Stereospecific Total Synthesis of Prostaglandins *via* Reaction of α-Alkylcyclopentenones with Organocuprates[1]

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Abstract: A highly stereospecific method for the construction of the prostanoic acid skeleton featuring conjugate additions of C-8 vinylcuprates to α-alkylated cyclopentenones is described. The versatility of this synthetic approach is illustrated by the syntheses of (±)-11,15-dideoxy-PGE_1, (−)-11-deoxy-PGE_1, (±)-15-deoxy-PGE_1, and (−)-PGE_1.

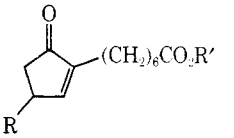
As many as five asymmetric centers are present in the natural prostaglandins. The incorporation of such asymmetry into a total synthesis constitutes a formidable synthetic objective since most chemical transformations performed in the laboratory yield statistical mixtures of optical enantiomers. Such mixtures may often be separated by reaction with an asymmetric resolving agent, which is often a natural product. However, resolution suffers from an inherent disadvantage in that only 50% of the enantiomeric mixture possesses the required natural absolute configuration. An alternative approach to the incorporation of asymmetry into a molecule makes use of chiral reagents to induce the required stereospecificity. In theory, the production of the required enantiomer can be achieved quantitatively by optical induction in contrast to the resolution method. Enzymes are excellent chiral organic reagents, capable of chemically modifying (metabolizing) a large variety of substrates. In particular, a reasonable approach to the total synthesis of natural products is the utilization of enzymes to introduce chirality into a synthetic prochiral substrate. Moreover, it is usually unnecessary to isolate such enzymes from their natural sources. That is, enzymatic transformations can be achieved by incubation of synthetic substrates with microorganisms.

The objective of the present study was the design of a *bioorganic total synthesis* of prostaglandins, wherein the required asymmetry might reasonably be introduced microbiologically. The present report details the successful development of a method for construction of the prostanoic acid skeleton which readily accommodates an asymmetric induction step. A detailed account of a completely stereospecific bioorganic total synthesis of (−)-prostaglandins E_1 and E_2 constitutes the subject of the accompanying paper.[3]

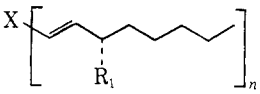
One approach to stereospecific synthesis, which has been successfully applied to prostaglandins, depends on the intermediacy of polycyclic structures for control of stereochemistry.[4] Thus, stereochemical relationships are enforced with the aid of covalent linkages which are ultimately severed to yield the desired monocyclic prostaglandin. The present report details the successful development of a highly stereospecific total synthesis of prostaglandins based on a more direct approach, which relies solely upon steric interactions to control the stereochemical course of the synthesis. Asymmetric centers are introduced consecutively around a five-membered ring. It was our intention that the first center of asymmetry might be introduced microbiologically. Therefore, we were led to devise a synthetic scheme involving an intermediate possessing only a single center of asymmetry in a five-membered ring. This intermediate must be converted into a prostanoic acid in which the additional ring substituents are present in one particular "natural" configuration.

Results and Discussion

It is well documented that vinyl "ate" complexes such as $(CH_2{=}CH_2)_2CuLiP(n\text{-}C_4H_9)_3$ efficiently transfer the vinyl group to the β-carbon atom of conjugated enones such as α-cyclohexenone to provide good yields of γ,δ-unsaturated ketones.[5] Based on this important observation, we devised a method for the construction of the prostanoic acid nucleus *via* the assembly of a "left-hand synthon," **1a,** with a "right-hand ate complex," **2a.**



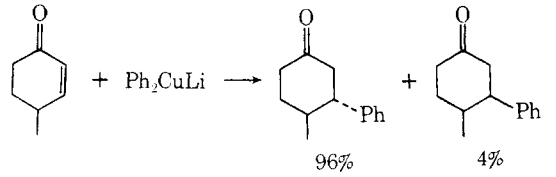
1a, R = OTHP; R′ = C_2H_5
b, R = OH; R′ = C_2H_5
c, R = H; R′ = CH_3



2a, X = I; R_1 = OH; n = 1
b, X = I; R_1 = $OCH(CH_3)OCH_2CH_3$; n = 1
c, X = Li; R_1 = $OCH(CH_3)OCH_2CH_3$; n = 2
d, X = Cu; R_1 = $OCH(CH_3)OCH_2CH_3$; n = 2
e, X = I; R_1 = H; n = 1
f, X = Li; R_1 = H; n = 1
g, X = Cu; R_1 = H; n = 2

Within the past few years, the syntheses of prostaglandins *via* conjugate additions of organometallic derivatives to substituted cyclopentenones have been the subject of intensive investigations.[6] In a series of communications, we described the synthesis of (+)-15-deoxyprostaglandin E_1,[6a] (−)-11-deoxyprostaglandin E_1,[6c] (−)-prostaglandin E_1[6b,d] (PGE_1), and (−)-prostaglandin E_2[6e] (PGE_2) *via* conjugate addition of lithium divinylcuprates to α-alkylated cyclopentenones. In this paper, we report the critical experimental details of our initial exploratory studies necessary for the successful elaboration of the prostanoic acid skeleton. We speculated that the required stereochemical relationships of the ring substituents could be achieved by suitable manipulation of steric interaction. We noted that these substituents in the E prostaglandins are in the thermodynamically most stable all-trans configuration. It is not unreasonable to expect that the attack by **2a** proceeds with a high degree of stereoselectivity from the least hindered side of **1a,** and that protonation of the resulting enolate would give rise to the thermodynamically more stable trans relationships of the two side chains. Conjugate additions of lithium diorganocuprates with substituted cyclic enones are known to proceed with exceedingly high stereoselectivity. Even a mere methyl

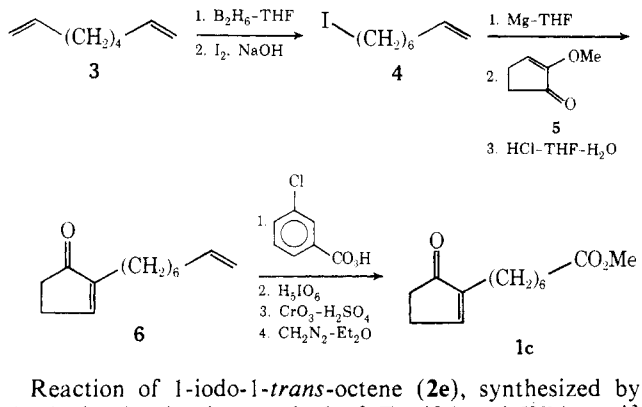
substituent in the γ position is sufficient to favor trans over cis adduct by 96:4.[7]



Ph = phenyl

To test the validity of these assumptions, we first studied the feasibility of carrying out the conjugate addition reaction using simple unfunctionalized model compounds such as **1c** and **2g.** The synthon **1c**[8] was prepared from the readily available starting material, octa-1,7-diene (**3**). The first step was the conversion of **3** into 8-iodo-1-octene (**4**) (75%) *via* the hydroboration procedure of Brown, *et al.*[9] The Grignard reagent from **4** was condensed with 2-methoxycyclopent-2-en-1-one[10] (**5**) to yield 2-(oct-7-enyl)cyclopent-2-en-1-one (**6**) according to the method of Ansell and Ducker.[11] The conversion of the olefin **6** into **1c** was accomplished in an overall yield of 42% *via* the following sequence of reactions. Treatment of **6** with *m*-chloroperbenzoic acid gave the epoxide; cleavage of the latter with periodic acid to the aldehyde,[12] followed by oxidation with Jones reagent and esterification with diazomethane yielded **1c** (Scheme I). Alternatively, the aldehyde may be oxidized using silver oxide.

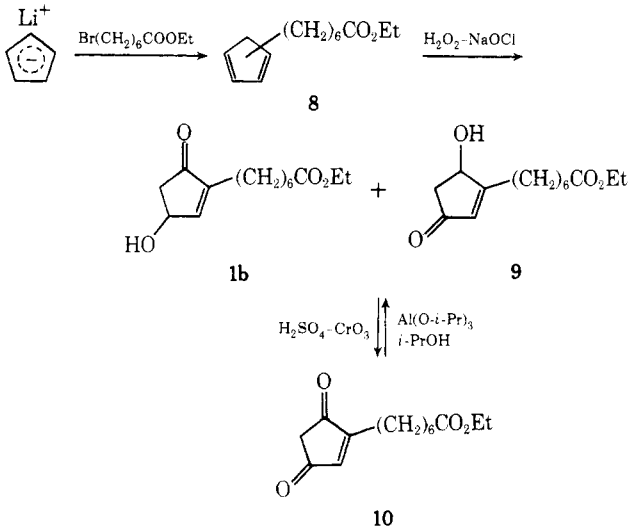
Scheme I



Reaction of 1-iodo-1-*trans*-octene (**2e**), synthesized by the hydroalumination method of Zweifel and Whitney,[13] with either fine lithium powder or dispersion in hexane afforded 1-lithio-1-*trans*-octene (**2f**). When **1c** was treated with 2 molar equiv of **2f** in the presence of 1 molar equiv of copper(I) iodide, no significant amount of conjugate addition took place,[14] probably because of the insolubility of CuI in ether. Therefore, we decided to use a soluble copper species such as the tri-*n*-butylphosphine-copper(I) iodide complex.[15] In this case, 1,4 addition proceeded readily and efficiently as evidenced by the isolation of (±)-11,15-dideoxyprostaglandin E_1 (**7b**) (75% from **1c**) after hydrolysis of the methyl ester with methanolic sodium hydroxide (Scheme IV).

