Total Synthesis of 3-Oxa-4,5,6-trinor-3,7-*inter-m*-phenylene Prostaglandins. 2. Conjugate Addition Approach

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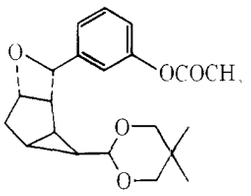
An alternative and more efficient total synthesis of optically active 3-oxa-4,5,6-trinor-3,7-*inter-m*-phenyleneprostaglandin E_1 (**2**) is described starting from the known protected lactone **7**. Lactone **7** was converted in six steps to α-methylenecyclopentanone (**13**), which was then condensed with lithium diarylcuprate (**16**) to give the 1,4-adduct **17** in good overall yield. Subsequent transformations (Scheme II) afforded **2** in 23–27% overall yield from **7**. The synthesis of enone **13** (Scheme I) involved the oxidative decarboxylation of an intermediary carboxylic acid (i.e., **10**), and the utility of **13** as an intermediate for the synthesis of the desired analogue was confirmed.

The preceding paper[1] in this series described the rationale for and the total synthesis of several optically active 3-oxa-4,5,6-trinor-3,7-*inter-m*-phenyleneprostaglandin analogues of the PGE_1 family (e.g., **2**) starting from the readily available and optically active tricyclic oxetane **1**. Although this



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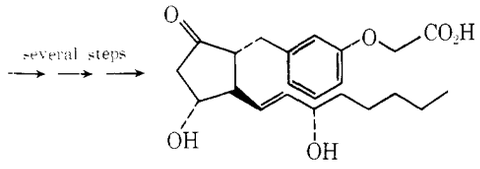

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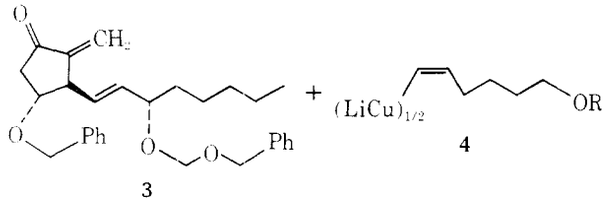
synthetic procedure was satisfactory for procuring initial quantities of the desired analogues for biological evaluation, it proved to have too many limitations. In particular, the final solvolytic ring-opening step to afford the methyl ester of **2** was low-yielding and required extensive chromatographic purification of the product mixture. For these reasons, an alternative and more efficient synthesis of *l*-3-oxa-4,5,6-trinor-3,7-*inter-m*-phenyleneprostaglandin E_1 (**2**) was developed and is reported herein.

Results and Discussion

Strategy. Recently, Stork and co-workers[2] described a novel total synthesis of prostaglandins which employed as a key step the conjugate addition of the lithium divinylcuprate **4** to the α-methylene ketone **3** to afford prostanoid **5**. It was



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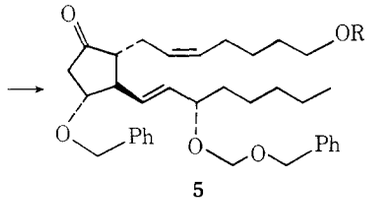

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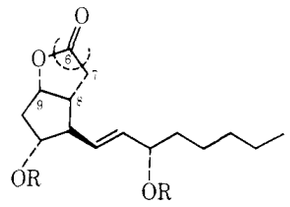
R = $CH(CH_3)(OCH_2CH_3)$

envisaged that if an optically active enone intermediate like **3** could be readily synthesized from an available and optically active intermediate (e.g., **6**[3,4]), then a new total synthesis of the biologically[1] and optically active 3-oxa-4,5,6-trinor-3,7-*inter-m*-phenyleneprostaglandins could be realized by the conjugate addition of an appropriate aryl organometallic reagent. The use of a suitably protected form of lactone diol **6** (e.g., **7**) to generate an α-methylenecyclopentanone moiety



6, R = H
7, R = THP

like **3** would necessarily require a one-carbon degradation (i.e., loss of C-6[5]) and subsequent oxidation of C-8 and C-9. Further, any degradation or oxidation conditions would have to be compatible with the other functional groups present in the molecule.

Synthesis. The successful synthesis of α-methylenecyclopentanone **13** is illustrated in Scheme I. Starting with the readily available and optically pure lactone bis(tetrahydropyranyl ether) **7**[3] the silylated acid **10** was prepared in 88% overall yield by (a) saponification of **7** to **8** with aqueous base, (b) silylation of **8** with *tert*-butyldimethylsilyl chloride[6] to **9**, and (c) selective basic hydrolysis of the silyl ester of **9**. The acid **10** was then subjected to the oxidative decarboxylation procedure of Kochi[7] to afford olefin **11** in 71% yield correcting for 45% of recovered starting acid **10**. The conversion of **10** to **11** was in general always in the range of 35–50%. This was attributed to the fact that acetic acid (a by-product of the reaction) effectively competed with acid **10** for coordination to lead(IV).[7] However, the reaction was relatively clean, and olefin **11** was easily separated from unreacted **10** by column chromatography and the acid was recycled. It is interesting to note that the oxidative decarboxylation conditions did not prove detrimental to the lower side chain of **10** or **11**. In addition, the procedure allowed the one-carbon degradation of C-6 and the oxidation at C-8 to be carried out simultaneously.

