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3-Oxa-15-cyclohexyl Prostaglandin DP Receptor Agonists as Topical Antiglaucoma Agents

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Abstract—A series of prostaglandin DP agonists containing a 3-oxa-15-cyclohexyl motif was synthesized and evaluated in several in vitro and in vivo biological assays. The reference compound **ZK 118.182** (9β-chloro-15-cyclohexyl-3-oxa-ω-pentanor $PGF_{2\alpha}$) is a potent full agonist at the prostaglandin DP receptor. Saturation of the 13,14 olefin affords **AL-6556**, which is less potent but is still a full agonist. Replacement of the 9-chlorine with a hydrogen atom or inversion of the carbon 15 stereochemistry also reduces affinity. In in vivo studies **ZK 118.182** lowers intraocular pressure (IOP) upon topical application in the ocular hypertensive monkey. Ester, 1-alcohol, and selected amide prodrugs of the carboxylic acid enhance in vivo potency, presumably by increasing bioavailability. The clinical candidate **AL–6598**, the isopropyl ester prodrug of **AL-6556**, produces a maximum 53% drop in monkey IOP with a 1 μg dose (0.003% w/w) using a twice-daily dosing regime. Synthetically, **AL–6598** was accessed from known intermediate **1** using a novel key sequence to install the *cis* allyl ether in the α chain, involving a selective Swern oxidative desilylation of a primary silyl ether in the presence of a secondary silyl ether. In this manner, 136 g of **AL–6598** was synthesized under GMP conditions for evaluation in phase I clinical trials.

Introduction

Glaucoma, a heterogeneous family of optic neuropathies, is one of the leading causes of blindness in the developed world. It is characterized by a specific pattern of visual field loss which is the result of the thinning of the ganglion cell layer of the retina and the cupping and excavation of the optic nervehead. Although the disease process and its causative factors are not completely understood, elevated intraocular pressure (IOP) is an important risk factor for loss of visual field due to optic nerve damage.[1,2]

Certain prostaglandins such as $PGF_{2\alpha}$ reduce IOP in man, but also cause conjunctival hyperemia, foreign-body sensation and ocular pain.[3] The development of potent, selective synthetic prostaglandin FP agonists as clinically effective IOP-lowering agents devoid of many of these side effects has been an important advance in the treatment of glaucoma.[3b,c]

Complementary to these findings was the discovery that PGD_2 and the selective synthetic DP prostaglandin agonist **BW 245C** (Fig. 1) lowered IOP in rabbits without causing the hallmark signs of ocular inflammation:

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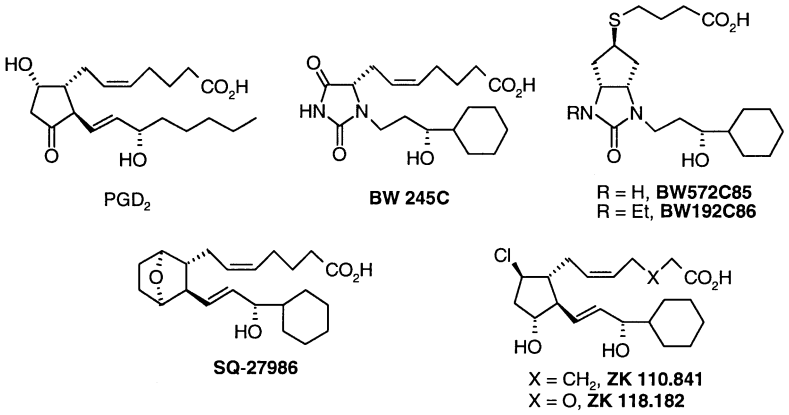


Figure 1.

hyperemia, flare and irritation.[4,5] Other investigators confirmed the IOP effect of PGD_2 in rabbits but suggested that the natural prostaglandin caused protein extravasation and eosinophil infiltration following topical ocular application. These investigators also reported that selective DP prostaglandin agonists such as **SQ-27986**, **BW 572C85**, and **BW 192C86** would lower intraocular pressure in rabbits and were essentially devoid of the inflammatory side effects demonstrated by PGD_2.[5a–d] Clinical trials with PGD_2 and **BW 245C** confirmed the efficacy of these compounds as ocular hypotensive agents. However in humans PGD_2 and **BW 245C** produced intense acute conjunctival hyperemia that was not predicted by the studies in rabbits.[5e]

We found that the potent, selective DP compound **ZK 110.841**[5f] and the metabolically more stable 3-oxa analogue **ZK 118.182**[5f,g] lowered IOP in Dutch belted (DB) rabbits. Repeated topical ocular application to the ocular hypertensive monkey produced a profound (40–50%) reduction in IOP. These compounds also caused intense acute conjunctival hyperemia in the guinea pig, a model that closely reproduces the ocular hyperemic effect of PGD_2 and **BW 245C** in the human.[5e] Based on these observations, a synthesis program was initiated to identify the structural features required for the potent ocular hypotensive activity of **ZK 118.182**. Below, we describe the studies leading to the identification of the clinical candidate **AL–6598** (Fig. 2) and the development of an efficient multigram GMP synthesis of this interesting compound.

Results and Discussion

Chemistry

Our synthetic route (Scheme 1) began with the known lactone **1**.[6] Methanolysis of **1** on a 500-g scale afforded diol **2**, which was protected as its bis THP ether **3** and then hydrogenated to afford 13,14-dihydro compound **4**. Alternatively, **2** could be hydrogenated directly in the basic aqueous extract from the methanolysis, and the resulting saturated diol then protected to form **4**. Reduction of **4** to the diol followed by Swern oxidation[7] of the bissilyl derivative **5** provided siloxy aldehyde **6**.[8] This route to **6** avoided problems of relactonization and overreduction encountered with γ-hydroxy ester intermediates.[9] Olefination[6a,10] of **6** gave enoate **7** (9:1 *Z*/*E*). In contrast, olefination of the lactol derived from **4** in this manner was plagued by intramolecular 1,4-addition of the liberated C-9 alkoxide onto the newly formed enoate to afford the corresponding tetrahydrofuran. On multigram scale we used pre-dried (over 4 Å molecular sieves) tris[2-(2-methoxyethoxy)ethyl]amine (TDA-1) as the K^+-complexing agent[11] in place of 18-crown-6[10] in order to avoid problems of cost, toxicity, separation, and disposal of the crown ether. Chromatographic separation of the *Z* and *E* isomers could be effected at this stage. We later observed greater ΔR_f for the *Z* and *E* isomers of diol **8**, affording more efficient separation.

Enoate **7** was elaborated to **AL–6598** along lines reported for the 13,14-dehydro series.[6] Reduction of **7** followed by desilylation gave diol **8**. Phase-transfer alkylation of **8** afforded hydroxy ester **9**, which we converted to the ophthalmically preferred isopropyl ester **10** by $Ti(OPr^i)_4$-mediated transesterification.[12] Mesylation of **10** followed by treatment with Bu_4NCl in hot toluene and removal of the THP groups afforded **AL–6598** after chromatographic separation from the 9-deschloro-$\Delta^{5,6,8,9}$ dienyl side product.[6a] Using these procedures, 136 g of **AL-6598** was prepared under GMP conditions for human clinical evaluation (14 steps, 13% overall yield).

We also synthesized **AL-6598** by way of a modified Sato sequence[13] (Scheme 2). Hydrogenation[14] of (*R*)-3-chloro-1-phenyl-1-propanol (**11**)[15] gave volatile cyclohexyl carbinol **12**, which was protected to form the saturated ω chain reagent **13**. Lithium-chlorine exchange (THF, 0 °C), mixed cuprate formation[16] and addition to chiral enone **14**[13] afforded methylene ketone **15**. A protecting group exchange via alcohol **16** gave silyl ether

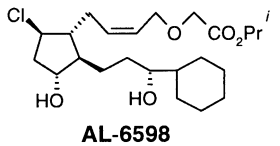
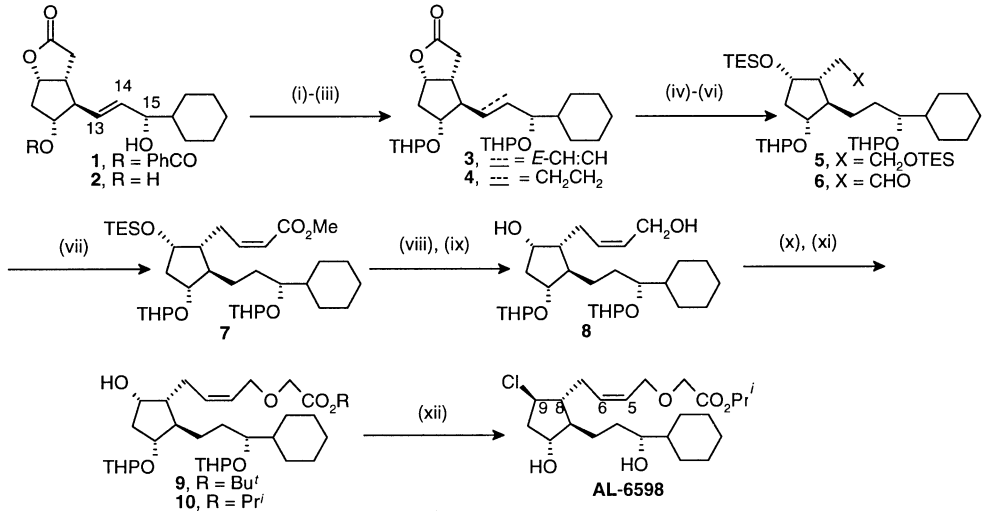


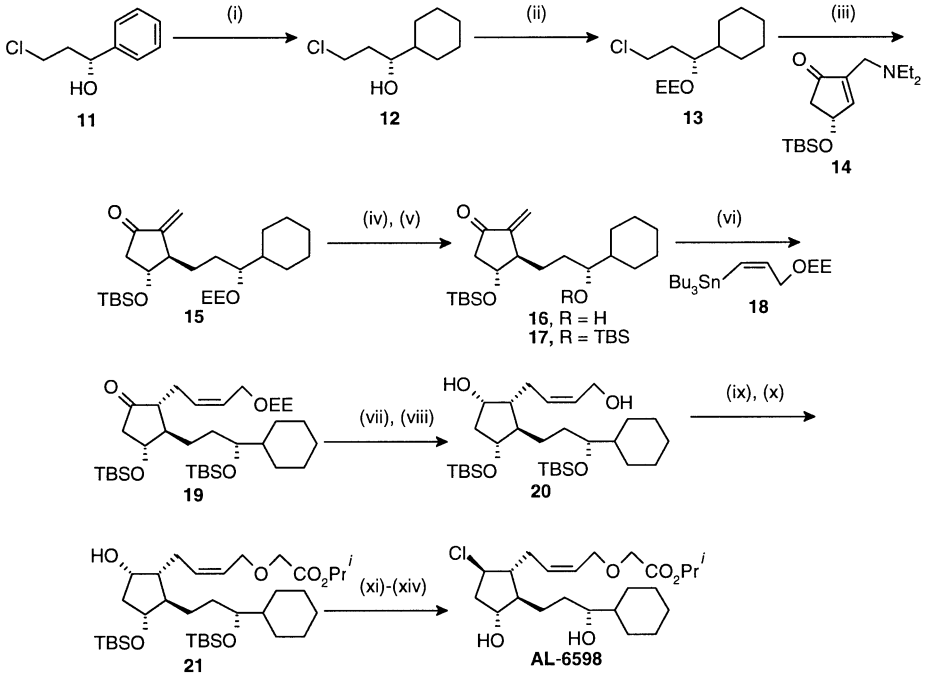
Figure 2.

17. By contrast, the TBDMS or TBDPS ether of **16** suffered O→C silyl migration when subjected to these Li–Cl exchange conditions.[17] For α chain installation we subjected Z-vinylstannane **18**[18a] to a stereospecific transmetalation with $Me_2Cu(CN)Li_2$[19] and added **17** to the resulting cuprate, affording ketone **19**. Reduction[13] of **19** was followed by removal of the EE group providing diol **20** which was elaborated as above to give **AL-6598**.

The 9-deoxy compound **22** was obtained by mesylation of alcohol **23**, $LiEt_3BH$ per-reduction of the mesylate to afford 9-deoxy-1-ol **24**, PDC/DMF oxidation to the corresponding 1-acid and esterification, deprotection, and saponification (Fig. 3). Attempted production of **22** by radical-mediated reductive dechlorination of 9-chloride **25** using Bu_3SnH/AIBN caused concomitant *Z* to *E* isomerization of the $\Delta^{5,6}$ olefin.[20] The 5*E* isomer **26** was constructed by Wittig reaction of lactol **27** with



Scheme 1. Conditions: (i) K_2CO_3, MeOH, 98%; (ii) DHP, TsOH, CH_2Cl_2, 5°C, 84%; (iii) 75 psi H_2, 10% Pd/C, EtOAc, 82%; (iv) $LiAlH_4$, THF, 0°C, 100%; (v) 3 equiv Et_3SiCl, NEt_3, CH_2Cl_2, cat DMAP, 73%; (vi) $(COCl)_2$, DMSO, CH_2Cl_2, −65 to −50°C, then NEt_3, 5°C, 87%; (vii) $(CF_3CH_2O)_2P(O)CH_2CO_2Me$, KHMDS, TDA-1, THF/toluene, −60 to −20°C, 69% pure Z olefin (crude, 8:1 *Z:E*); (viii) DIBAL-H, THF, −20 to 5°C, 97%; (ix) TBAF, THF, 0°C, 86%; (x) $BrCH_2CO_2Bu^t$, KOH, Bu_4NHSO_4, toluene/water, 86%; (xi) $Ti(OPr\text{-}i)_4$, *i*-PrOH, heat, 96%; (xii) (a) MsCl, pyridine, 0°C; (b) Bu_4NCl, toluene, 55°C; (c) AcOH/water, 65°C, 54% from **10** after HPLC purification.



Scheme 2. Conditions: (i) H_2, 5% Rh/Al_2O_3, MeOH, 55%; (ii) ethyl vinyl ether, PPTS, CH_2Cl_2, 97%; (iii) (a) Li, 4,4′-di-*t*-butylbiphenyl, THF, 0°C; (b) −45°C, **13**/THF; (c) lithium (2-thienyl)cyanocuprate/THF; (d) **14**/THF; 57% yield of **15** after quenching; (iv) PPTS, isopropanol, 77%; (v) TBSOTf, *i*-Pr_2NEt, CH_2Cl_2/DMF, 80%; (vi) MeLi, CuCN, THF, 0°C, then add **18**, rt, then cool to −78°C, then add **17**/THF, 10 min, aq NH_4Cl quench, 72%; (vii) L-Selectride, THF, −78°C, 56%; (viii) PPTS, isopropanol/ether, 76%; (ix) $BrCH_2CO_2Bu^t$, NaOH, Bu_4NHSO_4, toluene/water, 78%; (x) $Ti(OPr\text{-}i)_4$, isopropanol, heat, 75%; (xi) MsCl, pyr, 0°C; (xii) Bu_4NCl, toluene, heat; (xiii) HF, THF, 0°C to rt, 63% yield from **21** of **6598**/diene as a 3.5:1 mixture.

$Ph_3P{=}CHCO_2Me$ in the presence of acetic acid to afford the *E* enoate **28** (99%), the acidic conditions suppressing intramolecular 1,4-addition.[21] Compounds with the 15β alcohol relative stereochemistry, such as **29**, were synthesized from the 15-epimer[6] **30** of lactone **1**. The 15-methoxy acid **32** was prepared from the *t*-butyl ester **32** by selective *t*-butyldimethylsilylation of the C-11 hydroxyl, methylation of the C-15 hydroxyl, desilylation, and saponification. The primary amide **33** was prepared by NH_3/NH_4Cl treatment of **32**. The secondary and tertiary amides **34** and **35** were formed by Weinreb amination of **AL–6598** and **32**, respectively.

Pharmacology

The compounds in Table 1 were evaluated for their affinity and efficacy at the DP prostaglandin receptor and for IOP lowering effect in the Dutch belted rabbit and the ocular hypertensive monkey. The carboxylic acid was used in all in vitro studies since it is believed to be the pharmacologically active form of the compound. The isopropyl or *t*-butyl ester derivatives are prodrugs that facilitate corneal penetration and delivery of the carboxylic acid to aqueous humor. The esters were used in the in vivo experiments unless otherwise noted.

In vitro studies. The K_i and EC_{50} values for ligand binding to and functional activity at the DP receptor for relevant compounds are shown in Table 2. The parent compound **ZK118.182** is a high affinity potent full agonist at the DP prostaglandin receptor. The 5*E* (**26**) and 15β-hydroxy (**36**) isomers are over 400-fold less potent, the former being a full, and the latter a partial, agonist. The 9β-H compound **22** is also a full agonist, being about 25 and 90 times less potent than **ZK118.182** in binding and functional assays, respectively. The 1-alcohol derivative **37**, prepared as a carboxylic acid prodrug, has low affinity for the DP receptor, and is a weak partial agonist.

