Acetoxyfulvene Synthesis of Prostaglandins: an Alternative Synthesis of the Corey Aldehyde†

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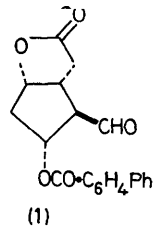
Summary A synthesis of the Corey aldehyde, a versatile prostaglandin precursor, from 6-acetoxyfulvene is described.

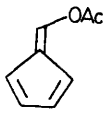
THE Corey aldehyde (**1**) is a key intermediate in prostaglandin synthesis[1,2,3] and has been used extensively in our laboratories for the preparation of prostaglandin analogues. The original synthesis of the aldehyde (**1**) required the construction of a bicycloheptene by means of a catalysed Diels-Alder reaction of 5-methoxymethylcyclopenta-1,3-diene with 2-chloroacrylonitrile. However, isomerisation of the 5-substituted cyclopenta-1,3-diene is a problem in this sequence; it can be overcome by the use of thallium cyclopentadienide[2] but this is a highly toxic and expensive reagent. We report here an alternative synthesis of the aldehyde (**1**) that overcomes these disadvantages.

6-Acetoxyfulvene (**2**)[4]‡ is used as starting material since the isomerisation of the 1,3-diene system is prevented by the presence of the exocyclic enol acetate group. A further advantage of this approach is that the enol acetate grouping in 6-acetoxyfulvene (**2**), which becomes the formyl group in the aldehyde (**1**), is introduced at the correct oxidation level. 6-Acetoxyfulvene (**2**) smoothly underwent an uncatalysed Diels–Alder reaction with 2-chloroacrylonitrile in refluxing benzene to give the enol acetate (**3**) (73% overall yield from cyclopentadiene) as a mixture of epimers at C(5), which upon hydrolysis with 2N-hydrochloric acid in acetone gave the products of kinetic control, the *anti*-aldehydes (**4**).§ This mixture was readily isomerised to the more stable *syn*-aldehydes (**5**) by prolonged treatment with 2N-hydrochloric acid and dioxan at 84 °C. The key intermediate *syn*-aldehydes (**5**) now contained the appropriate stereochemistry for the synthesis of the aldehyde (**1**).

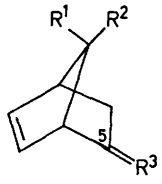
The aldehydes (**5**) were converted into the dimethyl acetals (**6**) [trimethyl orthoformate–*p*-toluene sulphonic acid; 62% overall from the enol acetates (**3**)] prior to hydrolysing the chloronitrile group with potassium hydroxide in dimethyl sulphoxide¶ to give the ketone (**7**)†† (67%), m.p. 43—45 °C. Baeyer–Villiger oxidation of the ketone (**7**) using alkaline hydrogen peroxide, and iodolactonisation of the resulting product with potassium iodide and iodine, gave the iodohydrin (**8**) (74%). The iodohydrin (**8**) was converted into the 4-phenylbenzoate (**9**) (74%), m.p. 156—157 °C, which was deiodinated with tri-n-butyltin hydride to yield the acetal (**10**) (93%), m.p. 115 °C. The dimethyl acetal function in (**10**) was readily hydrolysed using a two-phase system of concentrated hydrochloric acid and 2% propan-2-ol in chloroform to give the desired aldehyde (**1**) (79%). The aldehyde (**1**) was identical in all respects to a sample prepared by the method of Corey.[3]

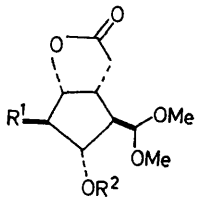


(**1**)



(**2**)





(**3**) R^1,R^2 = ═CHOAc; R^3 = Cl, CN
(**4**) R^1 = H; R^2 = CHO; R^3 = Cl, CN
(**5**) R^1 = CHO; R^2 = H, R^3 = Cl, CN
(**6**) R^1 = $CH(OMe)_2$; R^2 = H; R^3 = Cl, CN
(**7**) R^1 = $CH(OMe)_2$; R^2 = H; R^3 = O

(**8**) (R^1 = I; R^2 = H)
(**9**) (R^1 = I; R^2 = COC_6H_4Ph)
(**10**) (R^1 = H; R^2 = COC_6H_4Ph)

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‡ Prepared by reaction of sodium cyclopentadienide with ethyl formate and treatment of the resulting sodium salt of 5-formylcyclopenta-1,3-diene with acetyl chloride as given in ref. 4.

§ *Anti* is used here to indicate that the aldehyde function is on the opposite side of the one carbon bridge to that of the double bond. The *anti* configuration was indicated by the presence of a long range coupling (*J* 3Hz) of the C(7) *syn* proton to the C(6) *endo* proton in the n.m.r. spectrum *via* a "planar W" conformation. (See V. Mark, *Tetrahedron Letters*, 1974, 299). This coupling was absent in the *syn*-aldehyde (**5**).

¶ The method of conversion of the dimethyl acetals (**6**) into the lactone (**10**) is derived from that given in ref. 1.

†† The ketone (**7**) was resolved *via* the *d*-amphetamine salt of the hemiphthalate ester of the corresponding *endo*-alcohol. Crystallisation of the diastereoisomeric salts from propan-2-ol gave an enantiomerically pure salt which was converted back into the ketone (**7**), $\alpha^{24}_{\lambda} = -545°$ (*c* 0·156, $CHCl_3$) by standard methods.

[1] E. J. Corey, N. M. Weinshenker, T. K. Schaaf, and W. Huber, *J. Amer. Chem. Soc.*, 1969, **91**, 5675.
[2] E. J. Corey, U. Koelliker, and J. Neuffer, *J. Amer. Chem. Soc.*, 1971, **93**, 1489.
[3] E. J. Corey, S. M. Albonico, U. Koelliker, T. K. Schaff, and R. K. Varma, *J. Amer. Chem. Soc.*, 1971, **93**, 1491.
[4] K. Haffner, G. Schulz, and K. Wagner, *Annalen*, 1964, **678**, 39.