stirred for 3 h at this temperature. A 0.1% solution of triethylamine in hexane (0.5 mL) was added, and the mixture was evaporated. The residual material was chromatographed on a column of Florisil (1.2 g) by using a 1:1:0.001 mixture of hexane, ethyl acetate, and triethylamine as eluant to give **34** (6.9 mg, 97%) as a white solid: mp 35.0 °C (lit.[36d] mp 30–33 °C); TLC R_f 0.36 (6:3:1 ethyl acetate/cyclohexane/THF); IR ($CHCl_3$) 3600, 3560–3280, 1730, 1695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (t, 3, J = 6.5 Hz, CH_3), 1.1–2.5 (m, 22, 9 CH_2, 2 CH and 2 OH), 3.67 (s, 3, OCH_3), 3.7–4.2 (m, 3, 3 CHO), 4.58 (m, 1, vinyl), 5.55 (m, 2, vinyls); ^{13}C NMR ($CDCl_3$) δ 14.0, 22.6, 24.7, 25.1 (2 C), 31.7, 33.0, 33.6, 37.0, 40.6, 45.3, 51.4, 54.7, 73.0, 77.0, 83.4, 95.8, 131.8, 136.4, 154.6, 174.5; $[\alpha]^{21}_D$ +79.8° (c 0.27, $CHCl_3$) [lit.[36d] $[\alpha]^{25}_D$ + 78° (c 0.88, $CHCl_3$]. These spectral data and chromatographic behavior were identical with those of authentic specimen donated by Ono Pharmaceutical Co. and Teijin Co.

Acknowledgment. We are grateful to Ono Pharmaceutical Co., Teijin Co., and Sumitomo Chemical Co. for providing various authentic samples of PGs and starting materials as well as valuable information. We also appreciate Dr. C. H. Lin of Upjohn Co. for sending us IR and ^1H NMR spectra of **12** and **25**.

Triply Convergent Synthesis of (−)-Prostaglandin E_2 Methyl Ester†

Carl R. Johnson* and Thomas D. Penning

Contribution from the Department of Chemistry, Wayne State University, Detroit, Michigan 48202. *Received December 4, 1987*

Abstract: Enone **1**, prepared from cyclopentadiene, was obtained in optically pure form by resolution with (+)-*N,S*-dimethyl-*S*-phenylsulfoximine or by a procedure involving asymmetric semihydrolysis of *meso*-**3** catalyzed by electric eel acetylcholinesterase. The absolute configuration of (+)-**1** was assigned as *S,S* on the basis of a comparative optical rotary dispersion study. The lower prostanoid side chain was added to (+)-**1** as an organocopper reagent, the resulting enolate was alkylated with the upper side chain as the iodide, and the acetonide was reductively removed by treatment with Al(Hg) to produce the 11-hydroxy prostanoid, (−)-PGE_2, methyl ester.

A conceptually simple route to the biologically important 11-hydroxyprostaglandins (PGE's) is a triply convergent approach involving the coupling of the two side chains with a protected 4-hydroxy-2-cyclopentenone (Scheme I, path A).[1,2] Success of this convergent approach has been thwarted by equilibration of the initially generated enolate followed by elimination of the protected ring hydroxyl function under conditions conducive to alkylative introduction of the top side chain (Scheme I, path B).[3]

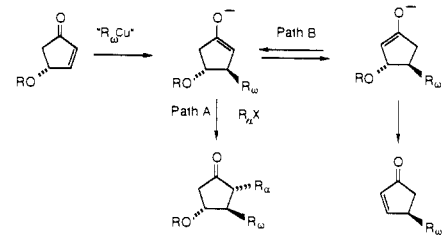
It appeared to us that a short and effective PGE synthesis might be achieved by design of a structural system that would suppress the offending enolate equilibration step. Our concept was to incorporate into the ring component a protecting group that would inhibit enolate equilibration to the undesired position. With this in mind, our attention turned to enone **1**. We postulated that the presence of the additional oxygen group constrained in the five-membered ring would eliminate enolate equilibration by a combination of dipole repulsion and angle strain, allowing alkylation to occur at the desired position. A selective deoxygenation at the 10-position would then furnish the PGE skeleton (Scheme II).

During the course of the work herein described, one solution to this equilibration/elimination problem appeared. Noyori and co-workers[4] found that the initially formed enolate (Scheme I) resulting from the addition of an organocuprate to a protected 4-hydroxy-2-cyclopentenone could be trapped at low temperatures as the *O*-(triphenylstannyl) derivative, which, in turn, could be directly alkylated[5] with a fivefold excess of $R_\alpha I$ in the presence of hexamethylphosphoramide. At about the same time as our preliminary disclosure[6] of the work herein described, an interesting, short, and convergent synthesis of PGE_2, based on the *O*-methyl derivative of the oxime of 4-[(*tert*-butyldimethylsilyl)oxy]-2-cyclopentenone, from the laboratories of Corey was revealed.[7]

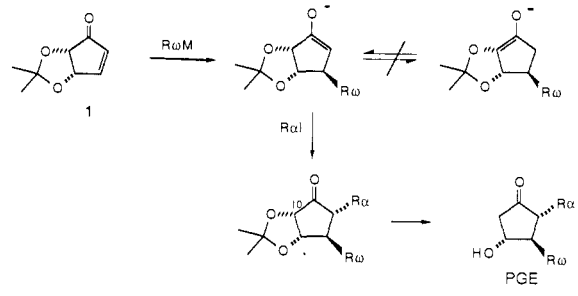
Results and Discussion

A. Synthesis of Enone 1. Cyclopentenone (±)-**1** has previously been prepared by a lengthy route from 2-cyclopentenone.[8]

Scheme I



Scheme II



Dugger[9] has reported on attempts to prepare optically active **1** from ribose, but the key transformations were unsatisfactory.

† Dedicated to Prof. E. J. Corey on the occasion of his 60th birthday.

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(2) For indirect variations of this approach, see: (a) Suzuki, M.; Yanagisawa, A.; Noyori, R. *Tetrahedron Lett.* **1984**, *25*, 1384. (b) Tanaka, T.; Toru, T.; Okamura, N.; Hazato, A.; Sugiura, S.; Manabe, K.; Kurozumi, S.; Suzuki, M.; Kawagishi, T.; Noyori, R. *Ibid.* **1983**, *24*, 4103. (c) Suzuki, M.; Kawagishi, T.; Noyori, R. *Ibid.* **1982**, *23*, 5563. (d) Suzuki, M.; Kawagishi, T.; Suzuki, T.; Noyori, R. *Ibid.* **1982**, *23*, 4057. (e) Donaldson, R. E.; Saddler, J. C.; Byrn, S.; McKenzie, A. T.; Fuchs, P. L. *J. Org. Chem.* **1983**, *48*, 2167. (f) Stork, G.; Isobe, M. *J. Am. Chem. Soc.* **1975**, *97*, 6260.

(3) (a) Davis, R.; Untch, K. G. *J. Org. Chem.* **1979**, *44*, 3755. (b) Patterson, J. W.; Fried, J. H. *Ibid.* **1974**, *39*, 2506.

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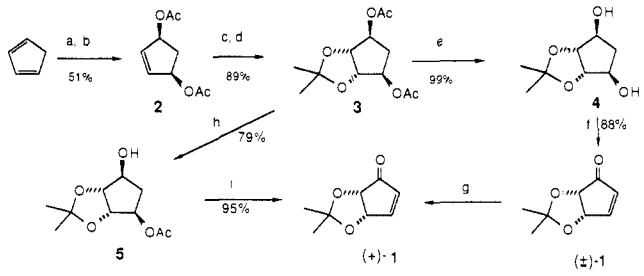
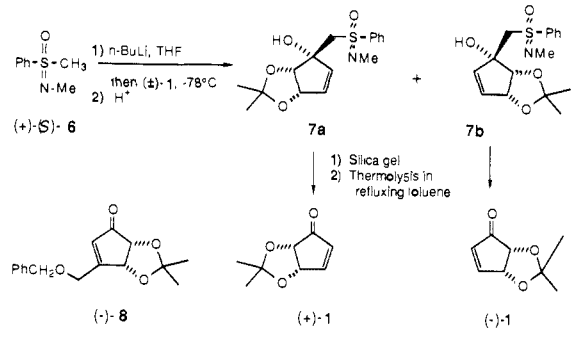
Scheme III[a]



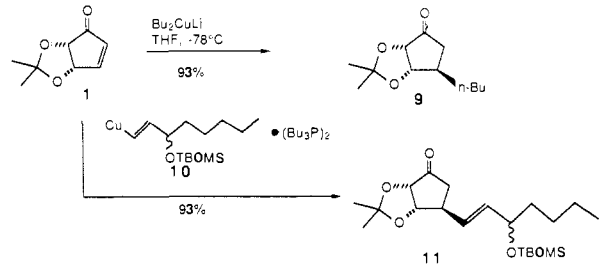
[a] (a) O_2, *hν*, rose bengal, thiourea, MeOH; (b) Ac_2O, pyridine, catalytic DMAP, CH_2Cl_2; (c) 1 mol% OsO_4, Me_3NO, THF, acetone; (d) acetone, catalytic TsOH; (e) KOH, MeOH; (f) dicyclohexylcarbodimide, DMSO, pyridine, trifluoroacetic acid, benzene; (g) (+)-*N*,*S*-dimethyl-*S*-phenylsulfoximine resolution, see Scheme IV; (h) electric eel acetylcholinesterase, H_2O, 25 °C; (i) CrO_2, H_2SO_4, acetone.

Scheme IV



We have prepared enone (±)-**1** from cyclopentadiene in six steps in an overall yield of 40% as shown in Scheme III. Addition of photochemically generated singlet oxygen to cyclopentadiene and in situ reduction of the adduct with thiourea yielded *cis*-2-cyclopentene-1,4-diol,[10] which was acetylated with acetic anhydride to yield diacetate **2**. Vicinal cis hydroxylation of **2** from the least hindered side with 1 mol % osmium tetraoxide and trimethylamine *N*-oxide[11] as reoxidant furnished the diol in 90% yield. Alternately, this oxidation could be accomplished in 71% yield with potassium permanganate under biphasic conditions.[12] Acid-catalyzed ketalization of the diol with acetone gave **3**. Treatment of **3** with potassium hydroxide gave diol **4** in 98% yield (from **2**). Oxidation/dehydration of **4** was best carried out by Moffatt oxidation[13] to produce **1** in 88% yield after chromatography (to remove the dicyclohexylurea byproduct). The six-step synthesis of **1** required only one chromatography—all other intemediates were purified by distillation or recyrstallization. The oxidation could also be achieved with chromium trioxide/pyridine complex in pyridine (Sarett's reagent).[14] Although no chromatography was required, the yields were slightly lower (70%), and the workup was more difficult.

Scheme V



Since it was ultimately desired to synthesize prostaglandins in enantiomerically pure form, enone **1** was required in optically pure form. Optical resolution of the enone was achieved by using a procedure based on our sulfoximine chemistry.[15] Addition of the lithium anion of optically pure sulfoximine (+)-**6** to enone (±)-**1** occurred with complete selectivity to the convex face and furnished only two diastereomeric adducts as ascertained by HPLC analysis (α = 1.37) (Scheme IV). These diastereomers were separated on a preparative scale by flash chromatography to give a 34% yield of **7a** and a 42% yield of **7b**. Thermolysis in refluxing toluene of **7a** and **7b**, separately, furnished (+)-**1** with $[\alpha]^{25}_D$ +71.8° (*c* 0.91, $CHCl_3$) and (-)-**1** with $[\alpha]^{25}_D$ -70.8° (*c* 0.925, $CHCl_3$), respectively, along with recovered sulfoximine (+)-**6**, which could be recycled.

The absolute configurations of (+)-**1** and (-)-**1** were determined by comparison of their optical rotary dispersion (ORD) curves with that of a similar optically pure compound, (-)-**8**,[16] of known absolute configuration. This enone had been synthesized from 5-*O*-benzyl-D-ribonolactone. The ORD curve of (-)-**8** exhibited a positive Cotton effect. The ORD curve of (-)-**1** also showed a positive Cotton effect, while (+)-**1** exhibited a negative Cotton effect. Since (-)-**1** and (-)-**8** both exhibited positive Cotton effects, they should have the same absolute configuration. The (+)-enone with the *S*,*S* configuration, therefore, was the enone needed for a synthesis of a PGE.

Although the above described resolution was quite effective, it suffered from the disadvantage inherent in resolutions—half of the product obtained had the wrong absolute configuration for the problem at hand. Consequently we turned to a study of the generation of (+)-**1** by asymmetric synthesis. On the basis of earlier studies[17] on enzymatic differentiation of the acetates of *meso*-**2**, we examined a number of esterase-catalyzed hydrolyses of *meso*-**3**. Success was variable until our attention was drawn to electric eel acetylcholinesterase by a report[17b] on the asymmetric hydrolysis of **2**. Indeed, treatment of **3** in aqueous suspension with commercially available electric eel acetylcholinesterase (ca. 1 mg of enzyme/g of **3**) provided monoacetate **5** (79%), which was oxidized with Jones reagent to enone (+)-**1** (95% yield, 98% optical purity) (Scheme III).

