Organic Process Research & Development **2002**, *6*, 138–145

Synthesis of the Potent Antiglaucoma Agent, Travoprost

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Abstract:

A commercial synthesis of the antiglaucoma agent, travoprost 2, is described. A total of 22 synthetic steps are required to provide the single enantiomer prostanoid, with the longest linear sequence being 16 steps from 3-hydroxybenzotrifluoride. The route is based upon a cuprate-mediated coupling of the single enantiomer vinyl iodide 13 and the tricyclic ketone 5, of high stereochemical purity, to yield the single isomer bicyclic ketone 15. A Baeyer−Villiger oxidation provides the lactone 16 as a crystalline solid, thus limiting the need for chromatographic purification. DIBAL-H reduction, Wittig reaction, esterification, and silyl group deprotection complete the synthesis of travoprost.

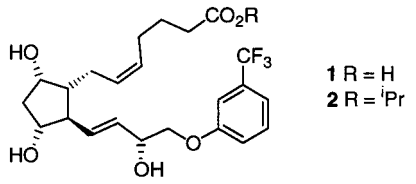

Figure 1.

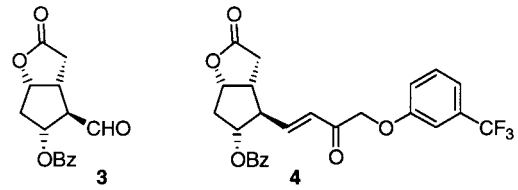

Figure 2.

Introduction

The prostaglandin analogue 16-[3-(trifluoromethyl)phenoxy]-17,18,19,20-tetranor $PGF_{2\alpha}$ **1** and its ester derivatives, in particular the isopropyl ester travoprost **2**, are potent drugs for the treatment of glaucoma and ocular hypertension (Figure 1).[1] Additionally, certain phenyl-substituted prostaglandin analogues are known to be potent and selective antiglaucoma agents.[2] Recently, novel analogues in which a cyclohexane unit[3] has replaced the cyclopentane core and a series containing a boronate[4] in the α-side chain have been synthesized. The racemic form of **1**, fluprostenol, was developed by ICI for use as a veterinary contraceptive agent.[5] The ICI synthesis commenced from the Corey lactone aldehyde **3**,[6] with the α- and *ω*-side chains being built up by Horner-Emmons/Wittig alkenylation reactions.

The biological profile and synthesis of **2** and its analogues have been described by Klimko et al.[1] Their synthetic strategy was based on the Corey lactone route wherein the cyclopentane ring embedded in a lactone intermediate of type **3** has relative stereochemistry correctly defined across four chiral centres (Figure 2). This approach has two major limitations (a) the reduction of the keto function in the *ω*-side chain of intermediate **4** using (−)-*B*-chlorodiisopinocampheylborane gave an insufficiently high diastereoisomeric excess, requiring the removal of the unwanted 15-(*S*) isomer by a difficult chromatographic separation, and (b) this route requires the purchase or synthesis of multikilogram quantities of the Corey lactone aldehyde **3**. Hence, an alternative route more amenable to the manufacture of kilogram quantities of travoprost **2** was sought.

Elegant three-component coupling methodologies have been developed for the synthesis of prostaglandins.[7] An alternative three-component, two-step variation has also been devised by Johnson.[8] Gooding describes the application of a three-component coupling to unnatural prostaglandins with (*E*)-CH═CHCH(OH)CH_2OPh as the *ω*-side chain, introduced by conjugate addition of a stannane-derived cuprate.[9] Other novel routes to prostaglandin analogues based on alkyne metathesis[10] and nickel-catalysed cyclisation[11] to form the cyclopentane core have appeared recently. From our experience in this area over the past six years we felt that none of these methods were suitable for a scaleable, commercial synthesis of travoprost **2**. In particular, none of these methods provided the rigorous control of all the stereocentres that we sought to satisfy the regulatory authorities. Therefore, an alternative synthetic strategy was required.

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(1) Klimko, P. G.; Bishop, J.; Desantis Jr., L.; Sallee, V. L. EP 0639563, 1995; *Chem. Abstr*. **1995**, *122*, 290579.
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(4) Feng, Z.; Hellberg, M. *Tetrahedron Lett*. **2000**, *41*, 5813.
(5) a) Mallion, K. B. U.S. Patent 3,935,240, 1976; *Chem. Abstr*. **1974**, *81*, 120097. (b) Bowler, J.; Crossley, N. S. U.S. Patent 4,321,275, 1982; *Chem. Abstr*. **1977**, *86*, 43256.
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(7) For some examples, see: Noyori, R.; Suzuki, M. *Angew. Chem., Int. Ed. Engl*. **1984**, *23*, 847; Morita, Y.; Suzuki, M.; Noyori, R. *J. Org. Chem*. **1989**, *54*, 1785; Suzuki, M.; Morita, Y.; Koyano, H.; Koga, M.; Noyori, R. *Tetrahedron* **1990**, *46*, 4809; Noyori, R.; Suzuki, M. *Chemtracts: Org. Chem*. **1990**, *3*, 173.
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(9) Gooding, O. W.; Beard, C. C.; Cooper, G. F.; Jackson, D. Y. *J. Org. Chem*. **1993**, *58*, 3681.
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Published on Web 02/07/2002

10.1021/op010097p CCC: $22.00

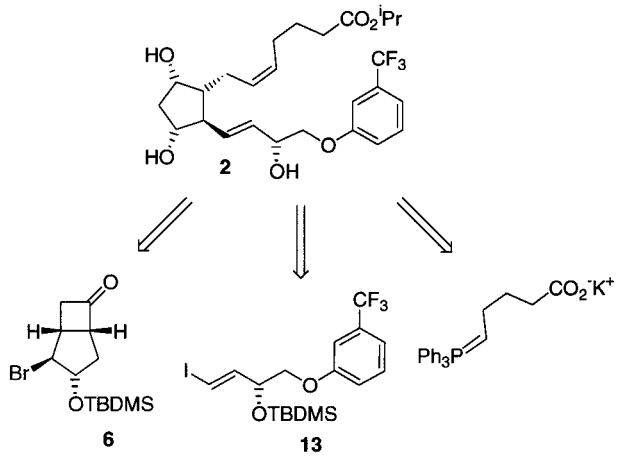


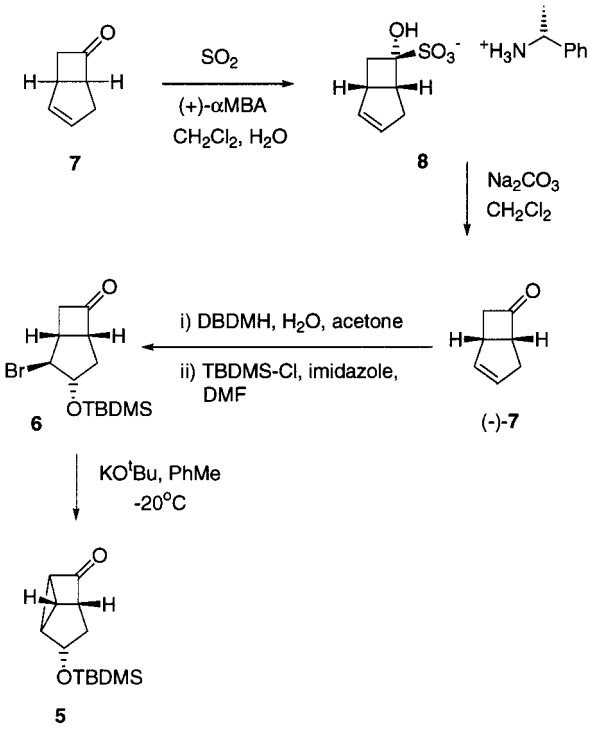
Figure 3.

