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# A Convergent Synthesis of the 11-Oxa Prostaglandin Analogue AL-12182

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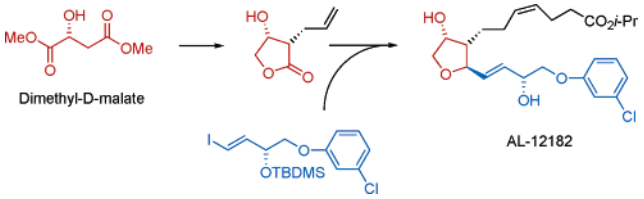
*Received November 4, 2004*




The 11-oxa prostaglandin analogue AL-12182 **1** has potent topical ocular hypotensive activity. A convergent and concise general synthesis of this class of prostanoid was developed employing a stereoselective coupling reaction between a tetrahydrofuran core electrophile and a nucleophilic omega side chain component, providing a route that should be suitable for commercial scale production. The tetrahydrofuran core was assembled from dimethyl D-malate using a stereoselective $\beta$-hydroxy ester dianion alkylation reaction.

## Introduction

11-Oxa prostaglandin analogues have been found to be effective agents for lowering intra-ocular pressure in the treatment of glaucoma.[1] These compounds exhibit mechanisms similar to $PGD_2$ **2** and $PGF_{2\alpha}$ **3** (Figure 1). An efficient synthesis of a compound of this class, AL-12182 **1**, was required with the potential for development to produce kilogram quantities as a pharmaceutical product.[2] Previous syntheses of 11-oxa prostaglandin analogues[1,3] have utilized (3a*R*,4*S*,6a*R*)-4-hydroxymethylhexahydrofuro[3,4-b]furan-2-one **4**, the oxa-analogue of the Corey lactone alcohol,[4] or functionally equivalent compounds as a key intermediate. The racemic synthesis of this core tetrahydrofuran unit by reaction of methyl 4,4-diethoxycrotonate and methylsodium glycolate has been described,[3a] but the reported syntheses of enantiomerically pure compounds of this type[3b–f] use carbohydrate starting materials to provide the four carbon atoms of the tetrahydrofuran ring and C13 of the $\omega$-chain. Thus, in the original patent route to AL-12182 **1** (Scheme 1),[1a] the Corey lactone alcohol equivalent **4** was synthesized from D-glucose, after which chemistry analogous to the latter stages of the Corey lactone route to carbocyclic prostanoids[4] was used. A later and more efficient, but conceptually similar, synthesis of AL-12182[1b] was based on the route developed by Hanessian[3d] starting with D-sorbitol. An essential feature of these routes is a C15 ketone reduction that typically provides the noncrystalline final product as a 7:1 mixture of diastereoisomers that require chromatographic separation.

Of particular concern to us was ensuring rigorous control of the stereochemistry of the molecule to simplify any subsequent regulatory submission for pharmaceutical substance.[5] Therefore, we sought an alternative general synthesis of 11-oxa prostaglandin analogues with this consideration in mind.[2] Comparing syntheses of classical (carbocyclic) prostanoids (Scheme 2), introduction of the $\omega$-chain by a C13–C14 bond-forming step

(1) (a) Selliah, R. H.; Hellberg, M. R.; Klimko, P. G.; Sallee, V. L.; Zinke, P. W. U.S. Patent 6,197,812; *Chem. Abstr.* **1997**, *127*, 135678. (b) Selliah, R. H.; Hellberg, M. R.; Sharif, A. N.; McLaughlin, M. A.; Williams, G. W.; Scott, D. A.; Earnest, D.; Haggard, K. S.; Dean, W. D.; Delgado, P.; Gaines, M. S.; Conrow, R. E.; Klimko, P. G. *Bioorg. Med. Chem. Lett*. **2004**, *14*, 4525–4528.

(2) Fox, M. E.; Jackson, M. EP Patent 1282627; *Chem. Abstr.* **2001**, *135*, 371564.

(3) (a) Vlattas, I.; Ong Lee, A. *Tetrahedron Lett*. **1974**, *15*, 4451–4454. (b) Corey, E. J.; Eggler, J. F. DE Patent 2739277; *Chem. Abstr.* **1978**, *89*, 5999. (c) Thiem, J.; Lüders, H. *Liebigs. Ann. Chem*. **1985**, 2151–2164. (d) Hanessian, S.; Guindon, Y.; Lavallée, P.; Dextraze, P. *Carbohydr. Res.* **1985**, *141*, 221–238. (e) Lourens, G. J.; Koekemoer, J. M. *Tetrahedron Lett*. **1975**, *43*, 3719–3722. (f) Arndt, R. R.; Koekemoer, J. M.; Lourens, G. J.; Venter, E. M. *S.-Afr. Tydskr. Chem*. **1981**, *34*, 121–127.

(4) Corey, E. J.; Cheng, X.-M. *The Logic of Chemical Synthesis*; Wiley: New York, 1989; p 250–266 and references therein.

(5) For a discussion of the issues in commercial scale prostanoid synthesis see McCague, R.; Lennon, I. C.; Fox, M. E.; Jackson, M. In *Handbook of Chiral Fine Chemicals Second Edition*; Ager, D. J., Ed.; Marcel Dekker: New York, in press; Chapter 30. *Commercial Synthesis of the Antiglaucoma Prostanoid Travoprost*.

10.1021/jo048035v CCC: $30.25 
Published on Web 01/26/2005

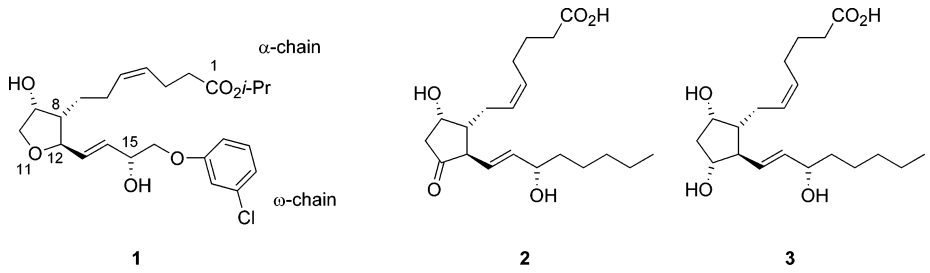
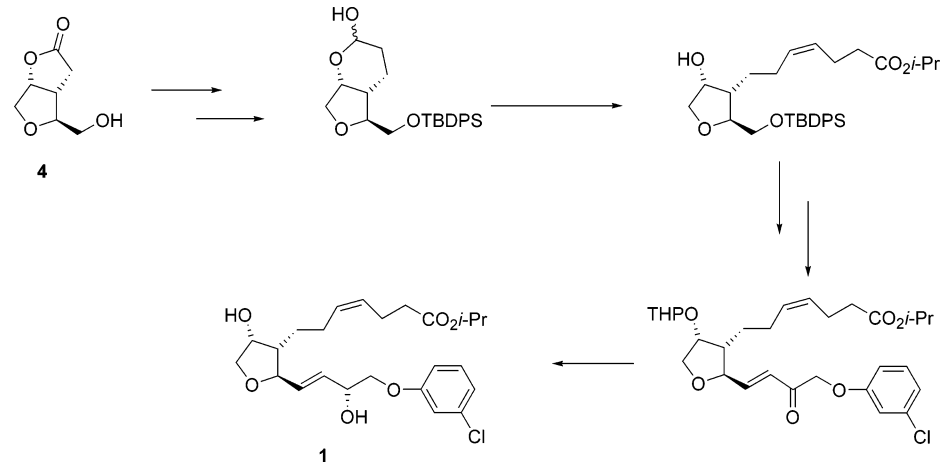
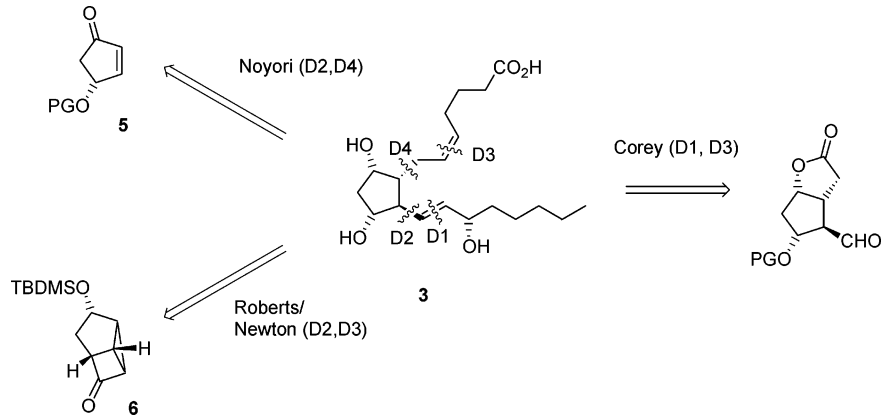



**FIGURE 1.** Structures of AL-12182 **1**, $PGD_2$ **2**, and $PGF_{2\alpha}$ **3** and numbering scheme for the prostanoid skeleton.

