Table I

solvent	temp, °C	catalysts[a]
THF	30–150	Et_2AlCl
benzene	80–150	$AlCl_3$
toluene	111	$BF_3 \cdot Et_2O$
xylenes	140	$TiCl_4$
methanol	65	$SnCl_4$
chloroform	61	

[a] The Lewis acid catalysts were used in a variety of solvents at room temperature or lower.

added 518 μL (3.1 mmol) of 6 N HNO_3 all at once with stirring. The reaction mixture was warmed to room temperature and stirred for 5 min. The red mixture was diluted with cold water and extracted 3 times with chloroform. The combined extracts were washed with brine and dried over sodium sulfate. Evaporation of the solvent under reduced pressure gave a "quantitative" yield of **2** free of starting material and byproducts according to its NMR spectrum. Significant decomposition of this material occurs within 24 h. NMR (60 MHz, $CDCl_3$) δ 2.07 (bs, 6 H), 2.12 (d, 3 H, J = 2.0 Hz), 2.20 (d, 3 H, J = 2.0 Hz) 3.70 (bs, 2 H), 5.94 (d, 1 H, J = 13.5 Hz), 6.25 (bs, 2 H), 7.46 (d, 1 H, J = 13.5 Hz); IR ($CHCl_3$) 3070, 1765, 1695, 1665, 1385, 1365, 1260, 1155, 925 cm^{-1}.

Trimethylsilyl Iodide Reaction with 16. This reaction was done in an NMR tube by dissolving 45 mg (0.01 mmol) of **16** in about 0.35 mL of $CDCl_3$. The tube was purged with argon and cooled to −78 °C, and 571 μL (0.404 mmol) of TMSI was added. The tube was allowed to warm to room temperature and the reaction followed in an NMR spectrometer. After 50 min the spectrum was identical with the spectrum of the bis(trimethylsilyl ether) of **14**, which was obtained in the cleavage of **13** by TMSI.

Diels–Alder Studies with 2. Table I lists the solvents, temperatures, and catalysts that have been tried. In each case the products formed under the reaction conditions listed in Table I were gross mixtures and could not be characterized. Usually polymeric precipitates were formed.

Acknowledgment. We thank Mr. Martin Weinand for his assistance with the preparation of starting materials. We are grateful to the National Science Foundation for support of this work through Grant CHE-79-17570.

Synthesis of 4,4,5,5-Tetradehydro and *cis*-4,5-Didehydro Prostacyclin Analogues

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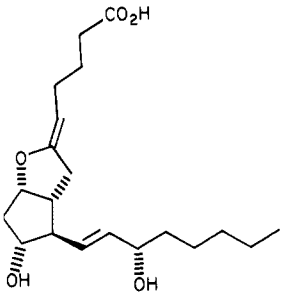
The synthesis of 4,4,5,5-tetradehydro and *cis*-4,5-didehydro prostacyclin analogues is described. The separation of the 6α and 6β isomers has been easily achieved at an early stage of the synthesis. The configuration of the 6α and 6β isomers has been determined by conversion of those isomers into 13,14-dihydro-6α-PGI_1 and 6β-13,14-dihydro-6β-PGI_1, respectively, via catalytic hydrogenation and correlation of the TLC mobilities of these isomers with authentic 13,14-dihydro-6α-PGI_1 and 13,14-dihydro-6β-PGI_1.

Introduction

It is well established that prostacyclin (PGI_2, 1) is both a potent inhibitor of platelet aggregation and a powerful vasodilator.[1] However, its inherent instability has attracted interest in the search for more stable analogues which will either mimic or split the biological profile of natural prostacyclin. One of the most logical variations has been to stabilize the enol ether functionality of the molecule. This objective has been achieved by converting the enol ether into the corresponding cyclic ether (PGI_1, **13b**)[2] or by shifting the double bond from C_{5-6} to C_{4-5} (*trans*-4,5-didehydro-PGI_1, **2**).[3] We report herein the straightforward synthesis of the 4,4,5,5-tetradehydro-PGI_1 analogues, **9a** and **9b**, and the *cis*-4,5-didehydro-PGI_1 analogues, **12a** and **12b**.

Results and Discussion

Since the *cis*-4,5-didehydro-PGI_1 analogues, **12a** and **12b**, could in theory be easily obtained from the partial hydrogenation of the corresponding 4,4,5,5-tetradehydro-PGI_1 analogues, **9a** and **9b**, the logical choice for the initial target



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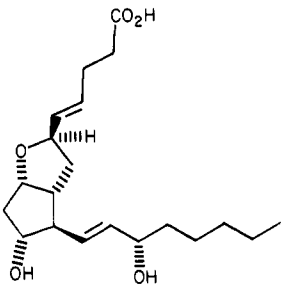

2

for the synthesis was the acetylenic analogues. From our previous synthetic work on 4,5-acetylenic prostaglandins[4] we were aware that the intermediate yne-one **4a** was easily obtainable in one step from the Corey lactone **3**. We decided, therefore, to approach the synthesis via this intermediate. The key problems in this approach involved the following: (a) separation of the C-6 epimers, (b) cyclization of the diols **5a** and **5b**, and (c) determination of the configuration at C-6.

As is shown in Scheme I the Corey lactone **3** was reacted with 1.5 equiv of [4-[(dimethyl-*tert*-butylsilyl)oxy]pentynyl]lithium at room temperature for 1 h to give 86% of pure yne-one **4a** after chromatographic purification.[4] The appearance of a strong IR band at 1680 cm^{-1} indicated that the equilibrium favored the conjugated yne-one rather than the cyclic lactol. Sodium borohydride reduction of yne-one

(1) (a) Moncada, S.; Gryglewski, R.; Bunting, S.; Vane, J. R. *Nature (London)* **1976**, *263*, 663. (b) Johnson, R. A.; Morton, D. R.; Kinner, J. H.; Gorman, R. R.; McGuire, J. C.; Sun, F. F.; Bunting, S.; Salmon, J.; Moncada, S.; Vane, J. R. *Prostaglandins* **1976**, *12*, 915. (c) Vane, J. R.; Bergstrom, S., Ed. "Prostacyclin"; Raven Press: New York, 1979.

(2) Johnson, R. A.; Lincoln, F. H.; Nidy, E. G.; Schneider, W. P.; Thompson, J. L.; Axen, U. *J. Am. Chem. Soc.* **1978**, *100*, 7690.

(3) (a) Corey, E. J.; Keck, G. E.; Szekely, I. *J. Am. Chem. Soc.* **1977**, *99*, 2006. (b) Nicolaou, K. C.; Barnette, W. E. *J. Chem. Soc., Commun.* **1977**, 331.

(4) Lin, C. H.; Stein, S. J. *Synth. Commun.* **1976**, 503.

