assume a value for k_r similar to that estimated by Saltiel[67] for stilbene triplet decay of $k_r = 1 \times 10^8$ sec^{-1}. The decay ratio, α, for 4-stilbazole is 0.5, and we can assume a similar value for NPE. Using these numbers eq 15 gives $k'_{et} = 2.5 \times 10^6$ sec^{-1} for energy transfer to *trans*-4-stilbazole and $k_{et}' = 1.1 \times 10^8$ sec^{-1} for energy transfer to *trans*-NPE. Absolute rate theory then gives $\Delta G^{\pm} = 9.3$ kcal/mol for 4-stilbazole and 6.0 kcal/mol for NPE. If there is no activation energy for triplet energy transfer beyond ΔE, the energy difference between the porphyrin triplet and the olefin triplet, these figures predict a triplet energy of 49–51 kcal/mol for *trans*-4-stilbazole and 46–48 kcal/mol for the triplet of *trans*-NPE; these values are very close to those expected by analogy to the case of stilbene. The fact that $\Delta G^{\pm}$ for energy transfer to *trans*-NPE exceeds $\Delta H^{\pm}$ for energy transfer to *cis*-NPE seems at first puzzling, since we have assumed that the azastilbene triplet is one state (or at least that the twisted and trans forms are nearly isoenergetic with a minimal barrier between them) and that activation of trans should have $\Delta G^{\pm} \sim \Delta H^{\pm}$. However since the *trans*-NPE ground state is more stable than the *cis*-NPE ground state, there is a 2–3 kcal/mol difference for the stilbenes,[73] such that activation to the triplet minimum from *cis*-NPE should require less energy than from *trans*-NPE by several kilocalories per mole.

From the calculated energies involved in the respective activation processes, we can conclude that energy transfer from porphyrin to complexed azastilbene yields a common excited triplet (or equilibrating, nearly isoenergetic triplets). Excitation of trans evidently yields a transoid triplet with little change in geometry; however, excitation of cis must involve a severe change in geometry or "nonvertical" process producing an excited state *at least* 8 kcal/mol lower in energy than the "spectroscopic" or cisoid excited state. Although the present results do not permit conclusions regarding the mechanism of nonvertical triplet energy transfer, the unravelling of the thermodynamic parameters provided by the intramolecular system gives a more complete and rather dramatic picture of the process and its potential.

Acknowledgment. We thank the U. S. Public Health Service (Grant No. GM 15,238) for support of this work.

(73) G. Fischer, K. A. Muszkat, and E. Fischer, *J. Chem. Soc. B*, 1156 (1968).

Synthesis of (±)-Prostaglandin E_1, (±)-11-Deoxyprostaglandins E_1, $F_{1\alpha}$, and $F_{1\beta}$, and (±)-9-Oxo-13-*cis*-prostenoic Acid by Conjugate Addition of Vinylcopper Reagents[1]

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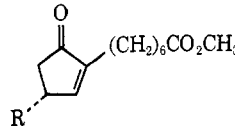
Contribution No. 405 from the Syntex Research Institute of Organic Chemistry, Palo Alto, California 94304. *Received May 11, 1972*

Abstract: The syntheses of (±)-PGE_1 and (±)-11-deoxyprostaglandins in the E_1 and F_1 series have been carried out by conjugate addition of bis(triethyl phosphite)copper(I) cyanide vinyllithium to the substituted cyclopentenones **1a** and **1b**, and subsequent elaboration of vinylamylcarbinol side chain *via* the intermediate carboxaldehydes **3b** and **3d**. The intermediate **3d** was also converted to (±)-9-oxo-13-*cis*-prostenoic acid (**6c**). These transformations are characterized by high yields and ease of operation.

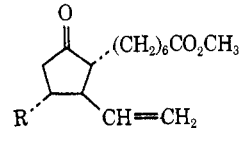
The synthesis of prostaglandins has been the subject of considerable synthetic effort during the past several years. In the course of this work a number of elegant syntheses of prostaglandins have been developed, but, in general, these approaches are lengthy and rather complex in nature.[2]

We now wish to report the synthesis of (±)-PGE_1 and (±)-deoxyprostaglandins which are characterized by ease of operation and high yields.

The basis of our work was the hypothesis that conugate addition of a vinylcopper reagent to an enone such as **1a** would provide the vinylated cyclopentenone **2a** with the correct steric configuration at the three asymmetric centers of the cyclopentenone ring. (Chiral compounds are not resolved. Only one enantiomer



1a, R = OTHP
1b, R = H
1c, R = OH
1d, R = OAc



2a, R = OTHP
2b, R = H

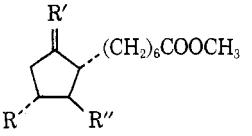
is depicted by the structures.) This stereochemistry was expected to be a result of addition of the vinyl species to the less hindered side of the 4-oxygenated cyclopentenone **1a** and protonation of the resultant enolate to give the thermodynamically more stable trans arrangements of the alkyl and vinyl groups.[3]

(1) Studies in Prostaglandins. IX. For part VIII see P. Crabbe, *Res. Prostaglandins*, 1 (4), 5 (1972).

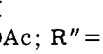
(2) For recent reviews see: *Ann. N. Y. Acad. Sci.*, **180** (1971); J. E. Pike, *Fortschr. Chem. Org. Naturst.*, **28**, 313 (1971).