**SCHEME 1. Summary of the Original Synthesis of AL-12182 1**




**SCHEME 2. Summary of Approaches to Carbocyclic Prostanoids**




(disconnection D1) as used in the Corey synthesis suffers from the requirement that establishment of the C15 stereochemistry is still necessary. On the other hand, there are alternative approaches that use a C12−C13 bond-forming step (disconnection D2 in Scheme 2) and thereby allow introduction of the entire $\omega$-chain, stereodefined at C15, as a nucleophilic reagent. In addition, this disconnection affords a more concise and convergent overall synthesis. The core moiety to which the $\omega$-chain component is coupled may be a cyclopentenone **5**, as in the three-component coupling route developed by Noyori and others,[6] or a tricycloheptanone **6**, as in the route developed by Roberts and Newton.[7] We have used this latter approach for the development of the manufacturing route to the prostanoid travoprost marketed by Alcon for glaucoma and ocular hypertension.[5,8]

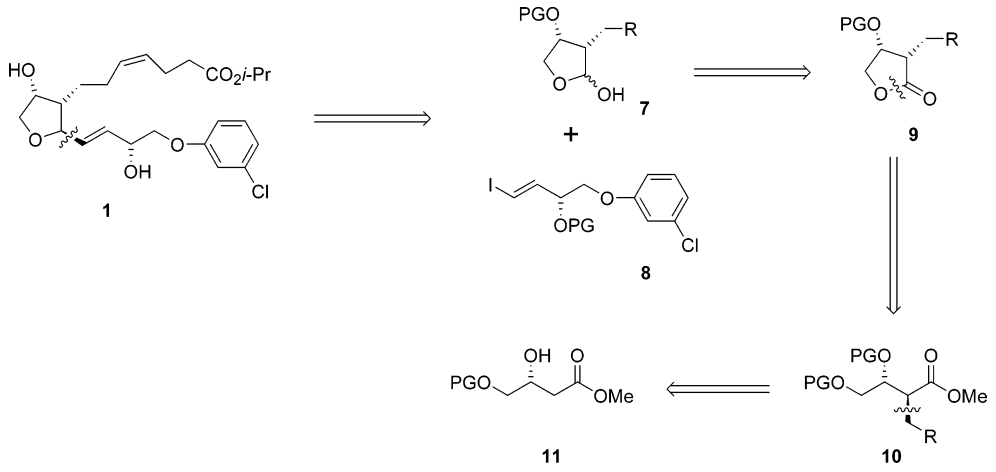
By analogy, we sought to extend this rationale to the synthesis of AL-12182 (Scheme 3). Application of the C12−C13 disconnection would entail a stereoselective *C*-glycosidation reaction of the lactol **7** requiring activation of the hydroxyl group to a leaving group and then displacement with a metalated $\omega$-side chain reagent. We were attracted to the activation method reported by a group at Merck to construct 2,5-substituted tetrahydro-

(6) (a) Noyori, R.; Suzuki, M. *Angew. Chem., Int. Ed. Engl*. **1984**, *23*, 847−876. (b) Morita, Y.; Suzuki, M.; Noyori, R. *J. Org. Chem*. **1989**, *54*, 1785−1787. (c) Suzuki, M.; Morita, Y.; Koyano, H.; Koga, M.; Noyori, R. *Tetrahedron* **1990**, *46*, 4809−4822. (d) Noyori, R.; Suzuki, M. *Chemtracts Org. Chem*. **1990**, *3*, 173−179.

(7) (a) Lee, T. V.; Roberts, S. M.; Dimsdale, M. J.; Newton, R. F.; Rainey, D. K.; Webb, C. F. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1176−1178. (b) Newton, R. F.; Roberts, S. M. *Tetrahedron* **1980**, *36*, 2163−2196. (c) Davies, J.; Roberts, S. M.; Reynolds, D. P.; Newton, R. F. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1317−1320.

(8) Boulton, L. T.; Brick, D.; Fox, M. E.; Jackson, M.; Lennon, I. C.; McCague, R.; Parkin, N.; Parratt, J. S.; Rhodes, D.; Ruecroft, G. *Org. Process Res*. **2002**, *6*, 138−145.

**SCHEME 3. Retrosynthetic Analysis of AL-12182 1 Based on a C12−C13 Disconnection**




furans with a high degree of trans-stereoselectivity and exemplified on a large scale.[9] In this method, the lactol is silylated, and then the silyl lactol ether is converted in situ to the 2-bromotetrahydrofuran with trimethylsilyl bromide. The bromide is displaced with an aryl Grignard reagent, effecting the desired C−C bond-forming step. The method gives mainly the trans-diastereoisomer in high selectivity even though the starting silyl ether was a mixture of diastereoisomers, the stereoconvergence suggesting an $S_N1$-like mechanism with stereocontrol provided by other residues on the tetrahydrofuran. We reasoned that the presence of two substituents on the same face of the five-membered ring in **7** would direct the attack of the side chain nucleophile to the opposite face in an analogous $S_N1$-like step, thus achieving the desired diastereocontrol. However, the effect of substituents on the stereochemical outcome of such C-glycosidation reactions of tetrahydrofurans can be subtle.[10]

We have recently published an efficient synthesis of the required single enantiomer $\omega$-chain iodide **8**[11] in which bioresolution of a precursor alkynol is used to establish the stereocenter. We expected that the lactol **7** could be made by reduction of the lactone **9**. Examination of the open-chain ester equivalent **10** of the lactone **9** reveals an antialdol relationship of the two remaining stereocenters, which could be established using the well-precedented protocol of dianion alkylation of the (*R*)-$\beta$-hydroxy ester **11**.[12] Hence, in our plan, starting with a simple chiral building block, both α and $\omega$ side chains would be introduced sequentially in stereoselective reactions, resulting in a highly convergent overall synthesis with a minimum number of linear steps. The synthesis of the single isomer hydroxy ester **11** has been reported by a wide variety of methodologies, including selective reduction of malic acid,[13a] oxidative degradation of L-arabinose,[13b] enzymatic hydrolysis of 3,4-epoxybutyrates,[13c] and bioreduction[13d] or asymmetric hydrogenation[13e−g] of the corresponding ketone, although some of these approaches may only be practical for the (*S*)-enantiomer ent-**11**.

## Results and Discussion

Our first objective was to obtain the key lactone intermediate **9**. Starting with dimethyl D-malate **12**, the ester group adjacent to the hydroxyl group was reduced chemoselectively with borane−dimethyl sulfide complex (Scheme 4).[13a] The primary hydroxyl group of the diol **13** was selectively protected with a *tert*-butyldimethylsilyl group[12d] (12:1 primary/secondary protection) to give the $\beta$-hydroxy ester **14** required for the stereoselective alkylation. In principle, it should be possible to introduce the entire α-chain in the stereoselective alkylation step using a suitable homoallylic alkylating agent. However, we expected this reaction to proceed much more readily if an activated alkylating agent was used. Therefore, we chose a stepwise construction of the α-chain, introducing the first three carbon atoms by alkylation with allyl bromide or 3-bromo-1-(trimethylsilyl)-1-propyne, both of which possess functionality suitable for elaboration to the full α-chain.[14] Both alkylating agents gave the antialdols **15** in a 20:1 diastereomeric ratio, but the reaction with

(9) Thompson, A. S.; Tschaen, D. M.; Simpson, P.; McSwine, D. J.; Reamer, R. A.; Verhoeven, T. R.; Shinkai, I. *J. Org. Chem*. **1992**, *57*, 7044−7052.

(10) (a) Larsen, C. H.; Ridgeway, B. H.; Jared, J. T.; Woerpel, K. A. *J. Am. Chem. Soc.* **1999**, *121*, 12208−12209. (b) Smith, D. M.; Tran, M. B.; Woerpel, K. A. *J. Am. Chem. Soc*. **2003**, *125*, 14149−14152.

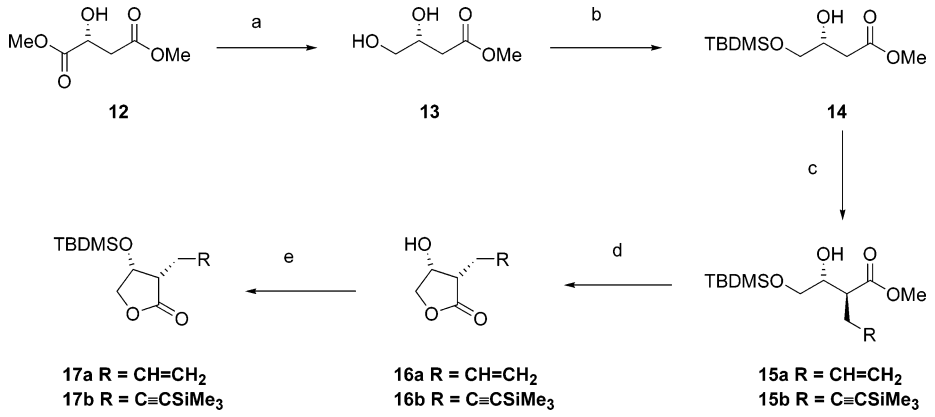
(11) Fox, M. E.; Jackson, M.; Lennon, I. C.; McCague, R.; Parratt, J. S. *Adv. Synth. Catal*. **2002**, *344*, 50−56.

(12) (a) Fräter, G.; Müller, U.; Günther, W. *Tetrahedron* **1984**, *40*, 1269−1277. (b) Barbier, P.; Schneider, F.; Widmer, U. *Helv. Chim. Acta* **1987**, *70*, 1412−1418. (c) Muraoka, O.; Tanabe; G.; Sano, K.; Minematsu, T.; Momose, T. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1833−1845. (d) Thomas, E. J.; Williams, A. C. *J. Chem. Soc., Perkin Trans. 1*, **1995**, 351−358.