At this point, the latent hydroxyl function of C-9[5] was selectively liberated with tetra-*n*-butylammonium fluoride in tetrahydrofuran.[6] Alcohol **12** was then oxidized with Jones reagent at −20 °C to the α-methylenecyclopentanone **13** in high overall yield. This unsaturated ketone, like **3**,[2a] was stable to chromatography on silica gel; however, it was not necessary to further purify the crude sample of **13** obtained from the

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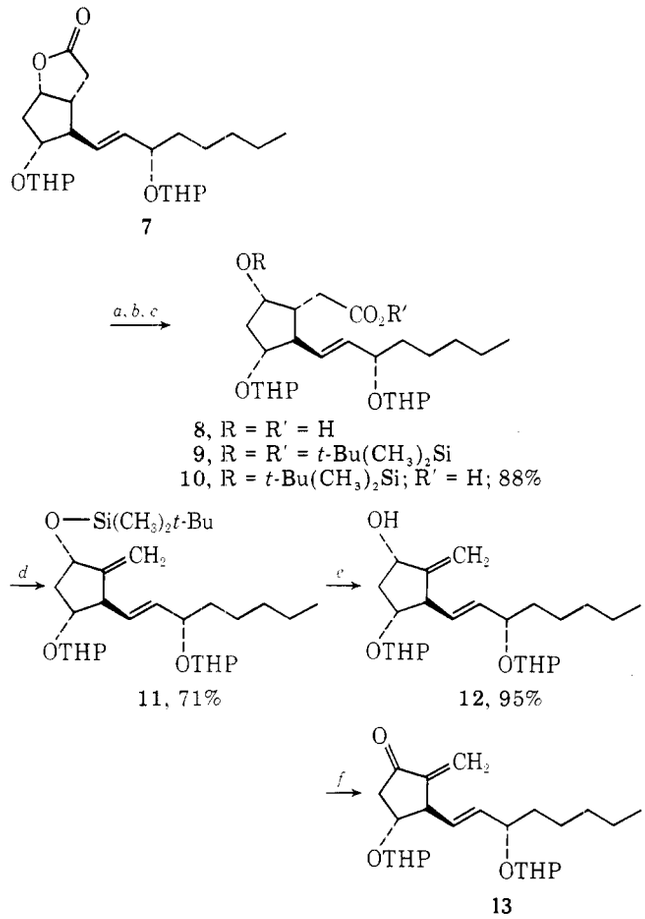
Scheme I



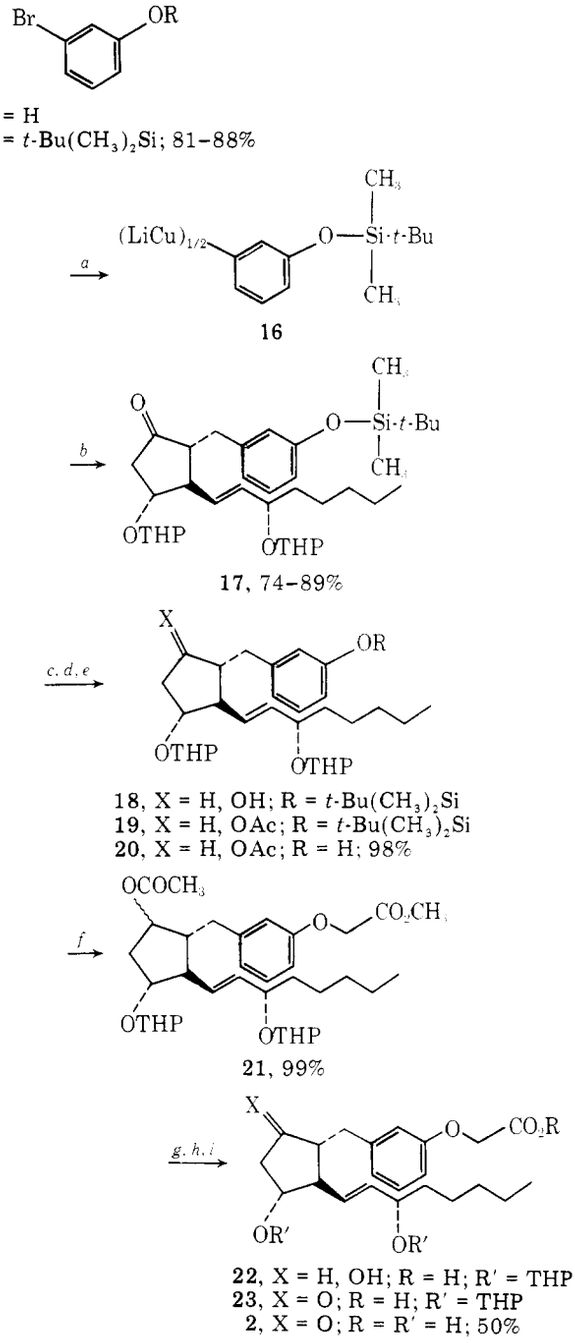
[a] NaOH, CH_3OH, H_2O; aq $KHSO_4$. [b] *t*-BuSi$(CH_3)_2$Cl, imidazole, DMF. [c] K_2CO_3, CH_3OH, H_2O. [d] $Pb(OAc)_4$, C_6H_6, $Cu(OAc)_2$, pyridine, 80 °C or *hν*. [e] $(n\text{-Bu})_4NF$, THF. [f] H_2CrO_4, acetone, −20 °C.

oxidation reaction since it was ≥90% pure (by TLC and NMR spectroscopy).

The synthesis of the requisite lithium diarylcopper reagent **16** and its condensation with α-methylenecyclopentanone **13** are illustrated in Scheme II. Commercially available *m*-bromophenol (**14**) was protected as its *tert*-butyldimethylsilyl ether **15**[6] and then metalated at −78 °C with 2 equiv of *tert*-butyllithium. The resulting aryllithium reagent was then added to a suspension of cuprous iodide–tri-*n*-butylphosphine complex in ether (−78 °C) to give the lithium diarylcuprate **16** as an orange-brown mixture. Addition of **13** to **16** at −78 °C followed by addition of the resulting enolate to a solution of glacial acetic acid in ether afforded ketone **17** in 74–89% isolated yield based on allylic alcohol **12**. The structure of **17** was supported by standard spectral data (see Experimental Section) and subsequent conversion to and comparison with known materials (vide infra).[1]

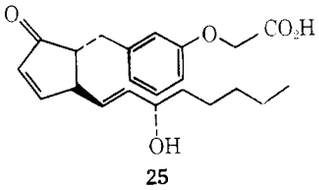
Continuing with the synthetic sequence in Scheme II, the phenol **20** was prepared from **17** in 98% overall yield by (a) reduction of the C-9 ketone function with sodium borohydride to give **18** as a mixture of epimers (ca. 1:1), (b) acetylation of **18** to give **19**, and (c) cleavage of the phenolic silyl ether with tetra-*n*-butylammonium fluoride. Alkylation of **20** with methyl bromoacetate gave diester **21** in essentially quantitative yield and this material was then transformed into optically active 3-oxa-4,5,6-trinor-3,7-*inter-m*-phenyleneprostaglandin E_1 (**2**) by (a) saponification with aqueous base to **22**, (b) Jones oxidation of the resulting C-9 alcohols to **23**, and (c) hydrolysis of the protecting groups in aqueous acid (40–50% overall from **21**). The sample of **2** so produced was identical

