Synthesis and Biological Activity of a Novel 11a-Homo (Cyclohexyl) Prostaglandin

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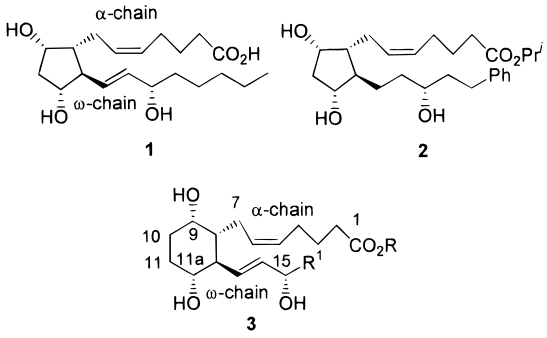
The racemic cyclohexane-for-cyclopentane ring substitution analogue of the potent prostaglandin FP agonist cloprostenol (**7**) was synthesized from cyclohexenediol **11** in 21 steps and 0.07% yield. In a prostaglandin FP receptor-linked second-messenger assay, racemic analogue **7** exhibited an EC_{50} value of 319 nM (72% response relative to cloprostenol); the corresponding values for $PGF_{2\alpha}$ and cloprostenol were 23 nM (91% relative response) and 1 nM (defined as 100% response), respectively. Key features of the synthesis were the selective manipulation of four hydroxyl groups to direct independent elaboration of the α and *ω* chains and a new method for synthesis of aryloxy-terminated *ω* chains involving Horner−Emmons elongation of an aldehyde to a methyl enone, regioselective bromination adjacent to the carbonyl, and phenoxide displacement of bromide.

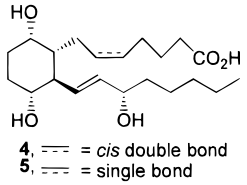
Introduction

Glaucoma, a leading cause of blindness in the developed world, is characterized by progressive degeneration of the optic nerve. While the disease process and causative factors thereof are not completely understood, it is known that high intraocular pressure (IOP), >21 mmHg, is an important risk factor positively correlated to loss of visual field resulting from nerve damage.[1] Certain compounds which are agonists at various prostaglandin receptors, such as $PGF_{2\alpha}$ (**1**), are known to be effective agents for lowering IOP in humans but frequently cause side effects such as conjunctival hyperemia, foreign-body sensation, and ocular pain.[2] The introduction of Xalatan (latanoprost, **2**), the corresponding acid of which is a potent and selective FP receptor agonist, as a clinically effective IOP-lowering agent devoid of many of the side effects of endogenous prostaglandins has been an important advance in the area.[3] As part of our research program directed toward the discovery of prostaglandin agonists as ocular hypotensives with reduced side effects,[4] we wish to report the synthesis and in vitro biological activity of a compound containing the 11a-homo (cyclohexyl) prostaglandin structural motif (**3**).

The replacement of the core cyclopentane ring of prostaglandin agonists with a cyclohexane ring should affect several physicochemical properties in a predictable fashion. First, the extra methylene group increases the lipophilicity of the molecule and the volume it occupies in the receptor binding site. Second, the well-known energetic preference of most cyclohexanes for a chair conformation with maximal equatorial placement of substituents contrasts with the more diffuse conformational population distribution of cyclopentanes;[5] thus, if the binding conformation of a cyclopentane FP agonist resembles a chair conformation of the corresponding cyclohexane, entropy considerations suggest that the cyclohexane analogue would be more potent. Third, the distances between several parts of the molecule would be expected to change (e.g., between the hydroxyl groups at carbons 9 and 11a). Cyclohexyl-for-cyclopentyl substitution could gauge the relative importance of these molecular features in affecting SAR.



We were mindful at the outset of our studies of two previously published reports concerning the synthesis of 11a-homo $PGF_{2\alpha}$ analogues **4**[6] and **5**.[7,8]



The authors' qualitative observations were that these ligands are less potent in the appropriate FP receptor-linked assay than is $PGF_{2\alpha}$. We felt that a better test for the viability of cyclohexyl FP receptor agonists would be to perform this modification on the a ligand known

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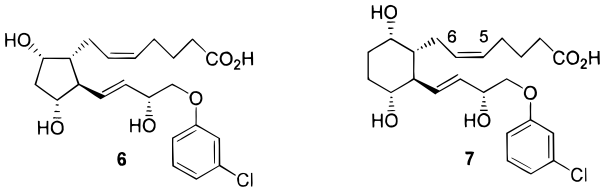
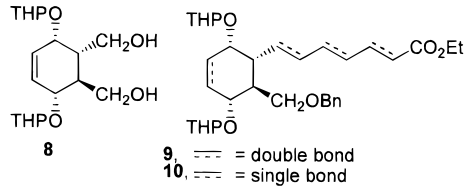
to be a more potent agonist at the FP receptor, namely cloprostenol (**6**).[9] Our target therefore was the cyclohexane analogue (**7**) of this compound.



Chemistry

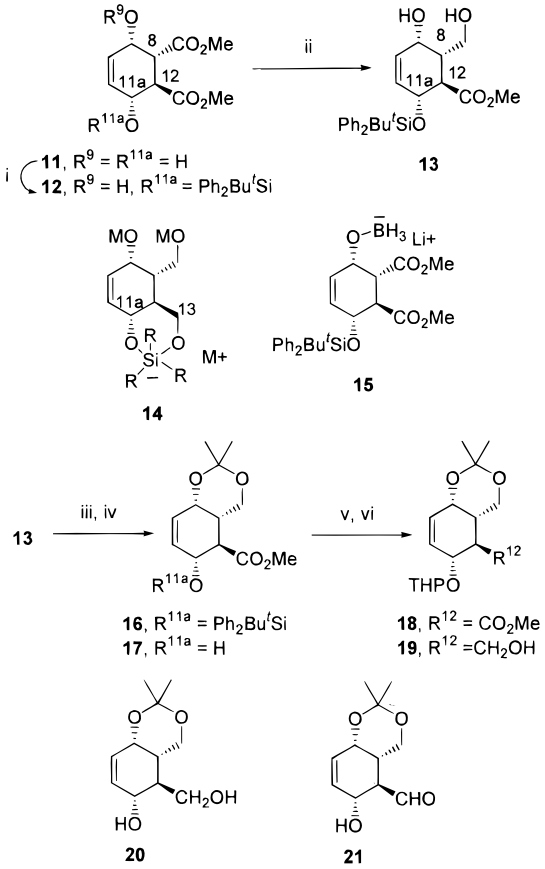
De Koning's synthesis of **5**[7] was appealingly simple: the cyclohexane core derived from the Diels–Alder cycloaddition of diacetoxybutadiene and dimethyl fumarate and the α and *ω* chains were installed using standard Horner–Emmons olefination chemistry. However, there were two significant problems with extending this strategy toward preparing **7**. First, efficient differential installation of the α and *ω* chains was hampered by the inability to protect selectively one of the two hydroxyls of intermediate **8**. Second, production of tetraene **9** by the Horner–Emmons condensation of triethyl phosphonosorbate with the appropriate aldehyde, followed by perhydrogenation to ester **10**, would not permit us to install the requisite cis-$\Delta^{5,6}$ olefin for **7**. Below we describe new methodology which allows efficient differential α and *ω* chain elaboration via selective hydroxyl protection and a new method for installing aryloxy-terminated *ω* chains.