(13) (a) Saito, S.; Hasegawa, T.; Inaba, M.; Nishida, R.; Fuji, T.; Nomizu, S.; Moriwake, T. *Chem. Lett*. **1984**, 1389−1392. (b) Bock, K.; Lundt, I.; Pederson, C. *Acta Chem. Scand. Ser. B* **1983**, *37*, 341−344. (c) Bianchi, D.; Cabri, W.; Cesti, P.; Francalanci, F.; Ricci, M. *J. Org. Chem*. **1988**, *53*, 104−107. (d) Hunt, J. R.; Carter, A. S.; Murrell, J. C.; Dalton, H.; Hallinan, K. O.; Crout, D. H. G.; Holt, R. A.; Crosby, J. *Biocatalysis and Biotransformations*, **1995**, *12*, 159−178. (e) For a review on $\beta$-ketoester hydrogenation see Ager, D. J.; Laneman, S. A. *Tetrahedron: Asymmetry* **1997**, *8*, 3327−3355. (f) Kitamura, M.; Ohkuma, T.; Inoue, S.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Ohta, T.; Takaya, H.; Noyori, R. *J. Am. Chem. Soc*. **1988**, *110*, 629−631. (g) Beck, G.; Jendralla, H.; Kesseler, K. *Synthesis* **1995**, 1014−1018.

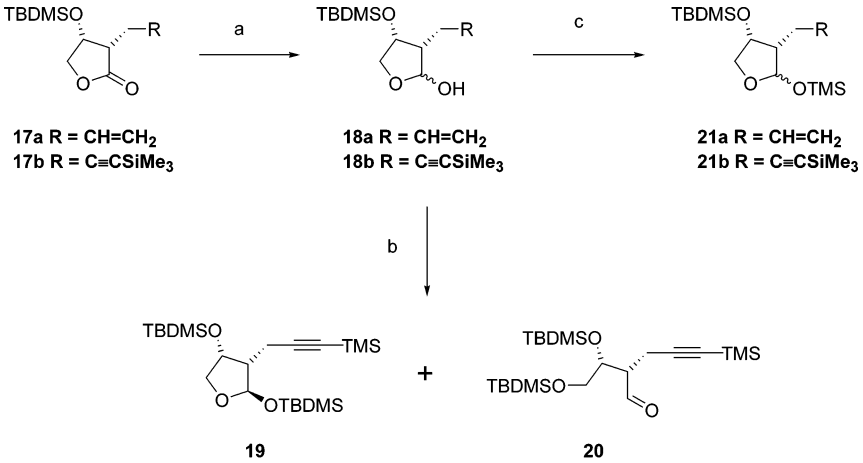
(14) For methods of hydration of a terminal alkyne to an aldehyde see Nicolaou, K. C.; Magolda, R. L.; Sipio, W. J.; Barnette, W. E.; Lysenko, Z.; Joullie, M. M. *J. Am. Chem. Soc*. **1980**, *102*, 3784−3793. (b) Pelter, A.; Smith, K.; Brown, H. C. *Borane Reagents*; Academic Press: New York, 1988. (c) Nicolaou, K. C.; Duggan, M. E.; Hwang, C.-K. *J. Am. Chem. Soc*. **1989**, *111*, 6676−6682 (b) Tokunaga, M.; Suzuki, T.; Koga, N.; Fukushima, T.; Horiuchi, A.; Wakatsuki, Y. *J. Am. Chem. Soc*. **2001**, *123*, 11917−11924. (c) Grotjahn, D. B.; Lev, D. A. *J. Am. Chem. Soc*. **2004**, *126*, 12232−12233.

**SCHEME 4. Synthesis of Key Lactones 17**[a]




[a] Conditions: (a) $BH_3$.DMS, $NaBH_4$ (cat), 89%; (b) TBDMSCl, $Et_3N$, DMAP (cat), $CH_2Cl_2$ 72%; (c) LDA, THF then 1.3 eq. DMEU then $CH_2$=$CHCH_2Br$ 82% **15a** or $Me_3SiC$≡$CCH_2Br$ 57% **15b**; (d) HCl, $H_2O$, DME 92% **16a**, 79% **16b**; (e) TBDMSCl, imidazole, DMF 76% **17a**, 90% **17b**.

**SCHEME 5. Synthesis of Silylated Lactols 21**[a]



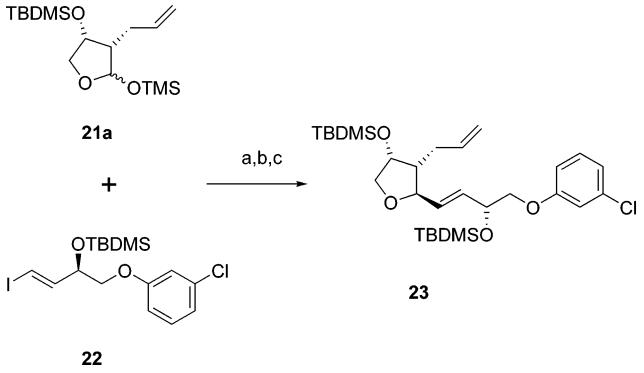

[a] Conditions: (a) DIBAL-H, toluene quant.; (b) TBDMSCl, imidazole, DMF, then Girard's reagent T 84%; (c) TMSCl, $Et_3N$, THF 93% **21a**, 98% **21b**.

allyl bromide was cleaner and the yield was higher. Removal of the silyl protecting group under acidic conditions gave the lactones **16**, after which protection of the hydroxyl group with a *tert*-butyldimethylsilyl group gave the crystalline lactones **17**. The presence of a crystalline intermediate at this stage in the synthesis is of particular advantage for a large-scale process; given that the early steps are clean and selective, this minimizes the need for chromatographic purification. The minor trans-diastereoisomer of the allyl-substituted lactone **17a** is a liquid, ensuring that crystallization is a highly effective method of purification for this compound. In addition to being suitable precursors for the cis-4-heptenoyl chain of AL-12182 **1**, the allyl and trimethylsilylpropargyl groups should be versatile precursors for elaboration to a variety of other substituents. In particular, oxidative cleavage of the double bond of the allyl substituent should provide an entry into the synthesis of analogues bearing a normal prostanoid α-chain with a C5−C6 cis-double bond.

Having successfully achieved an efficient synthesis of the key lactones **17**, we now turned our attention to the conversion to a suitable precursor for coupling of the ω-side chain. The lactones **17** were readily reduced to the lactols **18** with diisobutylaluminum hydride (Scheme 5). Silylation of the lactol **18b** with the *tert*-butyldimethylsilyl group, as employed by the Merck group,[9] gave a large quantity (15%) of the ring-opened aldehyde **20**. We reasoned that the greater steric crowding of the lactol **18b** compared to the Merck substrate slows the silylation of the lactol form relative to the hydroxy aldehyde form so that the ring-opened product **20** is favored despite the overwhelming predominance of the lactol form in the equilibrium mixture. Further evidence for this equilibration is provided by the fact that the starting lactols **18** exist as a 2:1 mixture of anomers but the silyl acetal **19** was obtained as a single anomer. The aldehyde **20** was removable by treatment of the mixture with Girard's reagent T. However, a more satisfactory solution to the problem of obtaining exclusively the silyl acetal form was to use the less bulky trimethylsilyl group. Thus, silylation of the lactols **18** with trimethylsilyl chloride gave the desired lactol silyl ethers **21** (4:1 mixture of anomers).

Next, we turned our attention to the activation and ω-side chain coupling reaction (Scheme 6). We decided to focus on the compounds bearing an allyl α-chain

**SCHEME 6. Key Coupling Reaction**[a]




[a] Conditions: (a) **21a**, TMSBr, $CH_2Cl_2$, −70 °C; (b) **22**, *tert*-BuLi, $Et_2O$, −70 °C then LiCu(2-thienyl)CN, THF; (c) add solution from (a) to (b), −70 °C, 63%.

precursor rather then the trimethylsilylpropargyl group because of the superior results obtained in the stereoselective alkylation step and the advantageous purification procedure available for the key lactone **17a**. The silyl lactol **21a** was treated with trimethylsilyl bromide at low temperature, after which smooth reaction took place with a higher order lithium cyanocuprate derived from iodide **22**[11] at low temperature (<−60 °C) to give the desired tetrahydrofuran **23** as a single diastereoisomer. Unlike the previously reported example,[9] we were not able to achieve coupling in our system using Grignard reagents with or without a copper catalyst.

Completion of the synthesis required elaboration of the α-chain (Scheme 7). In AL-12182, the α-chain olefin is transposed one position compared to typical prostanoids. Clean hydroboration of the terminal double bond of allyl tetrahydrofuran **23** to the alcohol **24** was achieved with 9-BBN, after which Swern oxidation[15] gave the desired aldehyde **25**. Attention was then focused on the Wittig reaction of the aldehyde **25**. A trans level of no more than 3.5% is acceptable in a pharmaceutical product of this type. Since removal of the trans-isomer from the final product **1** by chromatography was difficult, ensuring as high as possible a cis/trans ratio in the Wittig reaction was paramount. Initially, we used commercially available (3-carboxypropyl)triphenylphosphonium bromide with potassium *tert*-butoxide as the base. In a related Wittig reaction with the homologous (4-carboxybutyl)triphenylphosphonium bromide, we were routinely able to obtain a trans-content of 2−3%.[8] The acid **26** was converted to the isopropyl ester **27** with 2-iodopropane and DBU, and then the silyl protecting groups were removed with tetra-*n*-butylammonium fluoride. HPLC analysis of the final prostaglandin analogue **1** revealed the trans level to be an unacceptable 11%.

Therefore, we decided to change the order of steps and use the isopropyl ester **29**[16] in the Wittig reaction. Starting with 4-bromobutyric acid, the isopropyl ester **28** was readily prepared by esterification with isopropyl alcohol and catalytic sulfuric acid (Scheme 8). The phosphonium salt **29** was formed with triphenylphosphine in toluene.

(15) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165−185.
(16) Thum, O.; Hertweck, C.; Simon, H.; Boland, W. *Synthesis* **1999**, 2145−2150.

