Synthesis of PGE_1 and Various 10α-Hydroxyprostaglandins†

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Methods for the selective deprotection and/or reduction of compounds of type **2** to provide (7*E*)-7,8-didehydro-10α-hydroxy-PGE_1, (7*E*)-7,8-didehydro-10α-hydroxy-PGF_1, 10α-hydroxy-PGF_1, 10α-hydroxy-PGF_1, PGE_1, and 15-*epi*-PGE_1 as their racemic methyl esters have been examined.

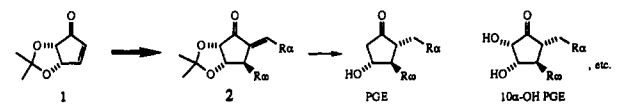
In the preceding article,[1] we noted the advantages of enone **1** as an intermediate for the synthesis of prostanoids and described our development of suitable procedures for the installation of side chains on **1** through conjugate addition and enolate trapping. The focus of the later process was an aldol reaction involving upper chain aldehyde synthons. The conversion of adducts **2** to typical prostaglandins and/or hydroxylated derivatives requires the reduction of the enone and/or a deoxygenation at C-10 (PG numbering); these matters are the subject of the present paper (Scheme I). The work described in this paper was carried out beginning with racemic **1**; information on the production of optically pure **1** is available in the preceding paper.

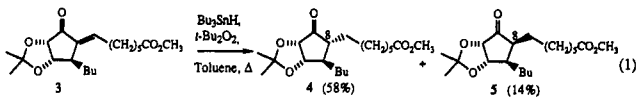
Results and Discussion

Model Studies in Reduction and Deoxygenation of Acetonide-Protected α-Alkylidenecyclopentanones 2. Conjugate reductions of α,β-unsaturated ketones can be achieved by the following: (i) catalytic hydrogenation; (ii) hydride-transfer reduction; (iii) electron-transfer reduction; and (iv) hydrogen atom (radical) transfer reduction. Hydride-transfer reduction is generally considered to be more selective in the reduction of olefins conjugated with carbonyls. A number of reagents have been used successfully for this purpose, including (1) simple transition-metal hydrides, e.g., $HFe(CO)_4$,[2] (2) "copper hydride" reducing agents,[3] and (3) transition-metal complex catalyzed hydride transfer from tin hydride[4] or silicon hydride.[5] The easily synthesized enone **3** was chosen for this model study. A number of reducing conditions were explored without success. When enone **3** was subjected to the following conditions the only result was recovered starting material: $Pd(Ph_3P)_4/Bu_3SnH$, $RhCl(PPh_3)_3/Et_3SiH$, $Pd(Ph_3P)_4/Ph_3SiH$, and $Bu_3SnH/ZnCl_2/Pd(Ph_3P)_4$.[6] Several "copper hydride" reagents were also explored, including $LiAlH(OMe)_3$/CuBr and DIBAL/MeCu/HMPA. The latter group gave no reaction at low temperature and led to decomposition when the reaction mixture was allowed to warm. The failure of these reductions may be the result of steric hindrance. The transition-metal complexes are known to exist as large aggregates in solution. This steric argument was supported by other results. Neither lithium dimethylcuprate nor sodium phenoxide added to this enone. Attempts to reduce this enone system with a variety of single electron transfer reduction methods also failed. This will be discussed later in more detail.

Hydrostannylation of conjugated ketones leading to saturated ketones has been achieved both by thermally and light-initiated additions.[7] Deuterium labeling studies suggested a hydrogen radical conjugate addition mechanism was involved. Thermal initiation of tributyltin hydride conjugate reduction has been reported in a prostaglandin synthesis.[8] Refluxing a toluene solution of enone **3** with 3 equiv of tributyltin hydride and 10 mol % of di-*tert*-butyl peroxide afforded 58% of trans product **4** and 14% of cis product **5** (eq 1).

Scheme I





The relative stereochemistry at C-8 of **4** and **5** was assigned on the basis of ^1H NMR chemical shifts. The β-proton is shielded relative to the α-proton due to its cis relationship to the adjacent butyl group.[9] In addition, the cis product **5** was equilibrated with catalytic sodium acetate in refluxing ethanol to an ca. 2:1 mixture of **4** and **5** to verify its identity as the thermodynamically less stable cis product.[10]

Selective reduction of α,β-unsaturated ketones to allylic alcohols generally is best accomplished by the combination of sodium borohydride and cerium chloride.[11] However, reduction of enone **3** with sodium borohydride in ethanol at 0 °C resulted in a quantitative yield of allyl alcohol **6** within 5 min. Use of cerium chloride is not necessary in this case. The relative stereochemistry at C-9 of **6** was assigned on the basis of ^1H NMR coupling. The coupling

† This paper is dedicated to Prof. Norman A. LeBel on the occasion of his 60th birthday.

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(3) A number of "copper hydride" reagents have been successful in the reduction of conjugated carbonyl compounds to saturated carbonyl compounds. For example: (a) $[n\text{-}(C_3H_7CCCuH]^-Li^+$. Boeckman, R. K.; Michalak, R. *J. Am. Chem. Soc.* **1974**, *96*, 1623. (b) [*N*-BuCuH[$^-Li^+$. Massamune, S.; Bates, G. S.; Georghiou, P. E. *Ibid.* **1974**, *96*, 3686. (c) $[LiAlH(OMe)_3$ + CuBr] and $[NaAlH_2(OCH_2CH_2OCH_3O_2$ + CuBr]. Semmelhack, M. F.; Stauffer, R. D.; Yamashita, A. *J. Org. Chem.* **1977**, *42*, 3180. (d) $(PPh_3)_2CuBH_4$. Fleet, G. W. J.; Fuller, C. J.; Harding, P. J. C. *Tetrahedron Lett* **1978**, *19*, 1437. Sorell, T. N.; Spillane, R. J. *Ibid.* **1978**, *19*, 2473. Sorrell, T. N.; Pearlman, P. S. *J. Org. Chem.* **1980**, *45*, 3449.
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(8) Suuki, M.; Kawagishi, T.; Suzuki, T.; Noyori, R. *Tetrahedron Lett.* **1982**, *23*, 4057.
(9) Donaldson, R. E.; Saddler, J. C.; Byrn, S.; Mckenzie, A. T.; Fuch, P. L. *J. Org. Chem.* **1983**, *48*, 2167.
(10) Posner, G. H.; Sterling, J. J.; Whitten, C. E.; Lentz, C. M.; Brunelle, D. J. *J. Am. Chem. Soc.* **1975**, *97*, 107.
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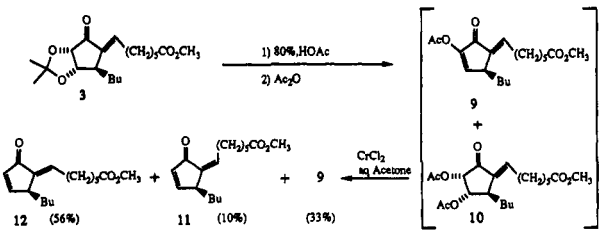
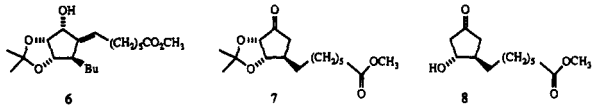
Scheme II



constant between the C-9 and C-10 hydrogens is equal to the coupling constant between the C-10 and C-11 hydrogens. This assignment is also in agreement with the prediction that the reagent should approach from the less hindered convex face of the bicyclic structure.



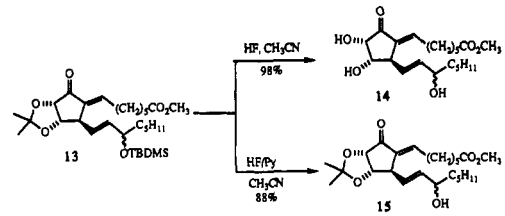
Reductive removal of alkoxy groups adjacent to carbonyl groups has been achieved by a number of reagents.[12,13] The utilization of aluminum amalgam for this purpose has been demonstrated by us in a PGE_2 synthesis.[12] The reduction of 7 to 8 proceeded in 80% yield in 8:1 THF/H_2O with 30 equiv of Al(Hg) (added in three portions). This reduction is slow and does not go to completion; it proceeds cleanly, and the recovered starting material 7 (13%) can be easily separated from product by flash chromatography.

