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# AL-12182, a novel 11-oxa prostaglandin analog with topical ocular hypotensive activity in the monkey

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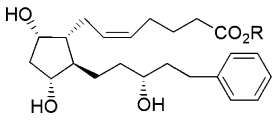
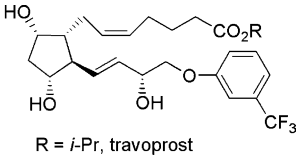
Dedicated to the memory of Dr. Tai-Lee Ke, our esteemed colleague and friend

**Abstract**—A series of 11-oxa prostaglandin analogs was evaluated for FP receptor binding and activation. Several compounds having aryloxy-terminated lower chains were found to be potent agonists. Topical ocular dosing of **AL-12182**, the isopropyl ester prodrug of the potent agonist **13**, lowered intraocular pressure in the monkey by 40% accompanied by minimal conjunctival hyperemia in the rabbit. **AL-12182** was synthesized on multigram scale starting with D-sorbitol.


Glaucoma, a heterogeneous family of optic neuropathies, is a leading cause of blindness in the developed world. 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] Endogenous prostaglandins (PGs) and their prodrugs, such as $PGF_{2\alpha}$ isopropyl ester, reduce IOP in man but also cause conjunctival hyperemia, foreign-body sensation, and ocular pain.[2] The development of prodrugs of potent, selective synthetic prostaglandin FP receptor agonists as clinically effective IOP-lowering agents devoid of many of these side effects has been an important advance in the treatment of glaucoma.[3] Thus latanoprost, the related $\Delta^{13}$ (*E*) ethyl amide bimatoprost, and the aryloxy-terminated compound travoprost[4] are prostaglandin analogs that have been introduced into clinical practice as active ingredients of topical IOP-lowering medications.



R = *i*-Pr, latanoprost
R = H, latanoprost acid



R = *i*-Pr, travoprost
R = H, travoprost acid

Further investigations have led to the exploration of compounds having an 11-oxa (i.e., tetrahydrofuran) structure instead of the cyclopentane core of endogenous PGs. Others have reported the synthesis of 11-oxa $PGF_{2\alpha}$ (**3**, Table 1) and of omega-chain modified analogs,[5–8] for example, the $PGF_{2\alpha}$ analog **1**[7] and the $PGE_2$ analogs **2**.[8] One report noted that **3** and its C9 epimer lacked FP receptor-linked bioactivity in an ex vivo smooth muscle contraction assay.[5] To the best of our knowledge no other biological data have been reported for 11-oxa prostaglandins, although typical PG-like systemic activities are suggested in patents.[8,9] We now report the results of in vitro and in vivo biological

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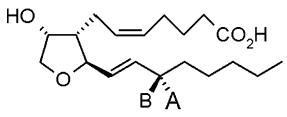
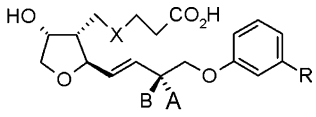
**Table 1.** FP receptor binding affinity and functional response




**3, 4**

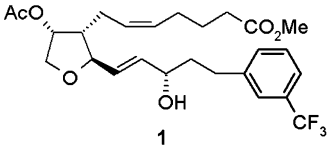



**5-16**

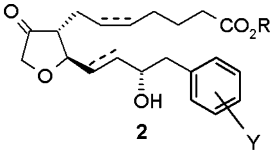
| Compound | X | A | B | R | $K_i \pm$ SEM,[a] nM | $EC_{50} \pm$ SEM,[a] nM (% response) |
|---|---|---|---|---|---|---|
| **3**[b] | — | OH | H | — | 6700 ± 620 | 2380 ± 214 (64) |
| **4**[c] | — | H | OH | — | >10,000 | >10,000 |
| **5** | *Z*—CH=CHCH$_2$ | OH | H | H | 640 ± 84 | 293 ± 45 (67) |
| **6** | *Z*—CH=CHCH$_2$ | H | OH | H | 2800 ± 560 | 573 ± 201 (49) |
| **7** | *Z*—CH=CHCH$_2$ | OH | H | Cl | 890 ± 270 | 58 ± 18 (84) |
| **8** | *Z*—CH=CHCH$_2$ | H | OH | Cl | 7300 ± 3000 | 194 ± 19 (67) |
| **9** | *Z*—CH=CHCH$_2$ | OH | H | CF$_3$ | 3100 ± 1400 | 187 ± 35 (74) |
| **10** | *Z*—CH=CHCH$_2$ | H | OH | CF$_3$ | >10,000 | 899 ± 101 (43) |
| **11** | *Z*—CH$_2$CH=CH | OH | H | H | 330 ± 100 | 57 ± 2 (83) |
| **12** | *Z*—CH$_2$CH=CH | H | OH | H | 5100 ± 2800 | 252 ± 6 (59) |
| **13** | *Z*—CH$_2$CH=CH | OH | H | Cl | 147 ± 36 | 23 ± 3 (88) |
| **14** | *Z*—CH$_2$CH=CH | H | OH | Cl | 820 ± 410 | 249 ± 66 (71) |
| **15** | *Z*—CH$_2$CH=CH | OH | H | CF$_3$ | 350 ± 140 | 67 ± 35 (88) |
| **16** | *Z*—CH$_2$CH=CH | H | OH | CF$_3$ | 9900 ± 180 | 781 ± 2 (61) |
| PGF$_{2\alpha}$ | — | — | — | — | 129 ± 12 | 24.5 ± 0.92 (92) |
| Latanoprost acid | — | — | — | — | 92 ± 14 | 34.4 ± 5.2 (75) |
| Travoprost acid | — | — | — | — | 52 ± 2 | 2.7 ± 0.28 (100) |