Scheme II



[a] *t*-BuLi, Et_2O, −78 °C; CuI–$(n\text{-Bu})_3P$, Et_2O, −78 °C. [b] Enone **13**, Et_2O, −78 °C; HOAc, Et_2O. [c] $NaBH_4$, CH_3OH, −25 to −5 °C. [d] Ac_2O, pyridine, 4-DMAP. [e] $(n\text{-Bu})_4NF$, THF. [f] $BrCH_2CO_2CH_3$, NaH, $CH_3OCH_2CH_2OCH_3$, 0 °C. [g] KOH, CH_3OH, H_2O, 40 °C. [h] H_2CrO_4, acetone, −30 to −15 °C. [i] H_3PO_4, H_2O, THF, 35 °C.

in all respects with an authentic specimen of **2**,[1] including an undepressed mixture melting point. In addition to the prostaglandin E_1 analogue **2**, significant quantities of 3-oxa-4,5,6-trinor-3,7-*inter-m*-phenyleneprostaglandin A_1 (**25**) were also formed during the hydrolysis of **23** to **2**.



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In summary, α-methylenecyclopentanone **13** has proved to be a versatile and useful intermediate for the total synthesis of 3-oxa-4,5,6-trinor-3,7-*inter*-*m*-phenyleneprostaglandins and is easily prepared in six steps from the known lactone **7** in ca. 60% overall yield.

Experimental Section

General. All melting points are corrected unless otherwise noted. Analytical data were obtained by the Physical and Analytical Chemistry Research Department of The Upjohn Co. IR spectra were obtained either on neat samples (oils) or on Nujol mulls (crystalline samples). Mass spectra were recorded at high or low resolution for derivatized (Me_3Si) or underivatized compounds at 70 eV. The NMR spectra were obtained on a Varian A-60D or T-60 spectrometer operating at 60 MHz on chloroform-*d* solutions containing internal tetramethylsilane. Thin layer chromatography (TLC) was conducted using Analtech (Uniplate) glass plates precoated with silica gel GF (250 μm). Where mixed solvents were used for chromatography, the composition is expressed as a percent by volume of the former in the latter. The solvent system A–IX[8] is the organic layer from an equilibrated mixture of 90 mL of ethyl acetate, 20 mL of acetic acid, 50 mL of 2,2,4-trimethylpentane, and 100 mL of water. The TLC plates were visualized first by UV light (Mineralight UVS-11), then by spraying with a vanillin–phosphoric acid solution or 50% aqueous sulfuric acid, followed by heating. Unless otherwise noted, column chromatography utilized neutral silica gel (E. Merck), 70–230 mesh. Acid-washed silica gel was Mallinckrodt CC-4. All solvents were reagent grade or reagent grade distilled from glass (Burdick and Jackson). All reagents were used as purchased and were reagent grade where available. Cuprous iodide was purified by the method of Kauffman and Teter[9] and dried in vacuo over phosphorus pentoxide before use.

3α,5α-Dihydroxy-2β-[3′(*S*)-hydroxy-*trans*-1′-octenyl]cyclopentane-1α-acetic Acid 3,3′-Bis(tetrahydropyranyl ether) 5-*tert*-Butyldimethylsilyl Ether (10). A 500-ml flask, equipped with a magnetic stirring bar, was charged with 10.30 g (23.59 mmol) of 3α,5α-dihydroxy-2β-[3′(*S*)-hydroxy-*trans*-1′-octenyl]cyclopentane-1α-acetic acid γ-lactone 3,3′-bis(tetrahydropyranyl ether) (**7**),[3] and 91 mL of methanol. The resulting solution was then treated with 91 mL of 1.0 N aqueous sodium hydroxide and stirred at 25 °C for 10–16 h. The reaction mixture was then concentrated in vacuo to one-half volume, diluted with 300 mL of brine, and cooled to 0 °C. The pH was then adjusted to 4–5 with ice-cold 1.0 N aqueous potassium bisulfate and the ice-cold aqueous mixture was quickly extracted with ethyl acetate (3 × 150 mL). The combined extracts were washed with brine, dried over sodium sulfate, and concentrated in vacuo to give 12.3 g of 3α,5α-dihydroxy-2β-[3′(*S*)-hydroxy-*trans*-1′-octenyl]cyclopentane-1α-acetic acid 3,3′-bis(tetrahydropyranyl ether) (**8**) as an oily foam.

The above sample of hydroxy acid **8** was immediately dissolved in 80 mL of *N*,*N*-dimethylformamide. The resulting solution was purged for several minutes with nitrogen and then treated with 14.32 g (95.00 mmol) of *tert*-butyldimethylsilyl chloride followed by 12.94 g (190.07 mmol) of imidazole. The reaction mixture was stirred at 40 °C for 4 h, cooled to 25 °C, diluted with 1000 mL of brine, and extracted with 1:1 diethyl ether–Skellysolve B (2 × 250 mL). The combined extracts were washed with ice-cold 1.0 N aqueous hydrochloric acid and brine, and dried over sodium sulfate. Concentration in vacuo gave crude 3α,5α-dihydroxy-2β-[3′(*S*)-hydroxy-*trans*-1′-octenyl]cyclopentane-1α-acetic acid *tert*-butyldimethylsilyl ester 3,3′-bis(tetrahydropyranyl ether) 5-*tert*-butyldimethylsilyl ether (**9**) as an oil.