Attempts to extend this Al(Hg) reduction to enone 3 lead to a complex mixture. Other reagents explored included SmI_2,[13] which gave the similar result as Al(Hg); chromous chloride ($CrCl_2$) and chromous acetate ($Cr(OAc)_2$) gave no reaction at all. An attempt to reduce both the enone and the C-10 oxygen substituent in one pot by zinc[14] in aqueous acetic acid resulted only in deprotection of the diol group. Reduction with lithium[15] in liquid ammonia in the presence of 1 equiv of NH_4Cl as a proton source also failed to give the desired product.

Since the enone survived treatment with $CrCl_2$, we thought that if we were able to make the 10-hydroxy group a better leaving group, we should be able to reduce the C-10 oxygen substituent and leave the enone intact. Deprotecting the diol group of enone 3 and acetylation gave a mixture of diacetate 10 and enol acetate 9. Diacetate 10 is unstable and eliminates acetic acid on standing to give 9. The mixture of 9 and 10 was treated with excess $CrCl_2$ in aqueous acetone to afford a mixture of dienones 11 and 12. Enol acetate 9 was not reduced under these conditions. The formation of 11 and 12 proved that $CrCl_2$ was able to reduce an α′-acetoxy group in an α,β-unsaturated ketone system, but the resulting β-acetoxy enone undergoes facile elimination to form a dienone (Scheme II). The formation of 7*Z* dienone 11 was unexpected.

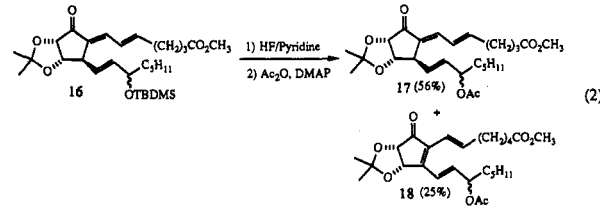
(±)-(7*E*)-7,8-Didehydro-10α-hydroxy-PGE_1, Methyl Ester (14). Removal of the *tert*-butyldimethylsilyl group from the 15-OH in the E-series prostaglandins caused problems in the early years of prostaglandin synthesis due to the highly sensitive β-hydroxycyclopentanone functionality. This problem has been solved by using an acetic acid/water/THF mixture,[16] aqueous hydrofluoric acid in acetonitrile,[17] and recently, hydrofluoric acid/pyridine in acetonitrile,[12,18-20] We encountered some difficulty in removing the acetonide protecting group due to the highly sensitive α,β-dihydroxycyclopentanone functionality. Although we found aqueous acetic acid gave good results for this purpose, the isolation of the diol from aqueous acetic acid was troublesome and we were not able to completely exclude dehydration. To a solution of enone 13 in CH_3CN at room temperature was added 50% aqueous hydrofluoric acid (corresponding to 5% (v/v) CH_3CN solution). The reaction, complete within 5 min, provided pure triol 14 in 98% yield as a mixture of epimers at C-15 (Scheme III).

Scheme III



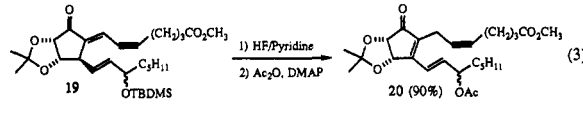
The desilylation of 13 was achieved by pyridine-buffered hydrofluoric acid in acetonitrile (Scheme III). The presence of 1% of pyridine in the hydrofluoric acid/acetonitrile solution is enough to inhibit the hydrolysis of the acetonide. This reaction is much slower than in the absence of pyridine. After 3 h at room temperature, 15 was obtained in 88% yield. A trace of triol 14 was seen by TLC, and small amount (5%) of 13 was recovered. If the reaction time was increased to allow the reaction to go to completion, the removal of the acetonide became a problem.

In a related study, the desilylation of 16 gave an unexpected result. After acetylation, 17 and 18 were obtained in an ca. 2:1 ratio (eq 2).



(2)

A similar olefin migration also occurred when compound 19 was subjected to the same conditions; rearranged compound 20 was the only product (eq 3). Addition of 10% of pyridine to the reaction suppressed isomerization, but the reaction became sluggish and was impractical.



(3)

(±)-(7*E*)-7,8-Didehydro-10α-hydroxy-PGF_1, Methyl Ester (23). Ketone 13 underwent 1,2-reduction with sodium borohydride to give a 95% yield of alcohol 21. The desilylation of silyl ether 21 under the standard conditions

(12) (a) Johnson, C. R.; Penning, T. D. *J. Am. Chem. Soc.* **1988**, *110*, 4726. (b) Johnson, C. R.; Penning, T. D. *Ibid.* **1986**, *108*, 5655.
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(17) Fitzsimmons, B. J.; Rokach, J. *Tetrahedron Lett.* **1984**, *25*, 3043.
(18) Tanaka, T.; Toru, T.; Okamura, N.; Bennai, K.; Sugiura, S.; Manabe, K.; Suzuki, M.; Kawagishi, T.; Noyori, R. *Tetrahedron Lett.* **1983**, *24*, 4103.
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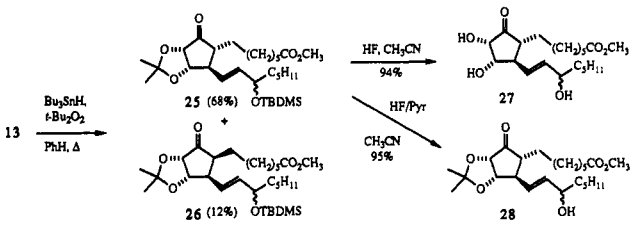
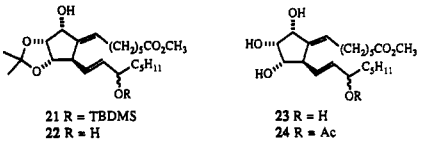
Scheme IV



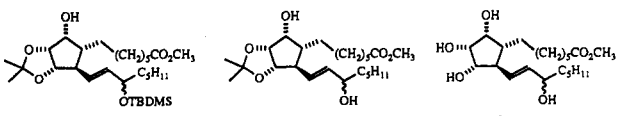
(HF/pyridine/CH_3CN) afforded diol **22** in 89% yield; in addition, 7% of silyl ether **21** was recovered. An attempt to deprotect the diol group in compound **21** by hydrofluoric acid in acetonitrile failed to give the desired product. The desilylation of **21** to give **22** was complete within minutes, as revealed by TLC; however, diol **22** gradually decomposed under these conditions to give numerous unidentified UV-active compounds.

The complete deprotection of the hydroxy groups of **21** was achieved by use of 80% aqueous acetic acid; tetraol **23** was obtained in 86% yield along with monoacetate **24** in 8% yield.

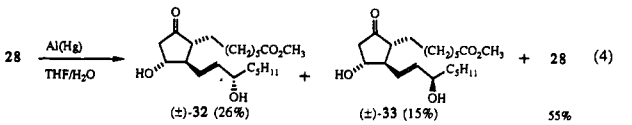


(±)-10α-Hydroxy-PGE$_1$, Methyl Ester (27). Reduction of **13** with tributyltin hydride in the presence of di-*tert*-butyl peroxide was carried out in refluxing benzene to afford a 68% yield of trans ketone **25**. In addition, cis product **26** was obtained in 12% yield. The latter can be equilibrated to a 2:1 mixture of **25** and **26** in the usual manner to provide an additional 7% of **25** after chromatography (75% overall). The reaction carried out in refluxing benzene took a longer time for completion than in refluxing toluene, but generally gave higher yields and a cleaner reaction mixture, which made product isolation easier. The desilylation of **25** with 5:1 aqueous HF/pyridine in acetonitrile at 25 °C afforded a 95% yield of alcohol **28**. The deprotection of **25** with 5% aqueous HF in acetonitrile removed both silyl and acetonide groups and afforded 94% of triol **27** (Scheme IV).

(±)-10α-Hydroxy-PGF$_1$, Methyl Ester (31). Sodium borohydride reduction of ketone **25** proceeded within 1 min and afforded a quantitative yield of alcohol **29**. Desilylation of **29** with HF/pyridine in acetonitrile afforded 92% of diol **30**. Hydrolysis of the acetonide and silyl groups of **29** with 80% aqueous acetic acid provided in 85% yield of tetraol **31**. A number of unidentified acetate derivatives also were obtained this reaction.