We next turned our attention to the reaction of the oxygenated left-hand synthon **1a** with **2g.** The synthetic sequence employed for the preparation of (±)-2-(6-carboethoxyhexyl)-4-hydroxycyclopent-2-en-1-one (**1b**) is outlined in Scheme II. Alkylation of lithium cyclopentadienide with ethyl 7-bromoheptanoate[16] in tetrahydrofuran at 25° afforded alkylated cyclopentadiene isomers,[17] represented as **8** in essentially quantitative yield. The diene **9** was used immediately in a 1,4 cycloaddition to chemically generated singlet oxygen by the reaction of sodium hypochlorite and hydrogen peroxide[18] at −10° in ethanol to give a mixture of hydroxycyclopentenones (20–40% yield) **1b**[19] and **9** in a ratio of 1:4. Reaction of the corresponding methyl ester in methanol at −10° improved the yield to 55%, but the ratio of **1b** to **9** remained unchanged. These positional isomers can be readily separated by column chromatography on silicic acid using benzene–ethyl acetate. Alternatively, this mixture was oxidized with Jones reagent at 0° to yield **10.** While reduction of **10** with lithium tri-*tert*-butoxyaluminum hydride afforded **1b** and **9** in a ratio of 1:9, reduction using aluminum isopropoxide on the other hand gave **1b** and **9** in a ratio of 2:1.

Scheme II

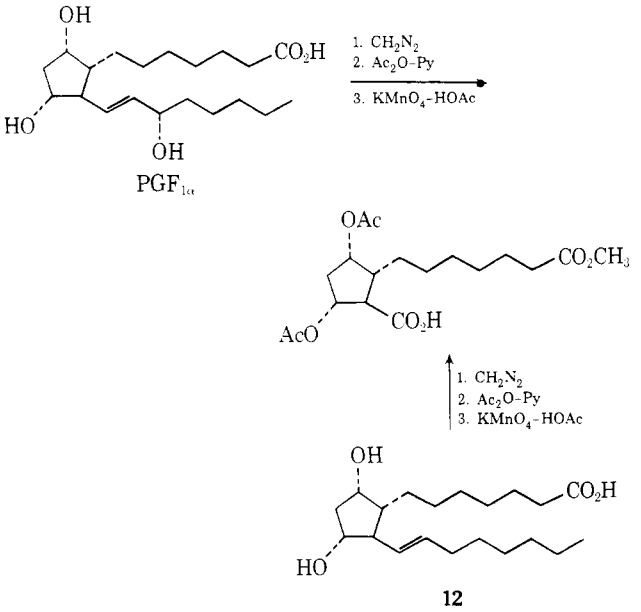


After conversion of **1b** into the tetrahydropyranyl ether **1a,** the latter was then treated with 2 molar equiv of 1-lithio-1-*trans*-octene (**2f**) in the presence of 1 molar equiv of tri-*n*-butylphosphine-copper(I) iodide complex in ether. After acidic hydrolysis of the protecting group,[20] (±)-15-deoxyprostaglandin E_1 ethyl ester **11a** (60% yield from **1b**) was obtained as the *sole* major product, accompanied by a small quantity of (±)-15-deoxyprostaglandin A_1 ethyl ester, an acid dehydration product of **11a.** This observation is consistent with the proposition that the vinyl cuprate attacked **1a** stereoselectively, most likely from the least hindered side. Hydrolysis of the ester grouping in **11a** was accomplished by its exposure to Baker's yeast for 13 hr yielding **11b.** The nmr spectrum of (±)-15-deoxyprostaglandin E_1 (**11b**) gave the following signals: δ 1.21 (t, 3, J = 6.7 Hz, CH_3), 4.13 (q, 2, J = 6.7 Hz, CH_3CH_2), 4.20 (m, 1, H-C-OH), 5.28 (d of d, $J_{12,13}$ = 7, $J_{13,14}$ = 16 Hz, $-C_{13}H=$), and 5.58 ppm (d of t, $J_{13,14}$ = 16, $J_{14,15}$ = 6 Hz, $=C_{14}H$); its infrared spectrum exhibited a band at 962 cm^{-1} (trans CH=CH). These data corroborate the fact that the trans stereochemistry of the double bond is maintained during the 1,4 addition, in agreement with the finding of others[5b] that the addition of both lithium di-*cis*- and di-*trans*-1-propenylcuprate to 2-cyclohexenone is completely stereospecific.

If (±)-**11a** was incubated with Baker's yeast for 48 hr or longer, two different polar compounds, **12** and **13,** were produced instead, the R_f values[21] (0.35 and 0.21, respectively) of which were identical with products derived from $NaBH_4$ reduction of (±)-**11b.** This observation suggested that not only was the yeast capable of hydrolyzing the ester grouping but also was capable of reducing the 9-keto function in (±)-**11a** to give two diastereomeric PGF_1 type compounds. The stereochemical assignment of the 9-hydroxyl group was made by subjecting $PGF_{1\alpha}$, $PGF_{1\beta}$, and **12** to the following series of reactions:[22] methylation of the carboxyls with dia-

zomethane, acetylation of the hydroxyl groups with acetic anhydride in pyridine, and oxidative cleavage of the double bond using $KMNO_4$ in acetic acid. The chromatographic behavior[21] of the resulting acid derived from **12** was found to be the same as the acid originating from $PGF_{1\alpha}$ but clearly different from the acid derived from $PGF_{1\beta}$. These degradative reactions (Scheme III) establish the chemical structure of **12** and **13** as 15-deoxyprostaglandin $F_{1\alpha}$ and 15-deoxy-*ent*-prostaglandin $F_{1\beta}$, respectively. It is interesting to note that under the same experimental conditions, the C-9 carbonyls in (−)-PGE_1 and (−)-PGE_1 methyl ester were reduced extremely slowly and poorly (<1%).

Scheme III



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In accord with our objective, our efforts were next directed to the preparation of an oxygen-functionalized[22] vinyl iodide **2a,** a precursor of the cuprate **2d.** Since **2e** was efficiently synthesized from 1-octyne *via* the hydroalumination method,[11] it was convenient to extend this process for the synthesis of **2a.** Reaction of (±)-1-octyn-3-ol with 1 mol equiv of diisobutylaluminum hydride (DiBAL) afforded a very small quantity of the desired (±)-3-hydroxy-1-iodo-1-*trans*-octene (**2a**). Instead, a large quantity of unreacted starting material was recovered, indicating that the major portions of the DiBAL reacted with the free hydroxyl function with the evolution of hydrogen. Furthermore, blocking of the hydroxyl group as the tetrahydropyranyl ether did not improve the extent of the hydroalumination reaction. However, when 2 mol equiv of DiBAL was used for hydroalumination, nmr analysis[23] of the crude reaction mixture showed the presence of only 25% of 1-octyn-3-ol remaining, accompanied by substantial quantities of vinyl iodide and alkyl iodide, formed in a ratio of 3:1. By heating the reaction mixture with triethylamine, the alkyl iodide is selectively destroyed permitting the isolation of the desired 3-hydroxy-1-iodo-1-*trans*-octene (**2a**) which is obtained on distillation of the crude material in a yield of 25% based on 1-octyn-3-ol. Although triisobutylaluminum (TRiBAL) reacts readily with hydroxyl functions with the evolution of isobutane, it is relatively inert toward triple bonds. To determine the optimum conditions for hydroalumination, a series of experiments was conducted on 1-octyn-3-ol using varying quantities of DiBAL and TRiBAL at different temperatures and times of reaction. It was found that the addition of 2 equiv of TRiBAL, followed by 1 equiv of DiBAL and heating at 56–58° for 2 hr gave the optimum yield of 3-hydroxy-1-iodo-1-*trans*-octene (**2a**) (47% on distillation) and reduced the formation of the alkyl iodide (ratio of 5.6:1). Substantial quantity (25–30%) of unreacted 1-octyn-3-ol was recovered, which may be recycled.