Saturation of the 13,14 olefin of **ZK118.182** to afford **AL-6556** causes a greater than 60-fold decrease in affinity and an almost 90-fold reduction in functional potency while maintaining full efficacy Within the series of 13,14-dihydro derivatives, the 15β-hydroxy (**38**), 5,6-dihydro (**39**), and the 9β-H (**40**) compounds have similar affinity for the DP receptor, being slightly less potent than **AL-6556**. In the functional assay, **39** and **38** are similar in potency to **AL-6556** and are partial and full agonists, respectively. Inversion of the carbon 15 relative stereochemistry from α to β in the 13,14-dihydro series surprisingly only slightly attenuates receptor affinity and functional potency, as compared to the marked decrease observed with this structural change in the 13,14-alkene series. The 9β-H compound **40** is a full agonist but has 2-fold lower affinity for the DP receptor and is 5-fold less potent than **AL-6556** in the functional assay.

The 15α-methyl ether **31** has low affinity for the DP receptor and is inactive in the functional assay, suggesting that the increased bulk of the methyl group is not tolerated and/or that the receptor requires a hydrogen bond donor for agonist activity. The amides **33**, **35**, and **41** and the 1-hydroxy derivative **42** were prepared as prodrugs. As expected, these compounds have low affinity for the DP receptor and are inactive at concentrations up to 100 μM in the functional assay.

In vivo studies. Compounds were evaluated for their effect on IOP in rabbits. Compounds having a favorable profile were advanced into the ocular hypertensive monkey. The rabbit and monkey IOP data are reported in Tables 3 and 4, respectively.

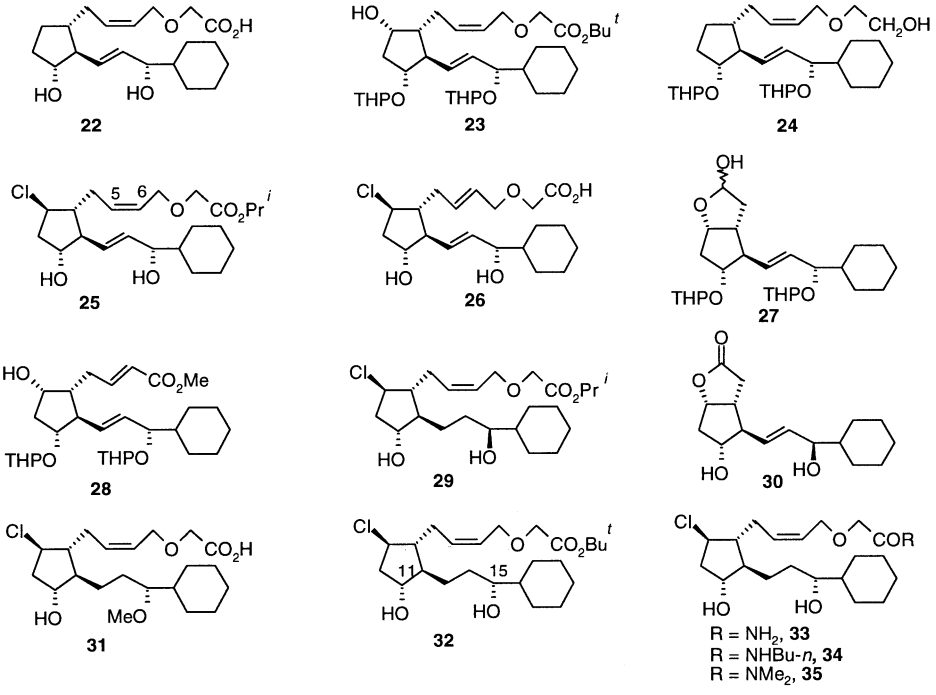
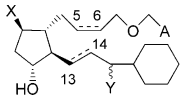


Figure 3.

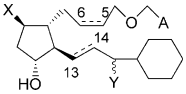
The carboxylic acid **ZK 118.182** causes a transient reduction in IOP in the rabbit following a 1-μg dose but produces a sustained reduction in IOP following a 20-μg dose. The compound also lowers IOP in the ocular hypertensive monkey following a 5-μg application. As expected the isopropyl (**25**) and *t*-butyl (**43**) ester prodrugs of **ZK 118.182** are much more potent than the acid in the rabbit and monkey, supporting the hypothesis that acid esterification facilitates corneal penetration and increases bioavailability. Following a 10-μg dose, the 5*E* ester **44** unexpectedly causes a large initial increase in IOP prior to exerting the expected ocular

Table 1. 3-Oxa-15-cyclohexyl prostaglandin analogues



Compd	A	5,6	X	13,14	Y
ZK 118.182	CO_2H	*Z*-CH=CH	Cl	*E*-CH=CH	α-OH
AL–6598	CO_2Pr^i	*Z*-CH=CH	Cl	CH_2CH_2	α-OH
AL–6556	CO_2H	*Z*-CH=CH	Cl	CH_2CH_2	α-OH
22	CO_2H	*Z*-CH=CH	H	*E*-CH=CH	α-OH
25	CO_2Pr^i	*Z*-CH=CH	Cl	*E*-CH=CH	α-OH
26	CO_2H	*E*-CH=CH	Cl	*E*-CH=CH	α-OH
29	CO_2Pr^i	*Z*-CH=CH	Cl	CH_2CH_2	β-OH
31	CO_2H	*Z*-CH=CH	Cl	CH_2CH_2	α-OMe
32	CO_2Bu^t	*Z*-CH=CH	Cl	CH_2CH_2	α-OH
33	$CONH_2$	*Z*-CH=CH	Cl	CH_2CH_2	α-OH
34	$CONHBu^n$	*Z*-CH=CH	Cl	CH_2CH_2	α-OH
35	$CONMe_2$	*Z*-CH=CH	Cl	CH_2CH_2	α-OH
36	CO_2H	*Z*-CH=CH	Cl	*E*-CH=CH	β-OH
37	CH_2OH	*Z*-CH=CH	Cl	*E*-CH=CH	α-OH
38	CO_2H	*Z*-CH=CH	Cl	CH_2CH_2	β-OH
39	CO_2H	CH_2CH_2	Cl	CH_2CH_2	α-OH
40	CO_2H	*Z*-CH=CH	H	CH_2CH_2	α-OH
41	CONHMe	*Z*-CH=CH	Cl	CH_2CH_2	α-OH
42	CH_2OH	*Z*-CH=CH	Cl	CH_2CH_2	α-OH
43	CO_2Bu^t	*Z*-CH=CH	Cl	*E*-CH=CH	α-OH
44	CO_2Bu^t	*E*-CH=CH	Cl	*E*-CH=CH	α-OH
45	CO_2Pr^i	*Z*-CH=CH	H	*E*-CH=CH	α-OH
46	CO_2Pr^i	*Z*-CH=CH	Cl	*E*-CH=CH	β-OH
47	CO_2Pr^i	*Z*-CH=CH	H	CH_2CH_2	α-OH
48	CO_2Bu^t	CH_2CH_2	Cl	CH_2CH_2	α-OH
49	CO_2Bu^t	*Z*-CH=CH	Cl	CH_2CH_2	α-OMe

Table 2. In vitro activities of 3-oxa-15-cyclohexyl prostaglandin DP receptor agonists



Compd	A	5,6	X	13,14	Y	DP affinity $K_i \pm$SEM[a] (μM)	DP activity $EC_{50} \pm$SEM[a] (μM)	DP activity Maximum response (%)
ZK 118.182	CO_2H	Z-CH=CH	Cl	E-CH=CH	α-OH	0.050±0.0088	0.014±0.0041	98
AL-6556	CO_2H	Z-CH=CH	Cl	CH_2CH_2	α-OH	3.2±0.46	0.80±0.18	92.5
22	CO_2H	Z-CH=CH	H	E-CH=CH	α-OH	1.2±0.45	0.89±.23	87
26	CO_2H	E-CH=CH	Cl	E-CH=CH	α-OH	35±2.5	0.94±0.22	93
31	CO_2H	Z-CH=CH	Cl	CH_2CH_2	α-OMe	25±17	>100,000	n.d.[b]
33	$CONH_2$	Z-CH=CH	Cl	CH_2CH_2	α-OH	140±60	>100,000	n.d.[b]
34	CONH-n-Bu	Z-CH=CH	Cl	CH_2CH_2	α-OH	n.d.[b]	n.d.[b]	n.d.[b]
35	$CONMe_2$	Z-CH=CH	Cl	CH_2CH_2	α-OH	110±13	>100,000	n.d.[b]
36	*CO_2H*	Z-CH=CH	Cl	E-CH=CH	β-OH	22±7.9	5.3±1.2	51
37	CH_2OH	Z-CH=CH	Cl	E-CH=CH	α-OH	66±15	14.8±4.5	43
38	CO_2H	Z-CH=CH	Cl	CH_2CH_2	β-OH	5.9±1.2	1.22±0.45	83.6
39	CO_2H	CH_2CH_2	Cl	CH_2CH_2	α-OH	7.2±0.79	1.3±0.36	52
40	CO_2H	Z-CH=CH	H	CH_2CH_2	α-OH	6.8±0.92	4.6±1.1	79
41	CONHMe	Z-CH=CH	Cl	CH_2CH_2	α-OH	110±12	>100,000	n.d.[b]
42	CH_2OH	Z-CH=CH	Cl	CH_2CH_2	α-OH	47±36	>100,000	n.d.[b]

[a]SEM, standard error of the mean.
[b]n.d., not determined.

hypotensive effect. The 9β-H analogue **45** at 0.1 and 0.3 μg topical ocular doses lowers IOP in the rabbit efficaciously but with a shorter duration of action than the corresponding 9β-chloride. The 15β-hydroxy compound **46** does not lower IOP in the rabbit at doses 100-fold higher than the ocular hypotensive dose of the 15α-hydroxy isomer **25**. The ineffectiveness, of **46** is consistent with the in vitro data for the corresponding acid. Interestingly, the 1-alcohol prodrug **37** does not lower IOP in the rabbit at doses well above those that

Table 3. Rabbit IOP data

Compd	Dose (μg)	Baseline IOP (mm Hg)	% Reduction ± SEM[a]			
			1 h	2 h	3 h	5 h
ZK 118.182	20	32.9	16.8 ± 5.2	22.6 ± 4.6	25.2 ± 1.3	23.8 ± 3.0
	1.0	32.2	18.7 ± 2.6	4.9 ± 5.2	5.4 ± 4.6	(+)[b] 6.9 ± 2.0
AL–6598	3	23.3	3.0 ± 5.9	9.9 ± 2.6	20.3 ± 3.1	22.6 ± 1.9
	1	29.6	13.9 ± 2.4	15.6 ± 2.1	11.5 ± 2.2	8.2 ± 2.2
25	0.03	24.6	24.1 ± 0.26	20.0 ± 2.1	14.3 ± 2.6	7.9 ± 1.9
	0.01	25.3	16.9 ± 13.1	13.0 ± 1.8	7.9 ± 1.2	5.1 ± 1.4
29	10	26.4	16.5 ± 4.4	14.7 ± 3.4	11.2 ± 3.3	12.9 ± 5.0
	1	26.7	16.3 ± 2.4	8.8 ± 3.5	5.0 ± 1.4	3.7 ± 2.9
33	30	24.9	4.9 ± 8.1	14.5 ± 4.7	21.6 ± 4.0	25.9 ± 3.2
	10	25.1	18.4 ± 2.8	14.3 ± 3.5	17.1 ± 2.6	24.2 ± 1.1
34	30	28.1	5.1 ± 3.8	7.5 ± 2.6	13.1 ± 2.5	25.1 ± 4.2
	3	24.4	(+)[b] 0.9 ± 2.2	4.3 ± 3.6	(+)[b] 1.8 ± 4.4	6.0 ± 4.2
35	100	26.6	12.5 ± 3.1	14.2 ± 4.4	16.4 ± 3.5	26.5 ± 1.5
	3	24.8	10.2 ± 3.4	4.3 ± 4.0	12.8 ± 4.9	11.3 ± 5.2
37	3	26.6	6.4 ± 3.5	8.0 ± 3.0	8.5 ± 2.7	7.5 ± 3.8
	1	26.5	4.8 ± 0.85	9.7 ± 3.0	13.5 ± 2.7	8.1 ± 1.8
41	10	28.2	10.3 ± 3.3	16.3 ± 2.2	21.1 ± 2.7	29.0 ± 4.1
	3	27.5	13.4 ± 3.1	14.4 ± 4.2	12.6 ± 2.1	11.6 ± 2.3
42	10	28.1	0.9 ± 2.3	(+)[b] 0.2 ± 2.0	(+)[b] 5.1 ± 2.8	(+)[b] 7.3 ± 3.7
43	0.1	27.8	33.1 ± 3.5	28.2 ± 3.6	28.4 ± 3.1	22.5 ± 3.7
	0.03	32.5	10 ± 3.7	9.7 ± 3.7	8.9 ± 1.7	9.3 ± 3.0
44	10	24.6	(+)[b] 30.1 ± 8.3	8.8 ± 4.7	16.4 ± 4.8	19.2 ± 3.7
	1	24.6	17.6 ± 1.8	20.6 ± 1.6	14.3 ± 2.2	6.8 ± 2.3
45	0.3	21.8	32.7 ± 5.6	15.2 ± 6.3	10.2 ± 6.0	3.5 ± 5.9
	0.1	22.3	21.4 ± 3.6	9.6 ± 4.3	6.2 ± 3.3	0.1 ± 1.7
46	3	22.8	11.3 ± 3.7	9.8 ± 4.3	5.3 ± 5.8	1.4 ± 3.9
	1	21.6	1.5 ± 3.8	0.2 ± 2.7	10.7 ± 6.4	0.7 ± 3.9
47	3	27.0	20.0 ± 2	8.9 ± 2.4	7.6 ± 2.5	1.8 ± 2.5
	1	25.9	9.9 ± 3.5	4.3 ± 2.9	2.1 ± 4.1	2.7 ± 5.1
48	10	27.5	5.9 ± 7.3	n.d.[c]	6.9 ± 3.6	0.9 ± 3.6
	1	27.7	2.5 ± 3.4	n.d.[c]	(+)[b] 6.7 ± 3.9	(+)[b] 9.7 ± 4.4
49	10	26.6	0.6 ± 41	3.3 ± 2.6	2.8 ± 3.4	2.7 ± 3.6
	3	26.0	5.5 ± 2.2	4.0 ± 3.2	3.4 ± 3.4	0.8 ± 3.2

[a]SEM, standard error of the mean.
[b](+) = increase in IOP above baseline.
[c]n.d., not determined.

Table 4. Monkey IOP data

Compd	Dose (μg)	Baseline IOP (mm Hg)	Time after dose/dose number			
			16 h/4	2 h/5	4 h/5	6 h/5
			% Reduction in IOP ± SEM[a]			
ZK 118.182	5	30.3	12.6 ± 3.6	25.5 ± 4.5	30.6 ± 3.4	26.2 ± 4.6
AL–6598	1	38.7	41 ± 3.1	52.5 ± 5.4	48.1 ± 5.2	35.7 ± 5.5
	0.3	36.7	17.8 ± 4.5	35.8 ± 5.3	34.6 ± 5.1	31.3 ± 6.0
25	0.03	35.3	34.7 ± 3.6	46.3 ± 3.8	31.7 ± 6.9	31.6 ± 4.6
29	10	38.7	48.7 ± 4.9	52.1 ± 2.4	50.7 ± 2.9	45.7 ± 3.4
	3	32.3	30 ± 6.1	41.4 ± 5.33	33.6 ± 6.2	29.8 ± 7.3
	1	35.3	20.6 ± 6.4	25.0 ± 6.6	31.1 ± 5.2	22.2 ± 7.4
33	3	38.6	25.5 ± 7.6	42.2 ± 5.8	48.3 ± 5.7	35.9 ± 7.8
	1	37.0	1.3 ± 2.6	10.9 ± 3.9	15.7 ± 4.3	13.8 ± 3.8
34	3	37.6	21.6 ± 3.4	24.3 ± 3.6	18.4 ± 4.6	13.7 ± 4.0
35	30	32.3	3 ± 3.4	17.9 ± 5.1	14.0 ± 4.4	14.1 ± 4.8
37	0.3	33.3	35.2 ± 2.7	44.3 ± 3.1	35.8 ± 3.3	30.3 ± 2.5
42	3	37.8	28.0 ± 3.9	42.2 ± 4.9	33.7 ± 5.2	28.5 ± 4.4
43	1	31.3	47.6 ± 2.6	52.8 ± 3.3	54.7 ± 3.4	53.1 ± 4.1
	0.1	31.4	19.2 ± 2.9	24.4 ± 4.6	25.8 ± 3.6	21.1 ± 4.1

[a]SEM, standard error of the mean.

are efficacious for the esters. Unlike the observed lack of activity in the rabbit, **37** effectively lowers IOP in the monkey at a 0.3 μg dose. This observation suggests that the rabbit, unlike the monkey, does not metabolize 1-alcohol prostaglandin derivatives to the carboxylic acid when the compound is administered topically to the eye. The esters of the 13,14-dihydro derivative of **ZK 118.182** (**AL–6598** and **32**) are 10- to 100-fold less potent but are just as efficacious in reducing IOP in the rabbit and the monkey as the parent esters **25** and **43**. The 15β-hydroxy compound in the 13,14 dihydro series (**29**) produces a modest effect on IOP in rabbits and is active only at the early time points. In the ocular hypertensive monkey **29** is less potent than the 15α isomer **AL–6598** but is equally efficacious.

