Synthetic Studies on Cyclopentane Derivatives

Part I. Alternative Routes to dl-Prostaglandin-B1, and Dihydrojasmine

By Junki KATSUBE* and Masanao MATSUI

Department of Agricultural Chemistry,
The University of Tokyo, Tokyo
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An alternative route to dl-prostaglandin-B1, using the Grignard reaction of 2-(6'-tert-butyloxycarbonylhexyl)-3-methoxy-2-cyclopenten-1-one(XII) with 3-tetrahydropyranyloxy-1-octyne was developed.

An easy synthesis of dihydrojasmine was also described.

Prostaglandins were first discovered in semen and seminal vesicles by Goldblatt11 and von Euler21 in 1935. They are now known to be widely distributed in nature, to belong to a family of C20 unsaturated and oxygenated fatty acids and to play physiologically important roles.

Since Bergström and co-workers3a–e) established the structures, several synthetic routes to prostaglandins or their analogs have been developed by many groups.4a–k)

In view of their potent and diverse biological activities, we have also attempted to synthesize in a few steps naturally occurring prostaglandins from readily available chemicals.

In this paper, we report an alternative route to dl-prostaglandin-B1, PGB1, I as shown in Chart 1.

This synthetic scheme was based on the principle that PGB1-skeleton could be built up by the Grignard reaction of an acetylenic alcohol with 2-substituted-3-alkoxy-2-cyclopenten-1-one, that is, 2-substituted cyclopentane-1,3-dione enol ether.

But Hardegger et al.4f) and Klok et al.4k) quite recently reported a similar total synthesis of dl-PGB1 which involved the Grignard reaction...
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CHART 1.

of an acetylenic alcohol with 2-substituted-2-cyclopenten-1-one and further several steps such as allyl rearrangement and oxidation.

The starting material, ethyl 9-oxo-decanoate (II) was prepared by the method of Barger and that of McKennis. The latter method comprises the condensation reaction of methyl cadmium with 8-ethoxycarbonyl-octanoyl chloride which was also obtained from azelaic acid, an industrially available chemical.

The key intermediate, 2-(6'-carboxyhexyl)-cyclopentane-1,3-dione (VI) was synthesized by the method of Smith with modification. Namely, II was condensed with diethyl oxalate in the presence of sodium ethoxide in ethanol to yield 2-(6'-ethoxycarbonylhexyl)-5-ethoxalyl-cyclopentane-1, 3, 4-trione(III) as an acidic material. Heating III in ethanolic hydrochloric acid gave a de-ethoxalylated trione(IV), which was treated with aq. solution of semicarbazide hydrochloride and sodium acetate to give a crystalline semicarbazone(V).

III and IV were obtained as viscous oil, and they were used without further purification, but their structures were supported by their spectral data which were similar to those of the corresponding 2-methyl homologs.

The semicarbazone(V) was reduced to the 1, 3-dione(VI) by heating with potassium hydroxide in ethylene glycol.

The 1, 3-dione(VI) contains two acidic functions, carboxylic acid and enolic hydroxide, which were blocked selectively by the following reactions; VI was treated with ethereal diazomethane to give a methyl ester-methyl enol ether(VII), which was heated in aq. oxalic acid to yield a methyl ester-1, 3-dione(VIII). Saponification of VII in aq. sodium hydroxide followed by neutralization with an equivalent amount of cold dilute hydrochloric acid yielded a carboxy-methyl enol ether(IX). Furthermore, the 1, 3'-dione(VI) was obtained when IX was further hydrolyzed in hydrochloric acid.

Treatment of the 1, 3-dione(VI) with isobutene in the presence of a catalytic amount of sulfuric acid gave a tert-butyl ester-1, 3-thoxy-2-cyclopenten-1-one(XIX) with Grignard reagents was first attempted as model experiments (see Chart 2).

When XIX was reacted with an usual Grignard reagent, methyl magnesium iodide, followed by hydrolysis in dil. hydrochloric acid, 2-pentyl-3-methyl-2-cyclopenten-1-one(XX) was obtained in considerable yield.