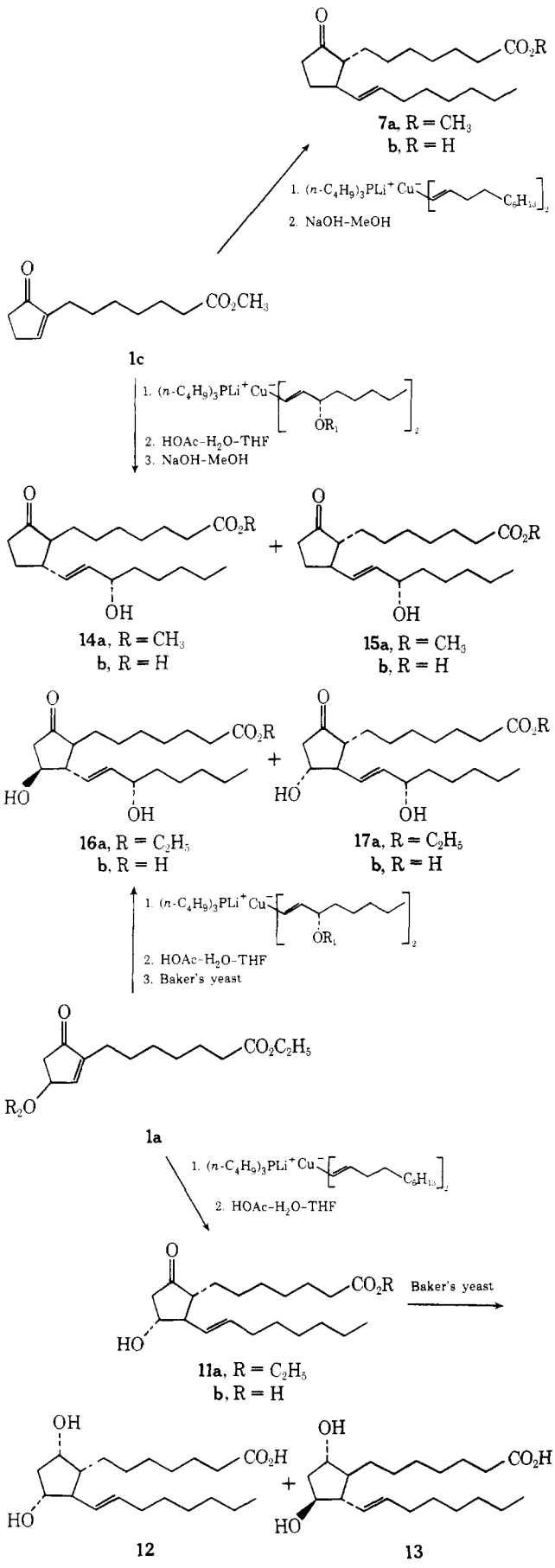
Having developed an adequate method for the preparation of the requisite (±)-iodovinylcarbinol, it was then necessary to prepare the chiral iodovinylcarbinol **2a** and convert it efficiently to the corresponding lithium species for the eventual formation of the cuprate reagent **2d.** This was accomplished by the transformation of (*S*)-1-octyn-3-ol[24] into 3(*S*)-hydroxy-1-iodo-1-*trans*-octene[25] (**2a**) which was in turn converted into 3(*S*)-(1-ethoxy)ethoxy-1-iodo-1-*trans*-octene (**2b**) using ethyl vinyl ether[22] in the presence of an acid catalyst. Treatment of **2b** with either fine lithium powder or dispersion in hexane afforded 3(*S*)-(1-ethoxy)-ethoxy-1-lithio-1-*trans*-octene (**2c**) in 55% yield.[26] *It should be emphasized that due to the extreme lability of* **2c**,[27] *it must be used immediately for the generation of the cuprate* **2d** *using a 0.5 molar equiv of tri-n-butylphosphinecopper(I) iodide.*

Treatment of **1c** with **2d** gave two diastereomeric prostanoic acids (60%) after acidic cleavage of the protecting group and basic hydrolysis of the ester grouping. These products were characterized as 11-deoxy-15-*epi*-*ent*-prostaglandin E_1 (**14b**) and 11-deoxyprostaglandin E_1[28] (**15b**) on basis of their spectral data and chromatographic behaviors[28] (Scheme IV). The circular dichroism (CD) spectrum of **14b** exhibited a positive Cotton effect ($\theta \times 10^{-3} = +7.5°$ at 296 nm), whereas the CD spectrum of **15b** afforded a negative cotton effect ($\theta \times 10^{-3} = -8.9$ at 296 nm), characteristic for the absolute configuration of C-8 of ent and natural prostanoic acids, respectively.[29] It is interesting to note that an excess of **14b** (55% *vs.* 45%) was consistently obtained in the conjugate addition reaction. The successful achievement of the conjugate addition of an oxygenated organocuprate to an unfunctionalized "left-hand synthon" **1c** prompted us to examine the reaction of the (−)-*trans*-divinylcuprate **2d** with (±)-**1a** for the synthesis of (−)-PGE_1. Two major diastereomeric products were obtained by reaction of (−)-**2d** with (±)-**1a** after acid hydrolysis of the protecting groups[20] and cleavage of the ester grouping with Baker's yeast (Scheme III). The first product was characterized as 15-*epi*-*ent*-PGE_1 (**16b**) on the basis of the following physical data. Its CD spectrum displayed a positive Cotton effect ($[\theta] \times 10^{-3} = +12.05$ at 296 nm), whereas its acid-dehydration[30] product, 15-*epi*-*ent*-PGA_1, uv λ_{max} 217 nm (ϵ 11,000), afforded a negative Cotton effect ($[\theta] \times 10^{-3} = 50.4$ at 231 nm), contrary to the CD curves of natural PGE_1 and PGA_1, respectively. Its nmr and mass spectrum and chromatographic behavior were also consistent with the assigned structure. The second product, mp 115–116°, was found to be identical (infrared, nmr and mass spectrum) with an authentic specimen of natural PGE_1 (**17b**) prepared by biosynthesis.[31] Aside from these major products,[32] no apparent 8-*iso*-PGE_1 and 11-*epi*-PGE_1 were detected.[33]

Conclusion

A highly stereospecific method for the construction of the prostanoic acid skeleton is reported. The synthesis depends on steric interactions to control the relative stereochemistry of the ring substituents. The present study clearly demonstrates the ability of the substituent at "C-11" (prostaglandin numbering) in the "left-hand synthon" such as **1a** to direct the attack of an octenylcuprate from the opposite face of the five-membered ring, and protonation of the resulting enolate selectively gives rise to the thermodynamically more stable stereoisomeric prostenoate. Thus, an intermediate

Scheme IV



possessing only a single center of asymmetry in a five-membered ring is converted in a single key step into a prostanoic acid in which the three-ring substituents at C-8, C-11, and C-12 are present exclusively in the required natural "all-trans" configuration. This transformation paves the way for a bioorganic total synthesis of optically active prostaglandins since a single center of asymmetry can readily be introduced microbiologically into a prochiral substrate as reported in the accompanying paper.[3]

Experimental Section[34]

8-Iodo-1-octene (4). Into a dry three-necked flask equipped with a septum stopper, thermometer-well adapter, pressure-equalizing dropping funnel, and magnetic stirrer were placed dry THF (200 ml/1 mol of octadiene) and 6.45 molar equiv of octadiene (**3**) (freshly distilled over CaH_2). A blanket of nitrogen was maintained at all times. Conversion to the trialkylborane was achieved by the dropwise addition of a solution of B_2H_6 in THF (1 molar equiv of hydride). The solution was stirred at 25° for 1 hr, then methanol (13 ml/mol of hydride) was added to destroy the excess hydride, followed by 0.28 molar equiv of iodine (added all at once) and 0.28 molar equiv of a 3 *M* solution of NaOH in methanol over a period of 5 min. After the reaction mixture was stirred for 15–20 min, it was poured into water containing $Na_2S_2O_3$ (1 g/50 ml of water) to remove excess iodine, and the aqueous layer was then extracted three times with pentane. The combined pentane extract was dried over $MgSO_4$. The pentane and most of the excess octadiene were evaporated, and the remaining material was distilled over CaH_2 under reduced pressure [bp 44–46° (0.2 mm)] to give 8-iodo-1-octene (**4**): ir 3080 (unsaturated CH), 2850 (saturated CH), 1640, 990, and 910 cm^{-1} (terminal vinyl group); nmr δ 2.00 (*m*, 2, $-CH_2CH{=}CH_2$), 3.18 (*t*, 2, J = 6.5 Hz, $I{-}CH_2$), 4.80–5.21 (m, 2, $CH{=}CH_2$), and 5.50–6.15 ppm (m, 1, $CH{=}CH_2$). *Anal.* Calcd for $C_8H_{15}I$: C, 40.35; H, 6.35. Found: C, 40.12; H, 6.87.

2-(Oct-7-enyl)cyclopent-2-en-1-one (6). 8-Iodo-1-octene (20.5 g, 0.086 mol) in 50 ml of THF was added dropwise to a mixture of 2.5 g of Mg turnings in 20 ml of dry THF with mechanical stirring (under a blanket of nitrogen). After completion of the addition (~1 hr), the mixture was refluxed for an additional 30 min. To this cooled Grignard reagent was added dropwise 9.5 g (0.085 mol) of 2-methoxy-2-cyclopenten-1-one (**5**), and the mixture was stirred at room temperature for 30 min. The resulting mixture was poured onto 200 g of chipped ice and 30 g of NH_4Cl; 100 ml of 2 *N* HCl was then added, and after shaking for 30 min, the product was extracted with several portions of ether (500 ml total). The combined extracts were washed with two 50-ml portions of saturated $NaHCO_3$, followed by 100 ml of saturated NaCl, and dried (Na_2SO_4). After evaporation of solvent, approximately 14 g of a crude residue was obtained.

