3β,25-diol; cf. (a) J. Weiss and M. Keller, *Experientia*, **6**, 379 (1950); (b) M. Keller and J. Weiss, *J. Chem. Soc.*, 2709 (1950); (c) B. Coleby, M. Keller, and J. Weiss, *ibid.*, 66 (1955); (d) G. R. Clemo, M. Keller, and J. Weiss, *ibid.*, 3470 (1950); (e) M. Kimura, M. Tohma, and T. Tomita, *Chem. Pharm. Bull.*, **20**, 2185 (1972); (f) *ibid.*, **21**, 2521 (1973); (g) A. L. J. Beckwith, *Proc. Chem. Soc., London*, 194 (1958). We have confirmed that HO· generated by ^{60}Co γ-radiolysis of aqueous cholesterol dispersions saturated with N_2O yields **3**, **5**, **7**, and **11–13**, and that neither sterol hydroperoxide **2**, **4**, and **8** nor **6**, **9**, **10**, and **14** were formed.

(30) (a) R. H. Steel and L. C. Cusachs, *Nature (London)*, **213**, 800 (1967); (b) W. H. Koppenol, *ibid.*, **262**, 420 (1976).

(31) D. R. Kearns, *Chem. Rev.*, **71**, 395 (1971) (on p 407), and references cited therein.

(32) (a) E. J. Bowen and R. A. Lloyd, *Proc. Chem. Soc., London*, 305 (1963); (b) E. J. Bowen, *Pure Appl. Chem.*, **9**, 473 (1964); (c) E. McKeown and W. A. Waters, *Nature (London)*, **204**, 1063 (1964); (d) E. McKeown and W. A. Waters, *J. Chem. Soc. B*, 1040 (1966).

(33) Failure to intercept $^1O_2$ in control experiments in systems involving H_2O_2 has been reported; cf. (a) E. J. Bowen, *Nature (London)*, **201**, 180 (1964); (b) J. A. Howard and K. U. Ingold, *J. Am. Chem. Soc.*, **80**, 1056 (1968); (c) ref 10.

(34) The rate of oxidation of H_2O_2 by NaOCl is greatly reduced in ^2H_2O, cf. ref 11c, and similar rate reduction in the disproportionation of H_2O_2 to $^1O_2$ may be the present case. Reliance on ^2H_2O enchancement of $^1O_2$ lifetime as evidence for $^1O_2$ action can only be had where enchancement effects are observed and not in their absence; cf. ref 11d.

(35) (a) A. A. Lamola, T. Yamane, and A. M. Trozzolo, *Science*, **179**, 1131 (1973); (b) F. H. Doleiden, S. R. Fahrenholtz, A. A. Lamola, and A. M. Trozzolo, *Photochem. Photobiol.*, **20**, 519 (1974); (c) D. A. Lightner and R. D. Norris, *N. Engl. J. Med.*, **290**, 1260 (1974); (d) K. Suwa, T. Kimura, and A. P. Schaap, Abstracts, International Congress on Singlet Oxygen and Related Species in Chemistry and Biology, Pinawa, Manitoba, Canada, Aug 21–26, 1977, p S-17; (f) A. F. P. M. De Goeij and J. Van Steveninck, *Clin. Chim. Acta*, **68**, 115 (1976).

(36) (a) G. O. Schenck, O. A. Neumüller, and W. Eisfeld, *Angew. Chem.*, **70**, 595 (1958); *Justus Liebigs Ann. Chem.*, **618**, 202 (1958); (b) B. Lythgoe and S. Trippett, *J. Chem. Soc.*, 471 (1959).

(37) (a) J. A. Waters and B. Witkop, *J. Org. Chem.*, **34**, 3774 (1969); (b) Y. Kondo, J. A. Waters, B. Witkop, D. Guenard, and R. Beugelmans, *Tetrahedron*, **28**, 797 (1972).

(38) L. L. Smith and F. L. Hill, *J. Chromatogr.*, **66**, 101 (1972).

(39) (a) E. H. Mosbach, M. Nierenberg, and F. E. Kendall, *J. Am. Chem. Soc.*, **75**, 2358 (1953); (b) E. Chicoye, W. D. Powrie, and O. Fennema, *Lipids*, **3**, 335 (1968).

(40) Literature melting points (except for **9**) are taken from J. Jacques, H. Kagan, and G. Ourisson, "Tables of Constants and Numerical Data", Vol. 14, Pergamon Press, Oxford, 1965.

(41) (a) H. B. Henbest and E. R. H. Jones, *J. Chem. Soc.*, 1792 (1948); (b) G. O. Schenck, K. Gollnick, and O. A. Neümuller, *Justus Liebigs Ann. Chem.*, 603, 46 (1957); (c) A. Nickon and J. F. Bagli, *J. Am. Chem. Soc.*, **83**, 1498 (1961).

(42) J. E. van Lier and L. L. Smith, *J. Chromatogr.*, **36**, 7 (1968).

(43) P. A. Plattner, H. Heusser, and M. Feurer, *Helv. Chim. Acta*, **32**, 587 (1949).

(44) Purification of **6** was fraught with unresolved homogeneity problems, as even the best (99% purity) stearic acid used contained demonstrable levels of fatty acid congeners as impurities, leading to octadecenoate, hexadecanoate, and hexadecenoate congeners of **6** as impurities in **6** revealed in CI mass spectral ions (methane or isobutane) *m/z* 283, 257, and 255, respectively.

(45) The component previously suggested as cholesta-4,6-dien-3β-ol found in aqueous sodium stearate dispersions of cholesterol and 5α-hydroperoxide **8**, cf. ref 7, was assigned the dienol identity from its chromatographic mobility, characteristic blue color with sulfuric acid, and ultraviolet light absorption. The component was in fact an unresolved mixture of dienone **10** and 7α-stearate **6** not then recognized as such.

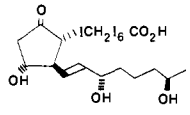
Total Synthesis of *dl*-19-Hydroxyprostaglandin E_1 and *dl*-13-*cis*-15-*epi*-19-Hydroxyprostaglandin E_1

Christoph Lüthy,[1] Peter Konstantin,[2] and Karl G. Untch*

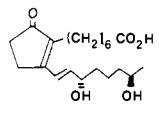
Contribution No. 495 from the Institute of Organic Chemistry, Syntex Research, Palo Alto, California 94304. *Received October 19, 1977*

Abstract: A total synthesis of *dl*-19-hydroxyprostaglandin E_1 (**34**) and *dl*-13-*cis*-15-*epi*-19-hydroxyprostaglandin E_1 (**35**) via the conjugate addition of the dioctenyl cuprate reagent **21** derived from *dl*-1-iodo-3-hydroxy-7-*tert*-butyldimethylsilyloxyoct-1-*cis*-ene (**14**) to *dl*-2-(6-carbomethoxyhexyl)-4-tetrahydropyranyloxycyclopent-2-en-1-one (**23**), followed by the stereospecific sulfenate–sulfoxide transformation on the resultant 13-*cis*-prostaglandin analogue, is reported. The preparation of the requisite *cis*-iodooctene **14**, prepared by two synthetic sequences starting from either α-methylcyclopentanone or acrylonitrile, is described as well as the separation of the C-19 α and β isomers.

Recently, two groups[3-6] have demonstrated that the major prostaglandin fraction in human semen consists of 19-hydroxyprostaglandin E_1 and 19-hydroxyprostaglandin E_2, together with lesser amounts of PGEs, PGFs, and 19-OH-PGFs.[7] Previously, in 1966, Hamberg and Samuelsson[8] had identified 19-OH-PGAs and 19-OH-PGBs in human semen, and later Hamberg[9] established the *R* configuration at C-19 for 19-OH-PGB_1 (**2**). These 19-OH-PGAs and -PGBs now are considered to have been artifacts resulting from dehydration during isolation and/or storage and analysis, since recent studies have shown that longer storage at a given temperature or storage at a temperature ≥0 °C of fresh seminal fluid results in a decrease in the amounts of 19-OH-PGEs with a concomitant increase in the amounts of 19-OH-PGAs and -PGBs. Although it has not yet been proven, it is highly likely that the naturally occurring 19-OH-PGEs have the 19 (*R*) configuration. The physiological role that these 19-OH-PGEs play in man or in primates[10] has not been yet established. It was therefore of interest to synthesize these prostaglandins for biological studies and evaluation.[11,12]



1



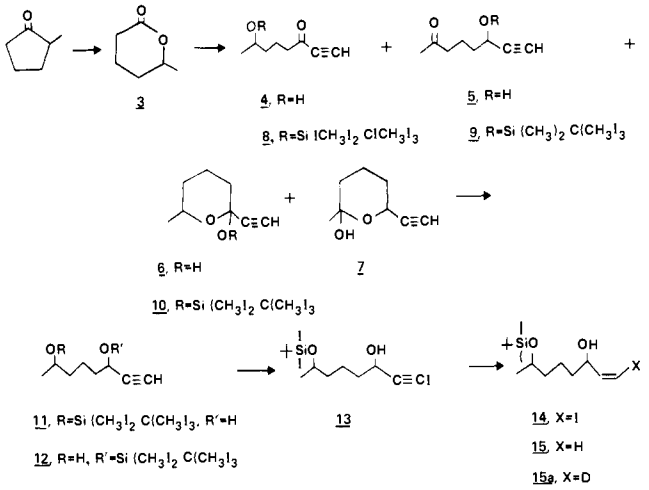
2

The total synthesis of *dl*-19-OH-PGE_1 reported here follows that which was developed in our laboratory,[13,14] which has as its key step the conjugate addition of the requisite functionalized *cis*-octenyl cuprate to the appropriate hydroxycyclopentenone, in order to take advantage of the high degree of stereochemical control at carbons 8, 11, 12, and 15. The stereospecific sulfenate–sulfoxide rearrangement[14] of the 13-*cis*-15β-hydroxy epimer provides the prostaglandin of natural stereochemistry, except the center at C-19 which is an equal mixture of 19α- and 19β-hydroxy isomers.

