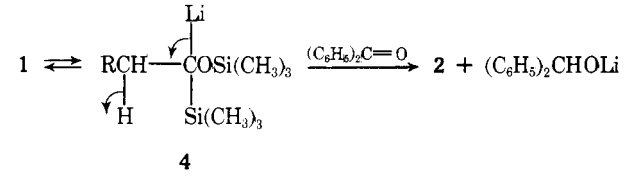
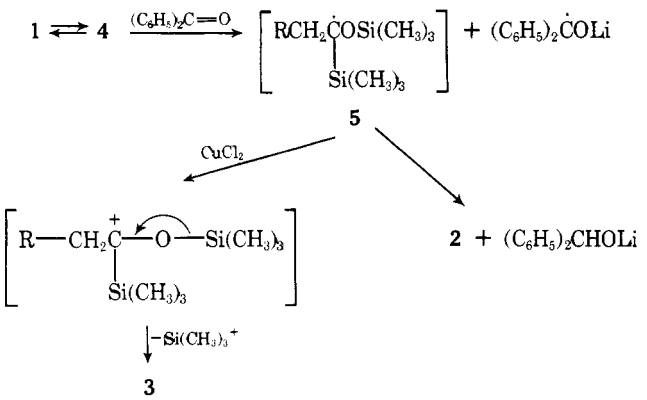
Scheme I



Scheme II



considered to be in equilibrium with **1**,[15] to yield the radical **5** and benzophenone ketyl. From the radical **5** thus formed, the β hydrogen is removed by the ketyl radical to afford **2** (Scheme II). In the case that the final step is somewhat retarded, the radical **5** is considered to be oxidized with oxygen, on quenching, to form the carboxylic acid, or with cupric chloride[16] to afford acylsilane **3** through the formation of the corresponding carbonium ion, followed by removal of trimethylsilyl group.

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(4) Silyl enol ether of acylsilane was previously prepared from the corresponding acylimidazole in 30~35% yield.[3e] It has also been found in our laboratory that the silyl enol ether is an excellent precursor to α-haloacylsilane, which is easily converted into α,β-unsaturated acylsilane.
(5) See also I. Kuwajima, T. Abe, and N. Minami, *Chem. Lett.*, 993 (1976).
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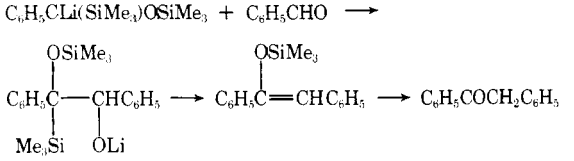
(9) The silyl enol ether obtained was composed of two geometrical isomers (5:1). Major (**2a**) and minor (**2b**) fractions have exhibited the following NMR spectra, respectively. **2a** (CCl_4): δ 0.20 (s, 9 H, $(CH_3)_3Si$), 0.26 (s, 9 H, $(CH_3)_3SiO$–), 3.50 (d, J = 8 Hz, 2 H, $C_6H_5CH_2CH$=), 5.67 (t, J = 8 Hz, 1 H, $C_6H_5CH_2CH$=), 7.30 (s, 5 H, aromatic protons). **2b** (CCl_4): δ 0.23 (s, 9 H), 0.31 (s, 9 H), 3.51 (d, J = 7 Hz, 2 H), 5.30 (t, J = 7 Hz, 1 H), 7.25 (s, 5 H). A mixture of **2a** and **2b** was obtained in ~1:5 ratio when 3-phenylpropionyltrimethylsilane was treated with lithium diisopropylamide, followed by silylation with trimethylchlorosilane.
(10) The reaction of this lithium alkoxide with cupric chloride was very slow and the corresponding acylsilane was isolated in 40% yield after stirring for 1 day at room temperature.
(11) *p*-Benzoquinone or ethyl azocarboxylate was also found to be less effective for this type of reaction.
(12) With lithium alkoxide of 1,1-bis(trimethylsilyl)benzyl alcohol, benzaldehyde reacts to give phenyl benzyl ketone (56%), which is probably formed through the following sequences. However, benzaldehyde remains unattacked with other alkoxides.