[a] SEM = Standard error of the mean.
[b] **3** = 11-oxa-PGF$_{2\alpha}$.
[c] **4** = 15-*epi*-11-oxa-PGF$_{2\alpha}$.

studies on a series of 11-oxa PGs culminating in the discovery of **AL-12182**, a highly effective topical ocular hypotensive agent in the monkey.

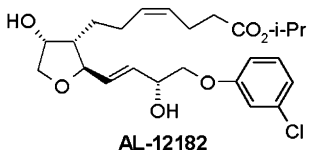



**1**




**2**

Y = H, F, Cl, Me, OMe, CF$_3$




**AL-12182**

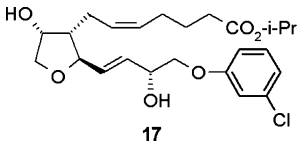
Table 1 summarizes our evaluation of the acids **3**–**16** for binding to an FP receptor expressed in bovine corpus luteum ($K_i$),[10] and for functional potency ($EC_{50}$ = effective concentration necessary for a compound to attain 50% of its maximal response) and efficacy via stimulation of FP receptor-linked phosphoinositide turnover in Swiss 3T3 mouse fibroblast cells.[11] The configuration of the omega chain carbinyl stereocenter was provisionally assigned based on $EC_{50}$ values in the FP functional assay, with the more potent diastereomer being designated as that having A = OH, B = H.[12] The standards PGF$_{2\alpha}$, latanoprost acid, and travoprost acid are included for comparison.

Compounds **11**–**16** feature a $\Delta^4$ double bond in the alpha chain.[13–15] Application of this structural perturbation to PGF$_{2\alpha}$ inhibited metabolic degradation in the monkey.[14] We are unaware of any prior report on the effect of this $\Delta^4$ modification on FP receptor response. In the present 11-oxa PG series this $\Delta^4$ modification increased FP receptor binding affinity and functional potency in two cases (**13** vs **7** and **15** vs **9**), while in one case (**11** vs **5**) little effect was observed. Acid **13** was comparable in potency and efficacy to PGF$_{2\alpha}$ and latanoprost acid.[16]

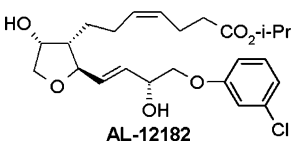
The favorable in vitro profiles of acids **7** and **13** led to the evaluation of their isopropyl ester prodrugs **17** and **AL-12182** in three animal models (Table 2). Conjunctival hyperemia (red eye), a side effect, was studied in New Zealand Albino rabbits. $RCH_{15}$ denotes the dose estimated to elicit 15% incidence of hyperemia over the 4 h course of the study.[4] As a preliminary assay of topical ocular potency and thus potential IOP-lowering effectiveness, the ability of a compound to constrict the cat pupil over time was measured and is expressed as an $ED_5$ value,[4] indicating the dose estimated to produce a 5 unit (mm h) difference in pupil diameter between the dosed and control eye. Acute IOP-lowering efficacy was measured in conscious ocular hypertensive cynomolgous monkeys.[4] The IOP reductions in Table 2 are the maxima observed for the indicated doses.