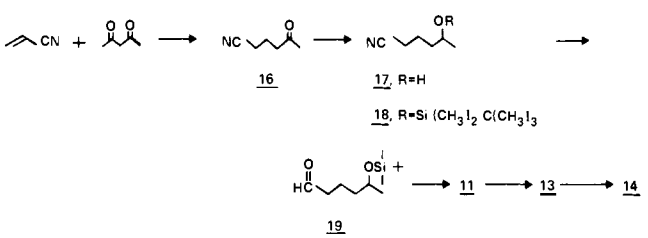
The required *cis*-iodovinylcarbinol **14** was prepared first by a six-step sequence as shown in Scheme I. Baeyer–Villiger oxidation of α-methylcyclopentanone with *m*-chloroperbenzoic acid gave lactone **3** in 74% yield after distillation. Linstead and Rydon[15] had previously synthesized this lactone in four steps (15% yield). Condensation of acetylenemagnesium bromide in tetrahydrofuran at 0 °C with lactone **3** gave, in only modest yield (30%), the hydroxy ketone **4** and the unexpected hydroxy ketone **5** in a ratio of ca. 2:1. The NMR spectrum of this mixture also exhibited resonances which were assigned to small

0002-7863/78/1500-6211$01.00/0

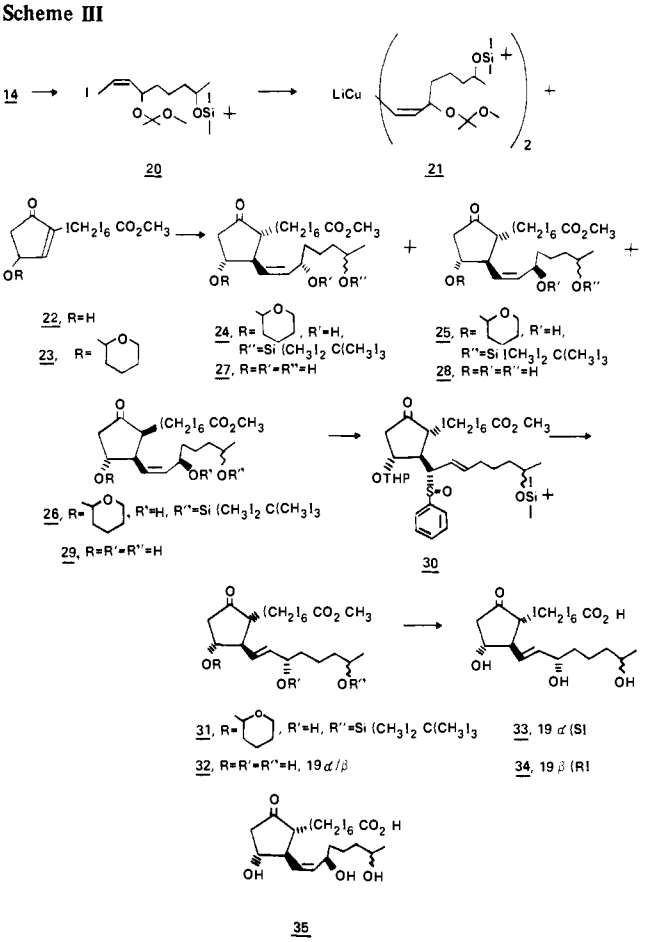
Scheme I



Scheme II



Scheme III



amounts (<10%) of cyclic hemiketals **6** and possibly **7** being present in equilibrium. This unusual formation of the hydroxy ketone **5** can be explained via a six-membered intramolecular hydride transfer in the magnesium bromide salt of the ynone **4.** This internal redox reaction could be providing a thermodynamic ratio of isomers; however, our data do not allow for this conclusion. Protection of the hydroxy groups of this mixture with *tert*-butyldimethylchlorosilane and an equivalent of imidazole afforded ketones **8** and **9** in 76% yield. Reduction of the mixture of **8** and **9** with sodium borohyride in ethanol provided a mixture of the corresponding alcohols which were separated by silica-gel chromatography to give **12** in 40% yield and **11** in 27% yield. The reaction of octynol **11** with the morpholine–iodine complex[16] at 45 °C for 24 h gave iodooctynol **13** in 82% yield, which was reduced with diimide[17] (methanol–dipotassium azodicarboxylate–acetic acid) to give the *cis*-iodooctynol **14** in 78% yield. A small amount (ca. 5%) of over-reduced iodooctanol was conveniently removed by treating the crude product with dimethylamine, followed by hydrochloric acid extraction of the resulting dimethylaminooctanol, as part of the workup procedure. This diimide reduction of an iodoacetylene to an iodo olefin was reported first from our laboratory[18] and we have carried it out successfully since with several other cases. To our knowledge, only iodoacetylenes provide high yields (75–90%) of iodo olefins by diimide reduction, whereas simple acetylenes give the corresponding saturated compounds.[19] This procedure is an excellent method for preparing terminal *cis*-iodo olefins free from any trans isomer, and it should be noted, for prostaglandin synthesis, that protection of the hydroxyl group is not required. Hydrogenation of an iodoacetylene using Lindlar catalyst gives no *cis*-iodo olefin but, rather, reductive elimination of the iodine.

Although the requisite *cis*-iodovinylcarbinol **14** for cuprate conjugate addition was in hand, the synthesis contained two poor-yielding steps and was complicated by giving a mixture of isomers in the second step. Therefore, another sequence was devised to prepare octynol **11** as shown in Scheme II. Base condensation of acrylonitrile and 2,4-pentanedione provided a 66% yield of distilled cyano ketone **16**,[20] which was reduced with sodium borohydride in methanol to give crude cyano alcohol **17** in 82% yield. Treatment of **17** with *tert*-butyldimethylchlorosilane and imidazole in dimethylformamide gave the crude protected cyano alcohol **18** in 84% yield. Purified **18** was obtained by distillation in 53% yield for two steps; **16** → **17** → **18**. Reduction of the nitrile **18** with diisobutylaluminum hydride gave hexanal **19** in 45% yield after distillation. The condensation of aldehyde **19** with lithium acetylide, prepared according to Midland,[21] at −78 °C in tetrahydrofuran gave a nearly quantitative yield of alcohol **11**, which was converted, without purification, to chromatographically pure *cis*-iodovinylcarbinol **14** by iodination and diimide reduction (see above) in an 82% overall yield for the three steps. Thus, synthesis of iodo alcohol **14** via Scheme I provided at 3.0% overall yield, whereas Scheme II gave **14** in a 17% overall yield. The 45% yield obtained for the reduction of nitrile **18** to aldehyde **19** might be improved since it is the result of a single attempt.

Successful generation of a divinyl cuprate reagent requires formation of the vinyllithium in high yield. Since each iodo olefin that we have studied seems to require somewhat different lithiation conditions, depending upon the nature of the oxygenated substitient, we carried out several experiments, varying time, temperature, and solvents, on the reaction of *n*-butyllithium with the *O*-methoxyisopropyl derivative **20**.

The amounts of olefin **15a** formed upon deuterium oxide quench was determined, and it was found that a reaction time of 90 min at −50 °C in hexane was required for high yield (≥70%) of olefin **15a.** The vinyllithium reagent, prepared in this manner in hexane, upon treatment with bis(trimethyl phosphite)copper(I) iodide in ether at −78 °C and warmed to −15 °C, gave the cuprate reagent **21** (see the Experimental Section).

The success of this total synthesis of 19-OH-PGE_1 depends to a large part upon the selection of appropriate hydroxyl-protecting groups. In order to carry out the last steps, which convert the 13-*cis*-15β-hydroxyprostaglandins to 13-*trans*-15α-hydroxyprostaglandins efficiently, the 11α- and 19-hydroxyl groups require protection while the 15-hydroxyl group should be free. For these reasons, we chose the more acid labile *O*-methoxyisopropyl group for C-15, the less acid labile tetrahydropyranyl group for C-11, and the *tert*-butyldimethylsilyl group for C-19. Very mild acid hydrolysis would provide the 15-hydroxyl group and retain the ethers at C-11 and C-19, and, in addition, further selective cleavage of the silyloxy group at C-19 with fluoride ion at a later stage in the synthesis remained a possibility.