(13) Existence of radical species other than benzophenone ketyl radical is definitely confirmed by measurement of ESR.
(14) For recent discussions about electron-transfer process involving carbonyl compounds, see H. O. House and P. D. Weeks, *J. Am. Chem. Soc.*, **97**, 2770, 2778, 2785 (1976); H. O. House, *Acc. Chem. Res.*, **9**, 59 (1976).
(15) About similar equilibrium between **1** and **4**, see, for example; A. G. Brook, *Acc. Chem. Res.*, **7**, 77 (1974).
(16) About oxidation of radical species with cupric salt, see J. K. Kochi, Ed., "Free Radicals," Wiley, New York, N.Y., 1973, Vol I, Chapter 11.

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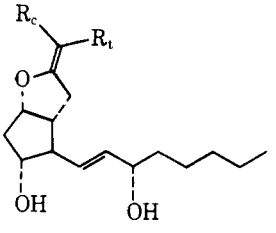
Synthesis and Stereochemistry of Prostacyclin and Synthesis of 6-Ketoprostaglandin $F_{1\alpha}$

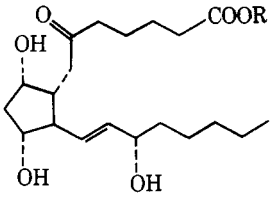
Sir:

The enzymatic transformation of the prostaglandin endoperoxides, PGH_2 and PGG_2, into a substance that inhibits platelet aggregation and causes relaxation of blood vessel walls was described recently by Vane and his colleagues.[1-4] Originally called prostaglandin X, this substance has been renamed prostacyclin.[5] The structure of prostacyclin, except for the stereochemistry of the C_5–C_6 double bond, has also been determined and accords with 9-deoxy-6,9α-epoxy-Δ^5-$PGF_{1\alpha}$ (**1**).[5] The enol-ether functionality of prostacyclin is rapidly hydrolyzed, even at pH 7.6, resulting in the formation of 6-ketoprostaglandin $F_{1\alpha}$ (**2**).[5] The isolation of 6-keto-$PGF_{1\alpha}$ from various biological tissues has been reported recently by several groups.[6-8] In this report, we outline the synthesis of both 6-keto-$PGF_{1\alpha}$ and prostacyclin and we assign stereochemistry to the C_5–C_6 double bond of prostacyclin.

When prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) methyl ester is treated (2 h, 5 °C) with iodine (2 equiv) in water in the presence of potassium iodide and sodium carbonate, or in methylene chloride in the presence of sodium carbonate, two less polar products are formed which we identified as iodo ether **3a** (90% yield aqueous; 45% yield, 90% if corrected for recovered starting material in CH_2Cl_2; high resolution mass spectrum of TMS derivative 638.2340, calcd for $C_{27}H_{51}Si_2O_5I$ 638.2322 and for $C_{21}H_{35}O_5I$, I 25.67, found 25.97)[9] and iodo ether **3b** (10% yield aqueous; 2% yield in CH_2Cl_2). Structure **3a** was assigned to the major new product on the following basis:

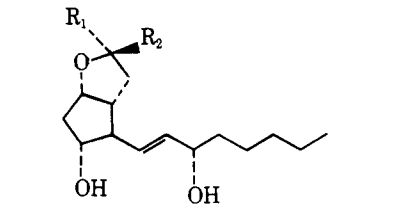


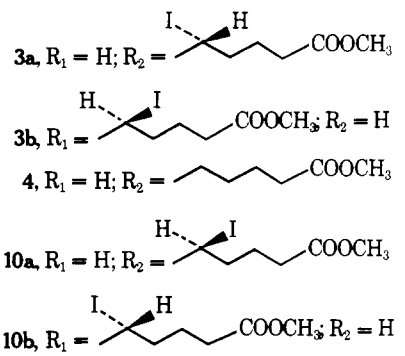
1, R_c = $-(CH_2)_3COOH$; R_t = H
8, R_c = $-(CH_2)_3COOCH_3$; R_t = H
9, R_c = $-(CH_2)_3COONa$; R_t = H
11, R_c = H; R_t = $-(CH_2)_3COOCH_3$
12, R_c = H; R_t = $-(CH_2)_3COONa$