This cyclopentenone(XX) is referred to dihydrojasmine10) which is closely related to jasmone, the primary odorous principle of jasmine flowers. Consequently, this Grignard reaction provided an easy synthesis of dihydrojasmine.11a-c)

The Grignard reaction of XIX with 3-tetrahydro-pyranoloxyl(THPO)-1-propyne in tetrahydrofuran, followed by hydrolysis in dil. hydrochloric acid or in aq. ammonium chloride was carried out to yield expected THPO-propynyl-cyclopentenone(XXI). The hydrolysis carried out in aq. ammonium chloride indicated that acidic condition was not necessarily essential for hydrolysis of the enolic ether of the intermediate, cyclopentenol which is shown in Chart 1.

The yne-enone system was confirmed by the

\[ \text{Chart 2.} \]

\[ \begin{align*}
\text{R}_3 & \quad \text{(R)} \\
\text{O} & \quad \text{(O)}
\end{align*} \]

\[ \begin{align*}
\text{R}_3 & \quad \text{(XIX)} \\
\text{OCH}_3 & \quad \text{CH}_3 \\
\text{C} & \quad \text{C-CH}_2\text{O}
\end{align*} \]

\[ \begin{align*}
\text{R}_3 & \quad \text{(XX)} \\
\text{C} & \quad \text{C-CH}_2\text{OH} \\
\text{O} & \quad \text{(XXII)}
\end{align*} \]

\[ \begin{align*}
\text{R}_3 & \quad \text{(XXXI)} \\
\text{C} & \quad \text{C-CH}_2\text{OH} \\
\text{O} & \quad \text{(XXXII)}
\end{align*} \]

\[ \begin{align*}
\text{R}_3 & \quad \text{(XXXIII)} \\
\text{C} & \quad \text{C-CH}_2\text{OH} \\
\text{O} & \quad \text{(XXXIV)}
\end{align*} \]

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following transformations; Treatment of XXI with methanol and a small amount of p-toluenesulfonic acid gave a hydroxy-propynyl cyclopentenone(XXII). Partial hydrogenation of XXI on palladized barium carbonate\(^{12}\) and quinoline\(^{13}\) followed by treatment with methanol and a small amount of p-toluenesulfonic acid gave a hydroxy-cis-propenyl-cyclopentenone(XXIII). Hydrogenation of XXI on palladium-charcoal gave a hydroxy-propyl-cyclopentenone(XXIV).

On the other hand, in the reaction of the methyl ester-methyl enol ether(VII) with the acetylenic Grignard reagent, it was proved that the ketonic carbonyl of the ring was less reactive than the methyl ester carbonyl from the fact that the intensity of the infrared absorption of the ester carbonyl(1740 cm\(^{-1}\)) had been weakened more rapidly than that of the ketonic carbonyl(1685 cm\(^{-1}\)) during the reaction.

Then, the carboxylic acid(IX) and the tert-butyl ester(XII) were used as starting materials, since these were thought to be less reactive to the Grignard reagents.

The Grignard reaction of IX with 3-THPO-1-propyne yielded desired THPO-propynyl cyclopentenone(XXIII), but a successful result was not obtained with 3-THPO-1-octyne.\(^{14}\)

On the other hand, the tert-butyl ester(XII) reacted with the Grignard reagent of 3-THPO-1-octyne to yield desired THPO-octynyl cyclopentenone(XXIV).

Partial hydrogenation of XIV on a small amount of palladized barium carbonate\(^{12}\) and quinoline\(^{13}\) gave THPO-cis-octenyl cyclopentenone(XV), which was successively treated with methanol and p-toluenesulfonic acid to yield hydroxy-cis-octenyl cyclopentenone(XVI). Treatment of XVI with trifluoroacetic acid gave a free acid, dl-PGB\(_{c}\)-cis isomer(XVII) and dl-PGB\(_{t}\)-cis isomer(XVIII) which was isomerized to dl-PGB(I) by treatment with 0.125N sodium hydroxide-methanol.\(^{4f}\)

Both dl-PGB\(_{c}\)-cis isomer(XVII) and dl-PGB\(_{t}\)(I) were obtained as crude oily materials, and purification was accomplished as dl-PGB\(_{t}\)-methyl ester(XVIII); The crude oily material obtained by esterification of dl-PGB\(_{t}\) with ethereal diazomethane was chromatographed on alumina to give the dl-PGB\(_{t}\)-methyl ester(XVIII).