To 9.4 g of the above residue, dissolved in 70 ml of anhydrous methanol, was added 2 ml of concentrated H_2SO_4, and the mixture was refluxed for 14 hr. The cooled mixture was neutralized by the addition of solid $NaHCO_3$. After removal of the methanol, 200 ml of water was added, and the resulting mixture was exhaustively extracted with ether (total of 600 ml). The combined extracts were washed with 150 ml of saturated aqueous NaCl, dried ($MgSO_4$), and concentrated, and the residual oil was distilled under reduced pressure. The fraction boiling at 87–89° (0.2 mm) was collected as pure 2-(oct-7-enyl)cyclopent-2-en-1-one (**6**) (4.3 g, 40–50% yield): ir (film) 1700 (C=O), 1630 (C=C), 995, and 905 cm^{-1} (terminal vinyl group); nmr δ 4.75–6.16 (m, 3, $-CH{=}CH_2$) and 7.16 ppm (m, 1, $-C(=O)C{=}CH$); uv λ_{max} 227 nm (ϵ 8600). *Anal.* Calcd for $C_{13}H_{20}O$: C, 81.21; H, 10.48. Found: C, 81.39; H, 10.51.

Epoxidation of 2-(Oct-7-enyl)cyclopent-2-en-1-one (6). To 1.77 g of **6**, dissolved in 8 ml of methylene chloride, was added dropwise a solution of *m*-chloroperbenzoic acid (1.7 g) in 20 ml of methylene chloride. The mixture was allowed to stand at 0° for 48 hr. After the usual work-up, the residue was chromatographed over a silicic acid–Celite (85:15) column. The column was eluted with a gradient system comprised of benzene and benzene–ethyl acetate (1:1) to yield 0.89 g of the epoxide and 0.96 g of unreacted **6**, which may be recycled: nmr no vinylic protons, δ 7.35 (m, 1, O=C—C=CH); the infrared spectrum showed absorption at 1700 cm^{-1} (O=C—C=C) and a small peak at 1740 cm^{-1} (saturated five-membered ring ketone). This latter absorption indicated that **6** was also con-

taminated with a small amount of the diepoxide. All attempts to resolve these two compounds on tlc in various solvent systems failed. So the epoxide was used as such for the periodic acid oxidation.

Periodic Acid Cleavage of the Epoxide. Periodic acid (15 g) was suspended in 1500 ml of anhydrous ether and stirred for 1 hr at room temperature. The remaining undissolved solid was filtered off, and 1450 ml of the filtrate (concentration 9 mg/ml) was added to a solution of the epoxide (12 g) in 100 ml of ether. After the mixture was stirred at room temperature for 1 hr, it was diluted with water, and the organic layer was separated and evaporated to afford 10.2 g of the crude aldehyde. The nmr spectrum showed the presence of an aldehydic proton at δ 9.76 as a triplet and an olefinic proton at δ 7.36. As this aldehydic compound was unstable, it was used immediately for the subsequent Jones oxidation.

Oxidation of the Aldehyde and Jones Reagent. The crude aldehyde (0.5 g) from the previous reaction was dissolved in 40 ml of acetone. After cooling to 0°, 3 ml of Jones reagent was added dropwise over a period of 15 min. After stirring the reaction mixture for 30 min at 0°, the excess Jones reagent was destroyed by the addition of 10 ml of isopropyl alcohol. After evaporation of the acetone on a rotary evaporator, the mixture was diluted with water (25 ml) and extracted with three 30-ml portions of ethyl acetate. The combined organic phase was washed with three 30-ml portions of 10% Na_2CO_3 solution. After acidification of the carbonate solution with 6 *N* HCl, it was exhaustively extracted with ethyl acetate. The ethyl acetate layer was washed with water, dried ($MgSO_4$), and evaporated to give 400 mg of the desired acid. The crude acid was chromatographed over a silicic acid–Celite (85:15) column. The column was eluted with a gradient system which consisted of benzene and benzene–ethyl acetate (7:3) to afford 290 mg of pure acid. Distillation of the acid under reduced pressure [bp 135–140° (0.03 mm)] afforded 2-(6-carboxyhexyl)cyclopent-2-en-1-one: mp 37–38°; ir ($CHCl_3$) 1710 (COOH, dimer) and 1700 cm^{-1} (C(=O)—C=C); nmr δ 7.30 (m, 1, olefinic proton) and 10.90 ppm (s, 1, COOH); uv λ_{max} 227 nm (ϵ 9000). *Anal.* Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.70; H, 8.65.

Oxidation of the Aldehyde with Silver Oxide. The aldehyde (200 mg) dissolved in 1 ml of diethyl ether was added dropwise to a suspension of Ag_2O in ether at 0°. The mixture was stirred for 1 hr, and the black precipitate was filtered off. The filtrate was extracted three times with methylene chloride to remove any unreacted aldehyde (39 mg). The aqueous layer was then acidified to pH 2 and exhaustively extracted with ethyl acetate. The combined ethyl acetate layers were dried (Na_2SO_4) and evaporated to yield 123 mg of the acid, mp 36–37°.

2-(6-Carbomethoxyhexyl)cyclopent-2-en-1-one (1c). The crude acid (7.2 g), dissolved in 50 ml of diethyl ether, was slowly treated with an ethereal solution of diazomethane until a yellow color persisted. The excess diazomethane was destroyed by the addition of a few drops of 2 *N* HCl. The organic layer was then washed successively with 10% $NaHCO_3$, water, and saturated NaCl solution. After drying of the ethereal layer (Na_2SO_4), the solvent was evaporated to give 7.8 g of a yellow oil, which was chromatographed over a silicic acid–Celite (85:15) column (17 × 1.5 in.). The column was eluted with a gradient system comprised of to 500 ml of benzene in the mixing chamber and 500 ml of benzene–ethyl acetate (7:3) in the reservoir flask, and 7-ml fractions were collected. Fractions 110–152 were pooled and evaporated to yield 5.2 g of **1c**, which was further purified by distillation under reduced presure [bp 105–106° (0.05 mm)]: ir (film) 1735 (CO_2CH_3), 1700 (C(=O)—C=C), 1630 cm^{-1} (C=C); nmr δ 3.63 (s, 3, CO_2CH_3) and 7.33 ppm (m, 1, olefinic proton); uv λ_{max} 227 nm (ϵ 10,900). *Anal.* Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.69; H, 8.84.

1-Iodo-1-*trans*-octene (2e). To a solution of 1-octyne (55 g, 0.5 mol) in dry heptane (100 ml) was added DiBAL (91 ml, 0.5 mol) while maintaining the temperature below 40°. When the exothermic reaction had subsided, the reaction mixture was heated for 2 hr at 50°. The heptane was then removed under reduced pressure (0.2 mm) and the residue obtained diluted with dry THF (200 ml). To this vinylalane solution at −50° was added a solution of iodine (127 g, 0.5 mol) in THF (200 ml). After allowing the reaction mixture to warm up to room temperature, the diisobutylalane [$Al(C_4H_9)_2$] was decomposed at 20–30° by the dropwise addition of 20% sulfuric acid (exothermic reaction). When the isobutane evolution had diminished, the reaction mixture was poured into ice–20% sulfuric acid. This mixture was extracted three times with pentane, and the combined extracts were washed successively with $Na_2S_2O_3$, saturated $NaHCO_3$, and saturated NaCl solutions and dried ($MgSO_4$). After evaporation of the pentane, the resulting liquid was stirred with CaH_2 to remove the final traces of water. Distillation over CaH_2 [56° (0.2 mm)] afforded 102 g of pure dry vinyl iodide (86% yield): ir (film) 1605 (C=C), 1465 (CH_3), and 940 cm^{-1} (CH=CH, trans); nmr δ 0.92 (m, 3, CH_3), 1.30 (m, 8, methylenes), 2.03 (m, 2, CH=CH—CH_2), and 5.83–6.78 ppm (m, 2, CH=CH). *Anal.* Calcd for $C_8H_{15}I$: C, 40.35; H, 6.35. Found: C, 40.19; H, 6.90.