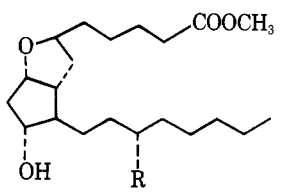


2, R = H
7, R = CH_3

NMR indicated that the methyl ester moiety was still intact (δ 3.65); the high resolution mass spectrum of the trimethylsilyl derivative indicated the presence of one iodine atom, two hydroxyl groups, and one ether oxygen. When the 11,15-bis(tetrahydropyranyl ether) of $PGF_{2\alpha}$ methyl ester (obtained from $PGF_{2\alpha}$, 11,15-bis(tetrahydropyran-2-yl ether)[10] by reaction with diazomethane) was treated with iodine (water, KI, Na_2CO_3), the same product was obtained after workup and removal of the tetrahydropyranyl ether groups; $PGF_{1\alpha}$ methyl ester, however, did not react under those conditions. These results suggested that the Δ^5 double bond and the hydroxyl group at C_9 participated in the reaction and that a reaction analogous to iodohydrin formation had taken place resulting in **3a**.[11] Reductive removal of iodine with tributyltin hydride yielded **4** (mp 43 °C; high resolution mass spectrum of TMS derivative 512.3356, calcd for $C_{27}H_{52}Si_2O_5$ 512.3353) which was hydrogenated (Pt, MeOH) to yield a mixture of two products. Gas chromatographic-mass spectral analysis of the trimethylsilyl derivatives established their structures as **5** (*m/e* 514 (M^+), 443 [$M^+ - (CH_2)_4CH_3$), 424 (M^+ − TMSOH), 334 (M^+ − 2TMSOH], 309 (M^+ − TMSOH − $(CH_2)_4CO_2CH_3$)) and **6** (*m/e* 426 (M^+), 336 (M^+ − TMSOH), 311 ($M^+ - (CH_2)_4CO_2CH_3$), 221 (M^+ − TMSOH − $(CH_2)_4CO_2CH_3$)). The predominant peaks at *m/e* 311 and 221 in the mass spectrum of the trimethylsilyl derivative of **6** clearly establish that the ether oxygen is linked to carbon 6 and not carbon 5; the iodine must therefore be on carbon 5 in iodo ether **3a**.[12] Removal of iodine from minor isomer **3b** gave an isomer of **4** (mp 71-73 °C).[12]