The above sample of **9** was dissolved in 300 mL of methanol and 100 mL of tetrahydrofuran and then treated with a solution of 10 g of potassium carbonate in 100 mL of water. The reaction mixture was stirred at 25 °C for 1 h, concentrated in vacuo to one-quarter volume and diluted with 300 mL of brine. The resulting aqueous mixture was cooled to 0 °C, adjusted to pH 4–5 with 1.0 M aqueous potassium bisulfate, and extracted with diethyl ether (2 × 150 mL). The combined extracts were washed with brine, dried over sodium sulfate, and concentrated in vacuo to give 18 g of crude acid **10** as an oil. A 48 mm × 48 in. column was slurry-packed with 600 g of acid-washed silica gel in 3% ethyl acetate in Skellysolve B. The sample of **10** was applied in Skellysolve B and eluted with 1 L each of 10%, 15%, 20%, and 25% ethyl acetate in Skellysolve B. Fractions were 50 mL each, and based on TLC homogeneity fractions 22–49 were combined to give 11.83 g (88%) of pure **10** as a viscous oil. The IR showed bands at 3700–2480 (CO_2H), 2980, 2890, 1735, 1715, 1252, 1200, 1181, 1128, 1110, 1074, 1020, 982, 870, 838, and 777 cm^{-1}. The NMR showed absorptions at δ 0.3 (bd, s, 6 H, silyl CH_3), 0.89 (s, 9 H, silyl *tert*-butyl), 0.7–2.8 (m, 29 H), 3.2–4.47 (m, 7 H), 4.68 (m 2 H), 5.27–5.72 (m, 2 H), 9.63 (m, 1 H). The mass spectrum exhibited peaks at *m/e* 583.3452 ($M^+ - C_4H_9$ of Me_3Si derivative; calcd for $C_{30}H_{55}Si_2O_7$: 583.3486), 539, 499, 481, 397, 382, 322, 305, 187, and 85. TLC using ethyl acetate in Skellysolve B showed one spot, R_f 0.14. Anal. ($C_{31}H_{56}O_7Si$) C, H.

3α-5α-Dihydroxy-2β-[3′(S)-hydroxy-*trans*-1′-octenyl]-1-methylenecyclopentane 3,3′-Bis(tetrahydropyranyl ether) 5-*tert*-Butyldimethylsilyl Ether (11). A 100-mL, three-neck flask, equipped with a magnetic stirring bar, reflux condenser, and a nitrogen inlet (a glass pipet placed below the surface of the reaction mixture), was charged with 2.20 g (3.87 mmol) of acid **10** and 35 mL of benzene. The resulting solution was treated with a mixture of 0.19 g of cupric acetate monohydrate and 1.16 mL of pyridine and then stirred at 25 °C until a homogeneous blue-green solution was produced (ca. 1 h). Then 5.03 g (11.34 mmol) of lead tetracetate was added and the resulting mixture was stirred at 25 °C in the dark for 1.5 h while maintaining a gentle nitrogen purge. The reaction mixture was heated to 80 °C (oil bath) over 20–30 min and heated with stirring and nitrogen purge at 80 °C for an additional 30 min. The reaction mixture was then cooled to ambient temperature, diluted with 300 mL of brine, and extracted with ethyl acetate (2 × 150 mL). The combined extracts were washed with brine, dried over sodium sulfate, and concentrated in vacuo to give 2.25 g of crude product mixture as an oil. A 28 mm × 36 in. column was slurry-packed with 225 g of silica gel in 3% ethyl acetate in Skellysolve B. The sample was applied in Skellysolve B and eluted with 500 mL each of 5%, 10%, 15%, 25%, 35%, and 45% ethyl acetate in Skellysolve B. Fractions were 20 mL each, and based on TLC homogeneity, fractions 44–63 were combined to give 0.80 g (40%) of pure **11** as an oil. Fractions 101–125 were combined to give 0.98 g (45%) of recovered acid **10** as an oil. For **11**, the IR showed bands at 3080, 1665, 1255, 1200, 1130, 1115, 1075, 1035, 1020, 1005, 975, 870, 835, and 775 cm^{-1}. The NMR showed absorptions at δ 0.08 (s, 6 H, silyl methyl), 0.92 (s, 9 H, silyl *tert*-butyl), 0.75–2.9 (m, 26 H), 2.9–4.5 (m, 7 H), 4.72 (m, 2 H), 4.93 and 5.17 (2m, 2 H, *exo*-methylene H), 5.33–5.64 (m, 2 H). The mass spectrum exhibited peaks at *m/e* 465.3034 ($M^+ - C_4H_9$; calcd for $C_{26}H_{45}SiO_5$: 465.3036), 420, 394, 381, 363, 326, 319, 279, and 85. TLC using 25% ethyl acetate in Skellysolve B showed one spot, R_f 0.64. Anal. ($C_{30}H_{54}O_5Si$) C, H.

3α,5α-Dihydroxy-2β-[3′(*S*)-hydroxy-*trans*-1′-octenyl]-1-methylenecyclopentane 3,3′-Bis(tetrahydropyranyl ether) (12). A 500-mL flask, equipped with a magnetic stirring bar, was charged with 28.94 g (55.35 mmol) of silyl ether **11** and 70 mL of dry tetrahydrofuran. The resulting solution was alternatively degassed and flushed with nitrogen (3×), cooled in an ice bath and then treated with 100 mL of 1.0 M tetra-*n*-butylammonium fluoride[10] in tetrahydrofuran. The reaction mixture was stirred at 5 °C under nitrogen for 2 h, diluted with brine, and extracted with ethyl acetate (2 × 250 mL). The combined extracts were washed with brine, dried over magnesium sulfate, and concentrated in vacuo to give 32.71 g of crude **12** as a dark red-brown oil. A 48 mm × 48 in. column was slurry-packed with 654 g of silica gel in 10% ethyl acetate in Skellysolve B. The sample was applied in Skellysolve B and eluted with 1000 mL each of 25%, 35%, 45%, 55%, and 65% ethyl acetate in Skellysolve B. The first fraction was 1000 mL and subsequent fractions were 50 mL each. Based on TLC homogeneity, fractions 35–60 were combined to give 21.38 g (95%) of pure **12** as a pale yellow solid. This material was then recrystallized from 200 mL of Skellysolve B at −20 °C to give 17.79 g of very pure **12** as a white solid: mp 83–84.5 °C (uncorrected); $[\alpha]_D$ + 45° (*c* 1.3755, EtOH). The IR showed bands at 3220, 3140, 1660, 1125, 1080, 1065, 1040, 1020, 1000, 970, and 910 cm^{-1}. The NMR showed absorptions at δ 0.88 (t, $J \sim 5$ Hz, 3 H), 0.6–2.8 (m, 24 H), 3.0–4.5 (m, 7 H), 4.70 (m, 2 H), 5.02 (m, 1 H, *exo*-methylene H), 5.20–5.62 (m, 3 H, olefinic H and *exo*-methylene H). The mass spectrum exhibited peaks at *m/e* 378.2591 (M^+ − THPOH; calcd for $C_{22}H_{38}SiO_3$: 378.2590), 379, 352, 294, 252, and 85. TLC using 25% ethyl acetate in Skellysolve B showed one spot, R_f 0.19. Anal. ($C_{24}H_{40}O_5$) C, H.