The tetrahydropyranyl-protected enone **23**[22] (1 equiv to 1.25 equiv of cuprate reagent) when added to the cuprate reagent **21** gave, after selective hydrolytic workup and careful column and high-pressure liquid chromatography, the 13-*cis*-15α-hydroxy compound **24** and the 13-*cis*-15β-hydroxy compound **25** in a 78% combined yield in a 17:83 (±1%) ratio and the 8β-15β-hydroxy epimer **26** in 6.6% yield.[23] The 8β epimers have not been observed by us previously when analogous conjugate additions using *cis*-divinyl cuprates have been carried out. However, in these previous cases 30% acetic acid was used to quench the reaction rather than ammonium sulfate which was used here. Another point of considerable interest is the degree of stereoselectivity observed during these *cis*-divinyl cuprate conjugate additons. In this report and in two other cases,[14] the ratios of 13-*cis*-15α-hydroxy to 13-*cis*-15β-hydroxy isomers vary from 17:83 to 2.5:97.5. These ratios reflect the more favorable transition state obtained between the (+) component of the (±)-cyclopentenone **23** and the (*R*)-*cis*-divinyl cuprate (such as **21**) than that obtained from the (−) component of the (±)-cyclopentenone **23** with the (*R*) cuprate, and thus the reaction leading to 13-*cis*-15β-OH-PGs proceeds considerably more rapidly than that which leads to 13-*cis*-15α-OH-PGs. Recently, Stork and Takahashi[24] have shown that (+)-cyclopentenone **23** reacts with a (±)-*cis*-divinyl cuprate (such as **21**) to give only a 13-*cis*-15β-OH-PG, stereospecifically. In their case there is none of the undesired enantiomer, (−)-cyclopentenone **23**, present to react with the excess divinyl cuprate after the (+) isomer has been depleted. For our purposes in this synthesis, however, the 15β-hydroxy isomer is used to convert the 13-cis-15β side chain to the 13-trans-15α of natural stereochemistry.

The remaining protecting groups of the prostaglandin analogues **24–26** were hydrolyzed with 65% aqueous acetic acid containing 10% tetrahydrofuran to give the 15α isomer **27** in 58% yield, the 15β isomer **28** in 90% yield, and the 8-epi-15β isomer **29** in 76% yield. Enzymatic hydrolysis with lipase, Type VII from *Candida cylindracea*, of 15β-hydroxy ester **28** gave 13-*cis*-15β-19α/β-OH-PGE_1 (**35**) in 60–90% yields. None of these 19α/β-hydroxyprostaglandin analogue pairs **27–29** and **35** showed any indication of separation with a variety of TLC and high-pressure LC systems.

The completion of this 19-OH-PGE_1 synthesis was carried out via the sulfenate–sulfoxide transformation without purification to the penultimate step. Treatment of the protected 15β isomer **25** with benzenesulfenyl chloride in the presence of triethylamine in ether gave the sulfoxide **30** which, when dissolved in methanol and treated with trimethyl phosphite at room temperature, afforded the 13-*trans*-15α isomer **31** which, in turn, was hydrolyzed with 65% aqueous acetic acid containing 10% tetrahydrofuran overnight to provide chromatographically pure *dl*-19α/β-OH-PGE_1 methyl ester **32** in an 82% overall yield for the three steps. This stereospecific transformation proceeds in remarkably high yield; approximately 94% per step. The mass spectrum (GC–MS) of the methyl oxime–trimethylsilyl ether derivative of **32** was essentially identical with that reported[3] for the corresponding derivative of natural 19-OH-PGE_1 methyl ester. Only slight differences of the relative intensities of the fragmentation peaks were noted. In addition, this mass spectrum was nearly the same as that reported[6] for the methyl oxime-trimethylsilyl ether derivative of natural 19-OH-PGE_2 trimethylsilyl ester after the subtraction of 56 mass units [−58, $Si(CH_3)_2$, +2, 2 H] for those fragmentation ions containing the upper chain. Finally, the methyl ester **32** was hydrolyzed enzymatically with lipase at pH 6.8 to give *dl*-19α/β-OH-PGE_1 in 95% yield, some of which was crystallized: mp 63–65 °C (subsequently, it was found that this solid is *one* of the C-19 epimers).

As in the 13-*cis*-19α/β-hydroxy cases, neither esters **32** nor acids **33/34** showed any indication of separation with several TLC and high-pressure LC systems. However, partial separation of the C-19 epimeric mixture was accomplished by using a preparative high-pressure LC system (Waters Associates, PrepLC/system 500) and collecting small fractions during the early and late parts of the elution curve, during cycles 3–5. Isomer I (less polar) of esters **32** of >80% purity[25] and isomer II of esters **32** of ca. 70% purity,[25] each containing the other, were obtained. Both of these esters **32**, isomers I and II, were hydrolyzed enzymatically using lipase at pH 6.8 to afford the acids **33/34**, isomers I and II, respectively. Purification by high-pressure LC provided *dl*-19-OH-PGE_1, isomer I, of 90% purity[25] (10% isomer II) and *dl*-19-OH-PGE_1, isomer II, of 80% purity[25] (20% isomer I).

These acids were crystallized to give isomer II, mp 62–64 °C, and isomer I, mp 89.5–91 °C. Mass spectra of the methyl oxime–trimethylsilyl ether–trimethylsilyl ester derivatives of **33/34**, isomer I, and **33/34**, isomer II, were identical with one another (both syn and anti isomer pairs) and nearly the same as that reported[6] for the corresponding derivative of naturally occurring 19-OH-PGE_2 after subtraction of 2 mass units from those fragmentation ions containing the upper chain. Thus, differentiation between the C-19 epimers could not be made.

This total synthesis provides *dl*-19-OH-PGE_1 in an approximately 10% overall yield from acetonitrile (prior to C-19 isomer separation). This same synthesis could be used to prepare optically active 19β-OH-PGE_1 (**1**) by using a (7*R*)-iodo-7-silyloxyoctene lower side-chain synthon.[26]

Experimental Section

Infrared (IR) spectra were recorded on a Perkin-Elmer 137 or a 237B grating spectrometer. Nuclear magnetic resonance (NMR) spectra were obtained with Varian A-60 and HA-100 instruments and with a Brucker WH-90 spectrometer in deuteriochloroform with Me_4Si as internal standard. Mass spectra were recorded on an Atlas CH 4 instrument and gas chromatographic mass spectra on a Varian CH 7 instrument coupled with a Hewlett-Packard HP F & M Scientific Model 402 gas chromatograph with a 1 m × 2 mm 3% SE-30 column at ca. 230 °C. Combustion analyses were performed by our microanalytical laboratory. Thin-layer chromatography (TLC) was carried out on Analtech (Uniplate) glass plates precoated with silica gel GF (250 μ).

5-Caprolactone (3). A mixture of α-methylcyclopentanone (58.8 g, 0.6 mol) and *m*-chloroperbenzoic acid (155.4 g, 0.9 mol) in 1.2 L of methylene chloride was stirred overnight at room temperature. The precipitate was collected by filtration (in vacuo), the filtrate was washed with 2 × 1 L of saturated $NaHCO_3$ solution and 2 × 500 mL of water, and the methylene chloride was removed with a rotary evaporator (in vacuo) to afford a yellow oil. Fractional distillation gave pure **3**: 50.6 g (74%); bp 100 °C (10 mm) [lit.[15] bp 107 °C (14 mm)]; IR (film) 1720 cm^{-1}; ^1H NMR δ 4.47 (m, 1 H), 2.49 (m, 2 H), 1.37 (d, 3 H, CH_3).

7-Hydroxyoct-1-yn-3-one (4) and 3-Hydroxyoct-1-yn-7-one (5). Methylmagnesium bromide (3 M) (Arapahoe Chemicals) in tetrahydrofuran–benzene was diluted with dry tetrahydrofuran to a 1 M solution. A stream of acetylene was flushed through 100 mL of the 1 M methylmagnesium bromide solution for 30 min, which resulted

in a dark red solution which, after transfer (N_2 atmosphere) to a dropping funnel, was added to 5-caprolactone (11.4 g, 0.1 mol) in 20 mL of tetrahydrofuran at 0 °C. The ice bath was removed and after stirring overnight at room temperature, 12 mL of a saturated solution of ammonium chloride was added slowly. A precipitate that formed was removed by vacuum filtration, layers were separated, the organic layer was dried over magnesium sulfate, and the solvents were removed with a rotary evaporator (in vacuo) to give a reddish brown oil (13.3 g). This residue was chromatographed on 150 g of silica gel, eluting with ethyl acetate-hexane (2:1, v/v), to give **4** and **5**; oil; 4.42 g (31%); IR (film) 3350, 3250, 2090, 1710, 1680 cm^{-1}; ^1H NMR δ 3.40-4.50 (complex m), (ca. 67%) 3.26 (s, $COC{\equiv}CH$), (ca. 33%) 2.15 (s, $COCH_3$), 1.20 (d, J = 6 Hz, CH_3), and signals assigned to cyclic hemiketal in equilibrium; GC-MS (70 eV) *m/e* (rel intensity) 125 (2) ($M^+ - CH_3$), 68 (100).