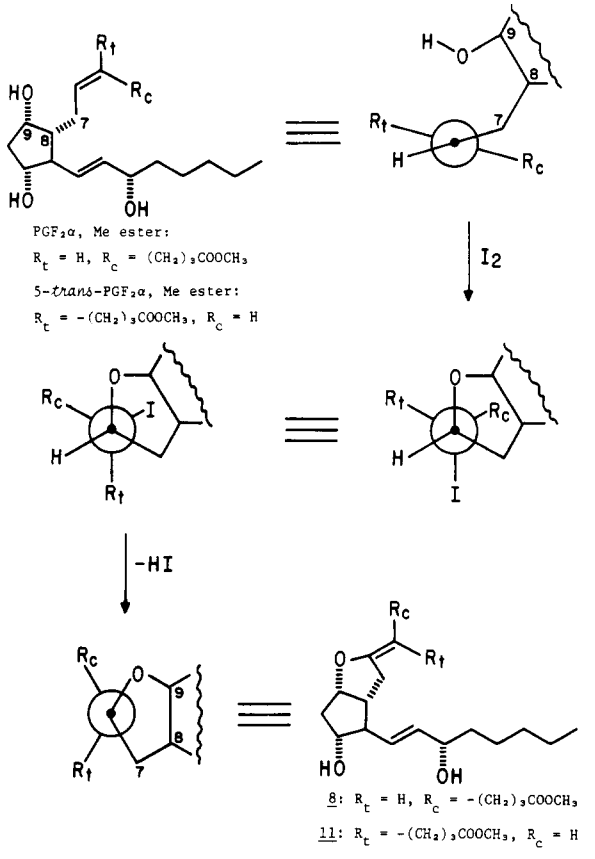
5, R = OH
6, R = H

Dehydrohalogenation of **3a** with silver carbonate in tetrahydrofuran in the presence of trace amounts of perchloric acid yielded **7** (80% yield; high resolution mass spectrum of trimethylsilyl derivative 600.3669, calcd for $C_{30}H_{60}Si_3O_6$ 600.3698; mp 68-74 °C, ether-hexane),[9,13] probably via **8** which was hydrated under the reaction conditions. 6-Keto-$PGF_{1\alpha}$ (**2**) was obtained by base hydrolysis of **7** (KOH, methanol; high resolution mass spectrum of trimethylsilyl derivative 658.3914, calcd for $C_{32}H_{66}Si_4O_6$ 658.3936; mp 60-105 °C, acetone-hexane).[9,13]

Reaction of iodo ether **3a** with 1,5-diazabicyclo[4.3.0]-non-5-ene (DBN, excess in benzene at 40 °C for 24-36 h) results in the formation of enol ether **8**. The product is isolated from this reaction simply by washing the organic phase with ice-water, drying and removing the solvent, and crystallizing from ether-hexane at −10 °C. The mushy crystals (80% yield) revert to a sticky gum at room temperature. The product is highly sensitive to moisture at acid pH, changing rapidly to 6-keto-$PGF_{1\alpha}$ methyl ester (**7**). Solutions in organic solvents can be stabilized by the addition of a few drops of triethylamine (Et_3N). When necessary, the product may be purified by column chromatography over Florisil using solvents containing Et_3N (0.1% is sufficient).[14] Enol ether **8** has the following physical properties: mass spectrum of bis(trimethylsilyl) derivative 510.3223, calcd for $C_{27}H_{50}Si_2O_5$ 510.3197, other ions at 495, 479, 439, 423.2724 ($M^+ - CH_2CH_2COOCH_3$, calcd for $C_{23}H_{43}Si_2O_3$ 423.2751), 349, 327, 323, 315, 313, 199, and 173; ^1H NMR ($CDCl_3$, δ), 5.54 (m, 2 H, -CH=CH-), 4.58 (m, 1 H, >CH-O), 4.16 (m, 1 H, >C=CH-), 4.00 (m, 1 H, $>C_{15}H$-O), 3.75 (m, 1 H, >CH-O), 3.65 (s, 3 H, $-OCH_3$), 0.87 (t, 3 H, J = 5 Hz, $-CH_3$); ^{13}C NMR ($CDCl_3$, ppm from Me_4Si), 174.6 (C_1), 154.6 (C_6), 136.4 (C_{14}), 131.7 (C_{13}), 96.9 (C_5), 83.7 (C_9), 77.2 (C_{11}), 73.0 (C_{15}), 54.9 (C_{12}), 51.5 (C_{21}), 45.8 (C_8), 40.7 (C_{10}), 37.1 (C_{16}), 33.6 (C_2), 33.2 (C_7), 31.8 (C_{18}), 25.3 (C_4), 25.2 (C_{17}), 24.7 (C_3), 22.6 (C_{19}), 14.0 (C_{20}); IR (ν, liquid melt) 3370 (OH), 1740 (C=O), 1695 cm^{-1} (O-C=C); TLC (silica gel,[14] 1:1 acetone-hexane) R_f 0.69. Enol-ether **8** has previously been converted to 6-keto-$PGF_{1\alpha}$ methyl ester by hydrolysis and to a crystalline γ-lactone by oxidative cleavage of the C_5-C_6 double bond.[5]

Other bases may be used to prepare **8** from **3a**. For example, reaction of **3a** with potassium superoxide[15] (KO_2, excess in DMF containing dicyclohexyl-18-crown-6 at 0-25 °C for 15 min) gives **8** (41% yield) following ether extraction and chro-

Scheme I



matography on Florisil. Conversion of enol ether **8** into the sodium salt **9**, considered to be the biological equivalent of prostacyclin,[5] was accomplished by saponification with 1 equiv of sodium hydroxide in methanol–water (1:1). Following lyophilization, **9** (100% yield) was obtained as a hygroscopic, free flowing white powder; IR (ν, mull) 3320 (OH),1693 (-O-C=C), 1555, 1470, cm^{-1} (CO_2-); stable for at least two months if kept dry at −30 °C.