Recently, an unusual microbiological approach to enone (+)-**1** has been reported by Hudlicky and co-workers.[18] When toluene vapor was passed over a cluture of *Pseudomonas putida*, 3-methyl-3,5-cyclohexadiene-1,2-diol was produced. Ozonolysis of the fermentation product followed by an internal aldol condensation gave enone (+)-**1** (eq 1).

B. Model Studies. To test the feasibility of our proposed approach to prostaglandins, three model reactions were examined: (1) the cuprate addition to **1**, (2) the regiospecific alkylation, and

(4) Suzuki, M.; Yanagisawa, A.; Noyori, R. *J. Am. Chem. Soc.* **1985**, *107*, 3348.
(5) (a) Nishiyama, H.; Sakuta, K.; Itoh, K. *Tetrahedron Lett.* **1984**, *25*, 223 and 2487. (b) See also: Binns, M. R.; Haynes, Rl K.; Lambert, D. E.; Schober, P. A. *Tetrahedron Lett.* **1985**, *26*, 3385.
(6) Johnson, C. R.; Penning, T. D. *J. Am. Chem. Soc.* **1986**, *108*, 5655.
(7) Corey, E. J.; Nimura, K.; Konishi, Y.; Hashimoto, S.; Hamada, Y. *Tetrahedron Lett.* **1986**, *27*, 2199.
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(11) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973.
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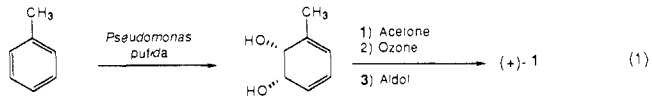
(15) (a) Johnson, C. R. *Aldrichimica Acta* **1985**, *18*, 3. (b) Johnson, C. R.; Zeller, J. R. *Tetrahedron* **1984**, *40*, 1225.
(16) Lim, M. I.; Marquez, V. E. *Tetrahedron Lett.* **1983**, *24*, 5559.
(17) (a) For example, see: Miura, S.; Kurozumi, S.; Toru, T.; Tanaka, T.; Kobayashi, M.; Matsubara, S.; Ishimoto, S. *Tetrahedron* **1976**, *32*, 1893. Laumen, K.; Schneider, M. *Tetrahedron Lett.* **1984**, *25*, 5875. (b) Deardorff, D. R.; Matthews, A. J.; McMeekin, D. S.; Craney, C. L. *Tetrahedron Lett.* **1986**, *27*, 1255.
(18) Hudlicky, T.; Barbieri, G.; Luna, H.; Kwart, L. D. Abstracts of Papers; 193rd National Meeting of the American Chemical Society, Denver, April 1987; American Chemical Society: Washington, DC; ORGN 28. Hudlicky, T.; Luna, H.; Barbieri, G.; Kwait, L. D. *J. Am. Chem. Soc.*, following paper in this issue.

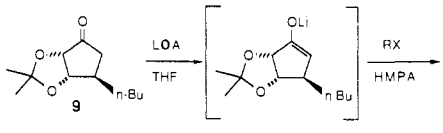


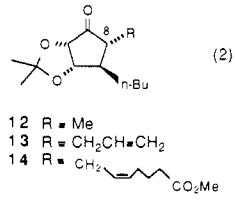
(3) the selective deoxygenation of the protected 10-hydroxy ketone (prostaglandin numbering).

Cuprate Addition Reaction. Addition of lithium dibutylcuprate to enone (±)-**1** proceeded cleanly at −78 °C in 93% yield to give ketone **9** by exclusive conjugate addition to the convex face (Scheme V). The trans relationship of the C-11 and C-12 protons (prostaglandin numbering) could clearly be seen from ^{1}H NMR decoupling studies of **9** by the lack of coupling between these protons ($J_{11,12}$ = 0 Hz). From inspection of molecular models, the 90° dihedral angle required for this can only be achieved when these protons are trans. DeShong[19] has noted a similar lack of coupling in a fused 5,5 system.

The stabilized organocopper reagent **10**[20] and (±)-**1** furnished a 93% yield of **11** as an inseparable mixture of two diastereomers (Scheme V). The reaction using the *tert*-butyldimethylsilyl-protected side chain was not only higher yielding, but was also much cleaner than the corresponding reaction using the trimethylsilyl-protected reagent.

Alkylation Reaction. The initial alkylation studies were carried out with iodomethane as the alkylating agent. The appropriate enolate of **9** could be regiospecifically generated with lithium diisopropylamide (LDA) in THF at −78 °C; alkylation of the enolate with an excess of MeI did not occur, even at 0 °C. Alkylation in the presence of HMPA (10 equiv), however, proceeded readily at −30 °C to yield the desired alkylation product **12** (eq 2). The necessity of HMPA in these direct alkylation reactions





(2)

had been previously noted.[4,5,21,22] The relative stereochemistry at C-8 (PG numbering) of **12** was assigned on the basis of ^{1}H NMR decoupling studies. Long-range coupling (1.5 Hz) was observed between the C-8 proton and both C-10 and C-11 protons. This coupling is observed only with this stereochemistry, since the coupled protons are held in the required "W" configuration. In addition, the chemical shift of the C-8 proton in **12** corresponded with that of the β C-8 proton in **9**. The β-proton (cis to the adjacent butyl group) is shielded relative to the α-proton.[23]

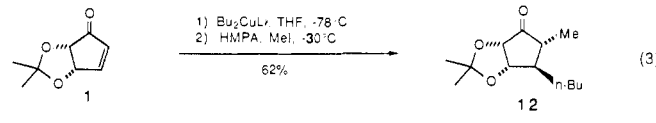
Relatively minor amounts of alkylation byproducts were isolated from the reaction mixture. The cis alkylation product, the C,C-dialkylation product, the O-alkylation product, and the C,O-dialkylation product could be separated relatively easily by flash chromatography and were all identified on the basis of their ^{1}H NMR spectra (see the supplementary material). The cis product was equilibrated with catalytic sodium acetate in refluxing methanol to ca. 10:1 trans/cis mixture.[22] Longer reaction times, higher temperatures, and increased amounts of HMPA or MeI all seemed to increase the amount of byproducts at the expense of the desired product **12**.

Alkylation of the enolate of **9** with allyl iodide in the presence of HMPA (eq 2) gave the desired product **13** in only 19% yield. As before, a number of byproducts were produced in the reaction, primarily the C,O-dialkylation product in 20% yield. Alkylation with allyl bromide gave similar results. As before, time and temperature seemed to be particularly critical factors in reducing the amount of byproducts.

Alkylation of the enolate of **9** was next attempted with the PGE_2 α side chain reagent, methyl *cis*-7-iodo-5-heptenoate, to see if the presence of the methyl ester in any way interfered with the alkylation. As before, the alkylation occurred only in the presence of HMPA and resulted in the production of only two products, the desired **14** (eq 2) and a C,O-dialkylation product. The presence of the ester seemed to have no detrimental effect on the reaction.

In an effort to eliminate the O-alkylation and dialkylation products, the alkylation of the tin enolate of **9** with methyl *cis*-7-iodo-5-heptenoate was attempted. Japanese workers[4,5a] have reported the clean monoalkylation of a cyclopentanone through the trialkylstannyl enolate in the presence of HMPA. The alkylation of the tributyltin enolate of **9** (generated by treatment of **9** in THF with LDA followed by tributylstannyl chloride) proceeded much more slowly, but much more cleanly, than the alkylation of the lithium enolate. The alkylation furnished a 25% yield of **14** and a 36% yield of recovered **9**. No evidence of any dialkylation products was found.

Although the yields of the desired alkylation products in these studies are relatively low, they compare reasonably well with the yields obtained by Posner[22a] (10–69%) in his studies of conjugate addition/alkylation of cyclopentenone. On the basis of these results, a more efficient one-pot conjugate addition/alkylation reaction was examined. Addition of lithium dibutylcuprate to (±)-**1** followed by addition of HMPA and MeI, afforded a 62% yield of the vincinally disubstituted **12** (eq 3). The reaction was



(3)

not only higher yielding but was also much cleaner than the alkylation reaction of **9** (eq 2); the effect of copper(I) in suppressing polyalkylation has been established by the work of Posner.[22b] The only other products produced in this reaction (eq 3) were the unalkylated product **9** and a minor amount of the cis product. This was particularly interesting since a large excess of MeI was used and the temperature was allowed to go as high as 0 °C, conditions that normally produce increased amounts of dialkylation products.

From these studies it was clear that alkylation could be achieved with reactive halides, and the procedure of a one-pot direct alkylation of the enolate generated by conjugate addition of an organocopper reagent was more effective than a procedure involving the independent generation of the enolate from a substituted ketone and LDA.

Deoxygenation Reaction. The feasibility of the cuprate addition reaction and the alkylation reaction had been demonstrated; there remained an examination of the crucial selective deoxygenation. Similar reductions had been accomplished with 2,3-epoxycyclopentanones[24] and α-acetoxycyclopentanones[25] with chromous chloride, chromous acetate, or aluminum amalgam (Al(Hg)).

Ketone **9** and was chosen for a model study of this reaction. Due to its mildness and ease of preparation, Al(Hg) was initially examined as the reducing agent in this reaction. The reduction

(19) DeShong, P.; Dicken, C. M.; Liginus, J. M.; Whittle, R. *J. Am. Chem. Soc.* **1984**, *106*, 5598.
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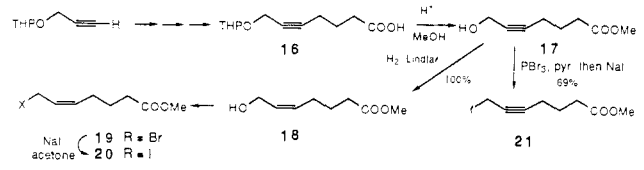
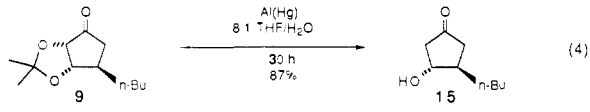
(21) Posner, G. H.; Whitten, C. E.; Sterling, J. J.; Brunelle, D. J. *Tetrahedron Lett.* **1974**, 2591.
(22) (a) Posner, G. H.; Sterline, J. J.; Whitten, C. E.; Lentz, C. M.; Brunelle, D. J. *J. Am. Chem. Soc.* **1975**, *97*, 107. (b) Posner, G. H.; Lentz, C. M. *Ibid.* **1979**, *101*, 934.
(23) Donaldson, R. E.; Saddler, J. C.; Byrn, S.; McKenzie, A. T.; Fuchs, P. L. *J. Org. Chem.* **1983**, *48*, 2167.
(24) Bundy, G. L.; Schneider, W. P.; Lincoln, F. H.; Pike, J. E. *J. Am. Chem. Soc.* **1972**, *94*, 2123. Also see: Cole, W.; Julian, P. *J. Org. Chem.* **1954**, *19*, 131.
(25) Mitscher, L. A.; Clark, G. W.; Hudson, P. B. *Tetrahedron Lett.* **1978**, 2553.

Scheme VI



of **9** to **15** proceeded in 87% yield in 8:1 THF/water when the Al(Hg) was added in two or three protions (eq 4). Other reaction



(4)

conditions were explored, but these particular conditions gave the best results. Evidently, the large quantities of aluminum salts produced in the reaction coat the metal after a period of time, so that the addition of separate portions of Al(Hg) was required. Acetic acid has been previously used to dissolve the aluminum salts and thus keep the metal surface relatively clean.[26] The addition of acetic acid to the mixture for reduction of **9** to **15** was not found to be advantageous. The trans stereochemistry of **15** could not be substantiated by high field ^{1}H NMR decoupling studies, but on the basis of the stereochemistry of **9**, it must be trans. The only other compound isolated from the reaction mixture was a small amount of **9**. No evidence was seen for any elimination products. Since Al(Hg) is so easily prepared and since such a high yield of **15** was obtained with it, no other reducing agents were explored.

Synthesis of the Side Chains. Iodide **20** was synthesized (Scheme VI) by using a modification of various approaches previously described.[2e,22,27] The carboxylic acid **16** was prepared on the basis of the description of Corey.[27] Treatment of **16** with catalytic acid in methanol concomitantly esterified the acid and deprotonated the propargyl alcohol to give **17**. This alkyne was contaminated with ca. 10% of the corresponding allene, which could be separated with difficulty by flash chromatography. This byproduct arose during acid treatment and could probably be eliminated by using diazomethane as in the original Corey procedure.

Initially, the catalytic semihydrogenation of **17** was carried out with 5% palladium on barium sulfate in the presence of a catalyst poison, quinoline. The progress of the reaction was carefully monitored by TLC, but a 20–30% yield of the *trans*-alkene was always produced. The problem of stereomutation of a *cis*-alkene by a palladium catalyst in the presence of hydrogen has been studied by Raphael.[28] He found that the semihydrogenation of 4-octyne over 10% palladium on barium sulfate gave a 40% yield of the *trans*-alkene, while with Lindlar's catalyst (palladium on calcium carbonate, poisoned with lead) only a 4% yield of the *trans*-alkene was obtained. Use of the Lindlar catalyst dramatically reduced the amount of *trans*-alkene produced. Since the isomerization of *cis*- to *trans*-alkene occurs after all the alkyne has been reduced, the reaction must be carefully monitored by TLC. The rate of the reaction could be controlled by running it in a hexane/EtOAc mixture (2:1) at 0 °C. Under these conditions, the reaction was completed in ca. 2–3 h. Reduction in this manner produced *cis*-alkene with a minimum of 95% purity. Alcohol **39** was converted to bromide **19** in one of two ways: with phosphorus tribromide and pyridine in ether (81%) or with carbon tetrabromide and triphenylphosphine in dichloromethane (97%).