Results and Discussion

We were attracted to a highly convergent approach to prostaglandin analogues involving addition of a cuprate reagent, incorporating the entire ω-side chain, to tricyclo-[3.2.0.0^{2,7}]heptanone **5** developed by Roberts and Newton.[12] This route required three synthons: the commercially available Wittig reagent (4-carboxybutyl)triphenylphosphonium bromide, the silyl-protected bromohydrin **6** to provide the cyclopentane core, and the vinyl iodide **13** to give access to the ω-side chain (Figure 3). Thus, **6** and **13** had to be prepared with high stereochemical purity.

The tricyclic ketone **5** was prepared from the TBDMS-protected bromohydrin **6**, which was in turn derived from bicyclo[3.2.0]hept-2-en-6-one **7** (Scheme 1).[13] The literature synthesis of **7** was readily scaled up to kilogram levels, except that we did not batch distill the intermediate dichlorobicyclo[3.2.0]hept-2-en-6-one, or **7**.[14] DSC analysis showed that the distillation of these materials could be hazardous principally because of decomposition of the residues. When heated at 10 °C/min in sealed aluminium pans, the crude dichlorobicycloheptenone decomposed exothermically from about 160 °C, the distilled material displayed two endotherms (probably due to evaporation), and the distillation residue decomposed exothermically from about 90 °C. The DSC results also showed that the distillation of **7** left an unstable residue, which degraded exothermically upon heating. Both of these materials were therefore purified by a short path wipe film distillation for any quantities above 50 g. The resolution of racemic bicyclo[3.2.0]hept-2-en-6-one **7** by forming diastereomeric salts of its α-hydroxysulfonic acid derivative with (+)-α-methylbenzylamine **8** and separation by crystallisation has been described.[15] To develop a synthesis capable of producing multihundred-gram to kilogram quantities of travoprost **2** we needed to operate this resolution at pilot-plant scale. The process developed at 5-L scale in the laboratory was subsequently transferred to 200-L vessels without any major process changes.

Scheme 1



The single enantiomer, bicycloheptenone (−)-**7** (99% ee), was liberated after treatment of the salt with aqueous sodium carbonate solution. This was carried out prior to the bromohydrin formation to minimise handling of the volatile bicycloheptenone, which had also shown a tendency to degrade at ambient temperature over short periods. Treatment of (−)-**7** with 1,3-dibromo-5,5-dimethylhydantoin in acetone/water gave the crude bromohydrin with excellent diastereoisomeric and regioisomeric control (<10% minor isomers). The rationale behind the highly selective bromohydrin formation in this system has been fully detailed.[16] The bromohydrin contained small amounts of hydantoin impurities that could not be readily removed by crystallisation, and consequently, the material was used crude. Silyl-protected **6** was readily recrystallised to provide analytically pure product in 38% yield from the salt **8**. The silyl-protected bromohydrin **6** was converted into the tricycle **5** as required.

Avoidance of awkward late-stage reduction to establish the required configuration of the C-15-OH functionality provides the major advantage of this route. The stereochemistry at C-15 is controlled by using a single enantiomer side chain derived from the acetylene **9**. The acetylene was derived from the racemic alcohol **10**[17] via a bioresolution sequence (Scheme 2).[18]

Enzymatic acylation of the racemic alcohol **10**, using Chirazyme L9, afforded the ester (*R*)-**11** and the alcohol (*S*)-**10** (Scheme 2). This mixture could be separated, after which basic hydrolysis of the butyrate ester (*R*)-**11** gave the desired

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(13) Grieco, P. A. *J. Org. Chem.* **1972**, *37*, 2363.
(14) The distillation of 7,7-dichlorobicylco[3.2.0]hept-2-en-6-one has been described. Minns, R. A. *Organic Syntheses*; Wiley & Sons: New York, Collect. Vol. 6, 1988, p 1037.
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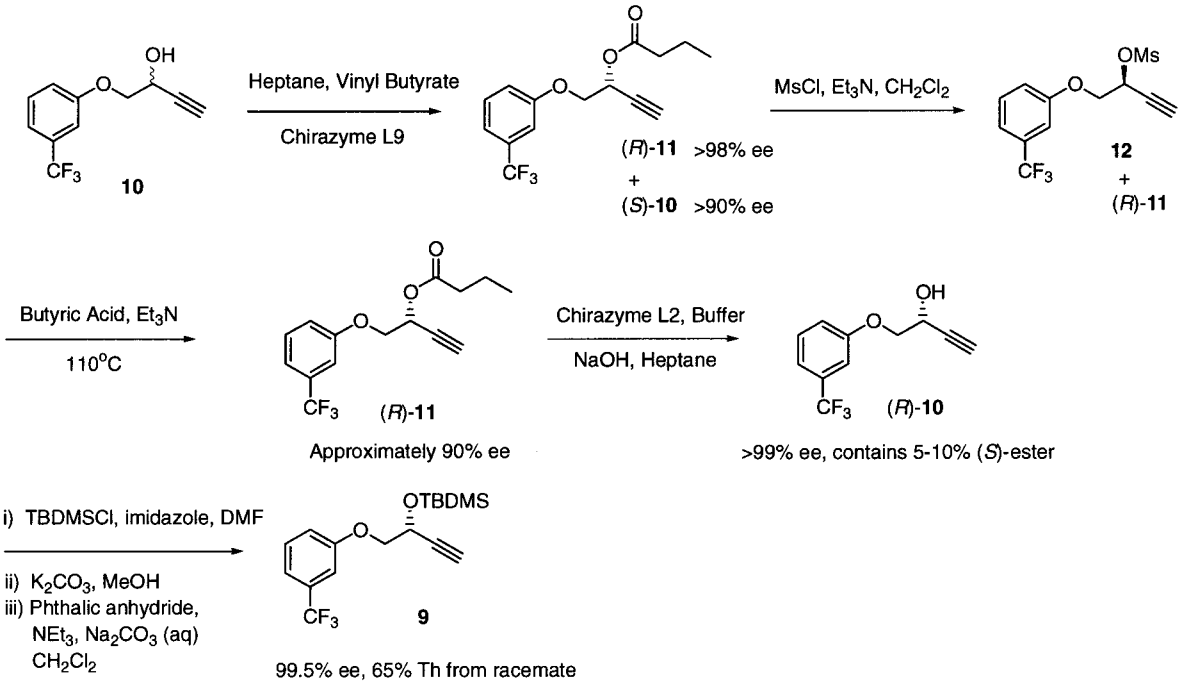
(17) Tolstikov, G. A.; Miftakhov, M. S.; Danilova, N. A.; Galin, F. Z. *Z. J. Org. Chem. USSR (Engl. Transl)*, **1983**, *19*, 1624−1631.
(18) Full details of this process are published elsewhere. (a) Fox, M. E.; Parratt, J. S. U.S. Patent 6,214,611; *Chem. Abstr*. **2000**, *133*, 309067. (b) Fox, M. E.; Jackson, M.; Lennon, I. C.; McCague, R.; Parratt, J. S. *Adv. Synth. Catal.* **2002**, *344*. In press.

