dation instrumentation support (CHE 76-05926; Bruker 200 MHz NMR) is also gratefully acknowledged. We thank Professor C. P. Casey (University of Wisconsin) for details of related studies in his laboratory.

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(15) (a) Isolated yield; (b) spectroscopic yield; (c) gas chromatographic yield.
(16) (a) Anal. Calcd for $C_9K_2O_9Re_2$: C, 15.38; K, 11.13; Re, 53.00. Found: C, 15.42; K, 11.42; Re, 53.12. IR (cm^{-1}, THF): 2033 (w), 2010 (m), 1966 (s), 1924 (s), 1880 (m), 1860 (m). (b) The reaction of $Re_2(CO)_{10}$ with 2 equiv of $Li(C_2H_5)_3BH$ yields a spectroscopically equivalent material believed to be $Li_2Re_2(CO)_8$.
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(23) NOTE ADDED IN PROOF. The 50.32-MHz ^{13}C NMR spectrum of **2** at −60 °C in THF-d_8 which is 0.06 M in $Cr(acac)_3$ (conditions for low temperature quadrupole decoupling) shows 5 carbonyl resonances (202.1, 198.6, 197.9, 193.0, 187.7 ppm; relative areas 1.6:1:2.8:2.6:0.7) indicating that **2** is likely the cis isomer.

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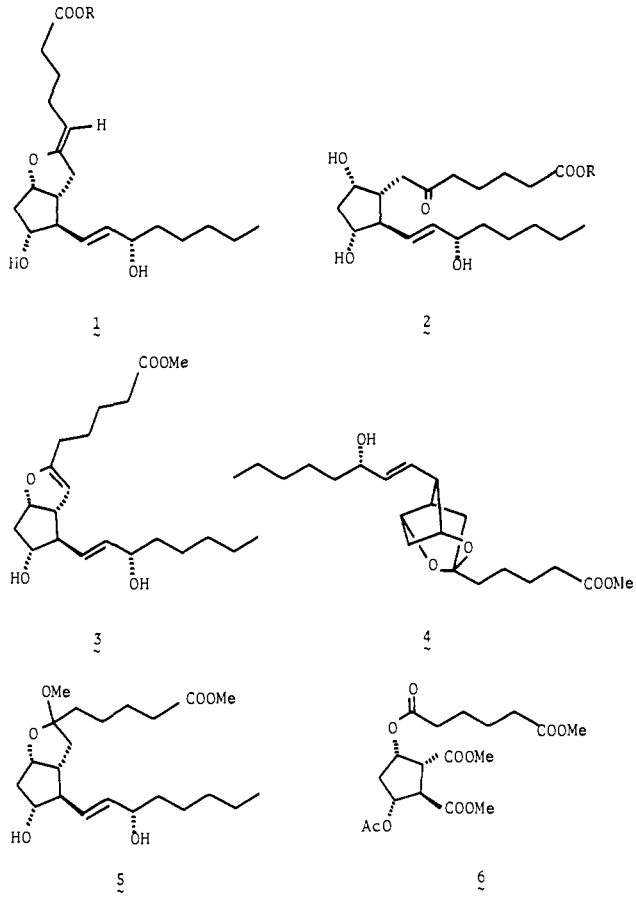
6,9α-Oxido-11α,15α-dihydroxyprosta-6,(*E*)-13-dienoic Acid Methyl Ester and 6,9α:6,11α-Dioxido-15α-hydroxyprost-(*E*)-13-enoic Acid Methyl Ester. Two Isomeric Forms of Prostacyclin (PGI_2)

Sir:

The isolation[1] and structural characterization[2] of prostacyclin (PGI_2, **1**, R = H) coupled with the discovery of its potential value in acute mycoardial ischemia[3] has opened a new chapter of prostaglandin research.[4] Prostacyclin is a rather unstable molecule in aqueous, acidic or neutral media, breaking down to 6-keto-$PGF_{1\alpha}$ (**2**, R = H), in equilibrium with its lactol form.[2a] The isolation of 6-keto-$PGF_{1\alpha}$ itself from various biological tissues has also been reported recently.[5] Although **2** does not appear to be as important biologically as



is the enol form **1**, the *possible regeneration* of **1** from **2** would be nonetheless deserving of careful chemical and biological study. Herein we report two isomeric forms (**3** and **4**) of prostacyclin both of which were derived chemically from 6-keto-$PGF_{1\alpha}$ and one of which showed a significant biological activity.