The physical properties of I and XVIII were identical with those in literatures.\(^{30, 4f}\)

**EXPERIMENTAL**

All melting points are uncorrected. The NMR spectra were recorded with a spectrometer JNM-4H-100 (Japan Electron Optics Lab. Co.), and all chemical shifts are given in the value, ppm (\(\delta\)) from TMS. The IR spectra were taken with a spectrophotometer IR-S (Japan Spectroscopic Co.). The UV spectra were taken with a spectrophotometer Cary-14 (Applied Physics Co.).

2-(6'-Ethoxycarbonylhexyl)-5-ethoxalyl-cyclopentane-1, 3, 4-trione(III). To an ethanolic solution of sodium ethoxide (6.0 g of Na in 80 ml of abs. EtOH) were added dropwise ethyl 9-oxo-decanoate (II, 25.3 g) and ethyl oxalate (38.0 g) with external cooling, followed by stirring at room temperature for 1 hr. After heating under reflux for 45 min, the resulting red-brown solution was cooled, to which 15.6N sulfuric acid (20 ml) was added.

The resulting precipitate (\(\text{Na}_2\text{SO}_4\)) was filtered off and washed with ethanol. The filtrate was concentrated in vacuo to give an oily residue, which was purified as follows: From an ethereal solution (250 ml) of the oily material, the acidic part was extracted with aq. sodium bicarbonate (5%). The oily acidic material was liberated by acidifying the sodium bicarbonate solution, which was extracted with ether and the extract was dried over magnesium sulfate. Evaporation of the solvent left 34.1 g of viscous oily III. \(\text{IR}_{\text{max}}(\text{cm}^{-1})\): 3300 - 3100, 1740, 1690, 1650, 1385. \(\text{NMR}_{\text{CDCl}_{3}}(\text{ppm})\): 4.13(2H, q, ester methylene), 4.4(2H, q, ethoxalyl methylene). UV\(_{\text{EtOH}}(m\mu)\): 252, 325.

2-(6'-Ethoxycarbonylhexyl)-cyclopentane-1, 3, 4-trione(IV). A mixture of III (19.1 g), 6N hydrochloric acid (40 ml) and ethanol (40 ml) was refluxed for 5 hr. After concentration of the reaction mixture, an oily residue was

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\(^{13}\) D. J. Cram and N. L. Allinger, \(J. \text{Am. Chem. Soc.}\), 78, 2518 (1956).

dissolved in ether, and the solution was washed with water and dried over magnesium sulfate.

Evaporation of the solvent left 16.4 g of oily IV. IR\text{\textsuperscript{\textit{\textnu}\textsubscript{max}}}(\text{cm}^{-1}): 3400–2600, 1735, 1680, 1650, 1390, 1200. NMR\text{\textsubscript{100Mc}}: 2.9(2H, s, methylene at 5-position), 4.1 (2H, q). UV\text{\textsubscript{\textlambda\textsubscript{max}}}(\text{\mu}\text{M}): 208, 276, 325.

2-(6'-Ethoxycarbonylhexyl)-cyclopentane-1, 3, 4-trione (IV). To an ethanolic solution(80ml) of 24.9 g of the trione(IV), was added with stirring an aq. semicarbazide solution(120ml) prepared from 11.1 g of semicarbazide-hydrochloride and 16.0 g of sodium acetate. After stirring for 1 hr, the reaction mixture was diluted with water(80ml) and allowed to stand overnight. The precipitated semicarbazone was filtered, washed with water and dried in vacuo, to give 20.6 g of yellow powdery V. For analysis, this crude semicarbazone was recrystallized from diethylformamide to give fine needles. mp 258–260°C (with decomp.). Anal. Found: N, 12.95. Calcd. for C\textsubscript{15}H\textsubscript{23}O\textsubscript{5}N\textsubscript{3}: N, 12.92%. IR\text{\textnu}(\text{cm}^{-1}): 3340, 3160, 3025, 1750, 1730, 1660, 1605, 1505, 1410, 1385, 1210, 1190.

2-(6'-Carboxyhexyl)-cyclopentane-1, 3-dione (VI). A mixture of 19.5 g of the semicarbazone(V) and potassium hydroxide(27 g) in ethylene glycol(195 ml) was gradually heated with stirring. During the initial 2 hr, the mixture was heated at 155–160°C, followed by heating at 190–195°C for further 8 hr.