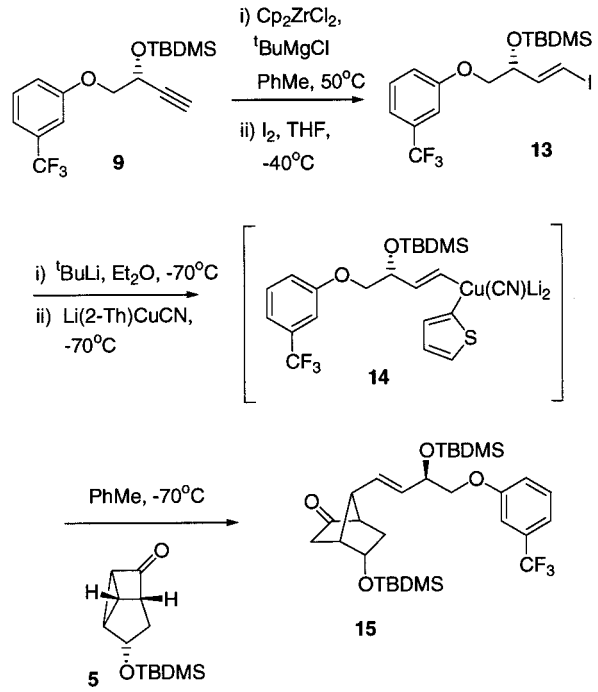
Scheme 2



alcohol (*R*)-**10** in >98% ee. In this case the maximum yield of **10** is 50%, with typical yields being 38−45%. To increase the throughput of material from this resolution we developed a mesylation and inversion process.[18] Reaction of the mixture of ester (*R*)-**11** and alcohol (*S*)-**10** with methanesulfonyl chloride gave a mesylate **12**/ester (*R*)-**11** mixture. Treatment of this mixture with butyric acid and triethylamine at 110 °C afforded the desired butyrate ester (*R*)-**11** with approximately 90% ee. Enzymatic hydrolysis of the ester, using Chirazyme L2, gave the alcohol (*R*)-**10** with >99% ee, containing some residual (*S*)-ester. The acetylene **9** was obtained in 58−65% yields from the racemate **10** and 99.5% ee after protection of the alcohol with TBDMSCl, basic hydrolysis of the residual ester and hemiphthalate formation. The final purification involved a base wash to remove the hemiphthalate and a simple filtration through a pad of silica gel.

The vinyl iodide **13** was prepared from the acetylene **9** via a hydrozirconation−iodination sequence (Scheme 3).[19] In this procedure the reactive zirconium reagent, ^{i}BuZrCp$_2$Cl,[19] is formed in situ from readily available zirconocene dichloride and *tert*-butylmagnesium chloride, thus avoiding the need for the more expensive Schwartz's reagent (Cp$_2$Zr(H)Cl). Vinyl iodide **13** was metalated with *tert*-butyllithium and then treated with lithium 2-thienylcyanocuprate. In our hands the use of *n*-butyllithium for the metalation failed to give satisfactory results. Fresh preparation of lithium 2-thienylcyanocuprate, by lithiation of thiophene with *n*-butyllithium followed by treatment with copper(I) cyanide, gave the most reproducible results. Reaction of alkenylcuprate **14** with tricycle **5** formed the bicyclic ketone **15**. The tricycle could be isolated as a low-melting, white solid on a small scale (<10 g), but on larger scale extensive decomposition

Scheme 3

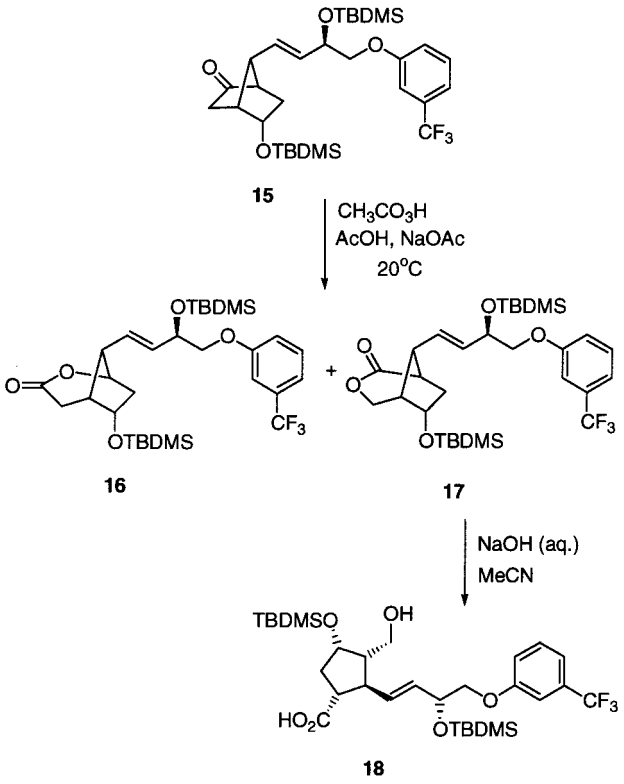


of the tricycle was observed upon drying. Therefore, tricycle **5** was used without purification as a concentrated toluene solution. The crude ketone **15** was semipurified by passing through a silica gel pad to provide **15** in greater than 90% chemical purity and 64% yield, and an analytically pure sample was obtained by silica gel chromatography.

The most problematic process step was the Baeyer−Villiger oxidation of the ketone **15**. The use of peracetic acid and sodium acetate in acetic acid resulted in a 3:1 mixture of regioisomeric lactones, **16** and **17** isolated as an oil (Scheme 4). This ratio is consistent with the Baeyer−Villiger oxidation of similar systems reported in the literature.[20] A

(19) Swanson, D. R.; Nguyen, T.; Noda, Y.; Negishi, E. *J. Org. Chem.* **1991**, *56*, 2590.