Based on its superior in vivo profile, **AL-12182** was selected for large-scale synthesis as a potential clinical candidate. We had prepared compounds **3**–**16** on ca. 10 mg scale from the known nonracemic pro-11-oxa analog of Corey lactone.[5–7] In turn, we had obtained this intermediate from D-glucose,[7] but found that the requisite anomeric deoxygenation sequences did not scale up well. We therefore adopted an alternative route reported by Hanessian et al.[5] that uses inexpensive

**Table 2.** Rabbit, cat, and monkey data




**17**




**AL-12182**

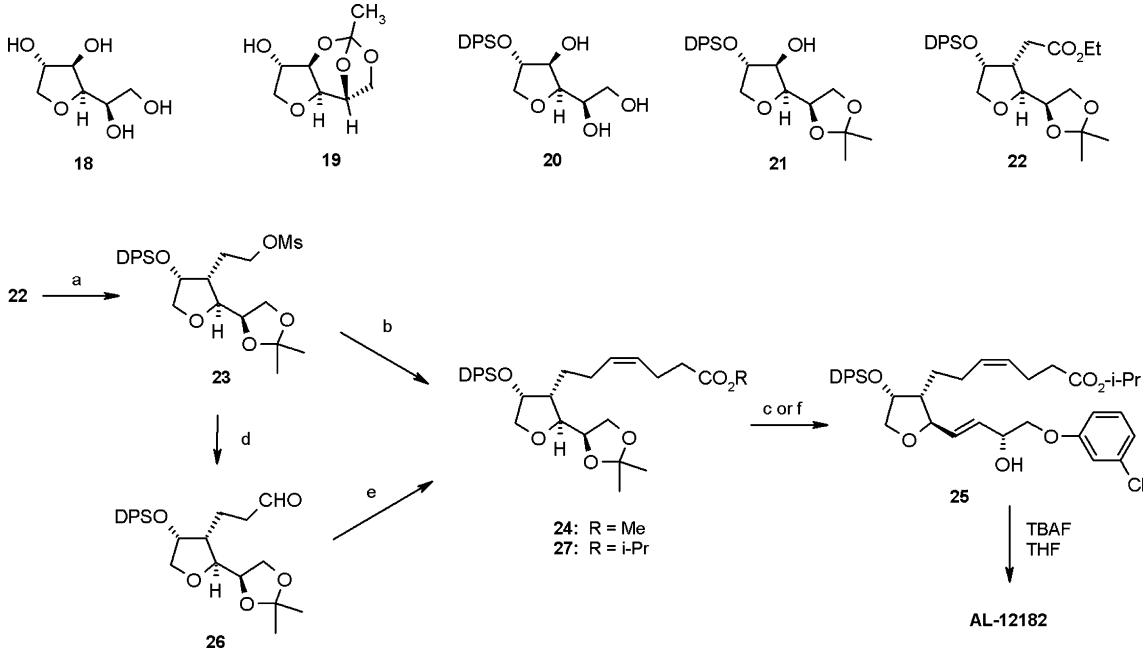
| Compound | $RCH_{15}$[a] | CPD,[b] $ED_5$ | MIOP,[c] % change (dose) |
|---|---|---|---|
| **17** | 30 μg | 0.8 μg | −15% (30 μg) |
| **AL-12182** | 30 μg | 0.2 μg | −40% (3 μg) |
| $PGF_{2\alpha}$ isopropyl ester | <0.1 μg | 0.03 μg | −38% (1 μg) |
| Latanoprost | 1.8 μg | 0.13 μg | −27% (3 μg) |
| Travoprost | 3 μg | 0.014 μg | −29% (0.3 μg) |

[a] $RCH_{15}$ = Dose estimated to elicit conjunctival hyperemia in 15% of the tested rabbits over 4 h.
[b] CPD = Cat pupil diameter constriction.
[c] MIOP = Monkey intraocular pressure.

D-sorbitol as the starting material and proceeds via tetrahydrofuran ester **22**. Our process research efforts led to expedited procedures[17] by which we prepared 3 kg of **22**. Thus the acid-catalyzed dehydration[18] of D-sorbitol (4 kg scale) was conducted in a concentrated melt followed by a nonaqueous workup to afford crystalline 1,4-anhydro-D-sorbitol (**18**) in 47% yield. The two-step conversion[5] of **18** to silyl ether **21** proved impractical on kilo scale due to nonoptimal discrimination among the hydroxyl groups, resulting in the formation of regioisomeric contaminants. In contrast, the conversion of **18** to *ortho* ester **19**[19] proceeded cleanly. Silylation of **19** was followed by stirring with Amberlyst 15 resin in MeOH–$H_2O$ to yield triol **20** without evidence of silyl migration. By means of this detour, crystalline **21** could be secured without resort to chromatography. Moffatt oxidation of **21**, Wittig condensation and hydrogenation of the resulting enoate gave **22** efficiently, as reported.[5]

On small scale, the synthesis of the $\Delta^4$ compounds **11**–**16** was accomplished by one-carbon extension of a pro-C6 aldehyde or lactol core structure using $Ph_3P{=}CHOMe$.[13–15] Two alternative sequences, considered to be more favorable for scaleup, were evaluated for advancing **22** to **AL-12182** on multigram scale.