Synthesis of 7. Cyclohexenediol **11**[7] was regioselectively silylated at the pseudoequatorial C-11a oxygen to afford **12** (Scheme 1).[10] Silylation of the pseudoaxial C-9 oxygen was not observed, even after 24 h in refluxing *N*,*N*-dimethylformamide (DMF). In contrast, tetrahydropyran-2-yl (THP) and methoxymethyl (MOM) protection proceeded nonselectively. The C-7 ester was reduced using $LiBH_4$ to afford diol **13**. Use of $LiAlH_4$, diisobutylaluminum hydride (DIBAL-H), or sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) resulted in reduction of the C-13 ester with concomitant desilylation of the C-11a position, probably facilitated by intramolecular silyl transfer[11] as depicted in **14**. The regioselectivity of the $LiBH_4$ reduction is likely due to intramolecular hydride delivery in alkoxyborohydride **15**.[12] This regioselective silylation–reduction sequence (**11** → **12** → **13**) allows efficient differentiation of the nascent α and *ω* chains.

The regiochemical result of this two-step procedure was determined by ^{1}H NMR spectroscopic analysis (200 MHz, $CDCl_3$) of **12** and **13**. For **12**, inspection of splitting patterns and coupling constants, together with decoupling experiments, permitted chemical shift assignment for the key protons at C-8 (δ = 2.87 ppm, dd, J = 4, 12 Hz), C-9 (δ = 4.38 ppm, m), C-11a (δ = 4.53 ppm, d, J = 9 Hz), and C-12 (δ = 3.12 ppm, dd, J = 9, 12 Hz). In **13**, H-8 appears at δ = 1.85 ppm, with couplings to an adjacent CH_2OH group, while the resonances for the protons at C-11a (δ = 4.58 ppm, d, J = 9 Hz) and C-12 (δ = 2.95 ppm, dd, J = 9, 12 Hz) were relatively unchanged.

Scheme 1[a]

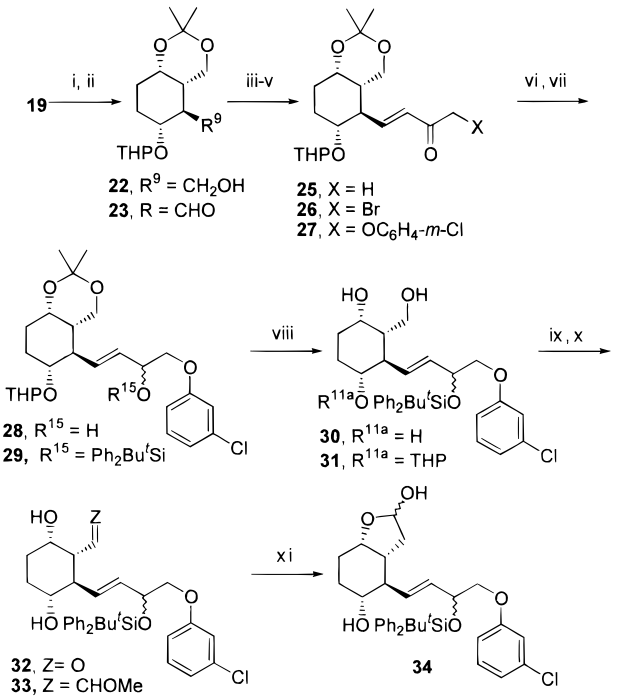


[a] (i) Ph_2Bu^tSiCl, DMF, imidazole, DMAP, imidazole, 82%; (ii) $LiBH_4$, THF, 84%; (iii) $Me_2C(OMe)_2$, *p*-TsOH, CH_2Cl_2, 86%; (iv) TBAF, THF, 80%; (v) DHP, *p*-TsOH, CH_2Cl_2, 98%; (vi) $LiAlH_4$, THF, 92%.

Protection of diol **13** afforded acetonide **16**, which was desilylated to alcohol **17** and reprotected as the C-11a THP ether **18**. Reduction of **18** to alcohol **19** was achieved using $LiAlH_4$. The protecting group interchange was necessary because desilylation invariably accompanied the reduction of **16** with a $LiAlH_4$, $LiBH_4$, DIBAL-H, or Red-Al, yielding diol **20**. Although **20** could be advanced to aldehyde **21**, the latter was too unstable to be of use.

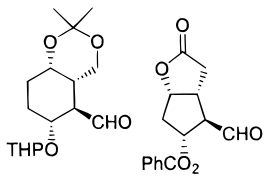
Hydrogenation of **19** was followed by oxidation of the resulting **22** to aldehyde **23** (Scheme 2). Attempted *ω* chain installation by Horner–Emmons condensation with dimethyl (3-chlorophenoxy)-2-oxopropylphosphonate under a variety of conditions afforded only recovered **23**. This result and the successful olefination of **23** using an alkyl-substituted *β*-ketophosphonate (vide infra) suggest that the addition of the phosphonate anion to the aldehyde is rate-limiting, with an alkyl-substituted *β*-ketophosphonate anion being reactive enough, and an aryloxy-substituted *β*-ketophosphonate anion being too stabilized, to add.[13] **23** is also markedly less reactive than cyclopentane aldehyde **24**, which readily condenses

Scheme 2[a]



[a] (i) H_2, Pd/C, EtOAC; (ii) Swern oxidation, 91% from **19**; (iii) $(MeO)_2P(O)CH_2C(O)CH_3$, NEt_3, LiCl, THF, 78%; (iv) TBSOTf, NEt_3, CH_2Cl_2, NBS, THF, 75%; (v) 3-chlorophenol, K_2CO_3, acetone, 48%; (vi) $NaBH_4$, $CeCl_3$, MeOH, 95%; (vii) Ph_2Bu^tSiCl, imidazole, DMAP, CH_2Cl_2, 86%; (viii) TsOH, THF, water, 38% of **30** and 36% of **31**; (ix) NCS, TEMPO, Na_2CO_3, CH_2Cl_2/water, Bu_4NCl, 39%; (x) $Ph_3P^+CH_2OMeCl^-$, $KOBu^t$, THF, 86%; (xi) TsOH, THf, water, 76%.

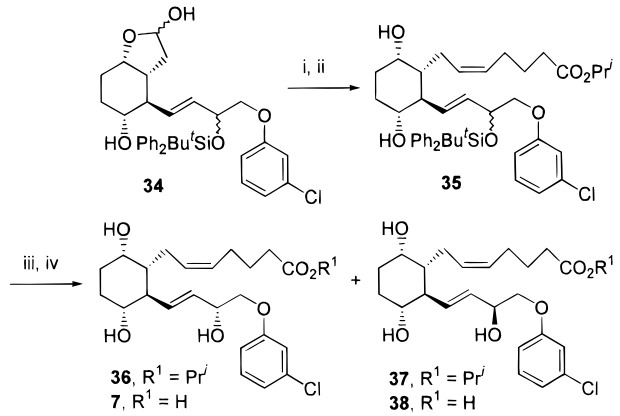
with both alkyl- and aryloxy-substituted β-ketophosphonates (LiCl, THF, NEt_3, 0 °C, 1 h).[4b]



These problems were eventually circumvented by exploiting the ability of 3-alkyl-substituted β-ketophosphonates to undergo successful Horner−Emmons olefination with **23**, coupled with the recognition that the C−O bond in the ω chain might be amenable to installation via phenoxide displacement of an α-halo ketone. In the event, olefination of **23** with dimethyl 2-(oxopropyl)phosphonate afforded methyl enone **25** (Scheme 3). Conversion of **25** to its kinetic silyl enol ether was followed by in situ bromination with NBS to provide α-bromo enone **26** in good yield. Treatment of **26** with 3-chlorophenol gave enone **27** containing the entire aryloxy-terminated ω chain. To the best of our knowledge, this type of procedure has not been disclosed previously in the prostaglandin synthetic literature and may find wider utility for constructing heteroatom-interrupted ω chains when the necessary phosphonate/phosphonium salt is not readily available and/or the Wittig procedure is unsuccessful.