We were pleased to find that the trans-level obtained in the Wittig reaction using the isopropyl ester **29** was much lower than with the free carboxylate. Thorough drying of the phosphonium salt **29** by heating under vacuum was essential. Both potassium *tert*-butoxide and potassium bis(trimethylsilylamide) in THF at −70 °C were suitable bases, with potassium potassium *tert*-butoxide giving **27** with 3.5−4.6% trans and potassium bis(trimethylsilylamide) giving **27** with 2.1−2.2% trans, which is well within the acceptable limit for this class of pharmaceutical product. Removal of the silyl protecting groups with tetra-*n*-butylammonium fluoride to give the oxa prostaglandin analogue **1** was clean and high yielding. Deprotection with acid in the final step would have been preferred from the point of view of avoidance of toxic materials in the final step of a pharmaceutical process, ease of workup, and product purification, but deprotection of bis-TBDMS ether **27** with HCl in isopropyl alcohol was much slower than for the corresponding deprotection of the carbocyclic $PGF_{2\alpha}$ prostaglandin analogue travoprost[8] and, in addition, the product **1** suffered slow degradation under these conditions.

Analysis of the final prostaglandin analogue **1** for diastereomeric excess and 4,5 cis/trans ratio was best carried out by HPLC. A 1:1 mixture of epimers at C15 for analytical development was readily made by using racemic ω-side chain iodide **22**. We were surprised to find that the 15-epi level was typically around 1% because the ω-side chain iodide **22** used was of >99% ee. However, on further investigation, we discovered that the commercial dimethyl D-malate used was <98% ee and hence that the 15-epi impurity observed was in fact the ent-15-epi isomer. Therefore, use of dimethyl D-malate of as high an enantiomeric excess as possible as a starting material is important in this synthesis.

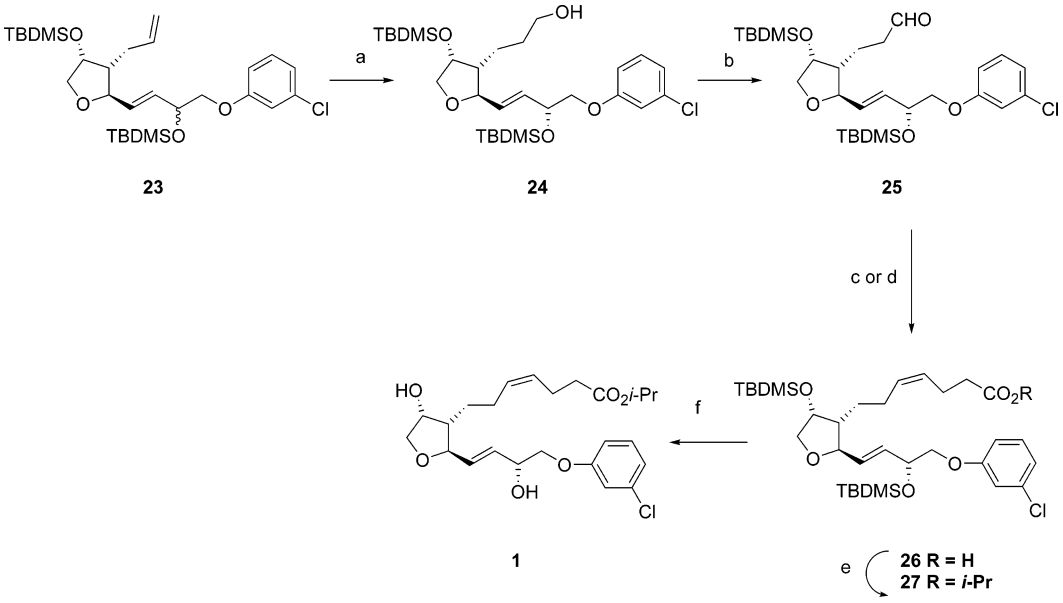
## Conclusions

A convergent and concise synthesis of the 11-oxa prostaglandin analogue AL-12182 **1** was demonstrated. The key steps in this route are a diastereoselective enolate alkylation and copper-mediated coupling reaction. With a longest linear sequence of 12 steps and an overall yield of 12% from dimethyl D-malate, this has the potential to form the basis for a viable manufacturing route to this compound. In particular, all of the four stereogenic centers are rigorously controlled. We expect this approach to be generally applicable to other 11-oxa prostaglandin analogues.

## Experimental Section

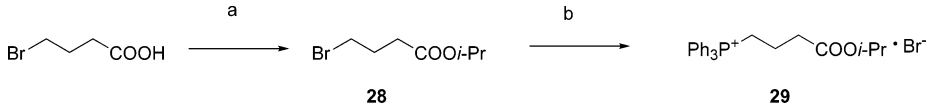
**(*R*)-Methyl 3,4-Dihydroxybutanoate (13).**[13a] Dimethyl D-malate **12** (50.05 g, 308.7 mmol) was dissolved in dry tetrahydrofuran (500 mL) under nitrogen. Borane dimethyl sulfide complex (10 M, 31.5 mL, 315 mmol) was added over 20 min (maintaining the temperature at 12−16 °C using a cold water bath). The solution was stirred for 1 h. Sodium borohydride (584 mg, 15.4 mmol) was added in five portions over 25 min (using cooling to keep the temperature below 20 °C). The mixture was stirred for 1 h, after which TLC (MTBE) showed no starting material. Dry methanol (150 mL) was added (slowly at first, hydrogen evolved) and the solution was stirred for 30 min. The solvent was evaporated and the residue was dissolved in methanol (100 mL). The solvent was evaporated again and the residue was azeotroped with toluene (3 ×

**SCHEME 7. Downstream Steps to AL-12182 1**[a]




[a] Conditions: (a) 9-BBN then $H_2O_2$, NaOH 78%; (b) $(COCl)_2$, DMSO, $Et_3N$, $CH_2Cl_2$, −70 °C 92%; (c) $Ph_3P^+CH_2CH_2CH_2COOH\ Br^-$, KO*t*-Bu, THF; (d) **29**, $K(N(SiMe_3)_2$, THF 94%; (e) DBU, *i*-PrI, THF 56%; (f) $Bu_4N^+\ F^-$ 84%.

**SCHEME 8. Synthesis of Phosphonium Salt 29**[a]




[a] Conditions: (a) *i*-PrOH, $H_2SO_4$ (cat), reflux 65%; (b) $PPh_3$, toluene, reflux, 57%.

50 mL) to give the crude diol **13** as colorless oil (41.9 g). The crude product was purified by passing through a pad of silica (100 g) eluting with ethyl acetate (1 L). The solvent was evaporated to give the diol **13** as a colorless oil (38.6 g, 274.6 mmol, 89%). $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 4.10 (m, 1H) 3.8−3.2 (m, 4H), 3.70 (s, 3H), 2.50 (m, 2H).

**Methyl (*R*)-4-(*tert*-Butyldimethylsilyloxy)-3-hydroxybutanoate (14).**[12d] The diol **13** (38.6 g, 275 mmol) was dissolved in dichloromethane (500 mL). Triethylamine (50 mL, 357 mmol) was added and the solution was cooled to 0 °C under nitrogen. A solution of *tert*-butyldimethylsilyl chloride (41.4 g, 275 mmol) in dichloromethane (100 mL) was added over 45 min. The mixture was allowed to warm to room temperature (over 3.5 h) and stirred overnight. TLC (ethyl acetate) showed diol **13** still present. (Dimethylamino)pyridine (1.98 g, 16.2 mmol) was added and the mixture was stirred for 6 h. Further *tert*-butyldimethylsilyl chloride (10.0 g, 66 mmol) was added and the mixture was stirred overnight. The reaction was quenched with water (250 mL). The organic layer was separated and washed with water (250 mL) and brine (250 mL), dried ($MgSO_4$), filtered, and evaporated. The residue was chromatographed (MTBE/heptane 1:4 to 1:1) to give the title compound **14** as a pale yellow liquid (49.7 g, 72%) (12:1 mixture of primary/secondary protected). $[\alpha]_D^{20}$ +9.9° (*c* 1.0, $CH_2Cl_2$). $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 4.10−4.00 (m, 1H), 3.70 (s, 3H), 3.65−3.50 (m, 2H), 2.88 (d, $J$ = 5 Hz, 1H), 2.52 (m, 2H), 0.90 (s, 9H), 0.08 (s, 6H).

**Methyl (2*S*, 3*R*)-2-Allyl-4-(*tert*-butyldimethylsilyloxy)-3-hydroxybutanoate (15a).** *n*-Butyllithium (2.5 M, 51.2 mL, 127.9 mmol) was added dropwise to a solution of diisopropylamine (19.5 mL, 139.5 mmol) in tetrahydrofuran (100 mL) at 0 °C under nitrogen (exothermic, temperature maintained at 0 to −5 °C with external cooling). The solution was stirred at 0 °C for 10 min and then cooled to −60 °C. A solution of the hydroxy ester **14** (14.44 g, 58.1 mmol) in tetrahydrofuran (30 mL) was added and residual ester was washed in with further tetrahydrofuran (10 mL) (the addition was exothermic causing the internal temperature to rise to −47 °C). The cold bath was removed and the reaction was allowed to warm to 0 °C. The mixture was then recooled to −60 °C. 1,3-Dimethyl-2-imidazolidinone (8.2 mL, 75.6 mmol) was added and after stirring for 5 min, allyl bromide (7.4 mL, 87.2 mmol) was added. The mixture was stirred below −50 °C for 30 min. The cold bath was removed and the reaction was allowed to warm to 10 °C over 1 h (TLC MTBE/heptane 1:3 showed no starting material). The reaction was quenched with saturated ammonium chloride (150 mL) (internal temperature rose to 23 °C). The organic layer was separated and the aqueous phase was extracted with MTBE (100 mL). The combined organic phases were washed with brine (100 mL), dried ($MgSO_4$), filtered, and evaporated. The crude product was passed through a short silica column (100 g), eluting with MTBE/heptane 1:6 to give the title compound **15a** as a pale yellow liquid (13.85 g, 48.0 mmol, 82%). $[\alpha]_D^{20}$ +6.5 (*c* 1.0, $CH_2Cl_2$). IR (neat) 3492, 1739 and 1642 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ ppm 5.84−5.64 (m, 1H), 5.13−5.00 (m, 2H), 3.83−3.74 (m, 1H), 3.69 (s, 3H), 3.66−3.57 (m, 2H), 2.94 (d, $J$ = 7 Hz, 1H), 2.74−2.64 (m, 1H), 2.50−2.28 (m, 2H), 0.88 (s, 9H), and 0.05 (s, 6H). EI 231 ([M-$^t$Bu]$^+$, 16), 117 (100). Anal. calcd for $C_{14}H_{28}O_4Si$: C, 58.3; H 9.8. Found: C, 58.5; H, 9.8.