As was seen with the 13,14-alkene analogue, application of the 9β-H derivative **47** to the rabbit eye results in a rapid onset of action that is brief in duration compared to corresponding 9β-Cl compound **AL–6598**. Both the 5,6,13,14-tetrahydro (**48**) and the 15-methoxy-13,14-dihydro (**49**) compounds are inactive at doses of 10 μg in the rabbit. As seen with the alkene series the 1-alcohol derivative **42** does not lower IOP at doses 3- to 10-fold higher than the effective dose of **AL–6598** in the rabbit. However, **42** is effective in lowering IOP in the monkey following a 3-μg dose.

The activity of the amide derivatives in the 13,14-dihydro series depends on the degree of substitution on nitrogen. The primary amide **33** and the secondary methyl amide **41** are 3- to 10-fold less potent than **AL–6598** in the rabbit IOP model. In the monkey the primary amide produces a profound reduction in IOP at a 3-μg dose. In the rabbit the *n*-butyl amide of **AL-6556** (**34**) appears to have a delayed onset of action with the maximum reduction in IOP at the 5-h observation point. The compound produces a modest reduction in IOP at 3 μg in the monkey, the only dose tested. In the rabbit the dimethyl amide **35** is active at doses that are 30- to 100-fold higher than that of the ester. It modestly reduces IOP in the monkey at 30 μg, the only dose tested. Since the amides are inactive in the in vitro functional assay, these observations suggest that the amides evaluated are being hydrolyzed to the pharmacologically active acid when applied topically to the eye, with increasing nitrogen substitution leading to slower cleavage. Irrespective of the nitrogen substitution pattern the amides are not cleaved as readily as the isopropyl or *t*-butyl esters.

Conclusions

A series of 3-oxa-15-cyclohexyl prostaglandins has been synthesized for evaluation in in vitro prostaglandin DP binding and functional assays and in in vivo rabbit and monkey IOP assays. All structural modifications to the parent compound **ZK 118.182** reduce receptor affinity and functional potency by 2–3 orders of magnitude, but many of these analogues maintain full agonist efficacy. Replacement of the 9-chlorine atom with a hydrogen or saturation of the 13,14 olefin affords full agonists with μM potency. Conversion of the carboxylic acid to an amide or reduction to the 1-alcohol completely abolishes in vitro efficacy. Interestingly inversion of carbon 15 hydroxyl stereochemistry from α to β greatly reduces functional potency and efficacy when the 13,14 alkene is present but only slightly affects these values when this position is saturated.

As reported with the prostaglandin FP derivatives, ester prodrugs enhance the potency of the compounds presumably by facilitating the corneal absorption of the compounds. These studies have shown that the 1-alcohol derivatives are also effective prodrugs for these analogues in the monkey, but not in the rabbit. The primary amide is potent and efficacious in the rabbit and monkey, while secondary and tertiary amides show reduced activity. The lack of potency and in some cases limited efficacy observed with these amide derivatives may be due to poor corneal penetration and/or slow rate of hydrolysis. The delayed onset of action of some of the amide derivatives suggests that the slow rate of hydrolysis may be reducing the bioavailability of the active carboxylic acid.

Based on the profound efficacy of these compounds as ocular hypotensive agents and additional preclinical studies demonstrating a positive effect on ocular blood flow one of these compounds, **AL–6598,** was selected for human clinical evaluation. The results of these studies will be reported in due course.

Experimental

Chemistry general methods

Abbreviations used include: DMAP, 4-(dimethylamino)pyridine; DIBAL-H, diisobutylaluminum hydride; TBAF, tetra-*n*-butylammonium fluoride. Unless otherwise noted, all ^{1}H NMR spectra were acquired in $CDCl_3$ solvent on a Varian Gemini 200 spectrometer operating at a field strength of 200 MHz, and all ^{13}C NMR and DEPT spectra were acquired in $CDCl_3$ on the same instrument operating at a field strength of 50.4 MHz. The compound **ZK 118.182** and its *t*-butyl ester **43** were kindly provided by Schering AG, Berlin, Germany. For reactions without added water, solvents used were anhydrous grade from Aldrich Chemical Company and were used without further purification. Unless otherwise stated, all reactions without added water were run under a positive pressure of nitrogen, and all temperatures quoted refer to external temperatures. 'Dry THF' refers to THF which was freshly distilled from potassium benzophenone ketyl. 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 staining with either ethanolic phosphomolybdic acid or 2% aq $KMnO_4$. 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 (LRMS) were acquired on

a Finnegan TSQ 46 triple quadrupole mass spectrometer when operated in the fast-atom bombardment (FAB) or chemical ionization (CI; isobutane as ionizing gas) modes and on a Voyager RP laser desorption time-of-flight mass spectrometer when using the matrix-assisted laser desorption ionization (MALDI) method. High resolution mass spectra (HRMS) were acquired in the CI mode using isobutane as the ionization gas at the University of Texas Mass Spectrometry Facility, Austin, TX, USA.

[3a*R*,4*R*(1*E*,3*S*),5*R*,6a*S*]-4-(3-Cyclohexyl-3-hydroxy-1-propenyl)-5-hydroxyhexahydro-2*H*-cyclopenta[*b*]furan-2-one (2). A mixture of [3a*R*,4*R*(1*E*,3*S*),5*R*,6a*S*]-4-[3-cyclohexyl-3-hydroxy-1-propenyl]-5-(benzoyloxy)hexahydro-2*H*-cyclopenta[*b*]furan-2-one (**1**) (500 g, 1.3 mol) and K_2CO_3 (180 g, 1.3 mol) in methanol (5 L) was stirred for 2 h. The pH of the mixture was adjusted to ca. 2 by the addition of 1 M aq HCl (2 L) and concentrated until the product separated as an oil. The aqueous phase was saturated with NaCl and was extracted with four portions of ethyl acetate. The combined organic extracts were washed with saturated NaCl, dried over sodum sulfate, and concentrated. The oily amber residue was triturated with 25% ether in hexane (1.5 L). Filtration and air drying of the white solid product afforded **2** (358 g, 98%). ^{13}C NMR δ 177.00 (C), 135.29 (CH), 131.11 (CH), 82.47 (CH), 77.37 (CH), 75.30 (CH), 55.25 (CH), 43.38 (CH), 42.44 (CH), 39.62 (CH_2), 34.04 (CH_2), 28.79 (CH_2), 26.42 (CH_2), 26.02 (CH_2), 25.94 (CH_2). MALDI LRMS, m/z for $(M+Na)^+$ at 303.

[3a*R*,4*R*(1*E*,3*S*),5*R*,6a*S*]-4-[3-Cyclohexyl-3-(tetrahydropyran-2-yloxy)-1-propenyl]-5-(tetrahydropyran-2-yloxy)-hydroxyhexahydro-2*H*-cyclopenta[b]furan-2-one (3). A 12-L three-neck round bottom flask was charged with diol **2** (524 g, 1.87 mol) and CH_2Cl_2 (5 L). The solution was cooled to 5 °C and 3,4-dihydro-2*H*-pyran (430 mL, 4.67 mol) was added in one portion. The catalyst *p*-toluenesulfonic acid monohydrate (2.5 g, 13 mmol) was added and the solution was stirred at 0 °C for 30 min. The reaction was quenched by the addition of saturated $NaHCO_3$ (1.5 L) and was stirred at room temperature for 2.5 h. The phases were separated, the aqueous phase was extracted with CH_2Cl_2 (1 L) and the combined organic layers were washed with saturated NaCl (500 mL) and dried over Na_2SO_4. The solvent was concentrated and 25% ether in hexane (4 L) was added to the oily residue. The mixture was concentrated until precipitation of a solid was evident. The solution was allowed to stand for 72 h. The white solid product was collected by filtration, washed with hexane, and air dried to provide of bis-THP ether **3** (513 g). The filtrate was concentrated and the oily residue was triturated with 25% ether in hexane to provide an additional lot of **3** (96 g). Repetition of this process afforded a third crop of **3** (37 g; total amount = 660 g = 79% yield). The remaining filtrate was concentrated and purified by chromatography with the corresponding filtrate from a 358 g run of this reaction. (total starting material for the two runs = 882 g = 3.14 mol). The chromatography was performed using 7 kg of silica gel eluting with 20% ethyl acetate in hexane. The total isolated from the two reactions was 1179 g (84% yield). MALDI LRMS, m/z 471 for $(M+Na)^+$.

[3a*R*,4*R*(3*R*),5*R*,6a*S*]-4-[3-Cyclohexyl-3-(tetrahydropyran-2-yloxy)propyl]-5-(tetrahydropyran-2-yloxy)hydroxyhexahydro-2*H*-cyclopenta[*b*]furan-2-one (4). A solution of **3** (658 g, 1.47 mol), in ethyl acetate (8.8 L) was transferred to a 20 L Buchi hydrogenation apparatus using vacuum. The catalyst (10% w/w Pd/C, 7.8 g) was added through the charging port via a small powder funnel. The system was sealed, purged three times with N_2, and stirred under 5 bar of H_2 for 20 h. After purging the system with N_2 the contents were removed and filtered through Celite. The reactor was washed with ethyl acetate (2×4 L) and filtered through Celite. The combined filtrates were concentrated to provide a white solid, which was triturated with hexane, filtered, and air dried to afford 446 g (67%) of **4**. The filtrate was concentrated and the residue was slurried with water, filtered, washed with hexane, and air dried to afford additional **4** containing a small amount of the isomeric 15-ketone (214 g total). This impure fraction was combined with a 335 g similar fraction from a hydrogenation run that started with 541 g (1.21 mol) of **3** (total starting material = 1199 g from the two runs), and the combined fractions were purified by chromatography on 7 kg of silica gel eluting with 1:1 hexane:ethyl acetate. The total amount of **4** isolated from both runs was 996 g (82% yield). MALDI LRMS, m/z for $(M+Na)^+$ at 473.

(9*S*,11*R*,15*R*)-11,15-Bis(tetrahydropyran-2-yloxy)-15-cyclohexyl-2,3,4,5,6,16,17,18,19,20-decanor-9-(triethylsiloxy)prostanol triethyl silyl ether (5). A 12 L three neck round bottom flask was charged with THF (3 L) and was cooled to 0 °C. $LiAlH_4$ (47 g, 1.24 mol) was added and the suspension was cooled to an internal temperature of 0 °C using a dry ice/*i*-PrOH bath. A solution of lactone **4** (561 g, 1.24 mol) in THF (2 L) was added to the stirred suspension over 60 min, maintaining the internal temperature between 0 and −3 °C. After stirring for 60 min the suspension was quenched by the sequential, slow addition of water (50 mL), 15% aq NaOH (150 mL), and water (50 mL). After stirring for an additional 30 min the mixture was filtered through Celite and the filter cake was washed with ethyl acetate (6 L). Saturated NaCl (1 L) was added to the filtrate and the layers were separated. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to afford 559 g (100%) of the diol (9*S*,11*R*,15*R*)-11,15-bis(tetrahydropyran-2-yloxy)-15-cyclohexyl-2,3,4,5,6,16,17,18,19,20-decanor-9-hydroxyprostanol, which was used in the next step without any further purification.

A 22 L three-neck round-bottom flask was charged with a solution of the diol reduction product from above (558 g, 1.23 mol) in CH_2Cl_2 (6 L). The reagents DMAP (1.5 g, 0.012 mol), NEt_3 (1012 mL, 7.37 mol), and Et_3SiCl (610 mL, 3.69 mmol) were added sequentially, resulting in the formation of a white precipitate. The suspension was stirred for 2.5 h and was quenched by the addition of water (2.5 L). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (1 L).

The combined organic layers were washed with saturated NaCl (4 L), dried over Na_2SO_4 and filtered, and the filtrate was concentrated to afford ca. 1016 g of a crude oil. Residual Et_3SiOH was distilled away using a Kugelrohr apparatus and the residue was purified by chromatography on a Kilo-Prep 250 liquid chromatograph eluting with 5% ethyl acetate in hexane to afford bissilyl ether **5** (613 g, 73%). ^1H NMR (characteristic peaks only) δ 4.62 (m, 2H), 4.15–3.25 (br m, 7H), 2.30–1.15 (br m, 18H), 0.95 (br t, 18H), 0.65 (br q, 12H). MALDI LRMS, m/z for $(M+Na)^+$ at 705.

(9*S*,11*R*,15*R*)-11,15-Bis(tetrahydropyran-2-yloxy)-15-cyclohexyl-2,3,4,5,6,16,17,18,19,20-decanor-9-(triethylsiloxy)prostanal (6). A 12-L three-neck round bottom flask was charged with $(COCl)_2$ (156 mL, 1.8 mol) and CH_2Cl_2 (1.6 L). The solution was cooled to an internal temperature of −55 °C and a solution of DMSO (323 mL, 4.5 mol) in CH_2Cl_2 (700 mL) was added over 1 h while maintaining the internal temperature below −50 °C. The mixture was stirred at an internal temperature of −60 °C for 1 additional hour and a solution of bissilyl ether **5** (613 g, 900 mmol) in CH_2Cl_2 (1.5 L) was added over another 1.5 h while maintaining the internal temperature below −55 °C. After an additional 3.5 h NEt_3 (752 mL, 5.4 mol) was added over 30 min as the internal temperature rose to −50 °C. After stirring at an internal temperature of −65 °C for 1.5 h the suspension was placed in a 5 °C refrigerator for 15 h. Water (3 L) was added to the reaction, the mixture was warmed to room temperature and was stirred for 30 min, and the phases were separated. The organic phase was washed with water (2×3 L) and saturated NaCl (2×2 L). The combined aqueous layers were extracted with CH_2Cl_2 (2×2 L) and the combined organic phases were washed with saturated NaCl (1 L), dried over Na_2SO_4, filtered, and concentrated. The residue was dissolved in 1:1 v/v ether/hexane (2 L) and washed with water (2×1 L) and saturated NaCl (1 L). The organic phase was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by chromatography in two portions on 7 kg of silica gel eluting with a 10% ethyl acetate→20% ethyl acetate in hexane gradient to afford aldehyde **6** (442 g, 87%). ^1H NMR δ 9.80 (br s, 1H), 4.62 (m, 2H), 4.20 (m, 1H), 3.85–3.60 (m, 3H), 3.40 (m, 3H), 2.80 (m, 1H), 2.45–2.05 (m, 4H), 1.95–1.10 (br m, 27H), 0.95 (br t, 9H), 0.55 (br q, 6H).

(5*Z*)-(9*S*,11*R*,15*R*)-11,15-Bis(tetrahydropyran-2-yloxy)-15-cyclohexyl-2,3,4,16,17,18,19,20-octanor-9-(triethylsiloxy)5-prostenoic acid methyl ester (7). A 12-L three-neck round-bottom flask was charged sequentially with THF (3 L), bis(2,2,2-trifluoroethyl) (methoxycarbonyl)-methylphosphonate (123 mL, 583 mmol), and pre-dried (over 4 Å molecular sieves for 1 week) tris [2-(2-methoxyethoxy)ethyl]amine (TDA-1; 561 mL, 1.75 mol). The brown solution was cooled to −65 °C (internal temperature) and $KN(SiMe_3)_2$ (1.166 L of a 0.5 M solution in toluene, 583 mmol) was added over 40 min while maintaining the internal temperature below −50 °C. The mixtuer was stirred for one h at an internal temperature of −65 °C before a solution of aldehyde **6** (301 g, 530 mmol) in THF (1.5 L) was added over 40 min while maintaining the internal temperature below −50 °C. After stirring at −50 °C for 1 h the mixture was warmed to −20 °C and maintained at that temperature for 15 h. Saturated NH_4Cl (2 L) was added and the mixture was warmed to room temperature. The suspension was filtered and the filter cake was washed with ethyl acetate (2 L). The phases of the filtrate were separated and the aqueous phase was extracted with ethyl acetate (2×1 L). Aqueous citric acid (10% w/v, 2 L) was added to the combined organic layers and the mixture was vigorously stirred for 10 min. The phases were separated and the organic phase was washed with saturated $NaHCO_3$ (2×2 L) and saturated NaCl (2 L), dried over Na_2SO_4, filtered, and concentrated to afford 430 g of crude product. Proton NMR analysis of the crude indicated an 8:1 ratio of Z:E isomers. The residue was first purified by passing through a 15% ethyl acetate in hexane solution of the residue through a sintered glass funnel containing 4 kg of silica gel to provide 311 g of a crude oil. This oil was further purified by chromatography on a KiloPrep 250 using a 10 cm tall×60 cm diameter silica gel cartridge of 32–63 μ KP-Sil silica gel eluting with 5% ethyl acetate in hexane to afford of *cis*-crotonate **7** (228 g, 69%) without any detectable *trans* diastereomer by proton NMR analysis. ^1H NMR δ 6.35 (m, 1H), 5.78 (broad d, $J=12$ Hz, 1H), 4.65 (m, 2H), 4.28 (m, 1H), 3.90 (m, 2H), 3.70 (s, 3H), 3.55–3.30 (m, 3H), 2.80 (m, 2H), 2.35–2.05 (m, 1H), 2.00–1.10 (broad m, 30H), 0.95 (broad t, 9H), 0.60 (broad q, 6H). MALDI LRMS, m/z for $(M+Na)^+$ at 645.

