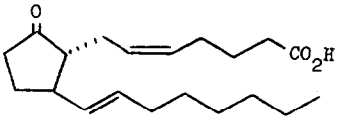
V



VI



VII



VIII

R :

a = CH_2CO_2Et

b = CH_2CHO

c = $CH_2CH\overset{c}{=}CHCH_2CH_2CH_2CO_2H$

5. (a). All new compounds reported have spectral and analytical data consistent with their assigned structures. (b). The yields of the products reported are for analytically pure compounds. (c). No effort was made to maximize the conjugate addition reaction.

6. The use of this reagent for the stereoselective conversion of PGE to PGFα derivatives was suggested by the observation of H. C. Brown and W. C. Dickason [J. Amer. Chem. Soc., 92, 709 (1970)] that 2-methylcyclopentanone could be reduced in 94% epimeric purity to the cis-2-methyl-cyclopentanol and was developed independently in these laboratories by R. E. Schaub. It has since been reported by E. J. Corey and R. K. Varma, [J. Amer. Chem. Soc., 93, 7319 (1971)].

7. E. J. Corey, N. M. Weinshenker, T. K. Schaaf, and W. Huber, J. Amer. Chem. Soc., 91, 5675 (1969).