Scheme 4



variety of oxidation systems were studied including *m*-chloroperbenzoic acid and various metal-catalysed reactions.[21] In all cases the ratio of regioisomers was similar to that outlined above. Extensive epoxidation of the ω-side chain olefin was also observed with most of these reagents. Using a tosyl group in place of the TBDMS group on the oxabicyclooctanone ring and carrying out the Baeyer−Villiger oxidation with peracetic acid, led to a 10:1 mixture of regioisomers, in favour of the desired isomer. Unfortunately, the tosylate intermediate was not suitable for the synthesis of travoprost **2**.

Conveniently, the minor and unwanted regioisomer **17** was selectively hydrolysed by treatment with aqueous sodium hydroxide in acetonitrile (Scheme 4).[22] The unreacted lactone **16** was separated from the hydroxy acid **18** by crystallisation to provide the desired product in 38% yield. Purification of the mother liquors by passing through a silica gel pad and crystallisation, led to a further crop. An overall yield of 47% of analytically pure, crystalline lactone **16** was obtained.[23]

Another key advantage of our route to travoprost **2** is the crystallinity of lactone **16**. This allows a high-purity, late-stage intermediate to be isolated without the need for careful chromatography. As the lactone was crystalline, we confirmed its structure and relative configuration by X-ray crystallography (Figure 4).[24]

Lactone **16** was converted to the target prostanoid **2** using conventional processes (Scheme 5). Reduction to the lactol

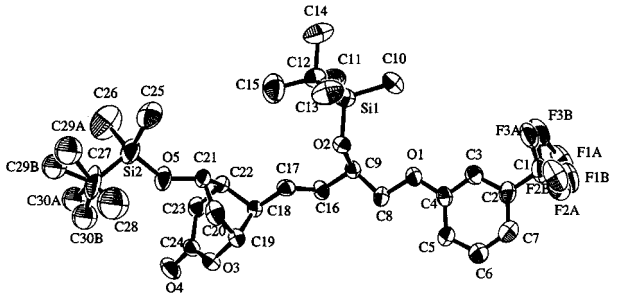
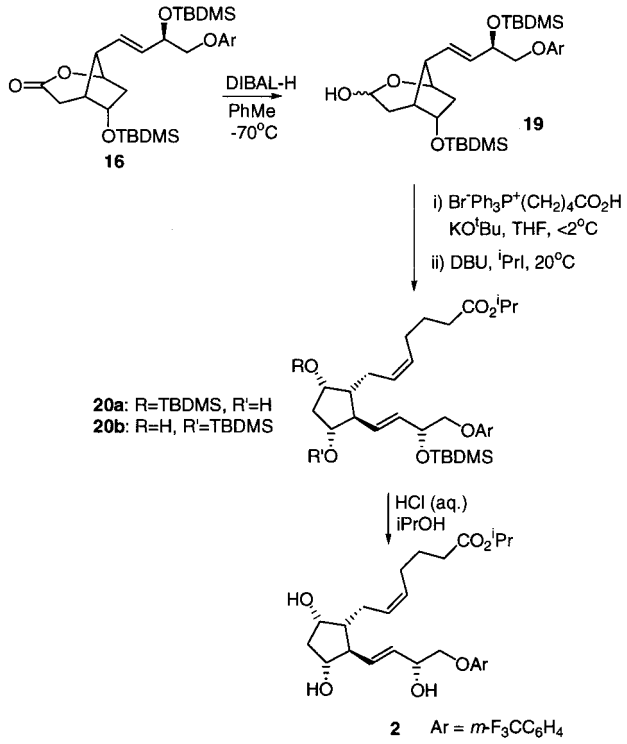


Figure 4. **ORTEP diagram of the molecular structure of lactone 16. Hydrogen atoms are omitted for clarity.**

Scheme 5



19 was achieved using diisobutylaluminium hydride at −70 °C. Wittig reaction with the ylide generated from (4-carboxybutyl)triphenylphosphonium bromide and potassium *tert*-butoxide followed by esterification using DBU and 2-iodopropane afforded the bis-silyl-protected prostanoids **20a** and **20b**. Carrying out the Wittig reaction at 0 °C limited the amount of trans isomer to 3% (whereas reaction at room temperature typically gave 5% trans isomer). The mixture of silyl compounds was also observed due to migration of the protecting group on the cyclopentane ring.[22,25] Deprotection using aqueous hydrochloric acid in 2-propanol

(20) Coleman, M. J.; Crookes, D. L.; Hill, M. L.; Singh, H.; Marshall, D. R.; Wallis, C. J. *Org. Process Res. Dev.* **1997**, *1*, 20.
(21) Gottlich, R.; Yamakoshi, K.; Sasai, H.; Shibasaki, M. *Synlett* **1997**, 971.
(22) Newton, R. F.; Roberts, S. M. *Tetrahedron* **1980**, *36*, 2163.
(23) Jackson, P. M.; Lennon, I. C. U.S. Patent 6,294,679; *Chem. Abstr.* **2000**, *133*, 309792.

(24) Crystal data for $C_{30}H_{47}F_3O_5Si_2$: colourless, monoclinic, $P2_1$, $a = 6.803(10)$ Å, $b = 32.53(4)$ Å, $c = 15.27(4)$ Å, $\beta = 90.24(10)°$, $V = 3380(10)$ Å^3, $Z = 4$, $d_{calc} = 1.181$ g/cm^3, $F(000) = 1288$, μ (Mo Kα) = 0.155 mm^{-1}, θ range 1.33−20.81° (Mo Kα), 123831 measured reflections on a Rigaku RAXIS diffractometer, 6797 independent reflections [R(int) = 0.052], the structure determination using direct methods (SHELXS86), R(F) = 0.0625, Rw = 0.1703 for 5791 reflections with $I > 2\sigma(I)$, GOF = 1.070. Crystallographic data for structure (**16**) reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as deposition No. CCDC-170249. Copies of the data can be obtained on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [e-mail: deposit@ccdc.cam.ac.uk, http://www.ccdc.cam.ac.uk].

(25) For a related example of silyl migration see: Torisawa, Y.; Shibasaki, M.; Ikegami, S. *Chem Pharm. Bull.* **1983**, *31*, 2607.

completed the synthesis of travoprost **2**. This material was isolated with good chemical purity, but was not of high enough purity for a bulk active. A simple purification to remove minor diastereoisomers and minor impurities was developed using a Biotage Prep 75-L chromatography unit. This provided travoprost **2** with excellent chemical purity, suitable for toxicology and clinical trials. This route has been developed further, with only minor modifications, to provide commercial quantities of travoprost **2**.