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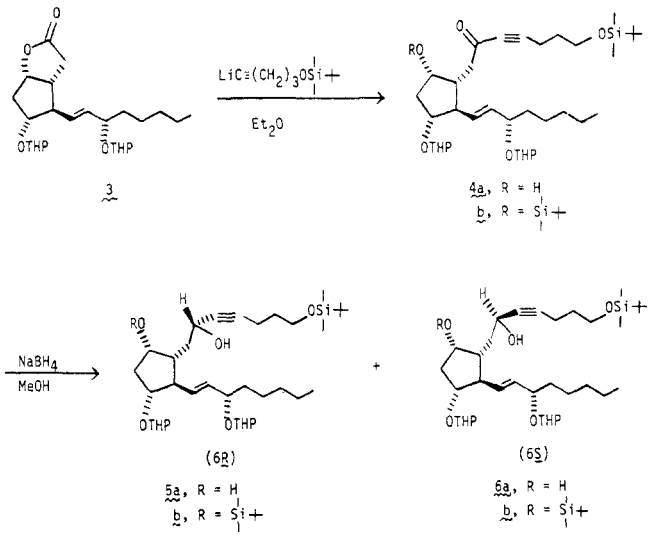
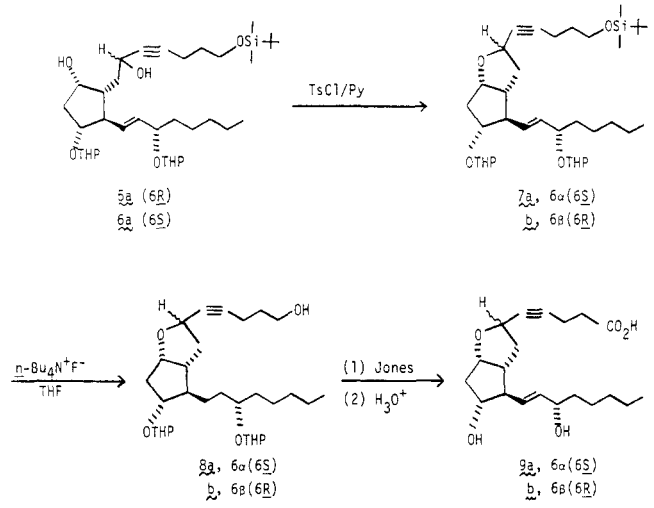
Scheme I



Scheme II

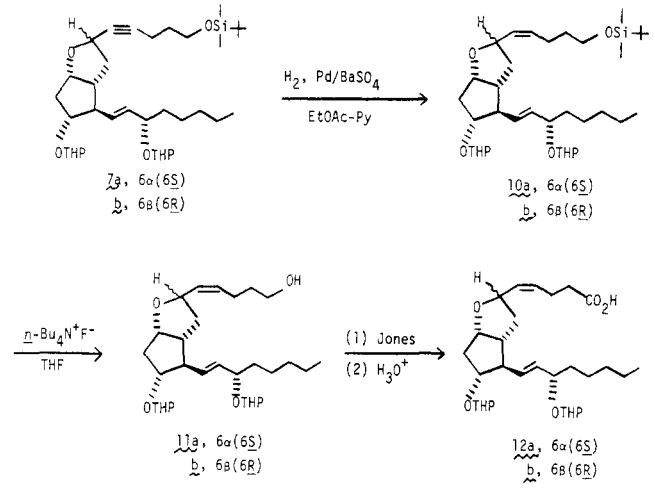


4a in methanol at −20 ∼−10 °C afforded two isomeric products **5a** (60%) and **6a** (28%) which were easily separable by HPLC. When the reduction was carried out with C-9 hydroxyl group protected yne-one **4b**, almost equal amounts of **5b** and **6b** were obtained.[5] The assignment of the stereochemistry at C-6 for **5a** and **6a** as 6*R* and 6*S*, respectively, was based on the stereochemical assignment of the final products, **9a** and **9b** (vide infra).

The next key step was the cyclization of the diols **5a** and **6a**. Our objective here was to selectively convert one of the hydroxyl groups (C-6 or C-9) into an appropriate leaving group such as tosylate. We felt that the relatively hindered C-9 hydroxyl group in the diols **5a** and **6a** would enable us to selectively convert the less hindered C-6 hydroxyl group into a monotosylate. We also expected that, due to the close proximity of C-6 and C-9 hydroxyl groups, the $C_{6,9}$ cyclic ether formation would occur readily via S_N2-type displacement, resulting in inversion of configuration at C-6. We found that when the reaction was carried out by adding 1 equiv of *p*-toluenesulfonyl chloride at periodic intervals of 0, 6, 24, and 48 h into a dilute pyridine solution containing the substrate (0.05 mmol of diol/mL of pyridine) and stirring the mixture for a total of 72 h at room temperature followed by stirring at 50 °C for 2–6 h, the cyclic ethers **7a** and **7b** were obtained in 70–88% yield.

The success of this key step enabled us to carry out the synthesis of all the desired analogues. As is indicated in Scheme II removal of the silyl protecting group,[6] Jones oxidation of the primary alcohols, and acid hydrolysis to remove the THP groups on **5a** and **6a** gave the final products, 4,4,5,5-tetradehydro-6α-PGI_1 **9a** and 4,4,5,5-tetradehydro-6β-PGI_1 **9b**, respectively. The products could be purified by HPLC either as the corresponding methyl esters or free acids. As for the synthesis of *cis*-4,5-didehydro-PGI_1 analogues (Scheme III), the acetylenic cyclic ethers, **7a** and **7b**, were converted into the corresponding *cis*-4,5-didehydro intermediates, **10a** and **10b**, respectively, by partial catalytic hydrogenation (5% $Pd/BaSO_4$ in EtOAC–Py). The same sequence as in the case of the 4,5-acetylenic series (**10** → **11** → **12**) gave pure *cis*-4,5-didehydro-6α-PGI_1 **12a** and *cis*-4,5-didehydro-6β-PGI_1 **12b** from 6α cyclic ether **10a** and 6β cyclic ether **10b**, respectively.