3-(*tert*-Butyldimethylsilyloxy)-1-bromobenzene (15). A 250-mL flask, equipped with a magnetic stirring bar, was charged with 10.0 g (57.80 mmol) of *m*-bromophenol, 40 mL of *N*,*N*-dimethylformamide, 17.42 g (115.60 mmol) of *tert*-butyldimethylsilyl chloride, and 15.74 g (231.20 mmol) of imidazole. The reaction mixture was stirred at 23 °C overnight, diluted with brine, and extracted with 3:1 Skellysolve B–methylene chloride (2×). The combined extracts were washed with brine (3×), dried over sodium sulfate, and concentrated in vacuo to give 29.07 g of oil which was distilled at reduced pressure to give 13.47 g (81%) of pure **15** as an oil: bp 66 °C (0.28 mm). The IR showed bands at 1590, 1570, 1475, 1295, 1270, 1240, 930, 840, 825, 810, and 780 cm^{-1}. The NMR showed absorptions at δ 0.20 (s, 6 H), 0.98 (s, 9 H), 6.58–7.48 (m, 4 H). The mass spectrum exhibited peaks at *m/e* 288, 286 (M^+), 232, 231, 230, 229, 150, 139, 137, and 135. The ul-

traviolet spectrum showed λ_{max}(*n*-hexane) 218 (sh, ϵ 9250), 267 (sh, ϵ 937), 272 (ϵ 1300), and 278 (ϵ 1150). Anal. ($C_{12}H_{19}BrOSi$) C, H.

3α-Hydroxy-5-oxo-2β-[3′(*S*)-hydroxy-*trans*-1′-octenyl]-1α-[*m*-(*tert*-butyldimethylsilyloxy)benzyl]cyclopentane 3,3′-Bis(tetrahydropyranyl ether) (17). A. Synthesis of 3α-Hydroxy-5-oxo-2β-[3′(*S*)-hydroxy-*trans*-1′-octenyl]-1-methylenecyclopentane 3,3′-Bis(tetrahydropyranyl ether) (13). A 2000-mL, three-neck flask, equipped with a mechanical stirrer, addition funnel, thermometer, and a nitrogen–vacuum connection, was charged with 40.0 g (97.90 mmol) of allylic alcohol **12** and 800 mL of acetone. The resulting solution was alternately degassed and flushed with nitrogen (2×) and cooled to −35 °C (internal temperature). Then added with stirring, 50 mL of 2.67 M Jones reagent during 5–10 min maintaining the internal temperature at or below −20 °C. The reaction mixture was stirred at −25 to −20 °C for 30 min, treated with 30 mL of isopropyl alcohol, and stirred for an additional 30 min at −25 to −20 °C. The reaction mixture was concentrated in vacuo at ≤30 °C to one-half volume, diluted with brine, and extracted with diethyl ether (3 × 350 mL). The combined extracts were washed with saturated aqueous sodium bicarbonate and brine, and dried over magnesium sulfate. Concentration in vacuo gave 40 g of enone **13** as a pale yellow oil. The IR showed bands at 2980, 2890, 1735, 1647, 1200, 1129, 1112, 1076, 1035, 1020, and 978 cm^{-1}. The NMR showed absorptions at δ 0.91 (t, J = 5 Hz, 3 H), 0.8–3.1 (m, 23 H), 3.1–4.4 (m, 6 H), 4.68 (m, 2 H), 5.11 and 5.98 (2m, 2 H, *exo*-methylene H), 5.47 (m, 2 H). TLC using 25% ethyl acetate in Skellysolve B showed one spot, R_f 0.44. Enone **13** was not further purified but used directly in part B.

B. Generation of Lithium Bis(3-*tert*-butyldimethylsilyloxyphenyl)copper (16). A 3000-mL, three-neck flask, equipped with a mechanical stirrer, serum stopper, and a nitrogen–vacuum connection, was charged with 600 mL of anhydrous diethyl ether, 24.8 g (122.58 mmol) of tri-*n*-butylphosphine, and 23.2 g (121.82 mmol) of cuprous iodide. The resulting mixture was alternately degassed and flushed with nitrogen (3×), stirred at 25 °C for 1 h, and then cooled to −78 °C (solution I).

A 2000-mL, three-neck flask, equipped with a magnetic stirring bar, serum stopper, 500-mL addition funnel (pressure equilibrated and graduated with a serum stopper at the top) and a nitrogen–vacuum connection, was charged with 360 mL of anhydrous diethyl ether. The system was alternately degassed and flushed with nitrogen (3×) and the flask was cooled to −78 °C. The addition funnel was then charged with 258 mL of 1.90 M *tert*-butyllithium in pentane (490.20 mmol) via a double-tipped needle with positive nitrogen pressure.[11] The *tert*-butyllithium solution was then added dropwise with stirring to the ether solvent in the flask (solution II).

A 500-mL flask, equipped with a magnetic stirring bar, was charged with 70.4 g (245.07 mmol) of aryl bromide **15** and 240 mL of anhydrous diethyl ether. The resulting solution was alternately degassed and flushed with nitrogen (3×), cooled to −78 °C, and added over 15 min to solution II via a double-tipped needle with positive nitrogen pressure.[11] The reaction mixture was then stirred at −78 °C for 1.75 h (solution III).