3-*tert*-Butyldimethylsilyloxyoct-1-yn-7-one (9) and 7-*tert*-Butyldimethylsilyloxyoct-1-yn-3-one (8). To a mixture of 7-hydroxyoct-1-yn-3-one (**4**), 3-hydroxyoct-1-yn-7-one (**5**) (2.89 g, 0.02 mol), and imidazole (1.4 g, 0.02 mol) in 40 mL of dry dimethylformamide (DMF), cooled to 0 °C, was added *tert*-butyldimethylchlorosilane (3.1 g, 0.02 mol), and the mixture was stirred for 3 h. Water (80 mL) and hexane (80 mL) were added; the organic layer was separated and combined with 2 × 80 mL of hexane extractions of the aqueous layer. The solvent was removed (in vacuo), after drying over sodium sulfate, to give a crude residue (4.3 g) which was chromatographed on silica gel (80 g), eluting with ethyl acetate-hexane (2:1, v/v) to afford **8** and **9**; oil; 4.0 g (76%); IR (film) 2100, 1720, 1690, 1250, 1090, 780 cm^{-1}; ^1H NMR δ 3.23 (s, $COC{\equiv}CH$), 2.42 (d, J = 2 Hz, $C{\equiv}CH$), 2.14 (s, $COCH_3$), 1.15 (d, J = 6 Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 208.6 (C-7), 85.3 (C-2), 72.4 (C-1), 62.6 (C-3), 43.3 (C-6), 37.8 (C-4), 29.7 (C-8), 19.5 (C-5), and low-intensity signals assigned to **10**.

3-*tert*-Butyldimethylsilyloxy-7-hydroxyoct-1-yne (12) and 3-Hydroxy-7-*tert*-butyldimethylsilyloxyoct-1-yne (11). To a mixture of 3-*tert*-butyldimethylsilyloxyoct-1-yn-7-one (**9**) and 7-*tert*-butyldimethylsilyloxyoct-1-yn-3-one (**8**) (4.0 g, 0.015 mol) dissolved in 500 mL of ethanol was added 4 × 300 mg of sodium borohydride, in portions, during a 20-h period at room temperature (followed by TLC). Any excess borohydride was destroyed by the addition of acetic acid (0.5 mL), and the solution was concentrated, treated with water (100 mL), and extracted with diethyl ether (3 × 100 mL). The ether solution, after drying over magnesium sulfate, was concentrated (in vacuo) to give an oil which was chromatographed on 400 g of silica gel, eluting with hexane-ethyl acetate (3:1, v/v). Pure **11**: oil; 1.1 g (27%); IR (film) 3400, 2100 (w), 1245, 780 cm^{-1}; ^1H NMR δ 4.40 (m, CHOH), 3.85 (m, CHOSi), 2.45 (d, J = 2 Hz, $C{\equiv}CH$), 1.60 (m, CH_2's), 1.13 (d, J = 6 Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 85.1 (C-2), 72.9 (C-1), 68.5 (C-7), 62.3 (C-3), 39.3 (C-4 or -6), 37.7 (C-6 or -4), 23.8 (C-8), 21.3 (C-5); GC-MS (70 eV) *m/e* (rel intensity) 199 (1) ($M^+ - C_4H_7$), 75 (100). Pure **12**: oil; 1.6 g (40%); IR (film) 3400, 2100 (w), 1255, 780 cm^{-1}; ^1H NMR δ 4.40 (m, CHOH), 3.85 (m, CHOSi), 2.42 (d, J = 2 Hz, $C{\equiv}CH$), 1.55 (m, CH_2's), 1.17 (d, J = 8 Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 85.6 (C-2), 72.2 (C-1), 67.9 (C-7), 62.7 (C-3), 38.9 (C-4 or -6), 38.5 (C-6 or -4), 23.4 (C-8), 21.3 (C-5); GC-MS (70 eV) *m/e* (rel intensity) 199 (1) ($M^+ - C_4H_7$), 75 (100). Anal. ($C_{14}H_{28}O_2Si$) C, H.

1-Cyano-4-pentanone (16). To sodium methoxide (9.5 g, 0.175 mol) in 400 mL of methanol (degassed with nitrogen), acrylonitrile (106 g, 2 mol) and 2,4-pentanedione (200 g, 2 mol) were added. The solution was refluxed for 4 h under a nitrogen atmosphere and stirred overnight at room temperature. Glacial acetic acid (20 mL) was added slowly, the solvent and unreacted acrylonitrile were removed on a rotary evaporator (in vacuo), and the residue was fractionally distilled to give **16** (147 g, 66%): bp 88 °C (0.8 mm); n^{25}_D 1.4303 [lit.[27] bp 64 °C (0.1 mm); n^{25}_D 1.4285]; IR (film) 2260, 1715, 1160 cm^{-1}; ^1H NMR δ 1.95 (m, 2), 2.15 (s, 3), 2.43 (dd, 2), 2.67 (dd, 2); MS (70 eV) *m/e* 111 (M^+). Anal. (C_6H_9NO) C, H, N.[28]

(±)-1-Cyano-4-*tert*-butyldimethylsilyloxypentane (18). 1-Cyano-4-pentanone (**16**) (55.5 g, 0.5 mol), dissolved in 100 mL of methanol, was treated with sodium borohydride (5.7 g, 0.15 mol) while stirring at 0 °C. After approximately 20 min, 90 mL of 2.5 N hydrochloric acid was added. The mixture was extracted with ether (3 × 100 mL), the extracts were washed with brine and dried over magnesium sulfate, and the solvent was removed on a rotary evaporator (in vacuo) to give **17**; an oil (46.2 g, 82%); IR (film) 3400, 2260, 1130, 1090 cm^{-1}. A purified sample was obtained by distillation: n^{25}_D 1.4385 [lit.[29] bp 106-108 °C (5 mm); n^{20}_D 1.4420]. Anal. ($C_6H_{11}NO$) C, H, N.[28] The crude material was dissolved in 100 mL of DMF and, at 0 °C, imidazole (33.5 g, 0.49 mol) and *tert*-butyldimethylchlorosilane (65 g, 0.43 mol) were added. After stirring for 4 h at room temperature, 100 mL of water was added and the mixture was extracted with hexane (200 mL, 3 × 100 mL), the combined organic layers were dried over magnesium sulfate, and the solvent was removed on a rotary evaporator (in vacuo) to give **18** (78.3 g, 84%). This material need not be purified further. Fractional distillation gave pure **18** (48.8 g, 53%): bp 92 °C (0.5 mm); IR (film) 2250, 1250, 1135, 1090, 1020, 835, 810, 775 cm^{-1}; ^1H NMR δ 3.85 (m, 1), 2.38 (m, 2), 1.63 (m, 4), 1.17 (d, J = 6 Hz), 0.89 (s, 9), 0.05 (s, 6); MS *m/e* 170.0994 ($M^+ - C_4H_9$; calcd for $C_8H_{16}NOSi$, 170.1001).

(±)-5-*tert*-Butyldimethylsilyloxyhexanal (19). (±)-1-Cyano-4-*tert*-butyldimethylsilyloxypentane (**18**) (47.2 g, 0.29 mol) was dissolved in 200 mL of dry toluene in a 2-L three-necked flask fitted with a gas inlet tube (nitrogen), thermometer, dropping funnel, and a mechanical stirrer. Slowly 460 mL (0.4 mol) of a 20% hexane solution of diisobutylaluminum hydride was added at −10 °C during 1 h. Stirring was continued for 1.5 h and then the reaction was quenched by the slow addition of 25 mL (0.6 mol) of methanol. This was followed by the very slow addition of a solution of 10% aqueous acetic acid (total 700 mL, 1.2 mol). The exothermic reaction was stirred vigorously and cooled with ice so that the temperature did not exceed 20 °C. The addition required 2 h and stirring was continued for an additional 3 h in order to disperse the resulting emulsion. The organic layer was decanted and washed with brine. The aqueous layer was extracted with toluene (2 × 200 mL), the combined organic fractions were dried over magnesium sulfate, and the solvent was removed on a rotary evaporator (in vacuo). The oily residue was fractionally distilled to give pure **19** (21.4 g, 45%): bp 78 °C (1.0 mm); IR (film) 2700, 1725, 1245, 1135, 1060, 1000, 835, 775 cm^{-1}; ^1H NMR δ 9.72 (t, J = 1.5 Hz, 1), 3.80 (m, 1), 2.40 (m, 2), 1.53 (m, 4), 1.10 (d, J = 6 Hz, 3), 0.85 (s, 9), 0.01 (s, 6).