(5*Z*)-(9*S*,11*R*,15*R*)-11,15-Bis(tetrahydropyran-2-yloxy)-15-cyclohexyl-9-hydroxy-2,3,4,16,17,18,19,20-octanor-5-prostenol (8). A 12-L four-neck round-bottom flask was charged with a solution of ester **7** (273 g, 440 mmol) in THF (2.7 L). The solution was cooled to an internal temperature of −20 °C and a 1.5 M solution of diisobutylaluminum hydride in toluene (880 mL, 1.32 mol) was added over 30 min while maintaining the internal temperature below 5 °C. The reaction was stirred for 2 h and was quenched by the addition of methanol (250 mL) and saturated Na K tartrate tetrahydrate (2 L). The mixture was warmed to room temperature and was extracted with ethyl acetate (2×2 L). The combined organic layers were washed with water (2 L) and saturated NaCl (2×2 L). The organic phase dried over Na_2SO_4, filtered, and concentrated, and the residue was dried under vacuum for 15 h using a Kugelrohr apparatus to afford alcohol (5*Z*)-(9*S*,11*R*,15*R*)-11,15-bis(tetrahydropyran-2-yloxy)-15-cyclohexyl-2,3,4,16,17,18,19,20-octanor-9-(triethylsiloxy)-5-prostenol (250 g, 97%), which was used in the next step without further purification. ^1H NMR δ 5.65 (m, 2H), 4.65 (m, 2H), 4.30–3.25 (br m, 5H), 2.40–2.05 (br m, 4H), 2.00–1.10 (br m, 32H), 1.00 (br t, 9H), 0.60 (br q, 6H). MS, m/z at 617 for $(M+Na)^+$.

A 12-L three-neck round-bottom flask was charged with a solution of the above-synthesized alcohol (542 g, 911 mmol) in THF (5 L). The solution was cooled to 0 °C and a 1 M solution of TBAF in THF (1.275 L, 1.275 mol) was added over 10 min. The reaction was stirred at 0 °C for 1 h and was quenched by the addition

of saturated NH_4Cl (5 L). The solution was extracted with ethyl acetate (2×4 L) and the combined organic phases were washed with saturated NaCl, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by chromatography on 4 kg of silica gel eluting with 50% ethyl acetate in hexane→100% ethyl acetate gradient to afford diol **8** (348 g, 86%). MS, *m*/*z* at 503 for $(M+Na)^+$.

(5*Z*)-(9*S*,11*R*,15*R*)-11,15-Bis(tetrahydropyran-2-yloxy)-15-cyclohexyl-9-hydroxy-3-oxa-16,17,18,19,20-pentanor-5-prostenoic acid *t*-butyl ester (9). A 12-L three-neck round-bottom flask was charged with *n*-Bu_4NHSO_4 (105.4 g, 320 mmol) and a solution of diol **8** (347 g, 720 mmol) in toluene (3.5 L). Sequential addition of *t*-butylbromoacetate (190 mL, 1.28 mol) and aqueous NaOH (2.542 L, prepared by the dilution of 1.116 L of 50% w/w NaOH with 1.426 L of water; 14 mol) was followed by stirring for 40 min. Saturated NH_4Cl (5 L) was then added, and the phases were separated. The aqueous layer was extracted with toluene (2×1.5 L) and the combined organic phases were washed with saturated NaCl (3 L), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by chromatography on 7 kg of silica gel eluting with a gradient of 30% to 50% ethyl acetate in hexane to afford ester **9** (353.3 g, 82%) as well as some impure material, which was repurified by chromatography under the same conditions to afford additional **9** (18 g; total = 371.3 g = 86%). ^1H NMR (200 MHz, $CDCl_3$) δ 5.65 (m, 2H), 4.62 (m, 2H), 4.16 (m, 1H), 4.10–3.75 (m, 3H), 3.95 (s, 2H), 3.45 (m, 2H), 2.50–0.90 (broad m, 35H), 1.46 (s, 9H). HRMS, *m*/*z* calcd for $C_{34}H_{59}O_8$ $[(M+H)^+]$, 595.4209; found, 595.4208.

(5*Z*)-(9*S*,11*R*,15*R*)-11,15-Bis(tetrahydropyran-2-yloxy)-15-cyclohexyl-9-hydroxy-3-oxa-16,17,18,19,20-pentanor-5-prostenoic acid isopropyl ester (10). A 12-L three-neck round-bottom flask was charged with a solution of *t*-butyl ester **9** (350 g, 588 mmol) in 2-propanol (3.5 L). Titanium (IV) isopropoxide (261 mL, 880 mmol) was added at room temperature and the mixture was refluxed for 1 h. The reaction mixture was then cooled in an ice bath and was treated with a saturated solution of sodium potassium tartrate tetrahydrate (5 L). The solution was extracted with ethyl acetate (4×2 L), the combined organic phases were washed with saturated NaCl (5 L), dried over Na_2SO_4, filtered, and concentrated, and the residue was purified by chromatography on 7 kg of silica gel eluting with a 20–50% ethyl acetate in hexane gradient to afford isopropyl ester **10** (329.8 g, 96%). ^1H NMR (characteristic peaks only) δ 5.80–5.52 (m, 2H), 5.15 (sep, *J* = 6 Hz, 1H), 4.03 (broad s, 2H), 1.27 (d, *J* = 6 Hz, 6H).

(5*Z*)-(9*R*,11*R*,15*R*)-9-Chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanor-5-prostenoic acid isopropyl ester (AL-6598). To a 0 °C solution of alcohol **10** (340 g, 585 mmol) in pyridine (3.4 L) was added methanesulfonyl chloride (91.5 mL, 1.18 mol). The reaction mixture was stirred at 0 °C for 15 min and at room temperature for 4 h, at which time *n*-Bu_4NCl (2.5 kg, 8.99 mol) and toluene (5.2 L) were added. After stirring at room temperature for 16 h the suspension was heated at 55 °C for 6 h. The heating source was removed, ice (1.8 kg) was added, and the mixture was stirred for 30 min before the phases separated. The aqueous layer was extracted with ethyl acetate (2×2 L) and the combined organic layers were washed with saturated NaCl (4 L), dried over Na_2SO_4, filtered, and concentrated to provide an oil. A stirred suspension of the oil in 3:1 v:v acetic acid:water (4.65 L) was heated to 65 °C for 3.5 h. The suspension was cooled to room temperature and poured into water (18 L), and the mixture was extracted with ethyl acetate (3×4 L). The combined organic layers were washed with saturated $NaHCO_3$ to pH 7–8 and then with saturated NaCl, dried over Na_2SO_4, filtered, and concentrated to afford an impure sample of **AL–6598** (245 g) as a golden oil.

The oil was purified by chromatography on 7 kg of silica gel eluting with 40% hexane in *t*-butyl methyl ether to afford five 25–30 g fractions containing various ratios of **AL–6598** to the $\Delta^{5,6,8,9}$ diene elimination by-product (total, 160 g). These fractions were purified by HPLC using a CHIRALPAK®AD™ 10 cm diameter×50 cm length column eluting with 9:1 v/v hexane/2-propanol using a 200 mL/min flowrate. The total amount of **AL–6598** isolated after drying to a constant weight was 136.5 g (54% from alcohol **10**), with an average purity of 99% as measured by analytical HPLC. ^1H NMR δ 5.67 (m, 2H), 5.08 (sep, *J* = 6 Hz, 1H), 4.30–3.95 (m, 6H), 3.40 (m, 1H), 2.35 (m, 2H), 2.30–2.00 (m, 3H), 1.93–1.35 (m, 12H), 1.25 (d, *J* = 6 Hz, 6H), 1.22–0.90 (m, 6H); ^{13}C NMR δ 170.21 (C), 131.74 (CH), 126.77 (CH), 75.69 (CH), 75.25 (CH), 68.73 (CH), 67.64 (CH_2), 66.70 (CH_2), 61.20 (CH), 54.23 (CH), 51.20 (CH), 44.44 (CH), 43.65 (CH), 31.64 (CH_2), 30.17 (CH_2), 30.08 (CH_2), 29.32 (CH_2), 28.01 (CH_2), 26.50 (CH_2), 26.27 (CH_2), 26.16 (CH_2), 21.78 (CH_3). HRMS, *m*/*z* calcd for $C_{23}H_{40}O_5Cl$ $[(M+H)^+]$, 431.2564; found, 431.2569.

(5*Z*)-(9*R*,11*R*,15*R*)-9-Chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanor-5-prostenoic acid *tert*-butyl ester (32). Alcohol **9** (280 mg, 0.47 mmol) was dissolved in 4.0 mL of a 61:1.2:1.0 v:v:v mixture of CH_3CN/CCl_4/pyridine and then PPh_3 (180 mg, 0.70 mmol) was added. The reaction was stirred for 17 h was then treated with 1:1 ether/hexane (10 mL). The suspension was filtered, the filtrate was concentrated, and the residue was purified by chromatography on silica gel eluting with 40% ether in hexane to afford the 9β chloride (5*Z*)-(9*R*,11*R*,15*R*)-11,15-bis(tetrahydropyran-2-yloxy)-9-chloro-15-cyclohexyl-3-oxa-16,17,18,19,20-pentanor-5-prostenoic acid *tert*-butyl ester (90 mg, 34%; R_f 0.47, 40% ether in hexane) free from the $\Delta^{5,6,8,9}$ diene by-product.

A solution of this compound (80 mg, 0.13 mmol) in 65% aqueous acetic acid (7 mL) was heated at 65–70 °C for 45 min. The reaction was cooled to room temperature and was concentrated. The residue was dissolved in anhydrous ethanol and was concentrated, and the residue purified by chromatography on silica gel eluting with 40% hexane in ethyl acetate to afford **32** (60 mg, 100%; R_f 0.4, 40% hexane in ethyl acetate). ^1H NMR δ 5.69 (m, 2H), 4.32–3.85 (m, 5H), 3.38 (m, 1H), 2.50–1.95 (m, 5H), 1.95–0.80 (br m, 29H), 1.43 (s, 9H); ^{13}C NMR

δ 169.9 (C), 131.7 (CH), 126.8 (CH), 82.0 (C), 75.6 (CH), 75.1 (CH), 67.9 (CH_2), 66.6 (CH_2), 54.2 (CH), 51.0 (CH), 44.3 (CH), 43.7 (CH), 31.4 (CH_2), 30.3 (CH_2), 30.1 (CH_2), 29.3 (CH_2), 28.1 (CH_2), 28.0 (CH_2), 26.5 (CH_2), 26.3 (CH_2), 26.1 (CH_3). HRMS, *m*/*z* calcd for $C_{24}H_{42}O_5Cl$ [$(M+H)^+$], 445.2720; found, 445.2716.

(5*Z*)-(9*R*,11*R*,15*R*)-9-Chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanor-5-prostenoic acid (AL-6556). A solution of **32** (133 mg, 0.299 mmol), methanol (20 mL), water (2.0 mL), and lithium hydroxide monohydrate (50 mg, 1.2 mmol) was stirred for 17 h and was then added to 75 mL of 2:1 $CHCl_3$/0.1 M HCl. The layers were separated, the aqueous phase was extracted with $CHCl_3$ (3×25 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated to afford **AL-6556** (99 mg, 85%). ^{13}C NMR δ 173.17 (C), 132.77 (CH), 126.03 (CH), 75.68 (CH), 75.24 (CH), 66.89 (CH_2), 66.40 (CH_2), 61.32 (CH), 54.12 (CH), 50.62 (CH), 43.95 (CH_2), 43.33 (CH), 30.92 (CH_2), 30.73 (CH_2), 29.89 (CH_2), 29.30 (CH_2), 27.95 (CH_2), 26.44 (CH_2), 26.25 (CH_2), 26.09(CH_2). HRMS, *m*/*z* calcd for $C_{20}H_{34}O_5Cl$ [$(M+H)^+$], 389.2094; found, 389.2090.

(1*R*)-3-Chloro-1-cyclohexylpropanol (12). A solution of (1*R*)-3-chloro-1-phenylpropanol[15b] (**11**; 4.25 g, 25 mmol) in methanol (20 mL) containing 5% w/w Rh/Al_2O_3 (750 mg) was hydrogenated at 60–65 psig on a Parr shaker for 6.5 h. The solution was diluted with ethyl acetate, filtered, and concentrated. The residue (4.0 g of an oil) consisted of a 61:37:2 ratio of **12**, 1-chloro-3-cyclohexylpropane (deoxy-**12**), and (1*R*)-1-cyclohexylpropanol (deschloro-**12**) [diagnostic ^1H NMR signals (DMSO-d_6): for **12**, δ 3.30 (m, 1H), 3.68 (2 overlapping t, $J=5.2$ Hz, and 7.0 Hz, 2H), 4.48 (d, $J=5.9$ Hz, 1H, exchanges with D_2O); for deoxy-**12**, δ 3.58 (t, $J=6.6$ Hz, 2H); for deschloro-**12**, δ 0.83 (t $J=7$ Hz, 3H), 3.05 (m, 1H), 4.12 (d, $J=5.9$ Hz, 1H, exchanges with D_2O)]. Chromatographic purification of this oil on 150 g of silica gel eluting with 25% ethyl acetate in hexane afforded **12** (2.32 g, 55%) containing 2–3% of deschloro-**12**. HPLC analysis (Chiralcel OD, 250×4.6 mm, 95:5 hexane–*i*-PrOH) of the benzoate of **12** showed 97.6% ee.

(1*R*)-3-Chloro-1-cyclohexylprop-1-yl 1-ethoxyethyl ether (13). Ethyl vinyl ether (EVE; 10 mL) was added to a stirred ice-cooled solution of alcohol **12** (4.89 g, 27.7 mmol) and pyridinium *p*-toluenesulfonate (PPTS; 40 mg, 0.16 mmol) in CH_2Cl_2 (40 mL, pre-dried over 4 Å molecular sieves). After 10 min a further 200 mg (0.8 mmol) of PPTS and 8 mL of EVE were added, and the solution was allowed to warm to room temperature. After 1 h, the solution was filtered through a 2.5 cm pad of silica gel (slurried with diethyl ether) on a 350 mL fritted funnel, eluting with diethyl ether. Concentration afforded **13** (6.69 g, 97%). ^1H NMR δ 4.7 (2 overlapping q, $J=5.3$ Hz, 1H), 3.4–3.8 (m, 5H), 1.32 and 1.30 (2 overlapping d, $J=5.3$ Hz, 3H), 1.21 (t, $J=7$ Hz, 3H), 2.0–0.9 (m, 13H).