To conclude, we have demonstrated that the tricycle rearrangement route[12] to prostanoids can be developed to provide a commercially viable route to the antiglaucoma agent, travoprost **2**, with rigorous control of all five stereocentres. The longest linear sequence was 16 steps from 3-hydroxybenzotrifluoride, and yields in the range of 4.0−6.9% were achieved. In total, 22 synthetic steps were required, and a total of 450 g of travoprost was synthesised for clinical trials. We are now using this route for the manufacture of travoprost **2** to provide low-kilogram quantities of the active pharmaceutical ingredient.

Experimental Section

General Procedures. Melting points were determined on an Electrothermal capillary apparatus and are uncorrected. ^{1}H NMR spectra were recorded at 200 MHz (Bruker AM200) or 400 MHz (Bruker DPX 400). ^{13}C NMR spectra were recorded at 100 MHz. Chemical shifts (δ) are quoted in ppm, and coupling constants (J) are given in Hz. Optical rotations were determined using a Perkin-Elmer 341 polarimeter and are given in 10^{-1} deg cm^2 g^{-1}. IR spectra were recorded using a Perkin-Elmer 1600 series FTIR. Mass spectra were recorded using a Navigator LC/MS system, or a Hewlett-Packard GC/MS. Analytical thin-layer chromatography was performed on Merck silica gel precoated plates and visualised using ceric ammonium molybdate or potassium permanganate solution.

(−)-6-Hydroxybicyclo[3.2.0]hept-2-en-6-sulfonic Acid (+)-α-Methylbenzylamine (1:1) Salt (8). (+)-α-Methylbenzylamine (7.30 kg, 60.2 mol), CH_2Cl_2 (86.3 kg) and demineralised water (1.2 kg) were charged to a 200-L nitrogen-purged vessel. The mixture was agitated, and sulfur dioxide gas (17.4 kg, 272 mol) was charged to the vessel with stirring in the temperature range 18−23 °C. (±)-Bicyclo[3.2.0]hept-2-en-6-one **7** (6.50 kg, 60.1 mol) was charged to the vessel, followed by CH_2Cl_2 (5.2 kg), maintaining the temperature of the vessel contents below 25 °C during this addition. The reaction mixture was stirred at 18−23 °C until crystallisation was observed. The contents of the vessel were cooled to between 0 and 5 °C, and the mixture was stirred overnight within this temperature range. The resulting solid was collected by filtration and washed with CH_2Cl_2 (5.2 kg). The solid was washed once more with CH_2Cl_2 (5.2 kg). The damp cake [9.75 kg, estimated dry weight 8.1 kg, 43.3%; liberated (−)-bicycloheptenone was 75% ee] was charged back to the vessel, and 2-propanol (20.3 kg) was added. The mixture was heated to 67 °C. The hazy solution was circulated through an in-line 5 μm filter to give a clear solution. The circulation lines were flushed clear of product using 2-propanol (1.9 kg). The batch was cooled to 0−5 °C and held at this temperature overnight (17 h) and then collected by filtration. The product was washed with 2-propanol (1.8 kg). The wet cake [7.00 kg, estimated dry weight 4.62 kg, 24.7%; liberated (−)-bicycloheptenone, 89% ee] was charged to the vessel with 2-propanol (11.6 kg) and heated to 67 ± 5 °C to give a solution. The mixture was cooled to 0−5 °C and left to stir overnight. The product was collected by filtration and washed with 2-propanol (1.6 kg). The 2-propanol wet cake [5.45 kg, estimated dry weight 4.34 kg, 23.2%; liberated (−)-bicycloheptenone, 97% ee] was charged to the vessel with 2-propanol (10.9 kg) and heated to 65 ± 5 °C, at which point the solids dissolved. The solution was cooled to 0−5 °C and stirred overnight. The resulting slurry was collected by filtration. The wet cake was washed with 2-propanol (1.2 kg) and collected. The wet cake was dried to constant weight to give the final product **8** (4.25 kg, 22.7%), mp 127 °C (lit.[15] 86−88 °C); $[\alpha]_D^{23}$ −14.8 (*c* 5, water).

^{1}H NMR (200 MHz, d_6-DMSO) δ 7.55−7.35 (5H, m, ArH), 5.72 (2H, m), 4.40 (1H, q, J = 8.0), 3.25 (1H, m), 2.92−2.62 (3H, m), 2.25 (1H, dd, J = 16.0, 10.0), 1.51 (1H, m), and 1.48 (3H, d, J = 8.0); Liberated (−)-bicycloheptenone 99% ee, [GC, Chirasil Dex CB, 90 °C, hold for 10 min, ramp to 200 °C at 30 °C/min, retention time: 5.52 min (−); 6.09 min (+)].

1(*R*)-2-*exo*-Bromo-3-*endo*-*tert*-butyldimethylsilyloxybicyclo[3.2.0]heptan-6-one (6). Demineralized water (54 kg), Na_2CO_3 (10.26 kg, 96.8 mol), and (−)-6-hydroxybicyclo-[3.2.0]hept-2-en-6-sulfonic acid (+)-α-methylbenzylamine (1:1) salt **8** (9.00 kg, 28.9 mol) were charged to a 200-L nitrogen-purged vessel. The mixture was agitated. CH_2Cl_2 (12.0 kg) was charged to the reactor, and the mixture was stirred for 15−20 min. The lower CH_2Cl_2 layer was separated, and the aqueous phase was extracted again with CH_2Cl_2 (12.0 kg). The combined CH_2Cl_2 extracts were charged to the vessel, and the vessel contents were adjusted to pH 1 by the controlled addition of hydrochloric acid (7.2%, 16.2 kg) over a 70-min period, maintaining the temperature in the range 8−16 °C. The CH_2Cl_2 layer was separated and washed with demineralised water (6 × 9.0 kg) and then with brine (21 kg). The CH_2Cl_2 solution was dried ($MgSO_4$) and filtered, and the solids were washed with CH_2Cl_2 (4.2 kg). The resulting solution was collected and concentrated by rotary evaporation to give an oil (3.1 kg, quantitative).

The oil (3.1 kg) was dissolved in acetone (10.7 kg) and charged to a vessel, and demineralised water (2.6 kg) was added. 1,3-Dibromo-5,5-dimethylhydantoin (4.14 kg, 14.5 mol) was charged to the reactor over 60−80 min, maintaining the temperature below 10 °C. The temperature was adjusted to 15−20 °C over 2 h, and the reaction mixture was held at this temperature overnight. The reaction mixture was quenched with 10% aqueous $Na_2S_2O_5$ solution (13.5 kg), maintaining the temperature of the mixture below 30 °C. The mixture was extracted with CH_2Cl_2 (3 × 12.0 kg). The CH_2Cl_2 extracts were washed with brine (22 kg) and dried ($MgSO_4$, 1.6 kg). The mixture was filtered, washed with CH_2Cl_2 (24 kg), and concentrated on a rotary evaporator to give the crude bromohydrin (4.75 kg, ∼88% purity = 4.18 kg actual, 62%),