Treatment of prostacyclin methyl ester (**1**, R = Me)[2a,6] in methanol with a small amount of acetic acid at 25 °C for 2 h, addition of excess triethylamine, extraction with ether, and concentration afforded the crude methoxy lactol **5**. The ^1H NMR and IR spectra of **5** indicated the absence of 5,6-olefinic unit.[7] The crude product was dissolved in hexamethylphosphoric triamide, and the mixture was heated at 180 °C for 14 min to effect elimination of methanol. The product was isolated from this reaction simply by extraction with ether, drying, and removing the solvent.[8] Purification of the acid-sensitive enol ether **3** was effected by column chromatography on silica gel (EtOAc–hexane–Et_3N, 50:50:0.1), and the product **3** so obtained as a colorless oil was >98% pure by GC analysis and exhibited fully consistent ^1H NMR (double-resonance technique) and IR spectra.[9] The same enol ether was prepared from 6-keto-$PGF_{1\alpha}$ methyl ester (**2**, R = Me) by an alternate sequence consisting of (1) trimethylsilylation by excess trimethylsilyldiethylamine (TMSDEA) at 25 °C for 12 h, (2) GC separation of the major component,[10] and (3) removal of the remaining trimethylsilyl groups (K_2CO_3–methanol, 0 °C for 1 h) to produce after column chromatography the pure enol ether **3** (44% yield from **2**).

Independent evidence for structure **3** was obtained by the clean hydrolysis of **3** to 6-keto-$PGF_{1\alpha}$ methyl ester,[11] a property paralleling that of PGI_2 methyl ester.[2a] Furthermore, oxidative cleavage of the C_6–C_7 olefinic unit of **3** was effected by (1) acetylation of **3** using acetic anhydride–pyridine at 25 °C for 18 h, (2) treatment with excess ozone in chloroform at −25 °C for 15 min followed by exposure to hydrogen peroxide–acetic acid at 50 °C for 12 h, and (3) esterification with

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diazomethane to furnish the pentaester **6**.[12]

Prolonged heating of either PGI_2 methyl ester or the regioisomer **3** afforded a small amount of nonpolar oily product. It appeared to us that this component might be the internal ketal **4** and ought to be accessible as a major product by a carefully controlled reaction conditions, and an experimental study was undertaken.

6-Keto-$PGF_{1\alpha}$ (**2**, R = Me, 0.95 g), upon treatment with powdered molecular sieve 4A (4 g)[13] and kiesel gel (4 g)[14] in dry methylene chloride (50 mL) with vigorous stirring at 25 °C for 4 h followed by filtration and purification by column chromatography, afforded the desired ketal **4** as a principal product (40% yield), whose structure was apparent from ^1H NMR and double-resonance ^1H NMR experiment as well as IR analysis.[15] Structure **4** was further confirmed by the following observations. (1) Hydrolysis of **4** with a mixture of acetic acid–water–tetrahydrofuran gave 6-keto-$PGF_{1\alpha}$ methyl ester. (2) Exposure of **4** to AcOD–D_2O–THF produced the 6-keto-$PGF_{1\alpha}$ methyl ester with no deuterium incorporation.[11] (3) Treatment of **4** with excess *p*-nitrobenzoyl chloride–triethylamine afforded the monobenzoate of allylic alcohol.[16] (4) Silylation of **4** with TMSDEA gave the monotrimethylsilyl derivative by mass spectral assay. (5) The methoxy lactol **5** was produced by methanolysis of **4**. Apart from being of considerable interest with regard to biological activity, the ketal **4** represents an internally protected form of 6-keto-$PGF_{1\alpha}$ methyl ester which allows a variety of useful selective transformations.

In the preliminary test, the *endo*-enol ether **3** shows the higher potency to natural PGE_1 in inhibiting platelet aggregation and the lower to PGI_2 methyl ester, while the internal ketal **4** was almost inactive.[17] Further study of the biological activities of **3** and **4** are in progress and will be published in due course.

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(7) ^1H NMR ($CDCl_3$): δ 3.13 and 3.21 (2s, 3 H, OCH_3), 3.66 (s, 3 H, $COOCH_3$).

(8) ^1H NMR analysis of the crude product revealed the presence of a small amount of PGI_2 methyl ester and its stereoisomer, which could be removed by careful column chromatography (TLC R_f value (ether–acetone–Et_3N, 75:25:0.1)): **1**, 0.41; **2**, 0.18; **3**, 0.43.

(9) ^1H NMR ($CDCl_3$): δ 2.22 (m, 1 H, C(12) H), 2.93 (m, 1,H, C(8) H), 3.76 (m, 1 H, C(11) H), 4.03 (m, 1 H, C(15) H), 4.65 (d, 1 H, C(7) H), 4.84 (m, 1 H, C(9) H), 5.47 (m, 2 H, C(13 and 14) H). IR ($CHCl_3$): 1665 cm^{-1} (enol ether).

(10) 5 mm × 1.5 m column of 5% SE-30 on Shimalite-W; column temperature, 260 °C; injection temperature, 280 °C; detector temperature, 260 °C; He, 1.6 kg/cm^2; t_r = 18 mm. Elimination of Me_3SiOH was effected during this operation.