Bromide **19** was converted to iodide **20** immediately prior to use with sodium iodide in acetone and was used without purification. It is very important that the reaction time be limited to under 10 min, since longer reaction times lead to appreciable amounts of the *trans*-alkene.[2e]

(26) Johnson, C. R.; Kirchhoff, R. A. *J. Am. Chem. Soc.* **1979**, *101*, 3602.
(27) Corey, E. J.; Sachdev, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 8483.
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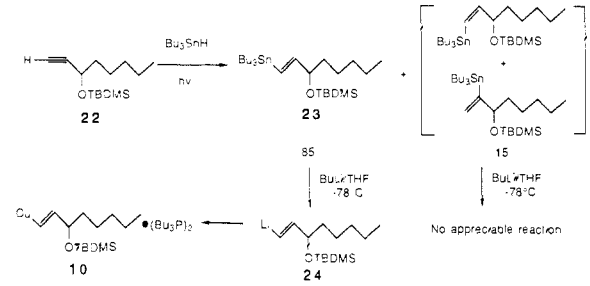
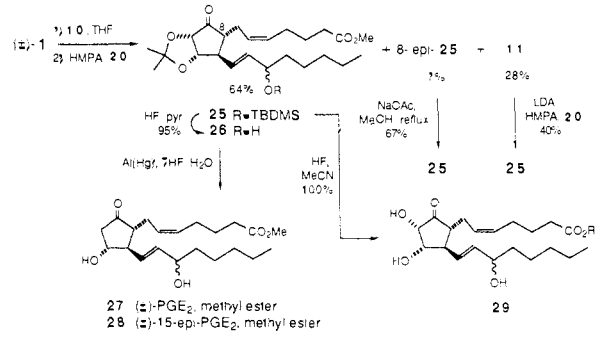
Scheme VII



Scheme VIII



The required lower chain synthon, vinylcopper reagent **10**, was synthesized as outlined in Scheme VI. The *tert*-butyldimethylsilyl ether **22**[29] was prepared from 1-octyn-3-ol. Irradiation (GE 275-W sunlamp) of **22** with exactly 1 equiv of tributyltin hydride[30] in the absence of solvent produced a mixture consisting of ca. 85% of the desired (*E*)-vinylstannanes **23** and 15% of a mixture thought to consist of the corresponding (*Z*)-vinylstannanes and a vinylstannane resulting from addition of tin hydride with the opposite regiochemistry (Scheme VII). These ratios could easily be calculated from the integration of the vinyl proton resonances in the ^{1}H NMR spectra. The thermally initiated addition of tributyltin hydride to 1-octyn-3-ol and its triethylsilyl ether have reportedly yielded only the (*E*)-vinylstannane.[31] The Searle group[32] has reported the generation of mixtures of (*E*)- and (*Z*)-vinylstannanes of ω-chain analogues both by the thermally and the light-initiated additions. The 85:15 ratio obtained in this reaction was independently verified in our laboratory.[33] Longer reaction times or higher temperatures did not change this ratio significantly. These mixtures were metalated with *n*-BuLi in THF at −78 °C (see below) to give one vinyllithium product (**24**). Under the reaction conditions the isomeric vinylstannanes are not transmetalated appreciably (Scheme VII). This selectivity has previously been notoed.[32] The presence of the undesired vinylstannanes, therefore, had no detrimental effect on the reaction. These vinylstannane mixtures were used as such and were found to be storable under argon at 0 °C without decomposition.

The transmetallation **23** to **24** must be run in THF, as it proceeds only very slowly in diethyl ether. The reaction temperature must also be kept below −50 °C, since at higher temperatures a 1,4 O- to C-silyl migration[34] occurs. Silyl ether (−)-(*S*)-**22**, resolved via a steroidal ester[35] and necessary for the efficient synthesis of optically pure prostaglandins, was converted

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(34) (a) Rücker, C. *Tetrahedron Lett.* **1984**, *25*, 4349. (b) Evans, D. A.; Tacacs, J. M.; Hurst, K. M. *J. Am. Chem. Soc.* **1979**, *101*, 371.
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to the vinylstannane mixture and transmetalated as described above.

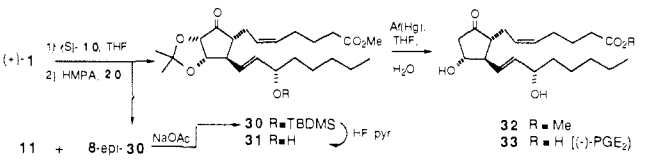
C. Synthesis of (±)-PGE_2 Methyl Ester. A stabilized organocopper reagent **10** generated from the *tert*-butyldimethylsilyl-protected vinyllithium **24** was added to enone (±)-**1**, followed by treatment with an excess of iodide **20** in the presence of HMPA to furnish **25**, as a mixture of two diastereomers, in 64% yield (Scheme VIII). The cis alkylation product (8-*epi*-**25**), isolated in 7% yield, could be epimerized at C-8 to provide additional **25**. A 28% yield of the unalkylation **11** was recovered. No evidence of any dialylation products was seen. Ketone **11** could be alkylated by sequential treatment with LDA and **20**, but the yield of **25** by this method was low.

It was desired to desilylate **25** without affecting the acetonide functionality, to provide **26**. Attempted desilylation with tetrabutylammonium fluoride[29] under the usual conditions resulted only in decomposition. Corey[29] has noted that the basicity of fluoride ion can cause problems in sensitive prostaglandin systems. He remedied the situation by using an acetic acid/water/THF mixture (3:1:1) to remove the *tert*-butyldimetylsilyl group. Under these conditions, the acetonide of **25** would also be removed, so this was not attempted. Recently, the addition of 2 equiv of acetic acid to the tetrabutylammonium fluoride has been mentioned to prevent decomposition in the desilylation of sensitive systems.[36] When **25** was submitted to these desilylation conditions, no reaction took place. When additional tetrabutylammonium fluoride was added, decomposition of **25** occurred. Desilylation of **25** did not occur with benzyltriethylammonium chloride and potassium fluoride dihydrate in acetonitrile.[37] Cesium fluoride in acetonitrile also failed to react.

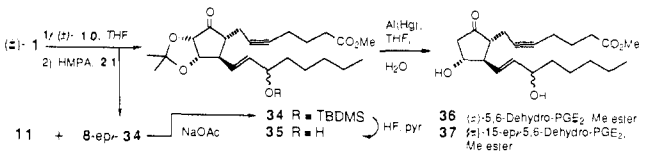
Aqueous hydrofluoric acid in aceonitrile has recently been reported[38] to be an excellent reagent for removal of the *tert*-butyldimethylsilyl protecting group, especially in sensitive prostaglandin systems. Silyl ether **25** was stirred in acetonitrile containing 5% of a 50% aqueous solution of HF at 25 °C to provide a quantitative yield of triol **29** as a mixture of two diastereomers epimeric at C-15 (Scheme VIII). These mild conditions evidently were still acidic enough to hydrolyze the acetonide relatively rapidly. The acid corresponding to **29** had been synthesized previously.[39] Noyori and others[4,40] have used hydrogen fluoride/pyridine in acetonitrile to successfully desilylate protected prostaglandins in excellent yields. Silyl ether **25** was cleanly desilylated in acetonitrile containing 1% pyridine and 6% of a 50% aqueous solution of HF at 25 °C to provide **26** as an inseparable mixture of two diastereomers in 95% yield. A trace amount of triol **29** was formed, and a minor amount of silyl ether **25** was recovered. The presence of the pyridine evidently buffers the solution enough so that hydrolysis of the acetonide does not occur to a significant extent.

Deoxygenation at C-10 of the PGE_2 precursor **26** was performed with aluminum amalgam in aqueous THF to furnish two diastereomers, (±)-PGE_2 methyl ester [(±)-**27**] and (±)-15-*epi*-PGE_2 methyl ester (**28**), which could be easily separated by flash chromatography (α = 1.60) (Scheme VIII). The reaction required addition of Al(Hg) in three or four portions over 30–40 h. The compound with the natural relative configuration at C-15, (±)-**27**, was always isolated in greater amounts (28–36%) than its C-15 epimer, (±)-**28** (18–25%). The reduction of the diastereomer of **26** that produced (±)-**27** seemed to proceed at a slightly faster rate than the reduction to produce **28**. Large amounts (35–47%) of starting ketone **26** were always recovered. No conditions could be found to drive the reaction to completion. Based on recovered

Scheme IX



Scheme X



starting material, (±)-**27** and (±)-**28** were produced in yields of 86–94% and in a ratio of ca. 1.6:1. Initially the assignments of (±)-**27** and (±)-**28** were made on the basis of their mobility on TLC. A number of investigators have reported the greater polarity of PGEs relative to their C-15 epimers on TLC.[31a,41] On the basis of these reports, the slower moving diastereomer was assigned the naturally configured structure (±)-**27** and the less polar diastereomer the epimeric structure (±)-**28**. These structural assignments were confirmed by comparison of the ^1H and ^{13}C NMR spectra of (±)-**27** and (±)-**28** with published spectral data for PGE_2.[42]

The aluminum amalgam reduction was also carried out on triol **29** to furnish a 70% yield of (±)-**27** and (±)-**28** in a 1.2:1 ratio. A minor amount of **29** was also recovered. This reduction seemed to proceed somewhat more rapidly than the reduction of **26**. This route to PGE_2 methyl ester was not as convenient as the route using **26** due to the difficulty in purifying the very polar triol **29**. Curiously, when the silyl ether **25** was submitted to these same reduction conditions, no reaction took place.

D. Synthesis of (−)-PGE_2 Methyl Ester. Optically pure (−)-PGE_2 methyl ester [(−)-**32**] was synthesized in the same manner as described above for (±)-PGE_2 methyl ester (Scheme IX). Addition of the organocopper reagent (*S*)-**10** derived from (*S*)-**22** to the resolved ketone (+)-**1**, followed by treatment with 1.5 equiv of iodide **20** in the presence of HMPA provided, after flash chromatography, a 46% yield of **30** as a single diastereomer as ascertained by ^{13}C NMR spectroscopy. The unalkylated product **11** was isolated in 25% yield. A minor amount of impure cis alkylation product (8-*epi*-**30**) was isolated also. The latter was equilibrated to a 2:1 mixture of **30** and 8-*epi*-**30** upon exposure to catalytic amounts of sodium acetate in refluxing methanol to provide another 7% of **30** (after flash chromatography). Alkylation product **30** was thus obtained in 53% overall yield.

Desilylation of **30** with 5:1 aqueous HF (50%)/pyridine in acetonitrile at 25 °C for 4.5 h afforded a 78% yield (90% based on recovered starting material) of alcohol **31** (along with a 14% yield of recovered **30**). If the reaction time was increased in an attempt to allow the reaction to go to completion, the loss of the acetonide became a problem.

Aluminum amalgam reduction of **31** with four portions of Al(Hg) over a period of 37 h provided, after flash chromatography, an 89% yield (98% based on recovered starting material) of (−)-PGE_2 methyl ester [(−)-**32**] along with 9% of recovered **27**. By TLC, ^1H and ^{13}C NMR, and IR analysis, (−)-**31** was identical with the previously prepared (±)-PGE_2 methyl ester [(±)-**27**]. Noyori[40a] has reported a synthesis of (−)-PGE_2 methyl ester with $[\alpha]^{20}_D$ −71.7° (*c* 1.04, MeOH), while an authentic sample he prepared by the esterification of commercial (−)-PGE_2 with diazomethane had $[\alpha]^{20}_D$ −71.1° (*c* 1.56, MeOH). Ester (−)-**32** synthesized by our route had $[\alpha]^{20}_D$ −71.8° (*c* 1.25, MeOH). Since

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(40) (a) Suzuki, M.; Kawagishi, T.; Noyori, R. *Tetrahedron Lett.* **1982**, *23*, 5563. Also see: Suzuki, M.; Yanagisawa, A.; Noyori, R. *Ibid.* **1984**, *25*, 1384. (b) Tanaka, T.; Toru, T.; Okamura, N.; Hazato, A.; Sugiura, S.; Manabe, K.; Kurozumi, S.; Suzuki, M.; Kawagishi, T.; Noyori, R. *Tetrahedron Lett.* **1983**, *24*, 4103.
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(42) (a) Kotovych, G.; Aarts, G. H.; Bigam, G. *Can. J. Chem.* **1980**, *58*, 1577. (b) Cooper, G. F.; Fried, J. *J. Proc. Natl. Acad. Sci. U.S.A.* **1973**, *70*, 1579.

the ester hydrolysis had been previously carried out enzymatically,[43] this represents a total synthesis of (-)-PGE_2.