which was then charged to a vessel with DMF (11.0 kg) and imidazole (2.4 kg, 35.2 mol). The mixture was stirred and cooled to 0−5 °C. *tert*-Butyldimethylsilyl chloride (3.5 kg, 23.4 mol) was charged in portions, maintaining the temperature below 5 °C. The reaction mixture was stirred overnight at 20 ± 2 °C. A further portion of *tert*-butyldimethylsilyl chloride (200 g, 1.34 mol) was charged, and the mixture was stirred for 2 h. The reaction mixture was quenched with demineralised water (36 kg) and extracted with heptane (12.3 kg, then 6.2 kg). The combined heptane extracts were washed with water (9.0 kg) and brine (9.0 kg). The heptane solution was dried ($MgSO_4$, 1.8 kg), and the slurry was filtered through a silica gel pad (0.84 kg). The resulting heptane liquors were concentrated under reduced pressure to give an oil (4.1 kg). The oil was charged to a vessel along with heptane (12.3 kg) and stirred to form a solution. The resulting solution was cooled to −27 ± 2 °C over 1 h and left to stir at −27 ± 2 °C for 1 h. The crystalline product was collected by filtration. Heptane (0.7 kg, precooled to −20 ± 2 °C) was charged to the vessel and then transferred to the filter cake. The solid was dried to constant weight to give **6** (3.53 kg, over two crops, 38%), retention time 26.3 min (GC, 25QC2/BP5, 60 °C for 5 min, ramp to 300 °C at 10 °C/min, hold for 25 min), $[\alpha]_D^{23}$ −0.7 (*c* 1.0, CH_2Cl_2); mp 58−62 °C, ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.51 (1H, d, J = 3.5), 4.21 (1H, s), 3.78 (1H, m), 3.33−3.13 (3H, m), 2.48 (1H, m), 2.20 (1H, d, J = 14), 0.85 (9H, s), 0.08 (3H, s), and 0.06 (3H, s).

3(*S*)-*endo*-*tert*-Butyldimethylsilyloxytricyclo[3.2.0.0^{2,7}]-heptan-6-one (5). KO^{t}Bu (114.2 g, 1.02 mol) was suspended in toluene (2 L) and cooled to −15 °C. The suspension was stirred under a nitrogen atmosphere, and a solution of the bromoketone **6** (250 g, 0.783 mol) in dry toluene (400 mL) was added over 1 h. The internal temperature was maintained at −10 to −20 °C. The mixture was stirred for 1 h before being warmed to room temperature, activated carbon (75 g) was added, and the mixture was stirred for 5 min. The mixture was filtered through Celite, and the cake was washed with toluene (2.5 L). The filtrates were concentrated under reduced pressure, at 20 °C, to an approximately 700-mL volume. This solution was used directly in the next step.

(*E*)-1-Iodo-4-(*m*-trifluoromethylphenoxy)-3(*R*)-*tert*-butyldimethylsilyloxy-1-butene (13). A dry 5-L three-necked flask was purged with nitrogen, and bis(cyclopentadienyl)-zirconium dichloride (459 g, 1.57 mol) and toluene (2 L) were added. The vessel was covered with aluminium foil to exclude light, evacuated, and purged with nitrogen. *tert*-Butylmagnesium chloride (2 M in ether, 785 mL, 1.57 mol) was added over 30 min (an exotherm from 20 to 28 °C was observed). The mixture was heated at 50 °C for 1 h (during which time isobutylene evolution was observed). Alkyne **9**[18] (450 g, 1.31 mol) in toluene (500 mL) was added, and heating was continued at 50 °C for 5 h. The reaction mixture was cooled to −40 °C (dry ice/acetone), and iodine (497 g, 1.96 mol) in THF (600 mL) was added over 35 min. The mixture was warmed to room temperature over 1 h. Aqueous $Na_2S_2O_5$ solution (1 M, 2 L) and heptane (3 L) were added (a bright-yellow dense precipitate was formed). The mixture was filtered through a No. 3 filter paper, and the filter cake was washed with heptane (1 L). The organic layer was separated, and the aqueous phase was extracted with heptane (1 L). The combined organic phases were washed with aqueous $Na_2S_2O_5$ solution (1 M, 3 L), saturated aqueous $NaHCO_3$ solution (2 L) (**Note:** effervescence; use care when adding bicarbonate solution), and brine (2 L). The organic phase was dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a brown oil. The residue was passed through a pad of activated aluminium oxide (Neutral Brockmann 1, 150 mesh, 750 g), eluting with heptane (6 L). The solvent was concentrated under reduced pressure, the residue was dissolved in heptane (1 L) and filtered through a No. 3 filter paper. The solvent was evaporated to provide the *iodide* **13** as a dark brown liquid (441 g, 72%), $[\alpha]_D^{23}$ −15.5 (*c* 0.96, CH_2Cl_2); IR ν_{max} (film) 1609, 1592, 1329, and 1130 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40 (1H, t, J = 8), 7.24 (1H, m), 7.11−7.04 (2H, m), 6.68 (1H, dd, J = 14, 5), 6.50 (1H, dd, J = 14, 1), 4.51 (1H, m), 3.91 (2H, d, J = 6), 0.92 (9H, s), and 0.11 (6H, s); *m*/*z* (GC/MS, EI) 415 (M − ^{t}Bu, 15), 288 (45), and 219 (100).

7-*anti*[4-(*m*-Trifluoromethylphenoxy)-3(*R*)-*tert*-butyldimethylsilyloxy-1(*E*)-butenyl]-5(*S*)-*endo*-*tert*-butyldimethylsilyloxybicyclo[2.2.1]heptan-2-one (15). A dry 10-L flange flask, fitted with an overhead stirrer, temperature probe, nitrogen inlet, and pressure-equalised dropping funnel, was purged with nitrogen and cooled to −70 °C. A solution of *tert*-butyllithium (1.7 M in pentane, 1013 mL, 1.72 mol) was added. The solution was recooled to −70 °C, and a solution of the vinyl iodide **13** (436 g, 0.923 mol) in diethyl ether (1.3 L) was added over 90 min, maintaining the internal temperature below −60 °C.

In the meantime, thiophene (75.2 mL, 0.94 mol) was placed in a dry 2-L three-necked flask, under a nitrogen atmosphere. THF (600 mL) was added, and the solution was cooled to −30 °C. *n*-Butyllithium (2.5 M in hexanes, 376 mL, 0.94 mol) was added over 20 min. The solution was stirred for 20 min at −20 °C, and then the resulting yellow solution was added to a suspension of copper(I) cyanide (84.15 g, 0.94 mol) in THF (800 mL) at −20 °C over 15 min. The resulting dark-brown solution was recooled to −10 °C and stirred for 20 min.