Stereorandom 1,2-reduction of **27** gave allyl alcohol **28**,[15] which was silylated to yield fully protected **29**.

Scheme 3[a]



[a] (i) $Ph_3P^+(CH_2)_4CO_2HBr^-$, $KOBu^t$, THF; (ii) acetone, DBU, isopropyl iodide, 58% from **34**; (iii) TBAF, THF, 33% of **36** and 20% of **37**; (iv) LiOH, MeOH, water, 37% of **7** and 78% of **38**.

Table 1. FP Receptor Functional Response and Binding Data for **8**, **9**, **37**, and **52**

compd	EC_{50}[a] ± SEM,[b] nM	max response, %[c]	N[d]	K_i[e] ± SEM,[b] nM[f]	N[d]
6[g]	1.0 ± 0.1	100	105	31 ± 3	9
1[g]	23.0 ± 5.0	91	11	119 ± 9	25
7	319 ± 32	72	2	1900 ± 920	2
38	2750 ± 250	50	2	56000 ± 9100	2

[a] Concentration at which 50% of the maximal stimulation of phosphoinositide turnover is observed. [b] Standard error of the mean. [c] Relative to cloprostenol (**6**). [d] Number of times the ligand has been evaluated in this system; each evaluation is the average of a triplicate run. [e] Inhibition binding constant. [f] The correlation coefficient for $-\log EC_{50}$ and $-\log K_i$ data for the above compounds was $r = 0.97$, $p < 0.00025$. [g] Data from ref 20.

Removal of the THP and acetonide groups was accomplished under acidic conditions to afford triol **30** and partially deprotected **31**; the primary alcohol of the former was oxidized chemoselectively using Einhorn's procedure[16] to give aldehyde **32**. Wittig reaction of **32** afforded enol ether **33**, which was hydrolyzed to provide lactol **34**.

Wittig condensation of **34** with $Ph_3P^+(CH_2)_4CO_2H\ Br^-$ was followed by alkylation of the resulting ene carboxylic acid with isopropyl iodide to yield ester **35** (Scheme 3). Desilylation of **35** with tetra-*n*-butylammonium fluoride (TBAF) followed by chromatographic purification afforded triol **36** and the less polar diastereomer **37**. Saponification of **36** and **37** provided acids **7** and **38**. Initially we had tentatively assigned the relative stereochemistry at C-15 for these compounds based on their relative chromatographic mobilities, with the faster eluting ester (i.e., **37**) being assigned the "natural" 15α (15*S**) relative configuration.[17] However, we revised our assignment once the EC_{50} values for **7** and **38** were determined, with the more potent acid being assigned the natural C-15α relative configuration.[18]

Pharmacology

The acids **7** and **38** were evaluated for their ability to stimulate FP receptor-linked phosphoinositide turnover in Swiss 3T3 mouse fibroblast cells and to bind to an FP receptor expressed in bovine corpus luteum, as per our recently published procedure.[9c] Table 1 summarizes the data, with inclusion of data for cyclopentane prostaglandins **1** and **6** for comparison purposes.

Two features worthy comment. First, note that **7** and **38** were synthesized as racemic mixtures, while **1** and **6** were tested as enantiomerically homogeneous samples. If it were assumed that the active enantiomer for the synthesized analogues accounted for all of the biological activity,[19] the effective EC_{50} values for **7** and **38** for direct comparison would be one-half those indicated in the table. Second, because of the somewhat equivocal relationship between C-15 relative stereochemistry and biological activity,[18] the C-15 relative stereochemical assignment should be considered tentative.

Conclusion

The cyclohexane-for-cyclopentane substitution analogue of the potent prostaglandin FP agonist cloprostenol was synthesized in 21 steps and 0.07% yield from cyclohexenediol **11**. This substitution leads to roughly a 300-fold drop in activity at the FP receptor. This indicates that the binding conformation of FP receptor agonists probably does not resemble closely a chairlike array typical of a cyclohexane and/or that the receptor volume occupied or the lipophilicity of the cyclohexane analogues has increased beyond an optimal value. Nevertheless, **7** is a sub-micromolar (partial) agonist at the FP receptor being only about 14 times less potent than $PGF_{2\alpha}$.[21]

Experimental Section

Chemistry: General Methods. All ^{1}H NMR spectra were acquired on a Varian Gemini 200 spectrometer operating at a field strength of 200 MHz. All ^{13}C NMR and DEPT spectra were acquired on the same instrument operating at a field strength of 50.4 MHz. For reactions without added water, solvents used were anhydrous grade from Aldrich Chemical Co. and were used without further purification. Unless otherwise stated, all reactions without added water were run under a positive pressure of nitrogen. Concentration refers to removal of solvent in vacuo on a rotary evaporator. Reactions were monitored by TLC on E. Merck silica gel 60 F_{254} plates, with visualization by UV light, or either phosphomolybdic acid or 2% aqueous $KMnO_4$ staining. Column chromatographic purifications were performed under positive air flow using 230−400 mesh silica gel from E.M. Science. Chromatography solvents used were HPLC grade from E.M. Science. Low-resolution mass spectra were acquired on a Finnegan TSQ 46 triple quadrupole mass spectrometer operating in the positive electrospray mode. High-resolution mass spectra were acquired in the FAB mode by Analytical Instrument Group, Raleigh, NC.

(1α,2α,3*β*,4α)-4-(*tert*-Butyldiphenylsiloxy)-2,3-bis-(methoxycarbonyl)cyclohex-5-en-1-ol (12). To a solution of diol **11**[7] (8.55 g, 37.2 mmol), imidazole (3.87 g, 56.9 mmol), 4-(dimethylamino)pyridine (DMAP; 630 mg, 5.16 mmol), and DMF (60 mL) was added *tert*-butyldiphenylsilyl chloride (TBDPSCl; 13.7 g, 49.9 mmol). After 4 h saturated NH_4Cl (80 mL) was added, the solution was extracted with ethyl acetate (3 × 90 mL), the combined organic layers were washed with water (2 × 100 mL) and saturated NaCl (2 × 100 mL), dried ($MgSO_4$), and concentrated, and the residue was chromatographed on a 22-cm tall × 53-mm diameter silica gel column eluting with 40% ethyl acetate in hexane to afford **12** as a viscous oil (14.27 g, 82%): ^{1}H NMR ($CDCl_3$) δ 7.72−7.62 (m, 4H), 7.45−7.30 (m, 6H), 5.65−5.60 (m, 2H), 4.53 (d, J = 9 Hz, 1H), 4.43−4.32 (m, 1H), 3.70 (s, 3H), 3.69 (s, 3H), 3.12 (dd, J = 12, 9 Hz, 1H), 2.87 (dd, J = 12, 4 Hz, 1H), 2.04 (d, J = 6 Hz, 1H), 1.02 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 174.64 (C), 171.88 (C), 136.02 (CH), 135.93 (CH), 134.02 (C), 133.94 (CH), 132.97 (C), 129.95 (CH), 129.85 (CH), 127.78 (CH), 127.65 (CH), 126.80 (CH), 71.74 (CH), 63.73 (CH), 52.22 (CH_3), 52.04 (CH_3), 47.27 (CH), 45.68 (CH), 26.77 (CH_3), 19.38 (C); MS *m*/*z* calcd for $C_{26}H_{33}O_6Si$ [$(M + H)^+$] 469.204215, found 469.20422.