(3) The preparation of γ,δ-unsaturated ketones *via* conjugate addition of bisvinyl(tri-*n*-butylphosphine)copper lithium to cyclohexenones has been reported by J. Hooz and R. B. Layton, *Can. J. Chem.*, **48**, 1626

To test this hypothesis the enone **1a** was prepared from **1b**[4] by allylic bromination and replacement of bromine by acetate to give **1d**,[5] followed by hydrolysis of the acetate with methanol in the presence of *p*-toluenesulfonic acid and conversion of the resultant carbinol **1c** to the tetrahydropyranyl ether **1a**. Reaction of **1a** with the reagent obtained from bis(trimethyl phosphite)copper(I) cyanide and 1 mol of vinyllithium at −78° in ethyl ether solution afforded the (±)-vinyl ketone **2a** in 46% yield. Subsequent steps to (±)-PGE_1 were carried out without further purification of intermediates. Thus, reduction of the vinyl ketone **2a** with sodium borohydride in methanol solution at room temperature, followed by acetylation with acetic anhydride in pyridine, gave the C-9 epimeric acetates **3a**. Ozonolysis of **3a** in methanol solution at −78°[6]



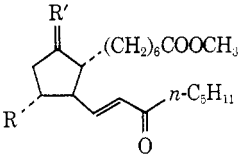
3a, R = OTHP; R′ =  OAc; R″ = CH=CH$_2$

3b, R = OTHP; R′ =  OAc; R″ = CHO

3c, R = H; R′ =  ; R″ = CH=CH$_2$

3d, R = H; R′ =  ; R″ = CHO

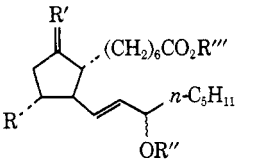
3e, R = OTHP; R′ =  ; R″ = CH=CH$_2$



4a, R′ =  OAc; R = OTHP

4b, R′ =  ; R = H

gave the unstable aldehydes **3b**, which were treated immediately with the anion of dimethyl 2-oxoheptylphosphonate[7] to give the α,β-unsaturated ketones **4a**. This material was reduced with zinc borohydride in glyme solution at 0°,[6] giving the C-15 epimeric alcohols **5a**. Treatment of this mixture with dihydropyran in



5a, R = OTHP; R′ =  OAc; R″ = H; R‴ = CH$_3$

5b, R = OTHP; R″ = THP; R′ =  OAc; R‴ = CH$_3$

5c, R = OTHP; R″ = THP; R′ =  OH; R‴ = H

5d, R = OTHP; R″ = THP; R′ = O; R‴ = H

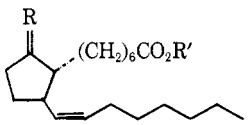
5e, R = OH; R″ = R‴ = H; R′ = O

5f, R = R″ = H; R′ = ; R‴ = CH$_3$

5g, R = R″ = H; R′ = O; R‴ = CH$_3$

5h, R = R″ = H; R′ = OH; R‴ = CH$_3$ (15 α series)

5i, R = R″ = H; R′ = OH; R‴ = CH$_3$ (15β series)



6a, R =  ; R′ = CH$_3$

6b, R = O; R′ = CH$_3$

6c, R = O; R′ = H

benzene solution in the presence of *p*-toluenesulfonic acid at room temperature yielded the bistetrahydropyranyl ethers **5b**. Saponification of the ester groups at C-9 and C-1 was carried out with sodium hydroxide in aqueous methanolic solution at room temperature. After acidification of the reaction mixture to pH 4, the acids of formula **5c** were isolated and oxidized with Jones' reagent[8] in acetone soution to give the ketones **5d**. Treatment of this mixture with 65% aqueous acetic acid at room temperature for 18 hr gave (±)-PGE_1 and (±)-15-epi-GPE_1. These compounds were separated by preparative tlc yielding (±)-PGE_1 (3.66% from **1a**) as a crystalline solid from ethyl acetate–hexane (mp 109–111°),[9] showing identical ir, mass spectral (as methyl ester), and tlc behavior with natural (−)-prostaglandin E_1 and the less polar (±)-15-epi-PGE_1 (3.2% from **1a**) as an oil.

In similar fashion, ketone **1b** was treated with the cuprate reagent described above[10] to yield the vinyl ketone **2b** in 66% yield (isolated as the semicarbazone; see the Experimental Section). This material was

(1970). Following the completion of this work, C. J. Sih, R. G. Salsman, P. Price, G. Peruzzotti, and R. Sood (*J. Chem. Soc., Chem. Commun.* 240 (1972)) reported the synthesis of (±)-15-deoxyprostaglandin E_1 by a similar route. After submission of this manuscript, C. J. Sih, P. Price, R. Sood, R. G. Salomon, G. Peruzzotti, and M. Casey (*J. Amer. Chem. Soc.*, **94**, 3643 (1972)) reported the synthesis of (−)-PGE_1 by addition of a functionalized organocopper reagent to **1a**.

(4) This compound, as the ethyl ester, has been reported by J. F. Bagli, T. Bogri, R. Deghenghi, and K. Wiesner, *Tetrahedron Lett.*, 465 (1966). We have prepared this product by a different route, *via* the enol acetate of 2-(6′-methoxycarbonylhexyl)-1-cyclopentanone, followed by bromination with NBS in aqueous THF at room temperature and dehydrobromination with lithium carbonate in pyridine solution at 90–100° for 1 hr. We thank Professor G. Stork for unpublished information from his laboratory.