After removal of the solvent by distillation in vacuo, to give 20.6 g of yellow powder V. For analysis, this crude semicarbazone was recrystallized from methanol(1.5 ml) and water(2.0 ml) was refluxed for 3 hr. The solid that deposited on cooling was filtered to give 0.54 g(88%) of crude VIII.

Recrystallization from hot water gave colorless leaflets, mp 116–118°C. Anal. Found: C, 65.36; H, 8.24. Calcd. for C\textsubscript{13}H\textsubscript{20}O\textsubscript{4}: C, 64.98; H, 8.02%. IR\text{\textsubscript{\textnu}}(\text{cm}^{-1}): 2600(broad, strongly hydrogen-bonded OH), 1745(ester CO), 1550(strongly hydrogen-bonded CO), 1375, 1350.

2-(6'-Methoxycarbonylhexyl)-cyclopentane-1, 3-dione (VIII). A mixture of 0.65 g of VII and oxalic acid(0.30 g) in methanol(1.5 ml) and water(2.0 ml) was added with stirring for 40 min. Ether(50 ml) was added to the resulting clear solution, and the mixture was neutralized with 2N hydrochloric acid(12.5 ml). After removal of the solvent by distillation in vacuo, to give 20.6 g of yellow powder V. For analysis, this crude semicarbazone was recrystallized from diethylformamide to give fine needles. mp 258–260°C (with decomp.). Anal. Found: N, 12.95. Calcd. for C\textsubscript{15}H\textsubscript{23}O\textsubscript{5}N\textsubscript{3}: N, 12.92%. IR\text{\textnu}(\text{cm}^{-1}): 3340, 3160, 3025, 1750, 1730, 1660, 1605, 1505, 1410, 1385, 1210, 1190.
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of isobutene-methylene chloride solution which had been prepared by trapping dry isobutene in cooled purified methylene chloride (50 ml).

After adding 0.5 ml of conc. sulfuric acid and a small amount of hydroquinone and plugging up with a rubber stopper, the pressure bottle was shaken for 5 hr and allowed to stand overnight.

After opening the bottle, the reaction mixture was dissolved in ether (150 ml) and poured on ice-cooled water (100 ml). The organic layer was washed with cooled water and dried over magnesium sulfate. About 0.2 g of unchanged VI separated from the organic layer was recovered. Removal of the solvent left a viscous oil, which was crystallized by treatment with hexane-ether in \( \ldots \) refrigerator.

By filtration 0.95 g of X was obtained, and from the mother liquor, XI was obtained as described in the next paragraph.

Colorless leaflets X, \( \text{mp 92}^{\circ} \text{C} \). Anal. Found: C, 67.80; H, 9.24. Calcd. for C\(_{16}\)H\(_{26}\)O\(_4\): C, 68.05; H, 9.28%. IR\(_{\text{max}}\) (cm\(^{-1}\)): 2600 (broad, strongly hydrogen-bonded OH), 1730 (ester CO), 1575 (hydrogen-bonded CO), 1375, 1265, 1175. NMR\(_{\text{max}}\): 1.42 (9H, s, methyls of tert-butyl ester), 2.1 (2H, t), 2.2 (2H, t), 2.48 (4H, s, ring methylenes).

The mother liquor was washed with aq. sodium bicarbonate and concentrated in vacuo to yield an oily material, which was chromatographed on 3 g of alumina (Wako Chem. Co.).

First, some oily material like paraffin was eluted and then a small amount of oily XI (about 0.1 g) was eluted by benzene. IR\(_{\text{max}}\) (cm\(^{-1}\)): 1730 (ester CO), 1690 (cyclopentenone CO), 1620 (enolic double bond), 1370, 1260 (enol ether), 1160. NMR\(_{\text{max}}\): 1.45 (9H, s, probably methyls of tert-butyl ether), 1.5 (9H, s, probably methyls of tert-butyl ester), 2.1 (2H, t), ca. 2.2 (2H, t), ca. 2.45 (2H, m, ring methylene), ca. 2.7 (2H, m, ring methylene). UV\(_{\text{max}}\) (\(\lambda_{\text{max}}\)): 236 (lit. 11c 235).