(±)-PGE$_1$, Methyl Ester ((±)-32) and (±)-15-*epi*-PGE$_1$, Methyl Ester (33). Deoxygenation at C-10 of **28** with aluminum amalgam in aqueous THF afforded diastereomers, (±)-PGE$_1$, methyl ester (**32**), and (±)-15-*epi*-PGE$_1$, methyl ester (**33**), which could be separated by flash chromatography (eq 4).



This reaction was run by addition of Al(Hg) in four portions over 50 h. The compound with the natural *S* configuration at C-15, (±)-**32**, was isolated in greater amounts (26%) than its C-15 epimer, **33** (15%). This phenomenon was also observed in our PGE_2 synthesis.[12] A large amount of starting ketone **28** (55%) was recovered. The overall yield of isolated products, based on recovered starting material, was 91%. The initial assignments of (±)-**32** and (±)-**33** were based on their mobility on the TLC plate. A number of investigators have reported the greater polarity of PGs relative to their C-15 epimers.[21-23] On the basis of these reports, the more polar compound with R_f = 0.2 (silica gel, 1:1 petroleum ether/EtOAc) was assigned as (±)-PGE$_1$, methyl ester ((±)-**32**), and the less polar compound (R_f = 0.3) was assigned as epimer **33**. These assignments were further confirmed by comparison of the ^1H NMR spectral data with that of PGE$_1$. The ^1H NMR spectrum of (±)-**32** was identical in all respects (except the methyl ester singlet) with a 400-MHz ^1H NMR spectrum of (−)-PGE$_1$.[24] The spectrum of **33** is similar to that of (±)-**32** with only slight differences in chemical shifts and coupling constants for the C-13, C-14, and C-15 protons.

The deoxygenation reaction was also carried out on triol **27** and silyl ether **25**. A large reaction rate difference was observed among these compounds. The deoxygenation of triol **27** was much faster than alcohol **28**; however, the resulting products are difficult to separate from starting triol. On the other hand, silyl ether **25** gave almost no reaction under the same reaction conditions. This phenomenon may be explained by the adsorptivity of the compound on the Al(Hg) surface. Triol **27**, with three hydroxy groups, may be strongly adsorbed on the Al(Hg) and therefore exhibits an enhanced reaction rate. Silyl ether **25** has no polar groups to attach to the metal surface, making the electron transfer from metal to the carbonyl group more difficult. The greater reactivity of the (15*S*)-OH isomer of alcohol **28** in comparison to the (15*R*)-OH isomer in Al(Hg) deoxygenation may be the result of a favored conformation of the (15*S*)-OH isomer in which the ring carbonyl group can be held more closely to the Al(Hg) metal surface.

Experimental Section[25]

Tributyltin Hydride Reduction of 3: 6-Butyl-5-(6′-carbomethoxyhexyl)-2,2-dimethyl-3aβ,5β,6α,6aβ-tetrahydro-4*H*-cyclopenta-1,3-dioxol-4-one (4). One drop of di-*tert*-butyl peroxide was added to a solution of enone **3** (81 mg, 0.23 mmol) and tributyltin hydride (200 mg, 0.69 mmol) in toluene (2 mL). The reaction mixture was refluxed in an oil bath for 1 h and then was cooled to room temperature. The cooled reaction mixture was diluted with 5 mL of benzene and washed with saturated aqueous KF (5 mL) and water (10 mL). The organic layer was dried over $MgSO_4$ and concentrated by rotary evaporation. Flash chromatography, first eluting with petroleum ether and then with 20:1 petroleum ether/EtOAc, furnished ketone **4** (47 mg, 58% yield) as a colorless oil: R_f = 0.7, 3:1 petroleum ether/EtOAc; ^1H NMR ($CDCl_3$) δ 4.41 (s, 2 H), 3.67 (s, 3 H), 2.30 (t, J = 7.5 Hz, 2 H), 2.03 (m, 2 H), 1.40 (s, 3 H), 1.34 (s, 3 H), 1.81–1.32 (m, 16 H), 0.93 (t, J = 6.7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 215.11, 174.29, 112.15, 81.20, 79.67, 52.59, 51.46, 43.33, 34.25, 34.12, 31.19, 29.42, 29.29, 29.00, 27.23, 27.00, 25.23, 24.95, 22.77, 13.99. Additionally, cis product **5** (11 mg, 14% yield) was also

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(24) Kotovych, G.; Aarts, G. H. M. *Can. J. Chem.* **1982**, *60*, 2617.
(25) For general experimental procedures see the preceding article. In ^{13}C NMR, • denotes a doublet due to two diastereomers.

obtained. Compound **5** (R_f = 0.8, 3:1 petroleum ether/EtOAc) was a colorless oil: ^1H NMR ($CDCl_3$) δ 4.65 (d, J = 6.0 Hz, 1 H), 4.10 (d, J = 6.0 Hz, 1 H), 3.67 (s, 3 H), 2.83 (m, 1 H), 2.35 (m, 1 H), 2.31 (t, J = 7.5 Hz, 2 H), 1.47 (s, 3 H), 1.35 (s, 3 H), 1.67–1.26 (m, 16 H), 0.92 (t, J = 6.7 Hz, 3 H). Compound **5** can be equilibrated to a 2:1 mixture of **4** and **5** by refluxing in an EtOH solution containing a catalytic amount of sodium acetate.

$NaBH_4$ Reduction of 3: Methyl (7*E*)-7-(6′-Butyl-4′a-hydroxy-2′,2′-dimethyl-3′aβ,5′,6′α,6′aβ-tetrahydro-4′*H*-cyclopenta-1′,3′-dioxol-5′-ylidene)heptanoate (6). Enone **3** (26 mg, 0.074 mmol) was dissolved in EtOH (0.5 mL) and cooled to 0 °C. $NaBH_4$ (6 mg, 0.16 mmol) was added, and the mixture was stirred for 5 min. The reaction was quenched by dropwise addition of 2 mL of saturated aqueous NH_4Cl solution. The resulting mixture was extracted with 5 mL of ether. The ether extract was dried over $MgSO_4$ and filtered. The filtrate was concentrated by rotary evaporation to give a quantitative yield of alcohol **6** as a colorless oil: IR (neat) 3504 (br), 2933 (s), 2859, 1740 (s), 1457, 1437, cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.55 (t, J = 6.8 Hz, 1 H), 4.52 (t, J = 5.7 Hz, 1 H), 4.35 (d, J = 5.7 Hz, 1 H), 4.31 (m, 1 H), 3.65 (s, 3 H), 2.59 (t, J = 7.0 Hz, 1 H), 2.29 (t, J = 7.4 Hz, 2 H), 2.07 (m, 2 H), 1.62 (p J = 7.3 Hz, 2 H), 1.34 (s, 3 H), 1.30 (s, 3 H), 1.50–1.23 (m, 10 H), 0.87 (t, J = 6.7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 174.16, 143.51, 123.88, 110.37, 82.86, 78.20, 72.75, 51.38, 44.42, 34.01, 32.48, 29.76, 29.44, 28.75, 28.36, 26.34, 24.83, 22.62, 13.91.