(1α,2α,3*β*,4α)-4-(*tert*-Butyldiphenylsiloxy)-2-(hydroxymethyl)-3-(methoxycarbonyl)cyclohex-5-en-1-ol (13). To a suspension of lithium borohydride (1.10 g, 52.4 mmol) in THF (50 mL) at 0 °C (bath temperature) was added a solution of **12** (14.27 g, 30.5 mmol) in THF (30 mL). After 2 h, the mixture was warmed to room temperature; and after 3 additional h, the solution was recooled to 0 °C (bath temperature). The reaction was then quenched by the dropwise addition of methanol (3 mL) and saturated citric acid (5 mL), each added over 15 min. The solution was warmed to room temperature, water was added (50 mL), the mixture was extracted with ethyl acetate (3 × 100 mL), dried ($MgSO_4$), filtered, and concentrated, and the residue was chromatographed on a 16-cm tall × 53-mm diameter silica gel column eluting with a 3:2 ethyl acetate:hexane to straight ethyl acetate gradient to afford **13** (11.24 g, 84%): ^{1}H NMR ($CDCl_3$) δ 7.78−7.62 (m, 4H), 7.50−7.30 (m, 6H), 5.64 (br s, 2H), 4.58 (d, J = 9 Hz, 1H), 4.25−4.17 (m, 1H), 3.85−3.40 (m, 2H), 3.64 (s, 3H), 2.95 (dd, J = 12, 9 Hz, 1H), 2.53 (t, J = 6 Hz, 1H), 2.28 (d, J = 6 Hz, 1 H), 1.90−1.78 (m, 1H), 1.01 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 174.67 (C), 136.04 (CH), 135.94 (CH), 134.02 (C), 133.77 (CH), 133.14 (C), 129.90 (CH), 129.82 (CH), 127.73 (CH), 126.67 (CH), 127.63 (CH), 71.69 (CH), 65.68 (CH), 63.24 (CH_2), 51.90 (CH_3), 46.70 (CH), 41.71 (CH), 26.82 (CH_3), 19.32 (C); MS *m*/*z* calcd for $C_{25}H_{33}O_5Si$ [$(M + H)^+$] 441.209906, found 441.20990.

(1α,6α,7*β*,8α)-8-(*tert*-Butyldiphenylsiloxy)-3,3-dimethyl-2,4-dioxa-7-(methoxycarbonyl)bicyclo[4.4.0]dec-9-ene (16). To a solution of **13** (11.24 g, 25.5 mmol) and 2,2-dimethoxypropane (3.71 g, 35.6 mmol) in CH_2Cl_2 (40 mL) at 0 °C (bath temperature) was added *p*-toluenesulfonic acid monohydrate (TsOH; 474 mg, 2.49 mmol). After 1 h, NEt_3 was added (500 mg, 5 mmol), saturated $NaHCO_3$ was added (50 mL), the phases were separated, the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL), the combined organic layers were dried ($MgSO_4$), filtered, and concentrated, and the residue was chromatographed on a 17-cm tall × 53-mm diameter silica gel column eluting with 30% ethyl acetate in hexane to afford **16** (10.5 g, 86%): ^{1}H NMR ($CDCl_3$) δ 7.75−7.60 (m, 4H), 7.43−7.30 (m, 6H), 5.72 (apparent doublet, J = 10 Hz, 1H), 5.59−5.48 (m, 1H), 4.55 (d, J = 9 Hz, 1H), 4.21−4.15 (m, 1H), 3.96 (dd, J = 12, 4 Hz, 1H), 3.64 (s, 3H), 3.50 (dd, J = 12, 3 Hz, 1H), 3.19 (dd, J = 12, 9 Hz, 1H), 1.75−1.62 (m, 1H), 1.43 (s, 6H), 1.00 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 175.14 (C), 136.04 (CH), 135.99 (CH), 134.00 (C), 133.20 (C), 129.83 (CH), 129.69 (CH), 127.68 (CH), 127.57 (CH), 125.36 (CH), 99.39 (C), 71.85 (CH), 62.79 (CH), 61.63 (CH_2), 51.79 (CH_3), 47.12 (CH), 35.28 (CH), 26.82 (CH_3), 19.90 (C), 19.35 (CH_3); MS *m*/*z* calcd for $C_{28}H_{36}O_5$ (M^+) 480.233378, found 480.23336.

(1α,6α,7*β*,8α)-3,3-Dimethyl-2,4-dioxa-7-(methoxycarbonyl)bicyclo[4.4.0]dec-9-en-8-ol (17). To a solution of **16** (10.5 g, 21.8 mmol) in THF (35 mL) was added a 1 M solution of tetra-*n*-butylammonium fluoride (TBAF) in THF (28 mL, 28 mmol). After 2.5 h, saturated NH_4Cl was added (45 mL), the solution was extracted with ethyl acetate (3 × 70 mL), dried ($MgSO_4$), filtered, and concentrated, and the residue was chromatographed on an 18-cm tall × 53-mm diameter silica gel column eluting with a 40% ethyl acetate in hexane to straight ethyl acetate gradient to afford **17** contaminated with some *tert*-butyldiphenylsilyl fluoride (4.04 g total, 80% nominal yield): ^{1}H NMR ($CDCl_3$) δ 5.95 (apparent doublet, J = 8 Hz, 1H), 5.82−5.75 (m, 1H), 4.42 (t, J = 8 Hz, 1H), 4.35−4.29 (m, 1H), 4.06 (dd, J = 9, 3 Hz, 1H), 3.77 (s, 3H), 3.61 (dd, J = 9, 2 Hz, 1H), 2.98 (dd, J = 9, 2 Hz, 1H), 1.94 (d, J = 5 Hz, 1H), 1.88−1.77 (m, 1H), 1.46 (s, 3H), 1.40 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 174.86 (C), 134.87 (CH), 126.40 (CH), 99.37 (C), 69.87 (CH), 62.82 (CH), 61.84 (CH_2), 52.05 (CH_3), 46.90 (CH), 34.84 (CH), 28.56 (CH_3); MS *m*/*z* calcd for $C_{12}H_{19}O_5$ [$(M + H)^+$] 243.12245, found 243.12245.