Solution III was added to solution I with vigorous stirring via a double-tipped needle at −78 °C.[11] The addition was carried out over 45–60 min with the following color change: white → yellow → tan → orange-brown. After the addition was complete, the reaction mixture was stirred at −78 °C for an additional 30 min.

C. Synthesis of 17. A 1000-mL flask, equipped with a magnetic stirring bar, was charged with 40 g of enone **13** and 400 mL of anhydrous diethyl ether. The resulting solution was alternately degassed and flushed with nitrogen (3×), cooled to −78 °C, and added to the above mixture of cuprate **16** (vigorously stirred) via a double-tipped needle with positive nitrogen pressure.[11] The addition was carried out over 60–80 min and the reaction mixture was then stirred for an additional 30–40 min at −78 °C. The resulting reaction mixture was then transferred into a rapidly stirred solution of 1000 mL of 7.6% glacial acetic acid in diethyl ether (precooled to −40 °C) via a ⅛-in. o.d. Teflon cannula and positive nitrogen pressure. After the transfer was complete, the resulting mixture was washed with brine (2 × 1000 mL), saturated aqueous sodium bicarbonate (3 × 1000 mL), and brine (1000 mL), and dried over magnesium sulfate. Concentration in vacuo gave 197.6 g of crude **17** as an oil.

The above product was combined with similar products obtained from runs employing 1, 5, and 20 g of allylic alcohol **12** (total of 161.54 mmol of **12**) to give 231.82 g of crude product which was purified as follows: a 110 mm × 48 in. column was dry-packed with 3000 g of silica gel (previously equilibrated with 300 mL of ethyl acetate). The sample was applied in Skellysolve B and eluted with 2 L each of 3, 10, 15, 15, 20, 20, 25, 30, 40, and 50% ethyl acetate in Skellysolve B. Fractions were 500 mL each, and based on TLC homogeneity, fractions 27–40 were combined to give 75.11 g (76%) of pure **17** as an oil. The IR showed bands at 2970, 2890, 1750, 1612, 1583, 1485, 1470, 1440, 1272, 1258, 1200, 1160, 1132, 1129, 1112, 1080, 1037, 1020, 976, 843, and 784 cm^{-1}. The NMR showed absorptions at δ 0.18 (s, 6 H), 0.90 (t, J = 5 Hz, 3 H), 0.98 (s, 9 H), 0.6–3.1 (m, 26 H), 3.2–4.4 (m, 6 H), 4.68 (m, 2 H), 5.50 (m 2 H), 6.52–7.42 (m, 4 H). The mass spectrum exhibited peaks at *m/e* 614.3982 (M^+; calcd for $C_{36}H_{58}O_6Si$: 614.4002), 557, 530, 529, 513, 512, 463, 455, 428, 410, 371, 357, 355, 353, 317, 246, 221, 159, and 85. TLC using 25% ethyl acetate in Skellysolve B showed three to four spots (diastereomeric THP mixture), R_f 0.25–0.37.

5αβ-Acetoxy-3α-hydroxy-2β-[3′(*S*)-hydroxy-*trans*-1′-octenyl]-1α-(*m*-hydroxybenzyl)cyclopentane 3,3′-Bis(tetrahydropyranyl ether) (20). A. Synthesis of 3α,5αβ-Dihydroxy-2β-[3′(*S*)-hydroxy-*trans*-1′-octenyl]-1α-[*m*-*tert*-butyldimethylsilyloxy)benzyl]cyclopentane 3,3′-Bis(tetrahydropyranyl ether) (18). A 1000-mL, three-neck flask, equipped with a magnetic stirring bar, addition funnel, thermometer, and a nitrogen–vacuum connection, was charged with 150 mL of absolute methanol and 2.52 g (66.65 mmol) of sodium borohydride. The resulting solution was alternately degassed and flushed with nitrogen (3×) and cooled to −30 °C (internal temperature). A solution of 27.3 g (44.43 mmol) of ketone **17** in 50 mL of methylene chloride was then added with stirring while maintaining the temperature of the reaction mixture at −30 to −25 °C. Residual **17** was rinsed in with 25 mL of methylene chloride and the reaction mixture was stirred at −30 to −25 °C for 1.5 h, diluted with 1000 mL of brine, and extracted with ethyl acetate (2 × 300 mL). The combined extracts were washed with brine (2 × 300 mL), dried over sodium sulfate, and concentrated in vacuo to give 27.8 g of crude **18** as an oil (ca 1:1 mixture of epimers). TLC using 50% ethyl acetate in Skellysolve B showed two spots, R_f 0.64 and 0.51.

B. Synthesis of 5αβ-Acetoxy-3α-hydroxy-2β-[3′(*S*)-hydroxy-*trans*-1′-octenyl]-1α-[*m*-(*tert*-butyldimethylsilyloxy)-benzyl]cyclopentane 3,3′-Bis(tetrahydropyranyl ether) (19). A 500-mL, three-neck flask, equipped with a magnetic stirring bar, addition funnel, thermometer, and a nitrogen inlet, was charged with 27.8 g of alcohols **18** (from part A) and 200 mL of pyridine. The resulting solution was purged with nitrogen for several minutes, cooled to 0 °C, and treated with 80 mL of acetic anhydride and 0.50 g of 4-(*N*,*N*-dimethylamino)pyridine. The reaction mixture was stirred at 8–10 °C for 20 min then at 20–25 °C for 3 h. The flask was immersed in an ice bath and 75 mL of anhydrous methanol was added at a rate such that the internal temperature was maintained at or below 35 °C. After stirring for an additional 30 min, the reaction mixture was diluted with 1000 mL of brine and extracted with ethyl acetate (2 × 300 mL). The combined extracts were washed with brine (300 mL), ice-cold 1 N aqueous hydrochloric acid (5 × 300 mL), saturated aqueous sodium bicarbonate (300 mL), and brine (300 mL), and dried over sodium sulfate. Concentration in vacuo gave 29.4 g of crude **19** as an oil. The IR showed the absence of a hydroxyl band and the appearance of a carbonyl band at 1745 cm^{-1}.