1-Lithio-1-*trans*-octene (2f). In a three-necked, round-bottom flask equipped with a wire blade mechanical stirrer and pressure-equalizing dropping funnel were placed 4–6 molar equiv of fine lithium powder and dry diethyl ether (2 ml/mmol of vinyl iodide) freshly distilled over $LiAlH_4$. An argon atmosphere was maintained at all times. To this rapidly stirred mixture, which was cooled in an ice bath, was added 1 molar equiv of 1-iodo-1-*trans*-octene (vinyl iodide) in dry diethyl ether (2 ml/mmol of vinyl iodide). After a few drops of the vinyl iodide in ether was added, a Gilman test was performed. If the test was negative, the addition of the vinyl iodide was stopped and the rapid stirring of the lithium solution continued. The Gilman test was performed at various intervals. When a positive test was obtained, the addition of the vinyl iodide was recommenced. The vinyl iodide solution was added over 1.5–2 hr. The solution was stirred with ice-bath cooling for an additional 4 hr. The solution of the vinyllithium was then transferred under argon through a glass wool filter (to filter out any unreacted lithium) to a storage bottle. The concentration of the vinyllithium solution was determined before use by the Gilman double titration procedure for alkyllithiums.[35]

(±)-11,15-Dideoxyprostaglandin E_1 (7b). A solution of copper(I) iodide–tri-*n*-butylphosphine complex (1.75 g, 3.0 mmol) in 2.5 ml of dry diethyl ether was treated with 22.5 ml of a 0.27 *M* solution (6.08 mmol) of 1-lithio-1-*trans*-octene in ether (added dropwise *via* syringe) at −78° under a blanket of argon. After stirring at −78° for 30 min, 450 mg (2 mmol) of **1c** was added dropwise *via* a syringe. This reaction mixture was stirred at −78° for 15 min and then allowed to warm to −23° (methanol–ice) and stirred at −23 to −10° for 1 hr. Finally, the mixture was allowed to warm to room temperature, whereupon the yellow solution began darkening after about 30 min. Twenty milliliters of 20% aqueous $(NH_4)_2SO_4$ solution was added and the mixture shaken in a separatory funnel. The phases were separated, and the organic phase was extracted with another portion of the $(NH_4)_2SO_4$ solution. The combined blue aqueous solution was extracted three times with ether, and the combined ethereal extract was washed with a saturated sodium chloride solution (50 ml) and dried ($MgSO_4$). After evaporation of the ether, the crude oily residue was chromatographed on 150 g of silica gel (Brinkmann), and the column was washed with 2 l. of chloroform–benzene (1:1). Elution of the column with pure chloroform afforded approximately 500 mg of the crude *dl*-11,15-dideoxyprostaglandin E_1 methyl ester (**7a**) which was treated with 400 mg (10 mmol) of NaOH in 20 ml of methanol–water (3:1). The mixture was stirred magnetically for 15 hr and the methanol was then removed by evaporation. The aqueous phase was diluted with 5 ml of water, and the resulting mixture was extracted with ether. The aqueous phase was then acidified with HCl and extracted with ether. The combined ethereal layers were dried ($MgSO_4$), and the solvent was removed to yield 255 mg of **7b** having the following characteristics: molecular ion at *m/e* 322.2505 (theory for $C_{20}H_{34}O_3$, 322.2507); nmr δ 5.5 ppm (m, 2, vinylic protons at C-13 and C-14); ir 1730, 1710, and 960 cm^{-1}; tlc mobility,[28] R_f 0.77.

2-(6-Carboethoxyhexyl)-4-hydroxycyclopent-2-en-1-one (1b) and 2-(6-Carboethoxyhexyl)-1-hydroxycyclopent-2-en-4-one (9). A solution of methyllithium (1.95 *M*, 0.65 mol, 333 ml) was added under nitrogen to a magnetically stirred solution of 60 ml (0.68 mol) of freshly distilled cyclopentadiene in 500 ml of dry tetrahydrofuran (THF) with ice-bath cooling. To this resulting white suspension, 120 g (0.54 mol) of ethyl 7-bromoheptanoate was added dropwise over a period of 30 min. The mixture was allowed to warm to room temperature and stirred for 3 hr. The resulting clear solution was poured into water and extracted with ether (3 l.). The extract was washed twice with water and once with saturated sodium chloride solution, dried ($MgSO_4$), and evaporated to dryness to

yield 119 g (0.54 mol) (100%) of 2-(6-carboethoxyhexyl)cyclopenta-1,4-diene (**8**): nmr δ 2.90 (m, 2) and 3.53–3.93 ppm (m, 3, olefinic protons).

The crude diene **8** (119 g, 0.54 mol) from the last reaction was dissolved in ethanol (6 l.). This was cooled to −10°, and to this chilled solution 30% hydrogen peroxide was added (125 g, 1.1 mol). To this mixture a solution of potassium hypochlorite (840 ml, 1.15 mol, 1.37 *N*) was added dropwise over a period of 2 hr. After stirring at −10° for an additional 30 min, the reaction mixture was acidified with 2 *N* HCl, and the ethanol was removed on a rotary evaporator. The residual oil was diluted with water and extracted with ether (3 l.). The extract was washed with water and saturated sodium chloride solution, dried ($MgSO_4$), and evaporated to dryness to yield 120 g of a yellow oil.

The yellow oil (20 g) was chromatographed over a silicic acid–Celite (85:15) column (1.5 × 25 in.). The column was washed with two volumes of benzene–ethyl acetate (8:2). The desired 2-(6-carboethoxyhexyl)-4-hydroxycyclopent-2-en-1-one (1.5 g) (**1b**) was eluted from the column with benzene–ethyl acetate (65:35); while the positional isomer, 2-(6-carboethoxyhexyl)-1-hydroxycyclopent-2-en-4-one (5 g) (**9**), was eluted from the column with benzene–ethyl acetate (55:45).

Compound **1b** (1 g) was purified by rechromatography on another silicic acid–Celite (85:15) column (0.75 × 16 in.). The column was eluted with a gradient system consisting of 400 ml of benzene–ethyl acetate (95:5) in the mixing chamber and 400 ml of benzene–ethyl acetate (65:35) in the reservoir; 7-ml fractions were collected. Fractions 53–94 were combined and evaporated to dryness to yield 884 mg of **1b:** uv λ_{max} 222 nm (ϵ 10,000); ir (Nujol) 3425, 1750, and 1710 cm^{-1}; nmr δ 1.21 (t, 3, J = 6.7 Hz, CH_3), 4.13 (q, 2, J = 6.7 Hz, CH_3CH_2), 4.93 (m, 1, H—C—OH), and 7.23 ppm (m, 1 vinyl H); molecular ion at *m/e* 254.1608 (theory for $C_{14}H_{22}O_4$, 254.1518).

Similarly, compound **9** (1 g) was repurified by chromatography over a silicic acid–Celite (85:15) column (0.75 × 15 ft). The column was eluted with gradient system consisting of 500 ml of benzene–ethyl acetate (95:5) in the mixing chamber and 500 ml of benzene–ethyl acetate (60:40) in the reservoir; 7-ml fractions were collected. The desired compound **9** resided in fractions 134–149 which were pooled to yield 798 mg of **9:** uv λ_{max} 224 nm (ϵ 13,500); nmr δ 1.22 (t, 3, J = 6.7 Hz, CH_3), 4.13 (q, 2, J = 6.7 Hz, CH_3CH_2), 4.88 (m, 1, J = 6 and 2.5 Hz, H—C—OH), and 5.98 ppm (m, 1, vinyl H); ir (Nujol) 3410, 1733, and 1695 cm^{-1}; molecular ion at *m/e* 254.1599 (theory for $C_{14}H_{22}O_4$, 254.1518).

(±)-2-(6-Carboethoxyhexyl)-4-(2-tetrahydropyranyloxy)cyclopent-2-en-1-one (1a). One drop of concentrated hydrochloric acid was added to a mixture of 3.2 g (13.3 mmol) of the hydroxy ester (**1b**) and 3.28 g (~40 mmol) of dihydropyran. The solution was shaken in order to effect mixing and was allowed to warm and stand at room temperature for 4 hr. Then, the solution was diluted with ether, and the resulting ethereal layer was washed successively with saturated $NaHCO_3$ and saturated NaCl solutions and dried ($MgSO_4$). Evaporation of the ethereal solution yielded 4.6 g of a yellow oil. This oil was chromatographed on a silicic acid–Celite (85:15) column (1.5 × 16 in.). The column was eluted with a gradient system consisting of 500 ml of benzene in the mixing flask and 500 ml of benzene–ethyl acetate (85:15) in the reservoir flask, and 7-ml fractions were collected. Fractions 68–120 were pooled and evaporated to dryness to give 2.7 g of **1a:** uv λ_{max} 222 nm (ϵ 9,500); ir (Nujol) 1740, 1720, and 1040 cm^{-1}; nmr δ 1.21 (t, 3, J = 6.7 Hz, CH_3CH_2CO), 3.75 (m, 2, $-COCH_2$), 4.13 (q, 2, J = 6.7 Hz, CH_3CH_2CO), 4.91 (m, 2, HCOCH), and 7.26 ppm (m, 1, vinyl H); molecular ion at *m/e* 338.2093 (theory for $C_{19}H_{30}O_5$, 338.2125).

2-(6-Carboethoxyhexyl)cyclopent-2-ene-1,4-dione (10). The oily mixture of hydroxycyclopentenones (7 g) (**1b** and **9**) was dissolved in 700 ml of acetone and cooled in an ice bath. To this solution was added 20 ml of Jones reagent dropwise (1 ml/min) under stirring. After 30 min, 15 ml of absolute methanol was added to destroy excess Jones reagent. The mixture was diluted with 500 ml of water, concentrated to 700 ml, and then extracted with three 250-ml portions of ether. The combined ethereal extract was washed with K_2CO_3, dried (Na_2SO_4), and evaporated to dryness to yield 4 g of an oily residue. The residue was chromatographed over a column (1.5 × 16 in.) containing silicic acid–Celite (85:15). The column was eluted with a gradient consisting of 500 ml of benzene–ethyl acetate (90:10) in the mixing chamber and 500 ml of benzene–ethyl acetate (70:30) in the reservoir flask; 7-ml fractions were collected. Fractions 128–141 were pooled and evaporated to yield **10:** mp 43–45°; nmr δ 1.21 (t, 3, J = 6.7 Hz, CH_3), 2.83 (s, 2, C-5, CH_2), 4.13 (q, 2, J = 6.7 Hz, CH_3CH_2), and 7.0 ppm (t, 1, J = 1, 1, and 1.5 Hz, vinyl H); uv λ_{max} 232 nm (ϵ 12,800); molecular ion at *m/e* 252.1461 (theory for $C_{14}H_{20}O_4$, 252.1362).