[3*R*(1*E*,3*R*),4*R*]-3-[3-Cyclohexyl-3-[(3-oxapent-2-yl)oxy]-propyl]-4-(*t*-butyldimethylsiloxy)-2-methylenecyclopentanone (15). Lithium wire (1% Na content, 3.2 mm diameter, 45 mg/cm:1.5 cm, 9.7 mg-atom) was added in 0.3 cm pieces to a stirred 0 °C (internal temperature) solution of 4,4′-di-*t*-butylbiphenyl (2.66 g, 10.0 mmol) and 5 mg of 2,2′-bipyridyl in dry THF (20 mL) under Ar. The mixture was titrated to a red endpoint with *n*-BuLi (2.5 M in hexane, 0.12 mL) and stirred for 15 h to form a deep blue-green solution of lithium 4,4′-di-*t*-butylbiphenyl. The solution was cooled to −45 °C (internal temperature) and a solution of chloride **13** (1.12 g, 4.5 mmol) in hexane (9.0 mL, pre-dried over 4 Å molecular sieves) was added dropwise via syringe, keeping the internal temperature below −40 °C. A yellow-green endpoint was observed. After 5 min, a solution of 0.25 M lithium (2-thienyl)cyanocuprate (20 mL, 5.0 mmol) was added dropwise while maintaining the internal temperature below −40 °C. A cherry-red endpoint was observed. After 10 min a solution of (4*R*)-4-(*t*-butyldimethylsiloxy)-2-[(diethylamino)methyl]cyclopent-2-en-1-one (**14**,[13] 1.12 g, 3.77 mmol) in dry THF (20 mL) was added dropwise while maintaining the internal temperature below −40 °C. The solution was allowed to warm to −20 °C and was then quenched into a rapidly stirring mixture of diethyl ether and saturated NH_4Cl. After several hours, the phases were separated and the aqueous layer was extracted with ethyl acetate. The combined organic phases were dried ($MgSO_4$), filtered, and concentrated, and the residue was purified by chromatography on 200 g of silica gel eluting with a gradient of 1:9 to 1:3 ethyl acetate/hexane to afford conjugate addition product **15** (950 mg, 58%). ^1H NMR δ 6.08 (s, 1H), 5.32 and 5.29 (both s, 2:3 ratio, total 1H), 4.68 (2 overlapping q, $J=5.2$ Hz, 1H), 4.12 (pentet, $J=5.2$ Hz, 1H), 3.55 (m, 2H), 3.30 (br q, $J=4$ Hz, 1H), 2.65 (br s, 1H), 2.62 (d of d, $J=17.8$ Hz, 5.8 Hz, 1H), 2.30 (d of d, $J=18.0$ Hz, 4.6 Hz, 1H), 1.30 and 1.29 (2 overlapping q, $J=5.3$ Hz, 3H), 1.20 and 1.17 (2 overlapping q, $J=7$ Hz, 3H), 1.9–0.8 (m, 15H), 0.87 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H).

[3*R*(1*E*,3*R*),4*R*]-3-(3-Cyclohexyl-3-hydroxypropyl)-4-(*t*-butyldimethylsiloxy)-2-methylenecyclopentanone (16). PPTS (250 mg, 1.0 mmol) was added to a solution of **15** (3.2 g, 7.3 mmol) in 1:1 diethyl ether/*i*-PrOH (100 mL). After 2 h the solution was added to saturated $NaHCO_3$ and was extracted with diethyl ether and ethyl acetate. The combined organic layers were washed with water and saturated NaCl, dried ($MgSO_4$), filtered, and concentrated, and the residue was purified by chromatography on 200 g of silica gel eluting with 25% ethyl acetate in hexane to afford alcohol **16** (2.05 g, 77%). ^1H NMR (DMSO-d_6) δ 5.83 (s, 1H), 5.30 (s, 1H), 4.21 (d, $J=5.5$ Hz, 1H, exchanges with D_2O), 4.12 (br q, $J=5$ Hz, 1H), 3.10 (br s, 1H), 2.65 (d of d, $J=18$ Hz, 6 Hz, 1H), 2.11 (d of d, $J=18$ Hz, 5 Hz, 1H), 1.8–0.8 (m, 15H), 0.79 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 203.89, 147.79, 117.36, 73.83, 71.74, 50.48, 46.34,43.35, 30.81, 28.92, 28.18, 27.66, 26.24, 25.99, 25.85, 25.62, 17.62,−4.64,−4.94.

[3*R*(1*E*,3*R*),4*R*]-3-[3-Cyclohexyl-3-(*t*-butyldimethylsiloxy)propyl]-4-(*t*-butyldimethylsiloxy)-2-methylenecyclopentanone (17). To an ice-cooled solution of alcohol **16** (1.53 g, 4.2 mmol) in a 4:3 mixture of CH_2Cl_2/DMF

(35 mL) under Ar was added via syringe $^{i}PrNEt_2$ (1.5 mL, 8.6 mmol), followed by $^{t}BuMe_2SiOTf$ (2.0 mL, 8.7 mmol). After 1.5 h, the mixture was diluted with diethyl ether and washed with water, saturated KH_2PO_4, and saturated NaCl. The organic layer was dried ($MgSO_4$), filtered, and concentrated, and the residue was purified by chromatography on 100 g of silica gel eluting with 10% diethyl ether in hexane to afford bissilyl ether **17** (1.60 g, 80%). ^{1}H NMR δ 6.08 (d, J = 2.2 Hz, 1H), 5.28 (d, J = 1.5 Hz, 1H), 4.09 (q, J = 5.7 Hz, 1H), 3.40 (br q, J = 5 Hz, 1H), 2.63 (br s, 1H), 2.62 (d of d, J = 18 Hz, 6 Hz, 1H), 2.30 (d of d, J = 18 Hz, 5 Hz, 1H), 1.8–0.9 (m, 15H), 0.88 (s, 18H), 0.08 (s, 3H), 0.06 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR δ 204.54, 147.59, 117.99, 76.43, 72.29, 51.29, 46.89, 43.14, 30.58, 28.67, 28.54, 27.78, 26.73, 26.51, 25.94, 25.73, 18.14, 17.95, −4.24, −4.36, −4.46, −4.79.

Z-3-(Tri-n-butylstannyl)-2-propen-1-yl (1′-ethoxy)ethyl ether (18). Pyridinium *p*-toluenesulfonate (1.00 g, 4.0 mmol) was added to a stirred solution of *Z*-3-(tri-*n*-butylstannyl)-2-propen-1-ol[18b] (3.18 g, 9.17 mmol) in 32 mL of ethyl vinyl ether and 16 mL of dichloromethane under argon. The mixture was stirred at 25 °C for 4 h, and then diluted with 40 mL of 9:1 (v/v) hexane–ethyl acetate. The suspension was decanted onto a pad of silica gel and eluted with 9:1 (v/v) hexane–ethyl acetate. Concentration in vacuo afforded 3.21 g (84%) of **18** as an oil: ^{1}H NMR ($CDCl_3$) δ 0.85–1.1 (m, 15H), 1.21 (t, J = 7, 3H), 1.35 (d, J = 5.5, 3H), 1.1–1.7 (m, 12H), 3.41–3.73 (m, 2H), 3.85–4.15 (m, 2H), 4.75 (q, J = 5.5, 1H), 6.06 (dt, J = 13, 1, 1H, $J_{Sn\text{-}H}$ = 64), 6.63 (dt, J = 13, 4, 1H, $J_{Sn\text{-}H}$ = 134); ^{13}C NMR ($CDCl_3$) δ 13.7, 15.3, 19.8 (CH_3), 10.5 ($J_{119Sn\text{-}C}$ = 343, $J_{117Sn\text{-}C}$ = 328), 27.3 ($J_{Sn\text{-}C}$ = 56), 29.2 ($J_{Sn\text{-}C}$ = 21), 60.6, 67.9 ($J_{Sn\text{-}C}$ = 38) (CH_2); 99.2, 131.5 ($J_{119Sn\text{-}C}$ = 366, $J_{117Sn\text{-}C}$ = 350), 144.4 (CH). Note: ^{117}Sn (7.6%) and ^{119}Sn (8.6%) satellites are unresolved except as indicated.

(5*Z*)-(11*R*,15*R*)-15-Cyclohexyl-11,15-di-*t*-butyldimethylsiloxy-9-oxo-2,3,4,16,17,18,19,20-octanor-5-prosten-1-yl 3-oxapent-2-yl ether (19). Methylithium (1.0 M in 9:1 cumene/THF, 0.80 mL, 0.80 mmol) was added dropwise to an ice-cooled suspension of CuCN powder (36 mg, 0.40 mmol) in dry THF (1.0 mL). After 5 min *Z*-$Bu_3SnCH{=}CHCH_2OCH(CH_3)OCH_2CH_3$ (**18**; 160 mg, 0.38 mmol) was added dropwise (0.5 mL of dry THF to rinse). The solution was allowed to warm to room temperature and was stirred for 1.5 h, then cooled to −78 °C. A solution of enone **17** (110 mg, 0.23 mmol) in dry THF (0.9 mL) was added dropwise. After 10 min, the mixture was added to saturated NH_4Cl and stirred for several hours. The solution was extracted with ethyl acetate, dried ($MgSO_4$), filtered, and concentrated, and the residue was purified by chromatography on 60 g of silica gel eluting with 10% ethyl acetate in hexane to afford **19** (100 mg, 72%). ^{1}H NMR δ 5.6 (m, 2H), 4.72 (q, J = 5.3 Hz, 1H), 4.1 (m, 3H), 3.6 (m, 2H), 3.39 (br q, J = 5 Hz, 1H), 2.42 (br t, J = 5.7 Hz, 2H), 2.59 (d of d, J = 18 Hz, 6 Hz, 1H), 2.15 (d of d, J = 18 Hz, 5 Hz, 1H), 1.9 (br s, 2H), 1.31 (t, J = 5.3 Hz, 3H), 1.21 (t, J = 7 Hz, 3H), 1.8–0.9 (m, 15H), 0.89 (s, 18H), 0.08 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H).

(5*Z*)-(9*S*,11*R*,15*R*)-15-Cyclohexyl-11,15-di-*t*-butyldimethylsiloxy-9-hydroxy-2,3,4,16,17,18,19,20-octanor-5-prosten-1-ol (20). L-Selectride® (1.0 M in THF, 2.5 mL, 2.5 mmol) was added dropwise to a −78 °C solution of ketone **19** (1.10 g, 1.62 mmol) in dry THF (10 mL) under Ar. After 45 min the cooling bath was removed and the solution was allowed to warm to room temperature and then cooled to 0 °C. Careful addition of 30% H_2O_2 (2 mL) was followed by warming of the solution to room temperature. Normal phase tlc analysis (12% ethyl acetate in hexane) showed the presence of a major, higher R_f spot and a minor, lower R_f spot, assigned as the 9α and 9β alcohols, respectively.[25] The mixture was added to saturated NH_4Cl and extracted with ethyl acetate and ether, and the combined organic layers were washed with 2 M $Na_2S_2O_3$, water, and saturated NaCl, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by chromatography on 75 g of silica gel eluting with 12% ethyl acetate in hexane to afford the 9α alcohol (5*Z*)-(9*S*,11*R*,15*R*)-15-Cyclohexyl-11,15-di-*t*-butyldimethylsiloxy - 9 - hydroxy - 2,3,4,16,17,18,19,20 - octanor-5-prosten-1-yl 3-oxapent-2-yl ether (560 mg, 56%). ^{1}H NMR (DMSO-d_6) 5.5 (m, 2H), 4.62 (q, J = 5.3 Hz, 1H), 4.30 (d, J = 5.2 Hz, 1H, exchanges with D_2O), 4.1–3.3 (m, 7H), 2.1 (septet, J = 7 Hz, 2H), 1.8–0.8 (m, 19H), 1.17 (d, J = 5.3 Hz, 3H), 1.08 (t, J = 7 Hz, 3H), 0.84 (s, 9H), 0.83 (s, 9H), 0.00 (s, 12H).

To a 0 °C solution of the above alcohol (550 mg, 0.90 mmol) in 1:1 diethyl ether/^{i}PrOH (16 mL) was added PPTS (40 mg, 0.16 mmol). The mixture was warmed to room temperature and stirred for 8 h. The solution was partitioned between ethyl acetate and saturated $NaHCO_3$, the organic phase was dried ($MgSO_4$), filtered, and concentrated, and the residue was purified by chromatography on 50 g of silica gel eluting with 25% ethyl acetate in hexane to provide diol **20** (370 mg, 76%). ^{1}H NMR δ 5.80 (br q, J = 9 Hz, 1H), 5.56 (d of t, J = 10.6 Hz, 4.6 Hz, 1H), 4.39 (t, J = 10.2 Hz, 1H), 4.05 (d, J = 17 Hz, 2H), 3.81 (d, J = 6 Hz, 1H), 3.4 (br s, 2H), 3.38 (br q, J = 4.7 Hz, 1H), 2.70 (q, J = 11.7 Hz, 1H), 2.05 (br d, J = 11.7 Hz, 1H), 1.9–0.7 (m, 19H), 0.88 (s, 18H), 0.07 (s, 3H), 0.02 (s, 3H). ^{13}C NMR δ 132.58, 129.09, 80.26, 76.46, 75.29, 57.34, 52.13, 42.97, 41.74, 32.15, 29.81, 28.71, 28.64, 27.88, 26.73, 26.55, 26.48, 25.95, 25.75, 18.19, 17.79, −4.21, −4.34, −4.71.

(5*Z*)-(9*S*,11*R*,15*R*)-15-Cyclohexyl-11,15-di-*t*-butyldimethylsiloxy-9-hydroxy-3-oxa-16,17,18,19,20-pentanor-5-prostenoic acid isopropyl ester (21). Ice-cold 25% NaOH (3.5 mL) was added to a vigorously stirring, ice-cooled solution of diol **20** (340 mg, 0.63 mmol) and *n*-Bu_4HSO_4 (21 mg, 0.06 mmol) in toluene (3.5 mL). *t*-Butyl bromoacetate (0.25 mL, 1.7 mmol) was added dropwise and the solution was allowed to warm to room temperature over 1 h. The mixture was diluted with diethyl ether, washed with water and saturated KH_2PO_4, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by chromatography on 25 g of silica gel eluting with 12% ethyl acetate in hexane to afford the *O*-alkylated product (5*Z*)-(9*S*,11*R*,15*R*)-15-cyclohexyl-11,15-di-*t*-butyldimethylsiloxy-9-hydroxy-3-oxa-16,17,18,19,20-pen-

tanor-5-prostenoic acid *t*-butyl ester (320 mg, 78%). ^{1}H NMR δ 5.65 (m, 2H) 4.20 (d, J = 6 Hz, 2H), 4.05 (m, 2H), 3.96 (s, 2H), 3.38 (br q, J = 5 Hz, 1H), 3.30 (d, J = 11 Hz, 1H, exchanges with D_2O), 2.4 (m, 1H), 2.2 (m, 1H), 1.48 (s, 9H), 1.9–0.8 (m, 19H), 0.88 (s, 18H), 0.08 (s, 6H), 0.02 (s, 6H).

To a solution of the above *t*-butyl ester (100 mg, 0.153 mmol) in *i*-PrOH (6 mL) under Ar was added $Ti(OPr^i)_4$ (0.2 mL). The solution was heated to 65–70 °C for 2 h and to reflux for 30 min, then cooled in ice, quenched with saturated sodium potassium tartrate, and extracted with diethyl ether. The organic phase was dried ($MgSO_4$), filtered, and concentrated. The residue was combined with the crude product from another run of 1/2 of the above scale and the whole was purified by chromatography on 20 g of silica gel eluting with 15% ethyl acetate in hexane to afford isopropyl ester **21** (110 mg, 75%). ^{1}H NMR δ 5.6 (m, 2H), 5.08 (septet, J = 6.3 Hz, 1H), 4.19 (d, J = 6 Hz, 2H), 4.03 (br s, 1H), 4.02 (s, 2H), 3.95 (br s, 1H), 3.33 (br q, J = 5 Hz, 1H), 3.3 (br s, 1H, exchanges with D_2O), 2.4 (m, 1H), 2.2 (m, 2H), 1.8–0.7 (m, 19H), 1.24 (d, J = 6.3 Hz, 6H), 0.86 (s, 18H), 0.05 (s, 6H), 0.01 (s, 3H), 0.00 (s, 3H).

(5*Z*)-(9*R*,11*R*,15*R*)-9-Chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanor-5-prostenoic acid isopropyl ester (AL-6598). Methanesulfonyl chloride (0.05 mL, 0.65 mmol) was added to a 0 °C solution of alcohol **21** (110 mg, 0.17 mmol) in pyridine (pre-dried over 4 Å molecular sieves, 1.0 mL) under Ar. The solution was allowed to warm to room temperature over 2.5 h. A suspension of $Bu_4NCl{\cdot}H_2O$ (1.0 g, 3.4 mmol) in toluene (1.5 mL) was added and the resulting mixture stirred at 55 °C overnight. The mixture was added to ice water and extracted with diethyl ether and the organic phase was washed with saturated NaCl, dried ($MgSO_4$), filtered, and concentrated. The residue was dissolved in THF (3 mL) and cooled to 0 °C. A premixed solution of THF (1.5 mL) and 48% HF (1.5 mL) was added dropwise. The solution was allowed to warm to room temperature over several hours until TLC analysis indicated complete desilylation. The mixture was added to saturated $NaHCO_3$ and extracted with ethyl acetate. The organic phase was dried ($MgSO_4$), filtered, and concentrated, and the residue was purified by chromatography on 15 g of silica gel eluting with 50% ethyl acetate in hexane to afford 45.4 mg (63%, calculated as the chloride) of **AL–6598** and its 9-deschloro-$\Delta^{5,6,8,9}$ diene by-product as a 3.5:1 molar mixture as measured by ^{1}H NMR spectroscopy (characteristic resonance for H-9 of the diene, δ = 5.3 ppm).