**Methyl (2*S*, 3*R*)-4-(*tert*-Butyldimethylsilyloxy)-3-hydroxy-2-(1-trimethylsilylpropargyl)butanoate (15b).** *n*-Butyllithium (2.5 M, 17.7 mL, 44.3 mmol) was added dropwise to a solution of diisopropylamine (6.75 mL, 48.3 mmol) in tetrahydrofuran (40 mL) at −10 °C under nitrogen (exothermic, temperature maintained at 0 to −5 °C with external cooling). The solution was stirred at 0 °C for 10 min and then cooled to −50 °C. A solution of the hydroxy ester **14** (5.0 g, 20.1 mmol) in tetrahydrofuran (10 mL) was added over 5 min and residual ester was washed in with further tetrahydrofuran

(5 mL) (the addition was exothermic causing the internal temperature to rise to −35 °C). The cold bath was removed and the reaction was allowed to warm to −10 °C. After 10 min, the mixture was recooled to −50 °C. 1,3-Dimethyl-2-imidazolidinone (2.8 mL, 26.2 mmol) was added and after stirring for 5 min, 3-bromo-1-(trimethylsilyl)-1-propyne (4.7 mL, 30.2 mmol) in tetrahydrofuran (15 mL) was added (immediate color change from yellow to dark brown) and the reaction was allowed to warm to room temperature over 3 h (TLC MTBE/heptane 1:3 showed no starting material). The reaction was quenched with saturated ammonium chloride (100 mL). The organic layer was separated and the aqueous phase was extracted with MTBE (100 mL). The combined organic phases were washed with water (50 mL) and brine (50 mL), dried ($MgSO_4$), filtered, and evaporated. The crude product was chromatographed (MTBE/heptane 1:4) to give the title compound **15b** as a light brown liquid (3.95 g, 11.0 mmol, 55%). IR (neat) 3508, 2178, 1738 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 3.94−3.88 (m, 1H), 3.72 (s, 3H), 3.70−3.67 (m, 2H), 2.98 (d, $J$ = 7 Hz, 1H), 2.82−2.75 (m, 1H), 2.61−2.58 (m, 2H), 0.90 (s, 9H), 0.11 (s, 9H), 0.08 (s, 6H). EI 301 ([M − $^t$Bu]$^+$, 4), 117 (100).

**(3*S*, 4*R*)-3-Allyl-4-hydroxytetrahydrofuran-2-one (16a).** The 2-allyl hydroxy ester **15a** (13.5 g, 46.8 mmol) was dissolved in 1,2-dimethoxyethane (100 mL). Aqueous hydrochloric acid (3 N, 60 mL) was added and the mixture was heated at 80 °C for 1 h (TLC MTBE/heptane 4:1 showed complete reaction). After cooling to room temperature, the aqueous phase was saturated with sodium chloride and the mixture was extracted with ethyl acetate (3 × 70 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and evaporated. The crude product (10 g) was filtered through silica (35 g), eluting first with 30% MTBE in heptane (to remove silicon byproducts) and then with neat MTBE to afford the lactone **16a** (6.11 g, 43.0 mmol, 92%). $[\alpha]_D^{20}$ +67.8 (*c* 1.0, $CH_2Cl_2$). IR (neat) 3444, 1759, 1642 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 5.90 (m, 1H), 5.25−5.10 (m, 2H), 4.55 (brs, 1H), 4.30 (m, 2H), 2.70−2.55 (m, 3H), and 2.50−2.40 (m, 1H). EI 123 (40), 79 (100).

**(3*S*, 4*R*)-4-Hydroxy-3-(1-trimethylsilylpropargyl)tetrahydrofuran-2-one (16b).** The hydroxy ester **15b** (4.2 g, 11.7 mmol) was dissolved in 1,2-dimethoxyethane (40 mL). Aqueous hydrochloric acid (2 N, 20 mL) was added and the mixture was heated at 80 °C for 75 min (TLC MTBE/heptane 3:1 showed complete reaction). After cooling to room temperature, the mixture was extracted with MTBE (2 × 30 mL). The combined organic extracts were washed with saturated sodium hydrogencarbonate solution (30 mL) and brine (30 mL), dried ($MgSO_4$), filtered, and evaporated. Heptane (10 mL) was added to the oily residue and the mixture was cooled in an ice bath. The crystalline solid was filtered, washed with heptane (2 mL), and dried to give the lactone **16b** (1.59 g, 7.5 mmol, 64%). mp 75 °C (onset by DSC). IR (Nujol) 3434, 2175, and 1768 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 4.75 (brs, 1H), 4.38 (m, 2H), 2.90−2.77 (m, 2H), 2.60 (dd, $J$ = 18, 12 Hz, 1H), 2.46 (brs, 1H), and 0.13 (s, 9H). EI 179 (100).

**(3*S*, 4*R*)-3-Allyl-4-(*tert*-butyldimethylsilyloxy)tetrahydrofuran-2-one (17a).** The hydroxy lactone **16a** (6.0 g, 42.2 mmol) was dissolved in dry dimethylformamide (10 mL) under nitrogen. Imidazole (4.78 g, 70.2 mmol) and then *tert*-butyldimethylsilyl chloride (7.05 g, 46.80 mmol) were added. The mixture was stirred at room temperature overnight and then partitioned between water (50 mL) and heptane (2 × 30 mL). The heptane extracts were dried ($MgSO_4$), filtered, and evaporated to give the crude product (10.5 g). This was crystallized from heptane (40 mL) at −15 °C to give the *title compound* **17a** as a white solid (7.60 g, 29.6 mmol, 70%). The mother liquors were concentrated and observed to solidify upon standing. The solid was dissolved in heptane (25 mL) and cooled in a $CO_2$/acetone bath to induce crystallization. The solid was filtered and washed with cold heptane (10 mL) to give a second crop of the lactone **17a** (646 mg, 2.5 mmol, 6%). The residue was chromatographed (MTBE/heptane 1:6 to 1:3) to give the title compound **17a** (746 mg, 2.9 mmol, 7%) [and the (3*R*,4*R*) diastereoisomer as a colorless oil (456 mg, 1.8 mmol, 4%)]. mp 48 °C (onset by DSC). $[\alpha]_D^{20}$ +88.0° (*c* 1.0, $CH_2Cl_2$). IR (Nujol) 1763, 1644 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 5.94−5.80 (m, 1H), 5.18−5.06 (m, 2H), 4.53 (t, $J$ = 3.5 Hz, 1H), 4.26 (dd, $J$ = 10, 3 Hz, 1H), 4.17 (d, $J$ = 10 Hz, 1H), 2.60−2.35 (m, 3H), 0.89 (s, 9H), 0.10 (s, 3H), and 0.08 (s, 3H). EI 199 ([M − $^t$Bu]$^+$, 4), 117 (100). Anal. calcd for $C_{13}H_{24}O_3Si$: C, 60.9; H, 9.4%. Found: C, 61.1; H, 9.5. (3*R*,4*R*) diastereoisomer $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ ppm 5.85−5.72 (m, 1H), 5.20−5.12 (m, 2H), 4.39−4.29 (m, 2H), 4.01−3.95 (m, 1H), 2.60−2.54 (m, 1H), 2.49−2.30 (m, 2H), 0.88 (s, 9H), 0.08 (s, 3H), and 0.06 (s, 3H).

**(3*S*,4*R*)-4-(*tert*-Butyldimethylsilyloxy)-3-(1-trimethylsilylpropargyl)tetrahydrofuran-2-one (17b).** The hydroxy lactone **16b** (1.57 g, 7.39 mmol) was dissolved in dry dimethylformamide (4 mL) under nitrogen. Imidazole (755 mg, 11.1 mmol) and then *tert*-butyldimethylsilyl chloride (1.33 g, 8.9 mmol) were added and the mixture was stirred at room temperature overnight (TLC MTBE/heptane 1:3 showed complete reaction). The mixture was partitioned between water (20 mL) and heptane (2 × 30 mL) and the combined organic phases were dried ($MgSO_4$). The solvent was evaporated and the residue was passed through a short silica column eluting with MTBE/heptane 1:8 to give the lactone **17b** (2.28 g, 7.0 mmol, 94%). mp 66 °C (onset by DSC). IR (Nujol) 2179, 1765 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 4.63 (t, $J$ = 3.51 Hz, 1H), 4.30 (dd, $J$ = 10, 3 Hz, 1H), 4.20 (d, $J$ = 10 Hz, 1H), 2.78−2.67 (m, 2H), 2.52 (dd, $J$ = 17, 12 Hz, 1H), 0.90 (s, 9H), 0.15 (s, 9H), 0.13 (s, 6H). EI 269 ([M − $^t$Bu]$^+$, 38), 117 (100).