(5) L. Heslinga, M. Van Gorkom, and D. A. Van Dorp, *Recl. Trav. Chim. Pays-Bas*, **87**, 1421 (1968).

(6) J. J. Pappas, W. P. Keaveney, E. Gancher, and M. Berger, *Tetrahedron Lett.*, 4273 (1966).

(7) E. J. Corey, N. M. Weinschenker, T. K. Schaaf, and W. Huber, *J. Amer. Chem. Soc.*, **91**, 5675 (1969).

(8) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

(9) Reported: 112–113°; H. L. Slates, Z. S. Zelamski, D. Taub, and N. L. Wendler, *J. Chem. Soc., Chem. Commun.*, **6**, 305 (1972).

(10) 1,4-Addition experiments on ketone **1b**, using bisvinyl(tri-*n*-butyl phosphite)copper lithium (ref 4) derived from 1 mol of vinyllithium and trimethyl phosphite copper iodide or the phosphine-free species (CH_2=CH)CuLi, gave the vinyl ketone **2b** in lower yields.

transformed into the cycloethylene ketal **3c** with ethylene glycol and a catalytic amount of *p*-toluenesulfonic acid. Ozonolysis[6] of this compound gave the aldehyde **3d** which, on reaction with the anion of dimethyl 2-oxoheptylphosphonate, followed by zinc borohydride reduction as described above, yielded a mixture of C-15 epimeric alcohols **5f**. Hydrolysis of this mixture in 65% aqueous acetic acid at room temperature yielded a 1:1 mixture of carbinols **5g**. This mixture was separated by chromatography on silica gel to yield the more polar 15α-alcohol (21.7%) and the less polar 15β-alcohol (32%), in addition to 32.3% of a mixture of 15α- and 15β-carbinols, for a total yield of 86% from **3c**. Hydrolysis of these compounds with 0.1 *N* aqueous sodium hydroxide in tetrahydrofuran solution at room temperature yielded (±)-11-deoxyprostaglandin E_1[11] and (±)-15-epi-11-deoxyprostaglandin E_1 respectively.

Sodium borohydride reduction of (±)-11-deoxyprostaglandin E_1 in methanol solution at room temperature gave a *ca.* 7:3 mixture of (±)-11-deoxyprostaglandin $F_{1\beta}$ and $F_{1\alpha}$[12,13] which were separated by preparative tlc.

Similarly, reduction of 15-epi-11-deoxyprostaglandins E_1 yielded a 7:3 mixture of 15-epi-11-deoxyprostaglandins $F_{1\beta}$ and $F_{1\alpha}$, which were also separated by preparative tlc.

Finally, the reaction of aldehyde **3d** with the ylide derived from triphenylheptylphosphonium bromide in dimethoxyethane–dimethyl sulfoxide solution yielded the olefin **6a** which, without purification, was transformed into the ketone by treatment with dilute hydrochloride acid in methanol to give **6b** in 77% yield after chromatography on silica gel.

Basic hydrolysis of **6b** in aqueous tetrahydrofuran gave the acid **6c** in 91.3% yield.

Experimental Section[14]

4-Hydroxy-2-(6′-methoxycarbonylhexyl)-2-cyclopenten-1-one (1c). A solution of 500 mg of 4-acetoxy-2-(6′-methoxycarbonylhexyl)-2-cyclopenten-1-one (**1d**) in 20 ml of methanol containing 75 mg of anhydrous *p*-toluenesulfonic acid was refluxed overnight. The reaction mixture was cooled to room temperature and 2 drops of triethylamine was added; then the mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with water and brine and dried over anhydrous sodium sulfate. Evaporation of the solvent gave an oil which was purified by preparative tlc in a 50% ethyl acetate–50% hexane system to give 250 mg of **1c** [mp 48–49.5°; λ_{max}^{MeOH} 222 mμ (ϵ 8120); ir 3415, 3860, 1735, 1685, and 1630 cm^{-1}; nmr 2.30 (d of d, J = 18.5, 2.5 Hz, H_5 cis), 2.80 (d of d, J = 18.7, 7.0 Hz, H_5 trans), 3.65 (s, 3 H, OCH_3), 4.90 (m, 1 H, H_{11}), 7.15 ppm (m, 1 H, H_{12})]. *Anal.* Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 65.07; H, 8.20.

4-Tetrahydropyranyloxy-2-(6′-methoxycarbonylhexyl)-2-cyclopenten-1-one (1a). A solution of 2.7 g of alcohol **1c** in 50 ml of benzene containing 2 ml of dihydropyran and 1 drop of phosphorus oxychloride was stirred at room temperature for 90 min. The reaction mixture was treated with a few drops of triethylamine, and the resulting solution was washed with brine and dried over anhydrous sodium sulfate. Evaporation of the solvent gave 3 g of crude **1a**. This material (1 g) was purified by chromatography on silica gel in an ethyl acetate–hexane system to give 600 mg of pure **1a** [oil; λ_{max}^{MeOH} 223 mμ (ϵ 10,200); ir 1710, 1740 cm^{-1}; nmr 3.65 (s, 3 H, OCH_3), 4.8 (br m, 2 H, H_{11}, C*H*O), 7.18 ppm (m, 1 H, H_{12})].