(11) The enol ether **3**, upon treatment with AcOD–D_2O–THF, produced the 7-*d*-6-keto-$PGF_{1\alpha}$ methyl ester: mass spectrum (after trimethylsilylation) *m/e* 511, 421, 350, 325, 278, 263, 217, 199, 173, 143. See ref 2b for the analysis of fragmentation pattern of 6-keto-$PGF_{1\alpha}$ methyl ester. The mass spectra of *5-d* derivative showed the following peaks: 511, 421, 350, 325, 277, 263, 217, 199, 173, 144.

(12) ^1H NMR ($CDCl_3$): δ 2.07 (s, 3 H), 3.32 (dd, 1 H), 3.57 (dd, 1 H), 3.68 (s, 3 H), 3.70 (s, 3 H), 3.74 (s, 3 H), 4.15–4.55 (m, 2 H). IR ($CHCl_3$): 1735 cm^{-1}. mass spectrum (after trimethylsilylation): *m/e* 402 (M^+), 371, 329, 297, 270, 242, 210, 200, 199, 182, 151, 143, 111.

(13) Freshly powdered and dried in vacuo at 160 °C for 2 h.

(14) Dried in vacuo at 160 °C for 2 h before use.

(15) ^1H NMR ($CDCl_3$): δ 1.90 (m, 2 H, C(7) H), 2.12 (m, 2 H, C(10) H), 2.80 (m, 1 H, C(12) H), 2.87 (m, 1 H, C(8) H), 4.00 (m, 1H, C(15) H), 4.33 (m, 1 H, C(11) H), 4.74 (m, 1 H, C(9) H), 5.44 (m, 2 H, C(13, 14) H). IR (liquid film): 3400 and 1735 cm^{-1} (no enol ether absorption). **4** was homogeneous by GC and TLC (R_f 0.56 (ether–acetone–Et_3N, 75:25:0.1)) analysis. Surprisingly, the NMR spectrum of **4** is almost identical with that of 6,9α-oxido-11,15-dihydroxyprosta-7,13-dienoic acid methyl ester (see C. Pace-Asciak and L. S. Wolfe, *Biochemistry*, **10**, 3657 (1971)), the synthesis of which is undergoing in our laboratories.

(16) ^1H NMR ($CDCl_3$): δ 5.47 (m, 1 H, C(15) H), 7.15–7.4 (AB, 4 H). IR (liquid film): no OH absorption.

(17) When compared with PGE_1, **3** was 11.7 times more potent as an inhibitor of platelet aggregation in ADP induced platelet rich plasma from rat.

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Conformational Equilibrium in the Backbone of Cyclic Tripeptides[1]

Sir:

NMR measurements and x-ray studies of cyclic tripeptides such cyclo[Pro_3],[2,3] cyclo[Hyp-Pro_2],[3] and cyclo[Sar_3][4] indicate a C_3 symmetric backbone conformation ("crown").[5] We have now synthesized the *N*-benzylglycine (Bzl·Gly) containing cyclic tripeptides of the general structure cyclo-[Pro_x-Bzl·Gly_{3-x}] (**1**, x = 0; **2** x = 1; **3**, x = 2) with the aim

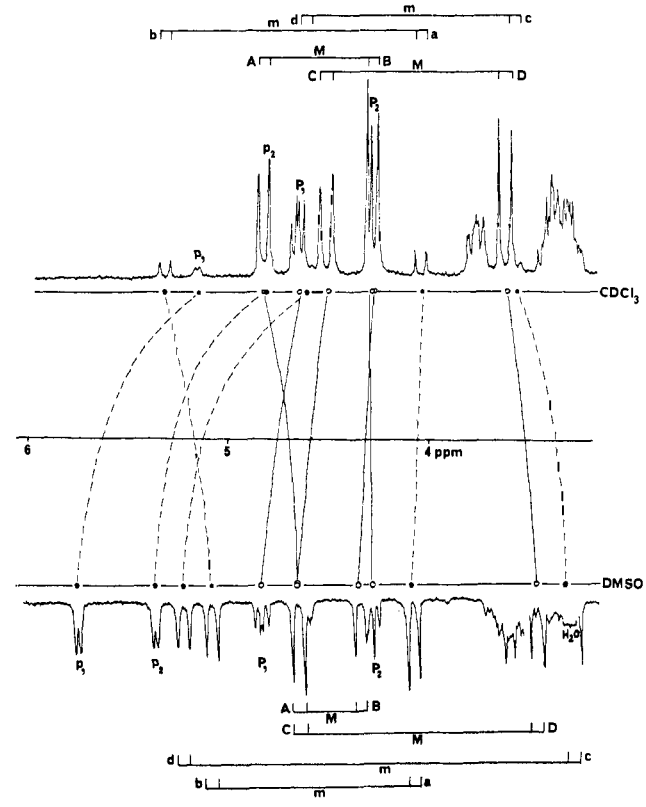

Figure 1. Part of the 270-MHz ^1H NMR spectrum of cyclo[Pro-Pro-Bzl·Gly] in $CDCl_3$ (top) and Me_2SO (inverted on bottom).

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