Lithium Aluminum Tri-*tert*-butoxy Hydride Reduction of 10. To a suspension of lithium aluminum tri-*tert*-butoxy hydride (freshly prepared from 30.4 mg (0.8 mmol) of $LiAlH_4$ and 237 mg (3.2 mmol) of *tert*-butyl alcohol in 2 ml of dry THF was added a solution of 100 mg of **10** (0.4 mmol) in 2 ml of THF at 0°. The reaction mixture was stirred at 0° for 30 min and at room temperature for an additional hour. The excess hydride was then quenched with 5 ml of 0.1 *N* HCl and extracted with ether. The ethereal layer was washed successively with 10% $NaHCO_3$ and saturated NaCl solutions and dried ($MgSO_4$). After evaporation of the solvent, 105 mg of residue was obtained. The positional isomers (**9** and **1b**) may be estimated from the nmr spectrum of the residue, which showed the vinylic protons at δ 5.98 in **9** and δ 7.23 in **1b** to be in a ratio of 9:1.

Aluminum Isopropoxide Reduction of 10. A solution of 220 mg (1 mmol) of freshly distilled aluminum isopropoxide [bp 130–140° (7 mm)] in 10 ml of anhydrous isopropyl alcohol (freshly distilled over CaH_2) was heated to reflux, and 100 mg (0.4 mmol) of the diketone (**10**) in dry isopropyl alcohol (1.5 ml) was added by syringe over a period of 15 min. The isopropyl alcohol was distilled slowly through a short path distillation apparatus over a period of 2 hr keeping the volume in the reaction flask constant by addition of fresh isopropyl alcohol. The remaining alcohol was removed on a rotary evaporator. Ether (20 ml) and water (5 ml) were added, and the mixture was acidified with 2 *N* HCl. The aqueous layer was extracted twice with ether. The combined ethereal extract was washed with water, dried ($MgSO_4$), and evaporated to afford a yellow gum (110 mg). An estimation of the ratio of the positional isomers may be made from the nmr spectrum of the gum, which showed the vinylic protons at δ 5.98 in **9** and δ 7.23 in **1b** as the isopropyl esters to be in a ratio of 1:2.

(±)-15-Deoxyprostaglandin E_1 Ethyl Ester (11a). A solution of tri-*n*-butylphosphine–copper(I) iodide complex (1.61 g, 4.1 mmol) in 21 ml of dry diethyl ether was treated with 34 ml of a 0.242 *M* (8.2 mmol) solution of **2f** in ether at −78° under a blanket of argon. After being stirred at −78° for 30 min, 1.33 g (3.99 mmol) of the tetrahydropyranyl ether derivative **1a** in 25 ml of dry diethyl ether was added dropwise to the yellow divinylcuprate solution. After the resulting solution was stirred at −78° for 15 min and then at −22 to −10° for 90 min, 28 ml of cold 20% aqueous $(NH_4)_2SO_4$ solution was added to complex the copper. The ethereal layer was separated from the blue aqueous layer, which was extracted three times with ether. The combined ethereal extracts were washed twice with a saturated NaCl solution and dried ($MgSO_4$). Evaporation of the ethereal extract afforded a reddish yellow oil, which was dissolved in 10 ml of acetic acid–water (65:35) and 1 ml of tetrahydrofuran[20] and was stirred at 30° for 12 hr. The solution was diluted with ether and washed with a saturated sodium bicarbonate solution until the washings were basic. The oily product obtained on evaporation of the ether was chromatographed over a silicic acid–Celite (85:15) column (0.75 × 14 in.). The column was eluted with a gradient system consisting of 400 ml of benzene in the mixing chamber and 400 ml of benzene–ethyl acetate (75:25) in the reservoir; 7-ml fractions were collected. Fractions 33–48 afforded 155 mg of ultraviolet positive material which had the following characteristics: nmr δ 1.21 (t, 3, J = 6.7 Hz, CH_3), 3.23 (m, 1, H at C-12), 4.13 (q, 2, J = 6.7 Hz, CH_3CH_2), 5.62 (m, 2, vinyl H at C-13 and C-14), 6.17 (m, 1, H at C-10), and 7.49 ppm (m, 1, H at C-11); uv λ_{max} 217 nm (ϵ 10,000); molecular ion at *m/e* 348.2682 (theory for $C_{22}H_{36}O_3$, 348.2664), consistent with *dl*-15-deoxy-PGA_1 ethyl ester.

Fractions 65–100 were pooled and evaporated to dryness to yield 717 mg of **11a** having the following characteristics: nmr (CCl_4, 100 mHz) δ 1.21 (t, 3, J = 6.7 Hz, CH_3), 4.13 (q, 2, J = 6.7 Hz, CH_3CH_2), 4.20 (m, 1, H—C—OH), 5.28 (d of d, $J_{12,13}$ = 7, $J_{13,14}$ = 16 Hz, $-C_{13}H=$), and 5.58 ppm (d of t, $J_{13,14}$ = 16, $J_{14,15}$ = 6 Hz, $=C_{14}H-$); ir (Nujol) 962 cm^{-1} (trans CH=CH); molecular ion at *m/e* 366.2814 (theory for $C_{22}H_{38}O_4$, 366.2769).

(±)-15-Deoxyprostaglandin E_1 (11b). To 15 g of Red Star dry yeast, dissolved in 500 ml of 0.1 *M* phosphate buffer, pH 7.0, was

added 500 mg of *dl*-15-deoxyprostaglandin E_1 ethyl ester (**11a**) in a 2-l. erlenmeyer flask. The reaction mixture was incubated on a rotary shaker at 25° for 13 hr. The reaction mixture was then acidified to pH 2.5 with 5 *N* HCl and extracted with 3 volumes of ethyl acetate three times. The combined ethyl acetate layer was dried (Na_2SO_4) and evaporated to dryness. The residue was chromatographed over a silicic acid–Celite (85:15) column (⅞ × 10 in.). The column was eluted with a gradient system consisting of 400 ml of benzene–ethyl acetate (95:5) in the mixing flask and 400 ml of benzene–ethyl acetate (50:50) in the reservoir flask; 7-ml fractions were collected. Fractions 22–40 contained 202 mg of recovered starting material, **11a**, whereas fractions 41–85 were pooled to yield 137 mg of *dl*-15-deoxyprostaglandin E_1 (**11b**): nmr (100 mHz) δ 4.08 (q, 1, *H*—C—OH), 5.29 (d of d, $J_{12,13}$ = 6, $J_{13,14}$ = 15 Hz, $-C_{13}H-$), and 5.69 ppm (d of t, $J_{13,14}$ = 15, $J_{14,15}$ = 6 Hz, $=C_{14}H-$); molecular ion at *m/e* 338.2389 (theory for $C_{20}H_{34}O_4$, 338.2456).

Yeast Reduction of 11a. To 300 mg of **11a** in 300 ml of 0.1 *M* phosphate buffer, pH 7.0, was added 9 g of Red Star dry yeast, and the reaction mixture was incubated for 48 hr at 27° on a rotary shaker (1 in. stroke, 125 rpm). The contents were then acidified with 5 *N* HCl to pH 2.5 and exhaustively extracted with ethyl acetate. The combined ethyl acetate layers were dried (Na_2SO_4) and evaporated to dryness. The residue was chromatographed over a silicic acid–Celite (85:15) column (0.75 × 15 in.), and 7-ml fractions were collected. Fractions 99–115 were combined to yield 55 mg of **12**: nmr δ 4.10 (m, 2, C-9 and C-11 H), 5.38 (m, 2, C-13 and C-14 H), and 6.0 ppm (broad s, 3, acid OH, C-9 and C-11 OH); $[\alpha]^{24}D$ +13.95° (*c*, 0.81, $CHCl_3$). Fractions 120–140 were pooled to give 83 mg of **13**: nmr δ 4.13 (m, 2, C-9 and C-11 H), 5.36 (m, 2, C-13 and C-14 H), and 5.75 ppm (broad s, 3, acid OH, C-9 and C-11 OH); $[\alpha]^{24}D$ +16.0° (*c* 0.70, $CHCl_3$).