In the first sequence, ester **22** was transformed to mesylate **23**, and the derived iodide (8 g scale) was reacted




**Scheme 1.** (DPS = diphenyl-*t*-butylsilyl). Reagents and conditions: (a) (1) $LiAlH_4$, $Et_2O$, 0° (90%); (2) MsCl, $Et_3N$, $CH_2Cl_2$, 0° (98%). (b) To give **24**: (1) NaI, $Me_2CO$, Δ (86%); (2) 4-pentynoic acid, $LiNH_2$, $NH_3$, −33°; add iodide in THF; quench with $NH_4Cl$; → pH 3; $CH_2N_2$, $Et_2O$ (73%). (3) $H_2$, $Pd(BaSO_4)$, py, −25° (86% of a 96:4 *Z*/*E* mixture, 0.5% overreduction, 6% recovered alkyne). (c) (1) **24**, $H_5IO_6$, EtOAc, 4 A MS (91%); (2) $(MeO)_2P(O)CH_2COCH_2OC_6H_4Cl$-*m*, $Et_3N$, LiCl, THF, 0° (69%); (3) (−)-$Ipc_2BCl$, THF, −15 to 0° (91% of an 88:12 *R*/*S* mixture); (4) $Ti(O\text{–}i\text{-}Pr)_4$, *i*-PrOH, Δ (100%). (d) (1) NaCN, $Me_2SO$, 45° (95%); (2) *i*-$Bu_2AlH$/hexane, toluene, −65°; 10% aq HOAc, → 0° (94%). (e) To give **27**: $Ph_3P^+(CH_2)_3CO_2\text{–}i\text{-}Pr$, $Br^-$, $NaN(SiMe_3)_2$, THF, 20°; add **26** in toluene, −68°, then → −20° (85% of a 97:3 *Z*/*E* mixture). (f) (1) **27**, $H_5IO_6$, *i*-PrOAc (99%); (2) $Ph_3P{=}CHCOCH_2OC_6H_4Cl$-*m*, HOAc, $CH_2Cl_2$ (90%); (3) (−)-$Ipc_2BCl$/heptane, THF, −45° (75% of a 93:7 *R*/*S* mixture, after desilylation).

with $LiC{\equiv}C(CH_2)_2CO_2Li$ in liquid $NH_3$.[20] The product was esterified and then semihydrogenated. Chromatography at this stage separated residual alkynyl ester. The resulting 96:4 mixture of enoate **24** and its *E* isomer was carried forward. One-flask acetonide hydrolysis–glycol cleavage[21] exposed the aldehyde function. Condensation[22] with the appropriate keto phosphonate,[13] reduction of the resulting enone with (−)-$Ipc_2BCl$[23] and subsequent transesterification[24] afforded alcohol **25**. Conversion of **25** to **AL-12182** entailed desilylation and a final chromatography to remove minor congeners.

For larger-scale synthesis we proceeded via aldehyde **26**. Condensation[25] of **26** (200 g) with $Ph_3P{=}CH(CH_2)_2CO_2$-*i*-Pr afforded ester **27**. The derived aldehyde was subjected to an acid-accelerated Wittig reaction,[26,27] and the resulting enone was reduced with (−)-$Ipc_2BCl$ at low temperature[28] to give **25**.[29] The configuration of the new carbinyl stereocenter in **25** was verified by *O*-methylmandelic ester analysis.[30,31] Pinene-derived byproducts were conveniently removed after desilylation of **25** to **AL-12182** (Scheme 1).

In conclusion, replacement of the hydroxymethylene (CHOH) group at the 11-position of the PG cyclopentane nucleus with an oxygen atom maintained potent (<100 nM) FP receptor-linked biological activity in many cases. **AL-12182**, the isopropyl ester prodrug of the $\Delta^4$ chlorophenoxy acid **13**, elicited minimal hyperemic response in the rabbit and profoundly lowered IOP in the ocular hypertensive monkey. A synthetic route beginning with D-sorbitol was employed to prepare >60 g of **AL-12182**.

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