Scheme III



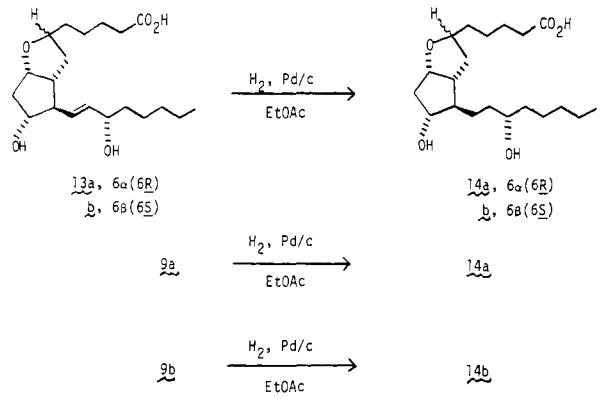
The configuration of isomers at C-6 was unambiguously determined by the following experiments. The less polar isomer **9a** was subjected to catalytic hydrogenation (10% Pd/C in EtOAC). The product obtained showed identical TLC mobility with the product obtained from hydrogenation of the authentic 6α-PGI_1 (**13** → **14a**, Scheme IV).[7] The ^1H NMR spectra of both hydrogenation products were identical. The chemical shift of the C-9 proton at δ 4.45–4.20 was indicative for the 6α isomer.[2] This isomer **5a** was thus assigned as (6*S*)-4,4,5,5-tetradehydro-6α-PGI_1. Accordingly, the less polar isomer **12a** in the vinyl series, obtained from the same intermediate **7a**, was also assigned as (6*S*)-4,5-*cis*-didehydro-6α-PGI_1. On the other hand when the more polar isomer **9b** was subjected to similar treatment the product obtained showed identical TLC mobility with the product obtained from the hydrogenation

(5) The stereoselectivity of this reduction was interpreted as a result of prior complexation of borohydride to C-9 hydroxyl group followed by internal hydride delivery to the C-6 ketone. One of the reviewers suggested, however, that it is not necessary to be the case. The reduction could occur from the opposite face of the carbonyl group, and the stereoselectivity can merely be a reflection of the distribution in the reaction medium of two different conformers of **4a**.

(6) Corey, E. J.; Venkatesuwarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

(7) The authentic samples **13a**, **13b**, and **14b** were kindly supplied by F. H. Lincoln and J. H. Kinner of these laboratories. They obtained 13,14-dihydro-PGI_1 **14b** from **13b** via the same procedure as the conversion of **13a** to **14a**. The hydrogenation products of **13b** showed two spots on TLC in A-IX, a major component (R_f 0.34) as **14b** and a minor component (R_f 0.46), presumably, as 13,14-dihydro-15-oxo-PGI_1.[9] The hydrogenation products of **13a** also showed two spots on TLC in A-IX, a major component (R_f 0.38) as **14a** and a minor component (R_f 0.49) as 13,14-dihydro-15-oxo-6α-PGI_1. There was no indication of the other isomer present in each of the hydrogenation products. The chemical shift of C-9 proton by **14b** was at δ 4.60–4.25, which differed from that of **14a** (at δ 4.45–4.20).

Scheme IV



of the authentic 6β-PGI_1 (**13b** → **14b**, Scheme IV). The ^1H NMR spectrum of this product showed peaks present at δ 4.60–4.25, identical with that of authentic **14b**.[7] Isomer **9b** was therefore assigned as (6*R*)-4,4,5,5-tetradehydro-6β-PGI_1. Again, the more polar isomer **12b** in vinyl series, obtained from the same intermediate **7b**, was also assigned as (6*R*)-4,5-*cis*-didehydro-6β-PGI_1. TLC analyses gave no indication whatsoever of the contamination by the corresponding isomer. These results clearly established the correct assignment on the configuration at C-6 for all the analogues synthesized.

Experimental Section

General Procedures. Melting points were obtained with a Thomas-Hoover melting-point apparatus (6406-K) and are uncorrected. Infrared spectra were recorded with either a Perkin–Elmer Model 137, 139 or a Digilab Model FTS-14D. The ^1H NMR spectra were obtained with a Varian A-60D or HFT-80 spectrometers employing tetramethylsilane as an internal standard. High-resolution mass spectra were obtained with a CEC 21-110E spectrometer. All TLC analyses were carried out by silica gel GF plates (2.5 × 8 cm, Analtech). Preparative HPLC columns used were prepared by packing silica gel 60 (40~63 μm, E. Merck) or CC-4 silica gel (Mallinkrodt) in various sizes of Michel–Miller columns (Ace Glass Inc.). The solvents were driven by either a Milton-Roy mini or D pump. The analysis of the fractions was done by TLC. Carboxylic acids were detected by TLC, employing A-IX[8] as the developing solvent.

4-[(Dimethyl-*tert*-butylsilyl)oxy]-1-pentyne. A round-bottomed flask equipped with a magnetic stirring bar was charged with 42 g (0.5 mol) of 1-pentyn-4-ol (Farchan Co.) and 100 mL of DMF. The solution was cooled to 0–5 °C under a nitrogen atmosphere. A solution of dimethyl-*tert*-butylchlorosilane (90 g, 0.6 mol) and imidazole (81.6 g, 1.2 mol) in 150 mL of DMF was then added. The resulting solution was allowed to warm to room temperature and stirred for 24 h. The solution was again cooled to 0–5 °C, treated with 10 mL of water, and stirred for 30 min. The product was extracted with hexane (2 L). The hexane layer was washed with water, 10% aqueous sodium bisulfate, saturated aqueous sodium bicarbonate, and brine, and dried over anhydrous magnesium sulfate. Filtration and concentration in vacuo followed by vacuum distillation gave 88 g (89%) of pure oil: bp 65 °C (9 mm); ^1H NMR (CCl_4, using $SiCH_3$ singlet in the molecule as an internal standard) δ 3.66 (t, J = 6 Hz, 2 H, CH_2O), 2.18 (t of d, J = 6, 2.5 Hz, 2 H, $CH_2C{\equiv}C$), 1.68 (d, J = 2.5 Hz, 1 H, $HC{\equiv}C$), 1.9–1.3 (m, 2 H, CH_2), 0.84 (s, 9 H, Si-*t*-Bu); IR (film) 3320, 2120, 1250, 1090, 970, 830, 770, 630 cm^{-1}; mass spectrum, m/e calcd for $C_{11}H_{21}OSi$ ($M^+ - 1$) 197.1362, found 197.1356.

2-Decarboxy-2-[[(dimethyl-*tert*-butylsilyl)oxy]methyl]-4,4,5,5-tetradehydro-6-oxo-$PGF_{1\alpha}$ 11,15-Bis(tetrahydropyranyl ether) (4a). A round-bottomed flask equipped with a magnetic stirring bar and a rubber septum was charged with 5.94 g (30 mmol) of 4-[(dimethyl-*tert*-butylsilyl)oxy]-1-pentyne and 100 mL of anhydrous ether (Mallinckrodt AR) under a nitrogen atmosphere. The solution was cooled to −10 °C and 18.7 mL (30 mmol) of *n*-butyllithium in hexane (1.6 M) was added dropwise over a period of 5 min. The solution was stirred for an additional 10 min. Another flask equipped with a magnetic stirring bar and a rubber septum was charged with 8.72 g (20 mmol) of lactone **3** and 400 mL of ether and the solution was cooled to 0–5 °C under a nitrogen atmosphere. The reagent solution prepared in the first flask was added dropwise over a period of 10 min via a double-tipped needle into the second flask containing the lactone. The reaction mixture was stirred at room temperature for 1 h. The color of the solution turned from light yellow to deep red. The reaction mixture was then quenched with 200 mL of saturated aqueous ammonium chloride and extracted with Skelly B–ether (1:2). The organic layer was washed with brine and dried over anhydrous magnesium sulfate. HPLC purification was carried out with 648 g of silica gel 60, eluting with Skelly B–ethyl acetate (3:1) for fractions 1–30 and 2:1 for fractions 31–80 and collecting 50-mL fractions. Fractions (48–80) homogeneous on TLC were combined and concentrated in vacuo to afford 11.0 g (86%) of pure yne-one **4a** (oil): ^1H NMR ($CDCl_3$) δ 5.56–5.18 (m, 2 H, CH=CH), 4.74–4.44 (m, 2 H, OCHO), 4.20–3.18 (m, 8 H, CHO, OH, CH_2O), 3.66 (t, J = 6 Hz, 2 H, CH_2OSi), 0.88 (t and s, 12 H, Si-*t*-Bu, CH_3); IR (film) 3500, 2220, 1680, 975 cm^{-1}; mass spectrum, m/e calcd for $C_{32}H_{53}O_7Si$ ($M^+ - C_4H_9$) 577.3560, found 577.3543; R_f 0.3 in hexane–ethyl acetate (2:1). This compound is labile at room temperature. Stability could be maintained for indefinite periods of time if stored in the refrigerator.