C. Synthesis of 20. A 250-mL three-neck flask, equipped with a magnetic stirring bar, serum cap, thermometer, and a nitrogen–vacuum connection was charged with 29.4 g of acetates **19** (from part B) and 100 mL of dry tetrahydrofuran. The resulting solution was alternately degassed and flushed with nitrogen (3×), cooled to 0 °C, and treated with 115 mL of 0.5 M tetra-*n*-butylammonium fluoride[10] in tetrahydrofuran. The reaction mixture was stirred at 3–10 °C for 45 min, diluted with 1000 mL of brine, and extracted with ethyl acetate (350 mL). The extract was washed with brine (300 mL), dried over sodium sulfate, and concentrated in vacuo to give 35.4 g of crude **20** as a dark oil. A 48 mm × 36 in. column was slurry-packed with 500 g of silica gel in 25% ethyl acetate in Skellysolve B. The sample was applied in methylene chloride and eluted with 1000 mL each of 25%, 35%, 45%, and 55% ethyl acetate in Skellysolve B. Fractions were 60 mL each, and based on TLC homogeneity, fractions 25–39 were combined to give 23.8 g of pure **20** (ea. 1:1 mixture of epimers) as an oil (98% overall from **17**). The IR showed bands at 3400, 2970, 2890, 1745, 1725(sh), 1604, 1590, 1240, 1131, 1114, 1075, 1021, and 974 cm^{-1}. The NMR showed absorptions at δ 0.88 (t, J = 5 Hz, 3 H), 1.80, 1.82, 2.07 (3 s, 3 H total, acetate CH_3), 0.8–3.1 (m, 26 H), 3.18–4.42 (m, 6 H), 4.47–5.23 (m, 3 H), 5.23–5.90 (m, 2 H), 6.42–7.30 (m, 4 H), 7.07 (bd, s, 1 H, OH, shifts downfield on cooling). The mass spectrum exhibited peaks at *m/e* 616.3820 (M^+ of trimethylsilyl derivative; calcd for $C_{35}H_{56}SiO_7$: 616.3795), 532, 514, 430, 370, 352, 326, 259, 179, and 85. TLC using 25% ethyl acetate in Skellysolve B showed two spots, R_f 0.09 and 0.13.

9-Deoxy-9(*RS*)-acetoxy-3-oxa-4,5,6-trinor-3,7-*inter-m*-phenyleneprostaglandin $F_{1\alpha}$ Methyl Ester 11,15-Bis(tetrahydropyranyl ether) (21). A 1000-mL three-neck flask, equipped with a magnetic stirring bar, thermometer, and a nitrogen–vacuum con-

nection, was charged with 23.83 g (43.75 mmol) of phenols **20**, 300 mL of 1,2-dimethoxyethane, and 20.04 g (131 mmol) of methyl bromoacetate. The resulting solution was alternately degassed and flushed with nitrogen (3×), cooled to 3–5 °C in an ice bath, and treated with stirring with 2.76 g of 57% sodium hydride dispersion in mineral oil (65.5 mmol) in small portions during 10 min. The reaction mixture was stirred at 5–10 °C for 2 h and then cautiously treated with 1 mL of glacial acetic acid. The reaction mixture was diluted with 1000 mL of brine and extracted with ethyl acetate (300 mL). The extract was washed with brine (300 mL), dried over sodium sulfate, and concentrated in vacuo to give 36.4 g of crude **21** as an oil. A 48 mm × 36 in. column was slurry-packed with 500 g of silica gel in 5% ethyl acetate in Skellysolve B. The sample was applied in Skellysolve B and eluted with 750 mL of 5% ethyl acetate in Skellysolve B followed by 1000 mL each of 10%, 15%, 30%, and 30% ethyl acetate in Skellysolve B. The first fraction was 900 mL and subsequent fractions were 60 mL each. Based on TLC homogeneity fractions 50–82 were combined to give 26.91 g of pure **21** as an oil (99%). This sample was a mixture of C-9 epimers. The IR showed bands at 2970, 2890, 1765, 1740, 1612, 1590, 1239, 1200, 1158, 1130, 1112, 1076, 1020, and 973 cm^{-1}. The NMR showed absorptions at δ 0.88 (t, J = 5 Hz, 3 H), 1.78, 1.82, 2.07 (3 s, 3 H total, acetate CH_3), 0.8–3.0 (m, 26 H), 3.12–4.33 (m, 6 H), 3.77 (s, 3 H, OCH_3), 4.43–5.23 (m, 3 H), 4.60 (s, 2 H), 5.23–5.83 (m, 2 H), 6.50–7.42 (m, 4 H). The mass spectrum exhibited peaks at m/e 616.3654 (M^+; calcd for $C_{35}H_{52}O_9$: 616.3611), 532, 514, 430, 370, 352, 326, 179, and 85. TLC using 15% acetone in methylene chloride showed a single broad spot, R_f 0.64. Anal. ($C_{35}H_{52}O_9$) C, H.

3-Oxa-4,5,6-trinor-3,7-*inter*-*m*-phenyleneprostaglandin E_1 (2). A. Synthesis of 9-Deoxy-9(*RS*)-hydroxy-3-oxa-4,5,6-trinor-3,7-*inter*-*m*-phenyleneprostaglandin $F_{1\alpha}$ 11,15-Bis(tetrahydropyranyl ether) (22). A 500-mL flask, equipped with a magnetic stirring bar, was charged with 22.36 g (36.25 mmol) of diester **21**, 50 mL of water, and 150 mL of 5% aqueous potassium hydroxide. The resulting mixture was stirred at 25 °C for 14 h, heated at 35–40 °C for 4 h, cooled to room temperature, and then transferred to a 2-L flask equipped with a magnetic stirring bar. The flask and its contents were cooled to 0 °C, stirring was started, and 1 M aqueous potassium bisulfate was added until pH 3 was obtained. The resulting mixture was diluted to 1000 mL with ice-cold brine, saturated with solid sodium chloride, and extracted with ethyl acetate (3 × 200 mL). The combined extracts were washed with brine, dried over sodium sulfate, and concentrated in vacuo to give 19.83 g of crude **22** as an oil.