3β-(6′-Carbomethoxyhexyl)-4α-hydroxycyclopentanone (8). Ketone **7** (207 mg, 0.69 mmol) was stirred in THF (12 mL) and water (1.5 mL). Granular aluminum (20 mesh, 0.19 g, 0.007 g-atom), which had been stirred for 1 min with 2% aqueous $HgCl_2$ (10 mL), filtered, and washed successively with water, ethanol, and diethyl ether, was added to the reaction mixture. Additional equal portions of aluminum amalgam was added to the reaction mixture after 22 h and 45 h. The mixture was stirred for another 20 h. The gray suspension was filtered, and the filtrate was poured into diethyl ether (15 mL) and water (15 mL). The organic layer was separated, dried over Na_2OS_4, and concentrated by rotary evaporation. Flash chromatography using 2:1 petroleum ether/EtOAc as eluent yielded starting ketone **7** (26 mg, 13%) and hydroxy ketone **8** (134 mg, 80%). Compound **8** was a colorless oil: IR (CCl_4) 3630 (w), 3483 (br), 2931, 2858, 1747 (s), 1437, 1363 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.07 (dd, J_1 = 5.4 Hz, J_2 = 3.3 Hz, 1 H), 3.59 (s, 3 H), 3.26 (d, J = 3.6 Hz, 1 H), 2.52 (m, 1 H), 2.46 (m, 1 H), 2.23 (t, J = 7.5 Hz, 2 H), 2.21 (m, 1 H), 2.08 (m, 1 H), 1.81 (dd, J_1 = 18.4 Hz, J_2 = 7.4 Hz, 1 H), 1.56 (m, 2 H), 1.25 (br, 8 H); ^{13}C NMR ($CDCl_3$) δ 216.61, 174.45, 74.12, 51.53, 46.85, 44.85, 43.08, 34.02, 32.90, 29.27, 28.95, 27.59, 24.83. Anal. Calcd for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15. Found: C, 63.95; H, 9.10.

Chromous Chloride Reduction of 10: Methyl (7*E*)-7-(2′-Butyl-5′-oxo-3′-cyclopenten-1′-ylidene)heptanoate (12). A solution of enone **3** (28 mg, 0.079 mmol) in 80% aqueous acetic acid (0.5 mL) was stirred at 85 °C for 15 min. The reaction mixture was cooled to room temperature, and the solvent and volatile material was removed in vacuo. The residue was dissolved in 1 mL of CH_2Cl_2 and was cooled to 0 °C. To this solution was added 0.05 mL each of pyridine and acetic anhydride. The ice bath was removed, and the reaction mixture was allowed to warm to room temperature, and stirred for another 2 h. The reaction mixture was diluted with 5 mL of ether and washed with three 2-mL portions of water. The organic layer was dried over Na_2SO_4 and filtered. The filtrate was concentrated by rotary evaporation to give a yellow oil. The ^1H NMR spectrum revealed that the crude product was a mixture of diacetate **10** and enol acetate **9**. The mixture was carried on to the chromous chloride reduction without separation. An acetone/water solution (2 mL, 2:1) of crude product mixture was stirred with $CrCl_2$ (110 mg, 0.9 mmol, purchased from Aldrich) at room temperature for 10 h. The reaction mixture was diluted with 5 mL of ether and was washed with 5 mL of water. The organic layer was dried over $MgSO_4$ and filtered. The filtrate was concentrated by rotary evaporation. The residue was purified by flash chromatograph (5:1, petroleum ether/EtOAc) to give dienone **12** (11 mg, 50% yield) as a colorless oil: R_f = 0.6, 5:1 petroleum ether/EtOAc; ^1H NMR ($CDCl_3$) δ 7.54 (ddd, J_1 = 6.0 Hz, J_2 = 2.6 Hz, J_3 = 0.7 Hz, 1 H), 6.53 (td, J_1 = 7.8 Hz, J_2 = 0.7 Hz, 1 H), 6.33 (dd, J_1 = 6.0 Hz, J_2 = 1.8 Hz, 1 H), 3.67 (s, 3 H), 3.47 (m, 1 H), 2.31 (t, J = 7.4 Hz, 2 H), 2.26 (m, 2 H), 1.80–1.20 (m, 12 H), 0.89 (t. J = 6.9 Hz, 3 H); HRMS calcd for $C_{17}H_{26}O_3$ ($M^{\cdot+}$) 278.1881, found 278.1885. Also isolated was the 7*Z* isomer **11** (2 mg, 9% yield) and enol acetate **9** (8 mg, 30% yield). Compound **11** was a colorless oil: R_f = 0.7, 5:1 petroleum ether/EtOAc; ^1H NMR ($CDCl_3$) δ 7.44 (dd, J_1 = 6.0 Hz, J_2 = 2.5 Hz, 1 H), 6.27 (dd, J_1 = 6.0 Hz, J_2 = 1.7 Hz, 1 H), 6.01 (t, J = 7.9 Hz, 1 H), 3.67 (s, 3 H), 3.27 (m, 1 H), 2.81 (q, J = 7.8 Hz, 2 H), 2.31 (t, J = 7.5 Hz, 2 H), 1.70–1.25 (m, 12 H), 0.90 (t, J = 6.7 Hz, 3 H). Compound **9** was a colorless oil: R_f = 0.5, 5:1, petroleum ether/EtOAc; ^1H NMR ($CDCl_3$) δ 7.26 (d, J = 2.9 Hz, 1 H), 6.63 (t, J = 7.8 Hz, 1 H), 3.66 (s, 3 H), 3.48 (m, 1 H), 2.32 (t, J = 7.5 Hz, 2 H), 2.28 (s, 3 H), 2.24 (m, 2 H), 1.90–1.20 (m, 12 H), 0.89 (t, J = 6.7 Hz, 3 H).

Desilylation of 13: Methyl (1″*E*,7*E*)-7-[6′-(3″-Hydroxy-1″-octenyl)-2′,2′-dimethyl-4′-oxo-3′aβ,5′,6′α,6′aβ-tetrahydro-4′*H*-cyclopenta-1′,3′-dioxol-5′-ylidene]heptanoate (15). Silyl ether **13** (45 mg, 8.4×10^{-2} mmol) was stirred in CH_3CN (3 mL) and cooled to 0 °C. Pyridine (0.1 mL) was added, followed by 50% aqueous HF (0.3 mL). The reaction mixture was warmed to room temperature and stirred for 3 h. The resulting 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 saturated aqueous NaCl (15 mL), dried over $MgSO_4$, and concentrated by rotary evaporation. Flash chromatography using 3:1 petroleum ether/EtOAc as eluent afforded starting silyl ether **13** (2 mg, 5% yield) and alcohol **15** (31 mg, 88% yield), as a mixture of two inseparable C-15 epimers. Alcohol **15** was a colorless oil: IR (CCl_4) 3620 (w), 3521 (br), 2990, 2934 (s), 2860, 1735 (s), 1647, 1457, 1437, 1383, 1221 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.89 (tt, J_1 = 7.6 Hz, J_2 = 1.6 Hz, 1 H), 5.66 (dt, J_1 = 15.4 Hz, J_2 = 6.0 Hz, 1 H), 5.50 (dt, J_1 = 15.4 Hz, J_2 = 5.7 Hz, 1 H), 4.50 (d, J = 5.0 Hz, 1 H), 4.42 (2d, J = 6.0 Hz, 1 H), 4.08 (br, 1 H), 3.71 (dt, J_1 = 5.8 Hz, J_2 = 6.0 Hz, 1 H), 3.66 (s, 3 H), 2.29 (t, J = 7.4 Hz, 2 H), 2.16 (q, J = 7.4 Hz, 2 H), 1.75–1.27 (m, 14 H), 1.35 (2s, 6 H), 0.87 (2t, J = 6.7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 202.61, 174.04, 143.48, 135.92, 135.79, 127.46, 112.01, 79.94*, 79.56, 72.09, 51.48, 43.86*, 37.40, 33.83, 31.65. 29.23, 28.83, 27.81, 27.36, 25.63, 25.01, 24.60, 22.54, 13.94; HRMS calcd for $C_{24}H_{38}O_6$ ($M^{\cdot+}$) 422.2668, ($M^{\cdot+}$ − OH) 405.2641, found 405.2636.