E. α-Side-Chain Variations. Two PGE_2 analogues, (±)-5,6-didehydro-PGE_2 methyl ester (**36**) and its C-15 epimer **37**, were synthesized by using this same approach (Scheme X). Addition of the racemic, stabilized organocuprate **10** to enone (±)-**1** followed by treatment with iodide **21** in the presence of HMPA provided, after chromatography, **34** as an inseparable mixture of two diastereomers in 40% yield. A large amount (ca. 40%) of the cis alkylation product 8-*epi*-**34** was isolated, along with 18% of the unalkylated product **11**. The cis product 8-*epi*-**34** was equilibrated to a 2:1 mixture of **34** and 8-*epi*-**34** in the usual manner to provide an additional 19% of **34** after chromatography (59% overall yield).

Silyl ether **34** was desilylated in acetonitrile containing 1% pyridine and 5% of a 50% aqueous solution of HF to provide, after flash chromatography, a 90% yield of **35** as a mixture of two diastereomers. These diastereomers were separable but were carried on as a mixture. Only trace amounts of triols resulting from removal of the acetonide were produced. Reduction of **35** with aluminum amalgam proceeded much more rapidly and cleanly than the analogous PGE_2 case. Addition of three portions of Al(Hg) over 25 h to an aqueous THF solution of **35** produced an easily separable (α = 1.53) mixture of diastereomers **36** and **37**. The synthesis of **36** had been previously described.[44] Noyori[40a] has converted the bis(*tert*-butyldimethylsilyl)-protected **36** to PGE_2 methyl ester by catalytic semihydrogenation and to PGE_1 methyl ester by selective catalytic hydrogenation.

The alkylation of the lithium enolate of **9** with the saturated methyl 7-iodoheptanoate was attempted, the product of which would lead to a synthesis of PGE_1. This alkylation was not successful. Alkylation with unactivated iodides in prostaglandin systems have previously given only low yield of alkylation.[4]

Conclusions

We have outlined a short and highly convergent synthesis of (-)-PGE_2 methyl ester. The overall yield based on cyclopentadiene is ca. 20%. The unique chemistry in this disclosue is associated with enone **1**. The special features of this synthon are (i) the residual five carbons of the cyclopentenone moiety are all functionalized and chemically differentiated, (ii) the shape of the bicyclo[3.3.0] system, especially with the augmentation by the *endo*-methyl of the acetonide, assures that additions will occur with clean diastereoface selectivity from the convex side, and (iii) the molecule is stable and readily accessible in enantiomerically pure form. We anticipate that synthon **1** and the concepts herein demonstrated involving the use of the acetonide grouping to control enolate regiochemistry and to mask an aldol will be applicable to the synthesis of a wide variety of targets.[45,46]

Experimental Section

***cis*-2-Cyclopentene-1,4-diol.**[10] A photochemical reaction vessel, equipped with a water-jacketed immersion well, was charged with methanol (4 L), freshly prepared cyclopentadiene (35 mL, 0.425 mol), thiourea (22 g, 0.289 mol), and rose bengal (0.40 g). After oxygen was bubbled through the mixture for 5 min, irradiation was begun with a 450-W tungsten–halogen lamp. After 3 h of vigorous stirring, the oxygen flow and the irradiation were terminated, and the suspension was allowed to stir in the dark for 16 h. Methanol was removed by rotary evaporation, and the resulting slurry was diluted with water (200 mL) and filtered. The filtrated was concentrated by rotary evaporation, and the brown oil was distilled (106–107 °C/0.4 Torr) to yield *cis*-2-cyclopentene-1,4-diol as a colorless oil (22.70 g, 53%): IR (neat) 3600, 3350 (br), 3060, 2995, 2935, 1400, 1235, 1110, 1060 (s), 995 (s), 870 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.98 (s, 2 H), 4.62 (dd, J_1 = 7 Hz, J_2 = 4 Hz, 2 H), 3.81 (br, 2 H), 2.6. (dt, J_1 = 14 Hz, J_2 = 7 Hz, 1 H), 1.53 (dt, J_1 = 14 Hz, J_2 = 4 Hz, 1 H). These data agree with published values.[10]

***cis*-3,5-Diacetoxycyclopentene (2).**[10] *cis*-2-Cyclopentene-1,4-diol (46.0 g, 0.459 mol), pyridine (112 mL, 1.385 mol), and acetic anhydride (130 mL, 1.375 mol) were dissolved in dichloromethane (600 mL) and cooled to 0 °C. 4-(Dimethylamino)pyridine (0.60 g) was added, the ice bath was removed, and the mixture was stirred at room temperature for 13 h. The mixture was poured into a separatory funnel and washed successively with two 200-mL portions of 3 N HCl, saturated aqueous $NaHCO_3$ (200 mL), and saturated aqueous NaCl (200 mL). The organic layer was dried over Na_2SO_4 and concentrated by rotary evaporation. Distillation (80–81 °C/0.9 Torr; lit.[10] 110–112 °C/8 Torr) provided a colorless oil (81.50 g, 96.4%): IR (neat) 3070 (w), 2990, 2945, 1740 (s), 1430, 1365 (s), 1230 (s), 1120, 1070, 1015, 985, 950, 900, 770 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.93 (s, 2 H), 5.38 (dd, J_1 = 7.4 Hz, J_2 = 3.8 Hz, 2 H), 2.73 (ddt, J_1 = 14.9 Hz, J_2 = 7.5 Hz, J_3 = 1.3 Hz, 1 H), 1.90 (s, 6 H), 1.57 (dt, J_1 = 14.9 Hz, J_2 = 3.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 170.00, 134.18, 76.14, 36.72, 20.53. These data agree with literature values.[10]

3α,5α-Diacetoxy-1β,2β-cyclopentanediol.[47] *cis*-3,5-Diacetoxycyclopentene (81.0 g, 0.440 mol) and osmium tetraoxide (1.0 g, 3.90 mmol) were stirred in THF (800 mL) and acetone (300 mL). A solution of trimethylamine *N*-oxide dihydrate (59.0 g, 0.530 mol) in water (90 mL) was added. The mixture was stirred at room temperature for 15 h. The THF and acetone were removed by rotary evaporation, and the aqueous mixture was poured into a separatory funnel containing saturated aqueous $NaHSO_3$ (100 mL). The aqueous layer was extracted with 10 100-mL portions of ethyl acetate. The combined extracts were dried over Na_2SO_4 and concentrated by rotary evaporation. Recrystallization yielded a white solid (85.9 g, 89.5%): mp 97.5–98.5 °C; IR ($CHCl_3$) 3530 (br), 3030, 3010, 2940, 1730 (s), 1370 (s), 1255 (s), 1100, 1080, 1040 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.97 (p, J = 3.8 Hz, 2 H), 4.12 (m, 2 H), 3.86 (br, 2 H), 2.79 (dt, J_1 = 15.4 Hz, J_2 = 7.8 Hz, 1 H), 2.09 (s, 6 H), 1.66 (dt, J_1 = 15.4 Hz, J_2 = 4.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 171.19, 77.90, 75.78, 33.76, 20.79.

4β,6-Diacetoxy-2,2-dimethyl-3aβ,5,6α,6aβ-tetrahydro-4*H*-cyclopenta-1,3-dioxole (3).[47] The above diol (20.0 g, 91.7 mmol) and *p*-toluenesulfonic acid hydrate ($TsOH\cdot H_2O$, 250 mg) were dissolved in dry acetone (1.5 L) and stirred for 60 h. The mixture was concentrated by rotary evaporation and the residue was dissolved in diethyl ether (300 mL), washed with water (100 mL), dried over Na_2SO_4, and concentrated by rotary evaporation to provide white, crystalline solid (23.4 g, 99%): mp 79.5–80.5 °C; IR ($CHCl_3$) 2985 (w), 2930 (w), 1735 (s), 1375 (s), 1240 (s), 1155, 1050 (s), 855 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.08 (dd, J1 = 5.6 Hz, J2 = 1.3 Hz, 2H), 4.62 (d, J = 1.5 Hz, 2 H), 2.41 (dt, J1 = 15.7 Hz, J2 = 5.5 Hz, 1 H), 2.05 (s, 6 H), 1.96 (dt, J1 = 15.7 Hz, J2 = 1.5 Hz, 1 H), 1.44 (s, 3 H), 1.28 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 169.74, 110.97, 84.09, 78.41, 34.07, 26.11, 23.75, 20.85.

2,2-Dimethyl-3aβ,5,6α,6aβ-tetrahydro-4*H*-cyclopenta-1,3-dioxole-4,6-diol (4).[47] A solution of KOH (17.0 g, 303 mmol) in MeOH (400 mL) was added to a solution of **3** (34.0 g, 132 mmol) in MeOH (700 mL), and the mixture was stirred for 30 min. The reaction mixture was adjusted to pH 8 with 1 N HCl (250 mL) and concentrated on a rotary evaporator to a volume of 300 mL. The solution was extracted with six 100-mL portions of diethyl ether. The combined ether extracts dried over Na_2SO_4 and concentrated by rotary evaporation. Recrystallization from CCl_4 yielded a white, crystalline solid (22.7 g, 99%): mp 135–136 °C; IR ($CHCl_3$) 3600, 3440 (br), 2980 (s), 2930 (s), 1420, 1385 (s), 1375 (s), 1260, 1155 (s), 1065 (s), 1045 (s), 960, 910, 860 (s), cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.65 (d, J = 1.8 Hz, 2 H), 4.25 (dd, J_1 = 6.6 Hz, J_2 = 4.4 Hz, 2 H), 2.82 (d, J = 6.8 Hz, 2 H), 2.15 (dt, J_1 = 14.6 Hz, J_2 = 4.4 Hz, 1 H), 1.87 (dt, J_1 = 14.7 Hz, J_2 = 1.7 Hz, 1 H), 1.43 (s, 3 H), 1.32 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 110.2, 86.1, 77.6, 37.1, 25.9, 23.6.

(±)-2,2-Dimethyl-3aβ,6aβ-dihydro-4*H*-cyclopenta-1,3-dioxol-4-one (1). Diol **4** (3.48 g, 20 mmol) was dissolved in dry benzene (80 mL) and dry DMSO (80 mL). Pyridine (2.4 mL, 30 mmol), trifluoroacetic acid (1.2 mL, 15 mmol), and 1,3-dicyclohexylcarbodiimide (DCC, 18.5 g, 90 mmol) were added in order, and the reaction mixture was stirred for 18 h. The mixture was filtered, and the filtrate washed with three 100-mL portions of water, dried over Na_2SO_4, and concentrated on a rotary evaporator. Flash chromatography with 10:1 hexane/EtOAc followed by recrystallization from pentane gave a white solid (2.70 g, 88%): mp 37.5–38.5 °C (lit.[8] mp 36–38 °C); IR ($CHCl_3$) 3020, 2990, 2930, 1725 (s), 1590 (w), 1455 (w), 1385 (s), 1375 (s), 1345, 1230, 1185, 1150, 1095 (s)e, 1065, 960, 910, 850 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.63 (dd, J_1 = 6.0 Hz, J_2 = 2.3 Hz, 1 H), 6.24 (dd, J_1 = 6.0 Hz, J_2 = 0.5 Hz, 1 H), 5.29 (ddd, J_1 = 5.5 Hz, J_2 = 2.3 Hz, J_3 = 0.65 Hz, 1 H), 4.49 (d, J = 5.5 Hz, 1 H), 1.43 (s, 6 H). These data agree with literature values.[8,44]

Reaction of (+)-*N*,*S*-Dimethyl-*S*-phenylsulfoximine [(+)-6] with (±)-1. 2,2-Dimethyl-4-[(*N*-methylphenylsulfonimidoyl)methyl]-

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(46) The chemistry described in this article is the subject of a patent application by Wayne State University.
(47) Kunnen, K. B. Ph.D. Dissertation, Wayne State University, 1985.

3aα,6aβ-dihydro-4H-cyclopenta-1,3-dioxol-4-ol (7a and 7b). A solution of *n*-BuLi in hexane (1.6 M) was added to a solution of (+)-**6** (2.54 g, 15.0 mmol) 99.5% ee)[15] and triphenylmethane (10 mg) in dry THF (100 mL) at 0 °C until an orange color persisted. The solution was stirred at 0 °C for 15 min and cooled to −78 °C. Enone (±)-**1** (2.31 g, 15.0 mmol) in dry THF (25 mL) was added slowly, and the reaction mixture was stirred at −78 °C for 1 h. The cold reaction mixture was poured into ether (50 mL) and saturated aqueous NH_4Cl (50 mL) in a separatory funnel. The layers were separated, and the aqueous layer was extracted twice with ether (50 mL). The combined ether extracts were dried over Na_2SO_4 and concentrated by rotary evaporation to yield a colorless gum. Analytical HPLC (65% EtOAc/35% hexane; 2 mL/min flow rate) showed two diastereomers (retention times 11.2 min and 14.7 min; ratio, 1.1/1; 1.37), which were separated by very careful flash chromatography with 2:1 hexane/EtOAc to give 2.02 g (42%) of the faster eluting diastereomer **7b** and 1.67 g (34%) of diastereomer **7a**.