3(*S*)-Hydroxy-1-iodo-1-*trans*-octene (2a). Two molar equivalents of TRiBAL were added to 1 molar equiv of 1-octyn-3(*S*)-ol in dry heptane (40 ml/100 mmol of 1-octyn-3(*S*)-ol) while maintaining the temperature between 10 and 20°. Then 1 molar equiv of DiBAL was added at 20°, and the resulting solution was heated at 56–58° for 2 hr. The heptane was then removed under reduced pressure (0.2 mm), and the residue obtained was diluted with dry THF (40 ml/100 mmol of TRiBAL and DiBAL). To this solution, cooled to −50°, was slowly added a solution of 3 molar equiv of iodine in dry THF (40 ml/100 mmol of iodine) while maintaining the temperature at about −50°. The iodine color disappeared at the beginning, and hydrogen gas was evolved. After 1 molar equiv of iodine was added, the gas evolution ceased, and the iodine color disappeared more slowly, the solution taking on a red color. After all the iodine had been added, the reaction mixture was allowed to warm up to room temperature, whereupon the diisobutylalane was decomposed at 20–30° by the dropwise addition of 20% H_2SO_4. When the isobutane evolution had diminished, the reaction mixture was poured into ice–20% sulfuric acid and extracted four times with pentane. The combined organic extract was washed successively with $Na_2S_2O_3$, saturated $NaHCO_3$, and saturated NaCl solutions and dried ($MgSO_4$). Evaporation of the solvent afforded a yellow oil. The nmr spectrum ($CDCl_3$) of the product, after all volatile material had been distilled off, showed that some of the saturated iodide, 3(*S*)-hydroxy-1-iodooctane, and possibly some diiodo-3(*S*)-hydroxyoctane were present. To remove these compounds, the reaction product was mixed with an excess (three to five times) of triethylamine and the mixture heated at *ca.* 80° for 6 hr. The excess triethylamine was evaporated off, water was added to the residue, and the mixture was shaken for some time. Most of the black oily residue dissolved in the water, and the total mixture was extracted five times with pentane. The combined pentane extract was washed successively with dilute HCl, saturated $NaHCO_3$, $Na_2S_2O_3$, saturated $NaHCO_3$, and saturated NaCl solutions and dried ($MgSO_4$). Distillation of the production [65° (0.1 mm)] obtained after evaporation of the pentane afforded 46.5% of 3(*S*)-hydroxy-1-iodo-1-*trans*-octene (**2a**): nmr δ 3.03 (s, 1, OH), 4.08 (m, 1, C-3 H), and 6.52 ppm (m, 2, C-1 H); ir (CCl_4) 3620 (OH), 1605 (C=C), and 940 cm^{-1} (trans CH=CH), $[\alpha]^{24}D$ +9.52° (*c*, 1.56, CH_3OH). *Anal.* Calcd for $C_8H_{15}IO$: C, 37.81; H, 5.95. Found: C, 37.78; H, 6.05.

3(*S*)-(1-Ethoxy)ethoxy-1-lithio-1-*trans*-octene (2c). One drop of concentrated hydrochloric acid was added to a mixture of 1.53 g (6 mmol) of **2a** and a fourfold excess of ethyl vinyl ether. The solution was mixed and allowed to stand at room temperature for 4 hr. The solution was then rapidly diluted with diethyl ether, washed successively with saturated $NaHCO_3$ and saturated NaCl solutions, and dried ($MgSO_4$). Removal of the solvent followed by distillation [89° (0.4 mm)] yielded 3(*S*)-(1-ethoxy)ethoxy-1-iodo-*trans*-1-octene (**2b**) as a colorless oil: nmr δ 3.50 (m, 2, OCH_2-), 3.98 (m, 1, HCO), 4.71 (m, 1, C-3 H) and 6.43 ppm (m, 2, C-1 and C-2 H).

Into a 25-ml three-necked round-bottom flask equipped with a mechanical stirrer (wire blade) and pressure-equalizing dropping funnel were placed 160 mg (23 mmol) of fine lithium powder and 10 ml dry diethyl ether (freshly distilled over $LiAlH_4$). A blanket of argon was maintained at all times. To this rapidly stirred mixture, which was cooled in an ice bath, was slowly added a solution of 652 mg (2 mmol) of **2b** in 8 ml of dry diethyl ether over a period of 2 hr. (After 0.5 ml of this solution had been added, a positive Gilman test was obtained.) The reaction mixture was rapidly stirred for another 3 hr. The resulting vinyllithium (**2c**) solution must be siphoned directly to the reaction flask for subsequent conjugate addition.

11-Deoxy-15-*epi*-*ent*-prostaglandin E_1 (14b) and 11-Deoxyprostaglandin E_1 (15b). The vinyllithium (**2c**) ether solution was prepared as described above, cooled to −20° (methanol-ice), then siphoned through a glass wool filter into a solution of 1.85 g (4.7 mmol) of tri-*n*-butylphosphine–copper(I) iodide complex in 8 ml of dry diethyl ether at −78° (Dry Ice–acetone), and the resulting yellow reaction mixture was stirred at −78° for 40 min. Then 996 mg (4.45 mmol) of 2-(6-carbomethoxyhexyl)cyclopent-2-en-1-one (**1c**) in 10 ml of dry ether was slowly added to this solution. The resulting mixture was stirred at −78° for 15 min, then allowed to warm to −23° (methanol-ice), and stirred at −23 to −18° for 1 hr. Twenty-five milliliters of cold aqueous 20% $(NH_4)_2SO_4$ solution was added and this mixture poured into 75 ml of the cold $(MH_4)_2SO_4$ solution in a separatory funnel and shaken well. The upper yellow layer was separated from the blue aqueous layer. The top organic layer was shaken with a further 25-ml portion of the cold $(NH_4)_2SO_4$ solution. The combined blue $(NH_4)_2SO_4$ solution was extracted three times with ether. The combined ethereal extract and yellow organic layer were washed with a saturated NaCl solution, dried ($MgSO_4$), and evaporated to give a yellow oil.

Forty-five milliliters of acetic acid–water (65:35) and 4.5 ml of THF were added to this oil, and the mixture was stirred at 31° for 6 hr. This solution was then evaporated to dryness and the product dissolved in ether, washed successively with saturated $NaHCO_3$ and saturated NaCl solutions, and dried ($MgSO_4$). Removal of the ether yielded a yellow oil.

A solution of 1.24 g (9 mmol) of potassium carbonate in 160 ml of methanol–water (1:1) was added to the above oil, and the resulting solution was stirred at room temperature for 2 days. The solution was concentrated, 50 ml of water added, and the resulting mixture extracted three times with ether. The aqueous solution was then acidified and the resulting solution extracted four times with ether. The ethereal extract was washed with a saturated NaCl solution, dried ($MgSO_4$), and evaporated to give a light yellow oily solid.

The oily solid (1.05 g) was chromatographed over a silicic acid–Celite (85:15) column (1.8 × 32 cm). The column was eluted with 400 ml of benzene–ethyl acetate (9:1) in the mixing chamber and 400 ml of benzene–ethyl acetate (6:4) in the reservoir chamber; 7-ml fractions were collected. Fractions 45–66 (483 mg) were combined and rechromatographed over a silicic acid–Celite (85:15) column (1.7 × 35 cm). The column was eluted with 300 ml of benzene–ethyl acetate (9:1) in the mixing chamber and 300 ml of benzene–ethyl acetate (6:4) in the reservoir chamber, and 5-ml fractions were collected. Fractions 83–110 were combined to afford 222 mg of pure 11-deoxy-15-*epi*-*ent*-PGE_1 (**14b**): mp 52–54°, recrystallized from ethyl acetate–pentane; $[\alpha]^{24}D$ +43.02° (*c*, 1.47, $CHCl_3$); ir 3430, 1735, 1710, and 970 cm^{-1}; nmr δ 0.89 (t, 3, *J* = 6 Hz, CH_3), 2.29 (t, 2, *J* = 7 Hz, CH_2CO_2), 4.06 (m, 1, *CH*OH), and 5.56 ppm (m, 2, CH=CH); *m/e* 338. The methyl ester of **14b** gave a molecular ion at *m/e* 352.2612 (theory for $C_{21}H_{36}O_4$, 352.2609).

Fractions 65–90 were pooled to yield 178 mg of 11-deoxy-PGE_1 (**15b**), mp 91–92°, $[\alpha]^{24}D$ −45.73° (*c*, 0.73, $CHCl_3$), whose ir, nmr, and mass spectra were identical with those of **14b**. *Anal.* Calcd for $C_{20}H_{34}O_4$: C, 70.97; H, 10.13. Found: C, 70.96; H,

10.13.