The freshly prepared lithium 2-thienylcyanocuprate solution, at −10 °C, was added to the vinyllithium solution at −70 °C over 20−30 min. The resulting solution was stirred for 30 min at −70 °C. The tricycle solution **5** (approximately 187 g in 600 mL toluene, + 100 mL THF added) was cooled to −70 °C and added to the cuprate solution **14** at −70 °C over 20 min. The mixture was stirred at −70 °C for 1 h, the cooling bath was removed from the reaction vessel, and saturated aqueous NH_4Cl solution (3 L) was added. The mixture was allowed to warm to room temperature with stirring (the aqueous layer became deep blue in colour, and a yellow/green precipitate formed). The mixture was filtered through a No. 3 filter paper, and the filter cake was washed with MTBE (1 L). The organic layer was separated, and the aqueous layer was extracted with MTBE (1 L). The combined organic layers were washed with brine (2 L), dried

($MgSO_4$), and decolourised with activated carbon. After 20 min the solution was filtered, the cake was washed with MTBE (2.5 L), and the filtrate was evaporated under reduced pressure.

The residue was taken up in heptane and passed through a plug of silica (1.5 kg), eluting with 2% EtOAc/heptane to 10% EtOAc/heptane to provide the pure ketone **15** as a yellow solid (293 g, 64%), mp 64−72 °C; $[\alpha]_D^{20}$ +35.9 (*c* 1.05, CH_2Cl_2); (Found: C, 61.50; H, 8.04. $C_{30}H_{47}F_3O_4Si_2$ requires C, 61.61; H, 8.10); IR ν_{max} (Nujol) 1738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 (1H, t, $J = 8$), 7.25 (1H, d, $J = 8$), 7.13 (1H, s), 7.07 (1H, d, $J = 8$), 5.86 (1H, dd, $J =$ 16, 8), 5.73 (1H, dd, $J = 16$, 6), 4.55 (2H, m), 3.90 (2H, d, $J = 7$), 2.80 (1H, m), 2.77 (1H, d, $J = 18$), 2.57 (2H, m), 2.45 (1H, m), 2.05 (1H, dd, $J = 18$, 4), 1.35 (1H, m), 0.95 (9H, s), 0.90 (9H, s), 0.15 (3H, s), 0.14 (3H, s), and 0.05 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.0, 158.8, 132.0, 131.5 (q, $J = 32$), 129.9, 127.8, 123.9 (q, $J = 270$), 118.0, 117.5, 111.1, 72.3, 71.3, 69.9, 54.4, 50.2, 46.2, 38.8, 33.4, 25.8, 18.3, 18.0, −4.7, −4.7, −4.9, and −4.9; *m*/*z* (GC/MS, EI) 527 (M − ^{t}Bu, 6), 409 (11), 219 (19), and 73 (100).

8-*anti*[4-(*m*-Trifluoromethylphenoxy)-3(*R*)-*tert*-butyldimethylsilyl-1(*E*)-butenyl]-6(*S*)-*endo*-*tert*-butyldimethylsilyloxy-2-oxabicyclo[3.2.1]octan-3-one (16). Ketone **15** (362.6 g, 0.62 mol) and NaOAc (170 g, 2.07 mol) were dissolved in glacial acetic acid (1.7 L). The reaction vessel was placed in a water bath at 20 °C, and peracetic acid (40% in dilute acetic acid, 176.7 mL, 0.93 mol) was added over a period of 20 min. The solution was stirred at room temperature for 3 h. More peracetic acid (30 mL) was added, and the solution was stirred for a further 2 h. The reaction mixture was poured onto water (2.5 L), and the products were extracted into MTBE (2 × 750 mL, and 500 mL). The combined organic extracts were washed with water (2 L). The aqueous phase was back-extracted with MTBE (500 mL). The combined organic extracts were neutralised with saturated Na_2CO_3 solution (500 mL), and water (2 L) was added to aid phase separation. The organic phase was washed with water (1 L) and brine (1 L), dried ($MgSO_4$), and evaporated under reduced pressure to give a yellow oil (363.8 g). The crude product (consisting of a 3:1 mixture of regioisomers) was dissolved in acetonitrile (1 L) at room temperature. Aqueous NaOH solution (1 M, 300 mL) was added, and the solution was stirred at room temperature for 2 h. Water (1 L) was added, and the product was extracted into MTBE (3 × 500 mL). The combined organic phases were washed with brine (500 mL), dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The residue was recrystallised from heptane (1 L) at −70 °C (cold bath temperature), filtered, and washed with cold (−70 °C, cold bath) heptane (2 × 200 mL). The solid was dried to give the *lactone* **16** as a white solid (141.2 g, 38%). The mother liquors were filtered through silica gel (1 kg), eluting with 20% CH_2Cl_2/heptane to remove baseline material. Recrystallisation from cold (−70 °C, cold bath) heptane (400 mL) gave a second batch of lactone (34 g, 9%), mp 77−78 °C; $[\alpha]_D^{20}$ −10.9 (*c* 1.05, CH_2Cl_2); (Found: C, 59.91; H, 7.90. $C_{30}H_{47}F_3O_5Si_2$ requires C, 59.97; H, 7.88); IR ν_{max} (Nujol) 1733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (1H, t, $J =$ 8), 7.22 (1H, d, $J = 8$), 7.10 (1H, s), 7.05 (1H, d, $J = 8$), 5.70 (2H, m), 4.52 (3H, m), 3.87 (2H, d, $J = 6$), 3.16 (1 H, d, $J = 18$), 3.00 (1H, d, $J = 6$), 2.56 (1H, dd, $J = 18$, 6), 2.46 (1H, m), 2.39 (1H, m), 1.88 (1H, dt, $J = 16$, 3), 0.95 (9H, s), 0.89 (9H, s), 0.10 (6H, s), and 0.04 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ (170.39, 158.75, 132.43, 131.92 (q, $J = 32$), 130.05, 127.87, 123.91 (q, $J = 270$), 118.06, 117.68, 111.11, 82.20, 72.26, 71.64, 71.10, 48.94, 42.48, 40.40, 33.05, 25.75, 18.30, 18.04, −4.64, −4.76, −4.88 and −5.10; *m*/*z* (GC/MS, EI) 543 (M − ^{t}Bu, 7), 219 (43), and 73 (100).