Diasteromer **7b** was a white solid: mp 71–73 °C; ^1H NMR ($CDCl_3$) δ 7.80 (d, J = 7.1 Hz, 2 H), 7.53 (m, 3 H), 5.81 (d, J = 5.7 Hz, 1 H), 5.66 (d, J = 5.7 Hz, 1 H), 5.65 (br, 1 H), 5.07 (s, 2 H), 3.55 (d, J = 14.3 Hz, 1 H), 3.06 (d, J = 14.3 Hz, 1 H), 2.56 (s, 3 H), 1.38 (s, 3 H), 1.36 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 136.96, 132.62, 132.88, 129.26, 128.98, 112.61, 83.68, 80.79, 62.43, 28.89, 27.47, 26.55; $[\alpha]^{25}_D$ −94.3° (*c* 1.19, $CHCl_3$, corrected for 99.5% pure (+)-**6**). Anal. Calcd for $C_{16}H_{21}NO_4S$: C, 59.42; H, 6.55. Found: C, 59.42; H, 6.92.

Diastereomer **7a** was a white solid: mp 73–75 °C; ^1H NMR ($CDCl_3$) δ 7.85 nd, J = 6.7 Hz, 2 H), 7.56 (m, 3 H), 6.03 (d, J = 5.8 Hz, 1 H), 5.88 (dd, J_1 = 5.8 Hz, J_2 = 1.4 Hz, 1 H), 5.53 (br, 1 H), 4.98 (d, J = 5.3 Hz, 1 H), 4.54 (d, J = 5.4 Hz, 1 H), 3.45 (d, J = 14.1 Hz, 1 H), 3.22 (d, J = 14.1 Hz, 1 H), 2.61 (s, 3 H), 1.41 s, 3 H), 1.33 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 137.32, 133.01, 132.00, 129.31, 129.08, 112.86, 83.12, 81.61, 79.99, 63.31, 28.94, 27.39, 26.45; $[\alpha]^{25}_D$ +111.8° (*c* 1.055, $CHCl_3$, corrected for 99.5% pure (+)-**6**). Anal. Calcd for $C_{16}H_{21}NO_4S$: C, 59.42; H, 6.55. Found: C, 59.16; H, 6.93.

Thermolysis of 7a and 7b. (−)- and (+)-Enone 1. A solution of β-hydroxysulfoximine (−)-**7b** (1.97 g, 6.09 mmol) in dry toluene (100 mL) was refluxed for 9 h. Concentration by rotary evaporation and flash chromatography with 6:1 hexane/EtOAc provided 0.91 g (97%) of (−)-**1** as a white solid with $[\alpha]^{25}_D$ −70.8° (*c* 0.925, $CHCl_3$). In an identical manner, (+)-**7a** (1.62 g, 5.01 mmol) was thermolyzed to give 0.755 g (98%) of (+)-**1** as a white solid with $[\alpha]^{25}_D$ +71.8° (*c* 0.91, $CHCl_3$). The dextrorotatory enantiomer was assigned the 3a*S*,6a*S* configuration, and the levorotatory enantiomer was assigned the 3a*R*,6a*R* configuration on the basis of a comparatived ORD study with (−)-**8**.[16]

Enzymatic Semihydrolysis of *meso*-4β,6-Diacetoxy-2,2-dimethyl-3aα,5,6a,6aβ-tetrahydro-4H-cyclopenta-1,3-dioxole (3) and Conversion of the Resulting Monoacetate 5 to (+)-(3a*S*,6a*S*)-2,2-Dimethyl-3aβ,6aβ-dihydro-4H-cyclopenta-1,3-dioxol-4-one [(+)-1]. The finely powdered meso diacetate **3** (12.9 g, 50 mmol) was stirred in 425 mL of a 0.58 M aqueous phosphate pH 6.9 buffer solution. Sodium azide (42 mg) (bacteriostat) and electric eel acetylcholinesterase (12–15 mg) (cholinesterase, acetyl from electric eel, type VI-S, Sigma Chemical Co.) were added, and the heterogeneous solution was stirred at 25 °C for 19 h. The nearly homogeneous reaction mixture was extracted with diethyl ether (5 × 100 mL), and the combined ether extracts were dried over Na_2SO_4 and concentrated by rotary evaporation. The colorless semisolid was flash chromatographed by using first 5:1 hexane/EtOAc, ten 1:1 hexane EtOAc, to provide (3α*S*,4*R*,6*S*,6α*R*)-4β-acetoxy-2,2-dimethyl-6-hydroxy-3aβ,5,6α,6aβ-tetrahydro-4H-cyclopenta-1,3-dioxole (**5**) as a white solid (8.5 g, 79%, 98% based on recovered **3** and **4**): ^1H NMR ($CDCl_3$) δ 5.05 (d, J = 5.2 Hz, 1 H), 4.58 (dd, J_1 = 5.7 Hz, J_2 = 1.1 Hz, 1 H), 4.52 (d, J = 5.7 Hz, 1 H) 4.18 (br, 1 H), 2.67 (br, 1 H), 2.28 (dt, J_1 = 15.2 Hz, J_2 = 5.3 Hz, 1 H), 2.01 (s, 3 H), 1.81 (dt, J_1 = 15.2 Hz, J_2 = 1.5 Hz), 1.35 (s, 3 H), 1.21 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 169.78, 110.61, 86.08, 84.17, 76.43, 36.19, 26.07, 23.71, 20.94; $[\alpha]^{25}_D$ −12.74° (*c* 0.95, $CHCl_3$). Also isolated was the diol **4** (1.25 g, 14%) (which could be reconverted to the diacetate and recycled) along with 0.63 g (5%) of recovered starting diacetate **3**.

The monoacetate **5** (8.3 g, 38.4 mmol) was dissolved in 450 mL of acetone and cooled to 0 °C. Jones reagent (22.1 mL of a 1.34 M solution, 29.6 mmol, see below) was added, and the reaction mixture was stirred at 0 °C for 15 min and at 25 °C for 4 h. Solid $NaHCO_3$ (1 g) and $NaHSO_3$ (1 g) were added, and the solution was filtered. The colorless solution was concentrated by rotary evaporation, the crude product was dissolved in diethyl ether (200 mL), and the solution was washed with saturated NaCl (150 mL). The layers were separated, and the aqueous layer was washed with 100 mL of diethyl ether. The combined ether extracts were dried over Na_2SO_4 and concentrated by rotary evaporation. Flash chromatography, first with 5:1 hexane/EtOAc, then with 2:1 hexane/EtOAc, provided the enone **1** as a white crystalline solid (5.65 g, 95%), mp 68–69 °C, $[\alpha]^{25}_D$ +70.49° (*c* 0.915, $CHCl_3$) (98%ee), along with recovered monoacetate **5** (0.35 g, 4%).

Jones reagent: CrO_3 (13.4 g, 0.134 mol) dissolved in 12 mL of concentrated sulfuric acid and diluted with distilled water to 100 mL.

6-Butyl-2,2-dimethyl-3aβ,5,6α,6aβ-tetrahydro-4H-cyclopenta-1,3-dioxol-4-one (9). To a slurry of purified CuI (0.35 g, 1.85 mmol) in dry THF (10 mL) was added *n*-BuLi (1.6 mL of a 1.6 M solution in hexane, 3.7 mmol) at −78 °C. The resulting mixture was allowed to warm to −20 °C, stirred for 1–2 min, and cooled to −78 °C. To this was added enone (±)-**1** (0.25 g, 1.62 mmol) in dry THF (2 mL). The mixture was stirred at −78 °C for 30 min and quenched with saturated aqueous NH_4Cl. The mixture was extracted with ether (3 × 15 mL), and the combined ether extracts were dried over Na_2SO_4 and concentrated by rotary evaporation. Flash chromatography with 35:1 hexane/EtOAc as the eluent yielded **9** as a colorless oil (0.32 g, 93%): IR (neat) 2980, 2950 (s), 2920 (s), 2850, 1755 (s), 1455, 1405, 1380 (s), 1370 (s), 1210 (s), 1150 (s), 1050 (s), 850 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.49 (d, J = 5.4 Hz, H10 (prostaglandin numbering)), 4.17 (d, J = 5.4 Hz, H11), 2.70 (dd, J_1 = 18.4 Hz, j_2 = 8.5 Hz, H8), 2.32 (q, J = 8.3 Hz, H12), 2.01 (dt, J_1 = 18.4 Hz, J_2 = 1.5 Hz, H8), 1.50–1.07 (m, 6 H), 1.39 (s, 3 H), 1.30 (s, 3 H), 0.86 (t, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 214.13, 111.95, 81.98, 77.99, 39.87, 36.64, 33.17, 29.20, 26.67, 24.71, 22.35, 13.70; HRMS, m/z 212.1404 (calcd for $C_{12}H_{20}O_3$ 212.1412). Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.97; H, 9.77.

6-[(1′*E*)-3′-[(*tert*-Butyltrimethylsilyl)oxy]-1′-octenyl]-2,2-dimethyl-3aβ,5,6α,6aβ-tetrahydro-4H-cyclopenta-1,3-dioxol-4-one (11). A solution of crude vinyltin reagent **23** (0.80 g, 1.50 mmol) in dry THF (5 mL) at −78 °C was treated with *n*-BuLi (1.20 mmol), and the mixture was stirred for 20 min. A solution of CuI·Bu_3P (0.47 g, 1.20 mmol) and Bu_3P (0.30 mL, 1.20 mmol) in dry THF (3 mL) was added, and the reaction mixture was stirred at −78 °C for 30 min. After addition of a solution of enone (±)-**1** (0.154 g, 1.00 mmol) in dry Et_2O (2 mL), the reaction mixture was stirred at −78 °C for 10 min and at −30 °C for 1 h. The usual workup procedure followed by flash chromatography with 50:1 hexane/EtOAc yielded **11** (0.370 g, 93%), a colorless oil, as an inseparable mixture of two diastereomers: ^1H NMR ($CDCl_3$) δ 5.56 (dd, J_1 = 15.7 Hz, J_2 = 5.3 Hz, J_3 = 2.2 Hz, H14), 5.49 (ddd, J_1 = 15.7 Hz, J_2 = 4.8 Hz, J_3 = 2.0 Hz, H13), 4.61 (d, J = 5.2 Hz, H10), 4.16 (d, J = 5.2 Hz, H11), 4.07 (m, H15), 3.10 (m, H12), 2.80 (ddd, J_1 = 18.1 Hz, J_2 = 8.4 Hz, J_3 = 0.8 Hz, H8), 2.22 (dd, J_1 = 18.1 Hz, J_2 = 0.8 Hz, H8), 1.51–1.13 (m, 8 H), 1.44 (s, 3 H), 1.35 (s, 3 H), 0.87 (2 s, t, J = 6.8 Hz, 12 H), 0.02–0.01 (2 s, 6 H); ^{13}C NMR ($CDCl_3$) δ 213.11*,[48] 135.74, 127.88, 112.31, 81.69*, 77.82, 72.72, 38.99, 38.39*, 38.07, 31.65, 26.77*, 25.76*, 24.87, 24.77, 22.48, 18.11, 13.91*, −4.40, −4.86. Anal. Calcd for $C_{22}H_{40}O_4Si$: C, 66.62; H, 10.16. Found: C, 66.62; H, 10.05.

6-Butyl-2,2,5-trimethyl-3aβ,5β,6,6aβ-tetrahydro-4H-cyclopenta-1,3-dioxol-4-one (12). To a slurry of purified CuI (0.162 g, 0.85 mmol) in dry THF (4 mL) was added *n*-BuLi (1.06 mL of a 1.6 M solution in hexane, 1.7 mmol) at −78 °C. The resulting mixture was allowed to warm to −20 °C, stirred for 1–2 min, and cooled to −78 °C. To this was added enone (±)-**1** (0.105 g, 0.68 mmol) in dry THF (2 mL). The mixture was stirred at −78 °C for 30 min, and HMPA (0.50 mL) and iodomethane (0.20 mL, 3.2 mmol) were added. The mixture was stirred at −78 °C for 30 min, at −30 °C for 30 min, and at 0 °C for 10 min. The reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with three 10-mL portions of diethyl ether. The combined ether extracts were washed with water (3 × 20 mL), dried over Na_2SO_4, and concentrated by rotary evaporation. The crude product was flash chroamtographed with 35:1 hexane/EtOAc to provide **12** as a colorless oil (0.096 g, 62%): R_f 0.40 (5:1 hexane/EtOAc); IR (neat) 2950 (s), 2920 (s), 2870, 2850, 1760 (s), 1455, 1380, 1210, 1155, 1070, 850 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.47 (dd, J_1 = 6.5 Hz, J_2 = 1.4 Hz, H10), 4.37 (dd, J_1 = 6.5 Hz, J_2 = 3.0 Hz, H11), 2.12 (dp, J_1 = 7.2 Hz, J_2 = 1.5 Hz, H8), 1.82 (dq, J_1 = 8 Hz, J_2 = 3 Hz, H12), 1.62–1.20 (m, 6 H), 1.37 (s, 3 H), 1.30 (s, 3 H), 1.14 (d, J = 7.0 Hz, 3 H), 0.90 (t, J = 7.0 Hz, 3 H); HRMS, m/z 226.1574 (calcd for $C_{13}H_{22}O_3$: 226.1568e. Byproducts produced in small amounts included **9** and the 5β-methyl diastereomer of **12**.