(±)-3β-Vinyl-4α-Tetrahydropyranyloxy-2α-(6′-methoxycarbonylhexyl)cyclopentan-1-one (2a). A solution of 1.7 g of bis(triethyl phosphite)copper(I) cyanide complex in 16 ml of a 1:1 mixture of tetrahydrofuran–ethyl ether at −78° was treated with 1 equiv of vinyllithium (commercial vinyllithium from Alfa Inorganics in tetrahydrofuran solution) in 6 ml of anhydrous ethyl ether under a nitrogen atmosphere and the mixture was stirred for 15 min. A solution of 600 mg of ketone **1a** was added over a period of 5 min. The reaction mixture was poured into a cooled mixture of methylene chloride and phosphate buffer at pH 7 with mechanical stirring. The organic layer was separated and the buffer extracted with more methylene chloride. The combined extracts were filtered through Celite, then washed with water and brine, and dried over anhydrous sodium sulfate. Evaporation of the solvent under reduced pressure gave an oil which was purified by silica gel chromatography to yield 300 mg of pure vinyl ketone **2a** [nmr 3.65 (s, 3 H, OCH_3), 3.7–4.4 (m, 3 H, H_{11}, CH_2O), 4.7 (m, 2 H, OCHO), 5.18 (m, 2 H, H_{14}), 5.75 ppm (m, 1 H, H_{13})]. *Anal.* Calcd for $C_{20}H_{32}O_5$: C, 68.15; H, 9.15. Found: C, 68.58; H, 9.15.

(±)-Prostaglandin E_1 and (±)-15-Epiprostaglandin E_1. A solution of 300 mg of vinyl ketone **2a** in 10 ml of methanol was cooled to 0° and then solid sodium borohydride was added gradually until no more starting material could be observed by tlc analysis (30% ethyl acetate–70% hexane system). The reaction solution was poured into water and extracted with ethyl acetate. The extracts were washed with water and brine and then dried over anhydrous sodium sulfate. The solvent was eliminated under reduced pressure to give the mixture of (±) isomeric alcohols **3e**. This residue was dissolved in 5 ml of benzene containing 2 ml of acetic anhydride and 1.5 ml of pyridine and the mixture was left at room temperature overnight. The solvents were removed under vacuum and the residue was dissolved in ethyl acetate; the resulting solution was washed twice with saturated sodium bicarbonate solution and then with water and dried over anhydrous sodium sulfate. The solvent was eliminated under reduced pressure and the residue of epimeric acetates **3a** was dissolved in 20 ml of methanol containing 200 mg of sodium acetate and ozonized at −70° until no more starting material was present as judged by tlc analysis (40% ethyl acetate–60% hexane system). The excess of ozone was blown out with nitrogen and 0.5 ml of dimethyl sulfide was added and the reaction solution stirred at −10° for 1 hr, at 0° for 1 hr, and then at room temperature for another hour. The reaction solution was poured into water and extracted with ethyl acetate. The organic extracts were washed with water and brine and dried over anhydrous sodium sulfate. Elimination of the solvent under reduced pressure gave 238 mg of unstable aldehydes **3b** (two spots in 40% EtOAc–60% hexane; R_f values 0.55 and 0.6) [nmr 2.0, 2.05 (2 × OAc), 3.65 (3 H, OCH_3), 9.73–9.79 ppm (CH=O)]. This material dissolved in 2 ml of dimethoxyethane was added to a previously prepared mixture of 200 mg of dimethyl 2-oxoheptylphosphonate and 37 mg of a 57% sodium hydride dispersion in 4.5 ml of dried dimethoxyethane. The mixture was stirred at room temperature under a nitrogen atmosphere for 1 hr and then poured into water and extracted with ethyl ether. The ether was washed with water and brine and dried over anhydrous sodium sulfate. The solvent was eliminated under reduced pressure to give the crude mixture of enones **4a**. This material was dissolved in 10 ml of anhydrous dimethoxyethane and treated with 1 ml of a 1 *M* solution of zinc borohydride in the same solvent at 0° for 6 hr. The excess reagent was destroyed with a saturated solution of sodium potassium tartrate. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with water and brine and dried over anhydrous sodium sulfate. The solvent was eliminated under reduced pressure and the mixture of epimeric alcohols **5a** was dissolved in 10 ml of benzene and treated with 0.5 ml of redistilled dihydropyran in the presence of a catalytic amount

(11) Assignment of configuration at C-15 has been based on direct comparison of alcohol **5g** with an authentic sample of (15*S*)-15-hydroxy-9-oxaprosta-13-*trans*-enoic acid, prepared by hydrogenation of (15*S*)-15-hydroxy-9-oxaprosta-10,13-*trans*-dienoic acid (PGA_1) with 5% Pd/C in methanol solution at −10 to −25°. These compounds showed no differences in their nmr, mass spectral, ir, and tlc behavior.

(12) The synthesis of (±)-11-deoxyprostaglandin F_1 as a mixture of stereoisomers has been reported; *cf.* J. F. Bagli, T. Bogri, R. Deghenghi, and K. Wiesner, *Tetrahedron Lett.*, 465 (1966), and M. P. L. Caton, E. C. J. Coffe, and G. L. Watkins, *ibid.*, 773 (1972).