2-Pentyl-3-methoxy-2-cyclopenten-1-one (XIX). A suspension of 2.8 g of 2-pentyl-cyclopentanone-1, 3-dione\(^{15}\) in ether was treated with ethereal diazomethane. Removal of the solvent left an oil, which was distilled under reduced pressure to give 2.95 g (97\%) of oily XIX, bp 110–115°C/0.7 mm Hg, \( \text{N} \)\(_{\text{mp}}\) = 1.4950. IR\(_{\text{max}}\) (cm\(^{-1}\)): 1685, 1630 (strong, enolic double bond), 1370, 1260 (enol ether). NMR\(_{\text{max}}\) : 3.9 (3H, s, methyl ether), \( \text{ca. 2.6} \) (2H, m, ring methylene), \( \text{ca. 2.3} \) (2H, m, ring methylene). UV\(_{\text{max}}\) (\(\lambda_{\text{max}}\)): 252.

2-Pentyl-3-methyl-2-cyclopenten-1-one (XX), dicyclohexano-tetrahydro-1,3-cyclohexadiene. To a solution of methyl magnesium iodide (990 mg, 0.006 mole) in ether (12 ml) was added dropwise 373 mg of XIX in ether (12 ml). After stirring for 1 hr at room temperature, the reaction mixture was refluxed for 2 hr, which was worked up in an usual manner to give 350 mg of crude oily XX.

This crude oil was considered from UV absorption to contain 263 mg (80\%) of XX. Distillation gave oily XX, bp 95°C (mainly)/3 mm Hg, \( \text{N} \)\(_{\text{mp}}\) = 1.4790. Anal. Found: C, 79.29; H, 11.06. Calcd. for C\(_{11}\)H\(_{18}\)O\(_2\): C, 79.46; H, 11.82%. IR\(_{\text{max}}\) (cm\(^{-1}\)): 1700, 1645, 1385, 1180. NMR\(_{\text{max}}\): ca. 2.4 (2H, m, ring methylene), ca. 2.2 (2H, m, ring methylene), 2.0 (3H, s, methyl at 3-position), 0.9 (3H, t). UV\(_{\text{max}}\) (\(\lambda_{\text{max}}\)): 252.

The semicarbazone (white prisms) melt at 176°C. Anal. Found: C, 64.34; H, 9.47; N, 18.73. Calcd. for C\(_{12}\)H\(_{21}\)ON\(_3\): C, 64.54; H, 9.48; N, 18.82%.

The 2, 4-dinitro-phenylhydrazone (red fine needles from 95% EtOH) melt at 120–122°C (lit. 11c 122°C). Anal. Found: N, 15.86. Calcd. for C\(_{17}\)H\(_{22}\)O\(_4\)N\(_4\): N, 16.18%.

2-Pentyl-3-(3'-THPO-1'-propynyl)-2-cyclopenten-1-one (XII). To a solution of ethyl magnesium bromide (0.05 mole) in abs. tetrahydrofuran (THF, 20 ml) was added dropwise 3-propyne (7.7 g, 0.055 mole), followed by heating under reflux for 5 min to yield the acetylenic Grignard reagent. Methoxy-cyclopentanone (XIII) prepared from 2-pentyl-cyclopentanone-1, 3-dione (1.68 g, 0.01 mole) was added to the Grignard reagent, followed by stirring at room temperature for 1 hr.

After heating under reflux for 0.5 hr, the resulting dark wine color solution was cooled and poured onto

\( \ldots \)

ether (250 ml) and 0.5N hydrochloric acid (150 ml), and the mixture was shaken for about 30 sec.

The organic layer was separated, washed with aq. sodium bicarbonate and water, and dried over magnesium sulfate.

Removal of the solvent and excess 3-THPO-1-propyne in vacuo gave a crude oily material, which was chromatographed on 50 g of alumina (Wako Chem. Co.) to yield oily XXI (1.4 g, 49% based on the 1,3-dione).

In the case of hydrolysis carried out in aq. ammonium chloride, XXI was also obtained in 50% yield based on XIX.

IR\textsubscript{max}(cm\textsuperscript{-1}): 2240 (triple bond), 1700 (cyclopentenone CO), 1615 (double bond), 1360, 1125, 1030.