2-Decarboxy-2-[[(dimethyl-*tert*-butylsilyl)oxy]methyl]-4,4,5,5-tetradehydro-6-hydroxy-$PGF_{1\alpha}$ 11,15-Bis(tetrahydropyranyl ether). Separation and Purification of 6*R* and 6*S* Isomers 5a and 6a. A two-neck round-bottomed flask equipped with a magnetic stirring bar was charged with 3.5 g (5.5 mmol) of yne-one **4a** and 100 mL of methanol. The solution was cooled to −20~−10 °C under a nitrogen atmosphere and 0.624 g (16.5 mmol) of sodium borohydride was added via a powder funnel. After the solution was stirred for 0.5 h, TLC showed the reaction to be complete. The mixture was treated with saturated aqueous ammonium chloride and methanol was removed in vacuo. The residue was extracted with ethyl acetate. The organic layer was washed with 10% aqueous sodium bisulfate, saturated aqueous sodium bicarbonate, and brine and dried over anhydrous magnesium sulfate. Filtration and concentration in vacuo afforded the crude product. The separation of 6*R* and 6*S* isomers **5a** and **6a** was carried out by HPLC through two columns packed with 324 g of silica gel 60, each connected in series, eluting with hexane–ethyl acetate (1:1) and collecting 50-mL fractions. The fractions homogeneous on TLC were combined and concentrated in vacuo. The less polar product (fractions 62–90, 2.1 g, 60%) was assigned as 6*R* isomer **5a**, whereas the more polar product (fractions 91–145, 1.0 g, 28.6%) was assigned as 6*S* isomer **6a**. Isomer **5a** (oil) showed the following: ^1H NMR ($CDCl_3$) δ 5.82–5.20 (m, 2 H, CH=CH), 4.84–4.60 (m, 2 H, OCHO), 4.60–3.28 (m, 10 H, CHO, CH_2O), 0.90 (s and t, 12 H, Si-*t*-Bu, CH_3); IR (film) 3400, 2220, 1670, 975 cm^{-1}; mass spectrum, m/e 370, 303, 299; R_f 0.33 in hexane–ethyl acetate (1:1). Anal. Calcd for $C_{36}H_{64}O_7Si$: C, 67.88; H, 10.13. Found: C, 67.87; H, 10.19. Isomer **6a** (oil) showed the following: ^1H NMR, IR, and mass spectra were all similar to **5a**; R_f 0.27 in hexane–ethyl acetate (1:1). Anal. Calcd for $C_{36}H_{64}O_7Si$: C, 67.88; H, 10.13. Found: C, 67.79; H, 10.26.

2-Decarboxy-2-(methyloxy)-4,4,5,5-tetradehydro-6-oxo-$PGF_{1\alpha}$ 1,9-Bis(dimethyl-*tert*-butylsilyl ether) 11,15-Bis(tetrahydropyranyl ether) (4b). A round-bottomed flask equipped with a magnetic stirring bar was charged with 17.2 g (26 mmol) of yne-one **4a** and 27 mL of DMF. A solution of dimethyl-*tert*-butylchlorosilane (8.1 g, 54 mmol) and imidazole (7.4 g, 108 mmol) in 27 mL of DMF was added at room temperature under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 3 h and at 40 °C for 1 h at which time TLC analysis showed no starting material remaining. The reaction mixture was treated with 5 mL of water, stirred for 0.5 h, and extracted with ether–hexane (1:1). The organic layer was washed with 10% aqueous sodium bisulfate, saturated aqueous sodium bicarbonate, and brine and dried over anhydrous magnesium sulfate. Filtration and concentration in vacuo afforded the crude product. Column chromatography, using 1 kg of silica

(8) Hamberg, M.; Samuelsson, B. *J. Biol. Chem.* **1965**, *241*, 257.
(9) Lin, C. H. *J. Org. Chem.* **1976**, *41*, 4045.

gel (63–200 μm, E. Merck), eluting with hexane–ethyl acetate (3:1), and collecting 200-mL fractions, yielded pure **4b** (fractions 8–12, 18.3 g, oil, 91%): ^{1}H NMR ($CDCl_3$) δ 5.70–5.25 (m, 2 H, CH=CH), 4.78–4.55 (m, 2 H, OCHO), 4.38–3.28 (m, 9 H, CHO, CH_2O), 0.88 (s and t, 21 H, Si-*t*-Bu, CH_3); IR (film) 2220, 1680, 975 cm^{-1}; mass spectrum, *m/e* calcd for $C_{38}H_{67}O_7Si_2$ ($M^+ - C_4H_9$) 691.4425, found 691.4454.