(13) The configuration at C-9 was determined by ^{13}C nmr studies. This analysis will be the subject of a separate report: M. Maddox, F. Alvarez, and L. Tökés, *J. Chem. Soc. Chem. Commun.*, submitted for publication.

(14) Nmr spectra were obtained on Varian A-60 and HA-100 spectrometers in deuteriochloroform solutions (10% w/v) containing tetramethylsilane as internal reference. Chemical shifts are reported as parts per million on the δ scale. We thank Dr. M. Maddox and Mrs. P. Nelson for these determinations. In the presentation of data, m = multiplet, s = singlet, d = doublet, d of d = doublet of doublets, d of t = doublet of triplets. The mass spectra were obtained with an Atlaswerke CH-4 spectrometer equipped with a direct inlet system. Spectra were measured at an ionizing potential of 70 eV and an acceleration voltage of 3 kV. We thank Mr. B. Amos and Dr. L. Tökés for assistance with these measurements.

of phosphorus oxychloride at room temperature for 1 hr. The mixture was diluted with benzene and treated with a few drops of triethylamine and then washed with water and brine and dried over anhydrous sodium sulfate. Evaporation of the solvent under reduced pressure gave the oily mixture of isomeric bis(tetrahydropyranyl) ethers **5b**. This mixture was dissolved in 2.4 ml of methanol and treated with 80 mg of sodium hydroxide dissolved in 0.6 ml of water at room temperature until tlc analysis indicated the absence of starting material. The mixture was diluted with water and extracted with ethyl acetate. The ethyl acetate extracts were backwashed with water (2 × 10 ml). The aqueous solution was acidified with oxalic acid to pH 4 and then extracted with ether (5 × 20 ml). The ethereal solution was washed with brine and dried over anhydrous magnesium sulfate. The solvent was eliminated under reduced pressure and the residue of the free acid **5c** was dissolved in 2.6 ml of acetone and cooled to −10° and then treated with 0.094 ml of Jones' reagent[8] over 5 min and stirred at −10° for 25 min more. The excess of reagent was destroyed by addition of 0.09 ml of isopropyl alcohol and the mixture stirred for 5 min more. The mixture was then diluted with 20 ml of ethyl acetate, washed with water (3 × 2 ml) and brine (2 ml) and dried over anhydrous magnesium sulfate. Elimination of the solvent gave 145 mg of the acid **5d** as an oil. This material was dissolved in 3.9 ml of 65% aqueous acetic acid and left at room temperature overnight. The solvents were removed at low temperature under high vacuum. The oil was applied to a 0.5 mm meter preparative plate and developed in benzene–tetrahydrofuran–formic acid (70:30:2) and developed twice. The appropriate bands were eluted with ethyl acetate to yield 24 mg of crystalline (±)-prostaglandin E_1 and 21 mg of oily (±)-15-epiprostaglandin E_1 homogeneous in tlc analysis. (±)-Prostaglandin E_1 showed mp 109–111°[15] and identical ir, nmr, mass spectral (as methyl ester), and tlc behavior with natural (−)-prostaglandin E_1. (±)-15-Epiprostaglandin showed to be a gum, less polar in tlc analysis than (±)-prostaglandin E_1. Otherwise its nmr, ir, and mass spectra were identical with those of (−)-prostaglandin E_1.

(±)-3β-Vinyl-2α-(6′-methoxycarbonylhexyl)cyclopentan-1-one (2b). A solution of 250.3 g of bis(triethyl phosphite)copper(I) cyanide in 1580 ml of a 1:1 mixture of tetrahydrofuran–ethyl ether was prepared, cooled to −78°, and with stirring, under a nitrogen atmosphere, treated with 277.3 ml of a 2 *M* commercial solution of vinyllithium in tetrahydrofuran in 920 ml of ethyl ether. The mixture was stirred for 10 min and then a solution of 45 g of ketone **1b** in 920 ml of ethyl ether was added during 30 min to the complex solution at −78° under a nitrogen atmosphere. The mixture was stirred for 10 min more and then poured into aqueous dilute hydrochloric acid and then the mixture was extracted with ether. The ether layer was washed with water and dilute sodium bicarbonate solution and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue distilled under high vacuum. The distillate weighing 76.4 g (containing mineral oil and triethyl phosphite) was diluted with 800 ml of methanol and treated with 140 ml of a solution of semicarbazide hydrochloride (11.1 g of semicarbazide hydrochloride in each 50 ml of water) and 120 ml of water containing 21 g of pyridine. The mixture was boiled gently on the steam bath for 30 min, cooled to room temperature, cooled under stirring in an ice bath water for 1 hr, and then diluted with water to a final volume of 5 l. The crystalline precipitate was collected by filtration and washed with water and then with hexane to yield, after drying, 45.5 g of the semicarbazone of **2b**, homogeneous in tlc analysis (5 and 10% methanol in methylene dichloride). The pure vinyl ketone **2b** was regenerated from its semicarbazone as follows: a solution of 85 g of semicarbazone was dissolved in 425 ml of acetic acid containing 213 ml of water and treated with 42.5 g of pyruvic acid and 42.5 g of sodium acetate. The mixture was heated on the steam bath for 90 min, cooled to room temperature, and diluted with 3 l. of water The mixture was extracted with ethyl acetate (3 × 1 l.), the organic extracts were combined and dried over anhydrous sodium sulfate, and after filtration the solvents were eliminated under reduced pressure. The residue was dissolved in 500 ml of hexane and filtered through 50 g of silica gel eluting first with hexane and then with hexane containing 5% of ethyl acetate until no more product was eluted. The combined eluates were concentrated under reduced pressure to give 61.7 g of pure vinyl ketone **2b**, homogeneous in tlc (25% EtOAc–75% hexane) (66% yield overall from **1b**) [*m/e* 252; ir 3085 (m), 2960 (sh), 2940 (s), 2865, 1740 (s), 1640 (m), 990 (s), 930 cm^{-1}; nmr 3.61 (s, 3 H, OCH_3), 4.85–5.25 (m, 2 H, $=CH_2$), 4.72 (m, 1 H, CH=)]. Elemental analysis was performed on the free acid. *Anal.* Calcd for $C_{14}H_{22}O_3$: C, 70.55; H, 9.31. Found: C, 70.10; H, 9.52.