Alkylation of 9 with 20: Methyl (5*Z*)-7-(6′β-Butyl-2′,2′-dimethyl-4′-oxo-3a′β,5′β,6′,6a′β-tetrahydro-4′H-cyclopenta-1′,3′-dioxol-5′-yl)-5-heptenoate (14). A solution of **9** (0.095 g, 0.448 mmol) in dry THF (2 mL) was added to a solution of LDA (0.50 mmol) in dry THF (4 mL) at −78 °C. After the mixture was stirred for 30 min at −78 °C, HMPA (0.20 mL, 1.15 mmol) and methyl *cis*-7-iodo-5-heptenoate (**20**) (0.15 g, 0.56 mol) in dry THF (0.5 mL) were added. The reaction mixture was stirred at −30 °C for 30 min, at −20 °C for 30 min, and at −5 °C for 15 min. The usual workup, followed by flash chromatography with 15:1

(48) The * at ^{13}C NMR data points indicates a doublet due to the presence of the two diastereomers associated with the hydroxylated center of the lower side chain.

hexane/EtOAc, furnished **14** as a colorless oil (43 mg, 27%): R_f 0.23 (5:1 hexane/EtOAc); IR (neat) 2955 (s), 2930 (s), 2860, 1755 (s), 1745 (s), 1455, 1440, 1380, 1370, 1215, 1155, 1060, 860 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.42 (J = 7.1 Hz, 2 H), 4.41 (q, J = 6.4 Hz, H10 and H11), 3.66 (s, 3 H), 2.47–2.24 (m, 4 H), 2.09 (m, 4 H), 1.70 (m, 2 H), 1.49–1.24 (m, 6 H), 1.41 (s, 3 H), 1.34 (s, 3 H), 0.91 (t, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 215.27, 173.94, 130.88, 127.21, 112.21, 81.12, 79.51, 52.40, 51.37, 42.53, 34.02, 33.46, 29.23, 28.50, 26.88, 26.59, 25.12, 24.73, 22.61, 13.84.

Also produced in the reaction was the C,O-dialkylated product (40 mg, 18%): R_f 0.29 (5:1 hexane/EtOAc); ^1H NMR ($CDCl_3$) δ 5.64 (m, 2 H), 5.34 (m, 2 H), 5.05 (m, H10), 4.48 (m, 2 H), 4.31 (d, J = 6.3 Hz, H11), 3.67 (2 s, 6 H), 2.96 (m, 1 H), 2.54 (m, 2 H), 2.32 (m, 4 H), 2.12 (m, 4 H), 1.79–1.22 (m, 10 H), 1.42 (s, 3 H), 1.35 (s, 3 H), 0.90 (t, 3 H).

Aluminum Amalgam Reduction of 9. *trans*-3-Butyl-4-hydroxycyclopentanone (15). Ketone **9** (0.100 g, 0.47 mmol) was stirred in THF (8 mL) and water (1 mL). Granular aluminum (20 mesh, 0.20 g, 0.0074 g-atom), which had been stirred for 1 min with 2% aqueoue mercuric chloride (10 mL), filtered, and washed successively with water, ethanol, and diethyl ether, was added to the reaction mixture. The mixture was stirred for 13 h. Another equal portion of aluminum amalgam was added, and the mixture was stirred for 21 h. The gray suspension was filtered, and the filtrate was poured into diethyl ether (10 mL) and water (10 mL). The organic layer was separated, dried over Na_2SO_4, and concentrated to rotary evaporation. Flash chromatography with 3:1 hexane/EtOAc as eluent furnshed **15** as a colorless oil (64 mg, 87%): IR (neat) 3430 (br), 2960 (s), 2920 (s), 2850 s), 1740 (s), 1460, 1400, 1335, 1145, 1070 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.19 (q, J = 5.9 H, 1 H), 2.61 (m, J_1 = 18.4 Hz, J_2 = 7 Hz, J_3 = 2 Hz, 1 H), 2.24 (m, J_1 = 18.5 Hz, J_2 = 6.0 Hz, J_3 = 1.5 Hz, 1 H), 2.13 (m, 1 H), 1.92 (dd, J_1 = 18.8 Hz, J_2 = 6.8 Hz, 1 H), 1..1 (br, OH), 1.69 (m, 1 H), 1.33 (m, 6 H), 0.93 (t, 3 H); ^{13}C NMR ($CDCl_3$) δ 216.19, 74.35, 46.74, 44.92, 43.01, 32.65, 29.94, 22.68, 13.89. Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.37; H, 10.43.

Methyl 7-Hydroxy-5-heptynoate (17).[27] A solution of acid **16**[27] (12.20 g, 54.0 mmol) and *p*-toluenesulfonic acid hydrate (200 mg) in MeOH (150 mL) was refluxed for 36 h. The reaction mixture was cooled and concentrated by rotary evaporation. The residue was dissolved in Et_2O (200 mL), washed with saturated, aqueous $NaHCO_3$ (100 mL) and water (100 mL), dried over Na_2SO_4, and concentrated by rotary evaporation. Distillation 103–105 °C/0.8 Torr) furnished **17** as a colorless oil (7.2 g, 85%). Alkyne **17** was contaminated with ca. 10% of a compound presumed to be methyl 7-hydroxy-4,5-heptadienoate. The allene could be separated from the desired alkyne by a tedious flash chromatography with 4:1 hexane/EtOAc. The allene [R_f 0.63 (2:1 EtOAc/hexane)] was characterized by multiplets at δ 5.38 and 4.09 in the ^1H NMR spectrum and by singlets at δ 92.81 and 91.34 in the ^{13}C NMR spectrum.

Alkyne **17**: R_f 0.68 (2:1 EtOAc/hexane); IR (neat) 3440 (br), 2950 (s), 2870, 2280 (w), 2220 (w), 1740 (s), 1440 (s), 1370, 1225, 1160, 1010 cm^{-1}; ^1H NmR ($CDCl_3$) δ 4924 (m, 2 H), 3.68 (s, 3 H), 2.44 (t, J = 7.4 Hz, 2 H), 2.29 (tt, J_1 = 6.9 Hz, J_2 = 2.1 Hz, 2 H), 1.83 (p, J = 7.1 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 173.65, 84.72, 79.34, 51.50, 51.02, 32.72, 23.61, 18.08. Anal. Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.74. Found: C, 61.37; H, 7.75.

Methyl *cis*-7-Hydroxy-5-heptenoate (18). Lindlar catalyst (palladium on calcium carbonate, poisoned with lead; 60 mg) was added to the solution of alkyne **17** (1.26 g, 8.07 mmol) in 2:1 hexane/EtOAc at 0 °C. Hydrogen was bubbled through the reaction mixture until TLC analysis indicated the disappearance of **17** (2–3 h). The mixture was filtered and concentrated to yield **18** as a colorless liquid (1.277 g, 100%): IR (neat) 3410 (br), 3015 (w), 2940 (s), 2860, 1740 (s), 1435, 1365, 1245, 1205, 1155, 1025, 1000 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.66 (dtt, J_1 = 10.9 Hz, J_2 = 6.8 Hz, J_3 = 1.4 Hz, 1 H), 5.44 (dtt, J_1 = 10.9 Hz, J_2 = 7.5 Hz, J_3 = 1.3 Hz, 1 H), 4.15 (dd, J_1 = 6.7 Hz, J_2 = 1.1 Hz, 2 H), 3.66 (s, 3 H), 2.32 (t, J = 7.3 Hz, 2 H), 2.12 (dq, J_1 = 7.5 Hz, J_2 = 1.1 Hz, 2 H), 1.99 (br, 1 H), 1.71 (p, J = 7.3 Hz, 2 H). A minor amount (ca. 3%) of methyl *trans*-7-hydroxy-5-heptenoate could be seen in the ^1H NMR spectrum at δ 4.09 The longer the reaction mixture was allowed to remain in contact with catalyst after reduction was complete, the greater the amount of trans product produced.

Methyl *cis*-7-Bromo-5-heptenoate (19). To a solution of alcohol **18** (1.48 g, 9.36 mmol) and carbon tetrabromide (3.40 g, 10.25 mmol) in dry CH_2Cl_2 (50 mL) was added triphenylphosphine (2.70 g, 10.30 mmol) in portions. The reaction mixture was stirred for 40 min, and MeOH (1 mL) was added. Concentration of a rotary evaporator, followed by flash chromatography with 50:1 hexane/EtOAc as eluent, gave **19** as a colorless oil (1.98 g, 96%): IR (neat) 3020 (w), 2945, 2860 (w), 1740 (s), 1435, 1370, 1200, 1165 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.77 (m, J_1 = 10.5 Hz, J_2 = 8.3 Hz, J_3 = 1.4 Hz, 1 H), 5.56 (m, J_1 = 10.6 Hz, J_2 = 7.5 Hz, 1 H), 3.98 d, J = 8.1 Hz, 2 H), 3.67 (s, 3 H), 2.34 (t, J = 7.4 Hz, 2 H), 2.19 (dq, J_1 = 7.5 Hz, J_2 = 1.4 Hz, 2 H), 1.74 (p, J = 7.3 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 173.55, 134.48, 126.26, 51.37, 33.06, 26.60, 26.01, 24.28. A minor amount (ca. 5%) of methyl *trans*-7-bromo-5-heptenoate could be seen in the ^1H NMR spectrum at δ 3.93.

Methyl *cis*-7-Iodo-5-heptenoate (20). To a solution of bromide **19** (0.29 g, 1.30 mmol) in dry acetone (10 mL) was added NaI (0.26 g, 1.70 mmol). The reaction mixture was stirred for 5 min, filtered, and poured into Et_2O (50 mL) and water (20 mL). The ether layer was separated, washed with three 20-mL portions of water, dried over Na_2SO_4, and concentrated by rotary evaporation to yield the iodide **34** (0.35 g, 100%). The iodide was used immediately without further purification. If the reaction mixture was stirred for longer than 5 min, isomerization of the *cis*- to the *trans*-allyl iodide began to take place.

Methyl 7-Bromo-5-heptynoate. A solution of alcohol **17** (1.95 g, 12.5 mmol) and pyridine (0.20 mL, 2.60 mmol) in dry Et_2O (15 mL) was cooled to 0 °C. Phosphorus tribromide (0.60 mL, 6.4 mmol) was added dropwise, and the reaction mixture was stirred at 0 °C for 30 min and at room temperature for 1 h. The mixture was poured into water (10 mL), and the organic layer was washed with two 10-mL portions of water. Drying over Na_2SO_4 and concentration by rotary evaporation furnished, after flash chromatography with 20:1 hexane/EtOAc, the bromide as a colorless oil (2.18 g, 80%): IR (neat) 3010 (w), 2950, 2300 (w), 2230, 1740 (s), 1435 (s), 1370, 1315, 1220 (s), 1160 (s), cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.89 (t, J = 2.3 Hzz, 2 H), 3.65 (s, 3 H), 2.40 (t, J = 7.4 Hz, 2 H), 2.29 (tt, J_1 = 6.9 Hz, J_2 = 2.3 Hz, 2 H), 1.80 (p, J = 7.1 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 173.23, 86.56, 76.10, 51.42, 32.56, 23.40, 18.23, 15.18.

Methyl 7-Iodo-5-heptynoate (21). Iodide **21** was prepared from the corresponding bromide (above) by the method described above for the corresponding allyl iodide **20** and was used immediately without further purification.

***trans*-3-[(*tert*-Butyldimethylsilyl)oxy]-1-(tributylstannyl)-1-octene (23).** A neat mixture of 3-[(*tert*-butyldimethylsilyl)oxy]-1-octyne (**22**) (2.05 g, 8.53 mmol) and tributyltin hydride (2.30 mL), 8.53 mmol) were irradiated with a 275-W GE sunlamp for 4 h to produce **23**: ^1H NMR ($CDCl_3$) δ 6.04 (d, J = 19.0 Hz, 1 H), 5.93 (dd, J_1 = 19.0 Hz, J_2 = 5.2 Hz, 1 H), 4.04 (dd, J_1 = 6.1 Hz, J_2 = 5.6 Hz, 1 H), 1.52, 1.34 (2 m, 26 H), 0.94 (m, 21 H), 0.07 (s, 3 H), 0.05 (s, 3 H). ^1H NMR analysis revealed that **23** was only 85% pure and presumably contained isomeric impurities (see Scheme IV).