(±)-3-Hydroxy-7-*tert*-butyldimethylsilyloxyoct-1-yne (11). In a 500-mL three-necked flask, fitted with two gas inlets, thermometer, and a rubber serum cap, was placed 140 mL of tetrahydrofuran (distilled from lithium aluminum hydride). A stream of acetylene, which was dried and purified by passing through a dry ice trap, a sulfuric acid trap, and a Drierite ($CaSO_4$) tube, was bubbled through the well-stirred THF solution at 0 °C for 1.5 h. The saturated solution was cooled to −78 °C and the flask was flushed with argon for 5 min. *n*-Butyllithium in hexane (82 mL, 1.6 M) was added slowly. No precipitate of the acetylene dilithium salt was observed. After 5 min, (±)-5-*tert*-butyldimethylsilyloxyhexanal (**19**) (9.47 g, 41 mol), dissolved in 15 mL of THF, was added in one portion. Stirring was continued for 30 min and then the temperature was raised to −10 °C. The reaction was quenched with 140 mL of saturated potassium dihydrogen phosphate solution. The organic layer was separated and the aqueous layer was extracted with ether (2 × 200 mL). The combined extracts were dried over potassium carbonate and the solvents removed on a rotary evaporator (in vacuo) to give crude **11** (12.0 g). Pure liquid **11**: IR (film) 3400, 2100 (w), 1245, 1130, 1040, 835, 780 cm^{-1}; ^1H NMR δ 4.40 (m, 1), 3.85 (m, 1), 2.45 (d, J = 2 Hz, 1), 1.12 (d, J = 6 Hz, 3); GC-MS (Me_3Si derivative) (70 eV) *m/e* (rel intensity) 313 (<1) ($M^+ - CH_3$), 271 (3) ($M^+ - C_4H_9$), 201 (8), 159 (16), 147 (100), 127 (15); MS *m/e* 199.1152 ($M^+ - C_4H_9$; calcd for $C_{10}H_{17}OSi$, 199.1154).

(±)-1-Iodo-3-hydroxy-7-*tert*-butyldimethylsilyloxyoct-1-yne (13). Iodine (16.1 g, 63 mmol) was dissolved in 200 mL of freshly distilled benzene at 45 °C and 17 mL of freshly distilled morpholine in 20 mL of benzene was added slowly to the well-stirred solution. The dark orange iodo-morpholino complex formed rapidly and after 10 min the crude acetylenecarbinol **11** (12.0 g, see above) was added and stirring continued at 45 °C for 24 h. After cooling, the hydriodide salt was removed by filtration (in vacuo) and washed with ether (3 × 25 mL). The combined filtrate and washes were washed with brine, with 10% sodium hydrogen phosphate, with 10% sodium thiosulfate, and with 5% sodium bicarbonate. The organic solution was dried over magnesium sulfate and the solvents were removed on a rotary evaporator (in vacuo) to give nearly pure **13** (18.9 g). Pure **13** is an oil: IR (film) 3300, 2170, 1245, 1130, 1090, 1020, 835, 805, 775 cm^{-1}; ^1H NMR δ 4.50 (m, 1), 3.82 (m, 1), 1.10 (d, J = 6 Hz, 3), 0.87 (s, 9), 0.01 (s, 6); ^{13}C NMR ($CDCl_3$) δ −4.65 and −4.36 [$Si(CH_3)_2$], 1.46 (C-1), 18.17 (SiC), 21.23 and 21.39 (C-5), 23.83 (C-8), 25.96 [$C(CH_3)_3$], 37.81 and 37.91 (C-6), 39.21 (C-4), 64.08 and 64.14 (C-3), 68.46 (C-7), 95.74 (C-2); GC-MS (Me_3Si derivative) (70 eV) *m/e* (rel

intensity) 397 (7) ($M^+ - C_4H_9$), 327 (10) ($M^+ - 1$), 307 (8), 253 (21), 159 (25), 147 (100); MS *m/e* 325.0122 ($M^+ - C_4H_9$; calcd for $C_{10}H_{18}O_2ISi$, 325.0123).

(±)-1-Iodo-3-hydroxy-7-*tert*-butyldimethylsilyloxyoct-1-*cis*-ene (14). The crude iodoacetylene (18.9 g, see above) was dissolved in 70 mL of methanol and 24.5 mL of pyridine and 12.0 g (62 mmol) dipotassium azodicarboxylate were added. Glacial acetic acid (7.5 mL) was added slowly (2 h, room temperature) and stirring continued overnight. An additional 18 g of dipotassium azodicarboxylate and 10.3 mL of glacial acetic acid were added (8 h). When no starting material could be detected by GLC (5 ft, SE-30) analysis of aliquots, 200 mL of ether was was added. Any remaining diimide precursor was destroyed by carefully adding 100 mL of 5% hydrochloric acid with vigorous stirring. The organic layer was separated and the aqueous layer was extracted with ether (2 × 100 mL). The combined organic layers were washed with 5% hydrochloric acid and with 5% sodium bicarbonate and dried over magnesium sulfate, and the solvents were removed on a rotary evaporator (in vacuo) to give an oil which was dissolved in 50 mL of ether and stirred with 12 mL of 40% aqueous dimethylamine to remove a small amount (ca. 5%) of overreduced material. The ether solution was washed with 5% hydrochloric acid (2 × 50 mL) and 5% sodium bicarbonate (50 mL) and dried over magnesium sulfate, and the ether was removed (in vacuo) to give crude iodo olefin **14** (15.63 g). Chromatography on silica gel (1.5 kg) with acetone–hexane (1:19, v/v) gave pure **14** (12.9 g, 82% for three steps, **19** → **11** → **13** → **14**) as an oil: IR (film) 3300, 1245, 1090, 1045, 835, 805, 775 cm^{-1}; ^1H NMR δ 6.24 (m, HC≡CH, 2), 4.41 (m, 1), 3.82 (m, 1), 1.09 (d, *J* = 6 Hz, 3), 0.85 (s, 9), 0.02 (s, 6); ^{13}C NMR ($CDCl_3$) δ −4.62 and −4.32 [$Si(CH_3)_2$], 18.17 (SiC), 21.20 and 21.30 (C-5), 23.80 and 23.90 (C-8), 25.98 [$C(CH_3)_3$], 36.05 (C-4), 39.56 (C-6), 68.56 (C-7), 74.45 (C-3), 82.28 (C-1), 143.56 (C-2); GC–MS (70 eV) *m/e* (rel intensity) 327 (9) ($M^+ - C_4H_9$), 235 (22), 193 (46), 108 (80). Anal. ($C_{14}H_{29}O_2ISi$) C, H.

1,4 Conjugate Addition of Cuprate 21 to Enone 23. (±)-2-(6-Carbomethoxyhexyl)-4-hydroxycyclopent-2-en-1-one (**22**) (2.59 g, 10.8 mmol) dissolved in 5 mL of methylene chloride was treated with distilled dihydropyran (1.2 mL, 13 mmol) and a catalytic amount (<1 mg) of *p*-toluenesulfonic acid at 0 °C (nitrogen atmosphere). After 15 min, analysis by TLC showed complete conversion. The solution was washed with 5% sodium bicarbonate and dried over magnesium sulfate, and the solvent was removed (in vacuo) to give a residue which was chromatographed on 300 g of silica gel, eluting with ethyl acetate–hexane (1:2, v/v). Pure **23** (2.75 g, 79%) was obtained. (±)-1-Iodo-3-hydroxy-7-*tert*-butyldimethylsilyloxyoct-1-*cis*-ene (**14**) (6.36 g, 16.5 mmol) was dissolved in 9 mL of 2-methoxyisopropene[30] and treated with a trace amount (<25 μg) of phosphorus oxychloride. The exothermic reaction was cooled with an ice bath and after 5 min (checked by TLC) 6 drops of triethylamine was added and the solvent removed (in vacuo) to give **20**, which was used without further purification. This protected compound was dissolved in 100 mL of dry hexane and transferred to a 500-mL three-necked flask, fitted with gas inlet, thermometer, 125-mL dropping funnel, a rubber serum cap, and magnetic stirring bar. The solution was cooled to −50 °C (argon atmosphere) and treated with 11 mL of 1.6 M *n*-butyllithium in hexane. Stirring was continued for 80 min at this temperature and, then, the reaction mixture was cooled to −78 °C. A solution of bis(trimethyl phosphite)copper(I) iodide (4.0 g, 9.1 mmol) in 80 mL of anhydrous ether was added slowly over a period of 20 min. Stirring was continued for an additional 40 min and then the reaction mixture was allowed to warm to −15 °C for 25 min, at which time an aliquot gave a negative Gilman test. After recooling to −78 °C, an etheral solution (20 mL) of protected enone **23** (2.14 g, 6.6 mmol) was added at once to the vigorously stirred cuprate solution. After 15 min the temperature was raised slowly to −10 °C and 80 mL of 20% ammonium sulfate was added. The organic layer was separated and washed five times with an ammonia–ammonium sulfate buffer solution (pH ~10.5) to remove copper salts. The organic layer was washed with brine and dried over magnesium sulfate, and the solvents were removed on a rotary evaporator (in vacuo). The oily residue was treated with 30 mL of a 1:1:1 mixture of 30% aqueous acetic acid, THF, and ether and stirred for 4 h (room temperature) to selectively cleave the methoxy isopropyl ether at C-15. An equal volume of ethyl acetate was added; the organic layer was separated, washed with 5% sodium bicarbonate, and dried over magnesium sulfate. Removal of the solvents on a rotary evaporator (in vacuo) gave an oily reaction mixture (6.87 g) which was chromatographed on 650 g of silica gel, eluting with a gradient of ethyl acetate–hexane (1:4 → 1:2, v/v). Based on analysis by TLC, appropriate fractions were combined to give five major fractions, designated fraction I (2.08 g, 54%), (±)-3-hydroxy-7-*tert*-butyldimethylsilyloxyoct-1-ene (**15**) [IR (film) 3350, 1625, 1240, 1125, 1035, 1000, 985, 835, 805, 770 cm^{-1}; ^1H NMR δ 5.95 (vinyl H, 1), 5.5–5.0 (vinyl H's, 2), 4.1 (br m, 1), 3.8 (br m, 1), 1.13 (d, *J* = 6 Hz, 3), 0.90 (s, 9), 0.05 (s, 6); GC–MS (70 eV) *m/e* (rel intensity) 201 (2) ($M^+ - C_4H_9$), 159 (15), 109 (55), 67 (100)]; fraction II (0.47 g); fraction III (1.23 g); fraction IV (1.63 g); and fraction V (0.24 g).