(±)-3β-Vinyl-2α-(6′-methoxycarbonylhexyl)cyclopentan-1-one Cycloethylene Ketal (3c). A solution of 70 g of vinyl ketone **2b** in 760 ml of benzene containing 76 ml of ethylene glycol was treated with 1.5 g of *p*-toluenesulfonic acid monohydrate under reflux overnight, using a Dean–Stark water separator. The reaction solution was cooled to room temperature and treated with 5 ml of triethylamine and then poured into saturated sodium bicarbonate solution and extracted with benzene. The organic extracts were washed with water and brine and dried over anhydrous sodium sulfate. The solvent was eliminated under reduced pressure and the resulting oil dissolved in hexane and filtered through 50 g of silica gel, eluting with the same solvent first and then with hexane containing 5% of ethyl ether. The eluates were combined and the solvents were eliminated under reduced pressure to give 76 g of **3c** (82.2%).

(±)-3β-Formyl-2α-(6′-methoxycarbonylhexyl)cyclopentan-1-one Cycloethylene Ketal (3d). A solution of 35 g of the vinyl ketal **3c** in 500 ml of methanol was transformed into **3d** in a similar manner as described above, to give 36.5 g of crude material. The unstable aldehyde **3d** exhibited: nmr 2.24 (br t, J = 7 Hz, 2 H, CH_2CO), 3.61 (s, 3 H, OCH_3), 3.90 (s, 4 H, OCH_2CH_2O), 9.6 ppm (d, J = 2 Hz, 1 H, CH=O).

(±)-9,15-Dioxo-13-*trans*-prostenoic Acid Methyl Ester Cycloethylene Ketal (4b). A solution of 36 g of aldehyde **3d** in 500 ml of anhydrous dimethoxyethane was treated as described for **3b** with a previously prepared mixture of 7.7 g of 56% sodium hydride dispersion, 41 g of dimethyl 2-oxoheptylphosphonate in 1.5 l. of dimethoxyethane, to give crude **4b**. A sample was purified by chromatography on silica gel in an ethyl acetate–hexane system and exhibited the following characteristics: oil; ir 2950, 2875, 1700, and 1635 cm^{-1}; uv λ_{max}^{MeOH} 230 mμ (ε 13,845); *m/e* 394; nmr 2.17 (t, J = 7 Hz, 2 H, $CH_2C(=O)CH=CH$), 2.51 (t, J = 7 Hz, 2 H, $CH_2CO_2CH_3$), 3.65 (CO_2CH_3), 3.9 (A), 6.06 (d, J = 16 Hz, CH=), 6.65, 6.82 (d of d, J = 16, 9 Hz, CH=).

A

(±)-11-Deoxyprostaglandin E_1 and (±)-15-Epi-11-deoxyprostaglandin E_1 Methyl Esters (5g). A crude mixture of enone **4b** corresponding to 73 g of vinyl ketone **3c** was reduced with zinc borohydride as described before for **4a** to give, after isolation, a crude mixture of 15-epimeric alcohols **5f** which, without further purification, was hydrolyzed with 65% aqueous acetic acid as described above for **5d**, to yield the mixture of keto alcohols **5g**. After isolation in the usual manner, this mixture was chromatographed on 1600 g of silica gel using 5% ethyl acetate in hexane and increasing the polarity up to 8% ethyl acetate. The appropriate homogeneous fractions were combined and the solvents eliminated under reduced pressure to yield 18.8 g of **5g** in the 15α series and 27.8 g in the 15β series, plus 28 g of a mixture of 15α- and 15β-alcohols **5g**. (±)-11-Deoxyprostaglandin E_1 methyl ester proved to be more polar than its 15β epimer by tlc analysis and silica gel column chromatography and showed: ir 3470, 2960 (sh), 2935, 2860, 1740, and 960 cm^{-1}; *m/e* 352; nmr 0.88 (br t, J = 6 Hz, 3 H, CH_3), 2.25 (t, J = 7 Hz, CH_2CO_2), 3.63 (s, 3 H, OCH_3), 4.06 (m, 1 H, CHO), 5.6 ppm (m, 2 H, CH=CH). *Anal.* Calcd for $C_{21}H_{36}O_4$: C, 71.55; H, 10.30; O, 18.15. Found: C, 71.6; H, 10.41; O, 18.08.