**(3*S*,4*R*)-3-Allyl-4(*tert*-butyldimethylsilyloxy)tetrahydrofuran-2-ol (18a).** The lactone **17a** (5.0 g, 19.50 mmol) was dissolved in dry toluene (50 mL) and cooled to −70 °C under nitrogen. Diisobutylaluminum hydride in toluene (1.5M, 19.5 mL, 29.25 mmol) was added over 15 min (temperature was maintained below −60 °C) and the resulting mixture was stirred for 1.5 h. The reaction was quenched with methanol (5 mL) (vigorous frothing initially). Aqueous sulfuric acid (2 N, 75 mL) was added, maintaining the temperature below −30 °C. The mixture was allowed to warm to room temperature and the organic layer was separated. The aqueous phase was extracted with toluene (50 mL + 25 mL) (the second extract contained no product). The combined organic solutions were washed with aqueous sulfuric acid (2 N, 25 mL), water (3 × 30 mL, to pH 7), and brine (30 mL). The solution was dried ($MgSO_4$), filtered, and evaporated to give the lactol **18a** as a colorless oil (5.18 g, 20.04 mmol, 103%), 1.5:1 mixture of anomers. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 5.95−5.80 (m, 1H, both anomers), 5.30−5.00 (m, 3H, both anomers), 4.46−4.41 (m, 1H, major), 4.30 (t, $J$ = 3.5 Hz, 1H, minor), 4.16−4.03 (m, 1H, both anomers), 3.90 (dd, $J$ = 9, 3 Hz, 1H, minor), 3.82−3.69 (m, 1H, both anomers), 3.50 (brs, 1H, major), 2.42−1.97 (m, 3H, both anomers), 0.92 (s, 9H, both anomers), 0.10 (s, 3H, both anomers), 0.06 (s, 3H, both anomers).

**(3*S*, 4*R*)-4-(*tert*-Butyldimethylsilyloxy)-3-(1-trimethylsilylpropargyl)tetrahydrofuran-2-ol (18b).** The lactone **17b** (680 mg, 2.1 mmol) was dissolved in dry toluene (7 mL) and cooled to −70 °C under nitrogen. Diisobutylaluminum hydride in toluene (1.5M, 2.0 mL, 3.0 mmol) was added dropwise and the resulting mixture was stirred for 3 h. The reaction was quenched with methanol (1 mL) (vigorous frothing initially). Aqueous sulfuric acid (2 N, 10 mL) was added and the mixture was allowed to warm to room temperature. The organic layer was separated and the aqueous phase was extracted with MTBE (2 × 15 mL). The combined organic solutions were washed with aqueous sulfuric acid (2 N, 10 mL), water (3 × 10 mL, to pH 7), and brine (10 mL). The solution was dried ($MgSO_4$), filtered, and evaporated to give the lactol **18b** as a colorless oil (680 mg, 99%), 2:1 mixture of anomers. $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ ppm 5.28 (t, 1H, $J$ = 4 Hz, major), 5.19 (dd, 1H, $J$ = 12, 4.5 Hz, minor), 4.50 (m, 1H, major), 4.42 (t, 1H, $J$ = 3.5 Hz, minor), 4.18−4.04 (m, 1H, both anomers), 3.94 (dd, 1H, $J$ = 10, 3 Hz, minor), 3.75−3.63 (m, 1H, both

anomers), 2.98 (d, 1H, $J$ = 4 Hz, major), 2.57−2.15 (m, 3H, both anomers), 0.90 (s, 9H, both anomers), 0.16−0.07 (m, 15 H, both anomers).

**(3*S*,4*R*)-2,4-(*tert*-Butyldimethylsilyloxy)-3-(1-trimethylsilylpropargyl)tetrahydrofuran (19).** The lactol **18b** (1.18 g, 3.6 mmol) was dissolved in dry dimethylformamide (3 mL) under nitrogen. Imidazole (369 mg, 5.4 mmol) and then *tert*-butyldimethylsilyl chloride (600 mg, 4.0 mmol) were added and the mixture was stirred at room temperature overnight (TLC MTBE/heptane 1:3 showed no lactol). The reaction was quenched with water (15 mL) and extracted with heptane (3 × 15 mL). The combined organic phases were dried ($MgSO_4$), filtered, and evaporated to give the crude silyl acetal (1.59 g, 99%) as a colorless oil containing approximately 15% aldehyde **27** as an impurity. The silyl acetal **26** was dissolved in ethanol (25 mL). Girard's reagent T (300 mg, 1.8 mmol) and water (2 mL) were added and the mixture was stirred for 1 h (TLC MTBE/heptane 1:15 showed no aldehyde). The reaction mixture was partitioned between heptane (2 × 30 mL) and brine (30 mL). The combined organic phases were dried ($MgSO_4$). MTBE (5 mL) was added and the solution was filtered through silica, washing with 10% MTBE in heptane (50 mL). The solvent was evaporated to give the pure silyl acetal **19** (1.34 g, 84%) as a single anomer. IR (neat) 2176 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 5.29 (d, $J$ = 3 Hz, 1H), 4.54−4.48 (m, 1H), 4.09 (dd, $J$ = 9, 5 Hz, 1H), 3.63 (dd, $J$ = 9, 3 Hz, 1H), 2.48−2.36 (m, 1H), 2.25−2.17 (m, 2H), 0.90 (s, 18H), 0.12−0.08 (m, 21H). EI 385 ([M − $^t$Bu]$^+$, 7), 117 (64), 73 (100).

**(3*S*,4*R*)-3-Allyl-4-(*tert*-butyldimethylsilyloxy)-2-trimethylsilyloxytetrahydrofuran (21a).** The lactol **18a** (5.03 g, 19.50 mmol) was dissolved in dry tetrahydrofuran (50 mL) under nitrogen and the solution was cooled to 5 °C in an ice bath. Triethylamine (4.0 mL, 29.25 mmol) was added, followed by trimethylsilyl chloride (2.60 mL, 20.47 mmol) dropwise over 2 min (internal temperature rose to 7 °C). The mixture was stirred for 45 min, then allowed to warm to room temperature, and stirred for a further 75 min (TLC MTBE/heptane 1:4 showed very little lactol). The reaction was quenched with water (50 mL) and extracted with heptane (2 × 50 mL). The organic extracts were washed with brine (30 mL), dried ($MgSO_4$), filtered, and evaporated. The residue was filtered through a pad of silica, eluting with 5% MTBE in heptane (150 mL) to give the silyl acetal **21a** as a colorless oil (6.30 g, 19.05 mmol, 98%), approximately a 5:1 mixture of anomers. $[\alpha]_D^{20}$ +65.1 (*c* 1.0, $CH_2Cl_2$). IR (neat) 1641 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ (major anomer) 5.90−5.73 (m, 1H), 5.20−5.00 (m, 3H), 4.48−4.42 (m, 1H), 4.09 (dd, $J$ = 9, 4.5 Hz, 1H), 3.67 (dd, $J$ = 9, 3 Hz, 1H), 2.40−2.27 (m, 1H), 2.15−2.00 (m, 2H), 0.91 (s, 9H), 0.16−0.00 (m, 15H). EI 273 ([M − $^t$Bu]$^+$, 1%), 117 (100). Anal. calcd for $C_{16}H_{34}O_3Si_2$: C, 58.1; H 10.4. Found: C, 58.4; H, 10.35.

**(3*S*,4*R*)-2,4-(*tert*-Butyldimethylsilyloxy)-2-trimethylsilyloxy-3-(1-trimethylsilylpropargyl)tetrahydrofuran (21b).** The lactol **18b** (215 mg, 0.65 mmol) was dissolved in dry tetrahydrofuran (2 mL) at room temperature under nitrogen. Triethylamine (0.14 mL, 1.0 mmol) and then trimethylsilyl chloride (0.10 mL, 0.78 mmol) were added and the mixture was stirred for 1 h. The reaction was partitioned between heptane (20 mL) and water (10 mL). The heptane layer was washed with brine (10 mL), dried ($MgSO_4$), filtered, and evaporated to give the silyl acetal **21b** as a colorless oil (241 mg, 0.60 mmol, 93%), approximately a 4:1 mixture of anomers. $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ (major anomer) 5.29 (d, $J$ = 3 Hz, 1H), 4.50 (m, 1H), 4.09 (dd, $J$ = 9, 5 Hz, 1H), 3.61 (dd, $J$ = 9, 3 Hz, 1H), 2.50−2.42 (m, 1H), 2.30−2.15 (m, 2H), 0.90 (s, 9H), 0.10 (m, 24H).