(5*Z*,13*E*)-(9*R*,11*R*,15*S*)-9-Chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanor-5,13-prostadienoic acid isopropyl ester (25). Beginning with lactone **3**, the title compound was synthesized analogously to **AL–6598** in 9 steps and 2.6% yield. ^{13}C NMR δ 170.04 (C), 134.51 (CH), 132.64 (CH), 130.43 (CH), 127.58 (CH), 77.34 (CH), 75.40 (CH), 68.60 (CH), 67.60 (CH_2), 66.64 (CH_2), 59.64 (CH), 55.95 (CH), 53.36 (CH), 43.61 (CH), 43.57 (CH_2), 28.83 (CH_2), 28.70 (CH_2), 26.49 (CH_2), 26.06 (CH_2), 25.99 (CH_2), 21.82 (CH_3). HRMS, m/z calcd for $C_{23}H_{38}O_5Cl$ [$(M+H)^+$], 429.2408; found, 429.2389.

(5*Z*,13*E*)-(11*R*,15*S*)-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanor-5,13-prostadienoic acid isopropyl ester (45). To a vigorously stirring mixture of alcohol **23** (1.09 g, 1.84 mmol; synthesized analogously to its 13,14-dihydro congener **9**) and pyridine (11 mL) at 0 °C was added methanesulfonyl chloride dropwise (510 mg, 4.5 mmol). The reaction was stirred for 30 min at 0 °C and for 2 h at room temperature. Saturated NH_4Cl (40 mL) was added and the mixture was extracted with ethyl acetate (2×40 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated, and the residue was purified by chromatography on silica gel eluting with 1:1 hexane/ethyl acetate to afford the corresponding 9α mesylate (5*Z*,13*E*)-(9*S*,11*R*,15*S*)-11,15-bis(tetrahydropyran-2-yloxy)-15-cyclohexyl-9-(methanesulfonyloxy)-3-oxa-16,17,18,19,20-pentanor-5-prostenoic acid isopropyl ester (1.08 g, 87%, R_f 0.5 in 1:1 hexane:ethyl acetate).

To a THF (11 mL) solution of the mesylate at 0 °C was added dropwise a 1 M solution of $LiEt_3BH$ in THF (11 mL, 11 mmol) and the reaction was stirred overnight at room temperature. The mixture was poured into a 1:1 v/v mixture of ethyl acetate/saturated NH_4Cl (50 mL), the layers were separated, and the aqeuous phase was extracted with ethyl acetate (2×30 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated, and the residue was purified by chromatography on a silica gel eluting with 40% ethyl acetate in hexane to afford the 9-deoxy alcohol (5*Z*,13*E*)-(11*R*,15*S*)-11,15-bis(tetrahydropyran-2-yloxy)-15-cyclohexyl-3-oxa-16,17,18,19,20-pentanor-5,13-prostadienol (**24**; 642 mg, 79%, R_f 0.4 in 40% ethyl acetate in hexane).

To a solution of the above (560 mg, 1.12 mmol) in DMF (5 mL) was added PDC (1.32 g, 3.51 mmol). After 48 h, water (20 mL) was added and the mixture was extracted with ethyl acetate (4×20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was dissolved in acetone (20 mL) and DBU (780 mg, 5.12 mmol) was added. After 15 min isopropyl iodide (850 mg, 5.0 mmol) was added and the reaction was stirred for 20 h. Concentration of the mixture and chromatography of the residue on silica gel eluting with 20% ethyl acetate in hexane afforded (5*Z*,13*E*)-(11*R*,15*R*)-11,15-bis(tetrahydropyran-2-yloxy)-15-cyclohexyl-3-oxa-16,17,18,19,20-pentanor-5,13-prostadienoic acid isopropyl ester (238 mg, 38% R_f 0.4 in 20% ethyl acetate in hexane).

To a mixture of the above, bis THP ether (230 mg, 0.41 mmol), *i*-PrOH (18 mL), and water (2 mL) was added 12 M HCl (1 mL). After 2 h saturated $NaHCO_3$ (20 mL) was added and the mixture was extracted with ethyl acetate (3×20 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was purified by chromatography on a 25 cm tall×26 mm diameter silica gel column eluting with 40% hexane in ethyl acetate to afford 9-deoxy ester **45** (120 mg, 74%, R_f 0.25 in 40% hexane

in ethyl acetate). ^{13}C NMR δ 170.00 (C), 134.17 (CH), 132.73 (CH), 125.97 (CH), 77.92 (CH), 77.68 (CH), 68.47 (CH), 67.38 (CH_2), 66.73 (CH_2), 58.02 (CH), 43.44 (CH), 42.77 (CH), 32.15 (CH_2), 28.89 (CH_2), 28.80 (CH_2), 27.63 (CH_2), 26.51 (CH_2), 26.06 (CH_2), 25.94 (CH_2), 21.97 (CH_3). HRMS, *m*/*z* calcd for $C_{23}H_{37}O_5$ [$(M+H)^+$]. 393.2641; found, 393.2633.

(5*Z*,13*E*)-(11*R*,15*S*)-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanor-5,13-prostadienoic acid (22). A solution of **45** (61 mg, 0.15 mmol), lithium hydroxide monohydrate (60 mg, 1.43 mmol), methanol (1.1 mL), and water (0.5 mL) was stirred for 16 h. The reaction was quenched by the addition of 1 M HCl (5 mL) and was extracted with ethyl acetate (3×10 mL), dried over Na_2SO_4, filtered, and concentrated to afford **22** (43 mg, 81%). ^{13}C NMR δ 173.44 (C), 134.03 (CH), 133.63 (CH), 125.38 (CH), 78.00 (CH), 77.74 (CH), 66.31 (CH_2), 57.76 (CH), 43.22 (CH), 42.88 (CH), 32.14 (CH_2), 28.89 (CH_2), 28.77 (CH_2), 27.59 (CH_2), 26.48 (CH_2), 26.03 (CH_2), 25.97 (CH_2). MS, *m*/*z* calcd for $C_{20}H_{33}O_5$ [$(M+H)^+$], 353.2328; found, 353.2326.

(5*Z*)-(11*R*,15*R*)-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanor-5-prostenoic acid (40). To a 0 °C solution of alcohol **10** (400 mg, 0.69 mmol) in pyridine (4.0 mL) was added methanesulfonyl chloride (150 mg, 1.4 mmol). After 15 min at 0 °C, the reaction was warmed to room temperature and was stirred for 4 h. The mixture was then partitioned between ethyl acetate and saturated $CuSO_4$, and the organic layer was dried over $MgSO_4$, filtered, and concentrated to the crude 9α mesylate (480 mg crude).

The crude mesylate was dissolved in THF (2.0 mL) at 0 °C and a 1 M solution of $LiEt_3BH$ (2.7 mL, 2.7 mmol) was added. The reaction was stirred for 15 min at 0 °C and at room temperature for 18 h. The mixture was added to water (20 mL) and was extracted with ethyl acetate (3×20 mL), dried ($MgSO_4$), filtered, and concentrated. The residue was purified by chromatography on silica gel eluting with a 30–50% ethyl acetate in hexane gradient to afford (5*Z*)-(11*R*,15*R*)-11,15-bis(tetrahydropyran-2-yloxy)-15-cyclohexyl-3-oxa-16,17,18,19,20-pentanor-5-prostenol (337 mg, 94%; R_f 0.4, 1:1 ethyl acetate/hexane).

A solution of above alcohol (337 mg, 0.64 mmol), DMF (10 mL), and PDC (1.4 g, 3.84 mmol) was stirred for 40 h, at which time the mixture was poured into 1:1 water/saturated KH_2PO_4 (100 mL). The solution was extracted with ethyl acetate (5×50 mL) and the combined organic layers were washed with water (2×25 mL) and saturated NaCl (25 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was dissolved in $CHCl_3$ and was treated with exess ethereal CH_2N_2 until a yellow color persisted, at which time solvent and excess CH_2N_2 were removed by an N_2 stream. The residue was purified by chromatography on silica gel eluting with a 10–30% ethyl acetate in hexane gradient to afford (5*Z*)-(11*R*,15*R*)-11,15-Bis(tetrahydropyran-2-yloxy)-15-cyclohexyl-3-oxa-16,17,18,19,20-pentanor-5-prostenoic acid methyl ester (140 mg, 40%; R_f 0.7, 1:1 ethyl acetate/hexane).

A 0 °C solution of the above compound (140 mg, 0.25 mmol), methanol (10 mL), and water (0.5 mL) was treated with saturated HCl (10 drops). After 15 min the temperature was raised to room temperature. After an additional 30 min, $NaHCO_3$ was added to quench the reaction, and the mixture was partitioned between $CHCl_3$ and saturated $NaHCO_3$. The organic layer was dried (Na_2SO_4), filtered, and concentrated, and the residue was purified by chromatography on silica gel eluting with 50–100% ethyl acetate in hexane gradient to afford the deprotection product (5*Z*)-(11*R*,15*R*)-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanor-5-prostenoic acid methyl ester (86 mg, 95%; R_f 0.16, 1:1 ethyl acetate/hexane).

A solution of the above methyl ester (88 mg, 0.24 mmol), methanol (10 mL), water (0.5 mL), and lithium hydroxide monohydrate (100 mg, 2.38 mmol) was stirred for 26 h and was then partitioned between $CHCl_3$/1 M HCl. The organic layer was dried over Na_2SO_4, filtered, and concentrated to afford **40** (82 mg, 96%). ^{13}C NMR δ 172.92 (C), 134.87 (CH), 124.73 (CH), 78.53 (CH), 76.01 (CH), 66.54 (CH_2), 66.21 (CH_2), 52.67 (CH), 44.23 (CH), 43.41 (CH), 33.92 (CH_2), 33.56 (CH_2), 31.07 (CH_2), 29.33 (CH_2), 29.19 (CH_2), 28.97 (CH_2), 27.93 (CH_2), 26.52 (CH_2), 26.33 (CH_2), 26.18 (CH_2). LRMS, *m*/*z* at 377 for [$(M+Na)^+$].

(5*Z*)-(11*R*,15*R*)-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanor-5-prostenoic acid isopropyl ester (47). A solution of acid **40** (60 mg, 0.17 mmol) in acetone (6 mL) was treated with DBU (0.15 mL, 1.0 mmol). After 30 min, isopropyl iodide (0.10 mL, 0.84 mmol) was added and the reaction was stirred for 48 h. The mixture was concentrated and the residue was purified by chromatography on silica gel eluting with 30–50% ethyl acetate in hexane gradient to afford **47** (40 mg, 59%; R_f 0.25, 1:1 ethyl acetate/hexane). ^{1}H NMR δ 5.73–5.55 (m, 2H), 5.11 (septet, J = 6 Hz, 1H), 4.30–4.12 (m, 2H), 4.04 (app d, J = 2 Hz, 2H), 3.92 (br s, 1H), 3.38 (br s, 1H), 2.41–2.26 (m, 1H), 2.17–1.99 (m, 1H), 1.92–1.38 (m, 19H), 1.27 (d, J = 6 Hz, 6H), 1.22–0.93 (m, 4H); ^{13}C NMR δ 170.16 (C), 133.67 (CH), 125.52 (CH), 78.92 (CH), 75.95 (CH), 68.57 (CH), 67.45 (CH_2), 66.79 (CH_2), 53.27 (CH), 44.60 (CH), 43.59 (CH), 34.15 (CH_2), 33.38 (CH_2), 31.91 (CH_2), 29.58 (CH_2), 29.18 (CH_2), 27.94 (CH_2), 26.52 (CH_2), 26.31 (CH_2), 26.16 (CH_2), 21.80 (CH_3). LRMS, *m*/*z* at 418 for [$(M+Na)^+$].

(5*E*,13*E*)-(9*R*,11*R*,15*R*)-9-Chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanor-5,13-prostadienoic acid *tert*-butyl ester (44). To a solution of lactone **3** (5.7 g, 12.7 mmol) in THF (40 mL) at −78 °C was added dropwise a 1.5 M solution of DIBAL-H in toluene (11.5 mL, 17.2 mmol). After 2 h, the reaction was poured into saturated sodium potassium tartrate tetrahydrate (70 mL) and was stirred for 30 min to break the emulsion. The mixture was extracted with ethyl acetate (3×50 mL) and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated, and the residue was purified by chromatography on silica gel eluting with 1:1 ethyl acetate/hexane to afford [3a*R*,4*R*(1*E*,3*S*),5*R*,6a*S*]-4-[3-cyclohexyl-3-(tetrahydropyran-2-yloxy)propenyl]-5-

(tetrahydropyran-2-yloxy)-hexahydro-2*H*-cyclopenat[b] furan-2-ol (**27**; 4.7 g, 82%).

A mixture of **27** (5.1 g, 11.3 mmol), $Ph_3P{=}CHCO_2CH_3$ (6.6 g, 19.7 mmol), CH_2Cl_2 (50 mL), and glacial acetic acid (8 drops) were stirred overnight. The reaction was concentrated and the residue was purified by chromatography on a silica gel column eluting with 1:1 hexane/ethyl acetate to afford the *trans* crotonate (5*E*,13*E*)-(9*S*,11*R*,15*S*)-11,15-bis(tetrahydropyran-2-yloxy)-15-cyclohexyl-9-hydroxy-2,3,4,16,17,18,19,20-octanor-5,13-prostadienoic acid methyl ester (**28**; 5.7 g, 99%).

A mixture of **28** (5.7 g, 11.8 mmol), CH_2Cl_2 (150 mL), imidazole (1.46 g, 21.5 mmol), DMAP (500 mg, 4.1 mmol), and Me_2Bu^tSiCl (2.54 g, 16.9 mmol) was stirred for 1 h. Saturated NH_4Cl (50 mL) was added, the phases were separated, the aqueous layer was extracted with CH_2Cl_2 (2×50 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The residue was purified by chromatography on silica gel eluting with 20% ethyl acetate in hexane to provide the 9α silyl ether (5*E*,13*E*)-(9*S*,11*R*,15*S*)-11,15-bis(tetrahydropyran-2-yloxy)-9-(*t*-butyldimethylsiloxy)-15-cyclohexyl-2,3,4,16,17,18,19,20-octanor-5,13-prostadienoic acid methyl ester (6.05 g, 84%).

To a solution of the above silyl ether (6.0 g, 9.8 mmol) in THF (50 mL) at 0 °C was added dropwise a 1.5 M solution of DIBAL-H in toluene (16 mL, 24 mmol). The reaction was brought to room temperature and was stirred for 2 h, at which time saturated sodium potassium tartrate tetrahydrate (75 mL) was added. The mixture was stirred for 25 min to break the emulsion, the layers were separated, and the aqueous phase was extracted with ethyl acetate (2×50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated, and the residue was purified by chromatography on silica gel eluting with 25% ethyl acetate in hexane to yield the alcohol reduction product (5*E*,13*E*)-(9*S*,11*R*,15*S*)-11,15-bis(tetrahydropyran-2-yloxy)-9-(*t*-butyldimethylsiloxy)-15-cyclohexyl-2,3,4,16,17,18,19,20-octanor-5,13-prostadienol (4.28 g, 74%).

A mixture of the above alcohol (2.4 g, 4.1 mmol), water (25 mL), toluene (30 mL), NaOH (3.8 g, 95 mmol), Bu_4NHSO_4 (300 mg, 0.88 mmol), and $BrCH_2CO_2Bu^t$ (5.0 g, 26 mmol) was vigorously stirred overnight. The layers were separated, the aqueous phase was extracted with ethyl acetate (2×50 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The residue was purified by chromatography on silica gel eluting with 20% ethyl acetate in hexane to afford the *O*-alkylated product (5*E*,13*E*)-(9*S*,11*R*,15*S*)-11,15-bis(tetrahydropyran-2-yloxy)-9-(*t*-butyldimethylsiloxy)-15-cyclohexyl-3-oxa-16,17,18,19,20-pentanor-5,13-prostadienoic acid *tert*-butyl ester (1.48 g, 48%).

A solution of the above compound (1.4 g, 2.0 mmol) in THF (20 mL) was treated with a 1 M solution of TBAF in THF (6 mL, 6 mmol). After 2 h, saturated NH_4Cl (30 mL) was added, the phases were separated, and the aqueous layer was extracted with ethyl acetate (2×40 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated, and the residue was purified by chromatography on silica gel eluting with 1:1 hexane:ethyl acetate to afford 9α alcohol (5*E*,13*E*)-(9*S*,11*R*,15*S*)-11,15-bis(tetrahydropyran-2-yloxy)-15-cyclohexyl-9-hydroxy-3-oxa-16,17,18,19,20-pentanor-5,13-prostadienoic acid *tert*-butyl ester (450 mg, 38%).