(±)-15-Epi-11-deoxyprostaglandin E_1 methyl ester showed ir, mass spectra, and nmr identical with its 15α epimer. *Anal.* Calcd for $C_{21}H_{36}O_4$: 71.55; H, 10.30; O, 18.15. Found: C, 71.72; H, 10.37; O, 18.12.

(±)-11-Deoxyprostaglandin E_1 and 15-Epi-11-deoxyprostaglandin E_1. A solution of 300 mg of (±)-11-deoxyprostaglandin E_1 methyl ester in 31 ml of tetrahydrofuran containing 10 ml of water was treated with 21 ml of 0.1 *N* aqueous sodium hydroxide and the mixture stirred at room temperature overnight. Then 21 ml of 0.1 *N* aqueous hydrochloric acid was added, and most of the tetrahydrofuran was eliminated under reduced pressure. The reaction residue was diluted with water and extracted with ethyl acetate. The organic extracts were backwashed with water and dried over anhydrous sodium sulfate to give, after evaporation of the solvent

(15) Reported mp 112–113°: H. L. Slates, Z. S. Zelamski, D. Taub, and N. L. Wendler, *J. Chem. Soc. Chem. Commun.*, **6**, 305 (1972).

under reduced pressure, 250 mg of title compound showing: mp 82.5–85°; ir 3425, 2950 (sh), 2920, 2850, 1720, and 960 cm^{-1}; nmr 0.88 (br t, J = 6 Hz, 3 H, CH_3), 2.29 (t, J = 7 Hz, CH_2CO_2), 4.08 (m, 1 H, C*H*O), 5.55 ppm (m, 2 H, CH=CH); *m/e* 338. *Anal.* Calcd for $C_{20}H_{34}O_4$: C, 70.97; H, 10.13. Found: C, 72.04; H, 10.33.

Similarly, (±)-15-epi-11-deoxyprostaglandin E_1 was obtained from its methyl ester [mp 53–56°; ir, nmr, and mass spectra identical with that of (±)-11-deoxy-PGE_1]. *Anal.* Calcd for $C_{20}H_{34}O_4$: C, 70.97; H, 10.13. Found: C, 70.76; H, 10.29.

(±)-11-Deoxyprostaglandin $F_{1\alpha}$ and (±)-11-Deoxyprostaglandin $F_{1\beta}$. A solution of 500 mg of (±)-11-deoxyprostaglandin E_1 was dissolved in 30 ml of methanol and solid sodium borohydride was added portionwise until no more starting material could be detected by tlc analysis (40% ethyl acetate–60% hexane). The reaction solution was poured into water and extracted with ethyl acetate. The organic phase was washed with brine and dried over anhydrous sodium sulfate. The solvent was eliminated under reduced pressure and the residue purified *via* preparative tlc to yield 303 mg of (±)-11-deoxyprostaglandin $F_{1\alpha}$ methyl ester and 98 mg of its 9β epimer. Basic hydrolysis of these compounds in the usual manner yielded (±)-11-deoxyprostaglandin $F_{1\alpha}$ [mp 97–98.5°; ir 3400 (br), 3160 (br), 2970 (sh), 2930 (s), 2860 (sh), 1695 (s), 9.75 (s) cm^{-1}; nmr 2.31 (t, J = 7 Hz, CH_2CO), 4.00–4.30 (m, 2 H, C*H*OH), 5.18–5.49 ppm (m, 2 H, *CH=CH*); *m/e* 340. *Anal.* Calcd for $C_{20}H_{36}O_4$: C, 70.55; H, 10.66. Found: C, 70.63; H, 10.85] and (±)-11-deoxyprostaglandin $F_{1\beta}$ [mp 69–70.5°; ir 3460 (br), 3250 (br), 2990 (sh), 2970 (sh), 2950 (sh), 2880 (s), 1740 (s), 990 (s) cm^{-1}; nmr 2.3 (t, J = 7 Hz, 2 H, CH_2CO), 3.78–4.1 (m, 2 H, C*H*OH), 5.24 ppm (m, 2 H, *CH=CH*); *m/e* 322 (340 − H_2O). *Anal.* Calcd for $C_{20}H_{36}O_4$: C, 70.55; H, 10.66. Found: C, 70.61; H, 10.84].

(±)-15-Epi-11-deoxyprostaglandins $F_{1\alpha}$ and $F_{1\beta}$. Similarly, title compounds were prepared from (±)-15-epi-11-deoxyprostaglandin E_1 methyl ester [mp 102–103.5°; ir 3440 (br), 2930 (s), 2855 (sh), 1700 (s), 1640 (s), and 970 (s) cm^{-1}; nmr 2.3 (t, J = 7 Hz, 2 H, CH_2CO), 4.3–4.95 (m, 2 H, C*H*OH), 5.35–5.5 ppm (m, 2 H, *CH=CH*); *m/e* as the methyl ester 336 (354 − 18). *Anal.* Calcd for $C_{20}H_{36}O_4$: C, 70.50; H, 10.66; O, 18.83. Found: C, 70.50; H, 10.72; O, 18.83] and (±)-15-epi-11-deoxy prostaglandin $F_{1\beta}$ [mp 59.0–60.5°; ir 3400 (br), 3300 (br), 2940 (s), 2860 (sh), 1690 (s), and 970 (s) cm^{-1}; nmr 2.9 (t, 2 H, J = 7 Hz, CH_2CO), 3.8–4.1 (m, 2 H, C*H*OH), 5.48 ppm (m, 2 H, *CH=CH*); *m/e* as methyl ester 336 (354 − 18). *Anal.* Calcd for $C_{20}H_{36}O_4$: C, 70.50; H, 10.66. Found: C, 70.45; H, 10.65].