NMR\textsubscript{max}: 4.75 (H), 4.4 (2H, s, methylene of propynyl chain), ca. 3.7 (H, m), ca. 3.5 (H, m), ca. 2.55 (2H, m, ring methylene), ca. 2.3 (2H, m, ring methylene), 2.23 (2H, t), 0.9 (3H, t). UV\textsuperscript{max} (m\textlambda): 268.

2-Pentyl-3-(3'-hydroxy-propynyl)-2-cyclopentene-1-one (XXII). A mixture of 423 mg of XXI, p-toluenesulfonic acid (10 mg) and methanol (10 ml) was stirred at room temperature for 30 min, and allowed to stand overnight in a refrigerator. The reaction mixture was diluted with ether (100 ml), washed with aq. sodium bicarbonate and water, and dried over magnesium sulfate.

After removal of the solvent, the residual oil was chromatographed on 10 g of alumina (Wako Chem. Co.) with benzene-ethyl acetate (10:1) to give oily XXII (153 mg).

IR\textsubscript{max}(cm\textsuperscript{-1}): 3400, 2250, 1690, 1610, 1370, 1125, 1035.

NMR\textsubscript{100Mc}: 4.45 (2H, s, methylene of propynyl chain), ca. 2.5 (2H, m, ring methylene), ca. 2.3 (2H, m, ring methylene), 2.23 (2H, t), 0.9 (3H, t).

Semicarbazone (yellow prisms from EtOH), mp 147–9°C. Anal. Found: C, 63.94; H, 7.86; N, 15.47. Calcd. for C\textsubscript{14}H\textsubscript{21}O\textsubscript{2}N\textsubscript{3}: C, 63.85; H, 8.04; N, 15.96%.

Hydrogenation of XXI to 2-pentyl-3-(3'-hydroxy-1'-cis-propenyl)-2-cyclopenten-1-one (XXIII). A mixture of palladized barium carbonate (30 mg) and quinoline (10 mg) in methanol (4 ml) was shaken under hydrogen for about 1 hr.

To the poisoned catalyst system described above was added 300 mg of XXI, followed by hydrogenation under atmospheric pressure. The reaction was continued until the starting material (XXI) was almost consumed, monitoring with thin layer chromatography and by UV absorption shift from 268 m\textlambda to 278 m\textlambda.

After partial hydrogenation was completed, the reaction mixture was treated with methanol (8 ml) and p-toluene sulfonic acid at room temperature for 5 hr. The reaction mixture was then obtained with ether, washed with water, and dried over magnesium sulfate. Evaporation of the solvent left oily XXIII (175 mg). IR\textsubscript{max}(cm\textsuperscript{-1}): 3400, 1675, 1625, 1585, 1370, 1050.

NMR\textsubscript{100Mc}: 3.6 (2H, t), ca. 2.5 (4H, m, two methylene), ca. 2.3 (2H, m), ca. 2.1 (2H, m), ca. 1.75 (2H, m), ca. 1.3 (6H, m), 0.9 (3H, t).

Semicarbazone (yellow prisms from EtOH), mp 147–9°C. Anal. Found: C, 63.94; H, 7.86; N, 15.47. Calcd. for C\textsubscript{14}H\textsubscript{21}O\textsubscript{2}N\textsubscript{3}: C, 63.85; H, 8.04; N, 15.96%.

Hydrogenation of XXI to 2-pentyl-3-(3'-hydroxy-1'-cis-propenyl)-2-cyclopenten-1-one (XXIII). To a solution of ethyl magnesium bromide (0.0331 mole) in THF (10 ml) was added, followed by heating under reflux for 10 min to yield the acetylenic Grignard reagent.

When 1.0 g (0.00415 mole) of the carboxy-methyl enol ether (IX) in THF (5 ml) was added dropwise 3-THPO-1-propyne (5.6 g, 0.04 mole), followed by heating under reflux for 1 hr, there was poured on 0.4N hydrochloric acid (120 ml) and ether. The organic layer was separated, from which an acidic material was extracted with aq. sodium bicarbonate. Acidification of the sodium bicarbonate solution liberated an oily crude acid (XIII), which was esterified with ethereal diazomethane to give a crude oily methyl ester.