A solution of the above 9α alcohol (430 mg, 0.72 mmol), PPh_3 (350 mg, 1.34 mmol), and pyridine (112 mg, 1.42 mmol) in CH_3CN (6 mL) was treated with CCl_4 (240 mg, 1.55 mmol). After stirring overnight the reaction was concentrated and the residue was purified by chromatography on silica gel to afford a mixture of the 9β choride (5*E*,13*E*)-(9*R*,11*R*,15*S*)-11,15-bis(tetrahydropyran-2-yloxy)-9-chloro-15-cyclohexyl-3-oxa-16,17,18,19,20-pentanor-5,13-prostadienoic acid *tert*-butyl ester and the 9-deschloro-$\Delta^{5,6,8,9}$ diene by-product (formally derived by HCl elimination) (5*E*,13*E*)-(11*R*,15*S*)-11,15-bis(tetrahydropyran-2-yloxy)-15-cyclohexyl-3-oxa-16,17,18,19,20-pentanor-5,13,8(9)-prostatrienoic acid *tert*-butyl ester (362 mg, 82% calculated as the chloride).

A solution of the above compound mixture (310 mg, 0.51 mmol calculated as the chloride), THF (5 mL), water (1 mL), and acetic acid (9 mL) was heated at 65 °C for 1 h. The solution was concentrated and the residue was purified by chromatography on silica gel eltuing with 4:1 ethyl acetate:hexane to afford a mixture of **44** and the corresponding $\Delta^{5,6,8,9}$ diene side product (188 mg, 83% calculated as the chloride). This mixture was purified by reverse-phase HPLC to afford pure **44** (58 mg, 26% from the 9α alcohol). ^{13}C NMR δ 169.67 (C), 134.67 (CH), 133.09 (CH), 131.18 (CH), 128.56 (CH), 81.62 (C), 77.31 (CH), 75.04 (CH), 71.63 (CH_2), 67.59 (CH_2), 59.38 (CH), 56.34 (CH), 53.08 (CH), 43.38 (CH_2), 43.32 (CH), 33.88 (CH_2), 28.87 (CH_2), 28.77 (CH_2), 28.10 (CH_3), 26.48 (CH_2), 26.05 (CH_2), 25.97 (CH_2). HRMS, *m*/*z* calcd for $C_{24}H_{40}O_5Cl$ [$(M+H)^+$], 445.2535; found, 445.2574.

(5*E*,13*E*)-(9*R*,11*R*,15*R*)-9-Chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanor-5,13-prostadienoic acid (26). A solution of **44** (22 mg, 0.050 mmol), water (1 mL), methanol (2 mL), and lithium hydroxide monohydrate (17 mg, 0.41 mmol) was stirred for 20 h. Saturated citric acid (10 mL) was added and the solution was extracted with $CHCl_3$ (3×10 mL), dried (Na_2SO_4), filtered, and concentrated to afford **26** (19 mg, 98%). ^{13}C NMR δ 173.22 (C), 134.60 (CH), 132.94 (CH), 131.66 (CH), 128.44 (CH), 77.79 (CH), 75.24 (CH), 71.99 (CH_2), 66.59 (CH_2), 58.93 (CH), 55.42 (CH), 52.80 (CH), 43.29 (CH_2), 43.18 (CH), 32.77 (CH_2), 28.89 (CH_2), 28.83 (CH_2), 26.46 (CH_2), 26.00 (CH_2), 25.92 (CH_2). LRMS, *m*/*z* calcd for $C_{20}H_{31}O_5Cl$ (M^+), 386.1860; found, 386.1859.

(5*Z*)-(9*R*,11*R*,15*S*)-9-Chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanor-5-prostenoic acid isopropyl ester (29). Beginning with the 15β alcohol **30**,[6] the title compound was synthesized analogously to its 15*R* diastereomer **AL–6598** in 13 steps and 1.7%

yield. ^{13}C NMR δ 170.21 (C), 131.12 (CH), 127.19 (CH), 76.75 (CH), 75.44 (CH), 68.70 (CH), 67.67 (CH_2), 66.78 (CH_2), 61.02 (CH), 54.28 (CH), 51.18 (CH), 44.31 (CH), 44.19 (CH), 31.35 (CH_2), 31.19 (CH_2), 29.73 (CH_2), 27.60 (CH_2), 26.50 (CH_2), 26.31 (CH_2), 26.16 (CH_2), 21.80 (CH_3). CI LRMS, *m*/*z* calcd For $C_{23}H_{40}O_5Cl$ [$(M+H)^+$], 431; found, 431.

(5*Z*)-(9*R*,11*R*,15*S*)-9-Chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanor-5-prostenoic acid (38). A mixture of **29** (52 mg, 0.12 mmol), lithium hydroxide monohydrate (35 mg, 0.83 mmol), methanol (9 mL), and water (2 mL) was stirred for 24 h. A 1 M solution of HCl (2 mL) was added and the solution was extracted with CH_2Cl_2 (3×20 mL), dried (Na_2SO_4), filtered, and concentrated to afford **38** (33 mg, 71%). ^{13}C NMR δ 166.64 (C), 132.11 (CH), 126.56 (CH), 77.14 (CH), 75.63 (CH), 66.53 (CH_2), 61.02 (CH), 54.38 (CH), 51.16 (CH), 44.18 (CH), 44.10 (CH), 31.44 (CH_2), 31.27 (CH_2), 29.99 (CH_2), 29.13 (CH_2), 27.57 (CH_2), 26.47 (CH_2), 26.29 (CH_2), 26.14 (CH_2). HRMS, *m*/*z* calcd for $C_{20}H_{34}O_5Cl$ [$(M+H)^+$], 389.2095; found, 389.2089.

(5*Z*,13*E*)-(9*R*,11*R*,15*R*)-9-Chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanor-5,13-prostadienoic acid isopropyl ester (46). Starting with the 15*R* diol **30**,[6] the title compound was synthesized analogously to **AL–6598** in 12 steps and 0.88% yield. ^{13}C NMR δ 170.14 (C), 134.71 (CH), 131.60 (CH), 130.56 (CH), 127.41 (CH), 76.95 (CH), 75.44 (CH), 68.66 (CH), 67.57 (CH_2), 66.66 (CH_2), 59.63 (CH), 55.81 (CH), 53.42 (CH), 43.76 (CH_2), 43.64 (CH), 28.92 (CH_2), 28.67 (CH_2), 28.58 (CH_2), 26.51 (CH_2), 26.13 (CH_2), 26.05 (CH_2), 21.82 (CH_3). HRMS, *m*/*z* calcd for $C_{23}H_{38}O_5Cl$ [$(M+H)^+$], 427.2251; found, 427.2249.

(5*Z*,13*E*)-(9*R*,11*R*,15*R*)-9-Chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanor-5,13-prostadienoic acid (36). A solution of **46** (30 mg, 0.070 mmol), lithium hydroxide monohydrate (25 mg, 0.71 mmol), methanol (1 mL), and water (0.3 mL) was stirred for 22 h. Saturated KH_2PO_4 (6 mL) was added and the mixture was extracted with ethyl acetate (3×4 mL), dried (Na_2SO_4), filtered, and concentrated to afford **36** (20 mg, 74%). ^{13}C NMR δ 173.22 (C), 134.11 (CH), 132.44 (CH), 131.90 (CH), 126.37 (CH), 77.52 (CH), 75.20 (CH), 66.50 (CH_2), 66.03 (CH_2), 59.60 (CH), 56.34 (CH), 53.74 (CH), 43.93 (CH_2), 43.33 (CH), 29.09 (CH_2), 28.82 (CH_2), 28.63 (CH_2), 26.42 (CH_2), 26.05 (CH_2), 25.96 (CH_2). HRMS, *m*/*z* calcd for $C_{20}H_{32}O_5Cl$ [$(M+H)^+$], 387.1938; found, 387.1911.

(5*Z*)-(9*R*,11*R*,15*R*)-9-Chloro-15-cyclohexyl-11-hydroxy-15-methoxy-3-oxa-16,17,18,19,20-pentanor-5-prostenoic acid *tert*-butyl ester (49). To a solution of **32** (127 mg, 0.285 mmol, prepared analogously to its corresponding isopropyl ester **AL–6598**), imidazole (49 mg, 0.72 mmol), DMAP (10 mg, 0.082 mmol), and CH_2Cl_2 (5 mL) was added *t*-butyldimethylsilyl chloride (90 mg, 0.59 mmol). After 24 h saturated NH_4Cl (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3×10 mL), dried ($MgSO_4$), filtered, and concentrated. The residue was purified by chromatography on silica gel eluting with 20% ethyl acetate in hexane to afford the 11-siloxy derivative (5*Z*)-(9*R*,11*R*,15*R*)-11-(*t*-butyldimethylsiloxy)-9-chloro-15-cyclohexyl-15-hydroxy-3-oxa-16,17,18,19,20-pentanor-5-prostenoic acid *tert*-butyl ester (87 mg, 55%).

The silyl ether from above (80 mg, 0.14 mmol), 2,6-di-*t*-butylpyridine (100 mg, 0.52 mmol), CH_2Cl_2 (2 mL), and methyl trifluoromethanesulfonate (80 mg, 0.51 mmol) was refluxed for 24 h. After cooling to room temperature the solution was added to saturated $NaHCO_3$ (10 mL), extracted with CH_2Cl_2 (3×10 mL), dried ($MgSO_4$), filtered, and concentrated. The residue was purified by chromatography on silica gel eluting with 10% ethyl acetate in hexane to afford the 11-siloxy, 15-methoxy compound (5*Z*)-(9*R*,11*R*,15*R*)-11-(*t*-butyldimethylsiloxy)-9-chloro-15-cyclohexyl-15-methoxy-3-oxa-16,17,18,19,20-pentanor-5-prostenoic acid *tert*-butyl ester (35 mg, 44%).

The above compound (32 mg, 0.056 mmol) was dissolved in THF (1.5 mL) and TBAF (0.12 mL of a 1 M solution in THF, 0.12 mmol) was added. After 30 min saturated NH_4Cl (4 mL) was added, the mixture was extracted with ethyl acetate (3×5 mL), dried ($MgSO_4$), filtered, and concentrated. The residue was purified by chromatography on silica gel eluting with 40% ethyl acetate in hexane to afford **49** (24 mg, 94%). ^{13}C NMR δ 169.77 (C), 130.90 (CH), 127.43 (CH), 85.89 (CH), 81.69 (C), 76.05 (CH), 67.83 (CH_2), 66.56 (CH_2), 61.00 (CH_2), 57.83 (CH_3), 54.06 (CH), 51.92 (CH), 44.45 (CH_2), 40.65 (CH), 29.92 (CH_2), 29.83 (CH_2), 29.02 (CH_2), 28.42 (CH_3), 28.10 (CH_2), 26.64 (CH_2), 26.37 (CH_2). HRMS, *m*/*z* calcd for $C_{25}H_{44}O_5Cl$ [$(M+H)^+$], 459.2877; found, 459.2878.

(5*Z*)-(9*R*,11*R*,15*R*)-9-Chloro-15-cyclohexyl-11-hydroxy-15-methoxy-3-oxa-16,17,18,19,20-pentanor-5-prostenoic acid (31). A solution of **49** (12 mg, 0.026 mmol), lithium hydroxide monohydrate (10 mg, 0.24 mmol), methanol (4 mL), and water (0.5 mL) was stirred for 24 h. Saturated citric acid (5 mL) was added and the mixture was extracted with CH_2Cl_2 (4×5 mL), dried (Na_2SO_4), filtered, and concentrated to afford **31** (7.0 mg, 67%). ^{13}C NMR δ 172.46 (C), 132.26 (CH), 126.34 (CH), 86.21 (CH), 75.86 (CH), 66.64 (CH_2), 66.31 (CH_2), 61.07 (CH), 57.77 (CH_3), 53.77 (CH), 51.95 (CH), 44.36 (CH_2), 40.62 (CH), 30.44 (CH_2), 29.32 (CH_2), 29.02 (CH_2), 28.42 (CH_2), 27.97 (CH_2), 26.60 (CH_2), 26.33 (CH_2). HRMS, *m*/*z* calcd for $C_{21}H_{36}O_5Cl$ [$(M+H)^+$], 403.2251; found, 403.2261.

(5*Z*,13*E*)-(9*R*,11*R*,15*S*)-9-Chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanor-5,13-prostadienol (37). To a solution of **43** (41 mg, 0.093 mmol) in THF (5 mL) at 0 °C was added a 1.5 M solution of DIBAL-H in toluene (0.7 mL, 1.05 mmol). After warming to room temperature and stirring for an additional 1.5 h, saturated NH_4Cl (15 mL) was added. The mixture was extracted with ethyl acetate (3×15 mL), dried ($MgSO_4$), filtered, and concentrated, and the residue was purified by chromatography on silica gel eluting with ethyl acetate to afford **37** (21 mg, 68%). ^{13}C NMR

δ 134.59 (CH), 133.00 (CH), 129.61 (CH), 128.21 (CH), 128.21 (CH), 77.56 (CH), 75.16 (CH), 71.54 (CH_2), 67.93 (CH_2), 66.46 (CH_2), 61.76 (CH), 59.49 (CH), 55.85 (CH), 53.23 (CH), 43.43 (CH), 28.81 (CH_2), 28.56 (CH_2), 26.46 (CH_2), 26.94 (CH_2), 26.02 (CH_2), 25.57 (CH_2). HRMS, *m*/*z* calcd for $C_{20}H_{34}O_4Cl$ [$(M+H^+]$, 373.2146; found, 373.2101.

(5*Z*)-(9*R*,11*R*,15*R*)-9-Chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanor-5-prostenol (42). A solution of (5*Z*)-(9*R*,11*R*,15*R*)-11,15-bis(tetrahydropyran-2-yloxy)-9-chloro-15-cyclohexyl-3-oxa-16,17,18,19,20-pentanor-5-prostenoic acid *tert*-butyl ester (the C11,C15-bisTHP ether of **32**, 150 mg, 0.24 mmol) in THF (5.0 mL) was cooled to 0 °C and DIBAL-H (0.5 mL of a 1.5 M solution in toluene, 0.75 mmol) was added. After 2.5 h, saturated sodium potassium tartrate (10 mL) was added and the mixture was stirred at room temperature for 1 h to break the emulsion. The organic layer was separated and the aqueous phase was extracted with ethyl acetate (5×10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated, and the residue was purified by chromatography on silica gel eluting with 30% ethyl acetate in hexane to afford the alcohol (5*Z*)-(9*R*,11*R*,15*R*)-11,15-bis(tetrahydropyran-2-yloxy)-9-chloro-15-cyclohexyl-3-oxa-16,17,18,19,20-pentanor-5-prostenol (114 mg, 87%; R_f=0.15, 30% ethyl acetate in hexane).

The above alcohol (54 mg, 0.09 mmol) was heated at 70 °C for 1 h in 65% aqueous acetic acid. The mixture was concentrated and the residue was purified by chromatography on silica gel eluting with ethyl acetate to afford **42** (33 mg, 88% yield; R_f 0.15, ethyl acetate). ^{1}H NMR δ 5.68 (m, 2H), 4.08 (m, 4H), 3.74 (m, 2H), 3.42 (m, 1H), 2.37 (m, 2H), 2.35–1.90 (m, 4H), 1.85–0.90 (broad m, 18H). ^{13}C NMR δ 131.06 (CH), 127.52 (CH), 75.80 (CH), 75.54 (CH), 71.94 (CH_2), 66.38 (CH_2), 66.38 (CH_2), 61.82 (CH_2), 60.82 (CH_2), 54.05 (CH), 50.87 (CH), 44.69 (CH), 43.60 (CH), 31.29 (CH_2), 29.71 (CH_2), 29.46 (CH_2), 29.22 (CH_2), 28.08 (CH_2), 26.48 (CH_2), 26.28 (CH_2), 26.14 (CH_2). HRMS, *m*/*z* calcd for $C_{20}H_{36}O_4Cl$ [$(M+H)^+$], 375.2302; found, 375.2299.

(5*Z*)-(9*R*,11*R*,15*R*)-9-Chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanor-5-prostenoic acid amide (33). A mixture of **32** (42 mg, 0.09 mmol), NH_4Cl (130 mg, 2.4 mmol), and liquid NH_3 (2 mL) were heated in a sealed pressure tube to 70 °C. After 24 h the reaction was cooled to −78 °C, the vessel was opened, and the mixture was warmed to room temperature to evaporate the NH_3. The residue was dissolved in ethyl acetate, filtered, and concentrated, and the residue was purified by chromatography on Florisil eluting with a gradient of 50% ethyl acetate in hexane to 40% hexane in acetone to afford **33** (20 mg, 57%; R_f 0.13, 50% hexane in acetone). ^{13}C NMR δ 172.72 (C), 131.47 (CH), 126.81 (CH), 75.92 (CH), 75.68 (CH), 69.23 (CH_2), 66.71 (CH_2), 60.61 (CH), 54.03 (CH), 51.44 (CH), 44.65 (CH_2), 44.61 (CH_2),43.55 (CH), 31.55 (CH_2), 29.74 (CH_2), 29.34 (CH_2), 29.24 (CH_2), 28.04 (CH_2), 26.46 (CH_2), 26.27 (CH_2), 26.12 (CH_2). HRMS, *m*/*z* calcd for $C_{20}H_{35}NO_4Cl$ [$(M+H)^+$], 388.2255; found, 388.2252.