Deprotection of 13: (±)-(7*E*)-10α-Hydroxy-7,8-didehydroprostaglandin E_1, Methyl Ester (14). To a solution of silyl ether **13** (30 mg, 0.065 mmol) in CH_3CN (3 mL) was added 50% aqueous HF (0.15 mL), and the mixture was stirred at room temperature for 5 min. The reaction mixture was poured into 5% aqueous $NaHCO_3$ (10 mL) and ether (20 mL). The organic layer was separated and washed twice with 10-mL portions of water, dried over Na_2SO_4, and concentrated to yield triol **14** as a mixture of two C-15 epimers (21 mg, 98%, R_f = 0.18 and 0.25 (1:1 petroleum ether/EtOAc), respectively): IR (neat) 3415 (br), 2932, 2859, 1734 (s), 1653, 1457, 1437 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.92 (t, J = 7.5 Hz, 1 H), 5.70 (dd, J_1 = 15.6 Hz, J_2 = 6.2 Hz, 1 H), 5.50 (m, 1 H), 4.27 (d, J = 4.5 Hz, 1 H), 4.23 (d, J = 4.5 Hz, 1 H), 4.10 (m, 1 H), 3.65 (s, 3 H), 3.39 (m, 1 H), 2.92 (br, 1 H), 2.29 (t, J = 7.4 Hz, 2 H), 2.14 (2td, J_1 = 7.4 Hz, J_2 = 7.2 Hz, 2 H), 1.60 (p, J = 7.6 Hz, 2 H), 1.53–1.20 (m, 12 H), 0.87 (2t, J = 6.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 203.26, 174.12, 142.96*, 135.76, 134.23, 127.06*, 76.72, 72.60*, 72.16, 51.47, 46.06, 37.36, 33.81, 31.65, 28.90, 28.79, 27.74, 25.02, 24.57, 22.52, 13.91; MS calcd for $C_{21}H_{34}O_6$ ($M^{\cdot+}$) 382, found 346 ($M^{\cdot+}$ − 2 H_2O), 147, 107, 91, 67, 55, 43.

Methyl (5*E*,7*E*,1″*E*)-7-[6′-(3″-Acetoxy-1″-octenyl)-4′-oxo-2′,2′-dimethyl-3′aβ,5′,6′α,6′aβ-tetrahydro-4′*H*-cyclopenta-1′,3′-dioxol-5′-ylidene]-5-heptenoate (17). Silyl ether **16** (90 mg, 0.169 mmol) was stirred in CH_3CN (3 mL) and cooled to 0 °C. Pyridine (0.1 mL) and 50% aqueous HF (0.3 mL) were added. The cooling bath was removed, and the reaction mixture was allowed to warm to room temperature and then stirred for an additional 2 h. The reaction mixture was worked up in the same manner as described previously for **14** to give a yellow oil. The crude product was dissolved in 2 mL of CH_2Cl_2, and the solution was cooled to 0 °C. Acetic anhydride (0.03 mL, 0.32 mmol), pyridine (0.1 mL), and DMAP (5 mg, 0.04 mmol) were added, and the reaction mixture was warmed to room temperature over 1 h. The reaction mixture was diluted with 5 mL of CH_2Cl_2 and was washed three times with 5-mL portions of water. The organic layer was dried over $MgSO_4$ and filtered. The filtrate was concentrated by rotary evaporation. Flash chromatography (20:1, petrolem ether/EtOAc) furnished **17** (40 mg, 56% yield, a mixture

of two C-15 epimers) as a light yellow oil: R_f = 0.6, 3:1 petroleum ether/EtOAc; ^{1}H NMR ($CDCl_3$) δ 7.22 (ddd, J_1 = 11.0 Hz, J_2 = 4.7 Hz, J_3 = 1.9 Hz, 1 H), 6.25 (m, 1 H), 6.13 (m, 1 H), 5.73 (2dt, J_1 = 15.1 Hz, J_2 = 7.1 Hz, 1 H), 5.35 (m, 1 H), 5.18 (p, J = 7.0 Hz, 1 H), 4.52 (2d, J = 4.7 Hz, 1 H), 4.42 (t, J = 4.7 Hz, 1 H), 3.79 (m, 1 H), 3.65 (s, 3 H), 2.32 (t, J = 7.4 Hz, 2 H), 2.25 (q, J = 7.3 Hz, 2 H), 2.02 (2s, 3 H), 1.77 (p, J = 7.6 Hz, 2 H), 1.36 (s, 3 H), 1.35 (s, 3 H), 1.70–1.25 (m, 8 H), 0.86 (t, J = 6.7 Hz, 3 H). A minor product, **18** (18 mg, 25% yield), was also isolated. Compound **18**, a yellow oil with only four olefinic proton resonances in its ^{1}H NMR spectrum was assigned as **methyl (1″*E*,6*E*)-7-[6′-(3″-acetoxy-1″-octenyl)-2′,2′-dimethyl-3′aβ,6′aβ-dihydro-4′*H*-cyclopenta-1′,3′-dioxol-5′-yl]-6-heptenoate**: R_f = 0.63, 3:1 petroleum ether/EtOAc; ^{1}H NMR ($CDCl_3$) δ 6.87 (m, 1 H), 6.12 (m, 1 H), 5.66 (m, 1 H), 5.40 (m, 1 H), 5.18 (q, J = 7.0 Hz, 1 H), 4.49 (2d, J = 4.5 Hz, 1 H), 4.40 (2d, J = 4.5 Hz, 1 H), 3.66 (s, 3 H), 2.36 (q, J = 7.3 Hz, 2 H), 2.30 (t, J = 7.5 Hz, 2 H), 2.12 (p, J = 7.2 Hz, 2 H), 2.03 (2s, 3 H), 1.62 (p, J = 7.1 Hz, 2 H), 1.35 (s, 3 H), 1.25 (s, 3 H), 1.55–1.20 (m, 8 H), 0.87 (t, J = 6.7 Hz, 3 H).

(1″*E*)-5-(6′-Carbomethoxy-2′-heptynyl)-6-(3″-acetoxy-1″-octenyl)-2,2-dimethyl-3aβ,6aβ-dihydro-4*H*-cyclopenta-1,3-dioxol-4-one (20). Silyl ether **19** (41 mg, 0.077 mmol) was subjected to the same desilylation and acetylation conditions as described previously in the preparation of **17**. Flash chromatography (3:1, petroleum ether/EtOAc) furnished **20** (32 mg, 90% yield) as a mixture of two C-15 epimers. Compound **20**, a light yellow oil with only two olefinic proton resonances in its ^{1}H NMR spectrum, was assigned as the rearranged endocyclic enone isomer: R_f = 0.65, 3:1 petroleum ether/EtOAc; IR (CCl_4) 2935 (s), 2860 (s), 2293 (w), 1738 (s), 1720 (s), 1643, 1603, 1457, 1436 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.91 (dd, J_1 = 16.0 Hz, J_2 = 6.5 Hz, 1 H), 6.57 (dd, J_1 = 16.0 Hz, J_2 = 5.8 Hz, 0.5 H), 6.52 (dd, J_1 = 16.0 Hz, J_2 = 6.2 Hz, 0.5 H), 5.48 (q, J = 6.5 Hz, 1 H), 5.30 (t, J = 5.8 Hz, 1 H), 4.52 (d, J = 5.8 Hz, 1 H), 3.65 (s, 3 H), 3.15 (m, 2 H), 2.37 (t, J = 7.4 Hz, 2 H), 2.18 (m, 2 H), 2.12 (2s, 3 H), 1.76 (p, J = 7.3 Hz, 2 H), 1.71 (m, 2 H), 1.43 (s, 3 H), 1.32 (s, 3 H), 1.40–1.23 (m, 6 H), 0.89 (t, J = 6.7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 200.91, 173.50, 170.12, 160.66, 140.89, 135.90, 123.19*, 114.89*, 80.26, 76.05, 75.76, 73.92, 73.62*, 51.45, 34.19*, 32.81, 31.45, 27.46, 26.30, 24.68*, 23.95, 22.40, 21.05, 18.16, 13.87, 12.87. HRMS calcd for $C_{26}H_{36}O_7$ ($M^{\bullet+}$) 460.2407, found 460.2140.