**[2*R*, (1*E*,3*R*), 3*R*,4*R*]-3-Allyl-4-*tert*-butyldimethylsilyloxy-2-[3-*tert*-butyldimethyl-silyloxy-4-(3-chlorophenoxy)-1-butenyl]-tetrahydrofuran (23).** Anhydrous ether (20 mL) and *tert*-butyllithium (1.5 M, 22.8 mL, 34.3 mmol) were added to a 250-mL three-necked flask at −70 °C under nitrogen. A solution of the vinyl iodide **22**[11] (8.16 g, 18.6 mmol) in ether (30 mL) was added over 40 min (the internal temperature was maintained at −60 to −70 °C, a yellow solution is obtained initially which slowly darkens to orange/brown). The solution was stirred for a further 40 min after complete addition. The silyl acetal **21a** (4.73 g, 14.3 mmol) was dissolved in dry dichloromethane (35 mL) and cooled to −60 °C under nitrogen. Trimethylsilyl bromide (1.85 mL, 14.3 mmol) was added and the mixture was stirred for 1 h, maintaining the temperature below −60 °C. *n*-Butyllithium (2.5 M, 7.4 mL, 18.6 mmol) was added to thiophene (1.56 g, 18.6 mmol) in dry tetrahydrofuran (15 mL) at −30 °C under nitrogen. The thienyllithium solution was stirred for 20 min and then added to a suspension of copper(I) cyanide (1.66 g, 18.6 mmol) in tetrahydrofuran (15 mL) at −20 °C under nitrogen. The mixture was allowed to warm until a clear brown solution was obtained. The lithium 2-thienylcyanocuprate solution was added to the vinyllithium solution, keeping the temperature below −60 °C (dark brown solution, some solids present). After 10 min, the activated bromoether solution was added to the cuprate solution, keeping the temperature below −60 °C (clear yellow/brown solution resulted). After 2 h, TLC (MTBE/heptane 1:15) indicated complete reaction. The reaction was quenched with saturated ammonium chloride solution (100 mL) and was allowed to warm to room temperature. The mixture was diluted with water (50 mL) and then filtered through Celite. The organic layer was separated and the Celite was washed with MTBE (100 mL). This washing was also used to extract the aqueous layer. The combined organic phases were washed with water (50 mL), brine (50 mL), dried ($MgSO_4$), filtered, and evaporated to give a yellow oil (9.9 g). This was chromatographed (6% MTBE in heptane) to give the tetrahydrofuran **23** as a pale yellow oil (5.02 g, 9.1 mmol, 63%). $[\alpha]_D^{20}$ +43.9 (*c* 1.0, $CH_2Cl_2$). IR (neat) 1595 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.18 (t, $J$ = 8 Hz, 1H), 6.91 (d, $J$ = 7.5 Hz, 1H), 6.87 (d, $J$ = 7 Hz, 1H), 6.76 (dd, $J$ = 8, 2 Hz, 1H), 5.81−5.78 (m, 3H), 5.08−4.97 (m, 2H), 4.53 (m, 1H), 4.35 (t, $J$ = 4 Hz, 1H), 4.15 (m, 1H), 4.03 (dd, $J$ = 9, 3.5 Hz, 1H), 3.84 (d, $J$ = 6 Hz, 2H), 3.75 (d, $J$ = 9 Hz, 1H), 2.30 (m, 1H), 2.05 (m, 1H), 1.70 (m, 1H), 0.91 (s, 18H), 0.09 (s, 6H), 0.06 (s, 6H). $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 159.5, 136.9, 134.8, 132.3, 131.7, 130.2, 120.9, 115.7, 114.9, 112.9, 82.4, 75.7, 73.1, 72.4, 71.1, 50.9, 29.0, 25.8, 18.3, 18.0, −4.4, −4.6, −4.7, −5.0. APCI (positive) 575 ([M$^{35}$ClNa]$^+$, 2), 421 (48), 156 (69), 114 (100). Anal. calcd for $C_{29}H_{49}ClO_4Si_2$: C, 62.95; H, 8.9. Found: C, 63.0; H, 8.9.

**[2*R*, (1*E*,3*R*), 3*R*,4*R*]-3-{4-*tert*-Butyldimethylsilyloxy-2-[3-*tert*-butyldimethylsilyloxy-4-(3-chlorophenoxy)but-1-enyl]tetrahydrofuran-3-yl}-propan-1-ol (24).** The alkene **23** (2.43 g, 4.39 mmol) was dissolved in dry tetrahydrofuran (25 mL) under nitrogen. 9-BBN (0.5 M, 10.0 mL, 5 mmol) was added over 5 min (a cold water bath was used to maintain the temperature below 20 °C). The mixture was stirred for 2.5 h (TLC, MTBE/heptane 1:3 showed no starting material). The reaction was cooled in an ice bath to 5 °C. Sodium hydroxide solution (3 M, 2.0 mL) and hydrogen peroxide (27.5%, 2.3 mL) were added in small portions, keeping the temperature below 10 °C (addition of further sodium hydroxide (3 M, 0.2 mL) and hydrogen peroxide (27.5%, 0.3 mL) showed no further exotherm). The mixture was warmed to room temperature and stirred for a further 30 min. The reaction was poured into water (50 mL) and extracted with MTBE (3 × 30 mL) [brine (25 mL) was added to aid separation of phases]. The combined organic layers were washed with brine (2 × 30 mL), dried ($MgSO_4$), filtered, and evaporated. The residue was chromatographed (MTBE/heptane 1:4 to 1:2) to give the alcohol **24** as a colorless oil (1.96 g, 3.43 mmol, 78%). $[\alpha]_D^{20}$ +45.1 (*c* 1.0, $CH_2Cl_2$). IR (neat) 3446 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.19 (t, $J$ = 8 Hz, 1H), 6.90 (t, $J$ = 2 Hz, 1H), 6.86 (t, $J$ = 2 Hz, 1H), 6.75 (dd, $J$ = 8, 2 Hz, 1H), 5.77 (m, 2H), 4.53 (m, 1H), 4.34 (m, 1H), 4.05 (m, 1H), 4.01 (dd, $J$ = 9, 4 Hz, 1H), 3.86 (m, 2H), 3.76 (d, $J$ = 9.5 Hz, 1H), 3.62 (m, 2H), 1.65−1.4 (m, 4H), 1.25−1.15 (m, 2H), 0.91 (s, 18H), 0.11 (s, 3H), 0.10 (s, 3H),

0.09 (s, 3H), 0.08 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 159.5, 134.8, 132.5, 131.8, 130.2, 120.9, 115.0, 112.9, 82.8, 75.8, 73.1, 72.3, 71.0, 63.1, 51.1, 31.2, 25.8, 25.8, 20.7, 18.3, 18.0, −4.9, −4.6, −4.7, −5.0. APCI positive 595 ($[M^{37}ClNa]^+$, 43), 593 ($[M^{35}ClNa]^+$, 100). Anal. calcd for $C_{29}H_{51}ClO_5Si_2$: C, 61.0; H, 9.0. Found: C, 60.9; H, 9.0.

**[2*R*, (1*E*,3*R*), 3*R*,4*R*]-3-{4-*tert*-Butyldimethylsilyloxy-2-[3-*tert*-butyldimethylsilyloxy-4-(3-chlorophenoxy)but-1-enyl]tetrahydrofuran-3-yl}-propionaldehyde (25).** A solution of dry dimethyl sulfoxide (0.82 mL, 11.6 mmol) in dry dichloromethane (10 mL) was added over 5 min to a solution of oxalyl chloride (2 M in dichloromethane, 2.65 mL) in dichloromethane (20 mL) at −60 °C under nitrogen. Stirring was continued for 5 min, and then a solution of the alcohol **24** (2.76 g, 4.83 mmol) in dichloromethane (15 mL) was added over 5 min (maintaining the temperature below −60 °C). The alcohol was washed in with dichloromethane (5 mL) and the reaction was stirred for 40 min. Triethylamine (3.4 mL, 24.2 mmol) was added dropwise and after 15 min the reaction was allowed to warm to room temperature. Water (50 mL) was added and the mixture was extracted with heptane (2 × 50 mL). The combined organic phases were washed with hydrochloric acid (1 M, 50 mL), water (50 mL), aqueous sodium carbonate solution (5%, 50 mL), water (50 mL), and brine (50 mL), dried ($MgSO_4$), filtered, and evaporated. The residue was chromatographed (MTBE/heptane 1:4) to give the aldehyde **25** as a colorless oil (2.55 g, 4.47 mmol, 92%). $[\alpha]_D^{20}$ +47.0 (*c* 1.0, $CH_2Cl_2$). IR (neat) 1727 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.72 (m, 1H), 7.18 (t, *J* = 8 Hz, 1H), 6.91 (d, *J* = 8 Hz, 1 H), 6.86 (t, *J* = 2 Hz, 1H), 6.75 (dd, *J* = 8, 2 Hz, 1H), 5.82 (m, 2H), 4.53 (m, 1H), 4.32 (m, 1H), 4.12 (m, 1H), 4.04 (dd, *J* = 10, 4 Hz, 1 H), 3.85 (d, *J* = 6 Hz, 2H), 3.75 (d, *J* = 9 Hz, 1H), 2.44 (m, 2H), 1.90 (m, 1H), 1.70−1.50 (m, 2H), 0.90 (s, 18H), 0.10 (s, 6H), 0.08 (s, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 201.7, 159.5, 134.8, 133.0, 131.3, 130.2, 120.9, 114.9, 112.9, 82.7, 75.7, 73.0, 72.3, 71.0, 50.2, 42.2, 25.8, 25.7, 18.3, 18.0, 17.2, −4.3, −4.6, −4.7, −5.0. APCI (positive) 593 ($[M^{37}ClNa]^+$, 18), 591 ($[M^{35}ClNa]^+$, 41), 114 (100). Anal. calcd for $C_{29}H_{49}ClO_5Si_2$: C, 61.2; H, 8.7. Found: C, 61.35; H, 8.7.

**Isopropyl 4-Bromobutyrate (28).** 4-Bromobutyric acid (21.6 g, 129 mmol) was dissolved in 2-propanol (100 mL). Concentrated sulfuric acid (0.5 mL) was added and the mixture was heated at reflux for 2 h (TLC MTBE/heptane 1:3 indicated complete reaction). The solution was cooled to room temperature and concentrated under reduced pressure (70 mL of solvent was removed). The concentrate was dissolved in MTBE (150 mL) and washed with saturated sodium hydrogencarbonate (50 mL), water (50 mL), and brine (50 mL). The solution was dried ($MgSO_4$), filtered, and evaporated to give a yellow liquid (21.7 g, 80%). NMR showed minor impurities (a more polar spot was visible by TLC). The crude product was dissolved in heptane (100 mL) and washed with water (2 × 50 mL) (this removes most of the impurity). The heptane solution was dried ($MgSO_4$) and filtered through a pad of silica (14 g), washing through with heptane (100 mL). The solvent was evaporated to give the title compound **28** (17.5 g, 65%) as a colorless liquid. $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 5.00 (heptet, *J* = 6 Hz, 1H), 3.45 (t, *J* = 6 Hz, 2 H), 2.45 (t, *J* = 7 Hz, 2H), 2.16 (quintet, *J* = 7 Hz, 2 H) and 1.22 (d, *J* = 6 Hz, 6H).