Fractions II–V were mixtures and were rechromatographed by column chromatography and further purified by high-pressure LC (using ethyl acetate–hexane mixtures). Certain pure 11-OTHP diastereomers were isolated separately. By TLC and high-pressure LC analyses, appropriate combinations were made to give the following results (for yields, diastereomeric pairs taken together, physical data are given for a single separated diastereomer).

Fraction II′ (518 mg, 13.5%), methyl (±)-9-oxo-11-tetrahydropyranyloxy-15α-hydroxy-19α/β-*tert*-butyldimethylsilyloxyprost-13-*cis*-enoate (**24**): IR (film) 3350, 1730, 1240, 1125, 1030, 835, 775 cm^{-1}; ^1H NMR (isomer B) δ 5.68 (dd, *J* = 12 Hz, 1), 5.32 (dd, *J* = 12, 9 Hz, 1), 4.67 (m, 1), 4.44 (m, 1), 4.11 (m, 1), 3.9 (m, 1), 3.63 (s, 3), 1.17 (d, *J* = 6 Hz, 3), 0.87 (s, 9); MS (70 eV) *m/e* (rel intensity) 481 (<1) (M^+ − OTHP), 480 (<1) (M^+ − HOTHP), 423 (47) (M^+ − HOTHP − C_4H_9), 405 (21), 55 (100).

Fraction III′ (2.46 g, 64.5%), methyl (±)-9-oxo-11α-tetrahydropyranyloxy-15β-hydroxy-19α/β-*tert*-butyldimethylsilyloxyprost-13-*cis*-enoate (**25**): IR (film) 3350, 1730, 1250, 1130, 1025, 970, 835, 775 cm^{-1}; ^1H NMR (isomer A) δ 5.77 (dd, *J* = 11, 8 Hz, 1), 5.41 (dd, *J* = 11, 10 Hz, 1), 4.67 (m, 1), 4.33 (m, 1), 3.79 (m, 1), 3.76 (m, 1), 3.62 (s, 3), 1.09 (d, *J* = 6 Hz), 0.87 (s, 9); MS (70 eV) *m/e* (rel intensity) 480 (<1) (M^+ − HOTHP − C_4H_9), 405 (2), 84 (100).

Fraction IV′ (253 mg, 6.2%), methyl (±)-8-*epi*-9-oxo-11α-tetrahydropyranyloxy-15β-hydroxy-19α/β-*tert*-butyldimethylsilyloxyprost-13-*cis*-enoate (**26**): IR (film) 3350, 1730, 1245, 1130, 1020, 835, 775 cm^{-1}; ^1H NMR δ 5.60 (dd, *J* = 10, 8 Hz, 1), 5.17 (dd, *J* = 10, 10 Hz, 1), 4.62 and 4.80 (m's, THPO isomers), 4.39 (m, 1), 4.14 (m, 1), 3.79 (m, 1), 1.10 (d, *J* = 6 Hz, 3), 0.86 (s, 9); MS (70 eV) *m/e* (rel intensity) 480 (<1) (M^+ − HOTHP − C_4H_9), 405 (3), 85 (75), 84 (74).

Methyl (±)-9-Oxo-11α,15β,19α/β-trihydroxyprost-13-*cis*-enoate (28). The protected 13-*cis*-19-OH-PGE_1 **25** (921 mg, 1.58 mmol) was hydrolyzed overnight at room temperature (20 h) in 6 mL of 65% aqueous acetic acid containing 10% THF. The reaction mixture was poured over ice and 5% sodium bicarbonate, extracted with ethyl acetate, and dried over sodium sulfate. Removal of solvent (in vacuo) gave crude **28** (807 mg) which was chromatographed on 80 g of silica gel, eluting with ethyl acetate–methanol (19:1), v/v) to give pure **28** (549 mg, 90%) as an oil: IR ($CHCl_3$) 3300, 1730, 1150, 1100, 1065 cm^{-1}; ^1H NMR δ 5.70 (dd, *J* = 10.5, 8 Hz, 1), 5.41 (dd, *J* = 10.5, 8.5 Hz, 1), 4.35 (m, 1), 3.92 (m, 1), 3.75 (m, 1), 3.61 (s, 3), 2.6–2.9 (br m, 3), 2.1–2.4 (br m, 3), 1.15 (d, *J* = 6 Hz, 3) (see Table I[31]); MS (70 eV) *m/e* (rel intensity) 366 (1) ($M^+ - H_2O$), 247 (8), 167 (100). Anal. ($C_{21}H_{36}O_6$) C, H.

Methyl (±)-9-Oxo-11α,15α,19α/β-trihydroxyprost-13-*cis*-enoate (27). Following the same procedure that was used to convert **25** to **28**, **24** (136 mg, 0.23 mmol) gave pure **27** (52 mg, 58%) as an oil: IR ($CHCl_3$) 3350, 1735, 1115, 1070, 1000 cm^1; ^1H NMR δ 5.65 (dd, *J* = 10, 8 Hz, 1), 5.33 (dd, *J* = 10, 10 Hz), 4.41 (m, 1), 3.99 (m, 1), 3.77 (m, 1), 3.61 (s, 3), 2.5–3.0 (br m, 3), 2.1–2.4 (br m, 3), 1.16 (d, *J* = 6 Hz, 3);[31] MS (70 eV) *m/e* (rel intensity) 367 (3) (M^+ − OH), 366 (2) ($M^+ - H_2O$), 348 (11) ($M^+ - 2H_2O$), 297 (13), 279 (40), 247 (58), 167 (60), 55 (100); MS *m/e* 348.2302 ($M^+ - 2H_2O$; calcd for $C_{21}H_{32}O_4$, 348.2300).

Methyl (±)-8-*epi*-9-Oxo-11α,15β,19α/β-trihydroxyprost-13-*cis*-enoate (29). Following the same procedure that was used to convert **25** to **28**, **26** (112 mg, 0.19 mmol) gave pure **29** (55 mg, 75%) as an oil: IR ($CHCl_3$) 3350, 1735, 1160, 1110, 1070, 1000 cm^{-1}; ^1H NMR δ 5.58 (dd, *J* = 10.5, 8 Hz, 1), 5.19 (dd, *J* = 10.5, 10.5 Hz, 1), 4.40 (m, 1), 4.19 (m, 1), 3.75 (m, 1), 3.62 (s, 3), 3.26 (m, 1), 2.1–2.7 (br m, 5), 1.17 (d, *J* = 6 Hz, 3);[31] MS (70 eV) *m/e* (rel intensity) 366 (2) ($M^+ - H_2O$), 348 (10) ($M^+ - 2H_2O$), 247 (28), 167 (100). Anal. ($C_{21}H_{36}O_6$) C, H.