2-Decarboxy-2-(methyloxy)-4,4,5,5-tetradehydro-6-hydroxy-PGF$_{1\alpha}$ 1,9-Bis(dimethyl-*tert*-butylsilyl ether) 11,15-Bis(tetrahydropyranyl ether). Separation and Purification of 6*R* and 6*S* Isomers 5b and 6b. A round-bottomed flask equipped with a magnetic stirring bar and a dropping funnel was charged with 240 mL of methanol. The flask was cooled to −30 °C under a nitrogen atmosphere and 2.73 g (72 mmol) of sodium borohydride was added. Then 18.0 g (24 mmol) of yne-one **4b** in 240 mL of methanol was added over a period of 5 min. The reaction mixture was stirred at −20∼−10 °C for 1 h. Saturated aqueous ammonium chloride was added and the mixture was stirred for 10 min. After the mixture warmed to room temperature, methanol was removed under reduced pressure. The residue was extracted with ether and the ether layer was washed with saturated aqueous ammonium chloride, saturated aqueous sodium bicarbonate, and brine and dried over anhydrous magnesium sulfate. Filtration and concentration in vacuo afforded an oil which showed two spots on TLC, using chloroform–hexane–acetone (10:10:1) as an eluant. To show these two spots were epimers at C-6, 670 mg of this oil was subjected to HPLC separation, using 68 g of silica gel 60, eluting with chloroform–hexane–acetone (20:20:1), and collecting 20-mL fractions. The less polar isomer **5b** (fractions 10–12, 221 mg, oil, R_f 0.48) and the more polar isomer **6b** (fractions 18–55, 170 mg, oil, R_f 0.35) gave identical ^{1}H NMR, IR, and mass spectra. In addition a mixture of both isomers with the more polar compound predominating (fractions 13–17, 150 mg) was isolated. The spectral data for both isomers were as follows: ^{1}H NMR ($CDCl_3$) δ 5.72–5.26 (m, 2 H, CH=CH), 4.78–4.56 (m, 2 H, OCHO), 4.44–3.30 (m, 8 H, CHO, CH_2O, OH), 3.66 (t, J = 6 Hz, 2 H, CH_2OSi), 0.88 (s and t, 21 H, Si-*t*-Bu, CH_3); IR (film) 3440, 2220, 1670, 970 cm^{-1}; mass spectrum (as Me_3Si derivative), *m/e* calcd for $C_{45}H_{86}O_7Si_3$ (M^+) 822.5681, found 822.5663 for **5b** and 822.5655 for **6b**.

2-Decarboxy-2-[[(dimethyl-*tert*-butylsilyl)oxy]methyl]-4,4,5,5-tetradehydro-6α-PGI$_1$ 11,15-Bis(tetrahydropyranyl ether) (7a) and 2-Decarboxy-2-[[(dimethyl-*tert*-butylsilyl)oxy]methyl]-4,4,5,5-tetradehydro-6β-PGI$_1$ 11,15-Bis(tetrahydropyranyl ether) (7b). A round-bottomed flask equipped with a magnetic stirring bar was charged with 5.7 g (9.0 mmol) of diol **5a** and 180 mL of pyridine under a nitrogen atmosphere. One equivalent of *p*-toluenesulfonyl chloride (Aldrich; 1.7 g, 9.0 mmol) was added at intervals of 0, 6, 24, and 48 h (total addition of 4 equiv). After the mixture was stirred at room temperature for 72 h and at 50 °C for 2 h, the resulting brown colored solution was cooled to 0–5 °C and ice–water (ca. 18 mL) was added. The mixture was stirred at room temperature for 30 min and pyridine was removed in vacuo. The brown oil was extracted with ether, and the ether layer was washed with water, 10% aqueous sodium bisulfate, saturated aqueous sodium bicarbonate, and brine and dried over anhydrous magnesium sulfate. Filtration and concentration afforded an oil. Purification by HPLC was carried out over silica gel 60 (324 g), eluting with hexane–ethyl acetate (10:1) for fractions 1–40 and 5:1 for fractions 41–106 and collecting 50-mL fractions. The fractions (57–106) homogeneous on TLC were combined and concentrated in vacuo to afford the pure oil **7a** (4.2 g, 75%): ^{1}H NMR ($CDCl_3$) δ 5.78–5.26 (m, 2 H, CH=CH), 4.82–4.54 (m, 2 H, OCHO), 4.54–3.18 (m, 10 H, CHO, CH_2O), 0.88 (s and t, 12 H, Si-*t*-Bu, CH_3); IR (film) 2200, 980 cm^{-1}; R_f 0.54, 0.58 in hexane–ethyl acetate (2:1). The appearance of two spots on TLC was due to THP epimers.

For preparation of the corresponding isomer **9b**, 2.9 g (4.6 mmol) of diol **6a** and 92 mL of pyridine were used. The addition of *p*-toluenesulfonyl chloride was also carried out in four stages with each addition being 0.874 g (4.6 mmol). The reaction time was 72 h at room temperature and 6 h at 50 °C. After the same workup as described in the earlier experiment, the brown oil was purified by HPLC, using 166 g of silica gel 60, eluting with hexane–ethyl acetate (5:1), and collecting 50 mL fractions. Fractions (7–26) homogeneous on TLC were combined and concentrated in vacuo to give the pure oil **7b** (2.2 g, 78.6%): ^{1}H NMR and IR spectra were similar to those of cyclic ether **7a**; R_f 0.44 and 0.38 in hexane–ethyl acetate (3:1), R_f 0.35 and 0.30 for cyclic ether **7a** in the same solvent system.

Both isomers **7a** and **7b** appeared to be quite labile. After these compounds were stored in the refrigerator overnight, several spots (with streaking) appeared on TLC. Repeated purification by HPLC in an attempt to prepare an analytical sample for combustion analyses failed. These compounds were therefore used in the next step immediately after HPLC purification.

2-Decarboxy-2-(methyloxy)-4,4,5,5-tetradehydro-6α-PGI$_1$ 11,15-Bis(tetrahydropyranyl ether) (8a) and 2-Decarboxy-2-(methyloxy)-4,4,5,5-tetradehydro-6β-PGI$_1$ 11,15-Bis(tetrahydropyranyl ether) (8b). A round-bottomed flask equipped with a magnetic stirring bar was charged with 1.24 g (2.0 mmol) of cyclic ether **7a**, 4 mL (4.0 mmol) of tetra-*n*-butylammonium fluoride[6] in THF (1 M), and 20 mL of THF all under a nitrogen atmosphere. The brown solution was stirred at room temperature for 3 h, THF was removed in vacuo, and the residue was extracted with ether. The organic layer was washed with 10% aqueous sodium bisulfate, saturated aqueous sodium bicarbonate, and brine and dried over anhydrous magnesium sulfate. Filtration and concentration afforded a brown oil. HPLC purification was carried out over 52.5 g of silica gel 60, eluting with hexane–ethyl acetate (1:1) and collecting 40-mL fractions. The fractions (9–22) homogeneous on TLC were combined and concentrated in vacuo to give pure **8a** as an oil (0.9 g, 90%): ^{1}H NMR ($CDCl_3$) δ 5.78–5.32 (m, 2 H, CH=CH), 4.85–4.54 (m, 2 H, OCHO), 4.54–3.20 (m, 10 H, CHO, CH_2O); IR (film) 3450, 2240, 1635, 985 cm^{-1}; R_f 0.28 in hexane–ethyl acetate (1:1).

For preparation of the other isomer **8b** 1.24 g (2.0 mmol) of cyclic ether **7b** and 4 mL (4.0 mmol) of tetra-*n*-butyl ammonium fluoride in THF (1 M) were used. HPLC purification was carried out over 52.5 g of silica gel 60, eluting with hexane–acetate (5:1) and collecting 40-mL fractions. There was obtained the pure oil **8b** (fractions 15–30, 0.925 g, 86%): ^{1}H NMR and IR were similar to those of **8a**; R_f 0.22 in hexane–ethyl acetate (1:1), R_f 0.28 for alcohol **8a** in the same solvent. As in the case of **7a** and **7b**, these compounds were too labile to give consistent combustion analyses.