B. Synthesis of 3-Oxa-4,5,6-trinor-3,7-inter-*m*-phenyleneprostaglandin E_1 11,15-Bis(tetrahydropyranyl ether) (23). A 1000-mL three-neck flask, equipped with a magnetic stirring bar, thermometer, addition funnel, and a nitrogen–vacuum connection, was charged with 19.83 g of acid **22** (from part A) and 300 mL of acetone. The resulting solution was alternately degassed and flushed with nitrogen (3×), cooled to −25 °C (internal temperature), and treated with 38.6 mL of 2.67 M Jones reagent at a rate that maintained the internal temperature at −20 to −15 °C. The reaction mixture was stirred at −20 to −15 °C for 40 min, treated with 20 mL of isopropyl alcohol, and stirred for an additional 15 min at −20 to −15 °C. The reaction mixture was then diluted with ice-cold brine and extracted with diethyl ether (4 × 200 mL). The combined extracts were washed with brine (4 × 200 mL), dried over sodium sulfate, and concentrated in vacuo to give 20.68 g of crude **23** as a viscous oil. A 48 mm × 36 in. column was slurry-packed with 200 g of acid-washed silica gel in 50% ethyl acetate in Skellysolve B. The sample of **23** was applied in methylene chloride and quickly eluted with 50% ethyl acetate in Skellysolve B until 3000 mL of eluate were collected. Concentration in vacuo gave 17.46 g of semi-pure **23** as an oil. TLC using the A–IX system[8] showed a major spot at R_f 0.54.

C. Synthesis of 2. A 100-mL flask, equipped with a magnetic stirring bar, was charged with 17.46 g of acid **23** (from part B), and 260 mL of tetrahydrofuran. Then 140 mL of water was added followed by 21 mL of 85% phosphoric acid. The resulting solution was purged with nitrogen for 15 min, heated with stirring at 35 °C for 12 h, and cooled to room temperature. The reaction mixture was diluted with 1000 mL of brine, saturated with solid sodium chloride, and extracted with ethyl acetate (3 × 300 mL). The combined extracts were washed with brine (3 × 300 mL), dried over sodium sulfate, and concentrated in vacuo to give 17.38 g of crude product. A 48 mm × 36 in. column was slurry-packed with 520 g of acid-washed silica gel in 25% ethyl acetate in Skellysolve B. The sample was applied in methylene chloride and eluted with 1000 mL each of 25%, 35%, 45%, 65%, 75%, and 85% ethyl acetate in Skellysolve B followed by 2000 mL of acetone. The first fraction was 1000 mL and subsequent fractions were 60 mL each. Based on TLC homogeneity, fractions 25–65 were combined to give 8.98 g of a less polar mixture and fractions 67–94 were combined to give 5.62 g of pure **2** as a pale tan solid.

The less polar mixture from the above chromatography was recycled using 134 mL of tetrahydrofuran, 72 mL of water, and 11 mL of 85% phosphoric acid to give, after a similar chromatography, 5.4 g of a less polar mixture and an additional 1.45 g of pure **2** as a pale tan solid (total yield of 7.07 g; 50% overall from **21**).

The total sample of **2** (7.07 g) was dissolved in 100 mL of hot acetone, treated with 1.0 g of activated carbon for 10 min, and filtered through Celite washing well with acetone. The filtrate was then concentrated to ca. 100 mL total volume, heated to boiling, and treated with 200 mL of hot *n*-hexane. Pure **2** crystallized on standing at 25 °C to give 4.11 g of white microcrystals: mp 129.0–130.0 °C (undepressed on admixture with an independently synthesized sample of **2**[1]). Physical constants for **2** were reported in the preceding manuscript.[1]

3-Oxa-4,5,6-trinor-3,7-*inter*-*m*-phenyleneprostaglandin A_1 (25). The less polar chromatographic fractions from the previous experiment (part C) were rechromatographed over acid-washed silica gel with 30–50% ethyl acetate in Skellysolve B to give a pure specimen of **25** as an oil. The NMR showed absorptions at δ 0.88 (t, J = 5 Hz, 3 H), 0.6–1.9 (m, 8 H), 2.15–3.47 (m, 4 H), 3.97 (m, 1 H), 4.63 (s, 2 H), 5.28 (m 2 H), 6.12–6.33 and 7.38–7.60 (2 m, 2 H), 6.62–7.4 (m, 6 H, aryl H + CO_2H + OH). The mass spectrum exhibited peaks at m/e 516.2743 (M^+ of bistrimethylsilyl derivative; calcd for $C_{28}H_{44}Si_2O_5$: 516.2727), 501, 445, 426, 235, 199, and 173. TLC using the A–IX system[8] showed one spot, R_f 0.31.

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Registry No.—**2**, 65451-57-2; **7**, 37517-42-3; **8**, 65423-49-6; **9**, 65423-50-9; **10**, 65423-51-0; **10** Me_3Si ester, 65423-52-1; **11**, 65423-53-2; **12**, 65423-54-3; **12** Me_3Si derivative, 65423-48-5; **13**, 65423-55-4; **15**, 65423-56-5; **16**, 65453-04-5; **17**, 65423-57-6; 5α-**18**, 65423-58-7; 5β-**18**, 65451-49-2; 5α-**19**, 65423-59-8; 5β-**19**, 65451-50-5; 5α-**20**, 65423-60-1; 5β-**20**, 65451-51-6; **20** Me_3Si ether, 65423-61-2; (9*R*)-**21**, 65423-62-3; (9*S*)-**21**, 65451-52-7; (9*R*)-**22**, 65423-45-2; (9*S*)-**22**, 65451-47-0; **23**, 65423-46-3; **25**, 65451-48-1; **25** Me_3Si ester, 65423-47-4; *t*-$BuMe_2SiCl$, 18162-48-6; *m*-bromophenol, 591-20-8; acetic anhydride, 108-24-7; methyl bromoacetate, 96-32-2.

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