Methyl (±)-9-Oxo-11α-tetrahydropyanyloxy-13α-phenylsulfinyl-19α/β-*tert*-butyldimethylsilyloxyprost-14-*trans*-enoate (30). The protected 13-*cis*-19-OH-PGE_1 **25** (989 mg, 1.7 mmol) was dissolved

Table I. ^{13}C NMR (δ, $CDCl_3$) of 19-OH-PGE_1 Methyl Esters

carbon no.	27	28[a]	29	32	32 (I)	32 (II)	33/34 (I)[b]	33/34 (II)[b]
1	174.74	174.54	174.67	174.58	174.57	174.58	175.55	175.52
2	34.04	34.04	34.07	34.04	34.04	34.07	34.00	34.00
3	24.67	24.87	24.87	24.84	24.84	24.87	25.00	25.03
4	29.19	29.45	29.26	29.36	29.36	29.36	29.52	29.52
5	28.71	28.93	28.97	28.87	28.87	28.90	29.00	29.03
6	26.40	26.69	25.55	26.63	26.59	26.63	26.79	26.79
7	27.80	27.99	27.54	27.76	27.76	27.80	27.99	28.02
8	55.56	53.48	50.78	54.97	54.84	54.94	54.87	54.91
9	215.11	214.92	218.01	215.11	214.98	214.92	215.47	215.47
10	46.72	46.59	45.09	45.97	45.97	46.00	46.39	46.39
11	72.27							
	72.20	71.10	72.24	71.81	71.94	71.94	72.04	72.04
12	49.77	49.71	46.98	54.45	54.52	54.55	54.45	54.49
13	131.70							
	131.50	133.71	128.96	132.28	131.89	131.92	131.66	131.66
14	136.54							
	136.41	136.57	136.15	136.70	136.70	136.83	137.03	137.09
15	68.76	66.90 (I)	67.00	72.76 (I)	72.69		72.69	
	68.53	66.74 (II)	66.77	72.40 (II)		72.33		72.69
16	37.58	36.87 (I)	37.22	36.96 (I)	37.03		37.35	
		36.64 (II)	36.96	36.70 (II)		36.83		37.29
17	21.55	21.59 (II)		21.36 (II)		21.39		21.85
	21.33	21.49 (I)	21.52	21.26 (I)	21.26		21.78	
18	38.65	38.95 (I)	38.82	38.69 (I)	38.75		39.27	
		38.75 (II)	38.59	38.30 (II)		38.43		39.17
19	68.20	67.85 (I)	67.81	67.85 (I)	67.98		67.62	
	67.98	67.62 (II)	67.52	67.62 (II)		67.81		67.62
20	23.76	23.67 (II)	23.63	23.80 (II)		23.86		23.60
	23.60	23.57 (I)	23.57	23.60 (I)	23.67		23.54	
OCH_3	51.59	51.59	51.62	51.56	51.56	51.56		

[a] Isomers were partially separated; 60:40 and 40:60 mixtures of **28** (I) and **28** (II). [b] $CDCl_3$-CD_3COCD_3, acid.

in anhydrous ether and treated at 0 °C while stirring with triethylamine (9.94 mL, 6.8 mmol), followed immediately by the addition of benzenesulfenyl chloride (0.25 mL, 2.6 mmol). Stirring was continued at room temperature for 40 min and then the triethylamine hydrochloride was removed by suction filtration through a Celite pad. The solvents were removed on a rotary evaporator (in vacuo) to give the crude sulfoxide **30**. No further purification need be done. An analytical sample, from a separate preparation, was obtained by column chromatography, eluting with ethyl acetate–benzene (1:2, v/v), as an oil: IR (film) 1735, 1575, 1250, 1130, 1075, 1035, 975, 835, 775, 745, 685 cm^{-1}; ^1H NMR δ 7.2–7.6 (m, 5), 5.56 (m, 1), 5.05 (m, 1), 4.70 and 4.81 (m's, THPO isomers, 1), 4.08 (m, 1), 3.61 (s, 3), 1.05 and 1.06 (2 d's, J = 6 Hz, 3), 0.85 (s, 9); MS (70 eV) *m/e* (rel intensity) 480 (<1) ($M^+ - C_5H_8O - H_2O - C_6H_5SH$), 462 (1), 423 (2), 405 (2), 218 (57), 218 (57), 125 (95), 110 (85), 109 (100), 77 (80).

Methyl (±)-9-Oxo-11α-tetrahydropyranyloxy-15α-hydroxy-19α/β-*tert*-butyldimethylsilyloxyprost-13-*trans*-enoate (31). The crude sulfoxide **30** (see above) was stirred 30 min at room temperature in a mixture of 10 mL of methanol and 1 mL (8.5 mmol) of trimethyl phosphite. The mixture was transferred with ethyl acetate, washed twice with brine, and dried over magnesium sulfate. The solvents were removed on a rotary evaporator (in vacuo) to give an oil, **31** (1.465 g), which was used directly in the next step. An analytical sample from a separate preparation, obtained from chromatography on silica gel, gave pure **31** as an oil: IR (film) 3550, 1735, 1240, 1120, 1025, 970, 835, 775 cm^{-1}; ^1H NMR δ 5.64 (m, 2), 4.68 (m, 1), 4.07 (m, 1), 3.96 (m, 1), 3.77 (m, 1), 3.60 (s, 3), 1.08 (dd, J = 6 Hz, 3), 0.85 (s, 9); MS (70 eV) *m/e* (rel intensity) 480 (1) ($M^+ - C_5H_{10}O_2$), 462 (15) ($M^+ - C_5H_{10}O_2 - H_2O$), 423 (30) ($M^+ - C_5H_{10}O_2 - C_4H_9$), 405 (63), 373 (15), 330 (27); MS *m/e* 462.3156 ($M^+ - C_5H_{10}O_2 - H_2O$; calcd for $C_{27}H_{46}O_4Si$, 462.3165).

Methyl (±)-9-Oxo-11α,15α,19α/β-trihydroxyprost-13-*trans*-enoate (32). Following the same procedure that was used to convert **25** to **28**, **31** (1.465 g, see above) gave a crude oily residue (1.25 g) which was chromatographed on silica gel (120 g), eluting with ethyl acetate–methanol (19:1, v/v), to give pure **32** (537 mg, 82% for three steps, **25** → **30** → **31** → **32**) as an oil: IR ($CHCl_3$) 3300, 1735, 1150, 1070, 1010, 970 cm^{-1}; ^1H NMR δ 5.58 (m, 2), 4.09 (m, 1), 3.98 (m, 1), 3.78 (m, 1), 3.62 (s, 3), 2.69 (dd, J = 19, 7 Hz, 2), 2.0–2.35 (m, 3), 1.17 (d, J = 6 Hz, 3);[31] GC–MS (methyl oxime and Me_3Si derivative, syn and anti isomers) (70 eV) *m/e* (rel intensity) 629 (<1) (M^+), 614 (2), 598 (8), 508 (9), 470 (38), 380 (32) and 598 (3) ($M^+ - OCH_3$), 508 (3), 470 (4), 366 (45), 297 (93). Anal. ($C_{21}H_{36}O_6$) C, H.

(±)-9-Oxo-11α,15α,19α/β-trihydroxyprost-13-*trans*-enoic Acid (33/34). 19-OH-PGE_1 methyl ester **32** (189 mg, 0.49 mmol) was treated with 20 mL of a pH 6.8 buffer solution (sodium dihydrogen phosphate–potassium dihydrogen phosphate) and sonicated for 5 min to disperse the ester. The emulsion was stirred for 40 min at room temperature after the addition of 1.9 g of Sigma Lipase, Type VII from *Candida cylindracea*. The reaction mixture was transferred to a separatory funnel with ethyl acetate (25 mL) and acidified to pH 3.5–4.5 with hydrochloric acid. The organic layer was separated and dried over sodium sulfate and the solvent removed on a rotary evaporator (in vacuo) to give 19-OH-PGE_1 **33/34** (173 mg, 95%). Crystallization from ethyl acetate–acetone gave a crystalline solid: mp 63–65 °C; IR (KBr) 3400 (br), 2920, 2845, 1735, 1700 (sh) cm^{-1}; ^1H NMR (CD_3OD) δ 5.56 (m, 2), 4.01 (m, 1), 3.65 (m, 1), 2.63 (dd, J = 18, 7.5 Hz), 1.9–2.4 (m, 3), 1.12 (d, J = 6 Hz, 3); MS (70 eV) *m/e* (rel intensity) 352 (5) ($M^+ - H_2O$), 334 (13) ($M^+ - 2H_2O$), 316 (8) ($M^+ - 3H_2O$), 283 (3), 265 (22), 247 (78).

Separation of *dl*-19α/β-Hydroxyprostaglandin E_1 Methyl Esters 32. The C-19 epimers **32** were partially separated by preparative high-pressure LC. Using a Waters Associates, Prep LC/system 500 chromatography, **32** (324 mg) in ethyl acetate–methanol (19:1, v/v) was injected onto the column and after removal of a forerun and four cycles of the main peak, small cuts were made during the early parts of the elution curves of the fifth, sixth, and seventh cycles which gave 33, 63, and 28 mg of ester **32**, respectively. The remaining material was recovered from nine approximately equal cuts of the eighth cycle (200 mg). The 33 mg from the fifth cycle was shown to be **32**, isomer I (>80%, by ^{13}C NMR[25]), and one of the nine cuts (the third, chosen arbitrarily) of the eighth cycle (39 mg) was shown by ^{13}C NMR to be a mixture of **32**, isomers I and II (ca. 40/60). In a second separation, **32** (313 mg) in ethyl acetate–ethanol (90:10, v/v) was injected onto the column, the main broad peak was cycled twice, and small front and rear cuts of the elution curves were made during the third,

fourth, and fifth cycles to provide **32**, isomers I and II (33.4 mg, >85:<15 by ^{13}C NMR[25]), and **32**, isomers I and II (61.7 mg, 25:75 by ^{13}C NMR[25]). An 80% recovery of total material was realized.