(1′*E*)-6-[3′-(*tert*-Butyldimethylsiloxy)-1′-octenyl]-5-(6″-carbomethoxyhexyl)-2,2-dimethyl-3aβ,5,6aα,6aβ-tetrahydro-4*H*-cyclopenta-1,3-dioxol-4-one (25). Enone **13** (300 mg, 0.56 mmol) and tributyltin hydride (488 mg, 1.7 mmol) in dry benzene (6 mL) was deoxygenated by bubbling argon into the solution for 5 min. Di-*tert*-butyl peroxide (0.05 mL) was added to the resulting solution. The reaction mixture was refluxed in an oil bath for 2 h. Another equal amount of di-*tert*-butyl peroxide was added and the reaction mixture was refluxed for another 2 h. The resulting reaction mixture was cooled to room temperature, diluted with 10 mL of benzene, and washed with saturated aqueous potassium fluoride (5 mL) and water (10 mL). The organic layer was dried over $MgSO_4$ and concentrated by rotary evaporation. Flash chromatography, first eluting with 50:1 petroleum ether/EtOAc to remove tin compounds and then with 10:1 petroleum ether/EtOAc to furnish **25** (205 mg, 68% yield), gave a mixture of two C-15 epimers) as a colorless oil: R_f = 0.7 (5:1 petroleum ether/EtOAc); IR (neat) 2932 (s), 2858, 1744 (s), 1464, 1437, 1069 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.58 (2t, J = 5.5 Hz, 2 H), 4.45 (m, 1 H), 4.44 (m, 1 H), 4.09 (m, 1 H), 3.65 (s, 3 H), 2.64 (m, 1 H), 2.28 (t, J = 7.5 Hz, 2 H), 2.19 (m, 1 H), 1.42 (s, 3 H), 1.33 (s, 3 H), 1.83–1.23 (m, 18 H), 0.88 (2s, t, J = 6.7 Hz, 12 H), 0.038 (s, 3 H), 0.010 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 210.96, 174.16, 136.01*, 129.09, 112.65, 80.92*, 79.30, 72.95*, 52.57*, 51.36, 47.25*, 38.25, 34.02, 31.75, 29.67*, 29.21, 28.90, 26.99, 25.87, 25.22, 24.87*, 22.58, 18.23, 13.96, −4.78, −4.31; HRMS calcd for $C_{30}H_{54}O_6Si$ ($M^{\bullet+}$) 538.3689, ($M^{\bullet+}$ − *t*-Bu) 481.2985, found 481.2990.

Additionally, a cis product **26** (36 mg, 12%, a mixture of two C-15 epimers) was isolated. Compound **26** (R_f = 0.76, 5:1 petroleum ether/EtOAc) was a colorless oil: IR (neat) 2932 (s), 2858, 1743 (s), 1465, 1374 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.59 (2dd, J_1 = 15.1 Hz, J_2 = 6.7 Hz, 1 H), 5.04 (m, 1 H), 4.55 (2d, J = 5.6 Hz, 1 H), 4.15 (t, J = 6.0 Hz, 1 H), 4.03 (q, J = 5.9 Hz, 1 H), 3.66 (s, 3 H), 3.07 (t, J = 8.5 Hz, 1 H), 2.81 (m, 1 H), 2.29 (t, J = 7.5 Hz, 2 H), 1.60 (m, 2 H), 1.46 (s, 3 H), 1.34 (s, 3 H), 1.53–1.25 (m, 16 H), 0.86 (2s, t, J = 6.7 Hz, 12 H), 0.016 (s, 3 H), −0.018 (s, 3 H); ^{13} NMR ($CDCl_3$) δ 212.93, 174.20, 138.56*, 124.69*, 112.28, 80.55*, 77.85, 72.73*, 51.38, 47.27*, 43.45*, 38.28, 34.06, 31.79, 29.69, 29.27*, 27.22*, 26.51, 25.83, 24.89, 24.72, 24.57, 24.45, 22.59, 18.19, 13.96, −4.46*, −4.81*; HRMS calcd for $C_{30}H_{54}O_6Si$ ($M^{\bullet+}$) 538.3689, ($M^{\bullet+}$ − *t*-Bu), 481.2985, found 481.2989. The cis product **26** could be equilibrated to a 2:1 mixture of **25** and **26** with a catalytic amount of sodium acetate in refluxing EtOH (5 mL) for 10 h. The reaction mixture was concentrated by rotary evaporation. Flash chromatography, eluting with 10:1 petroleum ether/EtOAc, gave an additional 7% (21 mg) of **25** (overall yield of 75%).

Desilylation of 25: (1′*E*)-6-(3′-Hydroxy-1′-octenyl)-5-(6″-carbomethoxyhexyl)-2,2-dimethyl-3aβ,5,6aα,6aβ-tetrahydro-4*H*-cyclopenta-1,3-dioxol-4-one (28). Silyl ether **25** (57 mg, 0.106 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 4 h. The reaction mixture was worked up in the same manner as described previously to give crude **28**. Flash chromatography using 1:1 petroleum ether/EtOAc as eluent furnished **28** (43 mg, 95%; a mixture of two C-15 epimers) as a colorless oil: IR (neat) 3509 (br), 2931 (s), 2858, 1741 (s), 1734 (s), 1654, 1457 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.67 (m, 2 H), 4.48 (m, 2 H), 4.11 (q, J = 7.1 Hz, 1 H), 3.65 (s, 3 H), 2.64 (m, 1 H), 2.28 (t, J = 7.5 Hz, 2 H), 2.22 (m, 1 H), 2.20 (br, 1 H), 1.42 (s, 3 H), 1.33 (s, 3 H), 1.69–1.28 (m, 18 H), 0.88 (t, J = 6.7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 213.29*, 174.25, 135.54*, 130.60*, 112.92, 80.75*, 79.18, 72.24*, 52.60, 51.41, 47.74, 37.36*, 33.98, 31.69, 29.25, 29.04*, 28.79, 26.96, 26.76*, 25.19, 25.02, 24.75, 22.55, 13.94; HRMS calcd for $C_{24}H_{40}O_6$ ($M^{\bullet+}$) 424.2825, found 424.2830.

Deprotection of 25: (±)-10α-Hydroxyprostaglandin E_1, Methyl Ester (27). To a solution of silyl ether **25** (45 mg, 0.0836 mmol) in CH_3CN (3 mL) was added 50% aqueous HF (0.15 mL). The mixture was stirred at room temperature for 5 min. The reaction mixture was poured into saturated aqueous $NaHCO_3$ (10 mL) and ether (20 mL). The organic layer was separated and washed with two 10-mL portions of water, dried over $MgSO_4$, and concentrated to yield triol **27** (30 mg, 94%, a mixture of two C-15 epimers with R_f = 0.26 and 0.36 (1:2 petroleum ether/EtOAc), respectively): IR (neat) 3454 (br), 2933 (s), 2859, 1740 (s), 1457, 1437 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.67 (m, 2 H), 4.28 (m, 1 H), 4.11 (m, 2 H), 3.65 (s, 3 H), 2.85 (br, 2 H), 2.67 (m, 1 H), 2.28 (q, J = 6.5 Hz, 2 H), 2.17 (m, 1 H), 1.82 (m, 1 H), 1.67–1.28 (m, 16 H), 0.87 (t, J = 6.7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 216.21, 174.23, 134.83, 130.82*, 76.10*, 73.66*, 72.44*, 51.38, 48.32*, 47.77*, 37.33, 33.96*, 31.66, 30.66*, 28.81*, 28.56, 26.91, 25.00*, 24.51, 22.52, 13.90; HRMS calcd for $C_{21}H_{36}O_6$ ($M^{\bullet+}$) 384.2512, ($M^{\bullet+}$ − OH) 367.2484, found 367.2489.

Aluminum Amalgam Reduction of 28: (±)-Prostaglandin E_1, Methyl Ester ((±)-32) and (±)-15-*epi*-Prostaglandin E_1, Methyl Ester ((±)-33). Ketone **28** (78 mg, 0.184 mmol) was stirred in THF/H_2O (8:1, 15 mL), and aluminum amalgam (from 74 mg, 0.0028 g-atom of granular aluminum), prepared as described earlier, was added. Additional equal amounts of Al(Hg) were added after 9, 21, and 47 h. The reaction mixture was stirred for an additional 10 h and filtered; 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 petroleum ether/EtOAc and then with EtOAc, yielded starting ketone **28** (43 mg, 55%), (±)-PGE_1, methyl ester ((±)-**32**, 18 mg, 26%), and (±)15-*epi*-PGE_1 methyl ester ((±)-**33**, 10 mg, 15%). Compound (±)-**32** was a colorless oil: R_f = 0.2 (1:1 petroleum ether/EtOAc); IR (CCl_4) 3615 (w), 3410 (br), 2933, 2859, 1746 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.70 (dd, J_1 = 15.3 Hz, J_2 = 6.7 Hz, 1 H), 5.55 (dd, J_1 = 15.3 Hz, J_2 = 8.5 Hz, 1 H), 4.12 (q, J = 6.9 Hz, 1 H), 4.06 (q, J = 8.6 Hz, 1 H), 3.66 (s, 3 H), 2.81 (d, J = 3.0 Hz, 1 H), 2.74 (ddd, J_1 = 18.4 Hz, J_2 = 7.4 Hz, J_3 = 1.1 Hz, 1 H), 2.35 (dt, J_1 = 12.0 Hz, J_2 = 8.6 Hz, 1 H), 2.28 (t, J = 7.5 Hz, 2 H), 2.23 (dd, J_1 = 18.4 Hz, J_2 = 9.7 Hz, 1 H), 2.08 (br, 1 H), 2.00 (dtd, J_1 = 12.0 Hz, J_2 = 5.5 Hz, J_3 = 0.6 Hz, 1 H), 1.62–1.27 (m, 18 H), 0.89 (t, J = 6.7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 214.44, 174.21, 137.07, 131.04, 72.77, 72.06, 51.39, 46.01, 38.83, 37.45, 34.01, 31.69, 29.28, 28.84, 27.75, 26.57, 25.10, 24.81, 22.57, 13.93; HRMS calcd for $C_{21}H_{36}O_5$ ($M^{\bullet+}$) 368.2563, ($M^{\bullet+}$ − OH) 351.2535, found 351.2541. Compound (±)-**33**