(5*Z*)-(9*R*,11*R*,15*R*)-9-Chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanor-5-prostenoic acid *n*-butyl amide (34). A solution of Me_3Al (2 M in toluene, 0.58 mL, 1.6 mmol) was added to *n*-$BuNH_2$ (90 mg, 1.2 mmol) in toluene (1.5 mL). After 25 min a solution of **AL–6598** (106 mg, 0.246 mmol) in toluene (1.5 mL) was added. After 3 h the reaction was quenched by the addition of saturated KH_2PO_4 (3 mL). The mixture was extracted with ethyl acetate (2×4 mL) and the combined organic layers were dried (Na_2SO_4), decanted, and concentrated. The residue was purified by chromatography on silica gel eluting with ethyl acetate to afford **34** (56 mg, 51% yield). ^{13}C NMR δ 169.70 (C), 131.36 (CH), 126.88 (CH), 76.02 (CH), 75.70 (CH), 69.41 (CH_2), 566.75 (CH_2), 60.73 (CH), 54.12 (CH), 51.57 (CH), 44.66 (CH_2), 43.62 (CH), 38.72 (CH_2), 31.72 (CH_2), 29.80 (CH_2), 29.37 (CH_2), 29.32 (CH_2), 28.20 (CH_2), 26.58 (CH_2), 26.38 (CH_2), 26.23 (CH_2), 20.16 (CH_2), 13.84 (CH_3). HRMS, *m*/*z* calcd for $C_{24}H_{43}O_4NCl$ [$(M+H)^+$], 444.287856; found, 444.28784.

(5*Z*)-(9*R*,11*R*,15*R*)-9-Chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanor-5-prostenoic acid dimethyl amide (35). To a solution of **32** (101 mg, 0.22 mmol) in toluene (5 mL) was added 2 mL of a stock solution prepared by the addition of Me_3Al (2 M in toluene, 2 mL, 4 mmol) to a toluene (3 mL) solution of Me_2NH_2Cl (430 mg, 5.3 mmol). The reaction was heated at 60 °C for 27 h and was then cooled to room temperature. Toluene (50 mL) and saturated sodium potassium tartrate were added and the mixture was stirred for 1 h. The layers were separated, the aqueous phase was extracted with ethyl acetate (3×10 mL), and the combined organic layers were washed with saturated NaCl (3×10 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated, and the residue was purified by chromatography on Florisil eluting first with ethyl acetate and then with acetone to afford **35** (20 mg, 22%; R_f 0.12, ethyl acetate). ^{13}C NMR δ 169.25 (C), 132.38 (CH), 126.54 (CH), 75.45 (CH), 74.48 (CH), 68.47 (CH_2), 66.58 (CH_2), 62.00 (CH), 54.39 (CH), 50.50 (CH), 44.36 (CH_2), 43.62 (CH), 36.12 (CH_3), 35.55 (CH_3), 31.31 (CH_2), 30.89 (CH_2), 30.29 (CH_2), 29.40 (CH_2), 28.01 (CH_2), 26.57 (CH_2), 26.33 (CH_2), 26.17 (CH_2). HRMS, *m*/*z* calcd for $C_{22}H_{39}NO_4Cl$ [$(M+H)^+$], 416.2568; found, 416.2560.

(5*Z*)-(9*R*,11*R*,15*R*)-9-Chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanor-5-prostenoic acid N-methyl amide (41). To a solution of (5*Z*)-(9*R*,11*R*,15*R*)-9-Chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanor-5-prostenoic acid methyl ester (125 mg, 0.311 mmol; prepared in quantitative yield by treatment of the acid **AL-6556** with diazomethane) in toluene (5 mL) was added a stock solution (2.8 mL) prepared by the addition of 2 M Me_3Al (2.0 mL, 4.0 mmol) to a toluene (3 mL) suspension of $MeNH_3Cl$ (360 mg, 5.3 mmol). After stirring for 30 min the mixture was heated to 50 °C (bath temperature) overnight. The mixture was cooled to room temperature and diluted with toluene (50 mL) and then stirred with saturated sodium potassium tartrate for 1 h. The layers were separated, the aqueous phase was extracted with

ethyl acetate, and the combined organic layes were dried over $MgSO_4$, filtered, and concentrated. The residue was purified by chromatography on a 15 cm tall×20 mm diameter silica gel column using 1:1 ethyl acetate/hexane→ethyl acetate→20% acetone in ethyl acetate gradient elution to afford **41** (98 mg, 78%). ^{13}C NMR δ 170.48 (C), 131.42 (CH), 126.87 (CH), 75.92 (CH), 75.61 (CH), 69.35 (CH_2), 66.68 (CH_2), 60.64 (CH), 53.99 (CH), 51.43 (CH), 44.56 (CH_2), 43.52 (CH), 31.57 (CH_2), 29.69 (CH_2), 29.28 (CH_2), 29.22 (CH_2), 28.08 (CH_2), 26.47 (CH_2), 26.27 (CH_2), 26.12 (CH_2), 25.56 (CH_3). HRMS, *m*/*z* calcd for $C_{21}H_{37}NO_4Cl$ [$(M+H)^+$], 402.2411; found, 402.2413.

(9*R*,11*R*,15*R*)-9-Chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanorprostanoic acid *t*-butyl ester (48). A solution of **32** (23 mg, 0.052 mmol) in ethyl acetate (5 mL) containing 5% Rh/Al_2O_3 (8 mg) was stirred under 1 atmosphere pressure of H_2. The mixture was filterred through a pad of Celite and concentrated, and the residue was purified by chromatography on a on a 15 cm tall×10 mm diameter silica gel column eluting with a gradient of 30–60% ethyl acetate in hexane to provide **48** (18 mg, 77%). ^{13}C NMR 169.87 (C), 81.54 (C), 76.18 (CH), 71.40 (CH_2), 68.71 (CH_2), 61.85 (CH), 54.27 (CH), 52.69 (CH), 44.72 (CH_2), 43.65 (CH), 33.19 (CH_2), 31.74 (CH_2), 30.33 (CH_2), 29.80 (CH_2), 29.25 (CH_2), 28.11 (CH_3), 27.94 (CH_2), 26.48 (CH_2), 26.28 (CH_2), 26.12 (CH_2), 23.48 (CH_2). HRMS, *m*/*z* calcd for $C_{24}H_{44}O_5Cl$ [$(M+H)^+$], 447.2877; found, 447.2872.

(9*R*,11*R*,15*R*)-9-Chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanorprostanoic acid (39). A solution of **48** (7 mg, 0.02 mmol), $LiOH{\cdot}H_2O$ (5 mg, 0.12 mmol), methanol (0.5 mL), and water (0.2 mL) was stirred for 19 h. The mixture was partitioned between $CHCl_3$(20 mL)/0.1 M HCl (10 mL). The phases were separated and the aqueous layer was extracted with $CHCl_3$ (2×10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated to afford **39** (7 mg, 100%). ^{13}C NMR δ 172.89 (C), 76.42 (CH), 75.96 (CH), 71.35 (CH_2), 67.91 (CH_2), 61.68 (CH), 53.94 (CH), 52.29 (CH), 44.74 (CH_2), 43.36 (CH), 32.47 (CH_2), 31.20 (CH_2), 29.53 (CH_2), 29.45 (CH_2), 29.19 (CH_2), 27.99 (CH_2), 26.44 (CH_2), 26.25 (CH_2), 26.09 (CH_2), 23.21(CH_2). HRMS, *m*/*z* calcd for $C_{20}H_{36}O_5Cl$ [$(M+H)^+$], 391.2251; found, 391.2214.

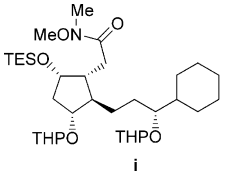
Biological assays

In vitro binding and functional activation of prostaglandin DP receptors. DP receptor binding affinity was determined using frozen thawed expired human blood platelets with [^3H]PGD_2 as the radioligand. Functional efficacy and potency was determined using embryonic bovine tracheal fibroblasts (EBTr) according to published methods.[22–24]

In vivo rabbit and monkey IOP studies. Rabbit IOP was measured in Dutch belted rabbits. The compound was instilled (1×30 uL) following a baseline IOP reading and IOP was measured 1, 2, 3, and 5 h following dosing. Monkey IOP studies were done using cynomolgus monkeys (*Macaca fascicularis*) that had previously had permanent ocular hypertension induced in the right eye by laser trabeculoplasty. All left eyes were normal and normotensive. The animals were trained to sit in restraint 'chairs' (designed for glaucoma studies) and conditioned to accept dosing and pressure measurements without chemical restraint. In the monkey IOP model the compound was instilled (1×30 uL) twice a day for a total of five doses. IOP was recorded 2, 4, and 6 h after the first dose, 16 h after the fourth dose, and 2, 4, and 6 h after the fifth dose. The reduction in IOP is reported as percent change from baseline measurements made prior to the initial dose. Compounds were generally formulated in a tromethamine/boric acid buffer containing 1.5% cremophor EL, 0.1% EDTA, and 0.01% benzalkonium chloride, pH 7.4.

References and Notes

1. Clark, A. F. *Emerg. Drugs* **1999**, *4*, 333.
2. Sugrue, M. F. *J. Med. Chem.* **1997**, *40*, 2793.
3. (a) Bito, L. Z. *Surv. Ophthalmol.* **1997**, *41* (Suppl. 2), S1. (b) Alm, A. *Prog. Retin. Eye Res.* **1998**, *17*, 291. (c) Linden, C.; Alm, A. *Drugs Aging* **1999**, *14*, 387.
4. Goh, Y.; Nakajima, M.; Azuma, I.; Hayaishi, O. *Jpn. J. Ophthalmol.* **1988**, *32*, 471.
5. (a) Goh, Y.; Nakajima, M.; Azuma, I. *Brit. J. Ophthalmol.* **1988**, *72*, 461. (b) Woodward, D. F.; Spada, C. S.; Hawley, S. B.; Williams, L. S.; Protzman, C. E.; Nieves, A. L. *Eur. J. Pharmacol.* **1993**, *230*, 327. (c) Matsugi, T.; Kageyama, M.; Nishimura, K.; Giles, H.; Shirasawa, E. *Eur. J. Pharmacol.* **1995**, *275*, 245. (d) Woodward, D. F.; Hawley, S. B.; Williams, L. S.; Ralston, T. R.; Protzman, C. E.; Spada, C. S.; Nieves, A. L. *Invest. Ophthamol. Vis. Sci.* **1990**, *31*, 138. (e) Nakajima, M.; Goh, Y.; Azuma, I.; Hayashi, O. *Graefe's Arch. Clin. Exp. Ophthamol.* **1991**, *229*, 411. (f) Thierauch, K.-H.; Stürzebecher, C. St.; Schillinger, E.; Rehwinkel, H.; Radüchel, B.; Skuballa, W.; Vorbrüggen, H.; *Prostaglandins* **1988**, *35*, 855. (g) Schulz, B. G.; Beckman, R.; Muller, B.; Schroder, G.; Maass, B.; Thierauch, K.-H.; Buchmann, B.; Verhallen, P. F. J.; Frohlich, W. *Adv. Prostaglandin Thromboxane Leukotriene Res.* **1991**, *21*, 21 B591. (h) Taisho Pharmaceutical Co. has disclosed the IOP lowering effect of several 9β-chloro-3-thia-15-cyclohexyl-13,14-alkynyl analogues of $PGF_{1\alpha}$. Sato, F.; Amano, T.; Kameo, K.; Tanami, T.; Mutoh, M.; Ono, N.; Goto, J. EP 737676A1.
6. (a) Buchmann, B.; Skuballa, W.; Vorbrüggen, H. *Tetrahedron Lett.* **1990**, *31*, 3425. (b) Buchmann, B.; Skuballa, W.; Vorbrüggen, H.; Radüchel, B.; Loge, O.; Elger, W.; Stürzebecher, C.-S.; Thierauch, K.-H. EP 299914 B1.
7. (a) Muzart, J. *Synthesis* **1993**, 11. (b) Hirst, G. C.; Johnson, T. O., Jr.; Overman, L. E. *J. Am. Chem. Soc.* **1993**, *115*, 2992.
8. (a) Alternatively, **4** was converted to **6** by DIBAL-H reduction of Weinreb amide **i**. Both of these routes also worked well with TBDPS instead of THP protection.



i

See: Conrow, R. E. US Patent No. 6,015,922 (Alcon). (b) Mills, S.; Desmond, R.; Reamer, R. A.; Volante, R. P.; Shinkai, I. *Tetrahedron Lett.* **1988**, *29*, 281.

9. Cooper, G. F.; Wren, D. L.; Jackson, D. Y.; Beard, C. C.; Galeazzi, E.; Van Horn, A. R.; Li, T. T. *J. Org. Chem.* **1993**, *58*, 4280.
10. Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.
11. (a) Soula, G. *J. Org. Chem.* **1985**, *50*, 3717. (b) For the use of TDA-1 as a superior alternative to 18-crown-6 in a Wittig reaction, see: Stafford, J. A.; McMurry, J. E. *Tetrahedron Lett.* **1988**, *29*, 2531. (c) The *Z* to *E* ratio was 4:1 without predrying of TDA-1, and 1:1 when TDA-1 was omitted.
12. Imwinkelried, R.; Schiess, M.; Seebach, D. Org. Synth, Coll.; Vol. VIII, p 201.
13. (a) Okamoto, S.; Katayama, S.; Ono, N.; Sato, F. *Tetrahedron: Asymmetry* **1992**, *3*, 1525. (b) Okamoto, S.; Kobayashi, Y.; Kato, H.; Hori, K.; Takahashi, T.; Tsuji, J.; Sato, F. *J. Org. Chem.* **1988**, *53*, 5590. (c) Chiral enone **14** was obtained from TCI Americas, Portland, OR, USA.
14. Stocker, J. H. *J. Org. Chem.* **1962**, *27*, 2288.
15. (a) Srebnik, M.; Ramachandran, P. V.; Brown, H. C. *J. Org. Chem.* **1988**, *53*, 2916. (b) Corey, E. J.; Reichard, G. A. *Tetrahedron Lett.* **1989**, *30*, 5207. (c) Available in 99% ee from Aldrich Chemical Company.
16. Lipshutz, B. H.; Kozlowski, J. A.; Parker, D. A.; Nguyen, S. L.; McCarthy, K. E. *J. Organomet. Chem.* **1985**, *285*, 437.
17. (a) Rücker, C. *Tetrahedron Lett.* **1984**, *25*, 4349. (b) Subsequent to our work a procedure was disclosed for Li-I exchange of the TBDMS-protected iodo analogue of **13**, using *t*-BuLi at −78 °C in diethyl ether: ref 5(h), example 23.
18. (a) A reaction medium consisting of 2:1 (v/v) EVE–CH_2Cl_2 saturated with PPTS proved optimal for conversion of the sterically hindered, acid-sensitive alcohol *Z*-$Bu_3SnCH{=}CH\text{-}CH_2OH$[18b] to **18**. (b) Corey, E. J.; Eckrich, T. M. *Tetrahedron Lett.* **1984**, *25*, 2419.
19. Behling, J. R.; Babiak, K. A.; Ng, J. S.; Campbell, A. L.; Moretti, R.; Koerner, M.; Lipshutz, B. H. *J. Am. Chem. Soc.* **1988**, *110*, 2641. This report describes the preparation of *E*-vinylcuprates.
20. Interestingly, this olefin isomerization did not occur during dechlorination of the corresponding 3-carba compound under the same conditions.
21. Claesson, A. *J. Org. Chem.* **1987**, *52*, 4414.
22. Crider, J. Y.; Xu, S. X.; Griffin, B. W.; Sharif, N. A. *Prostaglandins, Leukotrienes Essent. Fatty Acids* **1998**, *59*, 77.
23. Crider, J. Y.; Griffin, B. W.; Sharif, N. A. *Br. J. Pharmacol.* **1999**, *127*, 204.
24. Sharif, N. A.; Crider, J. Y.; Xu, S. X.; Williams, G. W. J. *Pharmacol. Exp. Ther.* **2000**, *293*, 321.
25. Suzuki, M.; Yanagisawa, A.; Noyori, R. *J. Am. Chem. Soc.* **1988**, *110*, 4718.