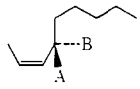
Enzymatic Hydrolyses of 19-Hydroxyprostaglandin E_1 Methyl Esters 28 and 32 (Isomers I and II). Each methyl ester (**28** and **32**, isomers I and II) was hydrolyzed with lipase according to the procedure for **32** to **33/34**. **28** (100 mg, using a pH 7.0 phosphate buffer) gave *dl*-13-*cis*-15-*epi*-19α/β-OH-PGE$_1$ (**35**) (86 mg, 87%) as an oil (hygroscopic): IR ($CHCl_3$) 3300, 1735, 1710, 1070, 1010 cm^{-1}; ^1H NMR δ 5.72 (dd, J = 10.5, 8 Hz, 1), 5.42 (dd, J = 10.5, 8.5 Hz, 1), 4.22 (m, 1), 3.96 (m, 1), 3.68 (m, 1), 1.17 (d, J = 6 Hz, 3). Anal. ($C_{20}H_{34}O_6 \cdot H_2O$) C, H. The ester **32** (isomer I) (58.5 mg, an isomer I:II, >85:<15 sample combined from selected fractions from the two separations, see above) gave *dl*-19-OH-PGE$_1$ (**33/34**, isomer I) (57.2 mg, >98% crude yield) which was purified by high-pressure LC to give **33/34** (isomer I:II, >90:<10[25]).[31] **32** (isomer II) (61.7 mg, an isomer I:II, 25:75 sample combined from selected fractions from the two separations, see above) gave *dl*-19-OH-PGE$_1$ (**33/34**, isomer II) (52.3 mg, 89% crude yield) which was purified by high-pressure LC to give **33/34** (isomer I:II, 20:80[25]).[31] The acid **33/34** (isomer II) was crystallized from ethyl acetate–acetone (ca. 95:5, v/v) to give a white solid: mp 62–64 °C. Anal. ($C_{20}H_{34}O_6 \cdot 0.5H_2O$) C, H. The acid **33/34** (isomer I) was crystallized from ethyl acetate–hexane (ca. 90:10, v/v) to give a white solid, mp 89.5–91 °C. Anal. ($C_{20}H_{34}O_6$) C, H.

Note Added in Proof. Recently, we have obtained ^{13}C NMR spectral data of (19*R*)- and (19*S*)-19-OH-PGE$_2$ methyl esters from Dr. John C. Sih, Upjohn Company, which enable us to make stereochemical assignments to our two racemic esters **32**, isomers I and II. The correlation of the two sets of values for the above-mentioned 19-OH-PGE$_2$ methyl esters with those for **32** (I) and **32** (II) is very good and completely consistent for carbons 13 through 20 (see Table I). Thus, **32** (I) corresponds to (19*S*), **32** (II) to (19*R*) and **33** is (±)-(19*S*)-19-OH-PGE$_1$, mp 89.5–91 °C (isomer I) and **34** is (±)-(19*R*)-19-OH-PGE$_1$, mp 62–64 °C (isomer II), the latter corresponding to the naturally occurring prostaglandin, assuming that (19*R*)-19-OH-PGB$_1$ was an artifact derived from 19-OH-PGE$_1$. We are most grateful to Drs. John C. Sih and John E. Pike, Upjohn Company, for kindly providing us with these NMR data.

Acknowledgment. We are grateful to Mrs. L. Kurz, Dr. M. Maddox, Mrs. J. Nelson, Mrs. A. Nitzen, Mr. H. Scharen, Mr. J. Smith, and Mrs. D. Wong for their assistance with analytical measurements. We thank Mrs. Sherri Ogden, Mass Spectrometry Laboratory, Department of Chemistry, University of California, Berkeley, for the high-resolution mass spectral measurements (determined with a Model CEC 110 mass spectrometer).

References and Notes

(1) Syntex Postdoctoral Fellow, 1976–1977.
(2) Syntex Postdoctoral Fellow, 1975–1976.
(3) P. L. Taylor and R. W. Kelly, *Nature (London)*, **250**, 665 (1974).
(4) I. Cooper and R. W. Kelly, *Prostaglandins*, **10**, 507 (1975).
(5) H. T. Jonsson, Jr., B. S. Middleditch, and D. M. Desiderio, *Science*, **187**, 1093 (1975).
(6) H. T. Jonsson, Jr., B. S. Middleditch, M. A. Schexnayder, and D. M. Desiderio, *J. Lipid Res.*, **17**, 1 (1976).
(7) P. L. Taylor and R. W. Kelly, *FEBS Lett.*, **57**, 22 (1975).
(8) M. Hamberg and B. Samuelsson, *J. Biol. Chem.*, **241**, 257 (1966).
(9) M. Hamberg, *Eur. J. Biochem.*, **6**, 147 (1968).
(10) R. W. Kelly, P. L. Taylor, J. P. Hearn, R. V. Short, D. E. Martin, and J. H. Marston, *Nature (London)*, **260**, 544 (1976).
(11) In ref 10, it is stated that Dr. N. S. Crossley of ICI Pharmaceuticals has synthesized *dl*-19-OH-PGE$_1$ and *dl*-19-OH-PGE$_2$, each as mixtures of α and β epimers at C-19.
(12) Since the completion of our synthesis, a report of the synthesis of (19*R*)-19-OH-PGEs and (19*R*)-19-OH-PGFs has appeared [J. C. Sih, *Prostaglandins*, **13**, 831 (1977)], and the effects of 19-hydroxyprostaglandins on oviductal and uterine motility have been reported: C. H. Spilman, K. K. Bergstrom, and A. D. Forbes, *Prostaglandins*, **13**, 795 (1977).
(13) A. F. Kluge, K. G. Untch, and J. H. Fried, *J. Am. Chem. Soc.*, **94**, 9256 (1972).
(14) J. G. Miller, W. Kurz, K. G. Untch, and G. Stork, *J. Am. Chem. Soc.*, **98**, 6774 (1974).
(15) R. P. Linstead and H. N. Rydon, *J. Chem. Soc.*, 2000 (1934).
(16) P. L. Southwick and J. R. Kirchner, *J. Org. Chem.*, **27**, 3305 (1962).
(17) S. W. Hamersma and E. I. Snyder, *J. Org. Chem.*, **30**, 3985 (1965).
(18) See ref 13, footnotes 3 and 4.
(19) (a) E. E. van Tamelen, R. S. Dewey, M. F. Lease, and W. H. Pirkle, *J. Am. Chem. Soc.*, **83**, 4302 (1961), ref 8; (b) E. J. Corey, D. J. Pasto, and W. L. Mock, *ibid.*, **83**, 2957 (1961); (c) K. Mori, M. Ohki, A. Sato, and M. Matsui, *Tetrahedron*, **28**, 3739 (1972).
(20) We thank G. Stork for providing experimental details for this reaction.
(21) M. M. Midland, *J. Org. Chem.*, **40**, 2250 (1975).
(22) The hydroxyenone **22** was prepared as described by F. S. Alvarez, D. Wren, and A. Prince, *J. Am. Chem. Soc.*, **94**, 7823 (1972), and A. F. Kluge, K. G. Untch, and J. H. Fried, *ibid.*, **94**, 7827 (1972), ref 20.
(23) In order to avoid confusion and to apply easily the α and β convention to designate configurations in prostaglandin structures, we, in ref 13 and 14, have written the lower chain of a 13-*cis*-prostaglandin as



where A $\neq$ B and is often H or OH. It is suggested now that 13-cis lower chains be written in this manner, by definition, as is the case for the C-17 chain in steroids, e.g., cholesterol. It is easily seen that the α and β designations readily convert to the Cahn–Ingold–Prelog *R*/*S* convention in that, in a 13-*cis*-15α-OH-PG, the C-15 has an *S* configuration as is the case of a 13-*trans*-15α-OH-PG; 15β-hydroxy has the *R* configuration at C-15 in both the 13-*cis*- and 13-*trans*-PG structures when so written. Only the C-13 and C-14 geometric centers differ between the two structures.
(24) G. Stork and T. Takahashi, *J. Am. Chem. Soc.*, **99**, 1275 (1977).
(25) A purity estimate of these isomers could only be judged from their ^{13}C NMR spectra; see Table I for chemical shift differences.
(26) The 1-cyano-4-pentanol **17** would be a reasonable candidate for resolution and conversion to a compound of known absolute stereochemistry. Alternatively, the iodo-*cis*-octene **14** could be prepared from naturally occurring material that would provide the *R* configuration at C-19 of the prostaglandin. Thus, fixing this one center and separation of diastereomers (**11**, **13**, or **14**) would dictate the configurations of all other centers of 19β-OH-PGE$_1$ prepared via this synthetic sequence, and no isomer separation would be required to obtain optically active 19β-OH-PGE$_1$ (**1**) which should be identical with that found to occur naturally in human and primate semen.
(27) C. J. Albisetti, Jr., N. G. Fisher, M. J. Hogsed, and R. M. Joyce, *J. Am. Chem. Soc.*, **78**, 2637 (1956).
(28) We thank A. Van Horn for the samples used to measure the refractive indices and to obtain the elemental analyses.
(29) M. B. Braude, *Chem. Abstr.*, **52**, 20152*g* (1958).
(30) Prepared according to M. S. Newman and M. C. Vander Zwan, *J. Org. Chem.*, **38**, 2910 (1973).
(31) See Table I for ^{13}C NMR data.