Methyl (5*Z*)-7-[6-[(1*E*)-3-[(*tert*-Butyldimethylsilyl)oxy]-1-octenyl]-2,2-dimethyl-4-oxo-3aβ,5β,6α,6aβ-tetrahydro-4*H*-cyclopenta-1,3-dioxol-5-yl]-5-heptenoate (25). Method A. Alkylation of 11. A solution of ketone **11** (0.17 g, 0.429 mmol) in dry THF (2 mL) was added to a solution of LDA (0.50 mmol) in dry THF (4 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 30 min, and HMPA (0.15 mL, 0.86 mmol) and a solution of iodide **20** (0.16 g, 0.60 mmol) in dry THF (1 mL) were added. The mixture was stirred at −78 °C for 10 min and at −30 °C for 3 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (5 mL) and poured into ether (15 mL) and water (10 mL). The organic layer was washed with three 15-mL portions of water, dried over Na_2SO_4, and concentrated by rotary evaporation. Flash chromatography with 15:1 hexane/EtOAc as the eluent afforded the starting ketone **11** (0.022 g, 13%), the cis alkylation product 8-*epi*-**25** (0.038 g, 16%), and the desired product **25** (0.072 g, 31%) as an inseparable mixture of two diastereomers. The product was a colorless oil with the following characteristics: IR (neat) 2990 (w), 2960 (se, 2935 (s), 2860, 1760 (s), 1750 (s), 1465, 1385, 1375, 1250, 1155, 1070, 965, 830, 770 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.57 (m, J = 15.4 Hz, H13 and H14), 5.41 (m, H5 and H6), 4.47 (m, H10 and H11), 4.09 (q, J = 5.8 Hz, H15), 3.66 (s, 3 H), 2.71 (m, J = 6 Hz, H12)8 2.42 (m, 1 H), 2.30 (m, J = 7 Hz, 4 H), 2.05 (2 q J = 7 Hz, 2 H), 1.68 (m, J = 7 Hz, 2 H), 1.53–1.17 (m, 8 H), 1.42 (s, 3 H), 1.35 (s, 3 H), 0.90 (m, 12 H), 0.05 (s, 3 H), 0.02 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 213.20*,[48] 173.70, 135.78*, 130.90, 128.84, 126.60, 112.47, 80.70*, 79.10*, 72.72, 52.29, 51.23, 46.03, 38.06, 33.25, 31.59, 26.99, 26.81, 26.45, 25.71, 25.06, 24.70*, 24.54, 22.42, 18.05, 13.83, −4.38, −4.88; HRMS, m/z 536.3527 (calcd for $C_{30}H_{52}O_6Si$ 536.3533). Anal. Calcd for $C_{30}H_{52}O_6Si$: C, 67.12; H, 9.76. Found: C, 67.35; H, 9.87. The cis alkylation product (8-*epi*-**25**) could be equilibrated to a 2:1 mixture of **25** and 8-*epi*-**25** with catalytic sodium acetate in refluxing MeOH (5 mL) for 3 h. Concentration by rotary evaporation, followed by flash chromatography (15:1 hexane/EtOAc), gave the desired **25** (0.021 g, 9%) for an overall yield of 40% of **25**.

Method B. One-Pot Procedure. To the vinyllithium reagent **24** (from the transmetallation of the vinyltin reagent **23** (0.54 g, 1.02 mmol)) in dry THF (6 mL) at −78 °C was added a solution of CuI·Bu_3P (0.32 g, 0.82 mmol) and Bu_3P (0.20 mL, 0.80 mmol) in dry THF (2 mL). After

the mixture was stirred at −78 °C for 30 min, a solution of enone (±)-**1** (0.109 g, 0.71 mmol) in dry Et_2O (2 mL) was added. The reaction mixture was maintained at −78 °C for 10 min and at −30 °C for 1 h. HMPA (0.24 mL, 1.40 mmol) and a solution of iodide **20** (0.34 g, 1.27 mmol) in dry THF (2 mL) were added, and the mixture was stirred at −30 °C for 3 h. The reaction mixture was quenched with 20% aqueous ammonium sulfate (10 mL) and poured into ether (10 mL) and water (10 mL). The ether layer was separated, washed with three 15-mL portions of water, dried over Na_2SO_4, and concentrated on a rotary evaporator. Flash chromatography with 15:1 hexane/EtOAc gave the unalkylation ketone **11** (0.080 g, 28%), the cis alkylated 8-*epi*-**25** (0.026 g, 7%), and the desired **25** (0.240 g, 63%) with spectral characteristics identical with those described above. No evidence of dialkylation products could be seen in the reaction mixture.

Desilylation of 25. Methyl (5*Z*)-7-[6-((1*E*)-3-hydroxy-1-octenyl)-2,2-dimethyl-4-oxo-3aβ,5β,6α,6aβ-tetrahydro-4*H*-cyclopenta-1,3-dioxol-5-yl]-5-heptenoate (26). A solution of silyl ether **25** (0.056 g, 0.104 mmol) in CH_3CN (4 mL) was cooled to 0 °C. Pyridine (0.05 mL) was added, followed by 50% aqueous HF (0.25 mL). The reaction mixture was stirred at 0 °C for 30 min and warmed to room temperature. The progress of the reaction was monitored by TLC. Upon disappearance of the starting material (2–4 h), the mixture was poured into saturated aqueous $NaHCO_3$ (15 mL) and Et_2O (20 mL). The organic layer was separated, washed with water (2 × 15 mL) and with saturated aqueous NaCl (15 mL), dried over Na_2SO_4, and concentrated by rotary evaporation. Flash chromatography with 3:1 hexane/EtOAc furnished alcohol **26** (0.042 g, 95.5%): IR ($CHCl_3$) 3610 (w), 3510 (br), 3020 (w), 3000, 2960, 2940 (s), 2860, 1755 (s), 1735 (s), 1665 (w), 1455, 1440, 1385, 1375, 1240, 1150, 1065, 970, 855 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.67 (dq, J_1 = 15.5 Hz, J_2 = 3.5 Hz, 2 H), 5.42 (m, 2 H), 4.50 (m, H10 and H11), 4.12 (q, J = 5.6 Hz, H15), 3.67 (s, 3 H), 2.69 (m, 1 H), 2.30 (m, 3 H), 2.08 (2 q, J = 6.5 Hz, 2 H), 1.69 (p, J = 7.4 Hz, 2 H), 1.62–1.22 (m, 9 H), 1.45 (s, 3 H), 1.35 (s, 3 H), 0.90 (t, 3 H); ^{13}C NMR ($CDCl_3$) δ 212.49, 174.16, 135.64*,[48] 131.03, 130.05t, 126.61*, 112.97, 80.61, 79.02, 72.27*, 52.66*, 51.49, 46.89*, 37.20*, 33.35, 31.65, 26.92, 26.54, 26.42, 26.29, 25.06*, 24.61, 22.52, 13.94.

Aluminum Amalgam Reduction of 26. (±)-Prostaglandin E_2 Methyl Ester (27) and (±)-15-*epi*-Prostaglandin E_2 Methyl Ester (28). Ketone **26** (45 mg, 0.106 mmol) was stirred in THF (8 mL) and water (1 mL). Aluminum amalgam (from 0.044 g, 0.0016 g-atom of granular aluminum), prepared as described earlier, was added. Additional equal portions of Al(Hg) were added after 6 h and 13 h. The reaction mixture was stirred for an additional 12 h and filtered, and the filtrate was poured into ether (10 mL) and water (10 mL). The organic layer was separated, dried over Na_2SO_4, and concentrated by rotary evaporation. Flash chromatography, first with 1:1 hexane/EtOAc and then with EtOAc, yielded starting ketone **26** (20 mg, 45%), (±)-PGE_2 methyl ester (**27**; 13 mg, 34%), and (±)-15-*epi*-PGE_2 methyl ester (**28**) (7 mg, 18%). Compound **27** was a colorless oil: R_f 0.15 (2:1 EtOAc/hexane);[31a,41] IR ($CHCl_3$) 3620 (w), 3440 (br), 3010, 2960 (s), 2930 (s), 2860 (s), 1745 (s), 1460, 1440, 1245, 1155, 1070, 970, 905 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.68 (dd, J_1 = 15.3 Hz, J_2 = 6.8 Hz, H14), 5.57 (dd, J_1 = 15.3 Hz, J_2 = 7.9 Hz, H13), 5.38 (m, J = 6.9 Hz, H5 and H6), 4.13 (q, J = 6.6 Hz, H15), 4.07 (q, J = 7.7 Hz, H11), 3.82 (br, OH), 3.68 (s, 3 H), 2.95 (br, OH), 2.76 (ddd, J_1 = 18.4 Hz, J_2 = 7.4 Hz, J_3 = 0.8 Hz, H10), 2.36 (m, 5 H), 2.22 (dd, J_1 = 18.5 Hz, J_2 = 9.7 Hz, H10), 2.08 (m, 3 H), 1.73–1.47 (m, 4 H), 1.45–1.15 (m, 6 H), 0.87 (t, J = 6.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 214.06, 174.17, 136.96, 131.06, 130.88, 126.53, 72.90, 72.06, 54.49, 53.54, 51.53, 46.07, 37.28, 33.42, 31.67, 26.59, 25.14, 25.04, 24.67, 22.59, 13.97; HRMS (20 eV), m/z 348.2304 (calcd for $C_{21}H_{32}O_4$ (M − H_2O) 348.2300). The ^1H and ^{13}C NMR spectra were identical with literature spectra.[42]

Compound **28** was a colorless oil: R_f 0.24 (2:1 EtOAc/hexane); IR (identical with that obtained for **27**); ^1H NMR ($CDCl_3$) δ 5.75 (dd, J_1 = 15.4 Hz, J_2 = 6.1 Hz, H14), 5.61 (ddd J_1 = 15.3 Hz, J_2 = 8.3 Hz, J_3 = 0.6 Hz, H13), 5.41 (m, J = 7 Hz, H5 and H6), 4.14 (2 q, J = 8 Hz and 6 Hz, H11 and H15), 3.70 (s, 3 H), 2.78 (ddd, J_1 = 18.5 Hz, J_2 = 7.3 Hz, J_3 = 1.1 Hz, H10), 2.42 (m, 2 H), 2.34 (m, 2 H), 2.23 (dd, J_1 = 18.5 Hz, J_2 = 9.7 Hz, H10), 2.10 (m, 4 H), 1.78–1.24 (m, 12 H), 0.91 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 214.11, 174.41, 137.64, 131.00, 129.51, 126.54, 72.26, 72.14, 54.63, 53.14, 51.62, 46.26, 37.36, 33.39, 31.70, 26.64, 25.18, 24.91, 24.68, 22.59, 13.92; HRMS (20 eV), m/z 348.2303 (calcd for $C_{21}H_{32}O_4$ (M − H_2O) 348.2300).

Deprotection of 25. (±)-10-Hydroxyprostaglandin E_2 Methyl Ester (29a) and (±)-10-Hydroxy-15-*epi*-Prostaglandin E_2 Methyl Ester (29b). A solution of silyl ether **25** (0.052 g, 0.097 mmol) and 50% aqueous HF (0.15 mL) in CH_3CN (3 mL) was stirred at room temperature for 1 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$ (10 mL) and ether (15 mL). The organic layer was washed with two 10-mL portions of water, dried over Na_2SO_4, and concentrated to yield a mixture of triols **29** (0.037 g, 100%): R_f 0.19 (**29a**) and 0.28 (**29b**) (2:1 EtOAc/hexane), respectively; ^1H NMR ($CDCl_3$) δ 5.68 (m, 2 H), 5.42 (m, 2 H), 4.34 (m, 1 H), 4.13 (m, 2 H), 3.74 (s, 3 H), 3.49 (br, 3 H), 2.76 (m, 1 H), 2.57 (m, 1 H), 2.33 (m, 2 H), 2.09 (m, 4 H), 1.69 (p, 2 H), 1.59–1.22 (m, 8 H), 0.90 (t, 3 H). Compounds **29** were not separated. Assignment of the two products on TLC was made on the basis of reports in literature of the greater polarity of PGE analogues than 15-*epi*-PGE analogues.[31a,41]

(+)-(3a′*S*,3′′*S*,5′*R*,6′*R*,6a′*S*)-Methyl (5*Z*)-7-[6′-[(1′′*E*)-3′′-[(*tert*-Butyldimethylsilyl)oxy]-1′′-octenyl]-2′,2′-dimethyl-3a′,5′,6′,6′-tetrahydro-4′*H*-cyclopenta-1′,3′-dioxol-5′-yl]-5-heptenoate [(+)-30]. A solution of (1*E*,3*S*)-3-[(*tert*-butyldimethylsilyl)oxy]-1-(tributylstannyl)-1-octene [(*S*)-**23**] (1.35 g, 2.54 mmol; prepared from (3*S*)-[(*tert*-butyldimethylsilyl)oxy]-1-octyne (**22**)[49] and tributyltin hydride as previously described) in dry THF (15 mL) at −78 °C was treated with *n*-BuLi (1.35 mL of a 1.6 M solution, 2.16 mmol) and stirred at −78 °C for 20 min. A solution of CuI·Bu_3P (0.85 g, 2.16 mmol) and Bu_3P (0.54 mL, 2.16 mmol) in dry THF (5 mL) was added, and the reaction mixture was stirred at −78 °C for 30 min. A solution of enone (+)-**1** (0.295 g, 1.91 mmol) in dry ether (5 mL) was added, and the mixture stirred at −78 °C for 10 min and at −30 °C for 1 h. HMPA (0.66 mL, 3.79 mmol) and a solution of iodide **20** (0.85 g, 3.17 mmol) in dry THF (5 mL) were added. After being stirred at −30 °C for 3 h, the reaction mixture was poured into 20% aqueous ammonium sulfate (20 mL) and ether (20 mL). The ether layer was separated, washed with three 30-mL portions of water, dried over Na_2SO_4, and concentrated by rotary evaporation. Flash chromatography, using 100:1 hexane/EtOAc, slowly changing to 10:1 hexane/EtOAc, gave (+)-**30** (0.475 g, 46%) as a colorless oil with the following characteristics: IR and ^1H NMR identical with those of **25**; ^{13}C NMR ($CDCl_3$) δ 213.23, 173.82, 135.85, 130.97, 128.93, 126.72, 112.61, 80.74, 79.18, 72.82, 52.42, 51.33, 46.07, 38.16, 33.37, 31.69, 27.15, 26.90, 26.55, 25.80, 25.14, 24.83, 24.64, 22.51, 18.15, 13.88, −4.31, −4.81; $[\alpha]^{25}_D$ +7.55° (*c* 0.98 $CHCl_3$). Also isolated was the unalkylated product (+)-(3a*S*,6*S*,6a*S*)-6-[(1′-*Z*)-[3′-(*tert*-butyldimethylsilyl)oxy]-1′-octenyl]-2,2-dimethyl-3a,5,6,6a-tetrahydro-4*H*-cyclopenta-1,3-dioxol-4-one [(+)-**11**] (0.192 g, 25%) as a colorless oil with $[\alpha]^{25}_D$ +102.2° (*c* 1.15, $CHCl_3$), and the cis alkylated product 8-*epi*-**30** (0.120 g, 12%). Compound 8-*epi*-**30** was equilibrated to a mixture of **30** and 8-*epi*-**30** as previously described, and the mixture was flash chromatographed with 15:1 hexane/EtOAc to provide an additional 0.067 g (7%) of (+)-**30** for a total yield of 53%.