4,4,5,5-Tetradehydro-6α-PGI$_1$ (9a) and 4,4,5,5-Tetradehydro-6β-PGI$_1$ (9b). A round-bottomed flask equipped with a magnetic stirring bar was charged with 858 mg (1.7 mmol) of alcohol **8a** and 51 mL of acetone. The solution was cooled to −25∼−20 °C and 2.54 mL (6.8 mmol) of Jones reagent (2.67 M) dissolved in 17 mL of acetone was added dropwise over a period of 30 min. After being stirred for 1 h, the reaction mixture was quenched with 10% aqueous sodium bisulfite. Acetone was removed in vacuo and the residue was extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous sodium sulfate. Filtration and concentration afforded the crude oil. This oil was then dissolved in 34 mL of HOAc–H_2O–THF (20:10:3) and the mixture was stirred at 45 °C for 3 h and at room temperature for 18 h. After concentration in vacuo freshly prepared diazomethane in ether was added. The crude oil thus obtained after removal of ether in vacuo was purified by HPLC. With 52.5 g silica gel 60, elution with hexane–acetone (3:1) for fractions 1–40, and 1:1 for fractions 41–50, and collection of 50-mL fractions, there was obtained 266 mg (47%) of an oil (**9a methyl ester**): ^{1}H NMR ($CDCl_3$) δ 5.78–5.38 (m, 2 H, CH=CH), 4.84–3.46 (m, 4 H, CHO), 3.72 (s, 3 H, CO_2CH_3), 3.14 (br s, 2 H, OH), 2.56 (br s, 4 H, C=CCH_2CH_2CO); IR (film) 3400, 2250, 1740, 975 cm^{-1}; R_f 0.20 in hexane–acetone (2:1). This methyl ester was saponified as follows. A round-bottomed flask equipped with a magnetic stirring bar was charged with 168 mg (0.46 mmol) of **9a methyl ester**, 1.84 mL of 1 N KOH in MeOH, and 1.84 mL of MeOH. The solution was stirred at room temperature for 14 h. MeOH was removed in vacuo and the residue was acidified with 10% aqueous sodium bisulfate, saturated with sodium chloride, and extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous sodium sulfate. Filtration and concentration gave the crude oil. Chromatographic purification was carried out with 7 g of CC-4 silica gel, eluting with hexane–acetone (3:1) and collecting 10-mL fractions. Fractions (13–78) homogeneous on TLC were combined and concentrated in vacuo to give 135 mg (84%) of white solid **9a**. Recrystallization from ethyl acetate–cyclohexane afforded a white solid: mp 98–99 °C;

^{1}H NMR ($CDCl_3$) δ 6.72 (br s, 3 H, OH, CO_2H), 5.72–5.36 (m, 2 H, CH=CH), 4.98–3.30 (m, 4 H, CHO), 2.54 (br s, 4 H, C=C, $CH_2CH_2CO_2$); IR (film) 3460, 2250, 1755, 1690, 980, 975 cm^{-1}; mass spectrum (as Me_3Si derivative), m/e calcd for $C_{29}H_{54}O_5Si_3$ (M^+) 566.3279, found 566.3265; R_f 0.32 in A-IX. Anal. Calcd for $C_{20}H_{30}O_5$: C, 68.54; H, 8.63. found: C, 68.39; H, 8.49. Jones oxidation of **8b** was carried out following the same procedure as described above. The product obtained could also be purified directly as an acid instead of convertin to the methyl ester. Starting with 806 mg (1.6 mmol) of **8b** in 32 mL of acetone, the reaction was run at −20∼−15 °C. Jones reagent (2.67 M) was added at the beginning of the reaction (2.4 mL, 6.4 mmol) and after 0.5 h (also 2.4 mL). After being stirred an additional 0.5 h, the mixture was worked up as described previously. Hydrolysis of the oxidized product was carried out by stirring the crude oil in a solution of 4 mL of 1 N HCl and 16 mL of 2-propanol for 24 h at room temperature. The solution was then neutralized with saturated aqueous sodium bicarbonate and 2-propanol was removed in vacuo. The residue was acidified with 10% aqueous sodium bisulfate and extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous sodium sulfate. Filtration and concentration afforded the crude oil. Chromatographic purification was carried out with 52.5 g of CC-4 silica gel, eluting with hexane–acetone (3:1) and collecting 40-mL fractions. Fractions (39–60) homogeneous on TLC were combined and concentrated in vacuo to give the pure oil **9b** (202.5 mg, 36%): ^{1}H NMR ($CDCl_3$) δ 5.72–5.22 (m, 5 H, CH=CH, CO_2H, OH), 4.85–4.36 (m, 2 H, CHO at C-6 and C-9), 4.32–3.52 (m, 2 H, CHO at C-11 and C-15), 2.55 (br s, 4 H, C=$CCH_2CH_2CO_2$); IR (film) 3450, 2240, 1710, 970 cm^{-1}; mass spectrum (as Me_3Si derivative), m/e calcd for $C_{29}H_{54}O_5Si_3$ (M^+) 566.3279, found 566.3294; R_f 0.27 in A-IX. Anal. Calcd for $C_{20}H_{30}O_5$: C, 68.54; H, 8.63. Found: C, 68.28; H, 8.61.