(±)-9-Oxo-13-*cis*-prostenoic Acid Methyl Ester (6b). A solution of crude aldehyde **3d** (corresponding to 11.2 g of vinyl ketone **3c**) in 96 ml of dimethoxyethane was added to a previously prepared mixture of 2.98 g of 57% sodium hydride dispersion (previously washed with ether) and 30.63 g of triphenylheptylphosphonium bromide in 132 ml of dimethyl sulfoxide, dropwise at such a rate as to maintain the temperature around 25°. The reaction mixture was stirred at room temperature for 30 min after the addition was complete, and then poured into water and extracted with ethyl ether. The organic layer was washed with water and brine and then dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure, the residue dissolved in hexane, and the solution filtered through a short column of silica gel, eluting the product with 5% ethyl acetate–95% hexane. Evaporation of the solvent gave an oil which, without further purification, was dissolved in a mixture of 50 ml of methanol and 5 ml of water. The resulting solution was treated with 4 drops of concentrated hydrochloric acid and left at room temperature for 3 hr. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with water and brine and dried over anhydrous sodium sulfate. Evaporation of the solvent left an oily residue which was dissolved in hexane and filtered through 140 g of silica gel, eluting the product with 1% ethyl acetate–99% hexane, to yield 9.8 g of keto ester **6b** showing: ir 3000 (sh), 2920, 2845, 1655 (m), and 970 (m) cm^{-1}; nmr 0.87 (br t, 3 H, CH_3), 3.64 (s, 3 H, OCH_3), 5.24 (d of d, J = 11.0, 9.0 Hz, 1 H, H_{13}), 5.71 (d of t, J = 11.0, 7.0 Hz, 1 H, H_{14}); *m/e* 336. *Anal.* Calcd for $C_{21}H_{36}O_3$: C, 74.95; H, 10.78. Found: C, 74.68; H, 10.78.

(±)-9-Oxo-13-*cis*-prostenoic Acid (6c). A solution of 8.5 g of keto ester **6b** in 580 ml of tetrahydrofuran plus 190 ml of water was treated with 390 ml of 0.1 *N* sodium hydroxide solution for 26 hr at room temperature. The reaction solution was acidified with diluted hydrochloric acid and the product extracted with ethyl acetate. The organic layer was washed with water and brine and dried over anhydrous sodium sulfate. Elimination of the solvent under reduced pressure gave an oil, which was filtered through 100 g of silica gel in 5% ethyl acetate–95% hexane, eluting the product with the same solvent mixture. The homogeneous fractions were combined and the solvents eliminated under reduced pressure to yield 7.7 g of **6c** exhibiting: ir 2935, 1740, and 1705 cm^{-1}; nmr 0.87 (br t, 3 H, CH_3), 5.22 (d of d, J = 11.0, 9.0 Hz, 1 H, H_{13}), 5.40 (d of t, J = 11.0, 7.0 Hz, 1 H, H_{14}). *Anal.* Calcd for $C_{20}H_{34}O_3$: C, 74.49; H, 10.63. Found: C, 74.43; H, 10.83.

Synthesis of Prostaglandin Models and Prostaglandins by Conjugate Addition of a Functionalized Organocopper Reagent[1]

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Abstract: Two methods are described for the preparation of an oxygen functionalized vinylcopper reagent. Reactions of this reagent with cyclic and acyclic enones give products of 1,4 addition. The labile methoxyisopropyl group was used as an alcohol protecting group for ease of formation and removal. The influence of reaction conditions such as solvents and temperature on the mode of addition and yield is discussed. (*S*)-1-Iodo-*trans*-1-octen-3-ol (**16a**) was prepared from (*S*)-1-octyn-3-ol (**17**). The optically pure iodovinylcarbinol was converted to the cuprate **2** and 1,4 addition to the hydroxy-protected cyclopentenone **14c** afforded (−)-PGE_1 (**18b**).

Organocopper reagents have proven to be extremely useful species in forming carbon–carbon bonds.[3] In the majority of cases these reagents have been of the unfunctionalized variety. Notable exceptions, such as an amino functionalized reagent by Corey[4] and an oxygen functionalized reagent by Eaton,[5] have recently appeared. One approach to the synthesis of E-series

(1) (a) Studies in Prostaglandins. X. (b) For part IX, see F. S. Alvarez, D. Wren, and A. Prince, *J. Amer. Chem. Soc.*, **94**, 7823 (1972).
(2) Syntex Postdoctoral Fellow, 1971–1972.
(3) For a review of conjugate addition reactions see: G. H. Posner, *Org. React.*, **19** (1972).
(4) E. J. Corey, D. E. Cane, and L. Libit, *J. Amer. Chem. Soc.*, **93** 7016 (1971).
(5) P. E. Eaton and R. H. Meuller, *ibid.*, **94**, 1014 (1972).