(1α,6α,7*β*,8α)-3,3-Dimethyl-2,4-dioxa-7-(methoxycarbonyl)-8-(tetrahydropyran-2-yloxy)bicyclo[4.4.0]dec-9-ene (18). To a solution of **17** (4.54 g, 18.8 mmol) and 3,4-dihydro-2*H*-pyran (1.94 g, 23.0 mmol) in CH_2Cl_2 (40 mL) at 0 °C (bath

temperature) was added TsOH (336 mg, 1.77 mmol). After 30 min, NEt_3 was added (210 mg, 2.1 mmol), the mixture was concentrated, and the residue was chromatographed on 14-cm tall × 53-mm diameter silica gel column eluting with 40% ethyl acetate in hexane to provide **18** (6.00 g, 98%): MS *m/z* calcd for $C_{17}H_{27}O_6$ [$(M + H)^+$] 327.180623, found 327.18063.

(1α,6α,7β,8α)-3,3-Dimethyl-2,4-dioxa-7-(hydroxymethyl)-8-(tetrahydropyran-2-yloxy)bicyclo[4.4.0]dec-9-ene (19). To a suspension of lithium aluminum hydride (1.20 g, 31.6 mmol) in THF (25 mL) at 0 °C (bath temperature) was added dropwise a solution of **18** (5.99 g, 18.4 mmol) in THF (35 mL). After 2 h, methanol (10 mL) was added dropwise over a 15 min period, followed by saturated NH_4Cl (80 mL). The mixture was warmed to room temperature and extracted with ethyl acetate (3 × 100 mL), dried ($MgSO_4$), filtered, and concentrated to afford **19** (5.07 g, 92%): MS *m/z* calcd for $C_{16}H_{27}O_5$ [$(M + H)^+$] 299.185867, found 299.18585.

(1α,6α,7β,8α)-3,3-Dimethyl-2,4-dioxa-7-(hydroxymethyl)-8-(tetrahydropyran-2-yloxy)bicyclo[4.4.0]decane (22). A suspension of **19** (5.07 g, 17.0 mmol) and 10% w/w Pd/C (502 mg) in ethyl acetate (75 mL) was stirred under 1 atm of hydrogen gas overnight, filtered through Celite, and concentrated to afford 5.33 g of an oil containing **22** and about 5 wt % ethyl acetate, which was used in the next step without further purification: MS *m/z* calcd for $C_{16}H_{28}O_5$ (M^+) 300.19288, found 300.19287.

(1α,6α,7β,8α)-3,3-Dimethyl-2,4-dioxa-7-formyl-8-(tetrahydropyran-2-yloxy)bicyclo[4.4.0]decane (23). To a solution of oxalyl chloride (4.07 g, 32.1 mmol) in methylene chloride (20 mL) at −78 °C (bath temperature) was added dropwise over 15 min a solution of DMSO (3.5 g, 45 mmol) in CH_2Cl_2 (5 mL). After 40 min, a solution of **22** in CH_2Cl_2 (28 mL) was added dropwise over 10 min. After an additional 1 h, NEt_3 (8.13 g, 80.5 mmol) was added dropwise over 5 min, the white suspension was stirred at −78 °C for an additional 10 min and then warmed to room temperature, saturated NH_4Cl (40 mL) was added, the phases were separated, the aqueous layer was extracted with CH_2Cl_2 (2 × 75 mL), dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed on a 13-cm tall × 53-mm diameter silica gel column eluting with 40% ethyl acetate in hexane to afford **23** (4.61 g, 91% two-step yield from **19**): MS *m/z* calcd for $C_{16}H_{26}O_5$ (M^+) 298.17803, found 298.17804.

[1α,6α,7β(1*E*),8α]-3,3-Dimethyl-2,4-dioxa-7-(3-oxobutenyl)-8-(tetrahydropyran-2-yloxy)bicyclo[4.4.0]decane (25). To a solution of THF (50 mL), NEt_3 (5.37 g, 53.2 mmol), LiCl (2.59 g, 61.7 mmol), and dimethyl (2-oxopropyl)phosphonate (10.34 g, 62.3 mmol) was added a solution of aldehyde **23** (5.27 g, 17.7 mmol). After 72 h the reaction was quenched by the addition of saturated NH_4Cl (50 mL). Saturated NaCl (75 mL) was added, the layers were separated, the aqueous phase was extracted with ethyl acetate (2 × 200 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The residue was chromatographed on a 15-cm tall × 40-mm diameter silica gel column eluting with 2:1 hexane: ethyl acetate to afford **25** [4.66 g, 78%, R_f = 0.3 (40% ethyl acetate in hexane eluent)], as well as recovered **23** (808 mg, 15%; yield of **25** based on recovered starting material = 92%): MS *m/z* calcd for $C_{19}H_{31}O_5$ [$(M + H)^+$] 339.21719, found 339.21719.

[1α,6α,7β(1*E*),8α]-3,3-Dimethyl-2,4-dioxa-7-(4-bromo-3-oxobutenyl)-8-(tetrahydropyran-2-yloxy)bicyclo[4.4.0]-decane (26). To a solution of **25** (4.65 g, 13.7 mmol) and NEt_3 (2.18 g, 21.6 mmol) in CH_2Cl_2 (65 mL) at 0 °C (bath temperature) was added dropwise over 8 min *tert*-butyldimethylsilyl trifluoromethanesulfonate (4.72 g, 17.9 mmol). TLC analysis of the reaction after 30 min showed that no starting material remained and that a new spot attributable to the kinetic silyl dienol ether, R_f = 0.75 (40% ethyl acetate in hexane eluent), had appeared. After 1 h recrystallized (from water) *N*-bromosuccinimide (2.69 g, 15.1 mmol) was added dropwise as a solution in THF (35 mL) over 7 min. TLC analysis of the reaction after 8 min showed the predominant appearance of a new spot, R_f = 0.41 (40% ethyl acetate in hexane eluent), assignable to the product α-bromo ketone. After 20 min saturated $NaHCO_3$ (30 mL) and saturated NaCl (30 mL) were added, the layers were separated, the aqueous phase was extracted with CH_2Cl_2 (2 × 75 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed on a 15-cm tall × 40-mm diameter silica gel column eluting with 2:1 hexane:ethyl acetate to afford **26** (4.26 g, 75%): MS *m/z* (relative intensity) 441 [100, $(M + Na)^+$ for ^{79}Br], 439 [100, $(M + Na)^+$ for ^{81}Br].

[1α,6α,7β(1*E*),8α]-3,3-Dimethyl-2,4-dioxa-7-[4-(3-chlorophenoxy)-3-oxobutenyl]-8-(tetrahydropyran-2-yloxy)-bicyclo[4.4.0]decane (27). A solution of **26** (4.25 g, 10.2 mmol), acetone (150 mL), K_2CO_3 (1.92 g, 13.9 mmol), and 3-chlorophenol (1.65 g, 12.8 mmol) was vacuum degassed, refilled with argon, and refluxed under a nitrogen atmosphere for 16 h. The reaction was cooled to room temperature, saturated brine (100 mL) was added, and the solution was extracted with ethyl acetate (3 × 150 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated, and the residue was chromatographed on a 15-cm tall × 40-mm diameter silica gel column eluting with 40% ethyl acetate in hexane to provide **27** (2.27 g, 48%): MS *m/z* calcd for $C_{25}H_{33}O_6ClNa$ [$(M + Na)^+$] 487.186426, found 487.18643.