2-Decarboxy-2-(methyloxy)-*cis*-4,5-didehydro-6α-PGI$_1$ 11,15-Bis(tetrahydropyranyl ether) (11a) and 2-Decarboxy-2-(methyloxy)-*cis*-4,5-didehydro-6β-PGI$_1$ 11,15-Bis(tetrahydropyranyl ether) (11b). A mixture of 1.24 g (2.0 mmol) of cyclic ether **7a**, 124 mg of 5% Pd/$BaSO_4$, 4 mL of pyridine, and 36 mL of ethyl acetate was stirred under a hydrogen atmosphere (1 atm) at room temperature for 1 h. Filtration through a layer of Celite and concentration of the filtrate in vacuo gave the crude oil **10a**: ^{1}H NMR ($CDCl_3$) was similar to cyclic ether **7a** except the integration now indicated four protons at δ 5.78–5.26; IR (film) was also similar to cyclic ether **7a** except for the disappearance of a weak band at 2220 cm^{-1}; R_f 0.49, 0.45 in hexane–ethyl acetate (3:1) (R_f 0.35, 0.30 for cyclic ether **7a**). Due to the instability of this compound the desilylation was carried out without purification. A round-bottomed flask equipped with a magnetic stirring bar was charged with 1.2 g (2.0 mmol) of cyclic ether **10a**, 4 mL of tetra-*n*-butylammonium fluoride (1 M) in THF, and 20 mL of THF, all under a nitrogen atmosphere. The brown solution was stirred at room temperature for 3 h. THF was then removed in vacuo and the residue was extracted with ether. The ether layer was washed with water, 10% aqueous sodium bisulfate, saturated aqueous sodium bicarbonate, and brine and dried over anhydrous magnesium sulfate. Filtration and concentration afforded a brown oil. HPLC purification was carried out with 52.5 of silica gel 60, eluting with hexane-ethyl acetate (2:1) for fractions 1–30, and 1:1 for fractions 31–52 and collecting 50-mL fractions. The fractions (35–52) homogeneous on TLC were combined and concentrated in vacuo to give the pure oil **11a** (592 mg, 59%): ^{1}H NMR ($CDCl_3$) δ 5.85–5.08 (m, 4 H, CH=CH), 4.88–4.46 (m, 3 H, OCHO, C_6-H), 4.60–3.20 (m, 9 H, CHO, CH_2O), 2.94 (br s, 1 H, OH); IR (film) 3450, 975 cm^{-1}; R_f 0.27 in hexane–ethyl acetate (1:3) (R_f 0.41 for **8a**). Anal. Calcd for $C_{30}H_{50}O_6$: C, 71.11, H, 9.95; Found: C, 70.91; H, 9.79. The same procedure as described above was followed for preparation of **11b**. A mixture of 742 mg (1.2 mmol) of cyclic ether **7b**, 74 mg of 5% Pd/$BaSO_4$, 2.4 mL of pyridine, and 21.6 mL of ethyl acetate was stirred under a hydrogen atmosphere (1 atm) at room temperature for 1 h. After filtration and concentration **10b** was obtained as an oil: ^{1}H NMR and IR spectra were similar to cyclic ether **10a**; R_f 0.44, 0.39 in hexane–ethyl acetate (3:1) (R_f 0.51, 0.49 for cyclic ether **10a**). Oil **10b** was stirred in a solution of 2.4 mL of tetra-*n*-butylammonium fluoride (1 M) in THF and 12 mL of THF at room temperature for 3 h. The workup was the same as described for the preparation of **11a**. The crude oil obtained was purified by HPLC, using 52.5 g silica gel 60, eluting with hexane–acetone (5:1), and collecting 50-mL fractions. Fractions (15–18) homogeneous on TLC were combined and concentrated in vacuo to give the pure oil **11b** (562 mg 93%): ^{1}H NMR and IR spectra were very similar to **11a**. The C-6 and C-9 protons moved downfield to δ 5.0–4.3 in the NMR spectrum, however; R_f 0.37 in hexane–acetane (3:1) (R_f 0.31 for alcohol **11a**). Anal. Calcd for $C_{30}H_{50}O_6$: C, 71.11; H, 9.95; Found: C, 70.85; H, 9.83.

4,5-*cis*-Didehydro-6α-PGI$_1$ (12a) and 4,5-*cis*-Didehydro-6β-PGI$_1$ (12b). The Jones oxidation was carried out following the same procedure as described in the preparation of the acid **9b**. Starting with 506 mg (1.0 mmol) of alcohol **11a** the oxidized product was stirred in a mixture of 4 mL of 1 N HCl and 16 of mL 2-propanol at room temperature for 24 h. After similar workup procedure as described for the acid **9b** the crude oil obtained was purified with 52.5 g of CC-4 silica gel, eluting with hexane–acetone (2:1) and collecting 40-mL fractions. Fractions (10–31) homogeneous on TLC were combined and concentrated in vacuo to give pure *cis*-4,5-didehydro-6α-PGI$_1$ **12a** (206.7 mg, 59%). Crystallization from ethyl acetate–cyclohexane gave 134 mg of white solid: mp 91–92 °C; ^{1}H NMR ($CDCl_3$) δ 5.68 (br s, 3 H, OH, CO_2H), 5.75–5.25 (m, 4 H, CH=CH), 4.88–3.62 (m, 4 H, CHO), 2.44 (br s, 4 H, C=$CCH_2CH_2CO_2$); IR (film) 3500, 1710, 965 cm^{-1}; mass spectrum (as Me_3Si derivative), m/e calcd for $C_{29}H_{56}O_5Si_3$ (M^+) 568.3435, found 568.3408; R_f 0.26 in A-IX. Anal. Calcd for $C_{20}H_{32}O_5$: C, 67.86; H, 9.05. Found: C, 67.86; H, 9.05.

A similar procedure was used in th preparation of **12b**: ^{1}H NMR ($CDCl_3$) δ 5.93 (br s, 3 H, CO_2H), 5.72–5.25 (m, 4 H, CH=CH), 5.10–4.25 (m, 2 H, CHO at C-6 and C-9), 4.25–3.33 (m, 2 H, CHO at C-11 and C-15), 2.44 (br s, 4 H, C=$CCH_2CH_2CO_2$); IR spectrum was identical with acid 12a; mass spectrum (as Me_3Si derivative), m/e calcd for $C_{29}H_{56}O_5Si_3$ (M^+) 568.3436, found 568.3420; R_f 0.23 in A-IX. Anal. Calcd for $C_{20}H_{32}O_5$: C, 68.15; H, 9.15. Found: C, 67.75; H, 9.54.

13,14-Dihydro-6α-PGI$_1$ (14a). A mixture of 200 mg (0.564 mmol) of 6α-PGI$_1$ **13a**, 20 mg of 10% Pd/C, and 20 mL of ethyl acetate was stirred under a hydrogen atmosphere (1 atm) at room temperature for 4 h. The mixture was filtered through a layer of Celite and the filtrate was concentrated in vacuo. HPLC purification was carried out with 52.5 g CC-4 silica gel, eluting with hexane–acetone (2:1), and collecting 40-mL fractions. Fractions (7–15) homogeneous on TLC were combined and concentrated in vacuo to afford the pure oil **14a** (145 mg, 73%): ^{1}H NMR ($CDCl_3$) δ 5.22 (br s, 3 H, OH, CO_2H), 4.45–4.20; 4.14–3.42 (m, 4 H, CHO): IR (film) 3500, 1710 cm^{-1}; mass spectrum (as Me_3Si derivative), weak M^+ at 527, m/e calcd for $C_{28}H_{57}O_7Si_3$ ($M^+ - CH_3$) 557.3514, found 557.3512; R_f 0.38 in A-IX; a less polar product (minor component) with R_f 0.49 appeared to be 13,14-dihydro-15-oxo-6α-PGI$_1$ on the basis of prevous work.[9]

Determination of C-6 Configuration on 4,4,5,5-Tetradehydro-6α-PGI$_1$ 9a. A mixture of 16 mg of acid **9a**, 5 mg of 10% Pd/C, and 4 mL of ethyl acetate was stirred under a hydrogen atmosphere (1 atm) at room temperature for 2 h. The mixture was filtered through a layer of Celite and the filtrate was concentrated in vacuo to give 15.8 mg oil. This oil showed the identical R_f (0.38 in A-IX) on TLC as the authentic acid **14a** obtained in previous experiment. With silver nitrate impregnated TLC plates both products also had identical R_f values (0.35 in A-IX), whereas the starting material **13a** and the 6β isomer (13,14-dihydro-PGI$_1$, **14b**) had R_f values of 0.16 and 0.31, respectively. There was no indication of any contamination of 6β isomer. The NMR ($CDCl_3$) spectrum was identical with that of **14a** and no peaks present in δ 4.60–4.50 region. In both hydrogenations of acids, **13a** and **9a**, a less polar product (R_f 0.49), presumably 13,14-dihydro-15-oxo-6α-PGI$_1$, was also formed as a minor product.