was a colorless oil: R_f = 0.3 (1:1 petroleum ether/EtOAc); IR (CCl_4) 3620 (w), 3441 (br), 2933, 2860, 1745 (s), 1457, 1437 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.75 (dd, J_1 = 15.3 Hz, J_2 = 5.9 Hz, 1 H), 5.60 (ddd, J_1 = 15.3 Hz, J_2 = 8.5 Hz, J_3 = 0.7 Hz, 1 H), 4.17 (q, J = 5.8 Hz, 1 H), 4.08 (q, J = 8.8 Hz, 1 H), 3.66 (s, 3 H), 2.75 (ddd, J_1 = 18.5 Hz, J_2 = 7.5 Hz, J_3 = 1.2 Hz, 1 H), 2.38 (dt, J_1 = 12.0 Hz, J_2 = 8.5 Hz, 1 H), 2.29 (t, J = 7.4 Hz, 2 H), 2.23 (dd, J_1 = 18.5 Hz, J_2 = 9.6 Hz, 1 H), 2.02 (m, 2 H), 1.77 (br, 1 H), 1.57–1.27 (m, 18 H), 0.89 (t, J = 6.7 Hz, 3 H); HRMS calcd for $C_{21}H_{36}O_5$ ($M^{\cdot+}$) 368.2563, ($M^{\cdot+}$ – OH) 351.2535, found 351.2539.

Methyl (1″*E*,7*E*)-7′-(4′α-Hydroxy-6′-[3″-(*tert*-butyldimethylsiloxy)-1″-octenyl]-2′,2′-dimethyl-3′aβ,5′,6′α,6′aβ-tetrahydro-4′*H*-cyclopenta-1′,3′-dioxol-5′-ylidene)heptanoate (21). To a solution of enone **13** (76 mg, 0.142 mmol) in absolute ethanol (1 mL) at 0 °C was added $NaBH_4$ (6 mg). After being stirred for 5 min at 0 °C, the reaction mixture was poured into saturated aqueous NH_4Cl (2 mL) and extracted with two 5-mL portions of ether. The combined ether extracts were dried over $MgSO_4$ and concentrated by rotary evaporation to furnish **21** (75 mg, 95% yield, a mixture of two C-15 epimers) as a colorless oil: IR (neat) 3545 (br), 2954, 2931 (s), 2858 (s), 1743 (s), 1463, 1437, 1372 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.68 (t, J = 6.5 Hz, 1 H), 5.42 (m, 2 H), 4.51 (t, J = 5.6 Hz, 1 H), 4.44 (t, J = 4.4 Hz, 1 H), 4.28 (m, 1 H), 4.01 (q, J = 5.5 Hz, 1 H), 3.66 (s, 3 H), 3.28 (m, 1 H), 2.28 (t, J = 7.6 Hz, 2 H), 2.17 (dd, J_1 = 11.1 Hz, J_2 = 1.4 Hz, 1 H), 2.02 (m, 2 H), 1.61 (p, J = 7.4 Hz, 2 H), 1.36 (s, 3 H), 1.32 (s, 3 H), 1.40–1.23 (m, 12 H), 0.86 (2s,t, J = 6.7 Hz, 12 H), 0.007 (2s, 3 H), –0.027 (2s, 3H); ^{13}C NMR ($CDCl_3$) δ 174.12, 141.59*, 134.91, 127.22*, 125.12*, 110.55, 85.57, 82.89, 77.50, 72.97*, 51.35, 46.81, 38.25, 33.99, 31.72, 29.27, 28.76, 28.25, 26.38, 25.84, 25.83, 22.65, 18.19, 13.94, –4.33, –4.80; HRMS calcd for $C_{30}H_{54}O_6Si$ ($M^{\cdot+}$) 538.3689, ($M^{\cdot+}$ – *t*-Bu) 481.2985, found 481.2989.

Desilylation of 21: Methyl (1″*E*,7*E*)-7′-(4′α-Hydroxy-6′-(3″-hydroxy-1″-octenyl)-2′,2′-dimethyl-3′aβ,5′,6′α,6′aβ-tetrahydro-4′*H*-cyclopenta-1′,3′-dioxol-5′-ylidene)heptanoate (22). Silyl ether **21** (30 mg, 0.0557 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 4 h. The reaction mixture was worked up as described previously. Flash chromatography (3:1, petroleum ether/EtOAc) afforded recovered silyl ether **21** (2 mg, 7% yield) and diol **22** (21 mg, 89% yield, a mixture of two C-15 epimers) as a colorless oil: IR (neat) 3465 (br), 2932 (s), 2859, 1740 (s), 1457, 1437 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.70 (t, J = 7.4 Hz, 1 H), 5.50 (m, 2 H), 4.51 (dd, J^1 = 5.6 Hz, J_2 = 2.8 Hz, 1 H), 4.46 (d, J = 5.6 Hz, 1 H), 4.30 (m, 1 H), 4.04 (q, J = 6.3 Hz, 1 H), 3.65 (s, 3 H), 3.30 (m, 1 H), 2.29 (t, J = 7.5 Hz, 2 H), 2.19 (d, J = 10.8 Hz, 1 H), 2.02 (m, 2 H), 1.61 (p, J = 7.3 Hz, 2 H), 1.36 (s, 3 H), 1.31 (s, 3 H), 1.50–1.25 (m, 12 H), 0.87 (t, J = 6.7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 174.23, 141.42, 134.42*, 128.59, 125.44*, 110.63, 82.90, 78.55*, 72.99, 72.41, 51.40, 47.02*, 37.32, 34.00, 31.67, 29.18, 28.23, 27.71, 26.38, 25.01, 24.85, 24.80, 22.56, 13.94; HRMS calcd for $C_{24}H_{40}O_6$ ($M^{\cdot+}$) 424.2825, ($M^{\cdot+}$ – CH_3) 409.2590, found 409.2595.