15-*epi*-*ent*-prostaglandin E_1 Ethyl Ester (16a) and Prostaglandin E_1 Ethyl Ester (17a). The vinyllithium (**2c**) solution, prepared as described above and cooled to −20° (methanol–ice), was siphoned through a glass wool filter into a solution of 196 mg (0.5 mmol) of tri-*n*-butylphosphine–copper(I) iodide complex in 5 ml of dry diethyl ether previously cooled to −78° (Dry Ice–acetone). The resulting solution was stirred at −78° for 45 min, and then a solution of 170 mg (0.5 mol) of 2-(6-carboethoxyhexyl)-4-(2-tetrahydropyranyloxy)cyclopent-2-en-1-one (**1a**) in 5 ml of dry ether was slowly added. The reaction mixture was stirred at −78° for 15 min and then allowed to warm to −23° (methanol–ice) and stirred at −23 to −18° for 60 min. Fifteen milliliters of a cold 20% aqueous $(NH_4)_2SO_4$ was added, and this mixture was poured into 10 ml of cold $(NH_4)_2SO_4$ was added, and this mixture was poured into 10 ml of cold $(NH_4)_2SO_4$ in a separatory funnel and shaken. The two layers were separated, and the top organic layer was shaken with another 10-ml portion of the cold $(NH_4)_2SO_4$ solution. The combined blue aqueous $(NH_4)_2SO_4$ solution was extracted three times with ether. The combined organic layers were washed with a saturated NaCl solution, dried ($MgSO_4$), and evaporated to give an orange oil. This oily residue was dissolved in 8 ml of acetic acid–water (6.5:3.5) and 0.8 ml of THF and stirred at 31° for 5.5 hr. This solution was then diluted with ether and washed with a saturated $NaHCO_3$ solution until the washings were basic. It was then washed with a saturated NaCl solution, dried ($MgSO_4$), and evaporated to dryness to give an orange oil, which was chromatographed on a silicic acid–Celite (85:15) column (0.75 × 12 in.). The column was eluted with 500 ml of benzene–ethyl acetate (9:1) in the mixing flask and 500 ml of benzene–ethyl acetate (1:1) in the reservoir, and 6-ml fractions were collected. Fractions 111–136 were combined to yield 53 mg of **16a:** tlc mobility,[28] R_f 0.41; ir 3400 (OH), 1725 (ring carbonyl), 1695 (ester carbonyl), and 962 cm^{-1} (C=C trans); nmr ($CDCl_3$) δ 2.63 (broad s, 2, C-11 and C-15 OH), 4.13 (m, 2, C-11 and C-15 H), 4.15 (q, 2, J = 7 Hz, CH_3CH_2CO), and 5.71 ppm (m, 2, C-13 and C-14 H). Peak match for (M − 18) at *m/e* 364.2617 (theory for $C_{22}H_{36}O_4$, 364.2613). Fractions 157–240 were pooled to give 43 mg of **17a:** tlc mobility,[28] R_f 0.37; ir 3390 (OH), 1730 (ring carbonyl), 1692 (ester carbonyl), and 960 cm^{-1} (C=C trans); nmr ($CDCl_3$) δ 3.50 (broad s, 2, C-11 and C-15 OH), 4.10 (m, 2, C-11 and C-15 H), 4.16 (q, 2, J = 7 Hz, CH_3CH_2CO), and 5.61 ppm (m, 2, C-13 and C-14 H). *Anal.* Calcd for $C_{22}H_{38}O_5$: C, 69.07; H, 10.01. Found: C, 68.83; H, 9.98.

Hydrolysis of 17a with Bakers Yeast. To 97 mg of **17a** in 100 ml of 0.1 *M* phosphate buffer, pH 7.0, was added 3 g of dry yeast (Red Star), and the reaction mixture was incubated for 16 hr at 27° on a rotary shaker (1-in. stroke, 125 rpm). The reaction mixture was then acidified to pH 2.5 with 5 *N* HCl and extracted exhaustively with ethyl acetate. The combined ethyl acetate layers were dried (Na_2SO_4) and evaporated to dryness. The residue was chromatographed over a silicic acid–Celite (85:15) column (⅝ × 8 in.). The column was eluted with 300 ml of benzene–ethyl acetate (75:25) in the mixing flask and 300 ml of ethyl acetate in the reservoir flask, and 5-ml fractions were collected. Fractions 30–51 were combined to give 34 mg of unreacted **17a.** Fractions 54–95 were pooled to yield 49 mg of crystalline **17b.** Three recrystallizations from ethyl acetate–hexane afforded an analytical sample, mp 115–116°; $[\alpha]^{20}D$ −54.3° (*c* 1.0, THF); its infrared, nmr, and mass spectra were indistinguishable from that of biosynthetic PGE_1:[31] mp 114–115°; $[\alpha]^{20}D$ −55.2° (*c* 1.0, THF); mixture melting point gave no depression.

Using these same incubation conditions, **16a** was converted into **16b.**

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(90:4:6).

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Asymmetric Total Synthesis of (−)-Prostaglandin E_1 and (−)-Prostaglandin E_2[1]

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Abstract: A bioorganic asymmetric total synthesis of (−)-PGE_1 and (−)-PGE_2 has been accomplished *via* conjugate addition of organocuprates derived from *trans*-3(*S*)-hydroxy-1-iodo-1-octene (**3a**) to 2-(6-carbomethoxyhexyl)-4(*R*)-hydroxy-2-cyclopenten-1-one (**1a**) and 2-(6-carbomethoxy-*cis*-2-hexenyl)-4(R)-hydroxy-2-cyclopenten-1-one (**2a**), respectively. The chiral centers of these key synthons were introduced by the use of microbial enzymes. A variety of microbiological asymmetric oxidations and reductions were examined for the transformation of prochiral substrates into optically active prostaglandin synthons. Microbiological reactions are discussed and compared with the corresponding nonenzymatic reactions. The synthon **1a** was prepared from 2-(6-carbomethoxyhexyl)cyclopentane-1,3,4-trione (**4**) *via* the sequence: microbiological asymmetric reduction of the C-4 carbonyl in **4** yielding the *R* alcohol **5a** which may be converted into any number of suitable enolates **6** followed by reduction of the C-3 carbonyl and acid rearrangement. By an analogous sequence of reactions, **2a** was prepared from 2-(6-carbomethoxy-*cis*-2-hexenyl)cyclopentane-1,3,4-trione (**14**). The complementary octenyl synthon **3a** was synthesized *via* a modified hydroalumination method and *via* microbiological reduction of 1-iodo-1-*trans*-octen-3-one. A key step in the synthetic scheme for transformation of these synthons into prostaglandins involves the conjugate addition of octenylcopper reagents with cyclopentenones. The results of an extensive study of this key step are reported. The effects of reaction time and temperature on yield are delineated. The relative effectiveness and reactivities of various divinylcuprate, mixed cuprate, and vinylcopper reagents in the conjugate addition reaction are assessed.

In the accompanying paper,[1] details are given for the synthesis of (−)-prostaglandin E_1 (PGE_1) and related substances *via* the reaction of conjugated 2-alkylcyclopentenones with both unfunctionalized and oxygenated organocuprates. Further, the importance of the C-4 center (C-11 prostaglandin numbering) of **1a** in dictating the eventual stereochemistry of the substituents at C-12 and C-8 (prostaglandin numbering) of prostaglandins through steric interactions has been clearly demonstrated. We now report a bioorganic total synthesis of (−)-PGE_1 and (−)-PGE_2 wherein all the chiral centers are asymmetrically introduced.

Results and Discussion

Microbiological Induction of Asymmetry into the Cyclopentyl Synthon. Microbial enzymatic oxidation of unactivated (remote) centers in hydrocarbons is a well-known phenomenon. *A priori*, an asymmetric center might be introduced at any position in a prochiral substrate by, for example, microbial hydroxylation. Further, numerous microbial transformations occur at substrate centers which possess readily apparent activation toward the chemical reaction involved.

The allylic ring methylene of 2-(1-oxocyclopent-2-ene)-heptanoic acid methyl ester (**1d**) is activated toward oxidation. In fact, the desired 4-hydroxy-2-cyclopenten-1-one **1a** has been prepared in racemic form from **1d** by chemical oxidation. Moreover, microbiological hydroxylation of 2-alkyl-1-oxocyclopent-2-enes such as cinerone to cinerolone is known.[2] However, the optical purity of the resulting cinerelone was only of the order of 60%. In addition, we have found that fungi containing hydroxylases have a general proclivity toward degradation of the acid side chain of **1a**.[3] We therefore turned our attention to the use of yeast reductases for asymmetric induction.

Cyclopent-2-ene-1,4-diones are activated toward reduction. These vinylogous α-diketones readily undergo selective monoreduction with a variety of reagents to yield cyclopent-2-en-4-ol-1-ones.[4] Moreover, chemical reduction of 2,3-dialkylcyclopent-2-ene-1,4-diones often proceeds with very high regioselectivity for reduction of the least sterically hindered C=O bond. We therefore examined microbial reduction of 2-(1,4-dioxocyclopent-2-ene)heptanoic acid methyl ester (**1e**).

Initial experiments employing Baker's yeast for the reduction of **1e** indicated that reduction of the C=C bond accompanied C=O reduction. Saturation of α,β-unsaturated ketones is a very common microbiological transformation.[5] On the assumption that C=C and C=O reductions were catalyzed by two independent enzymes, we performed the microbiological reduction of **1e** in the presence of excess 2-cyclohexenone or methyl vinyl ketone, in order to competitively inhibit the reduction of the double bond. This strategy succeeded. Remarkably, however, our first experiment, performed with Baker's yeast, yielded mostly 3-(1-oxo-4-hydroxycyclopent-2-ene)heptanoic acid, the product of regioselective monoreduction of the most sterically hindered C=O bond. This result poignantly reflects the unusual steric demands of enzymatic reactions in comparison with those of more common laboratory reagents.

As most microorganisms provided only mixtures of the above product and the desired 2-(1-oxo-4-hydroxycyclopent-2-ene)heptanoic acid **1a** in low yields, we examined an alternate approach based on the observation that 2-(6-car-