Purification by chromatography on silica-gel (22 g) gave 501 mg of methyl ester of XIII. IR\textsubscript{max}(cm\textsuperscript{-1}): 2250, 1740, 1700, 1615, 1360, 1200, 1125, 1025.

NMR\textsubscript{100Mc}: 4.75 (H, m, methyne of tetrahydropyranyl ring), 4.4 (2H, s, methylene of propynyl chain), 3.5 (3H, s, methyl ester), ca. 3.8–3.3 (2H, m), ca. 2.55 (2H, cyclopentene ring methylene), 2.35–2.1
(6H, overlapping signals). \( \text{UV}_{\lambda_{\text{max}}}^{\text{EtOH}}(\text{mp}) = 269. \)

2-(6'-tert-Butyloxycarbonylhexyl)-3-(3'-THPO-1'-octynyl)-2-cyclopenten-1-one(XIV). To a solution of ethyl magnesium bromide (0.0288 mole) in THF (11 ml) was added dropwise 3-THPO-1-octyne (6.4 g, 0.305 mole) in THF (5 ml), followed by heating under reflux for 10 min to yield the acetylenic Grignard reagent. To the cooled acetylenic Grignard reagent was added the tert-butyl ester-methyl enol ether(XII) which was obtained from 1.715 g (0.0061 mole) of the tert-butyl ester-1, 3-dione(X). After stirring at room temperature for 0.5 hr and heating under reflux for 45 min, the resulting dark wine color clear solution was poured on a cooled solution of 0.2N hydrochloric acid (150 ml) and ether (250 ml).

After shaking for a short period, the organic layer was separated, washed with aqueous sodium bicarbonate and water, and dried over magnesium sulfate. Evaporation of the solvent in vacuo left a crude oil, which was chromatographed on alumina (100 g, Wako Chem. Co.).

Firstly excess 3-THPO-1-octyne was eluted with hexane, and then 700 mg of oily XIV was eluted with benzene-ethyl acetate (10:1). \( \text{ND}_{28} = 1.4912. \) Anal. Found: C, 73.61; H, 9.98. Calcd. for C_{29}H_{46}O_{5}: C, 73.38; H, 9.77%. \( \text{IR}_{\nu}^{\text{cm}^{-1}}: 2250, 1735, 1705, 1615, 1365, 1155, 1020. \) \( \text{NMR}_{\text{H}}^{\text{ppm}}: 4.8(\text{H, m, methyne of tetrahydropyranyl ring}), 4.55(\text{H, t, methyne of octynyl chain}), \text{ca. 3.8-3.3(2H, m), ca. 2.5(2H, m, cyclopentenone ring methylene), 2.35-2.0(6H, overlapping signals), 1.4(9H, s, methyls of tert-butyl ester), 0.9(3H, t). \text{UV}_{\lambda_{\text{max}}}^{\text{EtOH}}(\text{mp}) = 269(\varepsilon, 2.4 \times 10^4). \)

2-(6'-Carboxyhexyl)-3-(3'-hydroxy-1'-cis-octenyl)-2-cyclopenten-1-one(XVI). With the poisoned catalyst system prepared from palladized barium carbonate (170 mg) and quinoline (10 mg) in methanol (15 ml) as described before was partially hydrogenated 432 mg of XIV under atmospheric pressure, monitoring by thin layer chromatography and UV absorption. The methanolic solution of 3-THPO-cis-octenyl-cyclopentenone(XV) thus obtained was filtered to remove the catalyst, and the filtrate was allowed to stand overnight with p-toluenesulfonic acid (70 mg) in refrigerator, and then stirred at room temperature for 8 hr.