Determination of C-6 Configuration on 4,4,5,5-Tetradehydro-6β-PGI$_1$ 9b. A mixture of 3.5 mg (0.01 mmol) of acid **9b**, 1 mg of 10% Pd/C, and 1 mL of ethyl acetate was stirred under a hydrogen atmosphere (1 atm) at room temperature for 30 min. Filtration through a layer of Celite and concentration of the filtrate in vacuo gave an oil (3.5 mg). This oil showed the identical R_f (0.34 in A-IX) on TLC as that of the authentic 13,14-dihydro-6β-PGI$_1$ **14b**. There was no indication of any contamination of the 6α isomer. The NMR spectrum of this

product showed a multiplet present at δ 4.60–4.25, identical with that of **14b**.[7] As in the case of hydrogenation of **9a** a less polar product (R_f 0.46), presumably 13,14-dihydro-15-oxo-PGI$_1$, was formed as a minor product.

Registry No. 3, 37517-42-3; **4a**, 61604-78-2; **4b**, 61600-83-7; **5a**, 80186-31-8; **5b**, 80186-32-9; **6a**, 80186-33-0; **6b**, 80186-34-1; **7a**, 80186-35-2; **7b**, 80186-36-3; **8a**, 80186-37-4; **8b**, 80186-38-5; **9a**, 80186-39-6; **9a** methyl ester, 80186-40-9; **9a** TMS derivative, 80206-12-8; **9b**, 80186-41-0; **9b** TMS derivative, 80186-42-1; **10a**, 80206-13-9; **10b**, 80206-14-0; **11a**, 80206-15-1; **11b**, 80206-16-2; **12a**, 80227-15-2; **12b**, 80227-16-3; **13a**, 62777-90-6; **14a**, 75351-76-7; **14a** TMS derivative, 80186-43-2; 4-[(dimethyl-*tert*-butylsilyl)oxy]-1-pentyne, 80186-44-3; 1-pentyn-4-ol, 2117-11-5.

Stereoselective Synthesis of (22*R*)- and (22*S*)-22-Methylcholesterol

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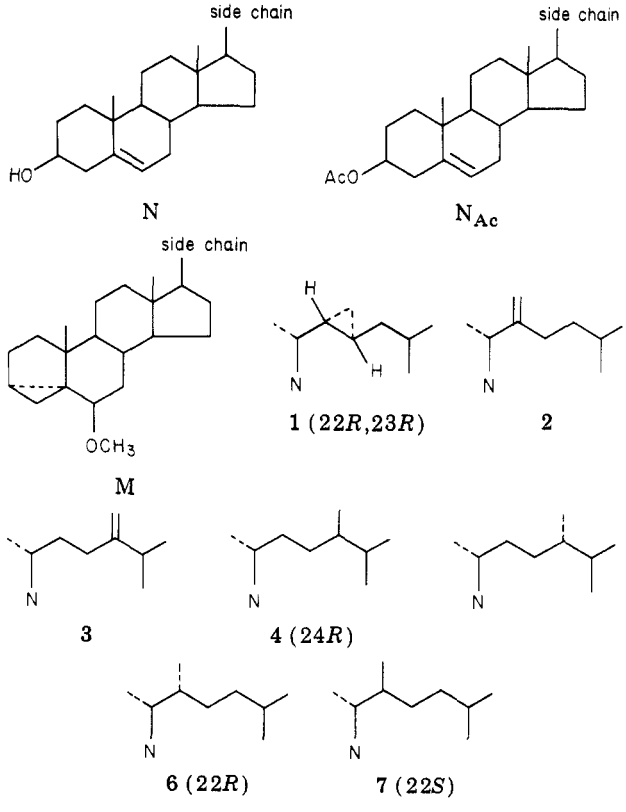
22-Methylcholesterol, though hitherto unknown, is likely to exist in nature in the marine environment. In order to facilitate its eventual recognition, stereoselective syntheses of the 22*R* and 22*S* isomers of 22-methylcholesterol were developed by using the Claisen rearrangement of appropriate precursors of established absolute configuration. An alternate approach involved hydroboration of an appropriate 22-methylene precursor, separation of the isomeric primary alcohols, mesylation, and lithium aluminum hydride reduction. Differentiation of these two isomers between themselves and from the common (24*R*)- and (24*S*)-22-methylcholesterols is possible on the basis of proton and ^{13}C NMR measurements as well as chromatographic mobility.

The recent isolation from marine organisms of (22*R*,23*R*)-22,23-methylenecholesterol (**1**)[2] and 22-methylenecholesterol (**2**)[3] (see chart I) represents the strongest indication to date that direct bioalkylation of 22-dehydrocholesterol is possible in nature. The occurrence of **1** and **2** had been predicted by us[4] and their eventual recognition was facilitated by prior synthesis of authentic reference compounds. By analogy to the existence[5] in nature of 24-methylenecholesterol (**3**) together with its two isomeric dihydro analogues, (24*R*)- (**4**) and (24*S*)-24-methylcholesterol (**5**), it is reasonable to assume that (22*R*)- (**6**) and (22*S*)-22-methylcholesterol (**7**) should also be naturally occurring. To expedite their eventual isolation from marine sources, we have undertaken their stereospecific synthesis in order to provide authentic reference compounds and to determine which physical method would be of greatest diagnostic utility.

Since knowledge of the C-22 stereochemistry is of great biosynthetic relevance, we selected a synthetic approach, which would not only be stereoselective, but would also establish the absolute configuration of the two 22-methylcholesterols (**6**, **7**). The stereospecific and regiospecific features of the Claisen rearrangement[6] have already been used to good advantage in the stereospecific introduction of certain substiuents into the steroid side chain,[7] and we have now adapted it to the synthesis of **6** and **7**.

Chart I



Our starting material, (22*E*)-6β-methoxy-3α,5-cyclo-5α-cholest-22-en-24-one (**8**),[8] was readily available from stig-

(1) (a) Postdoctorate fellow on leave from the Technical University, Gdansk, Poland. (b) Visiting investigator on leave from Shanghai Institute of Pharmaceutical Industrial Research, Shanghai, China.

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