[1α,6α,7β(1*E*,3*R*S),8α]-3,3-Dimethyl-2,4-dioxa-7-[4-(3-chlorophenoxy)-3-hydroxybutenyl]-8-(tetrahydropyran-2-yloxy)bicyclo[4.4.0]decane (28).** To a 0 °C (bath temperature) solution, open to air, of methanol (30 mL), cerium trichloride heptahydrate (2.54 g, 6.82 mmol), and **27** (2.26 g, 4.86 mmol) was added $NaBH_4$ (231 mg, 6.08 mmol) in 4 portions over 4 min. After 30 min the reaction was quenched by the cautious addition of saturated NH_4Cl (25 mL), the solution was warmed to room temperature, saturated NaCl (25 mL) was added, and the mixture was extracted with ethyl acetate (3 × 35 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to afford **28** [2.15 g, 95%; R_f = 0.27 (40% ethyl acetate in hexane eluent)] as a white foam: MS *m/z* calcd for $C_{25}H_{35}O_6ClNa$ [$(M + Na)^+$] 467.219969, found 467.21997.

[1α,6α,7β(1*E*,3*R*S),8α]-3,3-Dimethyl-2,4-dioxa-7-[4-(3-chlorophenoxy)-3-(*tert*-butyldiphenylsiloxy)butenyl]-8-(tetrahydropyran-2-yloxy)bicyclo[4.4.0]decane (29).** To a solution of **28** (2.15 g, 4.60 mmol), CH_2Cl_2 (19 mL), 4-(dimethylamino)pyridine (131 mg, 1.07 mmol), and imidazole (421 mg, 6.19 mmol) was added *tert*-butylchlorodiphenylsilane (1.58 g, 5.76 mmol). After 17 h saturated NH_4Cl (25 mL) was added, the layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated, and the residue was chromatographed on a 15-cm tall × 40-mm diameter silica gel column eluting with 20% ethyl acetate in hexane to provide **29** [2.80 g, 86%; R_f = 0.78 (40% ethyl acetate in hexane)]: MS *m/z* calcd for $C_{41}H_{53}O_6ClSiNa$ [$(M + Na)^+$] 727.319797, found 727.31982.

(13*E*)-(8*R,9*S**,11a*R**,12*R**,15*R*S**)-15-(*tert*-Butyldiphenylsiloxy)-16-(3-chlorophenoxy)-9,11a-dihydroxy-2,3,4,5,6,7,17,18,19,20-decanor-11a-homo-13-prosten-1-ol (30) and (13*E*)-(8*R**,9*S**,11a*R**,12*R**,15*R*S**)-15-(*tert*-Butyldiphenylsiloxy)-16-(3-chlorophenoxy)-9-hydroxy-11a-(tetrahydropyran-2-yloxy)-2,3,4,5,6,7,17,18,19,20-decanor-11a-homo-13-prosten-1-ol (31).** A solution of **29** (3.38 g, 4.79 mmol), THF (40 mL), water (7 mL), and *p*-toluenesulfonic acid monohydrate (382 mg, 2.01 mmol) was vacuum degassed with argon refill and refluxed under nitrogen for 4 h. The solution was cooled to room temperature, saturated $NaHCO_3$ (25 mL) and saturated NaCl (40 mL) were added, and the mixture was extracted with ethyl acetate (3 × 65 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated, and the residue was chromatographed on a 15 cm tall × 40 mm diameter silica gel column eluting with 60% ethyl acetate in hexane to afford the fully deprotected product **30** [1.19 g, 38%; R_f = 0.25 (60% ethyl acetate in hexane eluent)], the partially deprotected compound **31** [1.04 g, 29%; R_f = 0.4 (60% ethyl acetate in hexane eluent)], and a mixture of the two compounds (248 mg, 7%; total yield = 74%). For **30:** MS *m/z*

calcd for $C_{33}H_{41}O_5SiClNa$ [$(M + Na)^+$] 603.230716, found 603.23071. For **31:** MS *m/z* calcd for $C_{38}H_{50}O_6SiCl$ [$(M + H)^+$] 665.306031, found 665.30603.

(13*E*)-(8*R,9*S**,11a*R**,12*R**,15*R***S**)-15-(*tert*-Butyldiphenylsiloxy)-16-(3-chlorophenoxy)-9,11a-dihydroxy-2,3,4,5,6,7,17,18,19,20-decanor-11a-homo-13-prostenal (32).** To a vigorously stirring solution of **30** (1.19 g, 2.05 mmol), CH_2Cl_2 (22 mL). water (22 mL), Na_2CO_3 (130 mg, 1.22 mmol), Bu_4NCl (108 mg, 0.39 mmol), and 2,2,6,6-tetramethyl-*N*-piperidinyloxy free radical (TEMPO; 54 mg, 0.35 mmol) was added *N*-chlorosuccinimide (342 mg, 2.56 mmol) in one portion. After 2 h saturated $Na_2S_2O_3$ (10 mL) was added, the layers were separated, the aqueous phase was extracted with CH_2Cl_2 (2 × 25 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed on a 20-cm tall × 41-mm diameter silica gel column eluting with a 1:1 → 3:2 ethyl acetate:hexane gradient to afford **32** (459 mg, 39%): MS *m/z* calcd for $C_{33}H_{39}O_5SiClNa$ [$(M + Na)^+$] 601.215364, found 601.21539.

(13*E*)-(8*R,9*S**,11a*R**,12*R**,15*R***S**)-15-(*tert*-Butyldiphenylsiloxy)-16-(3-chlorophenoxy)-9,11a-dihydroxy-3,4,5,6,7,17,18,19,20-nonanor-11a-homo-1,13-prostadien-1-yl Methyl Ether (33).** To a suspension of $Ph_3P^+CH_2OCH_3\ Cl^-$ (1.10 g, 3.22 mmol) in THF (6 mL) at 0 °C (bath temperature) was added a 1 M solution of potassium *tert*-butoxide in THF (3.1 mL, 3.1 mmol). After 15 min a solution of **32** (450 mg, 0.78 mmol) in THF (6 mL) was added dropwise over 3 min. After one additional hour saturated KH_2PO_4 (15 mL) was added and the solution was warmed to room temperature. The mixture was extracted with ethyl acetate (3 × 25 mL), dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed on an 18-cm tall × 26-mm diameter silica gel column eluting with 1:1 ethyl acetate:hexane to afford **33** (406 mg, 86%): MS *m/z* calcd for $C_{35}H_{43}O_5SiClNa$ [$(M + Na)^+$] 629.246380, found 629.24640.

[1α,2*β*(1*E*,3*R*S**),3α,6α,8α*β*]-2-[3-(*tert*-Butyldiphenylsiloxy)-4-(3-chlorophenoxy)butenyl]-3,8-dihydroxy-7-oxabicyclo[3.3.0]nonane (34).** A solution of **33** (400 mg, 0.66 mmol), *p*-toluenesulfonic acid monohydrate (55 mg, 0.29 mmol), THF (12 mL), and water (4 mL) was vacuum degassed and refilled with argon. The mixture was then heated to reflux under a nitrogen atmosphere for 4 h. After cooling to room temperature, the solution was added to saturated $NaHCO_3$ (20 mL) and was extracted with ethyl acetate (3 × 25 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated, and the residue was chromatographed on a 26-cm tall × 26-mm diameter silica gel column eluting with a 1:1 → 3:2 ethyl acetate:hexane gradient to afford **34** (299 mg, 76%): MS *m/z* calcd for $C_{34}H_{41}O_5SiClNa$ [$(M + Na)^+$] 615.231167, found 615.23114.