The reaction mixture was diluted with ether, washed with water, and dried over magnesium sulfate. Evaporation of the solvent left a crude oily material, which was chromatographed on 8 g of alumina (Wako Chem. Co.) with benzene to give oily XVI (232 mg). \( \text{Np}^a = 1.4985. \) Anal. Found: C, 73.07; H, 10.38. Calcd. for C_{24}H_{40}O_{4}: C, 73.43; H, 10.27%. \( \text{IR}_{\nu}^{\text{cm}^{-1}}: 3450, 1730, 1690, 1635, 1585, 1370, 1220, 1160, 850. \) \( \text{NMR}_{\text{H}}^{\text{ppm}}: 6.325(\text{H, d, J=12 cps}), 5.75(\text{H, double d, J=12 cps, J=9 cps}), 4.5(\text{H, m, methyne of octynyl chain}), 2.75(2H, m, ring methylene), ca. 2.3-2.05(6H, overlapping signals), 1.4(9H, s, methyls of tert-butyl ester), 0.9(3H, t). \text{UV}_{\lambda_{\text{max}}}^{\text{EtOH}}(\text{mp}) = 278(\varepsilon, 2.65 \times 10^9). \)

2-(6'-Methoxycarbonylhexyl)-3-(3'-hydroxy-1'-trans-octenyl)-2-cyclopenten-1-one(XVIII). To 200 mg of the tert-butyl ester (XVI) was added trifluoroacetic acid (2.0 ml) with external ice cooling. The resulting solution was allowed to stand on for 2.5 hr with external ice cooling.

Then, the reaction mixture was dissolved in 150 ml of benzene-hexane (1:1) and the organic layer was washed with cooled water, and dried over magnesium sulfate. Evaporation of the solvent left an oily acidic material.

This oily material mainly contained dl-PGB1-cis isomer(XVII). \( \text{IR}_{\nu}^{\text{cm}^{-1}}: 3400-2600(\text{acid}), 1700(\text{broad, strong}), 1635, 1590, 1220, 1160. \) \( \text{NMR}_{\text{CDCl}_3}^{\text{ppm}}: 6.45(\text{H, d, J=12 cps}), 5.85(\text{H, double d, J=12 cps, J=9 cps}). \text{UV}_{\lambda_{\text{max}}}^{\text{EtOH}}(\text{mp}) = 278(\varepsilon, 2.4 \times 10^4). \)

2-(6'-Carboxyhexyl)-3-(3'-hydroxy-1'-trans-octenyl)-2-cyclopenten-1-one dl-PGB1(I). To the above-mentioned crude oily dl-PGB1-cis isomer(XVII) was added 10 ml of 0.125 N sodium hydroxide (50% EtOH-H2O) with external cooling.

The mixture was allowed to stand on at room temperature for 17 hr, followed by acidification with 5N hydrochloric acid with cooling.

An acidic oil separated was extracted with ether and the ether layer was washed with brine and dried over magnesium sulfate. Evaporation of the solvent in vacuo left a crude oily material, which was estimated to contain 64 mg of dl-PGB1 from UV absorption. \( \text{IR}_{\nu}^{\text{cm}^{-1}}: 3400-2600, \text{ca. 1700(broad), 1635, 1595, 1380, 1200, 970. \text{NMR}_{\text{CDCl}_3}^{\text{ppm}}: 6.275(\text{H, double d, J=16 cps, J=6 cps}), 6.275(\text{H, double d, J=16 cps, J=6 cps}). \text{UV}_{\lambda_{\text{max}}}^{\text{EtOH}}(\text{mp}) = 278 (\varepsilon, 2.68 \times 10^9). \)
methyl ester (XVIII), which was chromatographed on 8 g of alumina (Wako Chem. Co.).

Elution with benzene-ether (4:1) gave 41 mg of colorless oily XVIII. Anal. Found: C, 72.04; H, 10.05.
Caled. for C21H34O4: C, 71.96; H, 9.78%. IR$_{\text{max}}$ (cm$^{-1}$): 3450(OH), 1740 (methyl ester CO), 1690 (cyclopentenone CO), 1640, 1600, 1380, 1200, 970 (trans double bond); (lit. 1692, 1640, 1595, 970.) NMR$_{CDCl_3}$: 6.8(H, d, $J$=16 cps), 6.3(H, double d, $J$=16 cps, $J$=6 cps), 4.3(H, m, methyne of octenyl chain), 3.65 (3H, s, methyl ester), ca. 2.62H, m, ring methylene), ca. 2.45-2.2(6H, overlapping signals), 0.9(3H, t); [lit. 4 ethyl ester, 6.77(H, d, $J$=16 cps), 6.23(H, double d, $J$=16 cps, $J$=6 cps)]. UV$_{\text{EtOH}}$(m$\mu$): 278 ($\varepsilon$, 2.7 x 10$^4$).

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