To determine the stereochemistry of the C_5–C_6 double bond in prostacyclin, the double-bond isomer of enol ether **8** was prepared and the NMR spectra of the two isomers were compared. We reasoned that, if the reactions giving iodo ether **3a** and enol ether **8** are stereospecific as shown in Scheme I (i.e., trans addition and trans elimination), then application of this reaction sequence to 5-*trans*-$PGF_{2\alpha}$ methyl ester should give the isomeric enol ether. Accordingly, reaction of 5-*trans*-$PGF_{2\alpha}$ methyl ester[16] (0.005 mol) with iodine (0.005 mol) and sodium carbonate (0.010 mol) in CH_2Cl_2 (35 ml) gave a major iodo ether (**10a**, 0.0019 mol, mass spectrum of bis(trimethylsilyl) derivative calcd 638.2321, found 638.2333), a minor iodo ether (**10b**. 0.00033 mol, *m/e* calcd 638.2321, found 638.2327, and recovered starting material (0.0018 mol) following workup and chromatographic separation. Dehydroiodination of the major iodo ether (**10a**, 0.0035 mol) with excess KO_2 in DMF gave only isomeric enol ether **11** (0.00082 mol): mp 68–70 °C; ^1H NMR ($CDCl_3$, δ) 5.53 (m, 2 H, -CH=CH-), 4.67 (m, 1 H, -O-C=CH-), 4.52 (m, 1 H, >CH-O), 4.02 (m, 1 H, $-HC_{15}-O-$), 3.82 (m, 1 H, >CH-O), 3.67 (s, 3 H, $-OCH_3$), 0.88 (t, 3 H, J = 5 Hz, $-CH_3$); ^{13}C NMR ($CDCl_3$, ppm from Me_4Si) 174.3 (C_1), 155.9 (C_6), 136.4 (C_{14}), 131.3 (C_{13}), 95.9 (C_5), 83.0 (C_9), 77.3 (C_{11}), 72.9 (C_{15}), 55.5 (C_{12}), 51.4 (C_{21}), 45.6 (C_8), 40.4 (C_{10}), 37.2 (C_{16}), 33.4 (C_2), 31.7 (C_{18}), 30.5 (C_7), 26.9 (C_4), 25.7 (C_3), 25.2 (C_{17}), 22.6 (C_{19}), 14.0 (C_{20}); IR (ν, liquid melt) 3420 (OH), 1740 (C=O), 1690 cm^{-1} (-O-C=C); TLC (silica gel,[14] 1:1 acetone–hexane) R_f 0.65. Hydrolysis of **11** with aqueous pH 2 buffer in tetrahydrofuran (1:1)[5] gave 6-keto-$PGF_{1\alpha}$ methyl ester. Saponification of **11**, as described above for **8**, gave the sodium salt **12**.

Scheme I predicts that **8** and **11** will have the configurations of 5*Z* and 5*E*, respectively. Perusal of the NMR data for enol ethers reveals that the signals for the vinyl protons cis to the ether oxygen invariably are downfield from those for the isomeric trans protons.[17] Consequently, the finding of signals for the C_5 protons at δ 4.16 in **8** and at 4.67 in **11** confirms the assignment of the 5*Z* configuration to enol ether **8** and thereby to prostacyclin.

Finally, we note that enzymatically prepared prostacyclin methyl ester containing radiolabel[5] cochromatographs with **8** when a mixture of **8** and **11** is placed on a silica gel TLC plate and developed in 1:1 acetone–hexane.

