A Novel Approach to the Synthesis of Prostaglandin-F₁ Skeleton

Sir:

In a previous paper from our laboratories¹ a new synthetic route to prostaglandin-F₁ (PGF₁) skeleton utilizing a cyano-diacetate (VII) as a key intermediate was reported. Here we wish to report another novel synthetic approach to PGF₁ skeleton which includes oxidative cleavage of bicyclo (2, 2, 1) heptene (II) as a key step and merges in the latter stages with those developed earlier.²

A starting material, 9-carboethoxy-2-tran nonenonitrile (I) was synthesized from diethy suberate in four steps.² When I was subjected to the Diels-Alder reaction with cyclopentadiene at 150°C in an autoclave, an objective adduct (II) was obtained.

\[
\begin{align*}
C₂H₅OOC-(CH₂)₆-COOCC₃H₅ & \longrightarrow C₂H₅OOC-(CH₂)₆-CH=CH-CN \\
\text{(I)} & \\
\text{(IIa)} & \\
\text{(IIb)} & \\
\text{(IIa)} & \longrightarrow \text{(IIb)} & \longrightarrow \text{(III), (IV), (V), (VI), (VII)} & \longrightarrow \text{(VIII)} & \longrightarrow \text{(PGF₁)}
\end{align*}
\]

¹) Part 3, J. Katsube, H. Shimomura, E. Murayama, K. Toki and M. Matsui, in press, (Agr. Biol. Chem.).²) bp 102−105°C/0.1 mmHg, n₂₀°₀.₁₄₅₈₄₈.
A Novel Approach to the Synthesis of Prostaglandin-F₁ Skeleton

obtained (yield, 55%; conversion, 72%) which consisted of two stereoisomers, an exo-nitrile (IIa) and an endo-nitrile (IIb). IR:* 2250, 1735, 1245, 1180 for IIa and IIb. NMR (CCl₃):** 6.1-6.3 (olefinic, m, 2H) for IIa; 6.4 (dd, H) and 6.2 (dd, H) for IIb.³ The ratio of IIa and IIb was found to be about 4:1, and this predominance of the exonitrile (IIa) was expected from the similar cases in which α,β-unsaturated nitriles were used as dienophiles.⁴

The exo-nitrile (IIa) separated by column chromatography on silicagel was subjected to ozonolysis in methylene chloride at -60°-70°C, and the resulting ozonide was oxidatively decomposed by aq. performic acid to afford a diacid (III, in 83% yield). IR: 3200-2650, 2250, 1735, 1710, 1180.

The diacid (III) was chlorinated with phosphorus oxychloride in the presence of dimethylformamide in benzene to afford an acid chloride (IV). IR: 2250, 1795, 1730, 1180.

Treatment of IV with ethereal diazomethane gave a bis-diazoketone (V, IR: 3100, 2520, 2100, 1730, 1630, 1375, 1325), which was reduced by 48% hydroiodic acid to provide an objective oily diketone (VI, in about 30% yield). IR: 3200-2650, 2250, 1735, 1710, 1180.

The diketone (VI) was subjected to the Baeyer-Villiger oxidation with m-chloroperbenzoic acid (1.5 mole equiv.) in chloroform (3 w/v% solution) at 55°C for 72 hr. The objective cyano-diaceate (VII) was obtained in 25% yield after column chromatography on silica gel. IR: 2250, 1735, 1235, 1180. NMR (CCl₃): 5.2 (m, H) and 4.8 (m, H) due to two carboxylic methylene, 2.03 (s, 6H) due to two acetoxy methyl protons.

The present cyano-diaceate (VII) was proved to be essentially identical spectroscopically with that synthesized earlier.⁵

In a similar fashion as described earlier,⁶ VI was converted to an enone (IX) in two steps. The enone (IX) obtained thus was found to be composed of essentially only one stereoisomer, although the previous route had provided an isomeric mixture of the enone.⁷

Moreover, the present enone was found to be spectroscopically identical with the main isomer of the previous route. NMR (CDCl₃): 6.13 (d, J=16 cps, H) and 6.70 (dd, J=16.8 cps, H) due to olefinic, about 5.0 (a signal consisting of six peaks) due to two carboxylic methylene protons.

The stereochemistry concerning the asymmetric centers at the 9-, 11- and 15-position (PG number) remains uncertain,⁸ but the present pathway seems to be a fairly easy and stereo-controlled one for production of PGF₁₅ skeleton.⁹

Junki KATSUBE
Hiromi SHIMOMURA
Masanao MATSUI

Received September 14, 1971

Takazuka Research Laboratory,
Sumitomo Chemical Co.,
Takazuka-shi, Hyogo
*Department of Agricultural Chemistry,
The University of Tokyo,
Tokyo

Takazuka Research Laboratory,
Sumitomo Chemical Co.,
Takazuka-shi, Hyogo
*Department of Agricultural Chemistry,
The University of Tokyo,
Tokyo

Received September 14, 1971