(5*Z*,13*E*)-(8*R,9*S**,11a*R**,12*R**,15*R***S**)-15-(*tert*-Butyldiphenylsiloxy)-16-(3-chlorophenoxy)-9,11a-dihydroxy-17,18,19,20-tetranor-11a-homo-5,13-prostadienoic Acid Isopropyl Ester (35).** To a suspension of $Ph_3P^+(CH_2)_4CO_2H\ Br^-$ (458 mg, 2.16 mmol) in THF (6 mL) at 0 °C (bath temperature) was added a 1 M solution of potassium *tert*-butoxide in THF (3.3 mL, 3.3 mmol). After 15 min a solution of **34** (294 mg, 0.50 mmol) in THF (6 mL) was added. After an additional 1 h the reaction was warmed to room temperature and was quenched by the addition of 0.66 M citric acid (8 mL) to adjust the pH of the mixture to between 3 and 4. The solution was extracted with $CHCl_3$ (3 × 17 mL), the combined organic layers were washed with water (2 × 6 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was dissolved in acetone (12 mL) and the solution was cooled to 0 °C (bath temperature). DBU (600 mg, 3.94 mmol) was added, followed by the addition of isopropyl iodide (670 mg, 3.94 mmol) after an additional 30 min. The reaction was warmed to room temperature and was stirred for 72 h. Saturated citric acid was added (15 mL) and the mixture was extracted with 2:3 ethyl acetate:hexane (3 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated, and the residue was chromatographed on a 25-cm tall × 26-mm diameter silica gel column eluting with 2:3 ethyl acetate:hexane to afford **35** (210 mg, 58% from **34**): MS *m/z* calcd for $C_{42}H_{55}O_6SiClNa$ [$(M + Na)^+$] 741.334543, found 741.33453.

(5*Z*,13*E*)-(8*R,9*S**,11a*R**,12*R**,15*R**)-16-(3-Chlorophenoxy)-9,11a,15-trihydroxy-17,18,19,20-tetranor-11a-homo-5,13-prostadienoic Acid Isopropyl Ester (36) and (5*Z*,13*E*)-(8*R**,9*S**,11a*R**,12*R**,15*S**)-16-(3-Chlorophenoxy)-9,11a,15-trihydroxy-17,18,19,20-tetranor-11a-homo-5,13-prostadienoic Acid Isopropyl Ester (37).** To a solution of **35** (205 mg, 0.28 mmol) in THF (3 mL) was added a 1 M solution of tetra-*n*-butylammonium fluoride in THF (0.75 mL, 0.75 mmol). After 2 h saturated KH_2PO_4 was added (4 mL) and the solution was extracted with ethyl acetate (4 × 4 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated, and the residue was chromatographed on a 32-cm tall × 26-mm diameter silica gel column eluting with 20% hexane in ethyl acetate to afford **36** (43.9 mg, 33%) and **37** (27.5 mg, 20%). For **36:** ^{13}C NMR ($CDCl_3$) δ 173.56 (C), 159.28 (C), 135.06 (C), 134.83 (CH), 132.90 (CH), 130.30 (CH), 130.22 (CH), 128.88 (CH), 121.21 (CH), 115.07 (CH), 113.07 (CH), 72.60 (CH), 71.61 (CH_2), 70.87 (CH), 67.68 (CH), 65.30 (CH), 49.36 (CH), 44.35 (CH), 33.93 (CH_2), 31.08 (CH_2), 27.32 (CH_2), 26.56 (CH_2), 24.90 (CH_2), 21.80 (CH_3); MS *m/z* calcd for $C_{26}H_{37}O_6ClNa$ [$(M + Na)^+$] 503.217681, found 503.21820. For **37:** ^{13}C NMR ($CDCl_3$) δ 173.64 (C), 159.13 (C), 134.91 (C), 133.96 (CH), 133.15 (CH), 130.29 (CH), 128.86 (CH), 121.83 (CH), 115.03 (CH), 113.09 (CH), 72.35 (CH), 71.62 (CH_2), 70.30 (CH), 67.77 (CH), 65.32 (CH), 49.51 (CH), 44.45 (CH), 33.83 (CH_2), 31.03 (CH_2), 27.52 (CH_2), 26.99 (CH_2), 26.53 (CH_2), 24.84 (CH_2), 21.81 (CH_3); MS *m/z* calcd for $C_{26}H_{37}O_6ClNa$ [$(M + Na)^+$] 503.217681, found 503.21768.

(5*Z*,13*E*)-(8*R,9*S**,11a*R**,12*R**,15*R**)-16-(3-Chlorophenoxy)-9,11a,15-trihydroxy-17,18,19,20-tetranor-11a-homo-5,13-prostadienoic Acid (7).** A solution of **36** (29.0 mg, 0.0603 mmol), methanol (1.5 mL), and 0.5 M LiOH (0.5 mL, 0.25 mmol) was stirred for 24 h. The reaction was quenched by the addition of 0.5 M citric acid (1.50 mL, 0.75 mmol), extracted with $CHCl_3$ (3 × 3 mL), and the combined organic layers were washed with water (2 × 2 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was dissolved in acetonitrile (3 mL), filtered through a 0.45-μm nylon syringe filter to remove insolubles, and concentrated to afford **7** (9.8 mg, 37%): ^{13}C NMR ($CDCl_3$) δ 177.34 (C), 159.24 (C), 134.90 (C), 134.57 (CH), 132.80 (CH), 130.31 (CH), 128.85 (CH), 121.35 (CH), 115.14 (CH), 113.12 (CH), 72.62 (CH), 71.46 (CH_2), 70.81 (CH), 65.37 (CH), 49.52 (CH), 44.58 (CH), 32.90 (CH_2), 30.97 (CH_2), 27.24 (CH_2), 26.36 (CH_2), 26.41 (CH_2); MS *m/z* calcd for $C_{23}H_{31}O_6ClNa$ [$(M + Na)^+$] 461.170020, found 461.17047.

(5*Z*,13*E*)-(8*R,9*S**,11a*R**,12*R**,15*S**)-16-(3-Chlorophenoxy)-9,11a,15-trihydroxy-17,18,19,20-tetranor-11a-homo-5,13-prostadienoic Acid (38).** A solution of **37** (19.3 mg, 0.04 mmol), methanol (1.0 mL), and 0.5 M LiOH (0.33 mL, 0.16 mmol) was stirred for 24 h. The reaction was quenched by the addition of 0.5 M citric acid (0.96 mL, 0.48 mmol) and the mixture was extracted with $CHCl_3$ (3 × 3 mL). The combined organic layers were washed with water (2 × 2 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was dissolved in acetonitrile (3 mL), filtered through a 0.45-μm nylon syringe filter to remove insolubles, and concentrated to afford **38** (13.7 mg, 78%): ^{13}C NMR ($CDCl_3$) δ 176.89 (C), 159.12 (C), 134.94 (C), 134.56 (CH), 132.70 (CH), 130.34 (CH), 130.25 (CH), 128.81 (CH), 121.47 (CH), 115.12 (CH), 113.16 (CH), 72.38 (CH), 71.45 (CH_2), 70.75 (CH), 65.28 (CH), 49.70 (CH), 44.70 (CH), 32.36 (CH_2), 30.90 (CH_2), 27.11 (CH_2), 26.16 (CH_2), 24.34 (CH_2); MS *m/z* calcd for $C_{23}H_{31}O_6ClNa$ [$(M + Na)^+$] 461.170020, found 461.17001.