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(11) A subsequent literature search revealed that 2-(iodomethyl)tetrahydrofuran had similarly been prepared from 1-penten-5-ol; see V. I. Staninets and E. A. Shilov, *Ukr. Khim. Zh.*, **31**, 1286–1289 (1965); *Chem. Abstr.*, **64**, 12625–12626 (1966).
(12) The stereochemistry shown for structure **3a**, (5*R*,6*R*)-5-iodo-9-deoxy-6,9α-epoxy-$PGF_{1\alpha}$ methyl ester is assigned as a consequence of the assumed stereospecific iodo ether formation and subsequent elimination of HI during the synthesis of compound **8** (see Scheme I). An assignment of 5*S*,6*S* would also be compatible with this reaction sequence but would require a much more sterically hindered molecular conformation (easily seen in molecular models) during the reaction forming the iodo ether. The 5*S*,6*S* assignment is given to the iodo ether (**3b**) formed in minor yield (2–10%) in this reaction. It may also be expected that the exo configuration, which is pseudoequatorial with regard to the 2-oxabicyclo[3.3.0]octane ring system, will be the thermodynamically favored configuration for compounds that are epimeric at C_6. Similar reasoning is used for the assignment of stereochemistry to **10a**, (5*S*,6*R*)-5-iodo-9-deoxy-6,9α-$PGF_{1\alpha}$ methyl ester, and **10b**, (5*R*,6*S*)-5-iodo-9-deoxy-6,9α-$PGF_{1\alpha}$ methyl ester. An important feature distinguishing **3a** and **3b** as well as **10a** and **10b** is the presence of a multiplet (an ill-defined quartet, integrating for one proton) at δ 4.55 in the NMR spectra ($CDCl_3$) of **3a** and **10a** and the absence of any signal in this area of the NMR spectra of **3b** and **10b**. A similar contrast is seen in the spectrum of **4** (4.45) and its C_6 epimer (no signal).
(13) We attribute the wide ranging melting points found for **7** and **2** to the hemiketal hydroxy ketone equilibrium expected for 1,4-hydroxy ketones.
(14) The use of silica gel coated plates for thin layer chromatography is successful if the plate is developed immediately after spotting. Column chromatography on silica gel is unsuccessful, however, even if triethylamine is added to the solvent. 6-Keto-$PGF_{1\alpha}$ methyl ester is isolated from such attempted column purifications.
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Stabilization of One-Dimensional Conducting Materials by Carbonyl Ligands. Crystal and Molecular Structure of $Ir(CO)_3Cl$[1]

Sir:

We wish to report the characterization of $Ir(CO)_3Cl$, a one-dimensional highly conducting stoichiometric material in which chains containing short Ir metal–metal bonds of length 2.844 (1) Å are stabilized without mixed valency or charge transfer to interstitial anions within the lattice.

Recently controversy has arisen concerning the material originally characterized as $Ir(CO)_3Cl$ and later reported to be nonstoichiometric, $Ir(CO)_3Cl_{1.1}$. $Ir(CO)_3Cl$ was first synthesized by Hieber and Lagally[2] and later by Fischer and Brenner,[3] both groups reporting chemical analyses indicating a stoichiometric Cl content. Later Krogmann et al.[4] reported a preliminary x-ray structure of the Ir compound but gave the stoichiometry as $Ir(CO)_{2.93}Cl_{1.07}$ based on an unpublished chemical analysis. Since the structure of this compound involved stacked square planar groups and short Ir–Ir distances, it was described as similar to the partially oxidized cyanoplatinate compounds which share similar physical properties and structures. The reported chemical formulation was rationalized by suggesting that a small amount of $Ir(CO)_2Cl_2$ was incorporated into the crystal. Ginsberg[5] resynthesized this material and reported a chemical analysis consistent with the formulation, $Ir(CO)_3Cl_{1.1}$. He concluded that the excess Cl^- ion must reside interstitially within the crystalline lattice on the basis of Ir^{193} Mössbauer data which suggest Ir is present in a single-valence state and also magnetic susceptibility data which