Deprotection of 21: (±)-(7*E*)-10α-Hydroxy-7,8-didehydroprostaglandin F_1, Methyl Ester (23). A solution of silyl ether **21** (48 mg, 0.089 mmol) in 80% aqueous acetic acid (1 mL) was stirred at 85 °C for 20 min. The resulting mixture was cooled to room temperature. The solvent and volatile compounds were removed in vacuo. The resulting white solid was purified by flash chromatography using 10:1 Et_2O/MeOH to yield tetrol **23** (29 mg, 86% yield) as a mixture of two inseparable C-15 epimers: R_f = 0.36 (10:1 Et_2O/MeOH); IR (film) 3471 (s), 3315 (br), 2929 (s), 2855, 1735 (s), 1464, 1437 cm^{-1}; ^1H NMR (DMSO-d_6) δ 5.60–5.30 (m, 3 H), 4.47 (m, 1 H), 4.36 (m, 1 H), 4.10 (m, 1 H), 3.84 (m, 1 H), 3.66 (t, J = 7.6 Hz, 1 H), 3.56 (s, 3 H), 3.32 (s, 3 H), 2.94 (t, J = 6.3 Hz, 1 H), 2.26 (t, J = 7.4 Hz, 2 H), 1.89 (m, 2 H), 1.49 (p, J = 7.0 Hz, 2 H), 1.22 (m, 12 H), 0.84 (t, J = 6.7 Hz, 3 H); ^{13}C NMR (DMSO-d_6) δ 173.12, 134.66, 134.08*, 130.13*, 123.74, 75.96*, 73.07*, 70.68, 70.33*, 50.95, 48.95*, 37.45, 33.19, 31.22, 28.60, 28.21, 27.43*, 24.49, 24.27, 21.96, 13.69; MS calcd for $C_{21}H_{36}O_6$ ($M^{\cdot+}$) 384, found 366 ($M^{\cdot+}$ – H_2O), 348 ($M^{\cdot+}$ – 2 H_2O), 319, 133, 107, 91, 81, 67, 55 (100%). Additionally, a minor product **24** (R_f = 0.6, 10:1 Et_2O/MeOH) was isolated in 8% yield. Compound **24** was assigned as the 15-acetate derivative of **23**: ^1H NMR ($CDCl_3$) δ 5.87 (t, J = 7.0 Hz, 1 H), 5.59 (dd, J_1 = 15.5 Hz, J_2 = 6.7 Hz, 1 H), 5.41 (dd, J_1 = 15.5 Hz, J_2 = 7.1 Hz, 1 H), 5.18 (q, J = 6.7 Hz, 1 H), 4.29 (m, 1 H), 3.96 (m, 1 H), 3.89 (m, 1 H), 3.66 (s, 3 H), 3.35 (m, 1 H), 2.96 (br, 1 H), 2.67 (br, 1 H), 2.30 (t, J = 7.4 Hz, 2 H), 2.02 (2s, 3 H), 2.00 (m, 2 H), 1.60 (m, 2 H), 1.25 (m, 12 H), 0.87 (t, J = 6.7 Hz, 3 H).

Methyl (1″*E*)-7-[6′-[3″-(*tert*-Butyldimethylsiloxy)-1″-octenyl]-4α-hydroxy-2′,2′-dimethyl-3′aβ,5′,6′α,6′aβ-tetrahydro-4′*H*-cyclopenta-1′,3′-dioxol-5′-yl]heptanoate (29). To a solution of ketone **28** (107 mg, 0.2 mmol) in absolute ethanol (2 mL) at 0 °C was added $NaBH_4$ (10 mg). After being stirred for 10 min at 0 °C, the reaction mixture was poured into saturated aqueous NH_4Cl (5 mL) and extracted with two 5-mL portions of ether. The combined ether extracts were dried over $MgSO_4$ and concentrated by rotary evaporation to give **29** (107 mg, 100%; mixture of two C-15 epimers) as a colorless oil: IR (neat) 3536 (br), 2931 (s), 2858, 1742 (s), 1465, 1382, 1372 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.54 (ddd, J_1 = 15.2 Hz, J_2 = 6.0 Hz, J_3 = 2.4 Hz, 1 H), 5.42 (ddd, J_1 = 15.2 Hz, J_2 = 8.7 Hz, J_3 = 7.8 Hz, 1 H), 4.48 (dd, J_1 = 7.7 Hz, J_2 = 6.7 Hz, 1 H), 4.34 (dt, J_1 = 7.7 Hz, J_2 = 6.7 Hz, 1 H), 4.06 (q, J = 5.8 Hz, 1 H), 3.98 (m, 1 H), 3.65 (s, 3 H), 2.49 (m, 1 H), 2.45 (d, J = 1.4 Hz, 1 H), 2.28 (t, J = 7.6 Hz, 2 H), 1.53 (s, 3 H), 1.34 (s, 3 H), 1.61–1.27 (m, 18 H), 0.88 (s, 9 H), 0.87 (t, J = 6.7 Hz, 3 H), 0.037 (s, 3 H), 0.017 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 174.10, 136.29*, 129.65*, 113.83*, 85.72*, 80.19, 73.30*, 69.42, 51.39, 38.35, 34.05, 33.80, 31.78, 29.52, 29.08, 28.57, 27.72, 26.53, 26.22, 25.89, 24.91*, 24.62, 24.52, 22.59, 18.23, 13.96, –4.28, –4.76; HRMS calcd for $C_{30}H_{56}O_6Si$ ($M^{\cdot+}$) 540.3846, ($M^{\cdot+}$ – *t*-Bu) 483.3142, found 483.3145.

Desilylation of 29: Methyl (1″*E*)-7-[6″-(3″-Hydroxy-1″-octenyl)-4′α-hydroxy-2′,2′-dimethyl-3′aβ,5′,6′α,6′aβ-tetrahydro-4′*H*-cyclopenta-1′,3′-dioxol-5′-yl]heptanoate (30). Silyl ether **29** (46 mg, 0.085 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 5 h. The reaction mixture was worked up as usual. Flash chromatography using 1:1 petroleum ether/EtOAc as eluent furnished **30** (33 mg, 92% yield, a mixture of two C-15 epimers, R_f = 0.25, 0.33 (1:1 petroleum ether/EtOAc), respectively) as a colorless oil: IR (neat) 3510 (br), 2931 (s), 2858, 1740 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.54 (m, 2 H), 4.47 (m, 1 H), 4.35 (m, 1 H), 4.06 (dq, J_1 = 3.8 Hz, J_2 = 6.1 Hz, 1 H), 3.98 (m, 1 H), 3.64 (s, 3 H), 2.45 (m, 2 H), 2.27 (t, J = 7.4 Hz, 2 H), 1.51 (s, 3 H), 1.33 (s, 3 H), 1.59–1.28 (m, 19 H), 0.87 (t, J = 6.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 174.26, 135.76, 131.34*, 113.97, 85.51*, 80.06, 72.88*, 69.35*, 51.36*, 49.87, 37.30*, 33.98, 31.68, 29.34*, 28.97*, 27.51*, 26.40, 26.20, 25.16, 24.99, 24.78, 24.63, 22.54, 13.93; HRMS calcd for $C_{24}H_{42}O_6$ ($M^{\cdot+}$) 426.2981, ($M^{\cdot+}$ – CH_3) 411.2747, found 411.2750.

Deprotection of 29: (±)-10α-Hydroxyprostaglandin F_1, Methyl Ester (31). A solution of silyl ether **29** (50 mg, 0.092 mmol) in 80% aqueous acetic acid (1 mL) was stirred at 85 °C for 15 min. The resulting mixture was cooled to room temperature. The solvent and volatile materials were removed in vacuo. The resulting solid was purified by flash chromatography using 10:1 Et_2O/MeOH to yield **31** (30 mg, 85% yield, a mixture of C-15 epimers, R_f = 0.3 and 0.4, respectively (10:1 Et_2O/MeOH)), as a colorless oil: IR (neat) 3343 (br), 2927 (s), 2855, 1742 (s), 1463, cm^{-1}; ^1H NMR (DMSO-d^6) δ 5.36 (m, 2 H), 4.49 (dd, J_1 = 7.1 Hz, J_2 = 4.7 Hz, 1 H), 4.32 (m, 1 H), 4.10 (dd, J_1 = 4.5 Hz, J_2 = 1.3 Hz, 1 H), 3.86 (q, J = 4.8 Hz, 1 H), 3.81 (m, 1 H), 3.68 (q, J = 4.4 Hz, 1 H), 3.56 (s, 3 H), 3.51 (m, 1 H), 2.26 (t, J = 7.4 Hz, 2 H), 2.07 (m, 1 H), 1.51–1.22 (m, 19 H), 0.84 (t, J = 6.7 Hz, 3 H); ^{13}C NMR (DMSO-d_6) δ 173.22, 134.66*, 131.09*, 75.84*, 72.11, 71.71, 70.40, 53.97*, 50.99, 44.26, 37.46*, 33.20, 31.24, 28.97, 28.39, 27.35, 24.62, 24.41, 24.36, 22.03, 13.74; MS calcd for $C_{21}H_{38}O_6$ ($M^{\cdot+}$) 386, found 350 ($M^{\cdot+}$ – 2 H_2O), 280, 247, 109, 99, 81, 55 (100).

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Supplementary Material Available: ^1H NMR at 300 MHz for compounds **4, 6, 8, 11, 12, 14, 15, 17, 20–33** (11 pages). Ordering information is given on any current masthead page.