Pharmacology: General Methods. FP receptor binding assay: The bovine corpus luteum has been shown to express high-affinity [^{3}H]$PGF_{2\alpha}$ binding sites, in addition to [^{3}H]PGE_2 binding, which appear to have pharmacological characteristics of FP receptors.[19] Washed total particulate bovine corpus luteum membranes (20 mg/mL final) were incubated with [^{3}H]$PGF_{2\alpha}$ (0.9−1.5 nM) in Krebs buffer (pH 7.4) for 2 h at 23 °C in a total volume of 500 mL. Nonspecific

binding was defined with 1−10 μM unlabeled $PGF_{2\alpha}$ or fluprostenol. The assays were terminated by vacuum filtration (using Whatman GF/B glass fiber filter previously soaked in 0.3% polyethylenimine) and the data analyzed by a nonlinear, iterative, curve-fitting computer program.[19]

FP receptor-mediated phosphoinositide turnover assay: [^{3}H]Inositol phosphates ([^{3}H]-IPs) produced by agonist-mediated activation of phospholipase C in Swiss 3T3 cells expressing FP receptors were quantified by previously published procedures.[9c] Briefly, confluent 3T3 cells were exposed to 1.0−1.5 μCi of [^{3}H]-*myo*-inositol (18.3 Ci/mmol) in 0.5 mL of DMEM for 24−30 h at 37 °C. Then cells were rinsed once with DMEM/F-12 containing 10 mM LiCl, and the agonist stimulation experiment was performed in 0.5 mL of the same medium to facilitate accumulation of [^{3}H]IPs. Cells were exposed to the agonist or solvent for 60 min at 37 °C (triplicate determinations), followed by aspiration of the medium and immediate addition of 1 mL of ice-cold 0.1 M formic acid. The plates were kept cold and then frozen. Samples frozen up to one week were thawed prior to chromatographic separation of radiolabeled components. The cell lysates (0.9 mL) were loaded on columns packed with approximately 1 mL of AG 1-X8 anion-exchange resin. The elution procedure consisted of a wash with 10 mL of H_2O, then 8 mL of 50 mM ammonium formate, and finally 4 mL of 1.2 M ammonium formate with 0.1 M formic acid, which was collected in a scintillation vial. To this eluate was added 15 mL of scintillation fluid, and the total [^{3}H]IPs was determined by scintillation counting on a beta-counter. Data were analyzed by the sigmoidal fit function of the Origin Scientific Graphics software (Microcal Software, Northampton, MA) to determine agonist potency (EC_{50} value) and efficacy, relative to the standard cloprostenol.

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(15) Typically with nonracemic samples of cyclopentane prostaglandins, substrate control of diasteroselectivity is poor in the reduction of the C-15 ketone to the corresponding alcohol. Investigators have generally turned to reagent control using chiral reducing reagents (see for example: Corey, E. J.; Becker, K. B.; Varma, R. K. Efficient generation of the 15*S* configuration in prostaglandin synthesis. Attractive interactions in stereochemical control of carbonyl reduction. *J. Am. Chem. Soc.* **1972**, *94*, 8616. Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.-P.; Singh, V. K. A stable and easily prepared catalyst for the enantioselective reduction of ketones. Applications to multistep syntheses. *J. Am. Chem. Soc.* **1987**, *109*, 7925. Noyori, R.; Tomino, I.; Yamada, M.; Nishizawa, M. Asymmetric synthesis via axially disymmetric molecules. 7. Synthetic applications of the enantioselective reduction by binaphthol-modified lithium aluminum hydride reagents. *J. Am. Chem. Soc.* **1984**, *106*, 6717. See also ref 4b). However, in the case of a racemic sample as long as kinetic resolution is not operative, reagent control of C-15 stereochemistry using a chiral reducing agent will still give both 15α and 15β diastereomers. These types of reagents were not investigated, and no atttempt was made to optimize the diastereoselectivity of the reduction.

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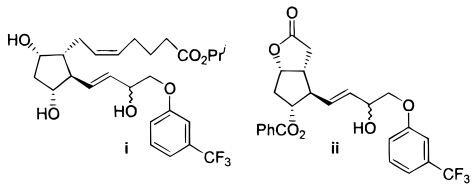
(17) Our unpublished observations with cyclopentane prostaglandins have been that under normal phase TLC conditions (silica gel, ethyl acetate/hexane mixtures as eluent), the natural 15α diastereomer (assigned as the more potent diastereomer in our FP receptor-linked functional assay;[9c] see ref 18 for a caveat)

usually elutes faster than the unnatural 15β diastereomer for species containing the complete α and ω chains (as in structure **i** below), while the opposite is usually observed for compounds containing a complete ω chain but with the α chain stored as a lactone (as in structure **ii** below).



For examples where the less polar epimer is assigned as the 15α diastereomer, see: (a) Corey, E. J.; Albonico, S. M.; Kelliker, U.; Shaff, T. K.; Varma, R. K. New reagents for stereoselective carbonyl reduction. An improved synthetic route to the primary prostaglandins. *J. Am. Chem. Soc.* **1971**, *93*, 1491. (b) Ref 18a. (c) Ref 18b. (d) Liljebris, C.; Selen, G.; Resul, B.; Stjernschantz, J.; Hacksell, U. Derivatives of 17-phenyl-18,19,20-trinorprostaglandin $F_{2\alpha}$ isopropyl ester: potential antiglaucoma agents. *J. Med. Chem.* **1995**, *38*, 289. For examples where the more polar epimer is assigned as the 15α diastereomer, see: (e) Corey, E. J.; Vlattas, I.; Andersen, N. H.; Harding, K. E. A new total synthesis of prostaglandins of the E_1 and F_1 series, including 11-epiprostaglandins. *J. Am. Chem. Soc.* **1968**, *90*, 3247. (f) Grieco, P. A.; Owens, W.; Wang, C.-L.; Williams, E.; Schillinger, W. J.; Hirotsu, K.; Clardy, J. Fluoroprostaglandins: synthesis and biological evaluation of the methyl esters of (+)-12-fluoro, (−)-*ent*-12-fluoro, (+)-15-*epi*-12-fluoro, and (−)-*ent*-15-*epi*-12-fluoroprostaglandin $F_{2\alpha}$. *J. Med. Chem.* **1980**, *23*, 1072. (g) Ref 18b. (h) Andersen, N. H. *J. Lipid. Res.* **1969**, *221*, 1251.

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(21) If it were assumed that all of the biological activity resided in one enantiomer of **7**, then that enantiomer of **7** would have an EC_{50} of 160 nM and thus would be one-seventh as potent an FP receptor agonist as $PGF_{2\alpha}$.

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