(−)-(3a′*S*,3′′*S*,5′*R*,6′*R*,6a′*S*)-Methyl (5*Z*)-7-[6′-((1′′E)-3′′-Hydroxy-1′′-octenyl)-2′,2′dimethyl-3a′,5′,6′,6a′-tetrahydro-4′*H*-cyclopenta-1′,3′-dioxol-5′-yl]-5-heptenoate [(−)-31]. A solution of (+)-**30** (0.470 g, 0.876 mmol) in CH_3CN (30 mL) was cooled to 0 °C. Pyridine (0.35 mL) was added, followed by 50% aqueous HF (1.75 mL). The reaction mixture was stirred at 0 °C for 10 min and at room temperature for 4.5 h. The mixture was poured into saturated aqueous $NaHCO_3$ (50 mL) and ether (50 mL). The ether layer was separated, washed with three 40-mL portions of water, dried over Na_2SO_4, and concentrated by rotary evaporation. Flash chromatography with 3:1 hexane/EtOAc as the eluent gave 0.064 g (14%) of starting silyl ether (+)-**30** and 0.288 g [78%; 90% based on recovered (+)-**30**] of (−)-**31** as a colorless oil: IR same as that of **26**; ^1H NMR ($CDCl_3$) δ 5.66 (dd, J_1 = 15.5 Hz, J_2 = 7.0 Hz, H14), 5.57 (dd, J_1 = 15.5 Hz, J_2 = 5.6 Hz, H13), 5.37 (m, H5 and H6), 4.46 (q, J = 6.7 Hz, H10 and H11), 4.06 (q, J = 6.0 Hz, H15), 3.63 (s, 3 H), 2.62 (dt, J_1 = 7.3 Hz, J_2 = 2.6 Hz, H12), 2.32 (m, 4 H), 2.26 (t, J = 7.4, 2 H2), 2.03 (dq, J_1 = 7.1 Hz, J_2 = 1.4 Hz, 2 H4), 1.63 (p, J = 7.4 Hz, 2 H3), 1.57–1.13 (m, 8 H), 1.38 (s, 3 H), 1.29 (s, 3 H), 0.84 (t, J = 6.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 212.49, 173.90, 135.44, 130.87, 129.95, 126.51, 112.76, 80.52, 78.90, 72.10, 52.47, 51.31, 46.67, 37.07, 33.24, 31.53, 26.78, 26.41, 26.35, 25.03, 24.94, 24.50, 22.39, 13.81; $[\alpha]^{25}_D$ −0.52° (*c* 2.29, $CHCl_3$). Anal. Calcd for $C_{24}H_{28}O_6$: C, 68.22; H, 9.06. Found: C, 68.08; H, 9.05.

(−)-Prostaglandin E_2 Methyl Ester [(−)-32]. To a solution of (−)-**31** (0.280 g, 0.66 mmol) in 8:1 THF/water (25 mL) was added Al(Hg) (from 0.18 g, 0.0066 g-atoms of granular aluminum). Additional equal portions of Al(Hg) were added after 10, 17, and 23 h. After being stirred for an additional 15 h, the reaction mixture was filtered, and the filtrate was poured into ether (20 mL) and water (20 mL). The ether layer was separated, dried over Na_2SO_4, and concentrated by rotary evaporation. Flash chromatography, first with 3:1 hexane/EtOAc and then with EtOAc, furnished (−)-**31** (0.025 g, 9%) and (−)-PGE_2 methyl ester (**32**) (0.216 g, 89%; 98% based on recovered (−)-**31**): $[\alpha]^{20}_D$ −71.8° (*c* 1.25, MeOH) [lit.[40a] $[\alpha]^{20}_D$ −71.7° (*c* 1.04, MeOH)]; IR, ^1H NMR, and ^{13}C NMR data were in agreement with literature values[42] and are described above for (±)-PGE_2 methyl ester (**27**).

(49) (3*S*)-[(*tert*-Butyldimethylsilyl)oxy]-1-octyne ($[\alpha]^{25}_D$ −47° (Et_2O)) was kindly provided by Dr. P. W. Collins, G. D. Searle and Co.

(±)-Methyl 7-[6-[(1*E*)-3-[(*tert*-Butyldimethylsilyl)oxy]-1-octenyl]-2,2-dimethyl-3aβ,5β,6α,6aβ-tetrahydro-4*H*-cyclopenta-1,3-dioxol-5-yl]-5-heptynoate (34). To the vinyllithium reagent **24** [from the transmetalation of the vinyltin reagent **23** (0.52 g, 0.98 mmol)] in dry THF (4 mL) at -78 °C was added a solution of CuI·Bu_3P (0.31 g, 0.78 mmol) and Bu_3P (0.19 mL, 0.78 mmol) in dry THF (2 mL). After the mixture was stirred at -78 °C for 30 min, a solution of enone (±)-**1** (0.11 g, 0.71 mmol) in dry Et_2O (2 mL) was added. The reaction mixture was stirred at -78 °C for 10 min and at -30 °C for 1 h. HMPA (0.25 mL, 1.43 mmol) and a solution of propargyl iodide **21** (0.30 g, 1.13 mmol) in dry THF (1 mL) were added, and the mixture was stirred at -30 °C for 3 h. The usual workup, followed by flash chromatography with 15:1 hexane/EtOAc, gave the unalkylated product **11** (0.087 g, 18%), the cis alkylated product (8-*epi*-**34**) (0.150 g, 39%), and the desired **34** (0.153 g, 40%; an inseparable mixture of two diastereomers) as a colorless oil: IR (neat) 2960 (s), 2940 (s), 2860, 1760 (s), 1745 (s), 1465, 1440, 1375, 1250, 1215, 1160, 1070, 970, 835, 775 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.68 (m, J = 15 Hz, H13 and H14), 4.57 (m, H10 and H11), 4.16 (m, H15), 3.71 (s, 3 H), 2.99 (m, H12), 2.48 (m, 3 H), 2.44 (t, J = 7.4 Hz, 2 H), 2.22 (tt, J_1 = 6.9 Hz, J_2 = 2.0 Hz, 2 H), 1.81 (p, J = 7.2 Hz, 2 H), 1.49-1.23 (m, 8 H), 1.45 (s, 3 H), 1.39 (s, 3 H), 0.93 (m, 12 H), 0.06 (2 s, 6 H); ^{13}C NMR ($CDCl_3$) δ 211.56*,[48] 173.57, 136.34*, 128.44*, 112.88*, 80.69, 80.60, 79.19, 77.07, 72.88, 51.72, 51.43, 46.18*, 38.21, 32.82, 31.74, 27.01, 25.85, 25.40, 24.92, 24.81, 24.06, 22.55, 18.38, 18.21*, 13.95, -4.24, -4.75; HRMS, m/z 534.3372 (calcd for $C_{30}H_{50}O_6Si$ 534.3376). The cis alkylation product was equilibrated as described above for 8-*epi*-**25**, and the mixture was flash chromatographed (15:1 hexane/EtOAc) to give 0.072 g (19%) of **34**, for an overall yield of 0.225 g (59%) of **34**.

Desilylation of 34. (±)-Methyl 7-[6-((1*E*)-3-Hydroxy-1-octenyl)-2,2-dimethyl-3aβ,5β,6α,6aβ-tetrahydro-4*H*-cyclopenta-1,3-dioxol-5-yl]-5-heptynoate (35). Silyl ether **34** (0.090 g, 0.168 mmol) was stirred in CH_3CN (3 mL) and cooled to 0 °C. Pyridine (0.10 mL) was added, followed by 50% aqueous HF (0.30 mL). The reaction mixture was warmed to room temperature and stirred for 3 h. The mixture was worked up in the same manner as described above to give crude **35** (0.068 g, 96%). Flash chromatography with 2:1 hexane/EtOAc furnished **35** (a mixture of two diastereomers) as a colorless oil: ^1H NMR ($CDCl_3$) δ 5.77 (m, J = 15 Hz, 2 H), 4.55 (m, H10 and H11), 4.18, (m, H15), 3.72 (s, 3 H), 2.97 (m, J = 3 Hz, H12), 2.51 (m, 3 H), 2.43 (t, J = 7.4 Hz, 2 H), 2.22 (tt, J_1 = 6.9 Hz, J_2 = 2.3 Hz, 2 H), 1.80 (p, J = 7.2 Hz, 2 H), 1.73-1.18 (m, 9 H), 1.44 (s, 3 H), 1.37 (s, 3 H), 0.91 (t, 3 H).

Aluminum Amalgam Reduction of 35. (±)-5,6-Didehydroprostaglandin E_2 Methyl Ester (36) and (±)-5,6-Dihydro-15-*epi*-prostaglandin E_2 Methyl Ester (37). Ketone **35** (18 mg, 0.043 mmol) was submitted to the usual Al(Hg) reduction conditions described above. After a total of 26 h, the reaction mixture was worked up to give a mixture of diols **36** and **37** (15 mg, 96%): R_f 0.19 and 0.29 (2:1 EtOAc/hexane), respectively;[31a,41] ^1H NMR ($CDCl_3$) δ 5.78 (2 dd, J_1 = 15.3 Hz, J_2 = 6.6 Hz and 5.9 Hz, 1 H), 5.64 (2 dd, J_1 = 15.3 Hz, J_2 = 8.3 Hz, 1 H), 4.17 (m, H11 and H15), 3.72 (s, 3 H), 2.81 (dd, J_1 = 18 Hz, J_2 = 7 Hz, 1 H), 2.73 (m, 2 H), 2.44 (t, J = 7 Hz, 2 H), 2.40-2.03 (m, 7 H), 1.83 (p, J = 7 Hz, 2 H), 1.67-1.23 (m, 8 H), 0.91 (t, 3 H); HRMS (CI conditions), m/z 365.2332 (calcd for $C_{21}H_{33}O_5$ (M + H) 365.2328). The product mixture was not further purified.

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Supplementary Material Available: General experimental information, experimental procedures, and spectral data on **13**, **14**, and **16** plus various byproducts (eq 2) (5 pages). Ordering information is given on any current masthead page.

Enantioselective Synthesis through Microbial Oxidation of Arenes.[1] 1. Efficient Preparation of Terpene and Prostanoid Synthons

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Abstract: *cis*-Toluenediol obtained by the microbial degradation of toluene by *Pseudomonas putida 39D* was shown to be a versatile chiral pool substrate in the formal total synthesis of $PGE_2\alpha$. Diol **1** was converted to enone **5** in three steps in an overall yield of 45%. A method for reliable oxidative cleavage of 1,3-dienes to 1,4-dicarbonyl compounds was implemented. Other transformations of **1** leading to terpenoid or cyclohexene oxide synthons **6**, **7**, and **4a** were also addressed. The isolation of three new arene diols, namely **28-30**, available via microbial oxidation of chlorobenzene, styrene, and phenylacetylene is reported, and their utility in the synthesis of functionalized cyclohexene oxides is indicated.

In 1970 Gibson and co-workers reported the enantioselective oxidation of toluene to *cis*-toluenediol (**1**) by a mutant of *Pseudomonas putida*, a soil bacterium.[3] Since that time many other simple arenes were shown to yield diols of this type through microbial oxidation techniques.[4] The possibility of utilizing arenes that are widely regarded as environmental pollutants in the preparation of optically pure natural products seemed intriguing, and we chose *cis*-toluenediol (**1**) as the initial substrate because

(1) Presented in part at the 194th National Meeting of the American Chemical Society, Denver, CO, April 1987, Abstract 28.

(2) Recepient of the National Institute of Health Research Career Development Award, 1984-1989.

(3) Gibson, D. T.; Hensley, M.; Yoshioka, H.; Mabry, T. J. *Biochemistry* **1970**, *9*, 1626. Diol **1** is now manufactured by ICI Pharmaceuticals and is available in multigram quantities [ICI Fine Chemicals, P.O. Box 42 Hexagon House, Blackley, Manchester M9 3DA, England].

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