**(3-Isopropoxycarbonylpropyl)triphenylphosphonium Bromide (29).**[16] Isopropyl 4-bromobutyrate **28** (16.0 g, 76.5 mmol) and triphenylphosphine (20.0 g, 76.5 mmol) in toluene (160 mL) were heated at reflux under nitrogen for 39 h. The phosphonium salt **29** separated as a white power. The mixture was allowed to cool (to approximately 40 °C), filtered, and the solid was washed with toluene (3 × 25 mL). The product **36** was dried under vacuum to give a white solid (20.7 g, 57%). mp 198 °C (onset by DSC). $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 7.85−7.60 (m, 15H), 4.89 (heptet, *J* = 6 Hz, 1H), 3.96−3.70 (m, 2H), 2.75 (t, *J* = 6 Hz, 2H), 1.95−1.75 (m, 2H), 1.13 (d, *J* = 6 Hz, 6H).

**Isopropyl [2*R*, (1*E*,3*R*), 3*R* (4*Z*), 4*R*]-7-{4-*tert*-butyldimethylsilyloxy-2-[3-*tert*-butyl-dimethylsilyloxy-4-(3-chlorophenoxy)but-1-enyl]tetrahydrofuran-3-yl}-hept-4-enoate (27).** The phosphonium salt **29** (3.92 g, 8.32 mmol, freshly dried by heating under high vacuum) was suspended in dry tetrahydrofuran (30 mL) and cooled to 0 °C under nitrogen. Potassium bis(trimethylsilyl)amide (0.5 M in toluene, 16.6 mL) was added dropwise over 5 min (temperature rose to 3 °C) and the resulting orange solution was stirred for 40 min and then cooled to −72 °C. A solution of the aldehyde **25** (2.37 g, 4.16 mmol) in tetrahydrofuran (30 mL) was added dropwise over 20 min, maintaining the temperature below −70 °C. The residues were washed in with tetrahydrofuran (5 mL) and the mixture was stirred for 1.5 h and then allowed to warm to 0 °C over 2 h. The reaction was quenched with saturated ammonium chloride solution (50 mL) (temperature rose to 13 °C) and water (20 mL) to dissolve salts. The organic layer was separated and the aqueous phase was extracted with ethyl acetate (50 mL). The combined organic phases were washed with water (50 mL) and brine (50 mL), dried ($Na_2SO_4$), filtered, and evaporated. The residue was chromatographed (ethyl acetate/heptane 1:10) to give the silyl protected prostaglandin analogue **27** (2.63 g, 3.88 mmol, 94%). $[\alpha]_D^{20}$ +23.9 (*c* 1.0, $CH_2Cl_2$). IR (film) 1731 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ ppm 7.18 (t, *J* = 8 Hz, 1H), 6.91 (d, *J* = 8 Hz, 1H), 6.87 (t, *J* = 2 Hz, 1H), 6.76 (dd, *J* = 8, 2 Hz, 1H), 5.80 (m, 2H), 5.34 (m, 2H), 5.01 (heptet, *J* = 6 Hz, 1H), 4.53 (m, 1H), 4.34 (m, 1H), 4.10 (m, 1H), 4.02 (dd, *J* = 9, 3.5 Hz, 1H), 3.84 (d, *J* = 6 Hz, 2H), 3.75 (d, *J* = 9 Hz, 1H), 2.30 (m, 4H), 2.08 (m, 2H), 1.65 (m, 2H), 1.27 (m, 1H), 1.22 (d, *J* = 6 Hz, 6H), 0.91 (s, 18H), 0.08 (s, 12H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 172.6, 159.5, 134.8, 132.4, 131.8, 130.7, 130.2, 128.0, 120.9, 114.9, 112.9, 82.7, 75.9, 73.0, 72.4, 71.1, 67.6, 50.7, 34.6, 25.8, 25.6, 24.2, 23.0, 21.9, 18.3, 18.0, −4.3, −4.6, −4.7, −5.0. APCI 705 ($[M^{37}ClNa]^+$, 49), 703 ($[M^{35}ClNa]^+$, 100). Anal. calcd for $C_{36}H_{61}ClO_6Si_2$: C, 63.45; H, 9.0. Found C, 63.45; H, 9.0.

**Isopropyl [2*R*, (1*E*,3*R*), 3*R* (4*Z*), 4*R*]-7-{4-*tert*-butyldimethylsilyloxy-2-[3-*tert*-butyl-dimethylsilyloxy-4-(3-chlorophenoxy)but-1-enyl]tetrahydrofuran-3-yl}-hept-4-enoate (27) by Wittig Reaction/Ester Formation.** 3-Carboxypropyltriphenylphosphonium bromide (268 mg, 0.62 mmol) was suspended in tetrahydrofuran (3 mL) under nitrogen and cooled to 3 °C. Potassium *tert*-butoxide (1 M in tetrahydrofuran, 1.25 mL) was added dropwise and the mixture was stirred for 40 min (a bright orange solution was obtained). The mixture was cooled to −2 °C and a solution of the aldehyde **25** (237 mg, 0.42 mmol) in tetrahydrofuran (2.5 mL) was added over 3 min (the residues were washed in with tetrahydrofuran, 0.5 mL). The reaction was stirred for 1 h (TLC MTBE/heptane 1:3 showed complete reaction) and then quenched with saturated ammonium chloride solution (20 mL). Water (10 mL) was added to dissolve salts and the mixture was extracted with ethyl acetate (2 × 20 mL). The combined organic phases were washed with saturated ammonium chloride solution (10 mL) and brine (10 mL), dried ($Na_2SO_4$), filtered, and evaporated to give a yellow oil (385 mg). The crude heptenoic acid **26** was dissolved in acetone (2 mL), and DBU (0.31 mL, 2.1 mmol) was added. After stirring for 5 min, isopropyl iodide (0.21 mL, 2.1 mmol) was added and the solution was stirred overnight (TLC MTBE/heptane 1:7 showed complete reaction). The mixture was partitioned between saturated potassium dihydrogen orthophosphate solution (15 mL) and ethyl acetate (2 × 20 mL). The organic phases were washed with brine (10 mL), dried ($Na_2SO_4$), filtered, and evaporated. The residue was chromatographed (MTBE/heptane 1:7) to give the *title compound* **27** (160 mg, 56%) as a colorless oil.

**Isopropyl [2*R* (1*E*,3*R*), 3*S* (4*Z*), 4*R*)]-7-{tetrahydro-2-[4-(3-chlorophenoxy)-3-hydroxy-1-butenyl]-4-hydroxy-3-furanyl}-4-heptenoate (AL-12182) (1).**[1] The silyl protected prostaglandin analogue **27** (2.40 g, 3.52 mmol) was dissolved in tetrahydrofuran (15 mL) (internal temperature 18 °C). Tetrabutylammonium fluoride (1 M in tetrahydrofuran, 10.5

mL) was added (temperature rose to 20 °C over 3 min) and the mixture was stirred at room temperature under nitrogen for 4 h (TLC ethyl acetate/heptane 3:1 indicated complete reaction). Water (50 mL) was added and the mixture was extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were washed with water (50 mL) and brine (50 mL), dried ($Na_2SO_4$), filtered, and evaporated. The residue was chromatographed (ethyl acetate/heptane 7:3) to give a faintly yellow oil (1.42 g, 3.13 mmol, 89%). Even after drying under high vacuum, small peaks at $\delta$ 0.9 were visible in the $^1$H NMR spectrum. The product was passed through a short silica column eluting with neat ethyl acetate to give AL-12182 **1** as a clear, colorless oil (1.29 g, 2.85 mmol, 81%). $[\alpha]_D^{20}$ +27.6 (*c* 1.0, EtOH). IR (film) 3416 and 1725 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.19 (t, $J$ = 8 Hz, 1H), 6.95 (d, $J$ = 8 Hz, 1H), 6.91 (t, $J$ = 2 Hz, 1H), 6.78 (dd, $J$ = 8, 2 Hz, 1H), 5.84 (m, 2H), 5.50−5.30 (m, 2H), 4.99 (heptet, $J$ = 6 Hz, 1H), 4.56 (m, 1H), 4.41 (m, 1H), 4.14−4.05 (m, 2H), 3.97 (dd, $J$ = 9, 4 Hz, 1H), 3.93−3.85 (m, 2H), 2.65 (brs, 2H), 2.50 (m, 1H), 2.36−2.22 (m, 4H), 2.00 (m, 1H), 1.75 (m, 1H), 1.52 (m, 1H), 1.43 (m, 1H), 1.22 (d, $J$ = 6 Hz, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ ppm 173.2, 159.2, 134.9, 132.7, 130.7, 130.6, 130.3, 128.1, 121.4, 115.1, 113.0, 82.2, 75.5, 72.6, 71.8, 70.1, 68.0, 50.9, 34.4, 25.8, 24.6, 22.7, 21.9, 21.9. APCI 477 ($[M^{37}ClNa]^+$, 25), 475 ($[M^{35}ClNa]^+$, 69), 247 (100).

**Acknowledgment.** This work was carried out in collaboration with Alcon Laboratories Inc., 6201 S. Freeway, Fort Worth, TX 76134. We are grateful for Mark DuPriest of Alcon for advice and helpful discussions. Analytical support was provided by Catherine Hill.

**Supporting Information Available:** HPLC chromatograms of AL-12182 **1** showing principle impurities. This material is available free of charge via the Internet at http://pubs.acs.org.

JO048035V