8-*anti*[4-(*m*-Trifluoromethylphenoxy)-3(*R*)-*tert*-butyldimethylsilyl-1(*E*)-butenyl]-6(*S*)-*endo*-*tert*-butyldimethylsilyloxy-2-oxabicyclo[3.2.1]octan-3-ol (19). The lactone **16** (180 g, 300 mmol) was dissolved in dry toluene (2 L), and the solution was cooled to −70 °C under nitrogen. DIBAL-H (1.5 M in toluene, 300 mL) was added dropwise over 1.5 h, and the solution was stirred for 3 h. The reaction was quenched with methanol (100 mL) at −70 °C. Dilute aqueous H_2SO_4 (2 N, 500 mL) was added, maintaining the temperature below −30 °C. The cold bath was removed, and after warming to ambient temperature, the mixture was extracted with MTBE (3 × 500 mL). The organic phases were washed with aqueous H_2SO_4 (2 N, 500 mL), water (500 mL), and brine (500 mL) and dried ($MgSO_4$). The mixture was filtered, and solvent was evaporated to give the *lactol* **19** (181 g, 100%) as a colourless oil, IR ν_{max} (film) 3428 and1724 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 9.78 (1H, s), 7.40 (1H, t, $J =$ 8), 7.20−7.05 (3H, m), 5.65 (2H, m), 4.50 (1H, m), 4.30 (1H, m), 3.95−3.86 (1H, m), 3.88 (2H, d, $J = 6.5$), 2.80 (1H, dd, $J = 19$, 10), 2.45−2.00 (4H, m), 1.78 (1H, m), 1.60 (1H, br), 0.90 (18H, s), 0.06 (6H, s), 0.04 (3H, s), and 0.00 (3H, s).

(5*Z*,13*E*)-(9*S*,11*R*,15*R*)-11-Hydroxy-9,15-bis-(*tert*-butyldimethylsilyloxy)-16-(*m*-trifluoromethylphenoxy)-17,18,19,20-tetranor-5,13-prostadienoic Acid, Isopropyl Ester (20a) and 9-Hydroxy-11,15-bis-(*tert*-butyldimethylsilyloxy)-compound (20b). KO^{t}Bu (1 M in THF, 1.8 L) was added to a stirred solution of (4-carboxybutyl)triphenylphosphonium bromide (402 g, 0.907 mol) in dry THF (3 L) under nitrogen whilst maintaining the temperature below 10 °C. After 30 min the mixture was cooled to 0 °C, and a solution of the lactol **19** (181 g, 0.30 mol) in dry THF (2.5 L) was added over 30−45 min, while maintaining the temperature below 2 °C. The mixture was stirred for 1.5 h. TLC (EtOAc/pentane 1:4) showed complete reaction of the lactol. The reaction was quenched with saturated NH_4Cl (1 L), and the mixture was extracted with EtOAc (1 L, then 2 × 500 mL). The organic phases were washed with water (1 L) and brine (1 L) and dried (Na_2SO_4, 250 g). The solvent was evaporated, and the crude prostadienoic acid was dissolved in acetone (2 L). DBU (280 g, 1.88 mol) was added. After 5 min, isopropyl iodide (306 g, 1.88 mol) was added, and the solution was stirred at room temperature for 20 h. TLC (EtOAc/pentane 1:4) showed complete consumption of the acid. Acetone was removed by rotary evaporation, and the residue was dissolved in EtOAc (3.5 L). The organic solution

was washed with saturated KH_2PO_4 (3.5 L). The aqueous layer was washed with EtOAc (1 L then 0.5 L). The combined organic phases were washed with brine (800 mL), dried with (Na_2SO_4, 210 g), and filtered. The solvent was removed under reduced pressure, and the residue was dissolved in 1:6 EtOAc/heptane (500 mL). The solution was passed down a flash column of silica (1.44 kg) in a sintered funnel. The product was eluted with 1:6 EtOAc/heptane (13 L). The solvent was evaporated to give the *title compounds* (**20a**+**b**) (209 g, 95%) as a colourless oil (Found: C, 62.76; H, 8.69. $C_{38}H_{63}F_3O_6Si_2$ requires C, 62.60; H, 8.71); IR ν_{max} (film) 3521 and 1731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (1H, t, $J = 8$), 7.18 (1H, d, $J = 8$), 7.10 (1H, s), 7.05 (1H, d, $J = 8$), 5.60 (2H, m), 5.40 (2H, m), 5.00 (1H, heptet, $J = 6$), 4.52 (1H, q, $J = 6$), 4.25−4.05 (2H, m), 3.90 (2H, m), 2.55 (1H, d, $J = 10$), 2.40−1.95 (7H, m), 1.80 (1H, d, $J = 15$), 1.65 (3H, m), 1.50 (1H, m), 1.20 (6H, d, $J = 6$), 0.90 (9H, s), 0.85 (9H, s), 0.10 (9H, s), and 0.05 (3H, s); *m*/*z* (CI) 729 (MH^+, 20), 597 (31), 435 (65), 303 (100), and (84).

(5*Z*,13*E*)-(9*S*,11*R*,15*R*)-9,11,15-Trihydroxy-16-(*m*-trifluoromethylphenoxy-17,18,19,20-tetranor-5,13-prostadienoic Acid, Isopropyl Ester (2). The silyl-protected compound (**20a**+**b**) (202 g, 277 mmol) was dissolved in 2-propanol (2.2 L). Aqueous HCl (2 N, 750 mL) was added over 30 min. The solution was stirred at room temperature for 2 h. TLC (100% EtOAc) showed complete deprotection had been achieved. Saturated aqueous $NaHCO_3$ solution (2 L) was added, and the mixture was extracted with EtOAc (1 L, then 2 × 0.4 L). The combined extracts were washed with brine (1 L), dried (Na_2SO_4), filtered, and evaporated. The residue was dissolved in EtOAc (200 mL). The solution (250 g) was chromatographed (100% EtOAc) in four portions on the Biotage 75 medium-pressure silica chromatography system. All relevant fractions were combined and concentrated to give the *title compound* **2** (97 g, 70%) as a colourless oil, $[\alpha]_D^{20}$ +14.6 (*c* 1.0, CH_2Cl_2); IR ν_{max} (film) 3374 and 1727 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 (1H, t, $J =$ 8), 7.22 (1H, d, $J = 8$), 7.15 (1H, s), 7.08 (1H, d, $J = 8$), 5.70 (2H, m), 5.40 (2H, m), 4.98 (1H, heptet, $J = 6.5$), 4.52 (1H, m), 4.18 (1H, m), 3.97 (3H, m), 3.25 (2H, br s), 2.60 (1H, br s), 2.38 (1H, m), 2.30−1.96 (7H, m), 1.76 (1H, dd, $J = 16$, 4), 1.65 (2H, quintet, $J = 7$), 1.55 (1H, m), and 1.20 (6H, d, $J = 6$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.57, 158.67, 135.45, 131.87 (q, $J = 32$), 130.02, 129.85, 129.75, 128.93, 123.89 (q, $J = 270$), 118.06, 117.82, 111.48, 77.77, 72.70, 71.99, 70.86, 67.72, 55.82, 50.24, 42.84, 34.00, 26.60, 25.48, 24.83, and 21.81; *m*/*z* (CI) 501 (MH^+, 21), 321 (34), 303 (44), and 249 (100).

Acknowledgment

We thank Dr. Madeleine Helliwell, Department of Chemistry, University of Manchester for determination of the X-ray crystal structure. We are grateful to Catherine Rippé and Sean Savage for the development of analytical methods, and Dr. John O'Rourke for DSC analysis.

Received for review October 15, 2001.

OP010097P